CEREBRAL PALSY: NEW DEVELOPMENTS

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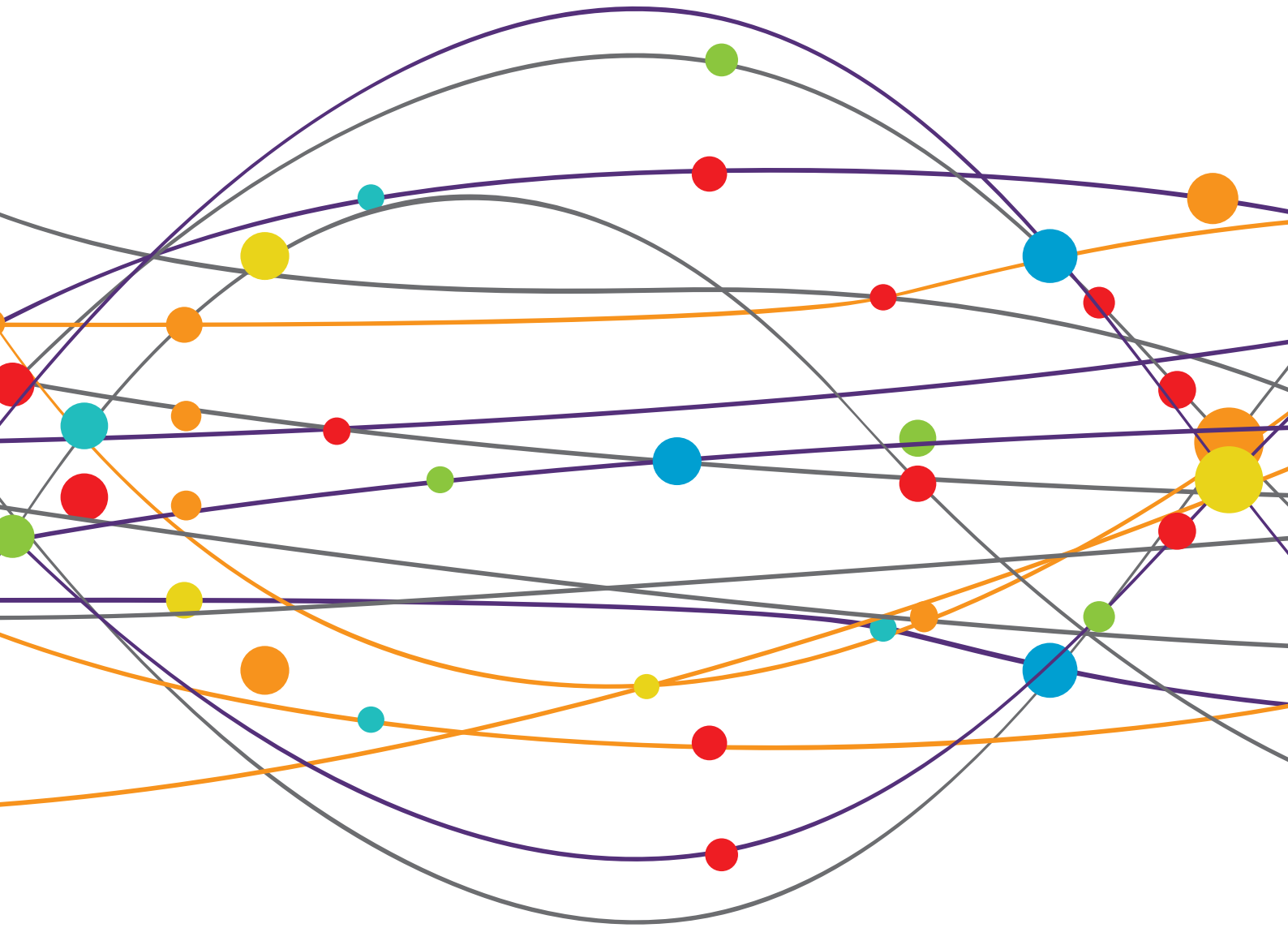

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CEREBRAL PALSY: NEW DEVELOPMENTS

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Editorial: Cerebral Palsy: New Developments

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Editorial on the Research Topic

Cerebral Palsy: New Developments

DEFINITION AND ETIOLOGY

Cerebral palsy (CP) is defined as a non-progressive permanent disorder of movement and posture attributed to disturbances in the developing fetal and infant brain (1). Diagnosis is based on clinical signs, not on causation. This definition was not modified when brain MRI demonstrated diverse lesions underlying CP phenotypes in 80% of patients (2, 3), nor when the development of a semi-quantitative scale (4) led to studies on CP characteristics, localization, extent, and severity of the brain lesions. Possible amplification and clarification of the definition is under discussion.

Genetic studies revealed that half of CP cases without environmental risk factors have pathogenic genomic deletions or duplications (5) raising questions whether this definition could withstand the discovery of mutations that disrupt brain development and confer risk for CP (6). For example, Beysen et al. reported three patients with spastic CP and genetically confirmed Aicardi-Goutières syndrome. MacLennan et al. argued that similarly to the diagnosis of epilepsy the clinical diagnosis of CP should remain, but prompt appropriate genetic investigation (7). Lewis et al., based on CP genomic data, proposed criteria for CP-associated genes through gene discovery, laboratory research, and clinical application. Horber et al., provided guidance for searching for genetic etiologies based on neuroimaging from the SCPE database. Predominantly white and gray matter injuries (around 50 and 20%, respectively) are considered acquired; genetic factors may increase vulnerability and are considered with positive family history and/or missing causative external factors. In maldevelopments and non-specific/normal findings (around 11% each), monogenic causes are likely. In miscellaneous MRI findings, a possible genetic origin may be considered. Wu F. et al. analyzed the most cited imaging articles in CP over three decades and concluded that multi-modality neuroimaging and high-level evidence-based methodologies could be used in future research to further elucidate pathophysiology, prognosis and efficacy of proposed treatments. Reviews emphasized the need for uniform procedures of MRI classification (8), image acquisition, and common outcome measures (9, 10). A common data language for research, such as the common data elements for CP proposed by the AACPDM, will facilitate comparison between studies (11).

EPIDEMIOLOGY

CP prevalence remained relatively stable over several decades; fluctuations reflected advanced perinatal and neonatal care. A decrease in the overall prevalence was preceded by reports on

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decreasing prevalence in low BW children (12–16). Also, severe CP prevalence is declining in preterm and low BW children with severity remaining unchanged in those extremely preterm or with very low BW (12, 13). Tracking the prevalence and clinical features of patients with CP is inherently related to the quality and amount of the collected data (17). Therefore, data from large population-based registries are valuable. Arnaud et al. examined the prevalence and severity of CP in 2,273 preterms, birth-years 2004-2010, from 12 population-based European registries; CP prevalence decreased except for extremely immature children, with the most severely affected showing a similar trend.

Of particular interest are the moderately and late preterm infants (32–34 and 34–36 weeks GA, respectively) representing the majority of all preterms (18) with higher risk than term infants in mortality, poor short-term and long-term outcomes, including impaired motor function (19). Smyrni et al. reported outcomes of a cohort of moderately and late preterm infants (191 out of 1,016 with CP), derived from a population-based registry. Moderately preterm-born with CP were more likely to have a history of N-ICU admission and require respiratory support than late preterm neonates. BW was a strong predictor for early neonatal problems in both groups. The majority in both groups had bilateral spastic CP, white matter lesions and comparable GMFCS levels.

FUNCTIONAL DEFICITS

Spastic CP is the prevailing type and the most amenable to treatment. Main neural impairments characterizing spastic CP include spasticity, decreased selective muscle control and poor postural stability. Secondary non-neural musculoskeletal impairments are altered intrinsic muscle structure, muscle contractures, and bony deformities. Muscle weakness is a predominant impairment highly associated with functional disability that depends both on neural activity and on intrinsic muscle structure. In fact, weakness and contractures are significant contributors to motor deficits and progressive disability with growth, characterizing this condition.

Hanssen et al., discussed the disproportional decrease of muscle size and strength around the knee and ankle joints in spastic CP and highlighted the large variability in the contribution of muscle size to muscle weakness. In a cross-sectional study of the development of lower limb strength in 160 ambulatory patients with bilateral spastic CP and 86 typically developing controls, aged 7–16 years, Darras et al., showed that patients exhibited lower strength values in lower limbs than controls, more pronounced in the severely impaired. A pattern of strength imbalance between antagonistic muscle groups was documented in all ages suggesting that strength imbalances are inherent to CP early on and do not develop with age.

De Beukelaer et al. compared medial gastrocnemius characteristics in Hereditary Spastic Paraparesis and Bilateral Spastic CP and found in both significantly smaller muscle volumes compared to controls concluding that treatment in these two conditions does not have to be different.

Altered muscle structure in CP relates to the pathophysiology of muscle contractures. Howard and Herzog review basic science and imaging studies which provide explanations for muscle stiffness and decreased muscle volume and length in CP. Concerns are expressed on the effect of botulinum toxin on muscle histology based on findings from preclinical animal models. It should be noted that no data exist on muscle histopathological alterations following other spasticity treatments such as, physiotherapy, orthoses, Intrathecal Baclofen and Selective Dorsal Rhizotomies.

Cognitive dysfunction is equally challenging as motor impairment but less studied. Intellectual disability epidemiology as related to imaging and clinical phenomenology is systematically monitored in large CP registries (20, 21). Himmelmann et al. examined structure-function relationships based on MRIs from 3,818 patients with CP (birth-years 1999-2009), from 20 European registers. The Impairment Index (22) showed worse associations of bilateral than unilateral compromise with motor impairment, intellectual disability, vision and hearing impairment and epilepsy. Associations between extent and localization of brain lesions and cognitive function are examined but heterogeneity of cognitive findings with similar MRI lesions and the effects of early brain plasticity raise questions as to the utility of this approach. Few studies assessed cognitive profiles or developmental trajectories of cognition in children with CP (23, 24). Intellectual disability is often overestimated. Tests need to be adapted so that cognition can be reliably assessed, especially in very young children and those with severe speech and motor impairments. Visual-spatial abilities, language and executive functions have been reported on, but other determinants of cognition, such as memory, are less studied (24, 25). In bilateral spastic CP uneven cognitive profiles to the advantage of verbal potential are shown; lower performance IQ is attributed to lower visual-spatial reasoning. Visual – perceptual impairment is reported in children with lower cognitive functioning, but also with normal cognition, unrelated to non-verbal cognitive functioning (26, 27).

NEW MANAGEMENT TRENDS

Treatments performed outside a rehabilitation setting gain popularity emphasizing the importance of parent empowerment in caring for their children. Constraint-induced movement therapy in unilateral CP is a program with proven efficacy given in the home environment or during intensive "camp" sessions (28). Wu C-L. et al. demonstrated feasibility of this program in preschool after botulinum toxin injections with improvements in self-care and hand function.

The need for caution in overestimating the abilities of children when tested in controlled environments is discussed. Wiedmann et al., illustrate the feasibility of measuring walking speed in children with CP with 3D accelerometers in real life and show that generally, patients and controls walk slower in a natural environment than in the lab.

During the COVID-19 outbreak remote assessments and treatments proved helpful but underutilized (29–31). The need to set up such initiatives increased (32). Telemedicine became the main communication route between care providers, patients and caregivers. Ben-Pazi et al. describe the accelerated telemedicine impact during the pandemic in CP care in terms of clinical accessibility, continuity of care, prevention, multidisciplinary approach, and participation. Studies need to examine if teleservices can prevent/reduce long-term comorbidities such as hip dislocation.

Technology has changed the scene for the treatment of CP however, some patients with painful syndromes may not be treated with advanced surgical procedures and palliative techniques may be required. Pain affects patients' quality of life and becomes challenging for patients, families, and physicians. Koch et al. presented four palliative options for severely painful spastic hip dislocation, in those with contraindications for reconstructive surgery. Case studies and technique comparisons show how old approaches can become new trends with high acceptability by patients and families.

Technological advances and societal changes create new ethical dilemmas for those involved in the care of patients with CP. Dan reviews principles of clinical bioethics and provides a theoretical approach toward organization of the clinician's thinking process and a constructive dialogue with patients and families.

CONCLUSION

CP, the most common cause of childhood disability, attracts researchers from different disciplines. It is a hot topic for neuroscientists as genetic research unveils the contribution of gene mutations to causation and a promising field for the study of brain structural connectivity and plasticity during development or post-intervention. The need to further elucidate pathophysiological mechanisms in order to develop neuroprotective treatments in those at risk for CP remains. Lastly, research on clinical issues, interventions, and outcomes served by many different medical and therapeutic disciplines, creates a unique setting for collaborative and multifaceted work for the purpose of improving quality of life in children with CP and their families. As a result, CP attracts researchers of neurodevelopment, technology experts, as well as from the therapeutic community and remains an "old" but always challenging problem for all.

AUTHOR CONTRIBUTIONS

AP contributed to the design of the editorial, analysis and interpretation of the submitted articles, drafting of the editorial, and finalizing. SM, EO, and HB-P revisited the content, added paragraphs and relevant references. All authors read and approved the article.

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MINI REVIEW
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Accelerating Telemedicine for Cerebral Palsy During the COVID-19 Pandemic and Beyond

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The effects of COVID-19 extend beyond the pandemic and are expected to transform healthcare in various ways, many of which remain unknown. With social distancing, telemedicine may become the preferred communication channel between caregivers and patients. Implications for cerebral palsy (CP) children are that this will pose a challenge within this transformation. CP, as a discreet entity, is not considered a risk factor. However, specific comorbidities in individuals with CP, such as chronic lung disease, are known as COVID-19 risk factors. The overall risk for the CP population is probably a factor of age and comorbidities. Staying at home for CP children is both a challenge and an opportunity. Escalation of behavioral conflicts or improved participation and equality within the household may emerge. Interestingly, restricted mobility for the general population narrows existing gaps of ambulation. Telemedicine is the primary way of providing services for chronic conditions during the pandemic and is expected to expand beyond pre-Coronavirus era use. The advantages of telemedicine vary, more so during pandemic times, according to severity, restrictions, and availably of telemedicine. A multidisciplinary therapeutic presence is more accessible with telemedicine, bringing together various specialties and approaches to the child's natural environment. Accessible, continuous care is expected to lower comorbidities, as demonstrated for other chronic conditions. Enhanced monitoring is crucial for younger children as devastating complications, such as hip dysplasia, could be minimized. Last but not least, we will discuss digital health care as an accelerator for participatory medicine, including networked patients and families, as responsible drivers of their health as full partners.

Keywords: telemedicine, telehealth, SARS-CoV-2, coronavirus, COVID-19, participatory medicine, digital health, cerebral palsy

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INTRODUCTION

Telemedicine—providing healthcare from a distance—is being exponentially transformed during the Coronavirus pandemic. Telemedicine is traditionally subdivided into being synchronous or asynchronous. Synchronous is defined as interactive video connections transmitting information in both directions simultaneously. Asynchronous telemedicine describes the store-and-forward transmission of medical data in separate time frames (1). Telemedicine services scale up with

global emergencies, such as the SARS epidemic in 2003 in China (2). Outside of crisis situations, the overall uptake of telemedicine has been slow and fragmented (3). The advantages of telemedicine became pronounced when it was harnessed to overcome the necessary COVID-19 distancing (4). As the number of COVID-19 cases increases in each country so too does the population's interest in telehealth (5). Acceptance of video-conferencing replacing in-person communication during the pandemic (6) is expected to transform services, especially healthcare.

There are three overlapping periods to consider during the outbreak: early, late, and post-pandemic. Most western countries are currently in the early phase, escalating existing available digital services and attempting to mitigate regulatory barriers (7). This requires abilities to rapidly expand telemedicine capabilities, increase providers' capacities, and update clinical workflows (8, 9). This quick integration is challenging for other, more conventional systems, as it takes 12–15 encounters for a provider starting tele-clinics to feel comfortable using in the ambulatory setting (9). The development of new products and services requires time, even now, with accelerated modes of funding and regulations (10). During the late phase, we expect that novel services and digital devices on the verge of development will enter the market and will be adopted for early use (11). As for the post-pandemic period, the healthcare systems will adopt innovations that proved real value for regular use. While expanding healthcare developments focuses on the current infectious patients, the revolution will also expand to non-infectious care of chronic patients.

This review will focus on telemedicine for children with CP during the outbreak and beyond. We will explore the challenges and opportunities of telemedicine in the CP arena, including practical tips (**Table 1**). Since clinicians' acceptance plays a crucial role in telemedicine integration (12), we share specific recommendations (**Table 2**) covering telemedicine set-up, patient examination, and clinical considerations for children with CP, and we do this also beyond standard recommendations for patients with movement disorders (13) and other conditions (9, 14).

ACCESSIBLE CARE

Telemedicine has already been demonstrated as being useful for chronic conditions (15), including movement disorders (16), but it until now has been underutilized for standard care despite the ubiquitous smartphone platform (2, 13). Technical hurdles on the patient's end could be addressed by virtual front desk conducting a pre-test. The gap seems more remarkable considering the limited and unequal accessibility for patients with CP compared to general population, including their need for mediators to access most tele and non-tele services. Paradoxically, tablets and smartphones improved accessibility to patients with CP to a multitude of online or application mediated activities, schooling, and entertainment (17–20).

Hospital telemedicine services are currently focused on reducing infection spread by providing tele-emergency services (21). Primary tele-healthcare services available before the pandemic (19) are expanding to manage the majority of home-isolated Coronavirus patients addressing diagnostic and treatment aspects (3, 8, 22–24), and some institutions show a significant increase in tele-consultations compared to pre-pandemic era (9). Left with a choice of not-consulting at

TABLE 1 | Challenges, opportunities, and tips for CP-focused telemedicine.

	Challenge	Opportunity	Tips
Accessible tele-clinic	Requires video conferencing skills/the child may have difficulty following	Less travel and work loss Functional assessment in the natural environment	Physical distancing is not emotional distancing Emphasize professional look, use reassuring mimicry, manipulate tone to convey the message Confirm that the child and family hear and see you especially during the discussion and recommendation
Continuous therapy	Less physical interaction with	Continuous, accessible, functional	Focus on longitudinal care plan per patient, planning several steps ahead Ask to document outcomes using synchronous and asynchronous (video clips) telemedicine Ensure proper reimbursement
Prevention	Increases care giver responsibility	Less travel for clinical appointments	Proactively initiate tele-follow-up to populations at risk to actively survey their condition and intervene appropriately to prevent deterioration Inform about specific risks with practical recommendations for homebased monitoring Point out red flags for deterioration
Multidisciplinary clinic	Requires more time and effective video- conferencing skills	Multiple specialists Child less intimidated	Use tele-clinics for an inclusive approach. Try to include both parents, community/school therapists, and a multidisciplinary medical team In the essence of time, focus each visit on one functional problem. Send background materials before the visit The deliverable of the multidisciplinary clinic should be a personalized, tailored, coordinated plan, including medical recommendations, physical treatments (PT, OT, ST), and educational-psychological therapies
Participatory medicine	Requires caregivers' responsibilities	Patient centric treatment	Focus on the child's and family's function goals and quality of life Plan a series of discrete steps to reach the discrete endpoint Provide indicators of success and hurdles

TABLE 2 | Tele medicine for CP-Practical recommendations.

	Unique issues	CP emphasis
Set-up	Visual impairment	Face should fill at least 1/3 of screen width White background Enhance mimicry
	Auditory impairment	Check that the sound is loud and clear several times during the conference Enhance vocal cues and variability
	Family and child	Wide shooting angle to include all participants or using different screens for each participant
	Comfortable environment	As the online visits may be long to ensure that all are comfortably seated
Examination	Physical disability	Two adults (parents) necessary for video examination one for manipulation and other for video recording
	Relaxing	Postponed stressful topics after the exam to ensure maximal relaxation Painful items should be postponed to the end of the exam
	Range of motion	Make sure that camera is 90 degrees to the angle assessed Consider requesting parents to take pictures and sending (asynchronous for formal ROM assessment
	Intellectual disability	Consider exposure of intimate undressing as poses an educational conflict
Clinician considerations	Emotional stress	Assess and treat the emotional aspects
	Chronic deteriorating condition	Follow up
	Recognizing problems	State demonstrate clear red flags
	Communication availably boundaries	Set clear communication rules on how to contact during routine and emergency

all vs. using telemedicine platforms, the "Philadelphia group" has clearly shown that patients preferred to use tele-visits rather than avoid clinical consultations (9). Individuals with CP are not specifically at risk from COVID-19, unless they suffer from comorbidities such as pulmonary disease or elevated blood pressure (25). However, to minimize exposure, many children stay home away from the daily treatments and services provided in rehabilitation schools and clinics. Elective consultations and paramedical treatment, including utilization of heavy equipment, walking aids, hydrotherapy services, and more, are diminished if not ceased. While much emphasis is on medical or physical risk and deterioration, the emotional comorbidity is relatively neglected. Individuals with chronic disabilities, including CP, have higher rates of anxiety and depression (26), and this is expected to worsen during the pandemic, even more so when most of them are far from their professional therapists. Increased stress worsens hypertonia and impairs daily life. Lack of physical treatment undermines function even further.

The result for the last months has been in most countries, that complex medical care for children with CP, that traditionally take place in outpatient clinics and institutions cannot be accessed. Telemedicine is thus one of the preferred and most accessible platforms for these children. Many children use tablets and computers almost independently or with minimal aid for social communication and learning; some can use smartphones. Proper instruction on how to use familiar technology for CP- tele-healthcare can therefore minimize gaps in physical and mental health when matching clinical needs to available opportunities (**Tables 1**, **2**).

CONTINUITY OF CARE

Children with CP require continuous care, both paramedical and medical (27). Many patients take chronic medications, some of which need more monitoring than others, including blood tests and clinical examinations. Some patients are treated with Intrathecal Baclofen pumps and need routine refills of the pump to avoid withdrawal symptoms and increased spasticity. Following selective dorsal rhizotomy (SDR), continuous massive physiotherapy is needed to decrease tone and increase functionality. Serial Botulinum toxin injections are preplanned as a program of long-term treatment to improve the functional range of movement (28).

During the acute phase of the pandemic, many hospitals closed outpatient clinics and canceled so-called elective appointments, and remote platforms of urgency grading were initiated (9, 23, 29). While necessary procedures mandating face-to-face interaction should not be canceled, consultation before and after the procedure may be performed by telemedicine (7, 9). Tele-clinics can replace many of clinical encounters, such as adjusting medication, orthopedic monitoring, and neurosurgical evaluation (13, 17). During routine follow-ups, we check by observation motor symptoms, stiffness, and spasticity as compared to "regular status," range of motion of limbs (any change in range, position), and increased difficulty in dressing/undressing. Non-motor issues such as pain, sleep, feeding, and communication could be easily evaluated by telemedicine in individuals with CP (16, 17, 20). Finally, it is required to address the relevancy and urgency of medical treatment in any chronic patient. Spasticity related emergencies are not common, and most surgical procedures in patients with CP are considered elective. Telemedicine can assist in identifying and prioritizing medical assistance in surgical (9) emergencies (neurosurgery includeed) (29). For example, neurosurgical services prioritized according to urgency in three different classes (immediate treatment, treatment within 7–10 days, and treatment within a month) (29). Tele-Guide-lined and Structured Continuous Care (TGSCC) can be provided for each patient, shared among healthcare providers, with practically no limitations of geographical distances (9). During the acute phase of the pandemic the main contribution of TGSCC is to maximize family aid and interference guided by professionals.

During post-Corona era, this tool could still maximize monitoring of the chronic patient and provide consultation and follow-up as for adjusting physical therapy, medication management, and psychosocial management whenever traveling and face-to-face treatment is not mandatory (14).

Novel post-Corona services may enable prioritizing necessary procedural actual visits, using accessible telemedicine to focus on the specific inquiry for changes over time from baseline status.

PREVENTION

Non-progressive neurological damage defines CP but does not imply a uniform, unchanging clinical behavior. Individuals with CP exhibit alterations in muscle tone with resultant changes in tendon-muscle unit length over time (27, 28). Muscle tone increases with stress, interfering with activities-of-daily-living, including dressing, feeding, hygiene care, and speech and may also limit the range of motion (30). Ultimately, increased tone leads to skeletal changes, such as hip displacement and spinal scoliosis, that may eventually cause pain and dysfunction, impacting health, wellness, and quality-of-life. While immediate consequences of tone changes may be monitored and treated, the long-term effects are very gradual, subtle, and challenging to recognize. Routine monitoring was found as the most effective way to eliminate contractures and hip displacement (31), with home visits being more effective than scheduled outpatient follow-up (32–35).

In many countries, most healthcare resources during the pandemic are diverted to COVID-19-related needs and less to routine care and prevention. If this trend continues, care of the CP population may be compromised. With less therapy, there is a substantial risk of irreversible contractures and the development of deformities that may eventually require surgical intervention. Failure to follow hip surveillance guidelines may further jeopardize the care. It is difficult to estimate the length of time after which the reduction in treatments and clinical and radiographic follow-up will begin to instigate deterioration. Telemedicine is an effective and accessible platform to enable attention, follow-up, and treatment of children with CP. Physicians and therapists should use telemedicine and encourage families to tele-communicate with medical and paramedical staff led by both pre-planned and on-demand principles to prevent deterioration and maintain follow-up.

CP-UP provided ample evidence that surveillance based on the CP type, age, Gross Motor Function Scale (GMFCS) score, and findings on physical exam minimize the risk of hip displacement (1, 36). Tele-monitoring applications can transform these protocols into a decision-support-system combining medical history, physical examinations, and radiographs to provide follow-up recommendations for early detection and prompt interventions (37, 38). Coronavirus pandemic increased the use of home-based tele-monitoring for COVID-19 patients (3–5, 8, 10). We expect these services to expand to broader use beyond the pandemic and harness them to bridge the gaps of essential routine monitoring for populations at risk, for other functional assessments in the natural environment such as gait monitoring as a screening tool for referrals to gait laboratories and remote rehabilitation monitoring. These services are yet to be developed and would need to determine the best user experience and guidance to perform orthopedic goniometry and radiological surveillance. Tele-hip monitoring has specific challenges such as camera position in a 90-degree angle to reflect the true hip abduction and appropriate protection of sensitive exposed areas. Improved orthopedic (hip surveillance) and functional (gait recording) monitoring may lead to minimization and even prevention of deterioration in children with CP.

MULTIDISCIPLINARY APPROACH

The healthcare needs of the CP population are complex (27, 28). A multidisciplinary approach has therefore gained popularity in recent years, with well-documented benefits that include improved coordination of care and time use optimization for patients and their caregivers (17, 30). However, these multidisciplinary setups may become impossible at times when physical distancing is required to limit exposure during the pandemic, as contact between patients and caregivers is greater than regular clinics. To maintain the high quality of multidisciplinary clinics and their achievements over time for patients with CP, telemedicine may become an even more promising platform. Telehealth may especially be relevant as challenges for these patients and families are intensified by school closures, crowding at home, and decreased access to healthcare and therapies. Telemedicine used as a multidisciplinary tele-meeting consumes less time and effort for the families and is more effective for Tele-Guide-lined and Structured Continuous Care (TGSCC). It maintains the added value of multiple specialists assembled without jeopardizing the possibility of discussion and re-evaluation based on real time interaction with the patient and family with all healthcare providers, patients, and caregivers being in their protected environment (18, 39, 40). Such tele-contact also obviates the need for the use of personal protective equipment such as gloves and face masks, limits the risk of viral spread, and offers patients a more natural environment without compromising health care personnel and patients' safety (21).

In the post-pandemic period, we expect telemedicine to become more coordinated and patient-centric, providing tools of assessment and reimbursement of multidisciplinary tele-care (9, 12, 23, 24). This challenge extends beyond the technical platform of bringing together multiple people for a video conference (41).

PARTICIPATORY MEDICINE

Medical conduct is moving from paternalistic conduct to participatory medicine (42). The conservative way of managing the patient is transforming as technology-enabled families are connected via social media and are better informed than in the past by available self-research. The internet and tele-communication era lead to shifting to a more mutually inclusive healthcare (43, 44). Predictive, Personalized, Preventive, and Participatory (4P) medicine is advantageous with telemedicine tools (44). This movement, which used to exist in the periphery of medical care, is currently expanding, public healthcare awareness is rising, and participatory medicine is becoming accepted as citizens are requested to report their health status. Corona pandemic introduces innovative and crowdsourcing technology

utilizing participatory medicine. People choose to share their health status to help others on a broader scale via social media, even more than was available in the pre-coronavirus pandemic (9, 10). Some countries, like Taiwan, used big data from citizens to track and control COVID-19 spreading (24). This trend poses privacy challenges but introduces therapeutic opportunities that will extend beyond the current crisis (7, 9).

Participatory medicine is especially important in chronic disorders (4, 41). In terms of research, a patient-centric approach is on the rise when it comes to children with CP (13, 45, 46). The comparative effectiveness of interventions, physical activity, and understanding aging were leading themes, highlighting the need to focus on longitudinal research that includes outcomes related to participation and quality-of-life (46). We believe that implementation will grow with telemedicine expansion. This is an opportunity for a therapeutic presence shift in CP: from the hospital to home, from somatic emphasis to a holistic approach, and from the physical examination to functional observation in the natural environment. Moreover, telemedicine assists other stakeholders to be involved in the child's care as needed (47).

DISCUSSION

In this mini review, we covered focused aspects of telemedicine for children with CP and its recent developments during the Coronavirus pandemic. The social, psychological, economic, and health burden of the COVID-19 pandemic on patients with CP and their families is enormous. We believe that teleconsultations can address aspects of continuous CP care, such as managing medications and providing exercises in home environments, with increased participation of patients and families (44–46). Reports have shown that patients prefer visual tele-consults rather than phone or e-mail consultations (5, 7, 9). In some countries, the pandemic has imposed reconsidering telemedicine (21–24), as "locked-down" reality and restricted services expanded for non-urgent and non-infectious treatment (7, 9). In other countries, with different levels of severity and variability in restrictions in face-to-face medicine telemedicine use was more variable. Telemedicine expansion also depended on available technology.

Patients with CP may be clinically dynamic, even though CP is a chronic situation deriving from non-progressive neurological damage. When withdrawn from routine services, physical and emotional difficulties occur, increasing spasticity and causing consequent functional emotional and behavioral deterioration (26, 28, 30, 31). Currently, in our service, to maintain continuity, parents are sharing with healthcare professionals video clips of patients with CP in their home environment standing, sitting, walking, playing, and communicating, each according to her or his functional status.

Possible Disadvantages and Difficulties of Telemedicine for Patients With CP

Aside from the natural tendency to avoid changes, disadvantages often quoted were concerns regarding less personal approach, patients' security, confidentiality concerns, liability issues, need for medical report integration, decreased reimbursement and questions regarding intellectual property rights (2, 14, 22, 23, 34). This is particularly important with respect to safeguarding children and vulnerable adults. Important possible limitations of telemedicine discussed were verification of patient identity and location as well as a difficulty to obtain informed consent and a secure HIPAA-compliant platform (Health Insurance Portability and Accountability Act) (7, 9). These difficulties, may be overcome with implementing adopted strategies creating adjusted reimbursement methods and re-defining workflows (9, 12). Fortunately, there is a growing modification of the payment policy in response to COVID-19 globally (9, 23). We hope others will follow suit, and equivalent reimbursement would become the norm. Also, "myths" need to be overcome: "patients prioritize relationships over transactional care," "the physical examination is missing," "virtual visits are not sufficient," and more. Currently, not all medical and paramedical staff are familiar with the use of teleconferencing technologies in instructing, monitoring, and diagnosing individuals with CP and their needs. By minimal training this may be overcome (7–9, 13), together with engaging families to use familiar technology, routinely used for social communications, for medical purposes. Many low-income populations do not have computers, smartphones, or software to participate in video conferences; thus, with the expansion of services, providers should consider installing local telemedicine kiosks.

Last but not least, Telemedicine cannot completely substitute face-to-face clinics. However, it is most beneficial where conventional healthcare is lacking or impossible providing accessible, continuous care, with real-time visualization.

Changing the Concept and Using "Familiar Social Technology" in "Clinical Setup"

Despite telemedicine prospects and the extensive use of technology for social communication, many clinicians and healthcare systems were reluctant to adopt it as a standard way of providing care. This paper has discussed the advantages of telemedicine emphasizing accessibility, its potential to provide multidisciplinary care, and enhanced patient participation. We have also discussed the advantage of real-time visualization of patients and families, regardless of the geographical distance, and the availability of several experts when video conferencing in the same session without travel discomfort or risk. In order to successfully incorporate telemedicine in the post-Corona era, now is the opportunity to open new platforms and workflows of care for the post-Corona era and to address the reimbursement hurdle (e.g., only 20% of states in the US require payment parity between telemedicine and in-person services) (7). The next steps include ensuring equitable access to affordable telemedicine for CP patients and evaluation of quality assurance.

In this mini review, we speculated how telemedicine program growth would develop efficient workflows for individuals with CP, suggesting the implementation of the "Guide-lined and Structured Continuous Care" (TGSCC) platform. Such an approach should be patient-centric, taking into account the ability of the family to increase participation and take more daily responsibility and action,

a parameter that has been shown to contribute to non-CP patients effectively (7). An integrated decision–support system should be able to create a workflow allowing informative and visual input from the patient/family, assessing the status and diagnosing possible changes/deterioration, including instructional therapies by tele-guidance, reassuring, correcting and re-evaluating, and allowing access to medical consultation and therapists' guidance as needed. Utilization of services on the tele-media platform for medical consultations for CP may assist in minimizing deterioration and irreversible physical, functional, emotional, and behavioral damage as well as providing reassurance to families.

Further research is necessary to evaluate both medical and psychological aspects of a shift to telemedicine on patients, including CP, as well as on healthcare workers. Controlled studies are needed to evaluate in the long term the impact of clinical practice from an epidemiological point of view. Combining a multidisciplinary approach to the COVID-19 imposed telemedicine should be explored and popularized if proven effective. Improved communication technologies, with good quality of visual and sound data transfer, and re-definition of reimbursement criteria are mandatory components to facilitate high-quality telemedicine for individuals with CP in the future.

AUTHOR CONTRIBUTIONS

HB-P: conceptualized, formatted, and drafted the paper. RL and LB-A: contributed to the writing and revised the mini review. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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The Most Cited Original Articles in Brain Imaging of Children With Cerebral Palsy: A Bibliometric Analysis Between 1984 and 2019

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Objective: Brain imaging is important in diagnosing children with cerebral palsy (CP) and in identifying its etiology. To provide study navigation in this field, a bibliometric analysis was conducted by analyzing the most highly cited articles.

Methods: The Web of Science All Databases were used for literature search in this study. All original articles on imaging in children with CP were searched. Two reviewers screened the search results independently and eliminated articles based on exclusion criteria such as participants over 20 years old, topics referring to images outside of the brain, or trauma. According to descending order of yearly citation counts, the top 25% of all included articles were considered as highly cited articles. Information such as yearly citations, research purposes, imaging modalities, CP types, and study designs were recorded and analyzed.

Results: A total of 50 highly cited articles ranked by yearly citations (from 23.85 to 3.33, 1991–2018) were included in this study. Considering different research purposes, these studies were classified into three categories: diagnosis studies (n = 25; 1991–2017, median: 2011), mechanism studies (n = 15; 1999–2018; median: 2014), and prognosis and therapeutic effect studies (n = 10; 2008–2017; median: 2014.5). First, for diagnosis studies, 22 studies used single modality and three used multi-modalities; the majority of these studies focused on diagnostic value evaluation (n = 10) and image performance (n = 12) of a single type of CP (n = 15) by using descriptive (n = 14) or cross-sectional approaches (n = 10). Second, for mechanism studies, the ratio between single and multi-modality was 8:7; most of these studies concentrated on a single subtype of spastic CP (hemiplegia = 10, quadriplegia = 2) with a cross-sectional study design (n = 10). Third, regarding the prognosis and therapeutic effect studies, the single vs. multi-modality ratio was 5:5, and these studies were dedicated to the efficiency of constraint-induced movement therapy in children with hemiplegia; paired design trials (n = 6) and randomized controlled trials (n = 2) were used more frequently.

Conclusion: Studies using multi-modality and high-level evidence-based design to provide information regarding mechanism, prognosis, and therapeutic efficacy may be the potential future research direction in the field of CP research.

Keywords: bibliometric analysis, brain imaging, cerebral palsy, children, citation analysis, neuroimaging

INTRODUCTION

Cerebral palsy (CP) is a group of permanent movement disorders attributed to non-progressive disturbances occurring during fetal or infant brain development (1). The prevalence of CP for all live birth ranges from 2 to 3 per 1,000 live births (2). However, this prevalence varies for different regions or countries depending on income level, and a higher prevalence has also been reported in infancy compared to all live births (1, 2). Brain sonography, a diagnostic imaging tool, was the first technique used to detect brain lesions in CP patients at 1984 (3). Moreover, in 2004, the American Academy of Neurology and the Child Neurology Society jointly published a practice parameter recommending neuroimaging examination as a necessary evaluation procedure for CP children with uncertain etiology (4). In recent years, the field of neuroimaging has made significant progress in early and accurate CP diagnosis (5), mechanism of action, prediction of therapy effect, and prognosis (functionality) (6–8). Brain imaging has become one of the main focuses of CP research, with numerous articles published on this topic. In the current imaging evaluation era of CP, a substantial volume of literature comprising studies on varying topics and designs are available to neurologists, pediatric neurologists, pediatricians, and radiologists. However, due to the lack of quantitative research providing an overview of brain imaging studies in CP patients (9), it is challenging for students, residents, and researchers new to the field to identify the most important study areas and future direction. Therefore, distilling the newest and emerging research in this field through citation counts can help create an evidence-based approach to guide future study.

Bibliometric analysis was previously used to quantitatively survey knowledge development in imaging and neuroimaging fields (10). Compared to meta-analysis and systemic review, which both focus on specific questions such as study population, methods, and findings, the bibliometric analysis provides an overview of the study field from a different angle, by using bibliographic material such as yearly citations, authors' information, and impact factor (IF) of the publishing journals (11). These three types of studies have distinct focuses and provide information that can complement each other in a given field. According to our research, no previous bibliometric analysis has been done on brain imaging of children with CP. Thus, we have selected the bibliometric analysis method to quantitatively evaluate the knowledge structure and development of pediatric CP imaging, to highlight emerging themes and future study trends in this field.

This study aimed to perform a citation analysis of the most cited papers on brain imaging in children with CP and analyzed each paper individually according to imaging modality, year of publication, yearly citations, research purposes, study designs, country of origin of the first author, and IF of the journal.

MATERIALS AND METHODS

As our study was a retrospective bibliometric analysis of publicly available study literature, it was exempt from institutional review board approval.

Literature Search

To identify the most highly cited articles, we conducted a systematic literature search on CP brain imaging for children articles, published from November 4, 2019. We used the Web of Science All Databases (Clarivate Analytics, Philadelphia, United States), which included the MEDLINE database; the results were limited to the English language with no publication year limit. The searching topics were listed:

"cerebral palsy" or "brain paralysis" or "monoplegia" or "unilateral paralysis" or "diplegia" or "quadriplegia" or "tetraplegia" or "hemiplegia" or "hemiparesis" or "static encephalopathy"

and

"diffusion tensor imaging" or "DTI" or "diffusion kurtosis imaging" or "DKI" "neuroradiology" or "neuroimaging" or "brain imaging" or "brain CT" or "head CT" or "computed tomography" or "MRI" or "MR imaging" or "magnetic resonance imaging" or "DWI" or "diffusion-weighted imaging" or "MR perfusion" or "magnetic resonance perfusion" or "SPECT" or "PET" or "sonography" or "ultrasound" or "doppler" or "network" or "connect*" and "infant*" or "child*" or "pediatric" or "toddler*" or "bab*" or "trottie" or "kid*" or "neonate*" or "newborn*" or "adolescent*" or "teenager" or "juvenile*" or "teen*".

All original articles on imaging in children with CP were included. Exclusion criteria were articles concerning participants over 20 years old, or topics referring to images of the spinal cord, musculoskeletal, urinary systems, vascular ultrasounds, ultrasound-guided therapy, hemi-convulsion-hemiplegia syndromes, or trauma.

Screening of Highly Cited Original Articles

Two reviewers (Fan Wu and Jingjing Zhang) screened the search results independently. Full-text articles were retrieved and screened according to the inclusion and exclusion criteria. In case of doubt, a third reviewer (Heng Liu) participated in the screening. Two reviewers independently extracted data and stored them electronically in Microsoft Excel 2016. The results were downloaded to a local database. From a list of articles in descending order of yearly citations (total citation count divided

by the year difference between publication year and 2019), the top 25% were considered the most highly cited (12).

Data Analysis

For the most highly cited articles in the final analysis, the following information was collected and listed: yearly citations, total citations, research purposes, CP types, study designs, imaging modalities, subjects age, modality of study acquisition, country of the first author, publication journal, and journal IF. For descriptive analysis of the CP types, imaging modalities, study designs, author or publication information, and number and proportion of articles were listed.

RESULTS

Among 6,137 published articles, 202 on brain imaging in children with CP were identified based on our inclusion and exclusion criteria. A total of 50 articles were defined as the most highly cited articles according to the ranking number of yearly citations.

Top 50 Highly Cited Original Articles

Table 1 lists the bibliometric materials of the top 50 highly cited original articles, regarding particulars such as citation counts, imaging modalities, and author and publication information. The yearly citation counts ranged from 23.85 to 3.33 per year (median: 6/year), and the total citation counts were between 310 and 7 (median: 45.5 times). According to different research purposes, the articles were classified into three categories: CP diagnosis studies (25 articles, 50%), CP mechanism studies (15 articles, 30%), and CP prognosis and therapeutic effect studies (10 articles, 20%). Based on the above classification, we explored the imaging modalities, CP types, impaired functions, study designs, country of origin of the first author, and journal's IF of these articles.

Application of Imaging Modalities in the Top 50 Highly Cited Articles

Figure 1A shows the yearly publication count distribution of the top 50 highly cited original articles that applied single or multiple modalities. The article publication numbers showed an increasing trend over time. Thirty-five studies used single modality (CP diagnosis: $n = 22$; CP mechanism: $n = 8$; CP prognosis and therapeutic effect: $n = 5$), whereas 15 studies were multi-modality studies with a growth trend in the past 10 years (CP diagnosis: $n = 3$; CP mechanism: $n = 7$; CP prognosis and therapeutic effect: $n = 5$). Among multi-modality studies, multiple imaging modalities were applied in eight studies. Specifically, seven studies used two imaging modalities [structural magnetic resonance imaging (sMRI) (1991) and transcranial ultrasound (TCS) = 1, 1993; sMRI and diffusion tensor imaging (DTI) = 4, 2007–2015; DTI and functional MRI (fMRI) = 1, 2015; sMRI and fMRI = 1, 2016], and one study used three imaging modalities [DTI, sMRI, and diffusion-weighted imaging (DWI) = 1, 2017]. Seven studies combined an imaging modality with an electrophysiological modality [magnetoencephalography (MEG) = 2, 2014 and 2018; transcranial magnetic stimulation (TMS) = 5, 2010–2017]. Thus, combining an imaging modality with an electrophysiological modality could be a possible study direction for brain imaging studies in children with CP.

Figure 1B shows the yearly article counts of each image modality used in the top 50 highly cited original articles according to different research purposes. First, sMRI (1991) and TCS (1992) were used the earliest in CP diagnosis studies ($n = 25$), and DTI (29 times) and sMRI (29 times) were used the most. Second, computed tomography (CT) was applied as a complementary method to sMRI in six CP diagnosis studies to help identify imaging performance. Third, multi-modalities were applied more frequently in CP mechanism studies since 2011 (8/15 studies), especially DTI combined with other MR technologies, TMS and MEG. Last, the prognosis ($n = 1$) and therapeutic affect studies ($n = 9$) first appeared in 2008, and the utilization of multi-modality in these types of studies has increased remarkably from 2013 ($n = 5$).

CP Types, Impaired Functions, and Study Designs of the Top 50 Highly Cited Articles

Table 2 lists the article counts of CP types, impaired functions, and study designs of the top 50 highly cited articles, as well as their publication years and distribution among different research purposes. CP diagnosis studies were further classified into diagnostic value of imaging methods (1993–2014, median: 2007.5), brain image performance (1991–2012, median: 2008.5), imaging classification systems, and imaging post-processing applications (2011–2017, median: 2014). The CP mechanism studies (1999–2018, median: 2014) have been explored from the 1990's. The prognosis and therapeutic effect studies involved four distinct types of treatment (2008–2017, median: 2014.5) presenting with a number of increases in the past 10 years.

CP Types and Impaired Functions

Regarding the CP types, articles mainly focused on single CP type study, specifically spastic CP (SCP) (37/50, 74%) (**Table 2**). The single subtype studies constituted of approximately 78% (29/37) spastic CP studies, and hemiplegia constituted of 79% (23/29) single subtype studies. Limited to early imaging technological development, most studies concentrated on the diagnostic value of specific imaging methods in CP (8/10) or identified unique image performances and feature classification in different CP types or subtypes (13/15). The majority of CP mechanism studies focused on single subtype SCP, particularly hemiplegia (10/15) and quadriplegia (2/15). The prognosis and therapeutic effect studies concentrated closely on constraint-induced movement therapy (CIMT) (5/10), bimanual intensive rehabilitation (1/10), and hand function prediction (1/10) of children with hemiplegia. Moreover, an article on botulinum injection studied patients with quadriplegia (1/10), and the autologous cord blood infusion studies (2/10) were also performed in children with CP but did not mention any particular CP subtype.

Concerning impaired functions, 32 out of 50 articles included impaired function in their studies (64%). Hand or upper limb function (19/50, 38%) and sensorimotor pathway function (13/50, 26%) received the most attention from researchers. In addition, four articles described the relationship between brain structure changes and cognitive functions (including speech

TABLE 1 | The top 50 highly cited brain imaging articles in children with cerebral palsy ranked by yearly average citation.

Rank	Article name	Main author	Journal	IF (2018)	Brain imaging modality	Single modality; multiple modality	Age	Modality of study acquisition	Publication Year	No. of yearly citations	No. of total citations	Rank of total citations
1	Clinical and MRI correlates of cerebral palsy—the European cerebral palsy study	Bax, M.	*JAMA*	51.27	sMRI	Single	0.08–7.25 years	-	2006	23.85	310	1
2	Sensory and motor deficits in children with cerebral palsy born preterm correlate with diffusion tensor imaging abnormalities in thalamocortical pathways	Hoon, A. H. Jr.	*Developmental Medicine and Child Neurology*	3.53	DTI	Single	1.25–15 years	Sedation	2009	17.4	174	3
3	Quantitative diffusion tensor imaging in cerebral palsy due to periventricular white matter injury	Thomas, B.	*Brain*	11.81	DTI	Single	12–16 years	Awake	2005	13.21	185	2
4	Effect of autologous cord blood infusion on motor function and brain connectivity in young children with cerebral palsy: a randomized, placebo-controlled trial	Sun, J. M.	*STEM CELLS Translational Medicine*	5.96	DTI, sMRI, and DWI	Multiple	1–6 years	–	2017	12	24	37
5	Corticospinal tract diffusion properties and robotic visually guided reaching in children with hemiparetic cerebral palsy	Kuczynski, A. M.	*Human Brain Mapping*	4.55	DTI	Single	6–19 years	–	2018	11	11	48
6	Hand function in relation to brain lesions and corticomotor-projection pattern in children with unilateral cerebral palsy	Holmstrom, L.	*Developmental Medicine and Child Neurology*	3.53	sMRI and TMS	Multiple	7–16 years	–	2010	10.22	92	10
7	Function and neuroimaging in cerebral palsy: a population-based study	Himmelmann, K.	*Developmental Medicine and Child Neurology*	3.53	sMRI or CT	Single	4–8 years	–	2011	9.5	76	15
7	MRI classification system (MRICS) for children with cerebral palsy: development, reliability, and recommendations	Himmelmann, K.	*Developmental Medicine and Child Neurology*	3.53	sMRI	Single	–	–	2017	9.5	19	43
9	Quantitative diffusion tensor tractography of the motor and sensory tract in children with cerebral palsy	Yoshida, S.	*Developmental Medicine and Child Neurology*	3.53	DTI	Single	0.33–9 years	Partial sedation	2010	8.78	79	14
10	Diffusion tensor imaging in children with periventricular leukomalacia: variability of injuries to white matter tracts	Nagae, L. M.	*American Journal of Neuroradiology*	3.26	DTI	Single	1.33–13.25 years	Sedation	2007	8.75	105	8
11	Cerebral palsy in a term population: risk factors and neuroimaging findings	Wu, Y. W.	*Pediatrics*	5.4	sMRI or CT	Single	–	–	2006	8.62	112	5
12	Diffusion tensor imaging of periventricular leukomalacia shows affected sensory cortex white matter pathways	Hoon, A. H.	*Neurology*	8.69	DTI	Single	4–8 years	–	2002	8.47	144	4

(Continued)

TABLE 1 | Continued

Rank	Article name	Main author	Journal	IF (2018)	Brain imaging modality	Single modality; multiple modality	Age	Modality of study acquisition	Publication Year	No. of yearly citations	No. of total citations	Rank of total citations
13	Structural neuroplastic change after constraint-induced movement therapy in children with cerebral palsy.	Sterling, C.	*Pediatrics*	5.4	MRI	Single	2.08–7.50 years	Sedation	2013	7.83	47	22
14	Is outcome of constraint-induced movement therapy in unilateral cerebral palsy dependent on corticomotor projection pattern and brain lesion characteristics?	Islam, M.	*Developmental Medicine and Child Neurology*	3.53	sMRI and TMS	Multiple	8–16 years	–	2014	7.8	39	28
15	Cortical somatosensory reorganization in children with spastic cerebral palsy: a multimodal neuroimaging study	Papadelis, C.	*Frontiers in Human Neuroscience*	2.87	DTI, fMRI, and MEG	Multiple	4.75–17 years	Awake	2014	7.8	39	28
16	Assessment of the structural brain network reveals altered connectivity in children with unilateral cerebral palsy due to periventricular white matter lesions.	Pannek, K.	*NeuroImage-Clinical*	3.94	sMRI and DTI	Multiple	5–17 years	–	2014	7.4	37	30
16	Magnetic resonance imaging findings in a population-based cohort of children with cerebral palsy	Robinson, M. N.	*Developmental Medicine and Child Neurology*	3.53	sMRI	Single	5–7 years	–	2009	7.4	74	16
18	MRI structural connectivity, disruption of primary sensorimotor pathways, and hand function in cerebral palsy.	Rose, S.	*Brain Connectivity*	–	sMRI and DTI	Multiple	10.63 ± 3.00 years	–	2011	7.38	59	18
19	Population-based study of neuroimaging findings in children with cerebral palsy	Towsley, K.	*European journal of Pediatric Neurology*	2.5	sMRI or CT	Single	0–5.50 years	–	2011	7.25	58	20
20	Reorganization of the somatosensory cortex in hemiplegic cerebral palsy associated with impaired sensory tracts.	Papadelis, C.	*NeuroImage-Clinical*	3.94	MEG, sMRI, and DTI	Multiple	6–17 years	–	2018	7	7	49
21	Speech problems affect more than one in two children with cerebral palsy: Swedish population-based study	Nordberg, A.	*Acta Paediatrica*	2.27	sMRI or CT	Single	–	–	2013	6.67	40	26
22	Quantitative analysis of brain pathology based on MRI and brain atlases-applications for cerebral palsy	Faria, A. V.	*Neuroimage*	5.81	DTI	Single	4–13 years	Sedation	2011	6.5	52	21
23	Brain structural connectivity increases concurrent with functional improvement: evidence from diffusion tensor MRI in children with cerebral palsy during therapy	Englander, Z. A.	*NeuroImage-Clinical*	3.94	DTI	Single	1.10–5.10 years	–	2015	6.25	25	36
24	Sensory tractography and robot-quantified proprioception in hemiparetic children with perinatal stroke	Kuczynski, A. M.	*Human Brain Mapping*	4.55	DTI	Single	6–19 years	–	2017	6	12	46

(Continued)

TABLE 1 | Continued

Rank	Article name	Main author	Journal	IF (2018)	Brain imaging modality	Single modality; multiple modality	Age	Modality of study acquisition	Publication Year	No. of yearly citations	No. of total citations	Rank of total citations
24	Using diffusion tensor imaging to identify corticospinal tract projection patterns in children with unilateral spastic cerebral palsy.	Kuo, H. C.	*Developmental Medicine and Child Neurology*	3.53	DTI and TMS	Multiple	6.08–17.08 years	–	2017	6	12	46
24	Validity of semi-quantitative scale for brain MRI in unilateral cerebral palsy due to periventricular white matter lesions: relationship with hand sensorimotor function and structural connectivity	Fiori, S.	*NeuroImage-Clinical*	3.94	sMRI and DTI	Multiple	11.40 ± 3.10 years	–	2015	6	24	37
27	Neuroradiology can predict the development of hand function in children with unilateral cerebral palsy	Holmefur, M.	*Neurorehabilitation and Neural Repair*	3.76	sMRI or CT	Single	0.75–9 years	–	2013	5.83	35	31
28	Gastrointestinal manifestations in children with cerebral palsy.	Del, G. E.	*Brain & Development*	1.76	sMRI or CT	Single	0.50–12 years	–	1999	5.6	112	5
29	Capturing neuroplastic changes after bimanual intensive rehabilitation in children with unilateral spastic cerebral palsy: a combined DTI, TMS and fMRI pilot study	Bleyenheuft, Y.	*Research in Developmental Disabilities*	1.87	DTI, fMRI, and TMS	Multiple	6–9 years	–	2015	5.5	22	40
30	DTI-based three-dimensional tractography detects differences in the pyramidal tracts of infants and children with congenital hemiparesis	Glenn, O. A.	*Journal of Magnetic Resonance Imaging*	3.73	DTI	Single	0.83–3.67 years	–	2003	5.44	87	11
31	Diffusion tensor imaging study of the response to constraint-induced movement therapy of children with hemiparetic cerebral palsy and adults with chronic stroke	Rickards, T.	*Archives of Physical Medicine and Rehabilitation*	2.7	DTI	Single	2.10–7.60 years	Sedation	2014	5.4	27	34
31	Reliability of a novel, semi-quantitative scale for classification of structural brain magnetic resonance imaging in children with cerebral palsy	Fiori, S.	*Developmental Medicine and Child Neurology*	3.53	sMRI	Single	4–16.92 years	–	2014	5.4	27	34
33	Correlation of quantitative sensorimotor tractography with clinical grade of cerebral palsy	Trivedi, R.	*Neuroradiology*	2.5	DTI	Single	3–12 years	–	2010	5.11	46	24
34	Diffusion tensor MR imaging tractography of the pyramidal tracts correlates with clinical motor function in children with congenital hemiparesis	Glenn, O. A.	*American journal of Neuroradiology*	3.26	DTI	Single	0.54–17.44 years	–	2007	4.92	59	18
35	Neuroplastic sensorimotor resting state network reorganization in children with hemiplegic cerebral palsy treated with constraint-induced movement therapy.	Manning, K. Y.	*Journal of Child Neurology*	2.09	sMRI and fMRI	Multiple	6–18 years	Awake	2016	4.67	14	45

(Continued)

TABLE 1 | Continued

Rank	Article name	Main author	Journal	IF (2018)	Brain imaging modality	Single modality; multiple modality	Age	Modality of study acquisition	Publication Year	No. of yearly citations	No. of total citations	Rank of total citations
36	An Australian population study of factors associated with MRI patterns in cerebral palsy	Reid, S. M.	*Developmental Medicine and Child Neurology*	3.53	sMRI	Single	0.08–11 years	–	2014	4.4	22	41
37	MRI and clinical characteristics of children with hemiplegic cerebral palsy	Cioni, G.	*Neuropediatrics*	1.65	sMRI	Single	1–18.3 years	–	1999	4.25	85	12
38	Periventricular leukomalacia: Relationship between lateral ventricular volume on brain MR images and severity of cognitive and motor impairment	Melhem, E. R.	*Radiology*	7.61	sMRI	Single	1.50–12.50 years	–	2000	4.21	80	13
39	Autosomal recessive spastic tetraplegia caused by AP4M1 and AP4B1 gene mutation: expansion of the facial and neuroimaging features	Tuysuz, B.	*American journal of Medical Genetics Part A*	3.26	sMRI	Single	2.50–17 years	–	2014	4.2	21	42
40	Correlation between the degree of periventricular leukomalacia diagnosed using cranial ultrasound and MRI later in infancy in children with cerebral-palsy	Devries, L. S.	*Neuropediatrics*	1.65	sMRI and TCS	Multiple	0.92–2.67 years	Sedation	1993	4.19	109	7
41	Treatment-induced plasticity in cerebral palsy: a diffusion tensor imaging study	Trivedi, R.	*Pediatric Neurology*	2.33	DTI	Single	3–12 years	Sedation	2008	4.09	45	25
42	Diffusion tensor imaging demonstrates focal lesions of the corticospinal tract in hemiparetic patients with cerebral palsy	Son, S. M.	*Neuroscience Letters*	2.17	DTI	Single	0.90–7 years	–	2007	3.92	47	22
43	Diffusion MRI in corticofugal fibers correlates with hand function in unilateral cerebral palsy	Holmstrom, L.	*Neurology*	8.69	DTI	Single	7.20–17.30 years	–	2011	3.75	30	32
43	Resting state and diffusion neuroimaging predictors of clinical improvements following constraint-induced movement therapy in children with hemiplegic cerebral palsy.	Manning, K. Y.	*Journal of Child Neurology*	2.09	DTI and fMRI	Multiple	6–15 years	Awake	2015	3.75	15	44
45	Magnetic-resonance-imaging in children with spastic diplegia—correlation with the severity of their motor and mental abnormality	Yokochi, K.	*Developmental Medicine and Child Neurology*	3.53	sMRI	Single	3–10 years	–	1991	3.71	104	9
46	Athetotic and spastic cerebral palsy: Anatomic characterization based on diffusion-tensor imaging	Yoshida, S.	*Radiology*	7.61	DTI	Single	0.5–15 years	Partial sedation	2011	3.5	28	33
46	Effect of sensory and motor connectivity on hand function in pediatric hemiplegia	Gupta, D.	*Annals of Neurology*	9.5	sMRI, DTI, and TMS	Multiple	7.02–18.12 years	–	2017	3.5	7	49

(Continued)

TABLE 1 | Continued

Rank	Article name	Main author	Journal	IF (2018)	Brain imaging modality	Single modality; multiple modality	Age	Modality of study acquisition	Publication Year	No. of yearly citations	No. of total citations	Rank of total citations
48	Diffusion tensor imaging demonstrated radiologic differences between diplegic and quadriplegic cerebral palsy.	Chang, M. C.	*Neuroscience Letters*	2.17	DTI	Single	0.10–5.30 years	–	2012	3.43	24	37
49	MRI findings in patients with spastic cerebral palsy.1. Correlation with gestational age at birth	Okumura, A.	*Developmental Medicine and Child Neurology*	3.53	sMRI	Single	1–19 years	–	1997	3.36	74	16
50	Corticospinal dysgenesis and upper-limb deficits in congenital hemiplegia: a diffusion tensor imaging study	Bleyenheuft, Y.	*Pediatrics*	5.4	sMRI and DTI	Multiple	10–16 years	–	2007	3.33	40	26

TCS, transcranial ultrasound; sMRI, structural magnetic resonance imaging; DTI, diffusion tensor imaging; CT, computed tomography; fMRI, functional magnetic resonance imaging; TMS, transcranial magnetic stimulation; MEG, magnetoencephalography; DWI, diffusion-weighted imaging.

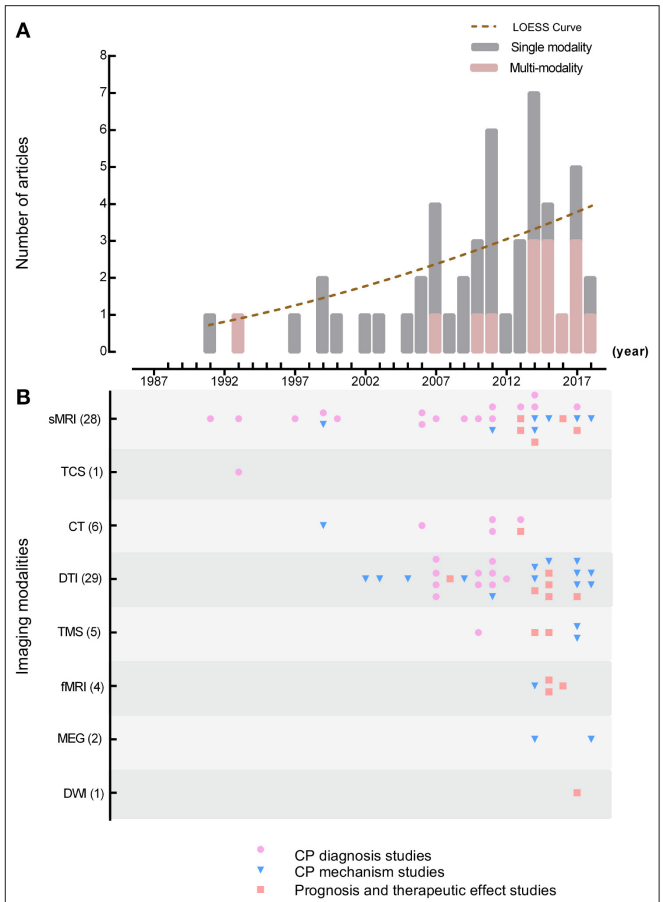

FIGURE 1 | Distribution of imaging modality and study topics. **(A)** Yearly article counts distribution of the top 50 highly cited original articles utilized single or multiple modality; **(B)** yearly article counts for each imaging modality used in the top 50 highly cited original articles classified by different research purposes. Different research purposes included CP diagnosis studies, CP mechanism studies, and CP prognosis and therapeutic affect studies. Study purposes are presented in different colors. sMRI, structural magnetic resonance imaging; TCS, transcranial ultrasound; CT, computed tomography; DTI, diffusion tensor imaging; TMS, transcranial magnetic stimulation; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; DWI, diffusion-weighted imaging.

function, 1991–2014). For different research purposes, the CP diagnosis studies focused on the correlation between brain image performance and impaired functions (12/25). CP mechanism studies were mostly concerned with the process of hand or upper limb and sensorimotor function (11/15). While therapeutic effect studies used CIMT (5/10), bimanual intensive rehabilitation (1/10), autologous cord blood infusion (1/10), and botulinum injection (1/10), the assessment of hand or upper limb function (5/10) or sensorimotor function (4/10) were also involved. However, only one study in development outcome prediction paid attention to hand function in hemiplegia.

Study Designs

Among the top 50 highly cited articles, 78% (39/50) were descriptive (19/50, 38%) and cross-sectional studies (20/50, 40%)

TABLE 2 | Cerebral palsy types, impaired functions, and study designs of the top 50 highly cited articles in different research purposes.

				CP diagnosis studies			CP mechanism studies	CP prognosis and therapeutic effect studies					Published year (median)	Total
				Diagnostic value of imaging method	Image performance	Imaging classification system and applications in CP		Autologous cord blood infusion	Constraint-induced movement therapy	Bimanual intensive rehabilitation	Botulinum injection	Prediction of function development		
CP types	Spastic CP	Single subtype:	Hemiplegia	1	5		10		5	1		1	1999–2018 (2014)	23
			Diplegia		2*								1991, 2012	2
			Quadriplegia		2*		2				1		2008–2014 (2010)	5
		Mixed subtypes:			1	2	1	1					2010–2015 (2014)	5
		Unclassified subtypes		1	2†								1997–2011 (2000)	3
	Athetoid CP				1†								2011	1
	Unclassified or multiple CP type mixed			8	1	1	2	1					1993–2017 (2009)	13
Impaired functions	Sensorimotor function			1	5*¶		3	1	2‡		1		1991–2017 (2008)	13
	Specific motor function	Hand or upper limb function-related		1#	4†		8		4‡	1		1	1999–2018 (2014)	19
		Lower limb function-related		1#	1†								1999, 2012	2
	Cognitive and function (including speech)			2#	2*¶								1991–2013 (1999.5)	4
Studies not related to impaired function				7	3	3	4	1					1993–2017 (2010.5)	18
Study designs	Descriptive study			10	2	2	5						1999–2017 (2011)	19
	Cross-sectional study				9	1	10						2000–2018 (2010.5)	20
	Case–control study				1								2007	1
	Cohort study											1	2013	1
	Non-randomized controlled trial								1				2016	1
	Paired design trial								4	1	1		2008–2015 (2014)	6
	Randomized controlled trial							2					2015, 2017	2
Published year (median)				1993–2014 (2007.5)	1991–2012 (2008.5)	2011–2017 (2014)	1999–2018 (2014)	2015, 2017	2013–2016 (2014)	2015	2008	2013	1991–2018 (2011)	
					1991–2017 (2011)					2008–2017 (2014.5)				
Total articles				10	12	3	15	2	5	1	1	1	50	

*The *, #, †, ¶, and ‡ symbols signify repeated counting of one article.*

(**Table 2**). The majority of the CP diagnosis and mechanism studies followed these two study designs. Furthermore, prospective design was adopted in a cohort study of prognosis (1/50, 2%) and in therapeutic effect evaluation studies (9/50, 18%). Specifically, therapeutic effect evaluation studies included six paired design trials (12%), two randomized controlled trials (4%), and one non-randomized controlled trial (2%).

Considering that the age range of children at the time of neuroimaging might affect the choice of study design, these subjects were divided into pre- (0–3 years) and post-myelination period (>3 years). Only one study included children at the pre-myelination period (11–32 months); 23 studies included children at the post-myelination period (23/50, 46%); 23 studies included children at both the pre- and post-myelination period, while 3 studies did not mention the children's age range.

Thirteen studies mentioned information on the modality of study acquisition (awake, natural sleep, sedation, and general anesthesia). Four studies reported that children were awake during the scanning (one article was published in 2005, ages: 12–16 years; three articles were published between 2014 and 2016, ages: 4.75–18 years); two mentioned that children were sedated at the age of 5 years or younger or have difficulty remaining still, while other children over 5 years were screened while awake (published between 2010 and 2011, ages: 0.33–15 years). Seven studies reported that all children included were sedated for the neuroimaging examination (published between 1993 and 2014, ages: 0.92–15 years), with five of them describing specific sedative drugs and doses in detail. From the above we can tell that only a few articles reported information on the modality of study acquisition. In articles including modality information of the study acquisition, the transition of obtaining images from sedated children to awake children can be observed. Thus, we believe that more attention needs to be paid on the safe acquisition of imaging data of children with CP.

Authors and Publications of the Top 50 Highly Cited Articles

First Author Countries

The country of affiliation of the first author is listed in descending order: USA (16/50, 32%), Sweden (7/50, 14%), Canada (5/50, 10%), Italy (4/50, 8%), Australia (4/50, 8%), Japan (4/50, 8%), Belgium (3/50, 6%), India (2/50, 4%), South Korea (2/50, 4%), England (1/50, 2%), Netherlands (1/50, 2%), and Turkey (1/50, 2%).

Journals

The top 50 highly cited articles were published in 27 journals. The top three journals with the most published articles on pediatric CP were *Developmental Medicine and Child Neurology* (12 articles, 24%), *NeuroImage: Clinical* (4 articles, 8%), and *Pediatrics* (3 articles, 6%). A full list of the article number and most recent journal IFs is shown in **Table 3**. The journals with the top three IFs in 2018 were *JAMA* (one article, 2%), *Brain* (one article, 2%), and *Annals of Neurology* (one article, 2%).

TABLE 3 | The impact factors and rank of journals which published articles on pediatric cerebral palsy.

Journal	No. of articles (%)	IF (2018)	Rank*
Developmental Medicine and Child Neurology	12 (24)	3.53	1
NeuroImage: Clinical	4 (8)	3.94	2
Pediatrics	3 (6)	5.40	3
Neurology	2 (4)	8.69	4
Radiology	2 (4)	7.61	5
Human Brain Mapping	2 (4)	4.55	6
American Journal of Neuroradiology	2 (4)	3.26	7
Neuroscience Letters	2 (4)	2.17	8
Journal of Child Neurology	2 (4)	2.09	9
Neuropediatrics	2 (4)	1.65	10
JAMA	1 (2)	51.27	11
Brain	1 (2)	11.81	12
Annals of Neurology	1 (2)	9.50	13
STEM CELLS Translational Medicine	1 (2)	5.96	14
Neuroimage	1 (2)	5.81	15
Neurorehabilitation and Neural Repair	1 (2)	3.76	16
Journal of Magnetic Resonance Imaging	1 (2)	3.73	17
Frontiers in Human Neuroscience	1 (2)	2.87	18
Archives of Physical Medicine and Rehabilitation	1 (2)	2.70	19
Neuroradiology	1 (2)	2.50	20
European Journal of Pediatric Neurology	1 (2)	2.50	21
Pediatric Neurology	1 (2)	2.33	22
Acta Paediatrica	1 (2)	2.27	23
American Journal of Medical Genetics Part A	1 (2)	2.20	24
Research in Developmental Disabilities	1 (2)	1.87	25
Brain & Development	1 (2)	1.76	26
Brain Connectivity	1 (2)	–	27

IF data were collected from Journal Citation Reports for the year 2018. No., number; IF, impact factor; JAMA, Journal of the American Medical Association.
**The journals ranked by number of articles and IF.*

DISCUSSION

Targeting the unclear focus of current studies and future directions in brain imaging for children with CP, our study demonstrated that the main topics of the highly cited articles were the identification and diagnosis of CP (44%) and understanding its mechanism using MR technologies (30%), with designs based on low-level evidence. Our results have also indicated that possible future directions in this field could be research on therapy effect evaluation and prognosis using multi-modalities, based on high-level evidence design (2008–2017,

median: 2014.5). Moreover, CP studies on the single subtype SCP and sensorimotor or upper limb-related function have also attracted considerable attention.

This study analyzed the bibliometric information of the top 25% of articles in order of yearly citation counts in brain imaging for children with CP, since brain imaging has first been applied in CP studies in 1984 (3). According to our research, there is still a lack of agreement on the standard of highly cited articles worldwide. Levitt et al. study mentioned that they chose the top 25% of yearly citation counts as highly cited articles due to it covering enough articles in the field while still meeting the definition of highly cited articles (12). Therefore, we chose the same standard, namely, the top 25%. **Figure 1** shows that no articles before 1991 were included, although no time limit was set for this study. According to the search results, only three articles were found before 1991, with yearly citation counts between 0.20 and 1.93, which did not qualify these articles for the top 25% of the list.

The selection of imaging techniques in CP studies changed from subjective and descriptive stages to objective and quantitative stages. Before the 21st century, TCS, sMRI, and CT were the first few technologies used in CP studies to help identify brain abnormalities and etiology (13). In the 2000's, with the development of imaging technology, DTI became the most frequently applied method to quantitatively analyze structural changes, mechanisms, and therapy effectiveness in CP children; it provided objective results for the detection of brain alterations (14, 15). From 2010 to 2018, the multi-modality approaches were more frequently used to assess therapy effectiveness and comprehensively discover mechanisms in children with CP (16–18). This was the result of a high clinical need for the discovery of the relationship between structure and function, in order to improve treatment evaluation (19, 20). The practice parameters from the American Academy of Neurology and the Child Neurology Society also recommend the use of MRI over CT in children with CP, due to its higher rate in identifying etiology and timing (4). Therefore, the application of new MR technologies became mainstream in brain imaging studies of children with CP. The historical trend in brain imaging modalities also reflects the rapid application of the new imaging techniques applied in CP studies. From the identification of lesions to the exploration of fiber pathways and the construction of brain networks, neuroimaging combined with TMS and/or MEG assisting the comprehensive evaluation of etiology, therapy effectiveness, and prognosis with multi-modality has become the route for future studies.

Among the CP diagnosis studies, the earlier descriptive studies have shown the diagnostic value of imaging examination in identifying the etiology for CP patients (21, 22). Meanwhile, the studies on image performance and features appeared to help understand the causes of CP and identify the relationship between brain abnormalities and clinical characteristics (13, 23). With the development of MR quantitative technology, studies mainly focused on the relevant relationship between structural changes and various functions including sensorimotor function, cognitive (including speech) function, and upper or lower limb function (14, 24). Recently, study focus has been shifted from etiology identification to systematically summarizing and classifying the correlation of brain abnormality with possible etiology (25, 26). The time of CP diagnosis has also been moved forward to 6 months of corrected age using MRI with a predictive sensitivity of 80–90% (5). Furthermore, new evidence suggests that 14% of CP cases have a genetic component (5). Utilizing molecular genetic techniques combined with neuroimaging to detect specific brain abnormalities has become a new tendency in CP studies (27).

CP studies have used new imaging techniques and multi-modality to explore CP mechanisms (19, 20). These studies concentrated mostly on CP subtypes, particularly hemiplegia, due to its extremely unique pathological mechanism (28). Congenital hemiparesis has become an ideal study model disorder due to its abnormal motor function only present on one side of the body, with the contralateral normal side serving as an internal control (29). Considering the significance of the upper limb and hand function for self-care ability in daily life, most of the studies deeply explored the changes in center-hand pathways and structural neuroplasticity (19, 20). Some studies also focused on sensorimotor function-related changes (15). However, very few studies have been found on the mechanism of impaired cognitive functions in children with CP, which needs to be explored in the future. Despite the high incidence of reports on SCP, further investigation is still needed on the mechanisms of other CP subtypes, and an evidence-based study is also essential.

Brain imaging was first implicated in therapeutic evaluation of children with CP in 2008 (30) among 50 highly cited articles. Since then, use of brain imaging to evaluate therapeutic effect in children with CP has been widely adopted. According to our study, nine articles on the evaluation of therapeutic effect were found after 2008, and seven articles have been published in the last 5 years. The utilization of imaging modality changed from single modality evaluation (30, 31) to multi-modality evaluation combined with a functional modality such as TMS (32). The treatments evaluated have also changed from single treatment efficacy evaluation (30, 31) to multiple treatment efficacy evaluation, accompanied by the development of possible treatment-specific biomarkers (33). Thus, we can conclude that the use of brain imaging techniques to evaluate therapeutic effect has become the current research focus and can lead the direction of future study.

The continental distribution of the first author includes North America, Europe, Australia, and Asia. The distribution is uneven with a trend toward developed countries. However, in developing countries, more attention is needed in the medical treatments of high-risk CP populations. Especially due to the financial constraints of low-level economies, the medical and social security systems are underdeveloped, which further affect quality of life of children with CP.

The journals *Developmental Medicine and Child Neurology*, *NeuroImage: Clinical*, and *Pediatrics* featured prominently among the top 50 journals, highlighting their important contribution in shaping the diagnosis, mechanism, and treatment of CP. Several well-known high-IF journals were included in the top 50, for example *JAMA*, *Brain*, and *Annals of Neurology*. It is worth mentioning that *JAMA* published the

most cited article in 2006. Although its original publication was 10 years ago, it still maintains the highest number of citations per year. It should also be noted that *STEM CELLS Translational Medicine* and *NeuroImage* have published two articles representing randomized clinical trials on autologous cord blood infusion.

Limitations

There are several limitations to this study. First, we searched the Web of Science All Databases to consider authority and relative comprehensiveness. The literature found in other databases and not included in the Web of Science All Databases was not highly cited. Second, this analysis contained all the original articles. The longer the period since the article was published, the greater the number of citations that can be found, regardless of its impact. To avoid this bias, we used yearly citations to better reflect the impact of the article. Third, the highly cited article only reflects the impact of the articles and the current focus of the field, but not the quality of the study. Thus, to fully evaluate a study field, information such as study design, rigor, or other measures need to be considered. Fourth, the rank of yearly citation counts might be affected by self-citations for some studies. However, the articles ranked after the top 50 most highly cited articles have limited yearly citation counts and do not affect our results. We will also try to avoid the effect of self-citation in our future studies. Last, the majority of highly cited articles in bibliometric studies are derived from overlapping lists of established journals indexed in major secondary databases. Some studies have reported that recently collected papers should have at least 2 years of historical accumulation of enough citation volume to establish bibliometric reliability (8). Therefore, our study can objectively reflect the hotspots and trends in all related studies up to 2017.

Conclusion

This study provides an important and comprehensive analyzation of the most cited articles in the field of imaging application in children with CP over the past 29 years. The future direction of this field may lead to multi-modality studies with high-level evidence-based design that investigate the mechanism, prognosis, and therapeutic efficacy of CP. These studies recognized the important study progress in this field and provided a valuable framework and direction toward diagnosis, mechanism, treatment, and prognosis of CP. By offering important insights into the historical trends in this highly active and promising field, these results might have a strong impact on future research.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

AUTHOR CONTRIBUTIONS

FW and XW performed the literature search, preliminary article analysis, drafted, and revised the paper. FW, HL, and JZ performed the literature search and screened articles. XW, MW, CL, ZZ, and XZ performed the literature search and download. FW, JY, XL, HJ, and TH analyzed the data and revised the draft manuscript. JY and HL oversaw the project and concept design, monitored the data collection, and revised the draft manuscript. All authors contributed substantially to the final article.

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A Pilot Study of Two Different Constraint-Induced Movement Therapy Interventions in Children With Hemiplegic Cerebral Palsy After Botulinum Toxin Injection During Preschool Education

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Introduction: To establish a pilot study on applying two low dose (40 h) constraint-induced movement therapy (CIMT) interventions in children with hemiplegic cerebral palsy (CP) after botulinum toxin (BoNT-A) injection during preschool education.

Methods: Five children with spastic CP (mean age: 5.31 years; Gross Motor Function Classification System level I and II) undergoing regular BoNT-A injections and rehabilitation programs were included. Participants were randomly allocated to one of two CIMT programs (40 h): a 2-week 4-hours/day CIMT program and a 4-week 2-hours/day CIMT program. One CIMT program was performed 1 month after a BoNT-A injection, and then the second program was implemented with the next injection. The outcomes were measured by changes in Goal Attainment Scaling (GAS), the grasp and Visual-Motor Integration (VMI) test in Peabody-Developmental Motor Scales (PDMS), the self-care scale on the Functional Skill Scale, and the Caregiver Assistance in Chinese Version of Pediatric Evaluation of Disability Inventory (PEDI-C), Anxiety and Oppositional Defiance Problems of Achenbach System of Empirically-Based Assessment before and after the CIMT interventions, and at every 2 months' follow-up thereafter.

Results: The mean age of the participants was 5.31 years, BMI was 16.7 (kg/m^2), VIQ was 86.4 ± 8.5, and dose of BoNT-A injection in the upper limb was 42 ± 26.6 units. Grasp, VMI, and self-care on the Functional Skill Scale were significantly better in the 4-week 2-hours/day CIMT program ($p < 0.001$, $p = 0.001$, $p < 0.001$). GAS, grasp, VMI, two 2 self-care scales of PEDI were significantly improved after the CIMT programs, and improvement continued for up to 4 months after the programs. There was no clinical evidence showing changes in the scores for anxiety and oppositional defiance problems during the study period.

Conclusions: The preliminary findings, although limited, suggest a potential therapeutic role for the school-based CIMT program after BoNT-A injection. The 4-week 2-hours/day CIMT program might be better than a 2-week 4-hours/day program in terms of self-care and hand function when performed in kindergarten in this pilot study. Furthermore, this pilot study provides valuable information; therefore, it is crucial to include more CP children and blinded assessors for hand function and ADL in the future study.

Keywords: cerebral palsy—diagnosis, therapy, constraint-induced movement therapy (CIMT), botulinum toxin (BoNT), rehabilitation—ot/pt, preschool education

INTRODUCTION

Cerebral palsy (CP) is the most common physical disability in childhood, and 39% of children with CP have hemiplegia (1–3). Hemiplegic CP children develop 90% of their hemiplegic hand function between the ages of 3 and 7 years (4), so preschool intervention is important to facilitate further development of hand function (5). Case-Smith, concluded that visual-motor interventions for children with developmental delays could improve visual-motor performance in the short term, and occupational therapy embedding both behavioral and learning principles appears to have positive effects on preschool children (3–5 years old) (6). Botulinum toxin A (BoNT-A) has been widely used to relieve the spasticity of CP children (7, 8). Occupational therapy after BoNT-A injection can improve hand function and functional skill performance in hemiplegic CP children (3). Constraint-induced movement therapy (CIMT) can facilitate hemiplegic hand function in stroke patients and CP children (9, 10). CIMT is child-active repetitive and structural training in the use of the hemiplegic upper limb by constraining the dominant hand (11). DeLuca et al., reported that pediatric CIMT at both moderate (63 h) and high doses (126 h) produced positive effects, and their findings refuted the hypothesis of differential dosage benefits (12). Novak, concluded that a period of 30–60 h of therapy within a 6–8-week period is needed to be effective (3).

Child-active approaches, for example, goal-directed training in hand function tasks (e.g., typing), that are designed to meet a goal meaningful to the child (3), are consistent with neuroscientific evidence with regard to inducing maximal neuroplasticity (13). Goal Attainment Scaling (GAS) is a method of scoring the extent to which the patient's individual goals are achieved in the course of intervention. GAS was first introduced in the 1960s by Kirusek and Sherman (14) for assessing outcomes in mental health settings (15, 16). GAS provides a useful measure of functional gains in response to rehabilitation and is more sensitive than global measures such as the Barthel Index (15). GAS could also offer the opportunity for a single interval measure with which to assess response to intervention with BoNT-A (15, 17). GAS has also shown promising qualities in pediatric rehabilitation (18).

This study was designed to be a pilot study employed for 4-week 2-hours/day and 2-week 4-hours/day CIMT (40 h) interventions in children with hemiplegic CP after a BoNT-A injection during preschool education, and to compare the effects and psychological stress of CP children relative to the two CIMT programs. The main hypothesis was that a low-dosage school-based CIMT (40 h) program could be performed smoothly in preschool and produce benefits in hand function and activities of daily living (ADL). The second hypothesis was that 2-week 4-hours/day CIMT would produce significantly greater benefits than 4-week 2-hours/day CIMT and less psychological stress.

MATERIALS AND METHODS

This study used a randomized crossover design with a "wash-out" period, and was conducted from June 2014 to December 2016. The study was approved, and ethical clearance was obtained from the hospital Institutional Review Board (IRB 130210). All participants and their parents provided written informed consent for participation.

Children with hemiplegic or quadriplegic spastic CP who were in a regular rehabilitation program with BoNT-A injections were invited to participate in this study. The enrolled children were classified as Gross Motor Function Classification System level I or II, were aged between 3 and 6 years old, with at least below average mentality, and were in mainstream preschool education; the extension of their hemiplegic wrist and metaphalangeal joint was $>10^{\circ}$. Children were excluded if they: (a) could not understand or cooperate with the CIMT program, (b) had joint contracture of an upper limb, and (c) could not actively extend their hemiplegic wrist. Based on a repeated ANOVA comparison of changes using an effect size of -0.8 for both groups, a significance (alpha) level of 0.05, and 80% power, we required six children for this pilot study.

Participants were randomized using a computerized random number and crossover-allocated to two different CIMT programs: one was a 2-week 4-hours/day program, and the other a 4-week 2-hours/day constraint program in preschool education.

After at least a 7-month "washout period," the children were crossed over to another CIMT program (19). The CIMT program was performed 1 month after BoNT-A injection at the involved upper limb, and was changed to the other program with the next BoNT-A injection. The CIMT program was carried out by preschool teachers during regular school activities, and an arm sling worn on the non-involved hand was used as a restraint. The child's occupational therapist was responsible for treatment planning and adjusting the plan according to the school programs. All children were asked to maintain their

ordinary treatments during the study period. Intramuscular injections of BoNT-A were performed by the same physiatrist (Dr. SF Liao), using 0.5–4 units of BoNT-A/kg/muscle group (Allergan PLC, Dublin, Ireland); the injection intervals depended on the spasticity condition of the children.

The outcomes were measured by any change in two playing goals and two self-care goals of the GAS, grasp, and visual-motor integration (VMI) in the Peabody-Developmental Motor Scales II (PDMS II), 73 functional skills and eight caregiver assistance self-care scales in the Chinese Version of the Pediatric Evaluation of Disability Inventory (PEDI-C), and anxiety and oppositional defiance problems in the Caregiver-Teacher Report Form (C-TRF)-Diagnostic and Statistical Manual (DSM)-oriented scales of the Achenbach System of Empirically-Based Assessment (ASEBA). Measurements were taken just before the BoNT-A injection (T0), 1 month after the injection (T1), shortly after the CIMT intervention (T2), and at 2 months (T3) and 4 months (T4) after CIMT. The measurements of PDMS II and GAS were performed by the child's occupational therapists, the PEDI-C records were maintained by the child's caregivers, and the C-TRF measurements were performed by the child's caregivers and school teachers. The measurements could not be blinded because the assessors (teachers, caregivers, and therapists) had to know the programs and how to operate them.

GAS included two playing goals and two self-care goals. The goals were decided by the occupational therapist, the preschool teachers, and the main caregiver. The goals were weighted by applying the factor of importance × difficulty, where importance of the goal to the patient was graded as 1 = fairly important, 2 = very important, and 3 = extremely important. Difficulty of achieving the goal was rated as 1 = probable, 2 = possible, and 3 = doubtful. Baseline scores were allocated as −1, if the goal was achieved as predicted, then scored 0 when evaluated at 2 and 4 months after CIMT. Achievement above the level predicted was scored at +1 ("somewhat better than expected") or +2 ("much better than expected"). No change or achievement below the expected level was scored as −1, and a worsening of the target function was scored as −2. GAS was calculated for the aggregated score of each patient's goals by applying the formula recommended by Kiresuk and Sherman (14).

The fine motor skills of the affected upper limb were evaluated using the grasping and VMI scores of the PDMS II. These scores can gauge improvement after the CIMT program. The C-TRF (1.5–5) DSM-oriented scales of the ASEBA can assess the children's behavioral/emotional problems from the perspectives of multiple informants (20). The anxiety and oppositional defiant problems in the C-TRF were used to evaluate the emotional stress of the CP children during the study period.

The Wechsler Preschool and Primary Scale of Intelligence-Revision-Chinese-language version (21) is used to assess the intelligence of children aged between 3 and 7 years; the scale includes a full-scale intelligence quotient, verbal intelligence quotient (VIQ), and performance intelligence quotient. The VIQ is used to determine intelligence status without interference by motor impairment. Children with a VIQ $\geqq$ 70 were included.

STATISTICAL ANALYSIS

Descriptive statistics (including mean, range, frequency, and percent) were used for demographic and clinical/treatment factors of interest. Comparisons of the two CIMT programs and the different times were carried out using Generalized Estimating Equations. Differences in the C-TRF-DSM scores between the caregivers and teachers were analyzed by Paired Samples *T*-test.

All analyses were performed using SPSS software version 22.0 for Windows (SPSS Inc., Chicago, IL). A $p < 0.05$ was considered statistically significant.

RESULTS

Five children finished the study; one child did not finish the program because his family moved to another city. The mean age of the participants was 5.31 years, BMI was 16.7 (kg/m^2) (22), VIQ was 86.4 ± 8.5, and BoNT-A dose injected into the upper limb was 42 ± 26.6 units. Four children had spastic hemiplegic CP and one child had spastic quadriplegic CP (**Table 1**). The brain MRI revealed one child had unilateral left periventricular leukomalacia (PVL), three had a porencephalic cyst in the right hemisphere, and one had a porencephalic cyst in the left frontoparietal lobe with PVL.

The GAS for the two playing goals and two self-care goals was significantly improved after the CIMT programs, and continued

TABLE 1 | Basic characteristics of participants at baseline.

Parameter	
No	5
Mean age (y)	5.31 ± 0.84
Female	2
Height (cm)	106.2 ± 4.9
Body weight (Kg)	18.3 ± 2.9
BMI (kg/m^2)	16.7± 2
Diagnosis, *n*	
Spastic hemiplegia	4
Spastic quadriplegia	1
Etiology-congenital	4
Traumatic	1
VIQ	86.4 ± 8.5
More-affected side, *n*	
Right	2
Left	3
Dose of BoNT-A (units) (number of injections)	
Upper limbs	42 ± 26.6
Pectoralis major	20 (1)
Biceps brachii	30 (1)
Brachialis	21.7 ± 6.8 (6)
Pronator teres	20.6 ± 4.6 (9)
Adductor pollicis	10 (4)
Lower limbs	56 ± 35.7

BMI, body mass index; VIQ, verbal intelligence quotient; BoNT-A, Botulinum toxin A.

TABLE 2 | Summary of outcome measures.

	T0-Before BoNT-A		T1-Before CIMT		T2-Shortly after CIMT		T3-2-month after CIMT		T4-4-month after CIMT		GEE		
	4h*2 w	2h*4w	4h*2 w	2h*4w	4h*2 w	2h*4w	4h*2 w	2h*4w	4h*2 w	2h*4w	Program *Time	Program	Time
PDMS II													
Grasp	44.5 ± 4.9	44 ± 5.6	42.5 ± 4.4$^{¢\$}$	47.8 ± 2.4	42.5 ± 4.4$^{‡\#}$	46.2 ± 4.4	46 ± 2$^{¢‡§}$	46.7 ± 2.1	46.7 ± 2.3$^{\$§\#}$	50 ± 2.8	P < 0.001*	P = 0.062	P < 0.001*
VMI	124 ± 8.5	126 ± 17	109.5 ± 20.6$^{¢\$}$	130.5 ± 12.5	111.8 ± 21.9$^{‡\#}$	124.8 ± 19.6	123.7 ± 10.7$^{¢‡}$	136.7 ± 7.8	121 ± 15.7$^{\$\#}$	141 ± 2.8	P = 0.001*	P = 0.202	P = 0.012*
PEDI-C													
Self-care	55 ± 1.4	55 ± 8.5	54.8 ± 5.3$^{¢\$}$	60 ± 1.2	54.7 ± 6.1$^{\#}$	64 ± 3.5	59.7 ± 3.8$^{¢§}$	65.5 ± 0.7	61.3 ± 2.3$^{¢§\#}$	66	*P < 0.001**	P =0.269	P < 0.001*
Caregiver assistant	20.5 ± 0.7	20.5 ± 7.8	22 ± 2.7$^{\&¢\$}$	24 ± 9.2	24.7 ± 3.1$^{\&\#}$	23.7 ± 7.5	25.3 ± 2.3$^{¢}$	33.5 ± 6.4	28.2 ± 6.7$^{\$\#}$	30	P = 0.153	P = 0.267	P < 0.001*
GAS	35.7 ± 0.3†	35.9 ± 0.4†			44.2 ± 7$^{†‡\#}$	44.3 ± 5.3$^{†‡\#}$	48.6 ± 6.5‡§	50.3 ± 5.5‡§	53.5 ± 11.7$^{§\#}$	52.1 ± 6.8$^{§\#}$	P = 0.856	P = 0.676	P < 0.001*
ABEBA-anxiety													
Teacher			2.67 ± 2.1$^{\&}$	3.7 ± 2.9	3.67 ± 2.1$^{\&}$	4 ± 2.6$^{‡\#}$	1.5 ± 0.7	0‡§	3 ± 2.6	1$^{\#§}$	P < 0.001*	*P = 0.204*	*P < 0.001**
Caregiver			4.3 ± 1.5	3.3 ± 3.2$^{¢\$}$	3 ± 2.6‡	4 ± 2.6$^{‡\#}$	4.3 ± 2.5‡	2.5 ± 3.5$^{¢‡§}$	3.5 ± 4.9	5$^{\$\#§}$	P < 0.001*	P < 0.001*	P < 0.001*
Oppositional defiant													
Teacher			1.33 ± 1.2	1.7 ± 2.9	2‡	1.3 ± 1.1	0‡§	1	1.7 ± 1.5§	1	P < 0.001*	P = 0.992	P < 0.001*
Caregiver			3 ± 2.6$^{¢}$	1.7 ± 2.9$^{\&}$	3.3 ± 2.1	4 ± 2$^{\&‡\#}$	2.3 ± 2.3$^{¢}$	3 ± 2.8‡§	3.5 ± 2.1$^{\#}$	4$^{\#§}$	P < 0.001*	P < 0.001*	P < 0.001*

*BoNT-A, Botulinum toxin A; PDMS II, Peabody-Developmental Motor Scales; VMI, visual-motor integration; PEDI-C, Chinese Version of Pediatric Evaluation of Disability Inventory; GAS, Goal attainment scaling; ABEBA, Achenbach System of Empirically Based Assessment. *P < 0.05. † P < 0.05 the data of T0 compared with T2. & P < 0.05 the data of T1 compared with T2. ¢ P < 0.05 the data of T1 compared with T3. $ P < 0.05 the data of T1 compared with T4. ‡ P < 0.05 the data of T2 compared with T3. # P < 0.05 the data of T2 compared with T4. § P < 0.05 the data of T3 compared with T4.*

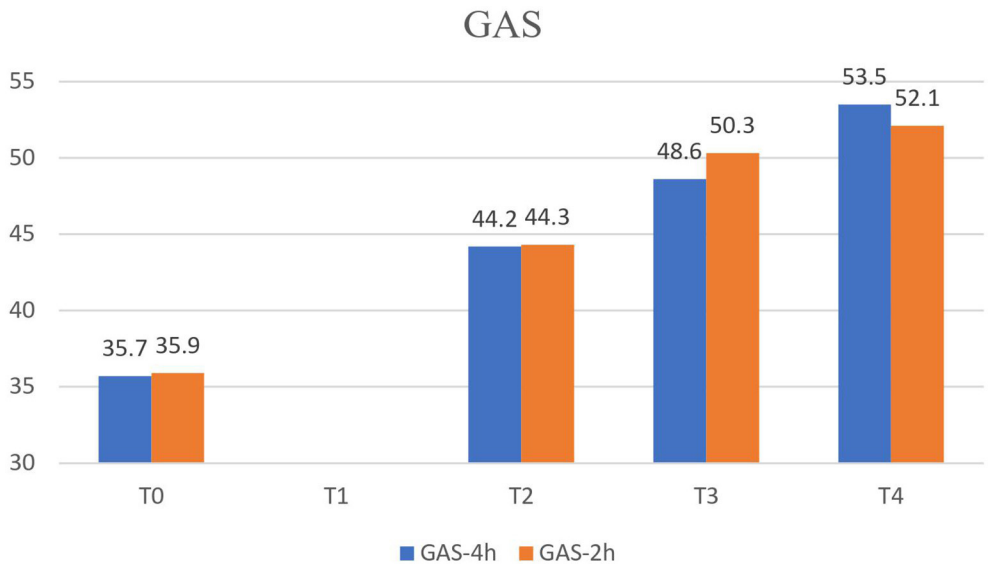

FIGURE 1 | GAS score showed improvement after the CIMT program. GAS, Goal attainment scaling.

to improve until 4 months after CIMT ($p < 0.001$). The GAS especially showed progressive improvement after the CIMT programs (**Table 2**, **Figure 1**), but there was no difference ($p = 0.856$) in the GAS between two 2 CIMT programs.

The grasp (**Figure 2A**) and VMI (**Figure 2B**) scores of the PDMS II were significantly better with the 4-week 2-hours/day CIMT program ($p < 0.001$, $p = 0.001$) (**Table 2**). The grasp and VMI scores of the two CIMT programs revealed significant improvement after the CIMT program, and continued improving until 4 months after the programs ($p < 0.001$, $p = 0.012$).

In terms of ADL, the self-care functional skill score (**Figure 3**) of the PEDI-C was significantly better with the 4-week 2-hours/day CIMT program ($p < 0.001$, **Table 2**). However, there was no difference in the caregiver assistance self-care scores between the two CIMT programs ($p = 0.153$, **Table 2**). The self-care functional skills and caregiver assistance scores were significantly improved at 2 months (T3) and 4 months (T4) after CIMT, but there was no difference in T2 compared with T1 and T0 (**Table 2**).

The anxiety and oppositional defiant disorder did not achieve clinical significance during the study period. Of interest, the anxiety and oppositional defiant disorder scores reported by the teachers were higher in the 4-week 2-hours/day CIMT ($p < 0.001$, $p < 0.001$) program, but the caregivers reported more stress in the 2-week 4-hours/day CIMT program ($p < 0.001$, $p < 0.001$). The anxiety and oppositional defiant disorder problems reported by the teachers were the highest shortly after CIMT, then gradually improved. In the caregiver's report, anxiety was in the subclinical range during T1 and T3, and oppositional defiant disorder was the highest during T2, then gradually improved (**Table 2**). We also compared the scores reported by the teachers and caregivers, and found that the caregivers gave higher scores than the teachers ($p = 0.016$, $p < 0.001$).

DISCUSSION

In our study, we found that the 40-h school-based CIMT program after BoNT-A injection could improve hand function, self-care, and GAS for 4 months, and thus the main hypothesis was corroborated. But the second hypothesis was subverted. The 4-week 2-hours/day CIMT program was more effective than the 2-week 4-hours/day CIMT program in improving hand function and self-care.

Galvin concluded that a combination of BoNT-A and occupational therapy was more effective than occupational therapy alone in reducing impairment and in improving activity-level outcomes and goal achievement. They also concluded that BoNT-A injections should not be used without follow-up therapy intervention (8). In a review article by Novak, CIMT was as effective as Bimanual Training (3). Different researchers have made various modifications to the CIMT program to make it more child-friendly, by reducing both the duration of the intensive training session for the paretic upper extremity and the restraint time for the non-paretic upper extremity. However, Novak suggested that a dose of 30–60 h of therapy within a 6–8-week period is needed to be effective (3). Our study found that 40-h school-based CIMT after BoNT-A is enough to show effectiveness. Most CIMT studies were performed at home (23) or in therapists' rooms (24). We performed the CIMT program in mainstream kindergarten and combined oriented goals with school-activities. Our results showed that both CIMT programs were well-tolerated and were performed smoothly. Another study found that using the 2 hours/day CIMT program in school-based settings can lead to improvements in quality of bimanual skill and movement patterns, but the CIMT program was performed in special education preschool in this study (25).

Goal-directed training that is designed to meet a goal meaningful to the child is an effective intervention in CP

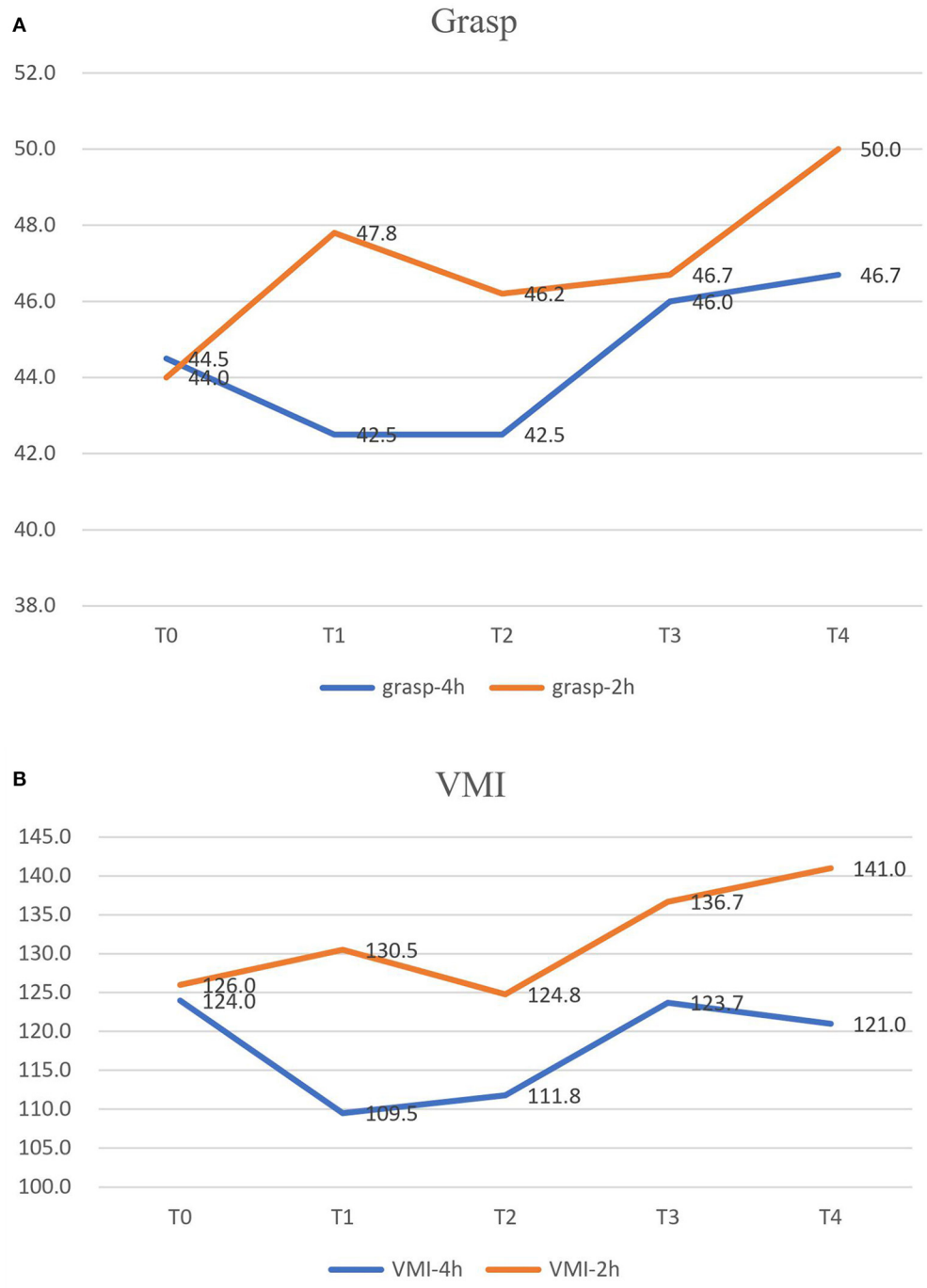

FIGURE 2 | The grasp **(A)** and VMI **(B)** scores of PDMS II were significantly better in the 4-week 2-h CIMT program. VMI, visual-motor integration; PDMS II, Peabody-Developmental Motor Scales II.

rehabilitation (3). In our study, GAS was used for two playing goals and two self-care goals that were chosen by the teacher, caregiver, and therapists. GAS was meaningful to the children and showed the child's progress and improvement after the CIMT program. GAS is a responsive method for individual goal-setting and for treatment evaluation (18), and shows promising qualities for use in CP evaluation.

Grasp and VMI functions were improved after two 40-h CIMT programs, and the improvement lasted 4 months. This is in agreement with a review article by Dong VA (26), in which the CIMT group gained more grasp function in the affected hand than the bimanual training group. Galvin found that a combination of BoNT-A and occupational therapy improved activity level outcomes and goal achievement, but did not

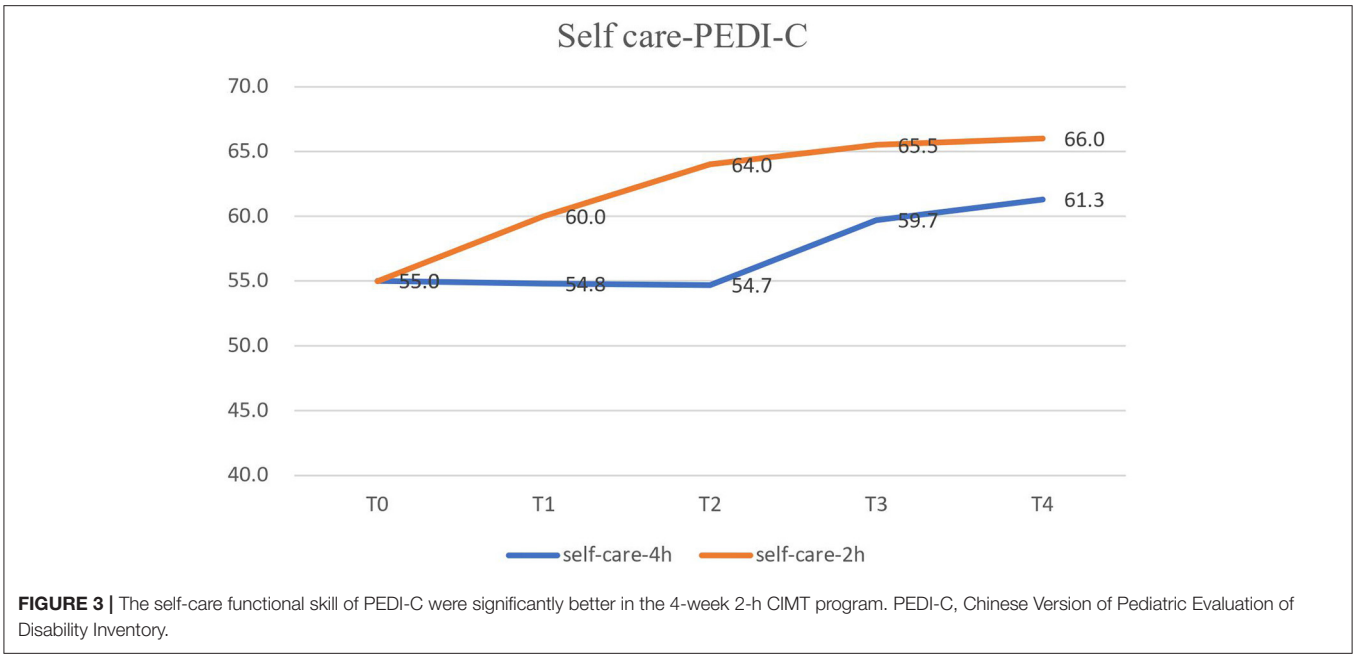

FIGURE 3 | The self-care functional skill of PEDI-C were significantly better in the 4-week 2-h CIMT program. PEDI-C, Chinese Version of Pediatric Evaluation of Disability Inventory.

improve quality of life or perceived self-competence (8). In our study, school-based CIMT after BoNT-A not only improved goal achievement and hand function, but also improved ADL.

The 4-week 2-hours/day CIMT program was more effective in improving grasp and self-care ADL. It might be that the 2-hours/day CIMT program is more accepted and comfortable for CP children than the traditional CIMT (at least 3 hours/day) program (25). Eliasson reported that the 2-hours/day modified CIMT program improved the children's ability to use their hemiplegic hand, and they experienced little frustration (27). In another study, Eliasson also reported that a 2-hours/day, 2-month Eco-CIMT program carried out by parents and preschool teachers influenced development more than ordinary therapy (19). In contrast, Lin KC et al. reported that a 3.5–4 hours/day, twice a week, 4-week CIMT program yielded higher parent–child dysfunctional interaction immediately after CIMT than that after the control intervention (23). We found that the 4-hours/day CIMT program was more stressful for CP children at home. However, the CP children showed more stress in the 2-hours/day CIMT program at school, which could be because of the longer program (4 weeks).

Overall, there was no significant clinical evidence in the scores for anxiety and oppositional defiant problems. This indicated our treatment programs administered in school did not aggravate the children's stress levels in the long run, as in Lin's study (23). The scores for anxiety and oppositional defiant problems evaluated by caregivers were higher than those in the teachers' report. It might be that the children tend to behave well in school but are more frustrated at home.

The novel finding of our study is that the low-level CIMT program could be performed smoothly by school teachers. Furthermore, the evaluation is multidisciplinary, including not only therapists, but also teachers and caregivers. Most CIMT studies were performed at home (23) or in therapists' rooms (24). Gelkop, N et al. also applied CIMT and hand-arm bimanual intensive therapy (HABIT) in a school-based setting, but the program was performed in a special education preschool and the therapy was handled by occupational therapists.

Our research had several strengths. First, we used a cross-over study design and long wash-out period, which could eliminate the bias of the children's personal and environmental differences, and the residual effect of the last BoNT-A injection. In this way, the children could maintain their regular BoNT-A injection and usual rehabilitation programs, but it would take longer (at least 1 year) to finish the program than in other studies (23, 25, 28). Second, GAS is well-established and has proven to be a useful scale to show the progress and improvement of children in the CIMT program. GAS was chosen by the teachers, caregivers, and therapists; the goals were meaningful to the children and allowed the medical staff and family members to be involved in the program.

This pilot study could be used in larger clinical studies. Cohen's *d* is determined by calculating the mean difference between two CIMT programs to determine the effect size of 0.34. Then, using a repeated ANOVA comparison of change with an effect size of 0.34 for both groups, three measurements, a significance (alpha) level of 0.05, and 80% power, 16 children would be required in a future study.

LIMITATIONS

This study has several limitations. First, the small sample size might limit the power and generalizability of the results to the population of children with CP. Second, we did not use a blinded study design. Therefore, there might be some measurement bias. In a further study with a larger sample size,

blinded measurements of PDMS and a measure for spasticity are suggested.

CONCLUSIONS

The results of this pilot study reveal a high rate of completion and adherence in the school-based CIMT program. The preliminary findings, although limited, also suggest a potential therapeutic role for the school-based CIMT program after BoNT-A injection. The 4-week 2-hours/day CIMT program seemed to be better than a 2-week 4-hours/day program in terms of self-care and hand function when performed in kindergarten in this pilot study. However, we must be attentive to the discomfort and emotional stress of the children when using the CIMT program. This pilot study provides valuable information; therefore, it is crucial to include more CP children and a blinded assessor for hand function and ADL in future studies.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board, Changhua Christian Hospital, IRB approval # 130210. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

C-LW, S-FL, and C-HL contributed to the study design. C-LW, C-HL, Y-TH, and Y-RL participated in data collection and analysis/interpretation. C-LW and S-FL participated in manuscript preparation. All authors revised and commented on the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Insights From Genetic Studies of Cerebral Palsy

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Cohort-based whole exome and whole genome sequencing and copy number variant (CNV) studies have identified genetic etiologies for a sizable proportion of patients with cerebral palsy (CP). These findings indicate that genetic mutations collectively comprise an important cause of CP. We review findings in CP genomics and propose criteria for CP-associated genes at the level of gene discovery, research study, and clinical application. We review the published literature and report 18 genes and 5 CNVs from genomics studies with strong evidence of for the pathophysiology of CP. CP-associated genes often disrupt early brain developmental programming or predispose individuals to known environmental risk factors. We discuss the overlap of CP-associated genes with other neurodevelopmental disorders and related movement disorders. We revisit diagnostic criteria for CP and discuss how identification of genetic etiologies does not preclude CP as an appropriate diagnosis. The identification of genetic etiologies improves our understanding of the neurobiology of CP, providing opportunities to study CP pathogenesis and develop mechanism-based interventions.

Keywords: cerebral palsy, genetics, genomics, neurodevelopmental disorders, neurogenetics

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INTRODUCTION

Cerebral palsy (CP) describes a disorder of motor function resulting from maldevelopment or injury to the developing brain. The motor disorders of CP are frequently accompanied by other associated impairments including intellectual disability, epilepsy and sensory impairments (1). CP is relatively common with an estimated prevalence of 1.3–1.9 cases per 1,000 live births in high income countries (2, 3). Whilst often described as a childhood disorder, CP is a lifelong condition. Although many risk factors have been recognized, for many individuals identifying the etiology of their CP can be difficult.

One example of the complexity of CP etiology is preterm birth. Babies born preterm have an increased risk of CP. However, not all babies born preterm go on to develop CP. Being born preterm puts an infant at-risk for additional complications, including respiratory injury (hypoxia, hypercarbia, or hyperoxia), infectious/inflammatory insults (sepsis or necrotizing enterocolitis), hemodynamic compromise (hypotension, intraventricular hemorrhage, or thrombosis). These factors can contribute to cell death in the brain or alter the maturation of neurons and glia, resulting in abnormal white matter tracts

(4) diminished cerebral volumes (5), or cerebellar hypoplasia (6). Further, genetic factors contribute to risk for preterm birth (7). Together this indicates the pathophysiology of CP may result from a combination of genetic, environmental, and genetic factors. Other CP risk factors, such as congenital anomalies or intrauterine growth restriction, may also reflect underlying genetic etiologies (8–11). Recognizing how genetic changes contribute to CP is a rapidly developing field with important themes.

GENETIC ETIOLOGIES OF CP

Relative Contribution of Copy Number Variants

Recent studies have implicated genetic factors as contributors or causes of CP, including single nucleotide variants (SNVs) and genomic copy number variants (CNVs). Putatively deleterious CNVs have been found in several CP cohorts, although estimates of molecular etiologic yield have varied considerably depending on study criteria (12–16). The initial study of 50 unselected CP cases using microarrays implicated novel variants in CP (12). Segel et al. (13) used microarrays to study an enriched cohort of 52 individuals with cryptogenic CP (i.e., no known cause). By applying American College of Medical Genetics & Genomics (ACMG) criteria to interpret their results, they identified 31% with pathogenic or likely pathogenic CNVs. Oskoui et al. (14) studied an unselected cohort of 147 individuals with CP using microarrays and evaluated detected CNVs using rigorous criteria based on ACMG guidelines. They found evidence for pathogenic or likely pathogenic CNVs in 9.6% of their cases. Zarrei et al. (15) assessed pathogenic or likely pathogenic CNVs in 97 individuals with otherwise unselected hemiplegic CP. When focusing on rare, *de novo* CNVs, they identified a molecular diagnostic yield of 7.2%. When they expanded their criteria to include inherited CNVs, known DECIPHER or ClinGen loci or CNVs that encompass genes known to play a role in NDD or brain/muscle disease, the potential yield rose to 23.7%. Finally, Corbett et al. (16) assessed CNV determination from whole exome data, finding an additional 3.7% of cases could be considered "solved" when CNVs are considered alongside SNVs.

In these studies, recurrent likely pathogenic CNVs were identified, such as a 2p25.3 deletion, 22q11.2 deletions and duplications, and Xp monosomy (**Table 2**). The relationship between a genetic deletion/duplication and CP can be complex. For example, 22q11.2 deletions can be associated with major congenital heart defects and polymicrogyria, with the cardiac abnormalities predisposing individuals to stroke and perioperative complications. Alternatively, 22q11.2 deletions are associated with dystonia in the absence of cardiac anomalies (17, 18). In addition, efforts to identify pathogenic CNVs are limited by clinical variability and microdeletion/microduplication boundaries that only partially overlap. Continued analysis and reporting of CNV findings alongside massively parallel SNV analyses are needed to expand knowledge of CNVs that can lead to CP.

Relative Contribution of SNVs

The foundational study conducted by McMichael et al. (10) sequenced 98 unselected CP trios and found that six (6%) had a *de novo* (4 cases) or inherited (2 cases) predicted deleterious variant in a known disease-associated gene. Eight (8%) harbored a potentially pathogenic variant in a novel candidate CP gene. Six of these were *de novo* and two were inherited. A small study conducted by Schnekenberg et al. (19) found *de novo* mutations by WES in 3 out of 4 cases with ataxic CP. Subsequently, Takezawa et al. (20) whole exome sequenced 17 CP trios. These cases represented full-term births without diagnostic MRI findings. Nine of the 17 (53%) cases had pathogenic or likely pathogenic variants in known disease-associated genes by ACMG criteria.

Although these initial studies laid the foundation for the field, there were challenges in reconciling findings in candidate genes with known Online Mendelian Inheritance in Man (OMIM; https://www.omim.org) genes. Limitations of these studies included small sample sizes and a lack of robust statistical methods and well-matched controls. An international collaborative publication (21) addressed several of these limitations, reporting the largest trio-based cohort to date using a rigorously vetted statistical approach supported by mechanistic and biological validations.

Advanced paternal age had previously been associated with risk for CP (22) and is known to be associated with *de novo* mutations. *De novo* mutations were found to be enriched 1.2-fold in CP cases compared to the expected value estimated from background germline mutation rate (21, 23). Models predict between 27 and 124 genes likely contribute to CP through a *de novo* mechanism (21), with the number of identified genes therefore anticipated to rise exponentially with the number of trios sequenced. Gene discovery for CP is a growing area of interest with a recent literature search reporting 57 published genetic studies on individuals described as having CP. However, many of these reports are case studies and some included cases which do not meet current consensus criteria for CP (24), complicating interpretation.

With the increase in our knowledge of the role that genetics play in CP, distinctions between genetic and environmental/acquired etiologies are blurring and mixed and multiple insults are increasingly recognized. In some cases, genetic risk factors predispose individuals to environmental insults. Such a predisposition has been described for hemorrhagic stroke due to *COL4A1* and *COL4A2* mutations (25) and hypotonia before birth causing delivery complications and perinatal asphyxia, exemplified by 1p36 deletion syndrome (26). Differences in genetic backgrounds, such as single nucleotide polymorphisms in glutamate transport (27) and COX-1/2 receptors (28), might also underly susceptibility to CP after exposure to environmental risk factors (29).

The long-recognized increased risk of CP for males (30) also provides evidence for complex interactions between genetic contributions, predisposition, and responses to brain injury. For instance, female rats have more dystonia-like outcomes, and males have more spasticity-like outcomes after the same hypoxic-ischemic injury (31). Together, this suggests differences

in genetics and subsequent physiology likely play a role in determining the development of CP in individuals exposed to environmental risk factors. Despite the considerable advances that have been made, the relative contribution of environmental vs. genetic causal factors remains unclear.

WHAT CONSTITUTES A CP-ASSOCIATED GENE?

Using careful case ascertainment to ensure sequenced individuals have CP is crucial for interpretation of genetic findings as either consistent with CP or not (24). Some cohorts may include individuals with progressive neurological impairments who do not fulfill the criteria for CP (32). Although these findings are important in their own right, genetic findings from individuals with rare pediatric movement disorders that do not meet the diagnostic criteria for CP should not be included in lists of CP-associated genes. Full reporting of the age of onset, movement disorder subtype, the presence or absence of neurodegeneration (including if there was follow-up over time and age of the last contact) and comorbidities will be necessary for the interpretation of the pathogenicity of variants in future cases presenting with mutations in those genes.

Determining whether a genetic variant or group of variants accounts for an individual's phenotype can be difficult without subsequent laboratory-based validation studies delineating the variant's effect on RNA or protein function. In some instances, the detection of multiple individuals in a CP cohort with predicted damaging variants in the same gene can provide strong statistical evidence for a *bona fide* association with CP if enrichment is present and consistent inheritance patterns are evident. A few CP-associated genes have clear loss-of-function variants, such as stop gain and frameshift variants in *CTNNB1* (21). Splice site variants can be challenging to interpret, but have been confirmed to affect mRNA sequence for *AMPD2* and *CTNNB1* as well as protein function in the case of *AMPD2* (20). However, most variants are missense mutations, and when bioinformatically predicted deleterious *de novo* missense mutations are systematically tested, many do not change protein function (33), highlighting the importance of experimental validation. *De novo* variants also can also contribute through gain of function or even change of function effects. For example, *FBXO31* and *RHOB* variants did not demonstrate loss of function deficits. However, when studied in more detail, gain/change of function mechanisms were identified (21). Given that many genes can have multiple functions, diverse localizations and myriad interactions, defects can be hard to detect in a single assay, making it more challenging to rule out candidate genes as well. *TUBA1A* missense variants, for example, can have subtle effects on microtubule shape and protein interactions, which may contribute to considerable phenotype heterogeneity (34). Even in some cases where genes have been shown to have an essential role in movement in model organism studies using zebrafish or Drosophila, the human variants were not tested to confirm variant-specific effects (21, 35).

The sheer number of genes that are being implicated in CP translates into a small but growing number of recurrent genes with a limited number of affected patients harboring variants in these genes. Larger cohorts with cases and controls utilizing methods to detect statistical enrichment of genes with deleterious variants are needed to overcome the recurrence gap. Gene matching platforms such as GeneMatcher (36) are going to be crucial for finding other patients with these rare genetic variants with clinical concordance. Current approaches to overcome limitations in identifying recurrent genes include using pathway enrichment and disease gene overlap to identify genes with a higher probability of contributing to CP pathology.

The criteria for identifying "a CP-associated gene" may vary based on the context prompting the question. Determining whether genetic variants explain an individual's clinical condition requires more stringent criteria than may be required for studying genetic networks contributing to the disease through multifactorial mechanisms. We propose a list of criteria for evaluating the level of evidence of CP genetic findings through the process of gene discovery, laboratory study, and finally, clinical application (**Table 1**). We hope that these proposed criteria will facilitate ongoing dialogue in the field amongst clinicians, basic scientists, and genomic researchers.

We have also reviewed the extant literature for cohort-based next-generation sequencing of CP. Our search strategies were expanded to include patients from cohorts of pediatric movement disorders with non-progressive spasticity, dystonia, ataxia, or chorea that meet CP diagnostic criteria (1) with WES sequencing since 2015. We curated 127 gene variants from WES cohort studies and 32 CNVs from array and WES studies (**Supplemental Table 1**). To determine which genes have strong evidence for causing CP, we identified genes that meet $\geq$1 criteria from all sections of **Table 1**. We found 18 genes and 5 CNVs meeting these criteria that have been described in 2 or more patients (**Table 2**).

Identifying genes responsible for "pure" movement disorder phenotypes has proved quite challenging, but themes are emerging. Genes causing the canonically progressive hereditary spastic paraplegia and the early onset, stable course of spastic CP overlap. Several of these genes, including *ATL1*, *SPAST*, and *AP4* complex members, converge on intracellular membrane trafficking and distribution, regulating the shape of organelles such as the endoplasmic reticulum (44). Genes causing mixed spastic-dystonic CP include *AGAP1*, *CTNNB1*, *FBXO31*, *KDM7A*, *KIF1A,* and *RHOB*, which indicates diverse biological processes can contribute to motor dysfunction. Genes crucial for basal ganglia development, *NKX2*-1, and cyclic nucleotide regulation in the striatum, including *GNAO1*, *ADCY5,* and *PDE10A* (45) have been identified in choreic CP. Finally, mutations in several ion channel genes have been found in ataxic CP patients including *KCNC3*, *ITPR1* (19) and *CACNA1A* (20, 41). Neurotransmission might be more broadly involved as mutations in *STXBP1*, a regulator of syntaxin, have also been found in ataxic CP (19, 20). Taken together, some CP motor subtypes and other motor disorders appear to share not only overlapping phenotypic features, but also overlapping genes and genetic pathways (46).

TABLE 1 | Proposed criteria for prioritizing potential CP-associated genes.

↑Increasing levels of confidence		Clinical features	Variant	Gene
	Gene discovery	Clinical phenotype is consistent with CP* (i.e., no progression, consistent movement disorder, early-onset).	1. Not widely represented in population (<0.001% MAF) 2. Inheritance pattern and family history consistent with segregation in family 3. Bioinformatic tools predict deleterious effect on protein function	1. Expressed in nervous system during development or regulates process known to contribute to CP (e.g., inflammation) 2. Mis_Z or pLI score indicates gene intolerance to random variation
	Research characterization Criteria met for gene discovery plus:	1. Similar phenotype (non-progressive, consistent movement disorder with early onset) in same gene identified in matching service (i.e., Genematcher).	1. Loss, gain, or change of function effect on protein verified in laboratory tests OR known LOF variant type (i.e., stop gain, frame shift) 2. Phenotype in patient tissues consistent with change in gene function 3. Statistical enrichment of predicted deleterious variants in this gene in cases compared to controls	1. Similar phenotype in a model organism with gene LOF 2. Present in protein complex with known disease-associated gene(s) 3. Shares molecular pathway with other CP-associated genes
	Clinical genetics Criteria met for gene discovery and research characterization plus:	Previous reports of the same gene (recurrence), with: 1. Motor symptoms consistent with CP or neurodevelopmental disorder (motor features unknown) 2. Patient findings (dysmorphic features, organ system involvement, etc.) consistent with previously reported findings	1. Same variant previously reported with similar symptoms 2. Variant in same functional domain as other disease-causing variants 3. Predicted pathogenic/likely pathogenic	1. Documented as a CP-associated gene in OMIM or included in clinical gene panel

Criteria indicate supportive evidence that support advancement to the next level of confidence. Criteria for each category and type of study ordered from most confidence to least confidence.

CP, cerebral palsy; HSP, hereditary spastic paraplegia; LOF, loss of function; MAF, minor allele frequency; NDD, neurodevelopmental disorder. pLI estimates the probability of a gene being loss of function intolerant.

**Rosenbaum et al. (1) and Smithers-Sheedy et al. (37).*

Adapted from the ACMG guidelines for evaluating variant pathogenicity in Richards et al. (38) taking into account steps and evidence in the process of confirming CP-association starting from gene discovery.

CP GENE FUNCTIONS AND PATHWAYS

Several case-control studies have used high-throughput-omics approaches to discover dysfunctional pathways and networks associated with CP. In other areas of disease research integrated-omics approaches have been used to consolidate genomic, epigenomic, and transcriptomic findings, but this approach has yet to be systematically applied to CP. Nonetheless, early findings are proving interesting.

Genomics

Genes with mutations detected in CP cluster into pathways governing neurite extension including the extracellular matrix, cell-matrix interactions, cytoskeletal dynamics, and Rho GTPase function. Several genes in these pathways cause locomotor impairments in Drosophila loss of function models (21), indicating that CP genes may regulate connectivity of central nervous system circuits regulating movement.

The concept that CP-associated genes regulate nervous system connectivity is further supported by the clinical and genetic overlap of CP with other neurodevelopmental disorders. Patients with CP often have intellectual disability (∼45%), epilepsy (∼40%), and autism (∼7%) (47, 48). Jin et al. (21) found a 1.7–2.0-fold enrichment of NDD genes among CP candidate genes detected by WES. Genetic pleiotropy has been described for several CP candidate genes. For example, *SCN8A* encodes a sodium channel with well-characterized mutations causing epileptic encephalopathies (49). Additionally, *de novo* mutations in *SCN8A* have been identified in CP (10) and intellectual disability without seizures (50). *KCNMA1* encodes a voltage and calcium gated potassium channel with different mutations associated with a spectrum of neurodevelopmental phenotypes including intellectual disability, developmental delay, axial and ataxic hypotonia, epilepsy, and dyskinesia (51, 52). The association of CP with known NDD genes deserves special mention as potential phenotypic expansions as in some cases, movement disorders have not been well-described previously (53). In most cases, the literature has not indicated the absence of a movement disorder but rather has remained silent on the issue, focusing instead on dysmorphic features, intellectual disability, etc. Thus, genetic disruption of brain development can result in CP, other neurodevelopmental disorders, or a combination.

TABLE 2 | Recurrent CP genes and copy number variants.

Gene/region	# of patients	Associated OMIM disorder	Primary movement type	Citations
AGAP1	3	–	Spastic dystonic	van Eyk et al. (35), McMichael et al. (10, 12)
AMPD2	2	Spastic paraplegia 63	Spastic	Takezawa et al. (20), Jin et al. (21)
AP4M1	8	Spastic paraplegia 50	Spastic-dystonic diplegia	Jin et al. (21), Jameel et al. (39), Verkerk et al. (40)
ATL1	5	Spastic paraplegia 3	Mostly spastic	Zouvelou et al. (41), Jin et al. (21)
CACNA1A	2	Episodic ataxia, type 2	Ataxic	Zouvelou et al. (41), Takezawa et al. (20)
COL4A1	2	Hemorrhage, intracerebral, susceptibility to	Spastic-dystonic w/generalized hypotonia, myoclonic jerks; ataxia	van Eyk et al. (35)
CTNNB1	5	Neurodevelopmental disorder with spastic diplegia and visual defects	Mostly spastic	Jin et al. (21), Cordeiro et al. (42)
FBXO31	2	Mental retardation, autosomal recessive 45	Spastic	Jin et al. (21)
ITPR1	2	Spinocerebellar ataxia 29, congenital non-progressive	Ataxic	Schnekenberg et al. (19)
KDM7A	2	–	Spastic dystonic	van Eyk et al. (35)
KIF1A	2	Spastic paraplegia 30	Spastic dystonic	van Eyk et al. (35)
MAOB	3	–	Spastic	van Eyk et al. (35)
NT5C2	3	Spastic paraplegia 45	Spastic diplegia	van Eyk et al. (35), Jin et al. (21), Naseer et al. (43)
RHOB	2	–	Spastic dystonic	Jin et al. (21)
SCN2A	2	Episodic ataxia, type 9	Spastic, ataxia, hyperkinesia	Cordeiro et al. (42), Takezawa et al. (20)
SPAST	7	Spastic paraplegia 4	mostly spastic	Takezawa et al. (20), Jin et al. (21), Zouvelou et al. (41)
STXBP1	3	Epileptic encephalopathy, early infantile, 4	Ataxic	Cordeiro et al. (42), Takezawa et al. (20)
TUBA1A	3	Lissencephaly 3	Spastic	Jin et al. (21)
dup Xp22.33	2	–	Hemiplegic	Zarrei et al. (15)
Del Xp22.33	2	–	Spastic, choreoathetotic	Oskoui et al. (11, 14), Corbett et al. (16)
Dup 2p25.3 (MYT1L)	2	MRD39	Spastic, choreoathetotic	Oskoui et al. (11, 14)
del 9p24.3 (KANK1)	2	Cerebral palsy, spastic quadriplegic, 2	Spastic	Oskoui et al. (11, 14), Segel et al. (13)
del 22q11.21	2	22q11.2 deletion syndrome		

Variants curated from literature of cohort-based WES and filtered to only include genes with at least one high-confidence variant meeting 1 or more criteria from each column in ***Table 1****.*

Epigenomics

Epigenomic analyses reveal alterations in axon guidance, actin cytoskeleton, and cell signaling with parallels to genomic findings. In monozygotic twins discordant for CP, pathway enrichment analysis for alterations in genome-wide DNA methylation at birth (54) shows changes in MAPK signaling, hypoxia-associated signaling, inflammation, cell adhesion, cytokine–cytokine receptor interaction, and Ras signaling. In unrelated individuals with CP, methylation differences have been identified in genes involved in axonal guidance, the actin cytoskeleton, insulin and ephrin receptors, crosstalk between dendritic cells and natural killer cells, TGF-β, Wnt, neuregulin, PI3K/AKT, and tight junction signaling (55). These findings support the notion that perinatal hypoxic-ischemia and inflammatory responses are associated with an eventual CP outcome. However, it is not clear whether a causal relationship exists, as these studies did not control for environmental risk factors, which could themselves account for the epigenetic changes. Additional cohorts studying many more epigenomes with careful attention to age, risk factors, and statistical methods are needed to determine if the changes are consistent, and how that relates to patient outcomes. Further studies linking genomic and epigenomic findings are also warranted.

Transcriptomics

Transcriptomic analysis of lymphoblastoid cell lines derived from 182 CP patients with a mix of environmental, genetic, and indeterminate etiologies revealed 387 significantly differentially expressed genes (56). Pathway enrichment analysis using this gene set demonstrated downregulated signal transduction and cell signaling pathways including brain-derived neurotrophic factor, upregulated immune function genes, and altered amyloid precursor protein A (APP) processing. Despite differing etiologies and age at the time of collection, the authors found overlap in dysregulation of MAPK signaling that aligned with findings from epigenetic studies. Many of the patients in this cohort have been reported in McMichael et al. (10) or Jin et al. (21) suggesting defects in genes that govern cell signaling (MAPK/PI3K/AKT) may lead to neuronal wiring defects and CP. One fascinating question regarding these findings is whether the observed difference in expression is primary (i.e. fundamentally related to the cause of CP) or secondary (i.e. a consequence of chronic spasticity/dystonia, muscle contracture, etc.) in nature.

Given these findings converge on neurotrophic and stress-response signaling pathways as well as cell adhesion, cytoskeletal maintenance, and actin dynamics, it will be important to replicate and further integrate these results. In the future, stratification of findings by etiology may reveal either consistent or disparate mechanisms. For both epigenetic and transcriptomic studies, the stage of development, time post-injury, and tissue type sampled will impact the resulting profiles. Harmonized study designs across—omics platforms will facilitate cross comparisons between epigenomics, transcriptomics, and proteomics, among other techniques. A serial study of individuals assessed using multiple techniques might be most revealing. Detailed catalogs of patient phenotypes will further facilitate interpretation of these complex findings and may help discern pathways which drives pathophysiology vs. those representing compensatory mechanisms.

GENETICS AND THE DIFFERENTIAL DIAGNOSIS OF CP

The international consensus definition for CP defines the disorder as "a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain" (1). In 2019 the International Cerebral Palsy Genomics Consortium (ICPGC) released a consensus statement reaffirming that CP is defined by clinical phenotype rather than etiology (57). Therefore, a CP diagnosis applies if the definitional criteria are met, regardless if there is a genetic etiology (37). However, a recent survey of physicians who treat people with CP across different specialties revealed variability in current clinical practice. When presented with a hypothetical scenario, only 67% would make a diagnosis of CP if there was a consistent clinical CP phenotype with a genetic cause identified (58). There is thus a need for more clinician awareness and training on genetic etiologies of CP and implications for clinical practice in order to avoid revisionist diagnosis for children who fit clinical criteria for CP.

It is also important for clinicians to be able to distinguish between CP and other disorders to plan treatment and care. Inborn errors of metabolism (IEM) appear early in life with different types of disordered movements, including hypotonia, dystonia, and chorea (59). The stakes are high: 67 of the 110 inborn errors of metabolism that can resemble CP are treatable (59). Therefore, there is a need to quickly and accurately identify the underlying etiology. We posit that CP is not currently, and should not be defined as an "untreatable" disorder. This begs the question: When is it CP and when is it an inborn error of metabolism?

We suggest considering IEM as a potential etiology of CP and using the following classifications based on whether the condition is stable or degenerative:

1. If after treating the metabolic disturbance, the disability resolves without permanent brain injury, the patient should be described as having a treatable IEM.
2. If after treating the metabolic disturbance, the injury to the brain and disability remain but does not worsen, the patient should be described as having CP with a neurometabolic etiology.
3. If the disability progresses, with or without treatment, the patient can be described as having a non-CP rare pediatric movement disorder caused by a degenerative IEM.

A diagnostic classification of both CP and an IEM would be similar to indicating that a person has epilepsy due to an underlying neurometabolic disorder. In many cases, this would be beneficial for access to treatments and services needed for the optimal patient care (37).

Genetic findings previously thought to singularly lead to neurodegenerative disorders have now been identified to lead to non-degenerative motor disorders that meet CP criteria. There is increasing evidence that different mutations in the same gene can lead to either degenerative or developmental phenotypes that probably reflect different effects on cellular biology. Careful phenotyping and follow up of patients with *SPAST* and *ATL1* mutations have revealed that some have phenotypes that are stable over decades (60, 61). *KCNC3* variants from infant-onset disease change channel gating properties and increase neuron excitability compared to variants from adult-onset disease, which were associated with reduced channel activity and high-frequency neuronal firing. Further, these effects can manifest with different temporal patterns, with the infant-associated variant disrupting dendrite and axon branching as a developmental feature absent from the adult-associated variant (62). Mutations in *TRIO* were recently shown to lead to distinct, domain-specific effects on development (63). This evidence suggests that manifestations may vary depending on the nature of a given mutation and potentially other moderating factors. A finding in a gene linked to a potentially progressive disorder should trigger a careful re-appraisal of the patient's phenotype and may influence testing, monitoring, and follow up, but should not reflexively prompt a revision of diagnosis unless clinically appropriate based on the patient's course.

ARE NEW GENETIC DISCOVERIES CHANGING THE TREATMENT OF CP?

New genetic findings are raising new questions. For instance, do genetic mutations disrupt brain development in consistent ways? What imaging findings indicate a genetic cause of CP? There have been several studies on brain malformations in movement disorders (64). Periventricular leukomalacia (PVL) detected by MRI has classically been interpreted as caused by perinatal stress (65). However, PVL was also detected in patients with *ATL1* and *RHOB* variants (21) and 5/12 patients with a neuroimaging finding of PVL had no pre- or perinatal risk factors or complications (66). This finding suggests that rather than representing a single etiology, PVL reflects white matter abnormalities where the timing can be either pre- or perinatal (67). In addition, individuals with CP often have structurally normal or mild, non-specific anatomic MRI findings (68). Functional MRI may add additional dimensionality to the understanding of brain connectivity (69). Compared to those with abnormal MRI findings, CP patients with normal MRIs are more likely to have been born at term and experienced an uneventful perinatal period. They are also more likely to have dyskinetic and diplegic CP types but show no differences in the severity of impairment or presence of comorbidities (70). More study is currently needed to determine how MRI could predict genetic contributions to CP.

Genetic findings can and will inform personalized medicine over time. For instance, in a randomized case-control clinical trial, polymorphisms in immune genes (*IL1β*, *PAI1*, *IL6R*) were associated with improved neurodevelopmental outcomes, including reduced rates of CP, after magnesium sulfate intervention in women at imminent risk of premature delivery (71). Genetic etiologies may also inform interventions such as deep brain stimulation (DBS). In some cases, DBS outcomes can be anticipated based on prior genetic findings (72, 73). Other genes may inform preventative or monitoring efforts to ensure optimal outcomes, such as avoiding head injury and managing cardiovascular risk factors in *COL4A1* patients. Due to increasingly compelling evidence that CP can have a genetic component, future studies should test whether using WES and CNV analysis can guide clinical care for CP. Surveys of patients and their families with disorders of unknown etiology support the use of WES as part of the diagnostic process, with the greatest benefit reported from those who obtained positive findings (74). This underscores the need for additional gene discovery and translational research to improve the interpretation of such tests and establish clinical guidelines for utilization in diagnostic assessment.

DISCUSSION

In summary, genetic etiology is a notable contributor to the development of CP, potentially through both disrupted brain development and dysregulated responses to risk factors. A small number of recurrent genes with strong evidence of pathogenicity have been described. However, there are likely hundreds more genes that await discovery and/or validation with large-cohort sequencing and follow up studies on the molecular consequences of patient-associated variants. Future studies will also be needed to provide a more in-depth analysis of the function of genes in individuals with overlapping phenotypes using platforms like Genematcher (36). A comprehensive list of all genes that have been identified for CP, not just those from cohort WES studies reviewed here, will be an essential development for the field, particularly as clinical CP sequencing panels are already being offered. Since CP-associated genes have not been systematically curated in OMIM, this represents an opportunity for the field. In the interim, the inclusion of NDD genes with or without previously described movement disorder phenotypes compatible with CP can serve as a surrogate.

Efforts to find genetic etiologies by CP motor type have been limited, in part due to genetic and phenotypic heterogeneity. Identifying CP-subtypes may become more feasible with meta-analysis with high numbers of patients with detailed clinical information provided for every individual in the cohort, facilitated by the International Cerebral Palsy Genomics Consortium (www.icpgc.org). Identifying genes that can cause specific motor types will be crucial for studying the mechanisms underlying those disorders as well as identifying pathways and other features to guide further gene discovery and the development of personalized treatments.

Progress in understanding CP pathology and developing new treatments has been impeded by the limited availability of animal models for functional studies. As monogenic forms of CP are increasingly identified, this will allow development of important genetic models to better understand changes to neurobiology and development in CP. Studies to date have identified relatively few genes as sequenced cohorts have been comparatively small, compounded by a relative lack of deep phenotyping. As more genetic studies are conducted, there will be an increased need for validation analyses to definitively link variants and genes with cerebral palsy. This improved characterization of individual genes will also facilitate subsequent gene discovery, pathways contributing to CP pathogenesis, and the development of targeted interventions. A better understanding of CP genomics will also enable the identification of risk genes contributing through a multifactorial, rather than strictly monogenic way. Together, the discovery of genetic factors relevant to CP provides new opportunities for detailed study driving development of treatments and interventions to improve the lives of people living with CP. Updating diagnostic criteria and practice parameters to incorporate indications for genetic testing and interpretation should be considered to provide clarity and guidance of how to classify CP considering the evolving genetic landscape.

AUTHOR CONTRIBUTIONS

SL conceptualized and wrote the manuscript. SS, BW, and AH contributed to literature review, variant curation, and drafting of the manuscript. SJ, HS-S, MF, and MK made intellectual contributions and edits. All authors approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.625428/full#supplementary-material

Supplemental Table 1 | Curated sequence variants from whole exome sequencing studies of cerebral palsy cohorts.

Supplemental Table 2 | Curated copy number variants from whole exome and microarray studies of cerebral palsy cohorts.

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frontiers in Pediatrics

ORIGINAL RESEARCH
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Accelerometric Gait Analysis Devices in Children—Will They Accept Them? Results From the AVAPed Study

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Aims: To assess children's acceptance to wear a 3D-accelerometer which is attached to the waist under real-world conditions, and also to compare gait speed during supervised testing with the non-supervised gait speed in every-day life.

Methods: In a controlled observational, cross sectional study thirty subjects with cerebral palsy (CP), with level I&II of the Gross Motor Function Classification System (GMFCS) and 30 healthy control children (Ctrl), aged 3–12 years, were asked to perform a 1-min-walking test (1 mwt) under laboratory conditions, and to wear an accelerometric device for a 1-week wearing home measurement (1 WHM). Acceptance was measured *via* wearing time, and by a questionnaire in which subjects rated restrictions in their daily living and wearing comfort. In addition, validity of 3D-accelerometric gait speed was checked through gold standard assessment of gait speed with a mobile perambulator.

Results: Wearing time amounted to 10.3 (SD 3.4) hours per day, which was comparable between groups ($T = 1.10$, $P = 0.3$). Mode for wearing comfort [CP 1, Range (1,4), Ctrl 1, Range (1,6)] and restriction of daily living [CP 1, Range (1,3), Ctrl 1, Range (1,4)] was comparable between groups. Under laboratory conditions, Ctrl walked faster in the 1 mwt than CP (Ctrl 1.72 ± 0.29 m/s, CP 1.48 ± 0.41 m/s, $P = 0.018$). Similarly, a statistically significant difference was found when comparing real-world walking speed and laboratory walking speed (CP: 1 mwt 1.48 ± 0.41 m/s, 1 WHM 0.89 ± 0.09 m/s, $P = 0.012$; Ctrl: 1mwt 1.72 ± 0.29, 1 WHM 0.97 ± 0.06, $P < 0.001$).

Conclusion: 3D-accelerometry is well-enough accepted in a pediatric population of patients with CP and a Ctrl group to allow valid assessments. Assessment outside the laboratory environment yields information about real world activity that was not captured by routine clinical tests. This suggests that assessment of habitual activities by wearable devices reflects the functioning of children in their home environment. This novel information constitutes an important goal for rehabilitation medicine.

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The study is registered at the German Register of Clinical Trials with the title "Acceptance and Validity of 3D Accelerometric Gait Analysis in Pediatric Patients" (AVAPed; DRKS00011919).

Keywords: wearables, cerebral palsy, gait speed, laboratory conditions, real-world conditions

INTRODUCTION

Successful rehabilitation enables patients to perform activities of daily living (ADL) in their own home setting. Therefore, to monitor the success of rehabilitation will ultimately require assessments in the patient's home setting. In this respect, there is an obvious knowledge gap, as rehabilitation success is typically assessed in a clinical setting, which can only indirectly reflect the patients' functioning in their free-living environment (1). This could lead to the result that patients are prepared to pass clinical assessments but fail in their ADL. Smart wearable devices present an appealing way to circumvent this.

Within the last decade, it has become possible to assess patients in their free-living environment (2). Such wearable devices have great potential for medicine, and assessment of physical activity through commercial companies is already widespread in the public domain (3). In the adult population, accelerometric devices are being used to attempt the assessment of, for example, daily physical activity, as a surrogate for the bones' mechanical environment (4), and as a predictor of hospitalization and mortality (5). Notably, accelerometric data can nowadays also be used to accurately derive real-world gait speed, walking distance (6) and walking and running activity (7), and if worn at the wrist they are well-tolerated in healthy infant population (8).

Children often have more difficulties in following verbal test instructions (9), even if they are as simple as to walk as fast as possible. It is therefore advisable in pediatrics to acquire information in an intuitive or implicit way. In the context of gait analysis, this could, for example, occur through 3D-accelerometric assessments of gait speed, as this would only require acceptance of a measurement device, but not adherence to a specific walking test. In previous studies, it was demonstrated that wearable gait analysis devices work not only in adults, but also in children (8, 10), at least as far as afixment of recording boxes is concerned, as well as obtaining readings of gait speed that are apparently meaningful. Hence, it seems very promising in pediatrics to expand functional assessments from laboratory settings to the real world. However, the crucial question is whether children would accept such measurements.

Cerebral palsy (CP) is the most common cause of impairment in children world-wide with an incidence of 2–3 out of 1,000 live births (11, 12). CP comprises a heterogeneous etiological group, that is often associated with permanent functional deficits, and with impaired development of movement and posture (13). The neuromotor deficits "are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior"(13), which introduce additional problems for testing physical functions in this patient group.

Rehabilitation of patients with CP at an early stage is paramount to the development of muscle and bone strength in early life, and thus for a healthy skeleton in the adult lifespan (14). One must also bear in mind that improving motor skills in children with cerebral palsy underpins cognitive development, non-verbal intelligence, word decoding and arithmetic function (15, 16).

Therefore, we were interested whether accelerometric data could also be collected in the assessment of children with and without CP. This question implies whether healthy children and pediatric patients and their parents would tolerate this type of measurement, and whether meaningful data can be collected. To have this information would not only be beneficial in CP children, for the reasons outlined above, but also in a wider pediatric population, given that lack of physical activity has been recognized as an increasingly important problem. Thus, we ventured to perform gait speed assessments with 3D-accelerometry recording boxes during a wearing-time of 1 week in children, to assess the children's acceptance of this novel approach (primary aim), to validate 3D-accelerometric assessment against a gold standard method, and to explore whether the laboratory-based assessment of maximal gait speed is related to gait speed in the children's habitual environment. No specific hypotheses were made *a priori* regarding any group difference in acceptance of 3D-accelerometric measurements.

SUBJECTS AND METHODS

Participants

Sixty participants aged 3–12 years were recruited between May and October 2018 for this controlled, monocentric, not randomized, observational, cross sectional study. Thirty children with CP were recruited among patients of our rehabilitation clinic, and 30 able-bodied control children (Ctrl) were recruited from CP-participants' and from hospital staff's families. Groups were age-matched through continuously monitoring anthropometric data throughout the recruitment process. One of the inclusion criteria for CP children was, amongst others, classification with Gross Motor Function Classification Scale (GMFCS) level I and II (full list given in **Table 1**). CP children were excluded from study participation when they had a vagus stimulator or a ventro-peritoneal shunt. Given that no prior experience existed, no formal sample size estimation was performed, and a number of 30 children per group was deemed as (a) small enough to be feasible with existing

Abbreviations: 1 mwt, 1-minute-walking test; 1 WHM, 1-week wearing home measurement; ADL, activities of daily living; CP, cerebral palsy; Ctrl, control children; GMFCS, gross motor function classification scale; LME, linear mixed effect model.

TABLE 1 | Inclusion and exclusion criteria.

	Inclusion criteria	Exclusion criteria
CP- group	-age 3–12 years -gross motor function classification scale (GMFCS) I&II -Patient of the Queen-Rania-Rehabilitation Center for Children, Center of Prevention and Rehabilitation, University of Cologne, Cologne, Germany -willingly to participate	-Vagus stimulator -ventriculo-peritoneal shunt
Control group	-age 3–12 years -healthy brother or sister of an included cerebral palsy (CP) child -related to a member of the staff of the Cologne Children's Hospital, University of Cologne, Cologne, Germany or of the Center of Prevention and Rehabilitation, University of Cologne, Cologne, Germany	-disability to appear for the baseline evaluation at the Queen-Rania-Rehabilitation for Children, Center of Prevention and Rehabilitation, University of Cologne, Cologne, Germany

resources, and (b) as large enough to assess effect sizes on the planned endpoints. The study flow is reflected in **Figure 3**.

All participants gave their written informed consent before study inclusion, where needed with support from their parents or through their parents. The study had been approved by the responsible local Ethical Committee, and it complied with the declaration of Helsinki. Before the study was commenced, it had been registered with the German clinical trials register (registration number DRKS00011919).

Study Flow and Data Acquisition

The primary aim of the study was to assess the children's acceptance of a waist-borne 3D-accelerometer within their habitual environment. Acceptance was operationalized as the amount of wearing time and also *via* a questionnaire. The second aim was to compare gait speed during supervised testing with non-supervised gait speed in every-day life. In addition, we planned to explore the data acquired in this study in order to generate novel hypotheses with regards to validity.

Data collection started no sooner than the day after participants had given their consent (see **Figure 1**). First, the 1-min-walking test (1 mwt) was performed on a standardized parkours representing "laboratory conditions." A 3D-accelerometric recording box (actibelt®, Munich) contained in a belt buckle was worn close to the child's body center of mass in proximity of the anterior symmetry axis (**Figure 2A**). During the 1 mwt, one operator followed the children's course as close as possible with a mobile perambulator (**Figure 2B**), and the distance measured thereby served to calculate gold standard walking speed. An acoustic start signal implemented in the study tablet was provided, and the children were instructed to walk as fast as possible, whilst avoiding running, along the outlined course. After the 1 mwt, the recording box was handed over for the 1-week wearing period at home (1WHM) for measurement under "real-world conditions." In addition to the recording box, we also handed over a questionnaire to assess wearing comfort (see **Table 2**). Acceptance of wearing was quantified as (a) hours of wearing per day, (b) wearing comfort as per questionnaire and (c) restriction in ADL (also per questionnaire).

Material

The 3D-accelerometric device used in this study was an actibelt® RCT2 recording box. It is containing a recording box (battery capacity: 1,000 mA, battery life: >35 days, storage capacity: 4 GB, interface: USB 2.0, built in sensor: 3D accelerometer, hall effect sensor) and a wearing belt placed close to the child's center of mass. The wearing belt was equipped with a magnetic closure contact used to verify the self-reported wearing time. Three of the children had been supported with a prototype of the next generation of belts. Specifications of the 3D-accelorometric components of these new devices are compatible with the other devices used in this study.

For the assessment of the gold standard speed, the walking path of each individual child was tracked during the 1 mwt wth mobile perambulator (M10, Geofennel, Baunatal, Germany) in order to measure the distance covered. By dividing the distance by the completion time (1 min by definition), one arrives at the gold standard speed. In order to identify discrepancies between the gold standard and gait speed as provided by the actibelt®, children also wore the actibelt® during the 1 mwt.

For the measurement protocol under laboratory conditions and data readout from the recoding boxes a tablet (Toshiba, AT10LE-A) with the corresponding study app (Trium Analysis GmbH, Munich, Germany) were used.

Subjects were weighted [standing scale, Kern, type MPB 300K100P (9V, 100 mA), Germany] without shoes in their daily clothing. Their height was measured by a mobile stadiometer, type Seca 213 (Seca, Germany).

Statistical Methods

For statistical analysis we used SPSS Statistics 24 (17) and the R-environment in its version 3.5.1 (18).

All data analyses followed the intent–to-treat principle, given that partly missing data (e.g., due to non-compliance or technical problems) should be reflected in the final analyses. Singular imputation was used for missing data, with mean for continuous variables (wearing time) and mode for ordinal variables (comfort and restriction).

Normal distribution was tested with Shapiro-Wilks and homogeneity of variances with Levene test. Wearing comfort and restriction in ADL data were statistically analyzed with the Whitney–Mann *U* test. Wearing time was tested with unpaired *t*-test. Pearson's correlation analyses was performed to assess commonality between gait speed by actibelt® and *via* gold standard in the 1 mwt. Bland-Altman plots were used in order to compare gait speed assessment with 3D-accelerometry against the gold standard. Statistically, the Bland-Altman plot data were then assessed with linear mixed effect (LME), using R's command "lme" from the package "nlme." LME models differ

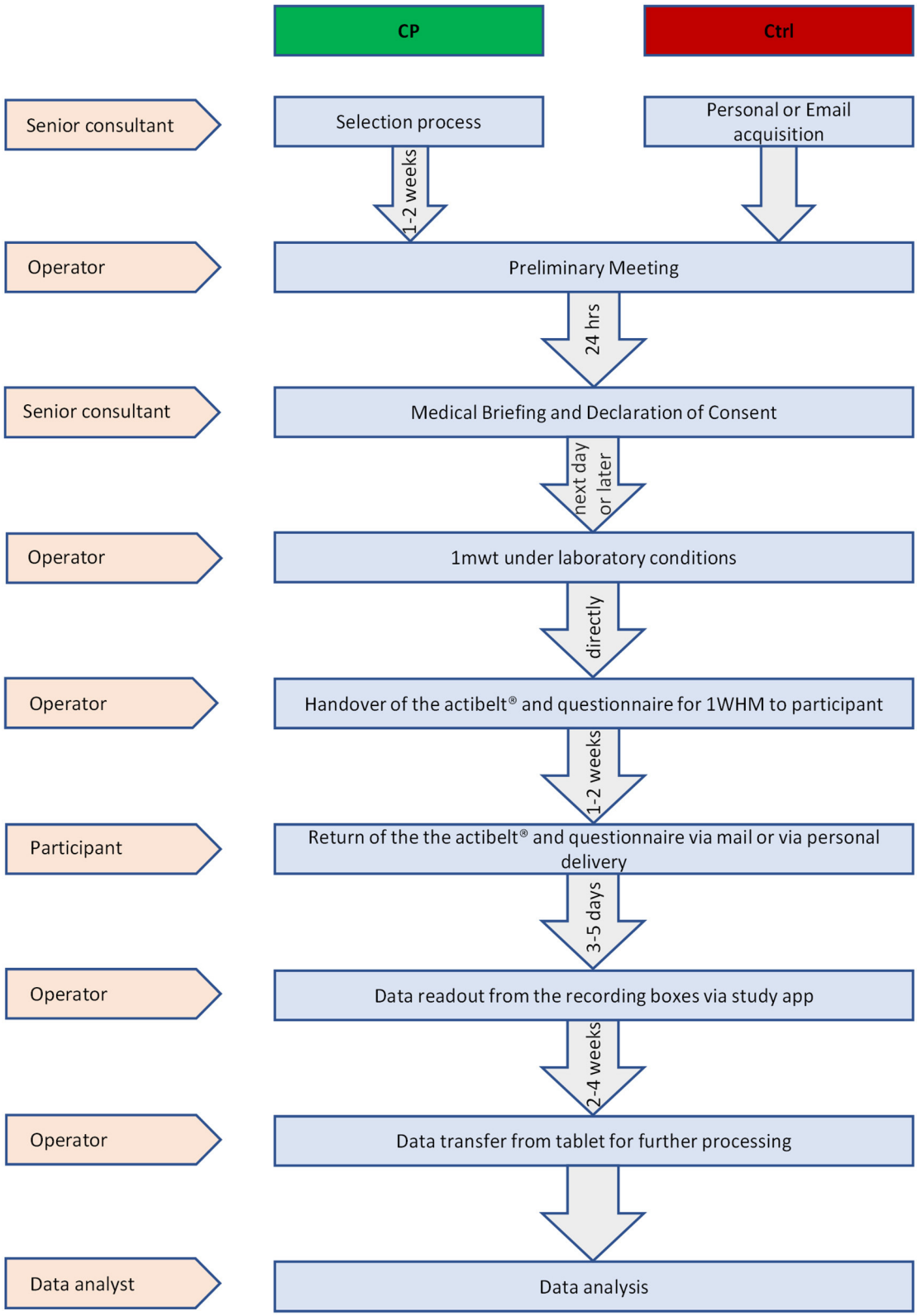

FIGURE 1 | Study flow.

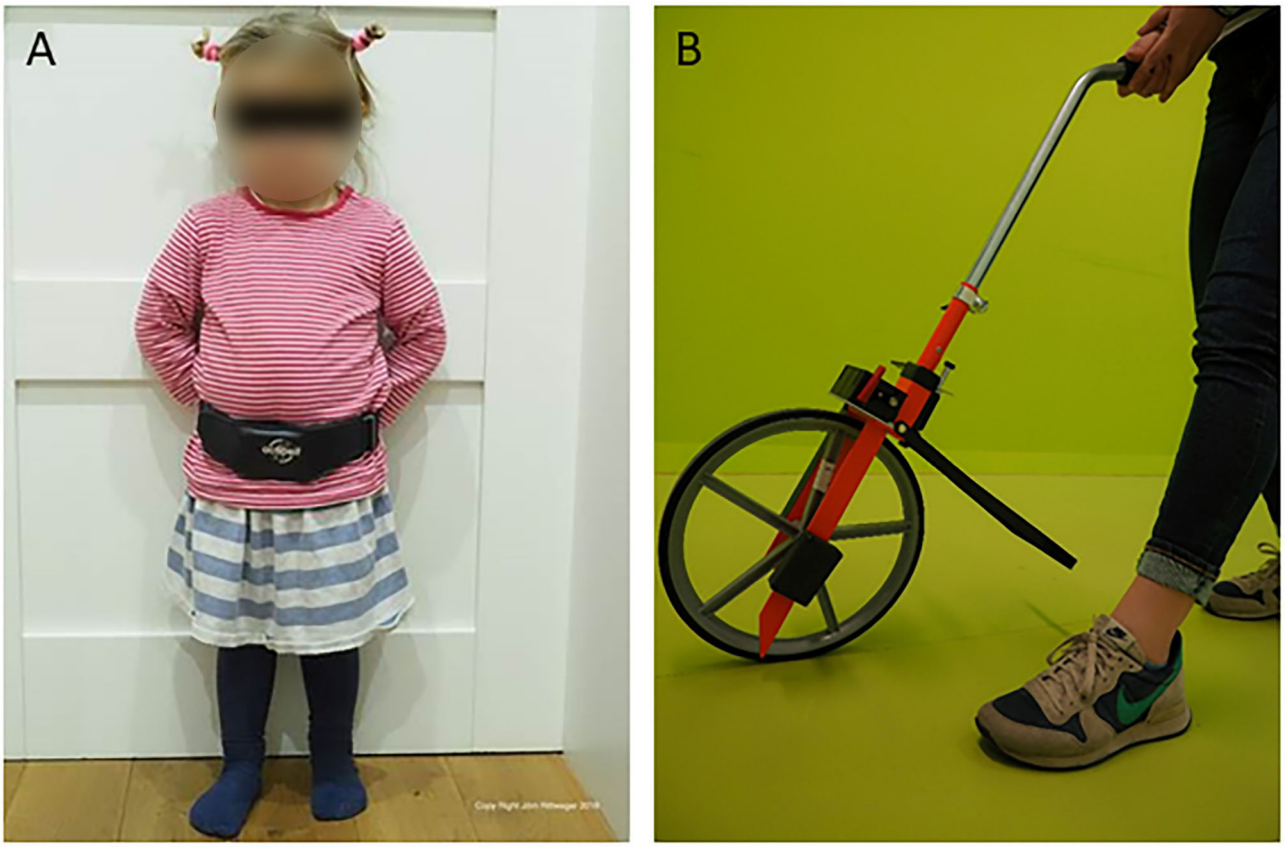

FIGURE 2 | (A) 3-year old child wearing an actibelt®. **(B)** Mobile perambulator used in this study.

TABLE 2 | Questionnaire Items.

Item	Scale
Which days had the accelerometric device been worn?	Date specification
How comfortable was wearing the accelerometric device?	1 = very comfortable 6 = very uncomfortable
How much has the accelerometric device restricted the child's ADL?	1 = no restriction 6 = very restricted
Has the child refused to wear the accelerometric device partially or completely? If so, are there some reasons?	Open answers possible
Are there some ideas how to improve the device?	Open answers possible

from traditional analysis of variance in that normal distribution is only assumed for the residuals, but not necessarily for the data themselves. This has, for example, the advantage that LME models can deal with non-normality in body dimensions by adjustments per individual. LME-models were constructed with y-data (i.e., differences in Bland-Altman plots) as dependent variable, subject as random effect and x-data (i.e., means in Bland-Altman plots) and group (CP or Ctrl) as fixed effects. Likewise, effects of height on gait speed on Bland-Altman y-data was assessed with such LME models. To check validity of LME models, we produced residual plots and Q-Q plots and found assumptions to be valid. Furthermore, partial regression analysis was performed, using the R-package r2glmm, in order to account for the relative contribution of group, height and gait speed on discrepancies between gold standard and actibelt-assessed 1 mwt speed.

Finally, differences between groups in laboratory speed and in real-world gait speed were tested with a paired *t*-test after normal distribution and homogeneity of variances were ascertained with Shapiro's test and with F-test, respectively.

Alpha-level was set at 0,05; all variables are expressed as mean ± standard deviation.

RESULTS

Recruitment Process

Out of 88 recruited children (67 *via* personal recruitment, 21 *via* email recruitment), 61 children performed the 1 mwt. In one child, it was found only after the 1 mwt that this child was occasionally using a walking aid, and all data were excluded from this child. In total, 21 children of the Ctrl group were recruited *via* email between July 2018 and August 2018. Thus, 60 children performed the 1 WHM (**Figure 3**).

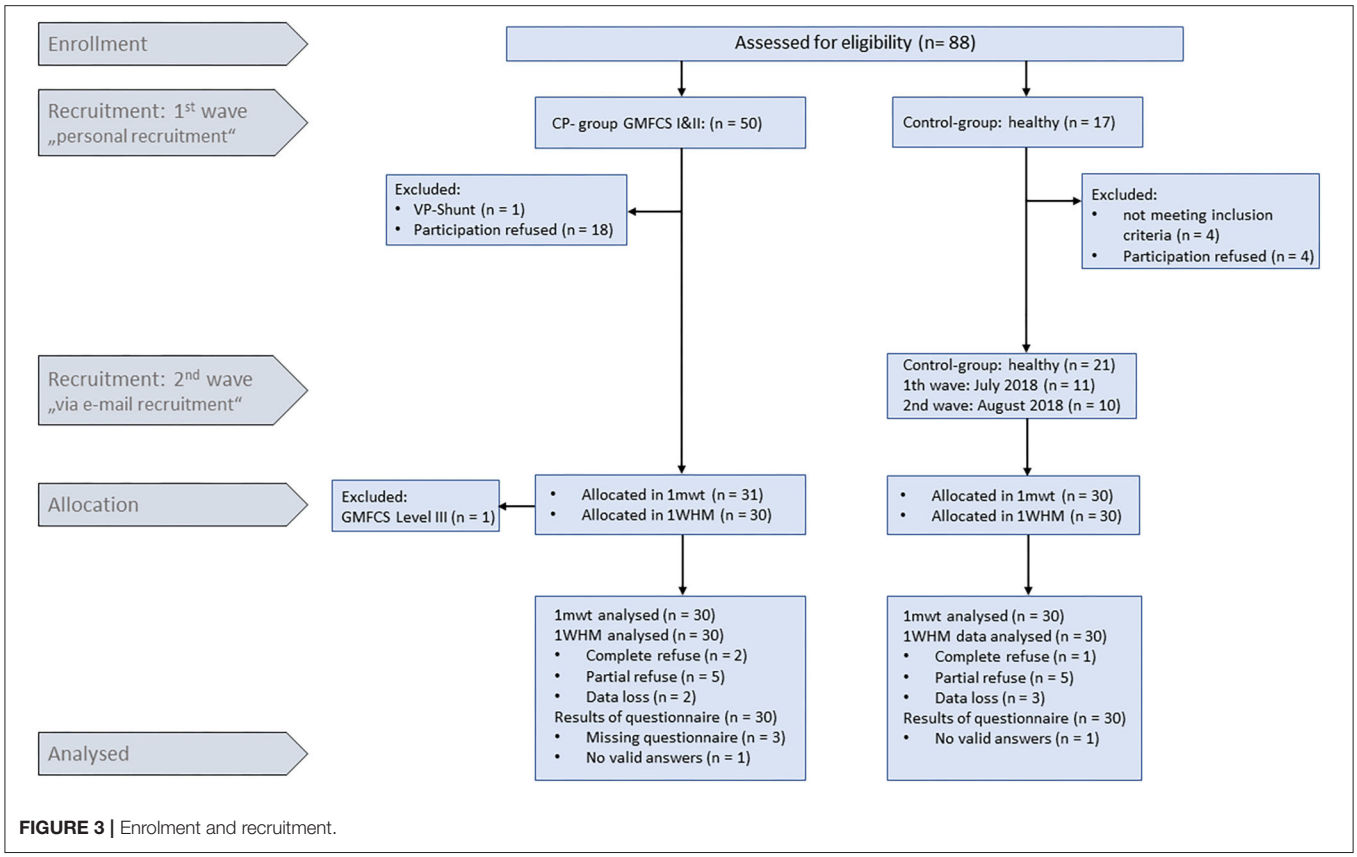

FIGURE 3 | Enrolment and recruitment.

Baseline characteristics of study participants ($n = 60$) are given in **Table 3**. Mean age ± SD in the Ctrl was 7.6 ± 3.0 years, and in the CP group 8.0 ± 3.1 years. For the Ctrl mean BMI ± SD was 16.5 ± 2.2. For the CP mean BMI was 15.7 ± 2.1.

Acceptance

The majority of participants rated no or only little restrictions in ADL in 93.3 and 90.0% of the CP and Ctrl groups, respectively (see **Figure 4**, no group difference, $U = 428$, $P = 0.9$). Wearing comfort was rated as "very comfortable" in 66.6% ($n = 20$) of cases in Ctrl, and 70% ($n = 21$) in CP. Only 3.3% ($n = 1$) of participants in Ctrl scored wearing comfort as "very uncomfortable," while none of the participants in CP scored it as "very uncomfortable" (no group difference, $U = 441$, $P = 0.7$). Wearing time amounted to 10.3 (SD 3.4) hours per day, which was comparable between groups ($T = 1.10$, $P = 0.3$).

In 8 cases we found a discrepancy between the actibelt® measured wearing time and the subject reported wearing time (5 Ctrl, 3 CP). In these cases, the recorded time from the actibelt® was used.

Accuracy of Gait Speed With Actibelt®

Although there was a significant correlation between walking speed assessed with actibelt® and with the gold-standard method [Person's r = 0.78, adjusted $R^2 = 0.60$, $F_{(1, 52)} = 81.4$, $P < 0.001$, dashed line in **Figure 5A**], the regression curves deviated from the line of identity [intercept = 0.74m/s as obtained from Pearson's regression, $P < 0.001$)]. When comparing both gait speed assessment methods in a Bland-Altman plot (**Figure 5B**), and when testing with an LME model built on those Bland-Altman data, a difference was found between the two methods [$F_{(1, 51)} = 3{,}574$, $P < 0.001$], suggesting that actibelt® over-estimated gait speed by 0.23 (SD 0.25) m/s. In addition, a significant linear trend [$F_{(1, 51)} = 86.0$, $P < 0.01$, see red line in **Figure 5B**] suggested that this over-estimation was greater at smaller gait speeds than at faster speeds. As gait speed scaled linearly with body height in both groups [**Figure 5C**, $F_{(1, 51)} = 28.1$, $P < 0.001$], we also explored the relationship between method-differences (= y-axis in **Figure 5B**) and body height. As can be seen in **Figure 5D**, the method-differences were inversely related to body height [$F_{(1, 51)} = 19.6$, $P < 0.001$], and regression lines were approaching 0 (meaning no difference) toward adult body height. Partial correlation analysis yielded significant contributions by group ($T = -2.7$, partial $R^2 = 0.13$, $P = 0.010$) and by body height ($T = -2.6$, partial $R^2 = 0.12$, $P = 0.013$), but not by gold standard speed ($T = -1.55$, partial $R^2 = 0.05$, $P = 0.13$), indicating that accuracy of the actibelt-derived gait speed was more affected by body stature than by gait speed.

Exploratory Analyses of Gait Speed

When comparing 1 mwt gait speed in both groups, we found a difference between CP and Ctrl under laboratory conditions ($P = 0.018$), indicating a 14.0% (95% CI: 3.1% to 25.0% greater gait speed in Ctrl than in CP ($P < 0.05$, **Figure 6A**). In

TABLE 3 | Group characteristics[a].

	Merged Groups			CP- group ($n = 30$)			Control group ($n = 30$)			*P*-value group differences
	Total	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**	
Distri-bution	60 (100%)	36 (60%)	24 (40%)	30 (50%)	20 (33.3%)	10 (16.7%)	30 (50%)	16 (26.7%)	14 (23.3%)	
Age (years)	7.8 ± 3.0	7.6 ± 2.9	8.0 ± 3.2	8.0 ± 3.1	7.1 ± 2.9	9.7 ± 2.8	7.6 ± 3.0	8.3 ± 2.9	6.9 ± 3.1	
BMI (kg/m²)	16.2 ± 2.2	16.1 ± 2.2	16.1 ± 2.1	15.7 ± 2.1	16.6 ± 2.1	16.0 ± 2.1	16.5 ± 2.2	16.8 ± 2.2	16.2 ± 2.1	
Comfort of wearing mode (range)	1 (1,6)	1 (1,4)	1 (1,6)	1 (1,4)	1 (1,3)	1 (1,4)	1 (1,6)	1 (1,4)	1 (1,6)	
Restriction of daily living mode (range)	1 (1,4)	1 (1,3)	1 (1,4)	1 (1,3)	1 (1,3)	1 (1,3)	1 (1,4)	1 (1,3)	1 (1,4)	
1 mwt gait speed (m/s)	1.42 ± 0.6	1.4 ± 0.7	1.5 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	1.2 ± 0.3	1.6 ± 0.3	1.6 ± 0.3	1.6 ± 0.4	<0.001
Average 1 WHM gait speed (m/s)	0.75 ± 0.4	0.69 ± 0.3	0.83 ± 0.5	0.64 ± 0.3	0.62 ± 0.3	0.66 ± 0.4	0.86 ± 0.3	0.79 ± 0.2	0.94 ± 0.4	<0.001
Maximum 1 WHM gait speed (m/s)	1.95 ± 0.22	1.98 ± 0.20	1.93 ± 0.24	1.87 ± 0.20	1.89 ± 0.19	1.82 ± 0.25	2.05 ± 0.18	2.08 ± 0.20	2.01 ± 0.17	0.0011
Total wearing time (hours/day)	10.3 ± 3.4	10.2 ± 3.2	10.5 ± 3.6	9.8 ± 3.4	9.6 ±3.8	10.4 ± 2.6	10.8 ± 3.2	11.0 ± 2.2	10.6 ± 4.3	0.3

[a] *The data contain the number (%) or mean ± SD.*

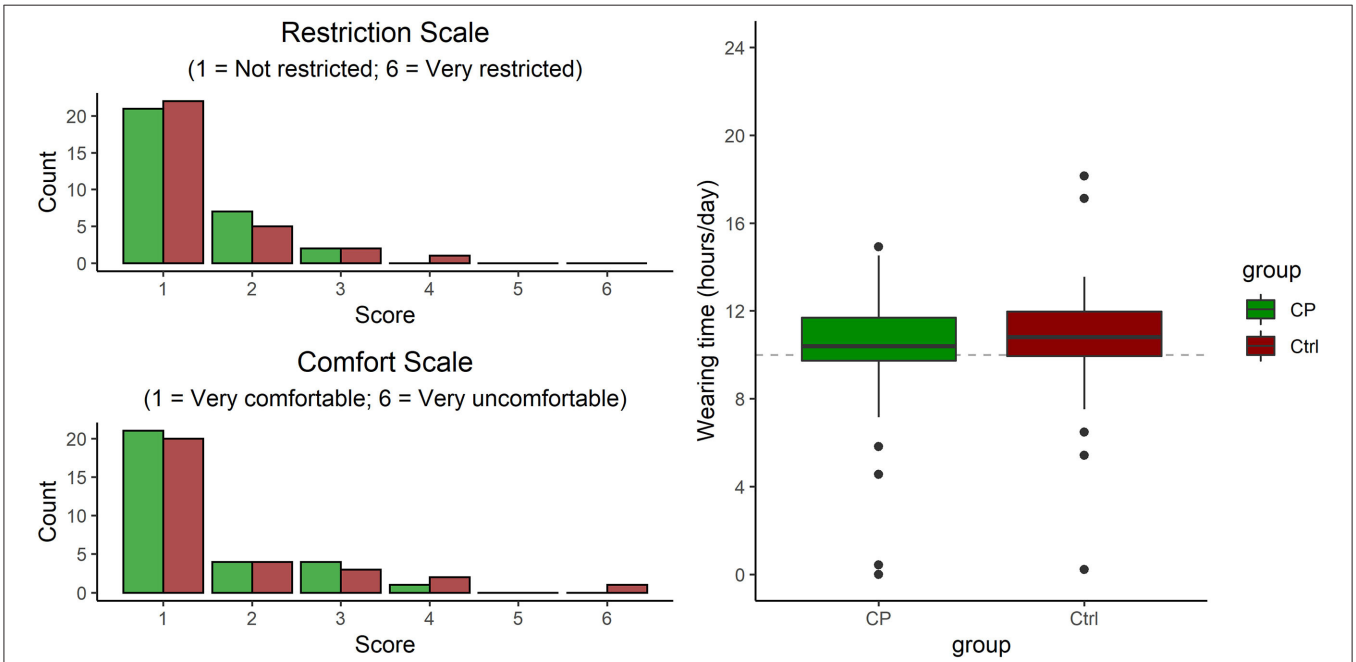

FIGURE 4 | Acceptance, in terms of rating of perceived restriction and of perceived comfort (both by questionnaire) and weekly wearing time (as read from the actibelt®).

comparing real-world gait speed (assessed *via* actibelt®) between both groups, there was likewise a higher speed in Ctrl than in CP ($P < 0.01$, **Figure 6B**).

Although there is a moderate correlation between real-world gait speed and 1 mwt gait speed [$P = 0.002$, $r = 0.26$ (CP), $r = 0{,}27$ (Ctrl), see **Figure 6C**] the regression line deviated very strongly from the line of equality (intercepts 0.79 m/s and 0.85 m/s for CP and Ctrl, respectively), indicating that both variables have different information content. In addition, four children from the CP group had greater walking speed under real-world conditions than during the 1 mwt, with the latter being a maximal test. As can be seen from **Figure 6D**, the 1

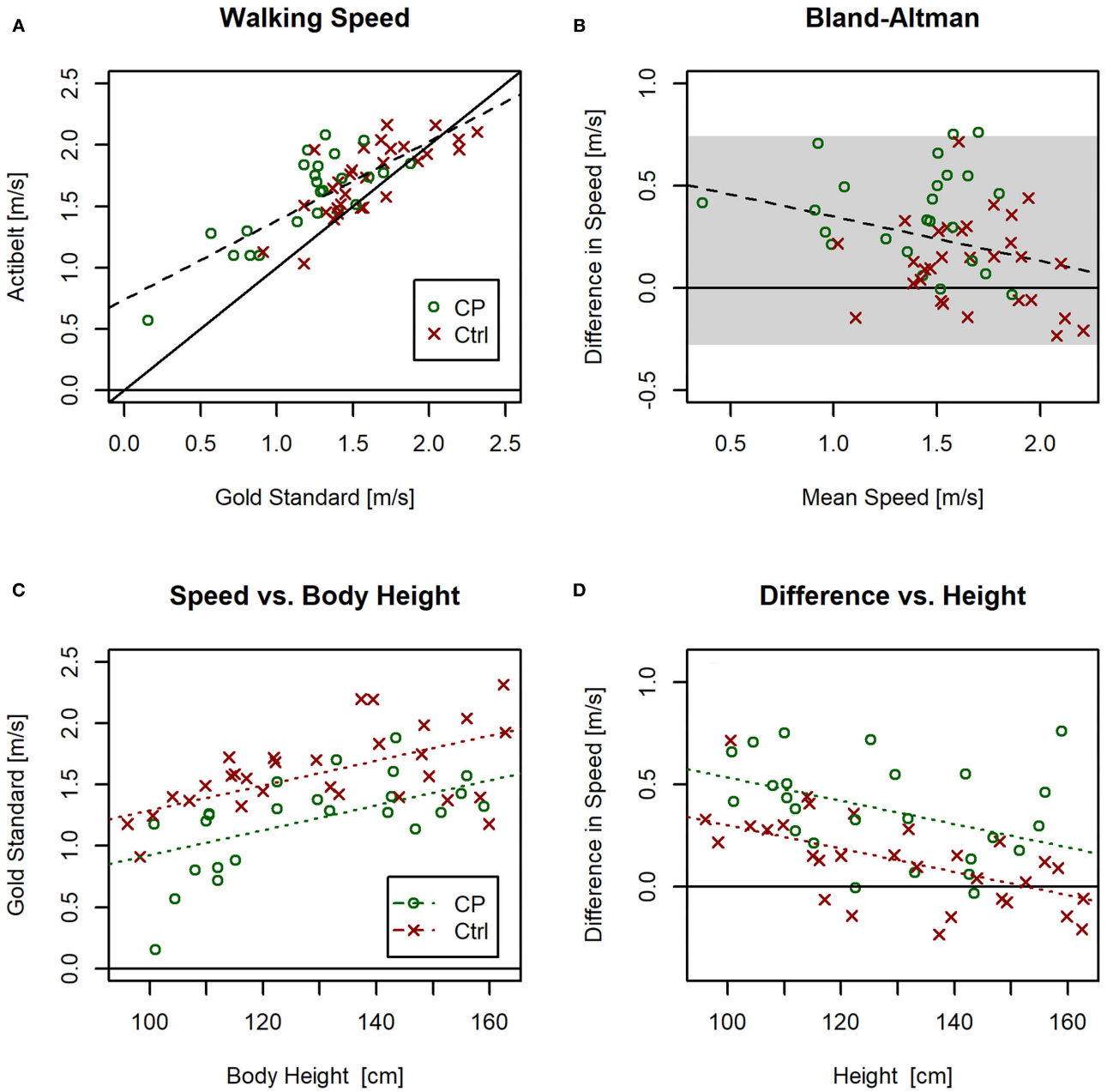

FIGURE 5 | (A) Correlation plot between gold standard walking speed and walking speed provided by actibelt® during the 1-min walking test (1 mwt). Dashed lines represent regression lines for the CP group (blue) and the Ctrl group (green). The black solid line is the line of identity. **(B)** Bland-Altman plot for 1 mwt gait speed assessed *via* actibelt® and *via* gold standard method; the gray shaded area marks the ±2SD range of differences, and the dashed line denotes a linear relationship ($P < 0.05$). For color code refer to sub-plot A**. (C)** 1 mwt gait speed assessed by gold standard method vs. body height; significant effects of gait speed were found for group and body height, but the interaction term was non-significant. **(D)** Difference in gait speed between the two methods vs. body height; significant effects on the method-difference were found for group and body height, but not for the interaction term. For line colors refer to legend in sub-plot C.

mwt:1 WHM speed ratio was unrelated to body height ($P = 0.13$), suggesting that factors other than stature account for sub-maximal gait speed during 1 mwt in some CP children. Finally, a somewhat stronger correlation was observed between maximum 1 WHM gait speed and 1mwt speed, both obtained *via* actibelt ($P = 0.004$, $r = 0.40$).

DISCUSSION

Data collected from this first effort in assessing children's acceptance of 3D-gait accelerometric devices aged 3–12 years yielded very good ratings of comfort, and also low ratings for restrictions in ADL. In the past, a wearing times of 10 h per

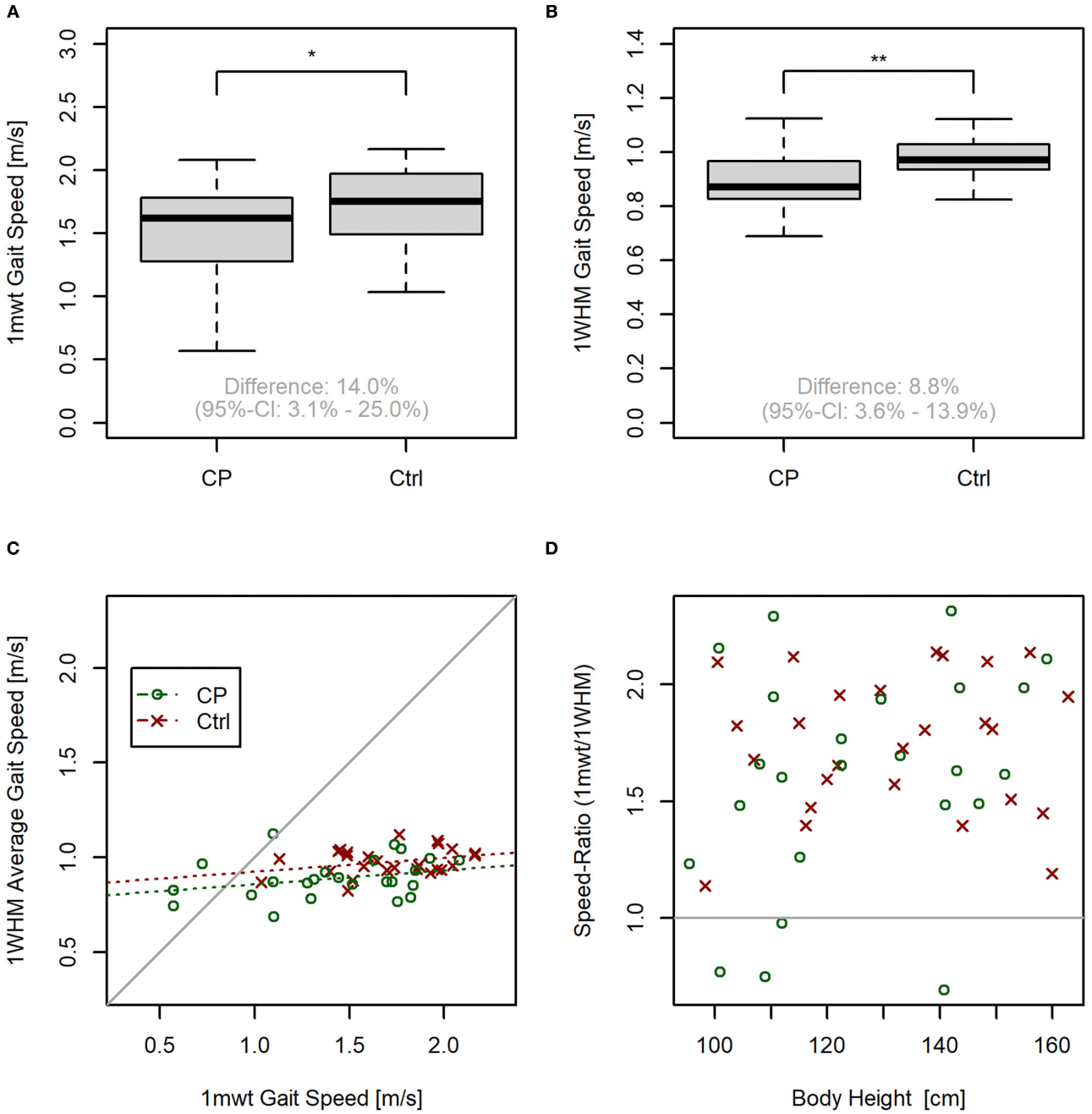

FIGURE 6 | Exploratory data analysis. **(A)** Boxplot for walking speed by group in the 1-min walking test (1 mwt). **(B)** Boxplot for walking speed by group under real-world conditions. **(C)** Correlation plot between actibelt® calculated speed under real-world conditions vs. 1 mwt. Dashed lines represent regression lines for the CP and Ctrl group. **(D)** Speed ratio (obtained by dividing 1 mwt-gait speed by real-world gait speed, both assessed *via* actibelt®) vs. body height. No significant correlation was found ($P = 0.13$). *$P < 0.05$; **$P < 0.01$. For symbol colors refer to legend in sub-plot C.

day had been regarded as the minimum, but this position has eroded and there is currently no generally accepted minimal wearing time for mobile sensor technology (19). Given that sleep is substantially longer in children than in adults, wearing times will always be shorter due to the shorter daily activity span. Results from this study demonstrate an average wearing times of 9.9 and 10.8 h in CP and control children respectively, which is considered as representative for daily activity in adults (20). This is all suggesting that children within this study have accepted wearable technology for gait speed assessment well-enough in order to provide meaningful outcomes. One could argue that CP children are already exposed to many therapeutic

interventions and additional measurements. On the one hand, this could reduce hesitance to accept another device, but it could also induce aversion against yet another measurement. It has therefore been established that no group differences were found for wearing comfort and for restrictions in ADL, suggesting that children with and without a medical condition showed similar acceptance. This lets us hope that these results can be generalized to a wider pediatric population, although future studies will of course have to demonstrate this point.

In addition, many parents mostly gave positive feedback regarding easiness of use and acceptancy by their children. Negative feed-back about the device only concerned coloring (black) and material, that induced sweating during summer period.

Previous studies have almost exclusively focused on adults. Thus, a recent systematic review (21) concluded that evidence for validity and reliability for body center worn accelerometery in adults with neurological diseases is limited, and numerous conflicts in generating reliable analyses have to be solved before these devices could be used under real world conditions.

With regards to the accuracy of the gait speed measurements in the 1-min walking test, it was found that actibelt® overestimates gait speed, as assessed with by the gold-standard method (see **Figure 5B**). This was evident especially at lower gait speeds, as previously also shown by Motl et.al. (22). This effect, in the population of this study, is mostly explained by variation in body height. However, it has to be noted here that existing algorithms have been validated on data from an adult population. Nevertheless, we conclude from the significant correlation between actibelt® and the gold standard method (**Figure 5A**) that accelerometric assessment of gait speed is principally possible also in children. One has to bear in mind here that the algorithm used to derive real-world walking speed was validated on data from an adult population (22). It therefore is possible that a validation study similar to that described by Aigner et al. (23) could remedy the problems. That this may be worthwhile is depicted in **Figure 6**: Gait speed differs between Ctrl and CP children both under laboratory and under real-world conditions. This was found both for the mean real-world speed as well as the maximal real-world gait speed, which confirms a recent study in patients with multiple sclerosis (24). A further look at **Figure 6C** suggests, that interindividual variation is lesser in the 1 WHM than in 1 mwt. We would anticipate, therefore, that within-group variation of both variables may also contain clinically meaningful information, that is, that gait speed assessment in CP children can help to judge severity of disease state and effectiveness of therapeutic strategies, or also compensatory strategies in CP children. Most importantly, assessment of real-world speed yields information that is complementary to the laboratory assessments. This is clearly evidenced by 4 children that had greater gait speed under real world conditions than when they gave their supposedly maximal effort in the 1 mwt. A trivial explanation for this surprising finding would be lack of motivation in the test. An alternative explanation would be that CP children can become over-excited during maximal efforts, and that augmented spasticity (25) during such tests limits their performance.

STUDY LIMITATIONS

As with any study, there are a number of limitations. First, this had been a pilot study. Readers can now derive effect sizes from our results for their own sample size calculations. For example, for wearing time, we arrive at a sample size estimate of $n = 99$ per group to find significant group difference ($\alpha = 0.05$, $\beta = 0.2$). Second, we should consider a possible selection bias. As we used two different recruitment mechanisms, that is, *via* personal contact for CP and merely *via* e-mail for Ctrl acceptance during 1 WHM is representative for both groups, but we are not able to evaluate how many healthy control children had refused participation in advance. This information, which is clearly linked to motivation, would have been helpful to judge whether the general interest in participating in a study was comparable between CP and Ctrl children. However, whilst this could have affected group differences in wearing time, we feel that such bias is unlikely to explain group differences in outcomes related to gait speed. Third, we registered the loss of two sets of data from the 1 WHM by losing the recording boxes during the reshipment process. One possible solution is to amend to the institutional address on the return envelope with a personal addressee from the research team. In having produced some invalid values in evaluation of wearing comfort and restriction of daily living we consider for future studies a more detailed written description for the use of the actibelt® and the questionnaire.

Moreover, we received feedback that recording boxes tended to slip down from their center of body mass. Thus, a solution could be to find alternatives and adaptations to the belt used by the children to position the recording box close to the body center of mass.

Another limitation regarded to the gold-standard measurement is that not having had a video recording and an accelerometer signal of the perambulator, as previously described elsewhere (23), the walking speed derived from the perambulator is given only by dividing the meters registered by the perambulator with the time to complete the test under the assumption it was always 60 s. This has some implications and limitations since it is operator-dependent and it has more room for mistakes compared to a more algorithm-based approach (accelerometer signal and video recording of toe-off/heel-strike of subjects during the test).

However, since the main objective of this study was to validate the acceptance of accelerometer in pediatric population with and without CP, more focus was given to ensuring a good compliance with the usage of the accelerometer in home environment.

CONCLUSION

In conclusion, this study has demonstrated that wearable accelerometric technology can be accepted also in a pediatric population.

Based on the discrepancy of the data we received from the recording boxes of the actibelt® and the reported wearing time from the questionnaire in several cases we may presume that accelerometric devices will prove as a useful assessment of the subject's behavior in real world.

However, some adjustments are probably necessary to further miniaturize hardware, and to extend software for application in children.

SUPPLIERS' LIST

Actibelt®: The actibelt platform is a joint development by Trium Analysis Online GmbH (Munich, Germany, www.trium.de) and the SLCMSR e. V. The Human Motion Institute (www.thehumanmotioninstitute.org).

Mobile perambulator: Geofennel, Baunatal, Germany.

Standing scale: Kern, Germany.

Stadiometer: Seca, Germany.

Study app: Trium Analysis GmbH, Munich, Germany.

Study tablet: Toshiba AT10LE, Tokyo, Japan.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of the University of Cologne (ID 17-184). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

MD, ES, and JR: conception of study. JR and ID: obtaining ethical approval. JR: study registration and running head. MG and ID: study implementation. IW, RL, ID, EA, and JR: data collection. MG: data analysis. IW, MG, and JR: statistical analysis and drafting manuscript. IW, MG, MD, ES, ID, and JR: interpretation. All co-authors: preparing and discussing final version of manuscript.

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Conflict of Interest: MG was employed by Trium Analysis Online GmbH and Sylvia Lawry Centre for Multiple Sclerosis Research e.V. at the time of the study. MD was employed by Trium Analysis Online GmbH. Trium Analysis Online GmbH, Sylvia Lawry Centre for Multiple and MD are owners of trademarks/design/patent/patent applications linked to actibelt technology (detailed list available upon request).

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Neuroimaging Patterns and Function in Cerebral Palsy—Application of an MRI Classification

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Background: Cerebral palsy (CP) is a disorder of movement and posture and every child with CP has a unique composition of neurological symptoms, motor severity, and associated impairments, constituting the functional profile. Although not part of the CP definition, magnetic resonance imaging (MRI) sheds light on the localization, nature, and severity of brain compromise. The MRI classification system (MRICS), developed by the Surveillance of Cerebral Palsy in Europe (SCPE), describes typical MRI patterns associated with specific timing of vulnerability in different areas of the brain. The classification has proven to be reliable and easy to use.

Aims: The aim of this study is to apply the MRICS on a large dataset and describe the functional profile associated with the different MRI patterns of the MRICS.

Materials and Methods: Data on children with CP born in 1999–2009 with a post-neonatal MRI from 20 European registers in the JRC-SCPE Central Registry was included. The CP classification and the MRICS was applied, and The Gross Motor Function Classification (GMFCS) and the Bimanual Fine Motor Function (BFMF) classification were used. The following associated impairments were documented: intellectual impairment, active epilepsy, visual impairment, and hearing impairment. An impairment index was used to characterize severity of impairment load.

Results: The study included 3,818 children with post-neonatal MRI. Distribution of CP type, motor, and associated impairments differed by neuroimaging patterns. Functional profiles associated with neuroimaging patterns were described, and the impairment index showed that bilateral findings were associated with a more severe outcome both regarding motor impairment and associated impairments than unilateral compromise. The results from this study, particularly the differences in functional severity regarding uni- and bilateral brain compromise, may support counseling and service planning of support of children with CP.

Keywords: cerebral palsy, neuroimaging, MRI pattern, associated impairments, functional profile, impairment index

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INTRODUCTION

Cerebral palsy (CP) is defined as a disorder of movement and posture affecting activity. In the latest definition, accompanying impairments are acknowledged (1). Every child with CP has a unique composition of neurological symptoms, motor severity, and accompanying impairments, constituting their functional profile. National guidelines have long recommended magnetic resonance imaging (MRI) as a diagnostic step after history taking neurological examination and examination of additional impairments (2). International guidelines also view MRI as part of the work-up (3). Although not part of the CP definition, MRI sheds light on the localization, nature, and extent of brain compromise. Whether the lesions affect cerebral hemispheres uni- or bilaterally will affect the capacity for plasticity and ultimately the outcome, and insults to core structures important for network building are also of importance (4). Typical MRI patterns have been identified and associated with specific timing of vulnerability in different localizations of the brain (5, 6). Several classifications of MRI findings in CP have been proposed (7–10). One is the MRI classification system (MRICS), developed by the Surveillance of Cerebral Palsy in Europe, SCPE (11, 12). A first report of European population-based results of the MRICS was recently published (13). The quality of the MRICS data relies on training of the register partners, who, guided by the Reference and Training Manual and annual exchange and discussions, do the classification of MRI reports and scans and are instructed to classify the neuroimaging pattern which most likely is the cause of the CP. Classifications done are validated by three pediatric neurologists with specific expertise in MRI (IK-M, VH, and KH). This classification has been proved to be reliable and easy to use in this way (12).

The structure–function relationship with regard to neuroimaging findings and CP has previously been addressed by the SCPE in the Reference and Training Manual[1] (14) and in a previous study (13), where the distribution of MRI patterns was reported by different gestational ages and CP subtypes.

Following this path, the aim of the present study was to apply the MRICS on a large population-based dataset and describe the functional profiles found, by the different MRI patterns of the MRICS. A second aim was to compare the outcome with respect to uni- and bilateral MRI findings.

MATERIALS AND METHODS

Study Population

Data were gathered from 20 geographically defined case registers across Europe. Children with CP born between 1999 and 2009 were included if they fulfilled clinical criteria after their 4th birthday. Children whose brain damage occurred after the neonatal period (beyond the 28th day after birth) were excluded. Children with a report of MRI performed after 1 month of age were then included.

Data Collection

The MRI classification (MRICS) of the SCPE was applied [**Table 1**; (12)]. The CP subtype was classified according to SCPE (11) into unilateral spastic CP (USCP), bilateral spastic CP (BSCP), dyskinetic CP, ataxic CP, or unknown. Gross motor function was classified according to the Gross Motor Function Classification (GMFCS) (15) and fine motor function according to the Bimanual Fine Motor Function (BFMF) classification (16, 17). Accompanying impairments were documented: Severe intellectual impairment was defined as an IQ below 50, tested or clinically estimated. Active epilepsy was defined as ongoing anti-epileptic medication. Severe visual impairment was defined as an acuity below 0.1 in the best eye, and severe hearing impairment was defined as hearing loss >70 dB on the better ear, before correction.

The recently suggested impairment index (18) was applied when uni- and bilateral neuroimaging patterns were compared: *Low impairment* was defined as being able to walk (GMFCS I–II), IQ ≥70, no visual impairment, no hearing impairment, and no epilepsy. *High impairment* was defined as inability to walk (GMFCS IV-V) and/or severe intellectual impairment (IQ <50), with or without one or more of the following impairments: severe visual impairment, severe hearing impairment, and active epilepsy. *Moderate impairment* included all other levels of impairment not defined as low or high [GMFCS I–II, IQ ≥70, but with one or more of the following impairments: severe visual impairment, severe hearing impairment, active epilepsy, OR GMFCS I–II with an IQ ≥50 and <70, with or without one or more of severe

TABLE 1 | The MRI classification system (12).

A. Maldevelopments

A.1. disorders of cortical formation (proliferation and/or migration and/or organization)

A.2. other maldevelopments (examples: holoprosencephaly. Dandy Walker malformation, corpus callosum agenesis, cerebellar hypoplasia)

B. Predominant white matter injury

B.1. periventricular leucomalacia, PVL (mild/severe)

B.2. sequelae of intraventricular hemorrhage (IVH) or periventricular hemorrhagic infarction (PVHI)

B.3. combination of PVL and IVH sequelae

C. Predominant gray matter injury

C.1. basal ganglia/thalamus lesions (mild/moderate/severe)

C.2. cortico subcortical lesions only (watershed lesions in parasagittal distribution/multicystic encephalomalacia) not covered under C3

C.3. arterial infarctions (middle cerebral artery/other)

D. Miscellaneous

(examples: cerebellar atrophy, cerebral atrophy, delayed myelination, ventriculomegaly not covered under B, hemorrhage not covered under B, brainstem lesions, calcifications)

E. Normal

Printed with permission. IVH, intraventricular hemorrhage.

Abbreviations: BFMF, Bimanual Fine Motor Function; BSCP, bilateral spastic cerebral palsy; CP, cerebral palsy; GMFCS, Gross Motor Function Classification System; MRI, magnetic resonance imaging; USCP, unilateral spastic cerebral palsy.

[1]https://eu-rd-platform.jrc.ec.europa.eu/scpe/reference-and-trainingmanual_en (accessed October 14, 2020).

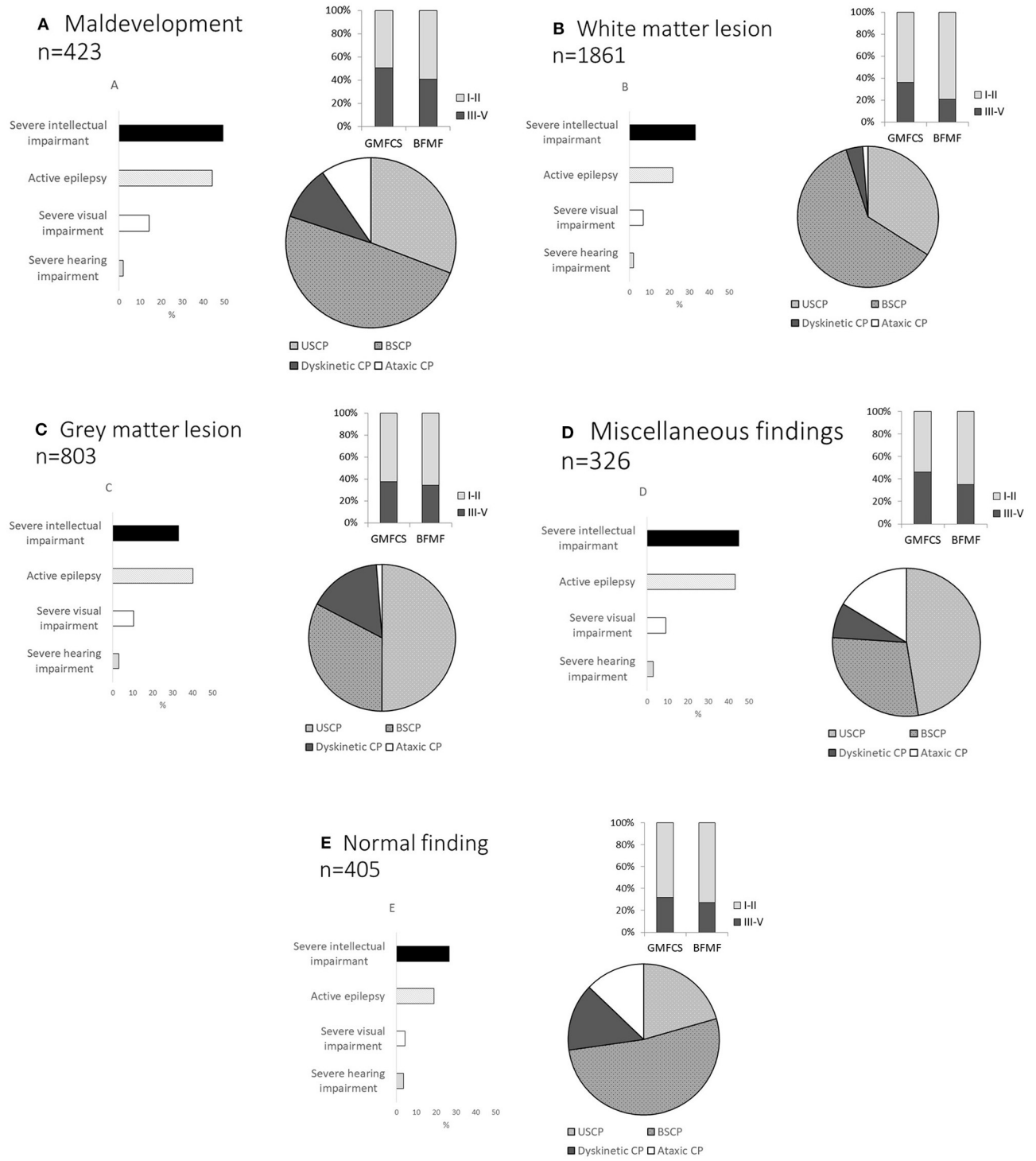

FIGURE 1 | Distribution of cerebral palsy (CP) type, gross and fine motor function, active epilepsy, severe intellectual impairment, severe visual impairment, and severe hearing impairment according to MRICS (12): **(A)** maldevelopment, **(B)** white matter injury, **(C)** gray matter lesion, **(D)** miscellaneous findings, and **(E)** normal finding on MRI, Gross Motor Function Classification System (GMFCS) levels I–V, Bimanual Fine Motor Function (BFMF) levels I–V. Unilateral spastic CP (USCP), bilateral spastic CP (BSCP), dyskinetic CP, and ataxic CP.

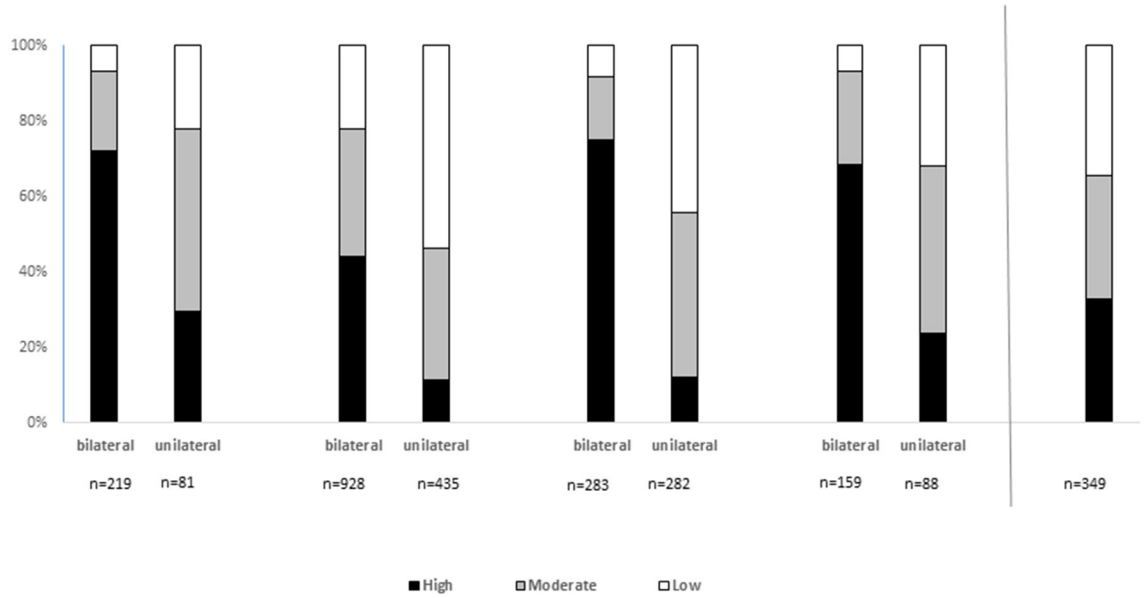

FIGURE 2 | Impairment index by neuroimaging pattern and by bilateral or unilateral findings in 2,824 children with cerebral palsy: *Low impairment* was defined as being able to walk (GMFCS I-II), IQ ≥70, no visual impairment, no hearing impairment, and no epilepsy. *High impairment* was defined as inability to walk (GMFCS IV–V) and/or severe intellectual impairment (IQ <50), with or without one or more of the following impairments: severe visual impairment, severe hearing impairment, and active epilepsy. *Moderate impairment* included all other levels of impairment not defined as low or high.

visual impairment, severe hearing impairment, and/or active epilepsy OR walking with aids (GMFCS III), with an IQ ≥50 with or without one or more of the following impairments: severe visual impairment, severe hearing impairment, and active epilepsy].

Statistical Analysis

Categorical variables were summarized as frequencies and percentages. To test for the association between imaging findings and clinical characteristics, chi-squared test or Fisher's exact test when appropriate was used. We also compared the distribution of CP types between children included in the study (with a post-neonatal MRI) and the children excluded in the study (with no report of post-neonatal MRI) using the chi-square test.

The level of statistical significance was set at 0.05.

RESULTS

There were 3,818 children with CP born 1999–2009 from 20 centers across Europe with an MRI performed in the post-neonatal period, while 5,415 children had no MRI report: in 1,720 (45%) children before 2 years of age (median age 12 months, interquartile range 8–16 months) and in 1,859 (49%) children at 2 years of age or later, MRI was performed. Age was unknown in 239 (6%) cases. The distribution of CP types was similar in the two groups (data not shown).

Of the 3,818 children, 1,320 (35.3%) had USCP, 1,930 (51.7%) had BSCP, 331 (8.9%) had dyskinetic CP, and 154 (4.1%) had ataxic CP, while CP type was unknown in 83 children.

The most common findings were white matter injury (49.1%) and gray matter injury (21.3%). MRI findings differed between CP types ($p < 0.001$).

Clinical characteristics, such as CP type, gross and fine motor function, presence of epilepsy, and severe intellectual, visual, and hearing impairment, are shown by neuroimaging pattern in **Figure 1**.

Distribution of motor and accompanying impairment differed between neuroimaging patterns and whether lesions were uni- or bilateral. The impairment index was applied in 2,824 children, for whom sufficient information about impairments and MRI was registered (**Figure 2**).

Neuroimaging Patterns

Maldevelopments

In 423 children, maldevelopment was found. This group had spastic CP in 77%, and severe intellectual impairment in 55%. Independent walkers (GMFCS I–II) comprised 47.4%, while 52.5% relied on wheelchair ambulation. Severe visual impairment was found in 14.2%, severe hearing impairment in 4.3% and active epilepsy in 46.2% (**Figure 1A**) Information on whether the lesion was uni- or bilateral was available in 338 children (**Table 2**).

TABLE 2 | Comparison of subtype and associated impairments according to bilateral and unilateral lesion in children with predominant maldevelopments on brain MRI.

Impairment	Localization of predominant maldevelopments			*P*-value*
	Bilateral *N* = 244 (%)	**Unilateral *N* = 94 (%)**	**Unknown *N* = 85**	
CP type				<0.001
Spastic bilateral	149 (63.1)	16 (17.2)	35 (45.4)	
Spastic unilateral	39 (16.5)	65 (69.9)	21 (27.3)	
Dyskinetic	25 (10.6)	6 (6.4)	11 (14.3)	
Ataxic	23 (9.7)	6 (6.4)	10 (13.0)	
GMFCS III–V	155 (64.6)	17 (18.3)	42 (56.2)	<0.001
BFMF III–V	124 (59.9)	24 (30.8)	24 (46.1)	<0.001
Epilepsy				0.40
Active	114 (48.5)	37 (40.7)	37 (45.7)	
Not active	15 (6.4)	8 (8.8)	3 (3.7)	
No epilepsy	106 (45.1)	46 (50.5)	41 (50.6)	
Severe intellectual impairment	147 (66.8)	21 (25.6)	41 (51.9)	<0.001
Severe visual impairment	40 (16.4)	2 (2.1)	18 (21.2)	<0.001
Severe hearing impairment	14 (5.7)	4 (4.3)	0 (–)	0.59

**The p-value corresponds to the comparison between bilateral and unilateral lesions. Unknown values were excluded from the comparison.*

TABLE 3 | Comparison of subtype and associated impairments according to bilateral and unilateral lesion in children with predominant white matter injury.

Impairment	Localization of predominant white matter lesions			*P*-value*
	Bilateral *N* = 1,058 (%)	**Unilateral *N* = 493 (%)**	**Unknown *N* = 310**	
CP type				<0.001
Spastic bilateral	850 (81.7)	86 (17.6)	182 (59.7)	
Spastic unilateral	129 (12.4)	389 (79.5)	106 (34.7)	
Dyskinetic	48 (4.6)	8 (1.6)	14 (4.6)	
Ataxic	13 (1.2)	6 (1.2)	3 (1.0)	
GMFCS III–V	510 (49.2)	48 (9.9)	117 (38.9)	<0.001
BFMF III–V	322 (38.2)	41 (10.6)	28 (25.9)	<0.001
Epilepsy				<0.001
Active	256 (25.4)	84 (17.7)	64 (21.9)	
Not active	74 (7.3)	23 (4.8)	22 (7.5)	
No epilepsy	678 (67.3)	367 (77.4)	206 (70.5)	
Severe intellectual impairment	299 (32.0)	45 (10.3)	60 (20.6)	<0.001
Severe visual impairment	86 (8.1)	15 (3.0)	26 (8.4)	<0.001
Severe hearing impairment	29 (2.7)	4 (0.8)	2 (0.6)	0.01

**The P-value corresponds to the comparison between bilateral and unilateral lesions. Unknown values were excluded from the comparison.*

White Matter Injury

Of 1,861 children, 94% had spastic CP, bilateral in almost two thirds of these cases. A majority, 63%, were independent walkers (GMFCS I–II). Only 23% (404/1,774) had active epilepsy, 6.8% had severe visual impairment, and 1% severe hearing impairment, while severe intellectual impairment was found in 24% (**Figure 1B**).

Information on whether the lesion was uni- or bilateral was available in 1,551 children. Children with bilateral white matter lesions mainly had BSCP, while in unilateral lesions, the majority had USCP. Severe intellectual impairment, severe visual and hearing impairments, and epilepsy were more common in children with bilateral than unilateral lesions (**Table 3**).

Gray Matter Injury

In this group of 803 children, bilateral lesions were found in 320, and unilateral in 322. The distribution as to uni- or bilateral was unknown in 150 cases (**Figure 1C**).

Uni- and bilateral gray matter lesions differed in outcome with a higher severity in terms of motor impairment and associated impairments for children with bilateral lesions (**Table 4**).

Children with bilateral gray matter lesions had the highest proportion of dyskinetic CP, 32% (101/320).

In children with unilateral gray matter lesions, spastic CP dominated (97.5%) and this was mainly unilateral.

Miscellaneous Findings

Miscellaneous findings on MRI were found in 326 children, 74.5% had spastic CP, 10.7% dyskinetic, and 10% ataxic CP. GMFCS levels were at III–V in 42.5%. Active epilepsy and severe intellectual impairment were common, found in 40 and 49.7% respectively (**Figure 1D**). Information on whether the lesion was uni- or bilateral was available in 270 children (**Table 5**).

Normal Finding

Children with normal findings on post-neonatal MRI had a spastic CP in 70% (283/405), were able to walk independently (GMFCS I–II) in 68%, had active epilepsy in 19% (74/405), and had severe intellectual impairment in 26.5% (94/405) (**Figure 1E**).

In summary, in children with maldevelopment, bilateral gray matter lesions, and miscellaneous findings on MRI, a more severe pattern of impairments was frequent, both regarding motor and associated impairments. In contrast, children with white matter injury and normal finding on MRI more often had a milder phenotype.

Children with bilateral white and gray matter lesions more frequently had a severe outcome than those with unilateral lesions.

The impairment index was applied in 2,824 children with sufficient information and revealed significant differences ($p < 0.001$, respectively) between uni- and bilateral MRI findings regardless of MRICS classification A through D, with a larger proportion of high impairment index in bilateral findings

TABLE 4 | Comparison of subtype and associated impairments according to bilateral and unilateral lesion in children with predominant gray matter injury.

Impairment	Localization of predominant gray matter lesions			*P*-value*
	Bilateral *N* = 320 (%)	**Unilateral *N* = 322 (%)**	**Unknown *N* = 161 (%)**	
CP type				<0.001
Spastic bilateral	178 (56.7)	30 (9.3)	51 (32.1)	
Spastic unilateral	32 (10.2)	284 (88.2)	82 (51.6)	
Dyskinetic	101 (32.2)	4 (1.2)	23 (14.5)	
Ataxic	3 (1.0)	4 (1.2)	3 (1.9)	
GMFCS III–V	232 (73.9)	13 (4.1)	56 (35.2)	<0.001
BFMF III–V	202 (74.3)	43 (16.6)	26 (54.2)	<0.001
Epilepsy				<0.001
Active	158 (50.3)	92 (29.6)	73 (49.0)	
Not active	30 (9.5)	30 (9.6)	11 (7.0)	
No epilepsy	126 (40.1)	189 (60.8)	69 (43.9)	
Severe intellectual impairment	179 (62.8)	30 (10.6)	56 (36.6)	<0.001
Severe visual impairment	48 (15.0)	7 (2.2)	29 (18.0)	<0.001
Severe hearing impairment	21 (6.6)	2 (0.7)	1 (0.6)	<0.001

**The P-value corresponds to the comparison between bilateral and unilateral lesions. Unknown values were excluded from the comparison.*

TABLE 5 | Comparison of subtype and associated impairments according to bilateral and unilateral lesion in children with miscellaneous findings on brain MRI.

Impairment	Localization of miscellaneous findings			*P*-value*
	Bilateral *N* = 175 (%)	**Unilateral *N* = 95 (%)**	**Unknown *N* = 56**	
CP type				<0.001
Spastic bilateral	104 (61.5)	23 (24.5)	23 (47.9)	
Spastic unilateral	17 (10.1)	66 (70.2)	10 (20.8)	
Dyskinetic	27 (16.0)	4 (4.3)	4 (8.3)	
Ataxic	21 (12.4)	1 (1.1)	10 (20.8)	
GMFCS III–V	110 (64.7)	15 (16.0)	26 (49.1)	<0.001
BFMF III–V	78 (52.7)	21 (25.0)	16 (42.1)	<0.001
Epilepsy				0.003
Active	79 (48.2)	30 (31.9)	32 (29.6)	
Not active	20 (12.2)	6 (6.4)	6 (11.1)	
No epilepsy	65 (39.6)	58 (61.7)	32 (59.3)	
Severe intellectual impairment	101 (63.5)	21 (23.6)	25 (52.1)	<0.001
Severe visual impairment	24 (13.7)	0 (–)	6 (10.7)	<0.001
Severe hearing impairment	9 (5.1)	3 (3.2)	1 (1.8)	0.55

**The p-value corresponds to the comparison between bilateral and unilateral lesions. Unknown values were excluded from the comparison.*

(**Figure 2**). Children with white matter lesions (B) overall had the least severe impairment load.

CP Types

Spastic CP was the most frequent in all MRI patterns. Less common CP types, such as dyskinetic CP and ataxic CP, were unevenly distributed. Most cases of dyskinetic CP were found in the group with bilateral gray matter injury.

Bilateral spastic CP was the most common CP subtype. Of the 1,118 children, severe motor and associated impairments were most frequent in those with maldevelopments or gray matter lesions (**Table 6**).

In unilateral spastic CP, two different neuroimaging patterns dominated: white matter lesion (B) and gray matter lesion (middle cerebral artery infarction) (C), emanating from different timing of compromise. The two groups had a similar profile of impairment index but differed with regard to prevalence of accompanying impairments (**Table 7**). Children with unilateral spastic CP and gray matter lesion or maldevelopment had a higher proportion of severe intellectual impairment and epilepsy than those with white matter lesions.

DISCUSSION

Neuroimaging is an important tool in disclosing clues to the background of CP. More than 80% of brain imaging in CP is abnormal in most studies. To achieve a common language regarding neuroimaging findings, the SCPE has suggested a classification describing the different patterns of abnormality, based on the timing of insult to the brain (12). This gives a possibility to investigate structure–function relationships and may help in predicting future impairments and increase the possibilities of prevention and treatment. Earlier studies have suggested a relationship between lesions occurring late in gestation and impaired speech and communication (19), and outcome of gross and fine motor function are also found to be related to timing of the lesion (4, 20, 21). Extent and topography of the lesions also play a role. Whether lesions affect cerebral hemispheres uni- or bilaterally is crucial for functional outcome. Following early brain lesions that are unilateral, the brain can refer to homotopic areas of the healthy hemisphere. This potential for reorganization is unique to the young brain. With respect to motor function, ipsilateral motor tracts can be recruited, but with relevant functionality only in earlier brain lesions, e.g., before the end of the third trimester of pregnancy or equivalent preterm age (22). Language can be reorganized to the right after early left hemispheric lesions up to early childhood age, as the representation of the language network is initially bilateral, whereas the young brain is more sensitive and vulnerable to lesions when these are bilateral and interfere with early network building (4, 23).

This study aimed to describe functional profiles by the neuroimaging patterns of the MRICS, using the large population-based database of the SCPE (11). A previous report from this database stated that the neuroimaging findings were mainly lesional, while maldevelopment, miscellaneous, and normal findings constituted smaller groups (13) and studies from national registers find similar results (24, 25). The present study

TABLE 6 | Comparison of associated impairments according to main lesion in children with bilateral spastic CP.

Impairment	MRI finding					*P*-value
	A *N* = 200	B *N* = 1,118	C *N* = 259	D *N* = 150	E *N* = 203	
GMFCS III–V	157 (80.1)	594 (54.0)	189 (74.4)	96 (66.7)	73 (36.9)	<0.001
BFMF III–V	118 (72.8)	319 (39.2)	137 (74.5)	69 (59.0)	31 (23.8)	<0.001
Epilepsy						<0.001
Active	109 (56.2)	282 (26.4)	143 (56.3)	65 (46.1)	35 (18.0)	
Not active	14 (7.2)	76 (7.1)	25 (9.8)	17 (12.1)	11 (5.7)	
No epilepsy	571 (36.6)	708 (66.4)	86 (33.9)	59 (41.8)	148 (76.3)	
Severe intellectual impairment	135 (73.0)	312 (31.3)	166 (70.0)	86 (64.2)	53 (29.3)	<0.001
Severe visual impairment	45 (22.5)	94 (8.4)	59 (22.8)	17 (11.3)	11 (5.4)	<0.001
Severe hearing impairment	10 (5.0)	24 (2.1)	12 (4.6)	7 (4.7)	5 (2.5)	0.05

TABLE 7 | Comparison of associated impairments according to main lesion in children with unilateral spastic CP.

Impairment	MRI finding					*P*-value
	A *N* = 125	B *N* = 624	C *N* = 398	D *N* = 93	E *N* = 80	
GMFCS III–V	8 (6.4)	15 (2.4)	7 (1.8)	7 (7.5)	0 (–)	0.002
BFMF III–V	16 (15.4)	30 (6.9)	43 (15.6)	9 (11.0)	2 (3.7)	0.001
Epilepsy						<0.001
Active	43 (35.2)	90 (14.9)	126 (32.6)	28 (30.1)	7 (8.9)	
Not active	10 (8.2)	27 (4.5)	32 (8.3)	7 (7.5)	6 (7.6)	
No epilepsy	69 (56.6)	485 (80.6)	228 (59.1)	58 (62.4)	66 (83.5)	
Severe intellectual impairment	19 (17.8)	38 (6.7)	40 (11.1)	15 (16.8)	3 (4.3)	<0.001
Severe visual impairment	3 (2.4)	18 (2.9)	9 (2.3)	2 (2.1)	0 (–)	0.62
Severe hearing impairment	6 (4.8)	7 (1.1)	3 (0.7)	1 (1.1)	1 (1.2)	0.01

shows that the impairment load in terms of occurrence of severe intellectual, visual, and hearing impairment and epilepsy, as well as in the distribution of gross and fine motor impairment, differs between neuroimaging patterns. Moreover, the severity of motor function and occurrence of associated impairments differs between children with unilateral and bilateral lesions, the latter associated with a more severe phenotype, in all neuroimaging patterns. As discussed above, homotopic areas in an unaffected hemisphere offer the possibility to reorganize and compensate for function, whereas vulnerability of the young brain to bilateral lesions is probably higher than in later age (4). This finding was supported when applying the impairment index (18), showing a significant difference in impairment load between uni- and bilateral maldevelopments or lesions, regardless of timing of event during gestation. It is noteworthy that unilateral white matter injuries (representing mostly periventricular hemorrhagic infarctions of preterm children, former IVH grade IV) present with the least impairment load, even less than unilateral gray matter injuries (e.g., arterial infarctions). We consider this an important aspect in the early counseling of the parents of a preterm child.

An increasing number of associated impairments have been recognized in children with CP. Recent contributions are neuropsychiatric disorders, reported to be associated with male sex, epilepsy, and intellectual disability in European children with CP (26). Other studies have pointed toward an association with white matter injuries (27, 28). Early insults to the brain may predict both attention and executive functioning (29, 30). Disruption of structural brain connectivity has been found, not only in the sensorimotor system but also in posterior brain regions, associated with intellectual impairment in individuals with dyskinetic CP (31). Thus, many factors affect the occurrence of impairment in children with early insult to the brain, and much is still unknown.

Limitations to this study must be recognized. The data came from the largest population-based database on children with CP worldwide. However, not all children had been subject to MRI. Also, there were missing data of whether the neuroimaging findings were uni- or bilateral. Information about intellectual impairment was in some cases based on estimation, often due to difficulties performing formal tests in severe cases.

However, the existing data provide a large basis to clarify structure–function relationships in the heterogeneous population of children with CP, illustrating that the proportion of severe impairments is clearly larger in children with bilateral lesions, consistent with previous findings (4). Moreover, the classification of MRI reports and scans was done and

validated in a structured and uniform way, strengthening data quality.

Further insights in the association between early brain compromise and clinical outcome in CP may be gained using a harmonized classification of neuroimaging findings such as the MRICS as a basis for research. As suggested earlier (12), additional information with regard to exact topography and extent of the brain lesions must be taken into account (32, 33). Such insights must be combined with additional knowledge about the child, for example regarding cognitive functioning (34).

We conclude that the distribution of motor and associated impairments differed between neuroimaging patterns in children with CP. A consistent finding was that bilateral lesions or maldevelopment more often gave a severe phenotype. This information may support individual counseling and planning of support of the child with CP.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the dataset is derived from the Central Database of JRC-SCPE, where requests should be directed. Requests to access the datasets should be directed to JRC-SCPE@ec.europa.eu.

AUTHOR CONTRIBUTIONS

KH drafted and revised the manuscript. VH, ES, JD, AP, and IK-M contributed to and critically revised several versions of the manuscript. The SCPE Collaboration contributed to and critically revised a final manuscript together with KH, VH, ES, JD, AP, and IK-M. All authors contributed to the article and approved the submitted version.

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The Role of Neuroimaging and Genetic Analysis in the Diagnosis of Children With Cerebral Palsy

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Cerebral magnetic resonance imaging (MRI) is considered an important tool in the assessment of a child with cerebral palsy (CP), as it is abnormal in more than 80% of children with CP, disclosing the pathogenic pattern responsible for the neurological condition. MRI, therefore, is recommended as the first diagnostic step after medical history taking and neurological examination. With the advances in genetic diagnostics, the genetic contribution to CP is increasingly discussed, and the question arises about the role of genetic testing in the diagnosis of cerebral palsy. The paper gives an overview on genetic findings reported in CP, which are discussed with respect to the underlying brain pathology according to neuroimaging findings. Surveillance of Cerebral Palsy in Europe (SCPE) classifies neuroimaging findings in CP into five categories, which help to stratify decisions concerning genetic testing. Predominant white and gray matter injuries are by far predominant (accounting for around 50 and 20% of the findings). They are considered to be acquired. Here, predisposing genetic factors may play a role to increase vulnerability (and should especially be considered, when family history is positive and/or causative external factors are missing). In maldevelopments and normal findings (around 11% each), monogenic causes are more likely, and thus, genetic testing is clearly recommended. In the miscellaneous category, the precise nature of the MRI finding has to be considered as it could indicate a genetic origin.

Keywords: diagnosis, classification, genetic analysis, cerebral palsy, magnetic resonance imaging

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INTRODUCTION

Cerebral palsies (CP) cover a group of diseases characterized by common clinical characteristics: CP is permanent, but not unchanging; it involves a disorder of movement and/or posture and of motor function; it is due to a non-progressive interference/lesion/abnormality; this interference/lesion/abnormality is in the developing/immature brain (1). Thus, it includes a number of conditions of different etiologies. The diagnosis of cerebral palsy is based on phenomenology, not on etiology (2).

Neuroimaging is not part of the diagnostic criteria, but it helps to understand the etiology or at least the pathogenesis of the underlying brain disorder. Magnetic resonance imaging (MRI) is abnormal in more than 80% of children with CP, disclosing the pathogenic pattern responsible for the neurological condition (2, 3). There is consensus on an international basis that cerebral MRI is important in the assessment of a child with cerebral palsy (4). MRI is recommended as the first diagnostic step after medical history taking and neurological examination (5). With the development of comprehensive genetic diagnostics, the genetic contribution to CP is increasingly discussed (6), and the question arises about the role of genetic testing in the diagnosis of cerebral palsy.

In a recent review, inconsistency of phenotypic definition of CP used by studies that investigated genetic causes of CP has been highlighted, which limits the quality and interpretation of study findings (7). The use of Surveillance of Cerebral Palsy in Europe (SCPE) guidelines (1) has been recommended for a precise diagnosis and classification.

We would like to discuss the role of genetic testing in relation to CP as phenotypically defined by SCPE and with respect to neuroimaging findings in children with CP. For classification of the latter, we also refer to guidelines established by the SCPE as described below.

The above given definition of SCPE excludes progressive disorders or non-cerebral diseases leading to a loss of motor function and underlines that the diagnosis of CP should be confirmed at around the age of 4 years. Subtypes of CP are defined according to clear neurological traits and recorded as spastic (unilateral and bilateral), dyskinetic, or ataxic CP. Furthermore, the SCPE network developed several tools including hierarchical trees (decision and classification trees), a standardized data collection form, and a Reference and Training Manual (1, 8, 9). For a full description, go to https://eu-rd-platform.jrc.ec.europa.eu/_en.

MRI Patterns—Distribution

The MRI classification system (MRICS) was developed and validated by SCPE, including a literature review and comparison to other classification systems (10). MRICS identifies typical MRI patterns in children with CP, associated with a specific timing of the brain compromise:

- *maldevelopments (category A)*, which originate in the first and partly in the second trimester of pregnancy.
- *predominant white matter injury (category B),* which typically arises in the early third trimester of pregnancy and especially characterize brain lesions of preterm born children with CP.
- *predominant gray matter injury (category C)* defines lesions arising in the late third trimester or around birth of a term or near to term born child with CP.
- findings not corresponding to one of the three categories are classified as *miscellaneous (category D)*.
- *normal findings (category E)*.

In a first analysis of MRI patterns in children with CP representative of the population, maldevelopments made up for around 11% of cases, predominant white matter injury accounted for 49% of cases, and predominant gray matter injury for 21%, whereas miscellaneous findings were reported in 8.5% and normal findings in another 10.5% of the cases (11). MRI patterns of children with unilateral spastic, bilateral spastic, and dyskinetic CP were mainly lesional (77, 71, and 59%), while children with ataxic CP had more maldevelopments, miscellaneous, and normal findings (together nearly 80%). The latter groups were also more frequent in term than in preterm born with CP (nearly 40% vs. 22 and 13% in children born with a gestational age of 32–36 weeks and <32 weeks).

These patterns, characterizing brain pathology in CP, may serve as guidance when discussing the contribution of genetic testing to the diagnosis of CP. In maldevelopments, monogenic causes are very likely to play a role (12, 13), which is probably also the case for normal findings. Predominant white and gray matter injuries are considered to be acquired, but predisposing genetic factors may increase vulnerability (14, 15). The group of miscellaneous findings has to be studied in more detail with the question whether findings indicate a genetic disease.

With this background, we will discuss the current evidence for genetic findings reported in CP with respect to the underlying brain pathology.

Genetic Testing in Cerebral Palsy

The presence of congenital anomalies in children with CP, the higher rates of CP in monozygotic than in dizygotic twins, and the higher risk of CP in consanguineous families compared with non-consanguineous first induced the discussion on a genetic background in the etiology of CP (16). A record-linkage study in three European regions with CP and congenital anomaly (CA) registers reported a higher prevalence of congenital anomalies among the CP population than in the general population. Prevalence was highest in children with ataxic CP (41.7%) and lowest in those with dyskinetic CP (2.1%); it was higher also among children born at term (13%) than among those born preterm (3.8%) (17). This indicates that genetic causes are more likely in the rare ataxic CP subtype and also more frequent in term than in preterm born children.

Increasing availability of comprehensive genetic testing such as microarray platforms and next-generation sequencing then has shed light on various genetic aspects linked to CP (15).

Genetic Testing Relevant for Individual Diagnosis

Here two different genetic categories are particularly relevant, copy number variations (CNVs), which can be assigned to a corresponding clinical phenotype, and sequence alterations in known CP-associated disease genes. The detection of mere genetic associations and vulnerability factors hardly plays a role in diagnostics as they are usually not robust enough.

- **Copy number variants (CNVs)** are understood as genomic deletions or duplications in copy number of genes. A minimum limit of CNV size of 50–100 kb is usually defined in the diagnostic setting. In a research environment and in special diagnostic cases, even significantly smaller CNVs can provide valuable information. Up to now, test methods of choice for detecting CNVs are mostly microarray technologies (such as

CGH arrays or SNP arrays), but the better availability of whole genome sequencing at decreasing costs provides an analysis tool for an easily accessible combined one-step evaluation for CNV and monogenic disease genes in the near future. A CNV can identify a diagnostically relevant genetic cause of CP either in itself as a contiguous gene deletion/duplication syndrome (e.g., 22q11.2) or by identifying a monogenic disease through a deletion/duplication in a listed CP-gene. Oskoui et al. (18) identified *de novo* CNVs in 7% of their unselected Canadian CP cohort of 115 patients. Overall, 9.6% of the families carried clinically relevant CNVs either explaining etiology of CP or possibly accounting for associated medical complication. Another study detected abnormalities in 7.2% of patients with hemiplegic CP (19). Segel et al. found *de novo* CNVs in 31% of their cohort of Israeli patients with CP of unknown etiology (20). The most recent study reported by Corbett et al. (21) revealed pathogenic and likely pathogenic CNVs in 3.7% of their unselected CP cohort of 186 patients, using exome analysis. In summary, depending on the cohort, a pathogenic or likely pathogenic CNV is found in about 4–30% of CP patients (22).

- **Genetic sequence alteration in genes with a listed CP-related phenotype (Single gene mutations)**. To date, a large number of genes have been identified as associated to a defined clinical phenotype compatible with CP. This includes genes causing brain malformations such as lissencephalies or polymicrogyrias, as well as genes coding for specific ion channels, which have been related to ataxic CP [ITPR1, KCNC3, and SPTBN2 (15, 23)], genes for inborn errors of metabolism, which may mimic CP (24), and many other genes, e.g., KANK1 [role in actin polymerization, related to a spastic CP phenotype, (25)], adaptor protein 4 complex (26), ADD3 (15), GAD1 [catalyzes the conversion of gamma-aminobutyric acid, a major neurotransmitter (26)], just to name a selection.

  Genetic analyses performed in CP cohorts showed a monogenic cause in ∼5% (27) to 15% (22) of cases, vastly differing between different subgroups. This factor may increase during the next years when comprehensive genetic analysis such as whole-genome sequencing (WGS) will be more broadly available and more CP genes presumably identified.

Genetic Research Studies

- **Single nucleotide polymorphisms (SNPs)** are non-rare specific genomic nucleotide exchanges. In contrast to the rare pathogenic sequence changes in monogenic disease genes, SNPs usually occur in a proportion of at least 1% in the general population. SNPs are often investigated in association studies, which are expected to provide indicators of predisposing factors for certain diseases and shed further light on the pathophysiology. In rare diseases, SNPs are not expected to have a sole causal effect but to act as vulnerability factors. They may gain further significance in the context of Polygenic Risk Score Assessments.

  In different studies, SNPs with susceptibility to thrombosis or hemorrhage have been suggested. However, a strong association to CP has not been found (15, 28). Apoprotein E is one of the most studied presumed risk factors. Whereas, the ApoE4 allele was associated with a severe clinical phenotype in some studies, other ApoE alleles were associated with reduced severity of CP (29). Larger studies found no association between ApoE and the risk of CP (30). The association between mutations in genes causing hereditary thrombophilia (antithrombin, Protein C, and Protein S) and CP due to perinatal stroke was weak (31).

- **Candidate cerebral palsy genes** Candidate genes are presumed to be monogenic disease genes for CP, but a verification of the causal effect by functional analyses is still missing. Candidate genes are usually identified in comprehensive genetic studies because they show rare sequence alterations [mostly in whole-exome sequencing (WES) or WGS] or located within a CNV (mostly in WGS or microarray). McMichael et al. (32) found novel candidate CP genes in 7% of an unselected CP cohort (183 cases) using WES.

Role of Genetic Analysis in the Different Brain Pathology Patterns

Maldevelopments

Maldevelopments occur early during brain development and are often due to gene abnormalities, which are relevant in specific periods of early brain development. Maldevelopments of cortical development are here of specific importance. They often lead to spastic CP, depending on their localization and extent. Neuronal proliferation, migration, and organization or post-migrational development depend on a complexity of genetic mechanisms, which are increasingly recognized. Accordingly, mutations of many genes have been described in patients with malformations of cortical development (33). A comprehensive discussion of genetic causes is beyond the scope of this paper, but some classical examples are mentioned and illustrate that the origin can be genetic or non-genetic:

- *The lissencephalies* (migration disorders) include agyria, pachygyria, and subcortical band heterotopia as part of a spectrum. Associated gene defects include the LIS1, DCX, RELN, ARX, or TUBA1 genes (33–35). Bilateral spastic CP is usually severe and accompanied by severe cognitive impairment, epilepsy, and cortical visual impairment, and children are microcephalic.
- *Proliferation defects* associated to megalencephaly may also cause severe bilateral spastic CP and can occur due to *de novo* germline and postmitotic mutations in AKT3, PIK3R2, and PIK3CA (36). The latter has also been reported with hemimegalencephaly and unilateral spastic CP (37).
- *Polymicrogyrias* are defects of organization or post-migrational development and are characterized by the appearance of an excessive number of small cortical folds. Although a number of genes have been associated, a larger part seems still unclear with respect to the underlying mechanism (38). A clear genetic origin is given when polymicrogyria occurs in conjunction with early manifesting inborn errors of metabolism such as peroxisomal disorders or mitochondrial disorders (33). Then the clinical picture is not one of a CP, and MRI in addition may disclose other abnormalities suggesting a progressive

disease. The origin of polymicrogyria is probably more often disruptive than genetic, for example, due to vascular events causing a schizencephalic pattern with clefts lined by polymicrogyric cortex (33). Additional calcifications and white matter abnormalities point toward an infectious origin such as cytomegalovirus (39). A pure symmetrical polymicrogyria may have a genetic background such as bilateral fronto-parietal polymicrogyria also called "frontal predominant cobblestone malformation," which can occur due to GPR56 mutations.

- *Focal cortical dysplasias* (FCDs) are probably mainly due to "abnormal post-migrational development". Evidence suggests that they can result from injury to the cortex during later stages of cortical development (33). Prenatal and perinatal insults including severe prematurity, bleeding, hydrocephalus, stroke, and others are reported in children with mild malformation of cortical development (40, 41).

Lesional Patterns (Predominant White or Gray Matter Injury)

As introduced above, research in CP has partly focused on genetic association studies, and an intriguing aspect is that genetically defined vulnerability factors can lead to neuroimaging abnormalities categorized as predominantly white matter or gray matter injuries (15), just as a genetic predisposition to stroke has long been recognized. However, studies have revealed no or only a small association between CP and the assumed genetic risk factors including mutations in genes causing hereditary thrombophilia.

A special role of the COL4A1 gene as a risk factor for lesional injuries has emerged in this context, which should be specially mentioned. Defects in the COL4A1 gene have been reported not only to increase the risk for stroke but also to occur in patients with prenatal brain lesions such as porencephaly and schizencephaly (42), accounting for 16 and 50% each in the latter series. Defects in the COL4A1 gene can be inherited (autosomal dominant with reduced penetrance) or occur *de novo*. As the phenotype mainly consists of a small (or large) vessel disease, which may involve the eyes and most commonly also other organs such as the kidneys, a thorough family assessment is important (43).

Miscellaneous Findings

The group "miscellaneous" refers to abnormal brain imaging findings, which cannot be allocated to the categories A, B, or C given above. SCPE registers are encouraged not only to code a finding but also describe it and give the MRI report. In its recent report, SCPE identified 8.5% of MRI findings as miscellaneous (11). For the purpose of this paper, we analyzed this group in more detail according to the additional descriptions given by the centers asking which findings could indicate a genetic cause. Findings were reported by SCPE registers from 18 European countries for children born between 1999 and 2009. Out of 3,818 MRI descriptions or written reports, 323 were coded as miscellaneous. No description was given for 22 cases (6.8 %).

Four groups of patterns could be characterized:

1. *Acquired patterns such as infections, tumor, or hemorrhage* represented 4.3% (14 cases) and included among others: prenatal infections (CMV, $n = 3$), encephalitis (Herpes, $n = 5$), tumor ($n = 2$), hemorrhage not covered by B or C (subdural/subarachnoidal hemorrhage).
2. *Brain injuries* that could not be classified into B or C as descriptions were too unspecific, such as "hypoxic injury," "widespread injury," represented 18.8% (61 cases).
3. Patterns which were *suggestive of a genetic background* accounted for 31.8% (103 cases): 83 cerebral/cerebellar atrophy and 20 myelination disorders (hypo- or demyelination).
4. *Unspecific patterns* such as thin corpus callosum, ventricular dilatation, arachnoid cysts, calcifications not specified as in context of a CMV-Infection, and other unspecific descriptions accounted for another 38% of this group (123 cases).

In groups 3 and 4, representing 70% of the miscellaneous group, genetic work-up certainly is to be recommended as further diagnostic procedure. Ideally, this should be done as WES with additional microarray analysis or WGS, as findings usually did not clearly indicate a specific monogenic disease.

Normal Findings

Normal MRI findings accounted for about 10.5% of CP cases in the SCPE report. It is of essential importance, as said before, to verify and re-consider whether diagnosis of CP is correct. A first pitfall could be the age at MRI. Mild periventricular leukomalacia (PVL) without reduction of white matter may not be evident in an MRI done before myelination is complete (see **Figure 1**). Mild basal ganglia and thalamus lesions appear in the neonatal period hyperintense on T1w images, after the first year they are reported as hyperintense on T2w images; in the transition phase, especially small lesions may be missed. Thus, in a child with mild spastic or dyskinetic CP and no major cognitive problems, a normal MRI before the age of 2 years should be repeated when myelination is complete.

Spinal origin of spasticity in a young child may be difficult to differentiate clinically from cerebral origin. In a child with spasticity of the legs and no comorbidities, a spinal MRI should be considered if cerebral MRI is normal, not to miss structural spinal pathology.

The next step then is genetic testing. Two disease entities may mimic especially spastic CP. Although progressive, they may start early with very slow progression. Hereditary spastic paraplegias (HSPs) are clinically and genetically heterogeneous. When starting early, the course is often very slowly progressive (44), MRI is usually normal in pure HSP, and bladder dysfunction may not be present. SPG3 is probably the genotype most often associated with these features (45, 46). However, comprehensive genetic testing is suggested as the majority of genetic subtypes, age of onset, and phenotypic expression are extremely broad (44). Dopa-responsive dystonias (DRDs) are the second entity, which should be considered in a child with mild spastic (or dyskinetic) CP, normal cognition, and normal MRI. As diagnosis has therapeutical consequences, this should be done early. DRDs typically manifest as limb-onset, diurnally fluctuating dystonia.

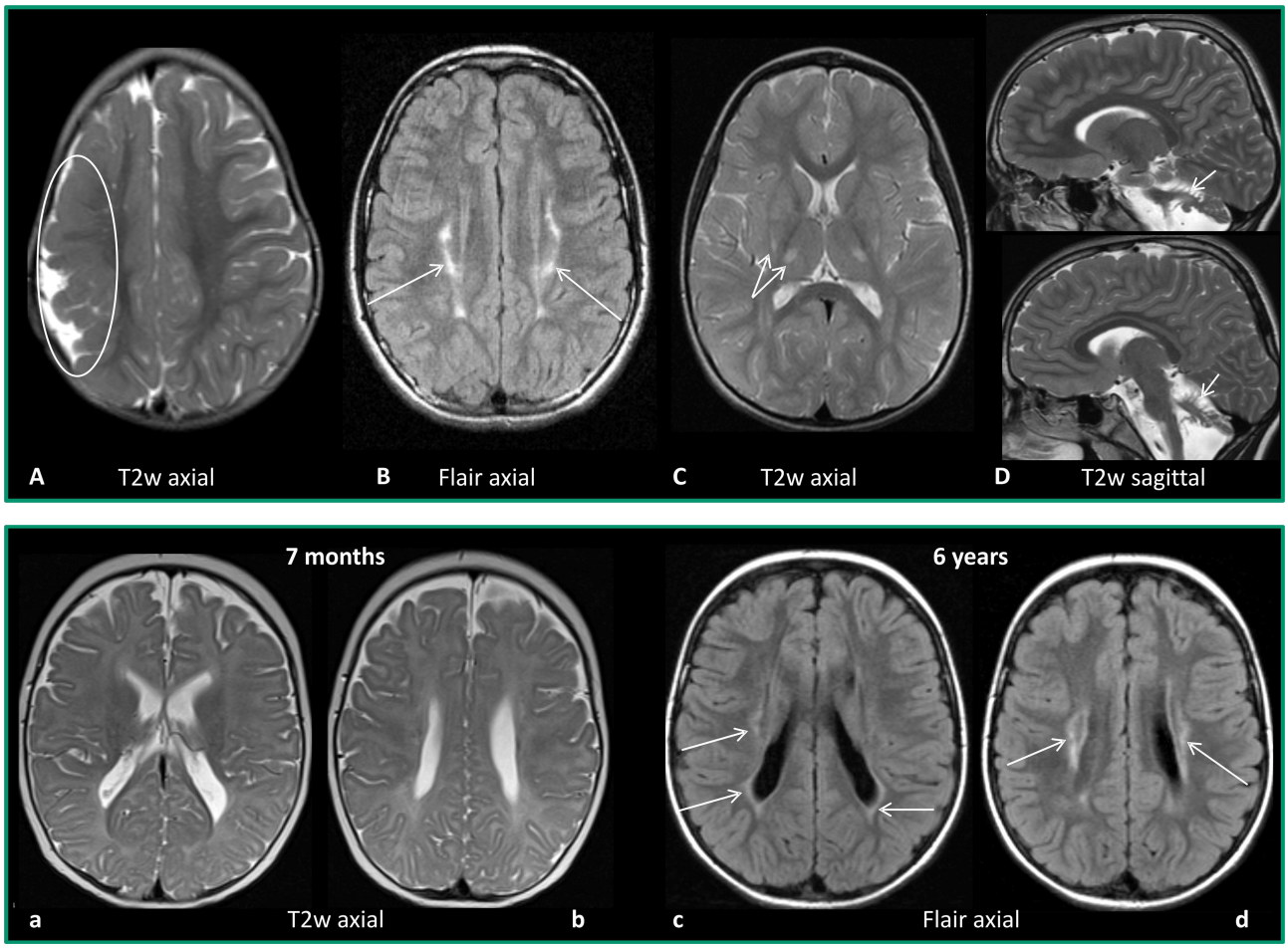

FIGURE 1 | Upper row: Examples for MRI patterns. **(A)** Maldevelopment: frontoparietal polymicrogyria right (encircled), 2 years old girl with US-CP left GMFCS I. **(B)** Predominant white matter injury: mild PVL (arrows), 12-year-old girl, preterm 32 weeks of gestation, BS-CP GMFCS I. **(C)** Predominant gray matter injury: mild basalganglia/thalamus lesions (double arrow), 3-year-old girl, placental ablation, dyskinetic CP GMFCS II. **(D)** Miscellaneous: cerebellar atrophy (arrows), 2-year-old boy, former preterm 26 weeks of gestation, ataxic CP, GMFCS I. Lower row: Example for difficulty of early diagnosis–PVL, former preterm, 32 weeks of gestation. **(a,b)** MRI at the age of 7 months: T2w axial images with no clear pathology. **(c,d)** MRI at the age of 6 years (BSCP, GMFCS III): axial FLAIR images reveal bilateral gliosis indicating PVL (arrows).

Autosomal dominant GTP cyclohydrolase 1 deficiency, also known as Segawa disease, is the most common and best-characterized condition (47). At disease onset, diurnal fluctuation may not yet be obvious, and with early onset, the neurological condition may be misdiagnosed as leg dominated bilateral spastic CP (48). As DRDs exhibit a rapid and clear response to levodopa treatment, a levodopa trial (mean 200 mg/day) may be used as the first diagnostic step, especially if genetic testing and cerebrospinal fluid neurotransmitter analysis are not easily available.

In ataxic CP presenting with normal MRI and normal cognition, some biochemical tests may be done before initiating broad genetic testing: serum AFP and ß-galactosidase as an indicator for Louis–Bar syndrome and GM1-gangliosidosis with late infantile onset, respectively.

A child with clinical signs compatible with CP of any subtype, a normal MRI but clear cognitive deficits always needs WGS or WES with microarray as a next diagnostic step.

CONCLUDING DISCUSSION

Genetic studies in children with CP often have the shortcoming that phenotypic definition is not very strict, and usually, no or little information is given on brain pathology. We have discussed genetic findings reported in CP with respect to the underlying brain pathology according to neuroimaging findings, based on the distribution of MRI findings from an analysis of children with CP phenotypically defined according to SCPE guidelines (11). Brain pathology is classified according to a specific timing of the brain compromise. With a view to these groups, the role of genetic contribution to the causation of CP can be discussed more specifically, summarized also in **Table 1**.

The largest groups are injuries predominantly of white or gray matter, accounting together for 70% of cases. Here genetic vulnerability factors may play a role. Up to now, evidence for their importance is not high. However, this needs

TABLE 1 | Recommendation for genetic work-up according to neuroimaging findings.

Pattern	Genetic work up recommended
A. Maldevelopments	**For monogenic diseases** "rule of thumb": disorders of cortical formation proliferation and migration defects are of genetic origin, whereas later defects such as organization or post-migrational defects (polymicrogyria) can be of genetic or non-genetic origin
B. Predominant white matter injuries C. Predominant gray matter injuries	**For genetic vulnerability factors** such as defects leading to thrombophilia or interfere with collagen formation, e.g., some collagenopathies. Contribution is low, thus, check family history, and whether causative external factors are missing
D. Miscellaneous	**For monogenic diseases** indicators are, e.g., disorders of myelination (such as hypomyelination) or cerebral atrophy, cerebellar atrophy
E. Normal	**For monogenic diseases** before initiating genetic testing check on a child with good cognition and mild spastic or dyskinetic CP - has MRI been done before the age of 2 yrs? - has spinal MRI been done? - consider a levodopa trial

further evaluation. If future studies on the genetic contribution to CP took up not only a more stringent definition of CP but also neuroimaging findings, results could be more conclusive, as indicated by the study centering on prenatal brain lesions, where a high proportion of COL41A defects could be identified, accounting for 16% of porencephalies and 50% of schizencephalies (42).

Malformations of the brain were reported in around 11% of children with CP. Here, cortical malformations play a specific role. As a "rule of thumb," malformations characterizing early disturbance of brain development such as proliferation and migration defects are mostly of genetic origin, whereas later defects such as organization or post-migrational defects have a higher probability for a non-genetic origin.

Miscellaneous findings are an intriguing group of findings. With higher quality of reporting (a process of regular training and feedback is ongoing in SCPE), the 20% of brain injuries coded in this category will hopefully be more specifically characterized in the future. For the other findings, which cannot clearly be allocated to an acquired condition, a genetic work-up is to be recommended. These findings also point out that diagnosis of CP has to be questioned in this group, as MRI findings do not clearly indicate a static brain disorder as the cause of the CP. SCPE considers an age of 4 years necessary for inclusion of a child as having CP allowing for a certain observation period to make it unlikely that a progressive disorder is misdiagnosed as CP. In times of readily available genetic testing, it is, however, advisable to already initiate a genetic work-up before, if MRI is not clearly indicating an acquired injury. This holds true also for the last group of MRI pattern, the normal findings. Here, in addition, quality and timing of the MRI has to be checked, as small lesions of white matter or diencephalon may go unrecognized before myelination is complete.

Taken together, the known contribution of genetic findings to the understanding of CP according to the literature is <30%. In addition, when considering the MRI findings reported from the SCPE database, it seems interesting that around 30% cannot be allocated to an acquired lesion; thus, a genetic origin has to be considered (maldevelopments, miscellaneous, and normal findings).

Hopefully, future genetic studies will be able to give more specific results while relying not only on a standardized phenotypical description of children with CP but also on their neuroimaging findings characterizing brain pathology. Polygenic risk scores are emerging approaches which will, hopefully, shed more light on the role of genetic vulnerability factors. In the meantime, we suggest some recommendations when to do a genetic work-up in a child with CP based on neuroimaging, which we do consider as the first diagnostic step after medical history taking and neurological examination. This may also have implications for molecularly informed treatment decisions, as neuroimaging findings may support early genetic work-up in children with slowly progressive and treatable disorders mimicking CP (24, 47). Against the background of the current data situation and decreasing examination costs, the application of comprehensive analysis methods such as exome analyses and genome analyses is preferable today to the targeted use of special gene panels or single gene analyses, provided that these are accessible. This applies both to a diagnostic framework and to research settings.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

VH: designed the manuscript, performed literature review and analyzed miscellaneous MRI data, drafted manuscript and performed revisions. UG: wrote section Genetic testing in CP, provided genetic expertise and reviewed the manuscript. ES: provided MRI data and expertise for MRI data analysis, reviewed the manuscript. CA: reviewed the manuscript. IK-M: conceived, designed and supervised the study, provided clinical expertise, participated in manuscript drafting and revision. KH: provided clinical expertise, supervised and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Moderately and Late Preterm Infants: Short- and Long-Term Outcomes From a Registry-Based Cohort

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Background: While most studies on the association of preterm birth and cerebral palsy (CP) have focused on very preterm infants, lately, attention has been paid to moderately preterm [32 to <34 weeks gestational age (GA)] and late preterm infants (34 to <37 weeks GA).

Methods: In order to report on the outcomes of a cohort of moderately and late preterm infants, derived from a population-based CP Registry, a comparative analysis of data on 95 moderately preterm infants and 96 late preterm infants out of 1,016 with CP, was performed.

Results: Moderately preterm neonates with CP were more likely to have a history of N-ICU admission ($p = 0.001$) and require respiratory support ($p < 0.001$) than late preterm neonates. Birth weight was significantly related to early neonatal outcome with children with lower birth weight being more likely to have a history of N-ICU admission [moderately preterm infants ($p = 0.006$)/late preterm infants ($p < 0.001$)], to require ventilator support [moderately preterm infants ($p = 0.025$)/late preterm infants ($p = 0.014$)] and not to have neonatal seizures [moderately preterm infants ($p = 0.044$)/late preterm infants ($p = 0.263$)]. In both subgroups, the majority of children had bilateral spastic CP with moderately preterm infants being more likely to have bilateral spastic CP and less likely to have ataxic CP as compared to late preterm infants ($p = 0.006$). The prevailing imaging findings were white matter lesions in both subgroups, with statistically significant difference between moderately preterm infants who required ventilator support and mainly presented with this type of lesion vs. those who did not and presented with gray matter lesions, maldevelopments or miscellaneous findings. Gross motor function was also assessed in both subgroups without significant difference. Among late preterm infants, those who needed N-ICU admission and ventilator support as neonates achieved worse fine motor outcomes than those who did not.

Conclusions: Low birth weight is associated with early neonatal problems in both moderately and late preterm infants with CP. The majority of children had bilateral spastic CP and white matter lesions in neuroimaging. GMFCS levels were comparable in both subgroups while BFMF was worse in late preterm infants with a history of N-ICU admission and ventilator support.

Keywords: cerebral palsy, moderately preterm, late preterm, premature birth, short term outcome, long term outcome, complication

INTRODUCTION

Prematurity is highly associated with neonatal mortality and morbidity and also constitutes a well-recognized risk factor for cerebral palsy (CP) and other lifelong effects on neurodevelopmental functioning and childhood/adulthood morbidity. According to the WHO, preterm birth is defined as any birth before 37 completed weeks of gestation and this can be further subdivided on the basis of gestational age (GA): very preterm (28 to <32 weeks), moderately preterm (32 to <34 weeks) and late preterm (34 to <37 weeks) (1, 2). So far, most studies on preterm birth have focused on very preterm infants as the group of preterm infants with the greatest risk of morbidity and mortality comprises those born at <32 weeks of gestation. However, this fact created a serious gap in the knowledge on the outcome of moderately (32 to <34 weeks GA) and late preterm infants (34 to <37 weeks GA) who represent the greatest number of infants born preterm. Over the past years there is a dramatic increase in studies focusing on moderately (32 to <34 weeks GA) and late preterm infants (34 to <37 weeks GA) highlighting that preterm infants born between 32 to <37 weeks of gestation are at higher risk of mortality and impaired short-term and long-term outcomes compared with infants born at term (3–6).

Several studies have shown that moderately and late preterm infants may suffer from respiratory distress syndrome (RDS) and other respiratory morbidities requiring respiratory support and neonatal intensive care unit (N-ICU) admission (7–9). Although respiratory issues tend to be transient in most moderately and late term neonates, some neonates may develop persistent pulmonary hypertension of the neonate (PPHN) or severe hypoxic respiratory failure (10). Additionally, moderately and late preterm infants are in higher risk of respiratory diseases and hospitalizations for respiratory infections in infancy and early childhood compared to their term peers (7, 11). Given that the last few weeks of gestation prepare the fetus for the transition from the intra-uterine life, the causes of respiratory distress observed in neonates even born after 32 weeks GA originate from the inability to adapt to the extra-uterine environment due to immature lung structure (7, 10). Neonatal seizures constitute another common complication in the newborn period. The incidence of neonatal seizures is typically associated with underlying brain injury and therefore adverse neurodevelopmental sequelae as well as high mortality rates with different aetiological profile in preterm compared to term infants and worse prognosis associated with younger gestational age (12, 13).

As far as long term sequelae is concerned, moderately and late preterm infants are reported to be at greater risk of CP and thus impaired motor function compared to term-born infants. The prevalence of CP rises with decreasing gestational age at birth and, additionally to motor manifestations, is frequently accompanied by cognitive and sensory impairment and epilepsy. The predominant abnormality among premature infants is spastic CP, mostly bilateral spastic (14). In terms of functional severity, Gross Motor Function Classification System (GMFCS) has been developed to provide a standardized classification of the patterns of motor disability in children with CP, with most of the patients distributed at GMFCS levels I-III compared to GMFCS levels IV-V (15–21). Several other assessments including the Bimanual Fine Motor Function (BFMF) Classification, the ABILHAND-Kids and the Manual Ability Classification System (MACS) have also been reported for fine motor function, but have not been studied extensively so far (22).

Abnormal neuroimaging findings are observed in the majority of children with CP. Based on the fact that CP is attributed to a non-progressive lesion or abnormality of the developing brain, the pathophysiology of CP depends on the time of occurrence of detrimental events during intra- and extra-uterine brain development. Disturbances during the first and second trimester of embryogenesis, when corticogenesis takes place, result in maldevelopments whereas disturbances during the third trimester when differentiation and "refining" events take place lead to predominant white matter injury mainly in the early third trimester and predominant gray matter injury in the late third semester when concerning cortical gray matter, basal ganglia and thalamus. However, given that CP is a clinical diagnosis, normal brain magnetic resonance imaging (MRI) does not exclude the diagnosis of CP (23–28). Previous studies confirmed that moderate and late preterm infants may exhibit important abnormalities such as severe intracerebral hemorrhage (ICH), ventriculomegaly and periventricular leukomalacia (PVL), albeit rarely, as well as smaller brain size, widespread white matter microstructural alterations and immature gyral folding compared with full-term peers (29–31).

Preterm birth has also been associated with an increased risk of epilepsy in childhood and intellectual disability with poorer neurodevelopmental outcomes of preterm infants at school age. The incidence of epilepsy has been shown to decrease with increasing gestational age but increases after 41 gestational weeks. In addition to intracranial hemorrhage and neonatal seizures, low Apgar score, N-ICU admission, respiratory support, antibiotic

treatment during neonatal period and a major congenital anomaly have been associated with increased risk of epilepsy (32).

Concerning developmental problems, it has been shown that preterm children are at significantly increased risk for adverse neurodevelopmental outcomes and intellectual disability compared to termborn peers. However, despite the fact that both early preterm and moderately-late preterm children have greater rates of developmental problems compared to

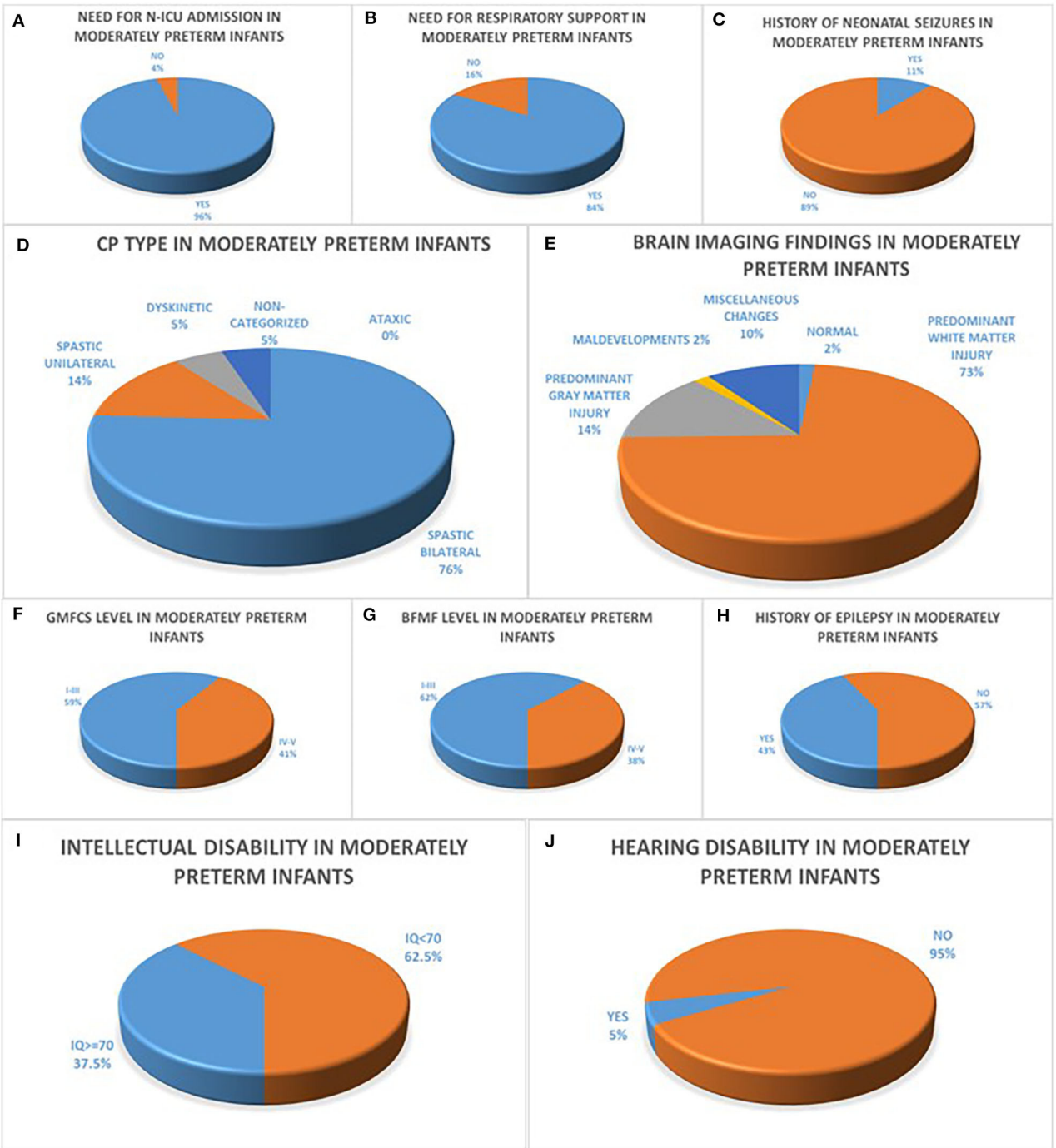

FIGURE 1 | (A–C) refer to the neonatal history of moderately preterm infants born at 32 to <34 weeks GA with CP concerning the history of N-ICU admission **(A)**, the need for respiratory support **(B)** and the history of seizures during the first 72 h after birth **(C)**. CP characteristics of moderately preterm infants are depicted in diagrams **(D–J)** with the majority of infants with available data presenting with bilateral spastic CP **(D)**, predominant white matter injury in brain MRI **(E)**, GMFCS levels I–III **(F)**, BFMF levels I–III **(G)**, no history of epilepsy **(H)**, intellectual disability with IQ < 70 **(I)** and no history of hearing disability **(J)**.

full-term born children before school entry, after school entry persistent developmental problems are observed solely in the subgroup of early preterm children, indicating that moderately-late preterm children may develop better adaptation capacities (33–35). Apart from gestational age, longitudinal growth in the first years of life has also been associated with neuropsychological functioning in moderately and late preterm children (36).

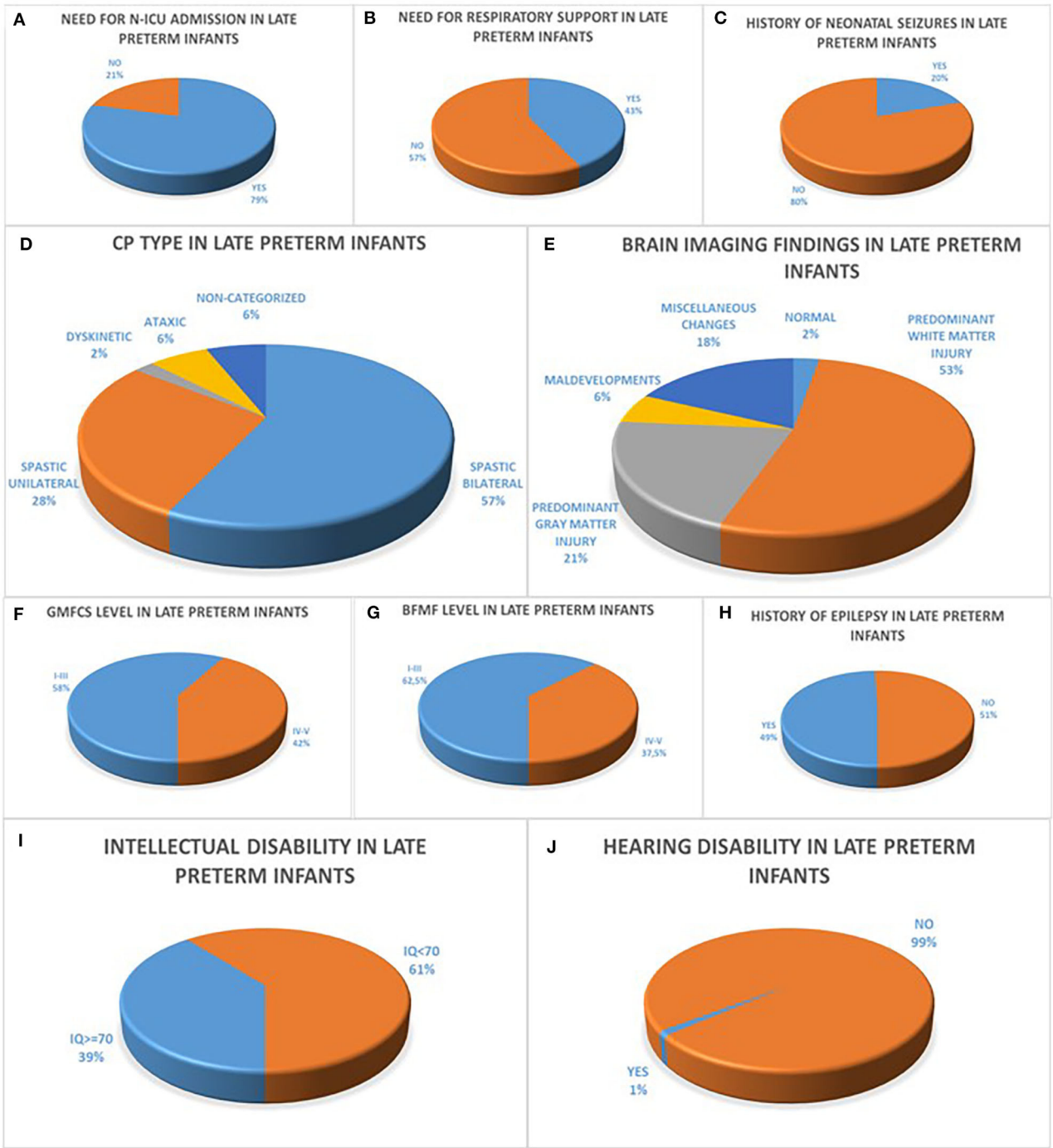

FIGURE 2 | (A–C) refer to the neonatal history of late preterm infants born at 34 to <37 weeks GA with CP concerning the history of N-ICU admission **(A)**, the need for respiratory support **(B)** and the history of seizures during the first 72 h after birth **(C)**. CP characteristics of moderately preterm infants are depicted in diagrams **(D–J)** with the majority of infants with available data presenting with bilateral spastic CP **(D)**, predominant white matter injury in brain MRI **(E)**, GMFCS levels I–III **(F)**, BFMF levels I–III **(H)**, no history of epilepsy **(H)**, intellectual disability with IQ < 70 **(I)** and no history of hearing disability **(J)**.

Given that moderately and late preterm infants represent a multitudinous, insufficiently studied and vulnerable to health and developmental problems population among preterm infants, we conducted a comparative analysis on the short- and long-term outcomes of moderately (32 to <34 weeks GA) and late preterm infants (34 to <37 weeks GA) born in Greece based on population-based data of the Greek CP Registry.

MATERIALS AND METHODS

In this retrospective comparative study, the participants' sample was drawn from the CP Registry of Attica-Greece. Data on 95 children born at 32 to <34 weeks GA and 96 children born at 34 to <37 weeks GA out of 1016 with CP, born between 1999–2006, were analyzed in terms of their need for N-ICU admission, respiratory support with endotracheal intubation or continuous positive airway pressure (CPAP) ventilation, and the occurrence of neonatal seizures during the first 72 h after birth. Moreover, the clinical classification of Cerebral Palsy (CP) in spastic CP (characterized by increased muscle tone and pathological reflexes, either unilaterally or bilaterally), dyskinetic CP (characterized by involuntary, uncontrolled, recurring, occasionally stereotyped movements of affected body parts) and ataxic CP (characterized by abnormal posture/movement and loss of muscular coordination) was assessed in children of both subgroups of moderately and late preterm infants (37). Furthermore, neuroimaging findings in MRI were categorized according to MRICS [MRI Classification System, proposed by the Surveillance of Cerebral Palsy in Europe (SCPE) network] (28). Additionally, gross motor function classification (GMFCS level) and bimanual fine motor function classification by assessing the child's ability to grasp, hold and manipulate objects in each hand separately (BFMF level), the incidence of epilepsy, intellectual disability [defined by an intelligence quotient (IQ) <70 in Wechsler Intelligence Scale for Children, fourth (WISC-IV) and fifth edition (WISC-V)] and hearing disability in childhood were studied as parameters of long-term outcome of moderately and late preterm infants (38–41).

The data were analyzed using the STATA 13 software package. Continuous variables (birth weight, Apgar score) were tested for normality using the Kolmogorov Smirnov test. Since they were not normally distributed, they were expressed as median values (range). Comparisons of continuous variables across groups of patients were based on Mann Whitney U test. When compared in more than two groups (e.g., MRI findings) Kruskall Wallis test was performed. Categorical data were presented as frequencies and percentages and were compared with chi-square or Fisher's exact test, as appropriate and *P*-values of <0.05 were a priori considered statistically significant.

Because of the fact that our study is retrospective, missing values were observed in several variables, due to incomplete data recording. All participants, though, had complete data in variables representing type of CP, GMFCS, and BFMF levels, the primary outcomes for the registry, and gestational age. Since our aim was to simply describe and compare the subgroups of

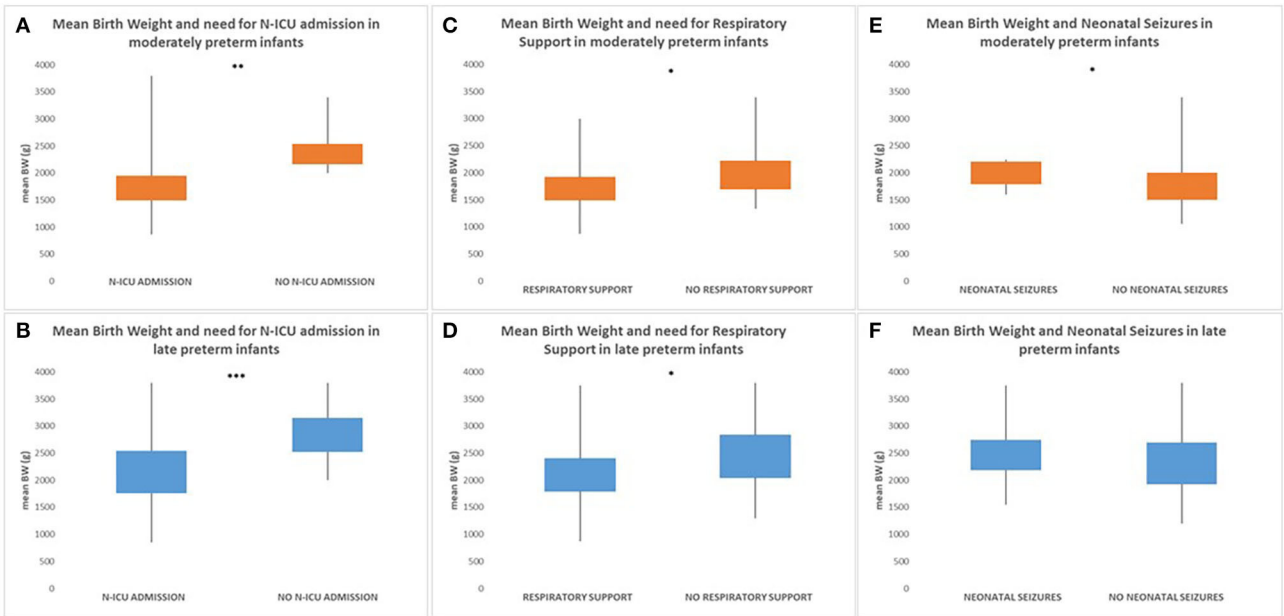

FIGURE 3 | Both moderately and late preterm infants with lower birth weight were more likely to have a history of N-ICU admission [32 to <34 weeks GA ($p = 0.006$) **(A)**/34 to < 37 weeks GA ($p < 0.001$) **(B)**] and to require respiratory support [32 to <34 weeks GA ($p = 0.025$) **(C)**/34 to < 37weeks GA ($p = 0.014$) **(D)**]. Additionally, moderately preterm neonates with higher birth weight were more likely to have seizures during the first 72 h after birth with statistically significant difference compared to moderately preterm neonates with lower birth weight [32 to <34 weeks GA ($p = 0.044$)] **(E)**, whereas there was not statistically significant difference in the late preterm population [34 to <37 weeks GA ($p = 0.263$)] **(F)**. (*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$).

patients with different gestational ages (moderately preterm and late preterm infants), no method for missing data was utilized.

RESULTS

Moderately Preterm Infants

Of the 95 infants in the moderately preterm population, sixty-one percent (61%) were boys, mean Birth Weight (BW) was 1,780 g (870–3,400 g) and mean Apgar score was 9 (3–10). Within the population of moderately preterm infants, of the 94/95 infants with available data concerning the need for N-ICU admission ninety six percent (96%) had a history of N-ICU admission, of the 86/95 infants with available data concerning the need for respiratory support eighty four percent (84%) underwent endotracheal intubation or CPAP ventilation and of the 72/95 infants with available data concerning the history of neonatal seizures eleven percent (11%) presented with seizures during the first 72 h after birth. The predominant CP type among moderately preterm infants was bilateral spastic CP in seventy six percent (76%), followed by unilateral spastic CP in fourteen percent (14%) and dyskinetic CP in five percent (5%) while none of the patients (0%) presented with ataxic CP and five percent (5%) of the subgroup of moderately preterm infants were non-categorized. Among the 59/95 of moderately preterm infants with available brain MRI, the prevailing neuro-imaging findings were predominant white matter lesions in seventy three percent

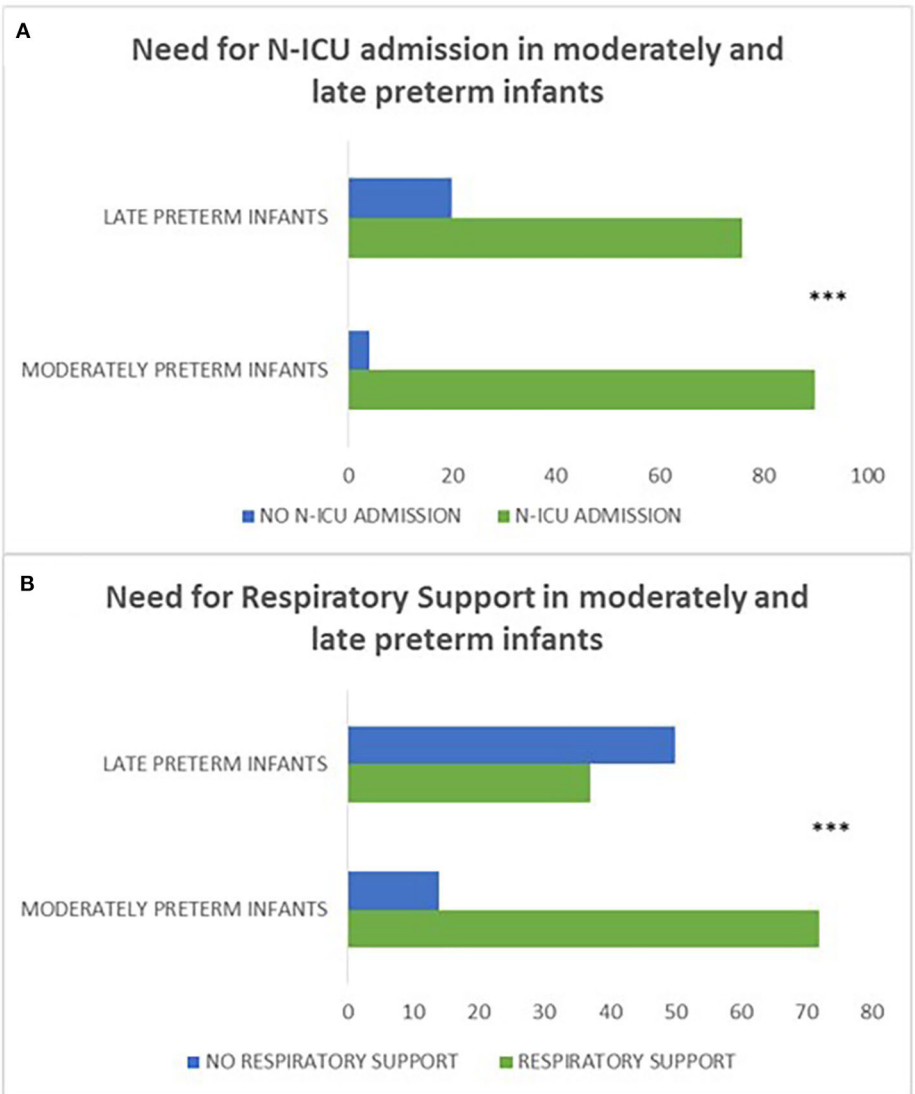

FIGURE 4 | (A, B) refer to the history of N-ICU admission and need for respiratory support in moderately preterm compared to late preterm neonates. Moderately preterm neonates were more likely to have a history of N-ICU admission ($p = 0.001$) **(A)** and require respiratory support ($p < 0.001$) **(B)** compared to late preterm neonates. (***$p \leq 0.001$).

(73%), followed by predominant gray matter lesions in fourteen percent (14%), miscellaneous changes in ten percent (10%), maldevelopments in two percent (2%) and normal imaging findings in two percent (2%) of the patients. The motor function status of moderately preterm infants was assessed concerning gross motor skills with fifty nine percent (59%) classified as GMFCS Level I-III and forty one percent (41%) classified as GMFCS Level IV-V and fine motor skills with sixty two percent (62%) classified as BFMF level I-III and thirty eight percent (38%) classified as BFMF level IV–V. Furthermore, among the 84/95 of moderately preterm infants with available data, forty three percent (43%) had a history of epilepsy and fifty seven percent (57%) did not. Among the 80/95 of moderately preterm infants with available IQ score sixty two point five percent (62.5%) were classified as intellectually disabled (IQ < 70) and among the 82/95 of moderately preterm infants with available hearing acuity test hearing disability was confirmed in five percent (5%) (**Figure 1**).

Late Preterm Infants

Sixty – four point six percent (64.6%) of all 96 late preterm infants were boys, mean BW was 2,310 g (850–3,800 g) and mean Apgar score was 9 (3–10). Within the population of late preterm infants, seventy nine percent (79%) were admitted in N-ICU during the neonatal period, of the 87/96 infants with available data concerning the need for respiratory support forty three percent (43%) of the patients required endotracheal intubation or CPAP ventilation and fifty seven percent (57%) did not and of the 81/96 infants with available data concerning the history of neonatal seizures twenty percent (20%) presented with seizures during the first 72 h after birth. The majority of late preterm infants had a diagnosis of spastic CP in eighty five percent (85%) classified as bilateral spastic CP in fifty seven percent (57%) and as unilateral spastic CP in twenty eight percent (28%) in the group of late preterm infants followed by ataxic CP in six percent (6%) and dyskinetic CP in two percent (2%) among late preterm infants while six percent (6%) of the patients

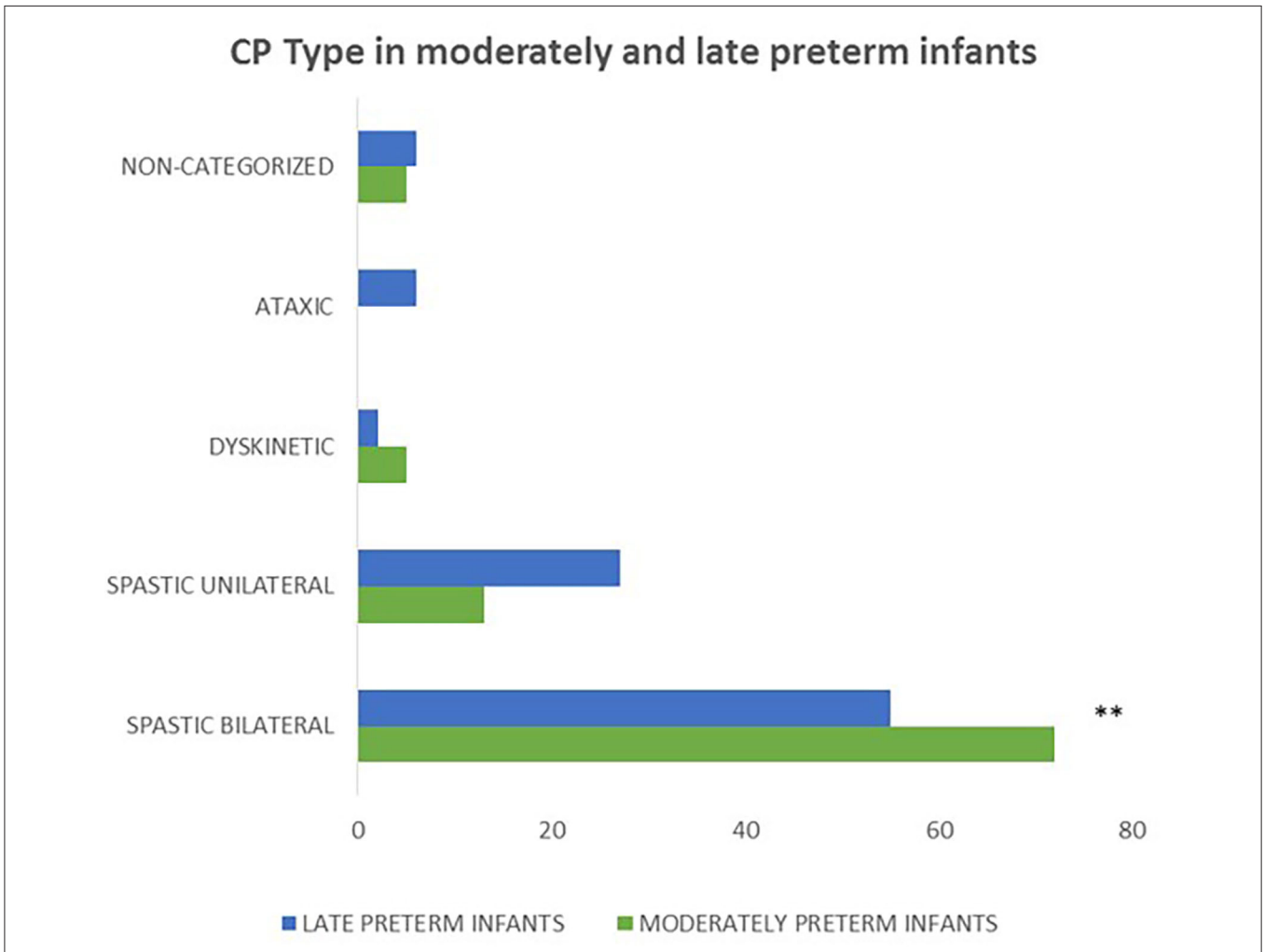

FIGURE 5 | Concerning the correlation of gestational age and CP type, moderately preterm infants presented more frequently with bilateral spastic CP compared to late preterms ($p = 0.006$) and none of the moderately preterm infants had ataxic CP. (**$p \leq 0.01$).

were not categorized. Among the 72/96 of late preterm infants with available brain imaging with MRI, the prevailing finding was predominant white matter injury in fifty three percent (53%) of the patients, followed by predominant gray matter injury in twenty one percent (21%), miscellaneous changes in eighteen percent (18%), maldevelopments in six percent (6%) and normal imaging findings in two percent (2%) in the late preterm population. The motor function status of late preterm infants was assessed concerning gross motor skills with fifty eight percent (58%) classified as GMFCS Level I-III and forty two percent (42%) classified as GMFCS Level IV-V and fine motor skills with sixty two point five percent (62.5%) classified as BFMF level I-III and thirty seven point five percent (37.5%) classified as BFMF level IV-V, similarly to the subgroup of moderately preterm infants. In addition, among the 89/96 of late preterm infants with available data, forty nine percent (49%) had a history of epilepsy and fifty one percent (51%) did not. Among the 87/96 of late preterm infants with available IQ score sixty one percent (61%) were classified as intellectually disabled (IQ $<$ 70) and among the 91/96 of late preterm infants with available hearing acuity test hearing disability was confirmed in one percent (1%) (**Figure 2**).

Birth Weight Is Related to Early Neonatal Outcome

Birth weight was significantly related to early neonatal outcome with both moderately and late preterm infants with lower birth weight being more likely to have a history of N-ICU admission [32 to <34 weeks GA ($p = 0.006$)/34 to <37 weeks GA ($p < 0.001$)] and to require respiratory support [32 to <34 weeks GA ($p = 0.025$)/34 to <37 weeks GA ($p = 0.014$)]. Additionally, moderately preterm neonates with higher birth weight were more likely to have seizures during the first 72 h after birth with statistically significant difference compared to moderately preterm neonates with lower birth weight, whereas there was not statistically significant difference in the late preterm population [32 to <34 weeks GA ($p = 0.044$)/34 to <37 weeks GA ($p = 0.263$)]. In the moderately preterm population, the mean BW of neonates who required N-ICU admission was 1,770 g (870–3,800 g) whereas the mean BW of neonates who did not was 2,235 g (2,000–3,400 g), the mean BW of neonates who required respiratory support was 1,750 g (870–3,000 g) whereas the mean BW of neonates who did not was 2,025 g (1,340–3,400 g), the mean BW of neonates who had seizures during the first 72 h after birth was 2,075 g (1,600–2,250 g) whereas the mean BW of neonates who did not was 1,980 g (1,060–3,400 g). In the late preterm population, the mean BW of neonates who required N-ICU admission was 2,200 g (850–3,800 g) whereas the mean BW of neonates who did not was 2,750 g (2,000–3,800 g), the mean BW of neonates who required respiratory support was 2,150 g (870–3,750 g) whereas the mean BW of neonates who did not was 2,515 g (1,300–3,800 g), the mean BW of neonates who had seizures during the first 72 h after birth was 2,450 g (1,550–3,750 g) whereas the mean BW of neonates who did not was 2,300 g (1,200–3,800 g) (**Figure 3**).

Gestational Age Is Related to Early and Late Outcome of Preterm Infants

Moderately preterm neonates were more likely to have a history of N-ICU admission ($p = 0.001$) and require respiratory support ($p < 0.001$) compared to late preterm neonates indicating that

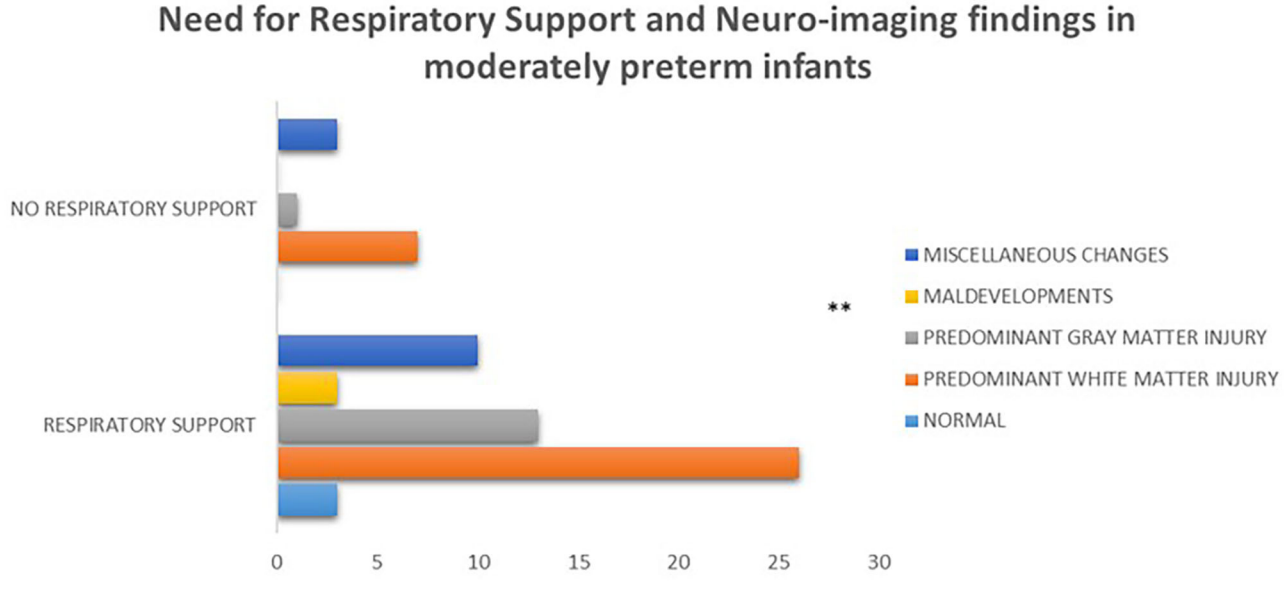

FIGURE 6 | Among the 59/95 of moderately preterm infants with available brain imaging the prevailing findings were white matter lesions, with statistically significant difference between moderately preterm infants who required respiratory support and mainly presented with this type of lesion vs. those who did not and presented with gray matter lesions, maldevelopments or miscellaneous findings ($p = 0.004$). (**$p \leq 0.01$).

gestational age serves a crucial role in the neonatal outcome of preterm infants (**Figure 4**).

Concerning the clinical classification of CP, moderately preterm infants presented more frequently with bilateral spastic CP compared to late preterms ($p = 0.006$). Moreover, in the moderately preterm population none of the neonates had ataxic CP indicating that moderately preterm infants have less frequently ataxic CP compared to late preterm infants (**Figure 5**).

Among the 82/95 of moderately preterm infants and the 91/96 of late preterm infants with available data concerning auditory acuity, auditory disorder was observed in five percent (5%, 4/82) and one percent (1%, 1/91) respectively ($p = 0.198$), indicating that hearing disorder is not a major disability in infants of either subgroup.

Among the 59/95 of moderately preterm infants and the 72/96 of late preterm infants with available brain imaging the prevailing findings were white matter lesions in both subgroups (43/59, 73% and 38/72, 53% respectively), with statistically significant difference between moderately preterm infants born at 32 to <34 weeks who required ventilator support and mainly presented with this type of lesion vs. those who did not and presented with gray matter lesions, maldevelopments or miscellaneous findings ($p = 0.004$) (**Figure 6**).

In addition, within the population of late preterm infants, those who needed N-ICU admission and respiratory support as neonates were more likely to achieve less favorable fine motor outcomes according to the BFMF scale ($p = 0.019$ and $p = 0.017$, respectively) (**Figure 7**).

DISCUSSION

Birth weight turned out to be significantly related to early neonatal outcomes of both moderately preterm (32 to <34 weeks GA) and late preterm infants (34 to <37 weeks GA) as neonates of both subgroups with smaller birth weight were more likely to have a history of N-ICU admission, require respiratory support and not to develop seizures during the first 72 h after birth. The higher incidence of N-ICU admissions and need for

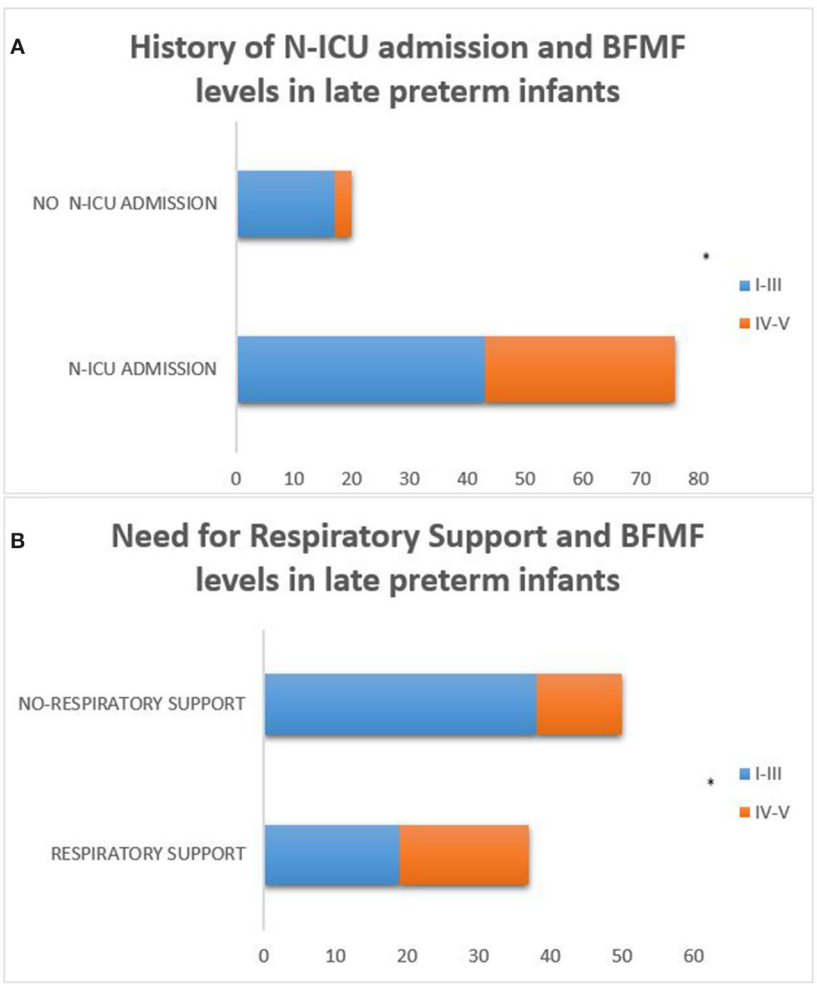

FIGURE 7 | Late preterm infants who needed N-ICU admission and respiratory support as neonates were more likely to achieve less favorable fine motor outcomes according to the BFMF scale [$p = 0.019$ **(A)** and $p = 0.017$ **(B)**, respectively]. (*$p \leq 0.05$).

respiratory support in moderately and late preterm neonates with lower birth weight in our study provides an indication of the predictive nature of birth weight and is similar to results of previous studies associating low birth weight with an increased risk of any emergency respiratory admission to hospital during the neonatal period, infancy and even later childhood until adulthood (11, 42–44).

In our cohort, moderately preterm infants were more likely to require respiratory support and have a history of N-ICU admission as neonates compared to their late preterm peers indicating that decreasing gestational age constitutes a negative prognostic factor for short term outcomes, in line with previous studies (7).

In both subgroups of moderately and late preterm infants, the predominant CP type was spastic CP (bilateral spastic CP followed by unilateral spastic CP), as expected based on current literature (14), and brain imaging revealed predominantly white matter lesions, as already highlighted in previous studies which documented intracranial hemorrhage (ICH), periventricular leukomalacia (PVL) as well as white matter microstructural alterations as the main neuroimaging finding in the population of moderately and late preterm infants (28–30).

Additionally, in the population of moderately and late preterm CP patients the classification of gross motor and fine motor function revealed comparable GMFCS and BFMF levels in both subgroups, with GMFCS and BFMF levels I-III in most patients. Several studies have been conducted so far concerning gross motor function in moderately and late preterm infants with CP indicating comparable results to ours, however, further studies are demanded in order to assess fine motor function in this population of infants as fine motor development of CP patients is poorly examined so far (16, 19–22).

Epilepsy and intellectual impairment were documented in high percentages, similar in both subpopulations of moderately and late preterm infants with CP, in accordance with current literature (32–35), whereas severe hearing disability was not observed in infants of either subgroup indicating further research needs as so far there are contrary existing literature data concerning hearing acuity in the population of moderately and late preterm infants (45, 46).

Our data support that moderately and late preterm infants constitute a population vulnerable for short-term complications and long-term unfavorable outcomes. Although, gestational age plays a crucial role for the short-term outcome and differentiates the clinical sequelae between moderately and late preterm infants during the neonatal period, the long-term outcomes of both subgroups of moderately and late preterm infants share common clinical features.

It is important to carry out further studies in order to follow up moderately and late preterm infants during prenatal neonatal period and childhood and to define prenatal and perinatal risk factors in order to improve obstetric and neonatal treatment practices that could lead to better short- and long-term outcomes.

Our study addresses the population of moderately and late preterm infants who represent the vast majority of infants born preterm and sheds light on short- and long-term outcomes of this subpopulation of CP patients providing data which appear to be consistent to current literature but also raise the necessity of further research.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

NS participated in the research design, the collection and statistical analysis of data and drafted the manuscript for intellectual content. MK, MG, HSt, FD, and GD participated in the collection of data. MP participated in the research design, the collection of data and revised the manuscript for intellectual content. EN participated in the research design, the collection and statistical analysis of data and revised the manuscript for intellectual content. HSk, HB, SM, ZD, AD, and MT participated in the diagnosis, treatment and follow up of patients, provided access to clinical data and revised the manuscript for intellectual content. AP conducted the research design, participated in the diagnosis, treatment and follow up of patients, provided access to clinical data, co-wrote the manuscript and revised the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

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REVIEW
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Skeletal Muscle in Cerebral Palsy: From Belly to Myofibril

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This review will provide a comprehensive, up-to-date review of the current knowledge regarding the pathophysiology of muscle contractures in cerebral palsy. Although much has been known about the clinical manifestations of both dynamic and static muscle contractures, until recently, little was known about the underlying mechanisms for the development of such contractures. In particular, recent basic science and imaging studies have reported an upregulation of collagen content associated with muscle stiffness. Paradoxically, contractile elements such as myofibrils have been found to be highly elastic, possibly an adaptation to a muscle that is under significant *in vivo* tension. Sarcomeres have also been reported to be excessively long, likely responsible for the poor force generating capacity and underlying weakness seen in children with cerebral palsy (CP). Overall muscle volume and length have been found to be decreased in CP, likely secondary to abnormalities in sarcomerogenesis. Recent animal and clinical work has suggested that the use of botulinum toxin for spasticity management has been shown to increase muscle atrophy and fibrofatty content in the CP muscle. Given that the CP muscle is short and small already, this calls into question the use of such agents for spasticity management given the functional and histological cost of such interventions. Recent theories involving muscle homeostasis, epigenetic mechanisms, and inflammatory mediators of regulation have added to our emerging understanding of this complicated area.

Keywords: cerebral palsy, skeletal muscle, muscle contractures, muscle morphology, spasticity, satellite cells, connective tissue, epigenetics

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INTRODUCTION

With respect to its musculoskeletal manifestations, cerebral palsy (CP) has been defined as a static encephalopathy, typified by muscle contractures (i.e., shortening) and bony deformities that are progressive with growth (1). The majority of children with CP exhibit a spastic motor type, whereby muscle stiffness increases proportional to the velocity of induced stretch (2, 3). The "spastic catch" that results, prior to the onset of fixed muscle shortening, has been referred to as a dynamic contracture, more commonly encountered in younger children with CP (4, 5). With time, the muscle develops a "static contracture" (i.e., the muscle becomes short) (6). As an overt manifestation of CP—associated with gait abnormalities, joint dislocations, seating issues, and impediments to activities of daily living (ADL)—muscle contractures (both dynamic and static) have been a convenient, and obvious, target for clinicians, both by nonsurgical and surgical means (7).

Given the natural history of muscle contracture development, with dynamic contractures preceding static, along with the concomitant development of bony deformities, it was natural to conclude that spasticity was the driving force behind these manifestations. As such, treatments focused on reducing spasticity, most notably injection with botulinum toxin, have been instituted at an early stage with the goal of preventing static contractures and bony deformities and thus orthopedic surgery (8). This treatment approach, effectively communicated by Dr. Mercer Rang in his three stages of CP (9) (**Figure 1**), has been recently referred to as the "Traditional View" (10, 11), providing an intuitive means by which these children have been treated over the last 25 years.

The "Traditional View" presupposed that skeletal muscle in CP was merely an end organ in CP, its abnormal activation causing protracted postures eventually leading to fixed contracture, all secondary to hypertonia from the primary brain insult. However, recent developments in our understanding of the CP muscle challenge that view. More than just an end organ, intrinsic changes in the CP muscle pathomorphology—including abnormalities in sarcomerogenesis, decreased satellite cell number and function, increased connective tissue and fat, highly elastic myofibrils, and ribosomal dysfunction—suggest a more localized role in the development of contracture (12–15). Indeed, epigenetics has become an important area of interest, with abnormalities in DNA methylation being correlated to the diagnosis of CP in general and more specifically to disordered ribosomal-mediated protein synthesis, proportional to disease severity (16, 17).

Coupled to clinical research showing that the treatment of spasticity does not reliably prevent the development of static muscle contractures and bony deformities or the need for orthopedic surgery, it is very likely that the *Traditional View* is incorrect, with primary muscle deformities developing in tandem with spasticity rather than as a result of abnormal muscle activation (18–24). Indeed, impaired muscle growth mismatched to more normal increases in bone length, along with significant increases in intramuscular connective tissue, would seem to be more primary determinants of static contracture development in CP.

As such, the goal of this review is to summarize what is currently known about the pathophysiology of the CP muscle and how it relates to the musculoskeletal manifestations of the disease. In addition, the effects of various common treatments on the intrinsic properties of the CP muscle will be explored.

THE CEREBRAL PALSY PHENOTYPE: POSITIVE AND NEGATIVE ASPECTS

Depending on the etiology of neurological insult, children with CP exhibit several different motor types, both hypertonic and hypotonic in nature. The most common motor type, and thus the most commonly investigated, is "spastic," with 86% of a population-based CP cohort being of this type (2). As a velocity-dependent increase in dynamic muscle stiffness, the manifestations of spasticity are readily appreciable both on physical examination and by parents. It is natural then to attribute these manifestations to the motor type itself, described above as the "Traditional View" and hence divert focus and resources to rectifying spasticity. In addition to the "positive" features of the upper motor neuron syndrome that typifies the CP phenotype (including spasticity, hyperreflexia, clonus, and muscle cocontraction), the negative features (most notably weakness but also poor selective motor control and balance) have been implicated as the primary determinants of gross motor function (5) (**Figure 2**). As will be discussed in the sections below, properties intrinsic to the sarcomere in the CP muscle seem to be causative in this respect, being both overlong and subject to a high rate of excursion.

According to Rang's Traditional View, it has been widely accepted that spastic muscles exert abnormal forces on growing bone, causing bony deformities—in the case of the hip—that include coxa valga (increased femoral neck-shaft angle), increased internal femoral torsion (anteversion), and acetabular dysplasia (i.e., hip displacement) (25). A recent population-based study of children with CP disputes this view, revealing persistent increases in femoral anteversion (present from birth) and coxa valga, both associated with disease severity according to the Gross Motor Function Classification System (GMFCS) (26). Another study showed no difference in the incidence of hip displacement, regardless of whether the motor type was hypertonic or hypotonic (27). Thus, current thinking suggests that abductor insufficiency and a lack of weight bearing are responsible for primary deformities of the proximal femur leading to hip displacement rather than from the positive features of CP (28).

With respect to ambulatory patients with CP, eccentric, antigravity muscles—such as the soleus—are of primary importance, modulating the site of application of the ground reaction force on the foot during weight bearing and allowing for biomechanically advantageous ambulation. Crouch gait, whereby the ankle is in substantial dorsiflexion, the knee and hip are flexed, and the ground reaction force is behind the knee develop as a consequence of either natural or iatrogenic weakness of the soleus. Necessitating high knee extension moments, this gait pattern has a high energy cost and is largely unsustainable (29). As will be discussed in later sections, understanding the mechanisms by which force is decreased—or potentially enhanced—in antigravity, eccentric muscles like soleus is important to avoid treatment interventions that might further compound the problem of muscle weakness in CP (e.g., aggressive surgical lengthening or chemical denervation).

Before one can understand the CP muscle, however, one must first understand typically developing muscle.

SKELETAL MUSCLE BASICS

Muscles are the engines of life. They allow us to move, to breathe, to play, and to function in everyday life. When muscles are properly trained and coordinated, they allow us to run 100 m in 9.58 s, play Liszt's "La Campanella," or perform a reverse 4 1/2 somersaults dive in the pike position. Muscles are the organs

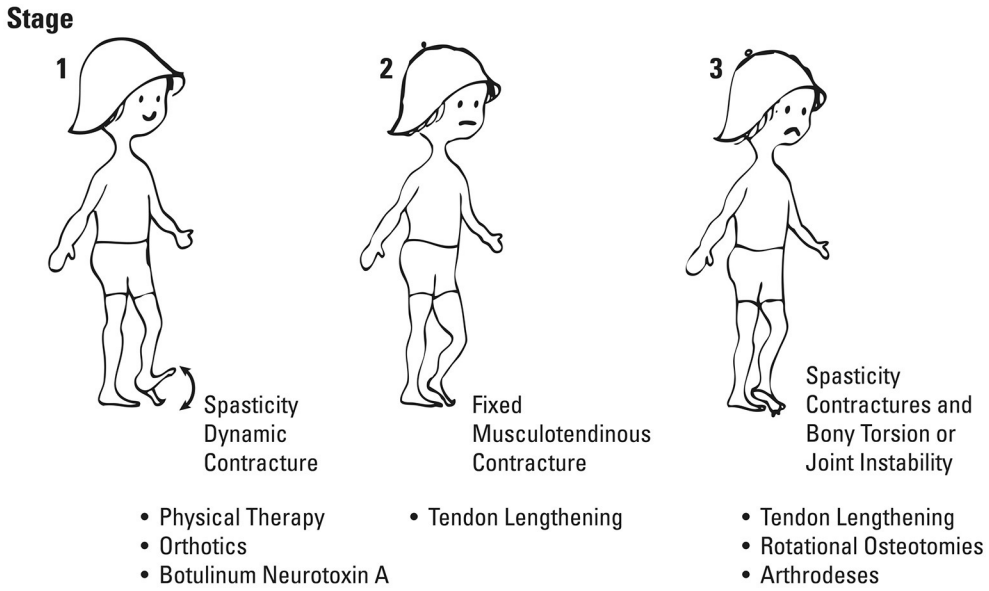

FIGURE 1 | Rang's three phases of cerebral palsy, the so-called "Traditional View," which emphasizes spasticity as a primary driver of both muscle and bony deformities. (Used with permission ©Bill Reid/Kerr Graham, RCH Melbourne).

of strength and power. Their intricate and highly specialized structure is aimed at producing mechanical work from metabolic energy in the most effective and most efficient manner.

Muscle Morphology

The basic contractile unit of a skeletal muscle is the sarcomere (**Figure 3**). Sarcomeres are repeating structures of intricately aligned contractile and structural proteins, bounded by the so-called Z-band. Sarcomeres are made up of the contractile proteins actin and myosin and a series of structural proteins including titin, nebulin, desmin, and dystrophin. The myosin (or thick) filament is located at the center of the sarcomere, while the actin (or thin) filament merges at either end of the sarcomere into the Z-bands from where it reaches toward the center of the sarcomere. Depending on the length of the sarcomere, which in turn depends on the length of the muscle, the actin and myosin filaments overlap to different degrees, which is an important consideration in the amount of force a sarcomere (or the muscle) can exert.

The myosin filament, as its name implies, is primarily made up of myosin molecules (**Figure 4**). Myosin molecules have a tail portion that forms the structural part of the thick filament and a globular head part that emerges from the thick filament and is used to attach to specific sites on actin and pull the actin past the myosin filament upon muscle activation and contraction. These globular head portions of the myosin molecule are referred to as cross-bridges. Cross-bridges in mammalian skeletal muscles are arranged in a uniform manner, with actin filaments arranged around each myosin filament in a hexagonal array (**Figure 5**), each half myosin filament supplying six actin filaments with cross-bridges, 60° apart from each other.

The actin filament is made up of two chains of serially linked actin globules (**Figure 6**). Actin also contains important regulatory proteins, so named because of their role in controlling myosin cross-bridge attachment to actin. The first of these regulatory proteins is the troponin tricomplex, which repeats every 36–39 nm on the actin filament. The troponin tricomplex consists of troponin C, troponin T, and troponin I proteins. Upon muscle activation, calcium is bound to troponin C, which in turn causes a conformational change in the troponin/tropomyosin complex, exposing the actin attachment site to the myosin cross-bridges, thus allowing contraction and force production.

Myofibrils are the contractile organelles in a muscle fiber, being made up of serially arranged sarcomeres (**Figure 7**). For typically developing human muscle, sarcomeres exert force most optimally at a length of ∼2.6 μm (30, 31). Therefore, each 1 mm (=1,000 μm) of myofibril contains about 400 sarcomeres perfectly aligned in series with each other. Since myofibrils can easily be several centimeters in length, a myofibril can contain thousands of sarcomeres. Myofibrils are between 0.5 and 1.0 μm in diameter and thus are ∼1/100th of the diameter of a human hair.

Muscle fibers are long and thin multinucleated cells of skeletal muscles (**Figure 8**). They typically contain several thousand myofibrils that lie in parallel to each other. Muscle fibers are surrounded by a cell membrane, the sarcolemma, and connective tissue, the endomysium that connects neighboring muscles fibers. The next greater structural entity is the muscle fascicle (**Figure 8**). Muscle fascicles are made of multiple muscle fibers, and they are contained within a connective tissue layer called perimysium. Finally, the whole muscle is made up of muscle fascicles. Muscles are surrounded by connective tissues that connect one muscle of a group to the other muscles in that same group. The connective

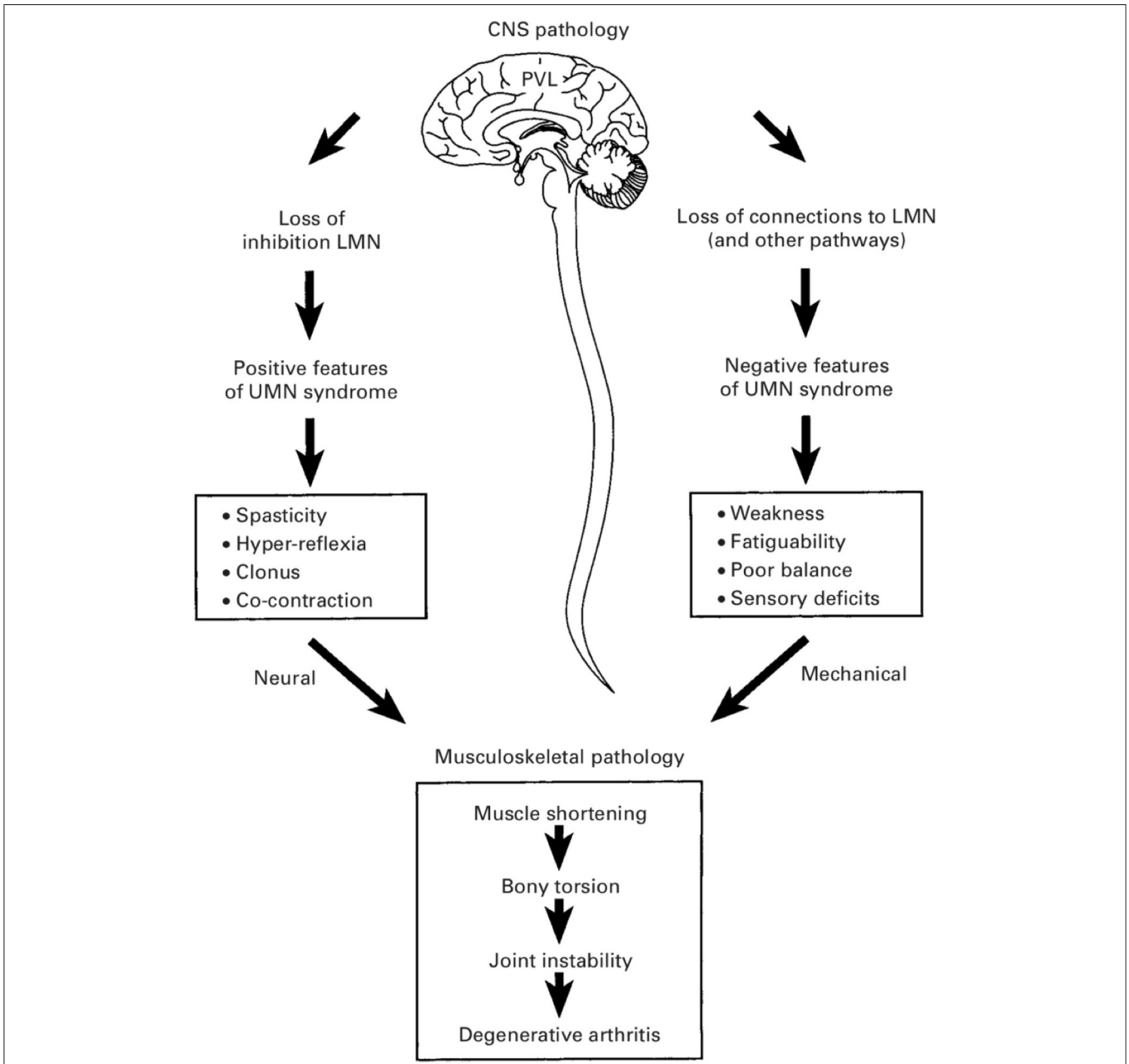

FIGURE 2 | Positive and negative features of the upper motor neuron syndrome in cerebral palsy (CP). The negative features—including weakness, poor balance, and impaired selective motor control—are considered to be more important determinants of gross motor function in CP and are more likely causes of bony deformities and joint instability. (Used with permission © Bill Reid/Kerr Graham, RCH Melbourne).

tissue layer closest to the muscle is referred to as the epimysium, and other layers of connective tissue are referred to generically as muscle fasciae.

Skeletal muscles have distinct arrangements of their fibers relative to the long axis of the muscle (**Figure 9**). Muscles whose fibers run essentially parallel to the long axis of the muscle are either referred to as fusiform or parallel fibered. When all fibers of a muscle are essentially aligned in the same direction and at a distinct angle to the long axis of the muscle, then the muscle is said to be unipennate. When there are two or more distinct fiber directions, a muscle is referred to as bipennate or multipennate. Examples of these different structural arrangements can be found in all animals, including humans: sartorius (parallel fibred), medial gastrocnemius (unipennate), rectus femoris (bipennate), and deltoid (multipennate). Typically, pennate muscles have shorter fascicles/fibers relative to the entire muscle length than parallel/fusiform muscles; thus, their fibers take up less volume and allow for more parallel fibers per volume than the fibers in

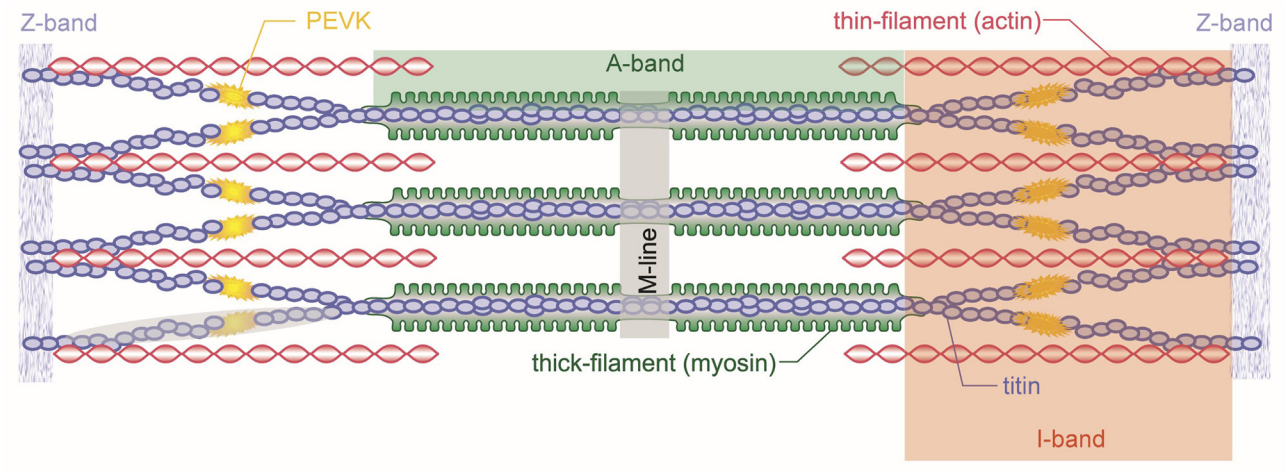

FIGURE 3 | Schematic representation of a skeletal muscle sarcomere. Shown are the contractile filaments actin and myosin and the structural protein titin. Sarcomeres are bordered by the Z-bands from which titin and actin emanate. Myosin is centered in the middle of the sarcomere and held in place by the titin filaments.

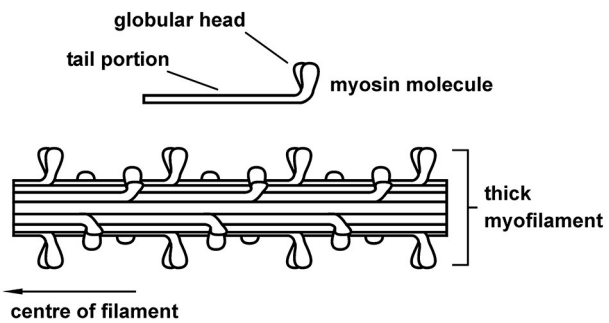

FIGURE 4 | Schematic representation of the thick (myosin) skeletal muscle filament comprised primarily of myosin proteins. Myosin had a tail portion that is incorporated into the main body of the thick filament and two globular heads that reach out from the myosin toward the actin filament. Cross-bridges form cyclic attachments with actin, pulling actin past the myosin filament, thereby producing muscle contraction and force.

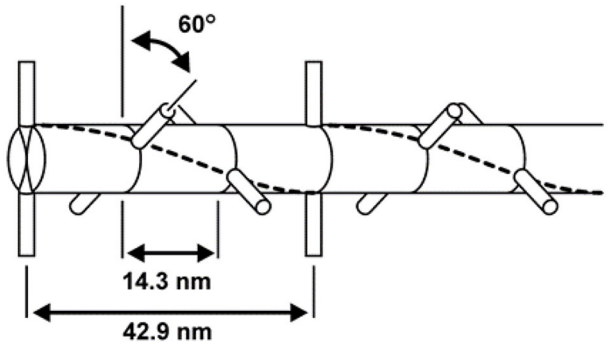

FIGURE 5 | Geometric arrangement of the cross-bridges on the myosin filament. Cross-bridges come in pairs that are offset by 180° and are arranged every 14.3 nm along the myosin filament. Neighboring pairs of cross-bridges are rotated by 60°; therefore, cross-bridges with the same orientation (and thus attaching to the same actin filaments) occur every 42.9 nm.

parallel muscles. Functionally, this means that for two muscles of equal volume, a pennate muscle has a greater maximal force capacity (maximal force depends on the physiological cross-sectional area of the muscle) but a smaller excursion range (excursion depends on the length of fibers) over which it can produce force than a parallel fibered muscle, while the work potential (area under the maximal force-length curve) for the two muscles of equal volume is the same.

Muscles in the human body, and in most mammals, are of mixed fiber type. On the most basic levels, muscle fibers are grouped into slow twitch (type 1) or fast twitch (type 2) fibers. Fast twitch fibers are typically further subdivided into type 2a, 2b, and 2x based on their myosin heavy chain gene expression. However, there are hybrid expressions of myosin heavy chains that make for a virtually continuous spectrum of fast twitch fibers, but these will not be discussed further. Metabolically, the slow twitch type 1 fibers and the fast twitch type 2a fibers rely primarily on oxidative metabolism for force and work production, while the 2b and 2x fast fibers rely primarily on glycolytic metabolism. Functionally, as the name implies, slow twitch fibers have slow twitch characteristics, slow force rise and relaxation, and a slow speed of unloaded (maximal) shortening relative to the fast twitch fibers. Therefore, even though the maximal isometric force per cross-sectional area of slow and fast twitch fibers is similar, force during shortening is much greater in fast compared to slow twitch fibers, resulting in a maximal power output that is three to four times greater in fast compared to slow twitch fibers. The low power output of the slow compared to fast twitch fibers is offset by their fatigue resistance allowing slow twitch fibers to perform submaximal work for a much longer period of time than the fast fatiguing fast twitch fibers.

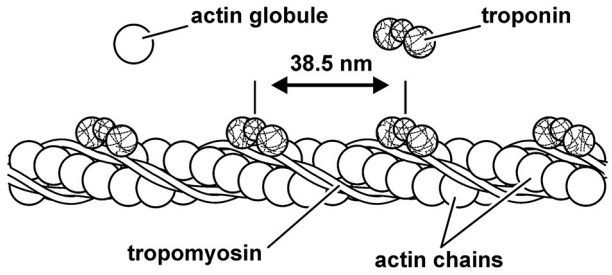

FIGURE 6 | Schematic representation of the thin (actin) filament. Actin is made up of two serially linked chains of actin globules and the repeating structures of the regulatory proteins tropomyosin and troponin. The regulatory protein troponin C binds calcium upon muscle activation, resulting in a configurational change of the troponin–tropomyosin complex that allows for cross-bridge attachment to actin.

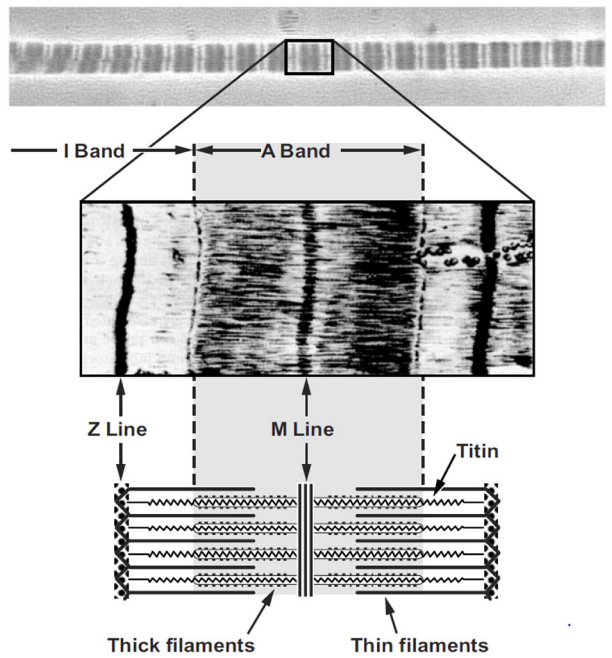

FIGURE 7 | Micrograph of a single myofibril (top panel) with the typical dark (A-band) and light (I-band) striation pattern and a corresponding sarcomere (middle panel) with a schematic representation of the sarcomere (bottom panel) including the appropriate labeling.

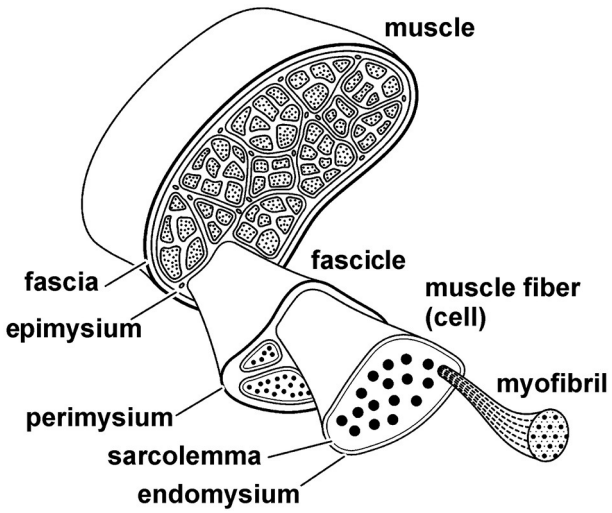

FIGURE 8 | Schematic structural hierarchy of a skeletal muscle. The entire muscle is made up of fascicles, fascicles are made up of fibers (cells), and fibers are comprised of myofibrils. Each structural entity of the muscle is surrounded by connective tissues that connect the various structural levels with each other and connect the entire muscle to other muscles, bones, and fascia. The connective tissue layers are referred to as the epimysium, perimysium, and endomysium, as indicated in the figure.

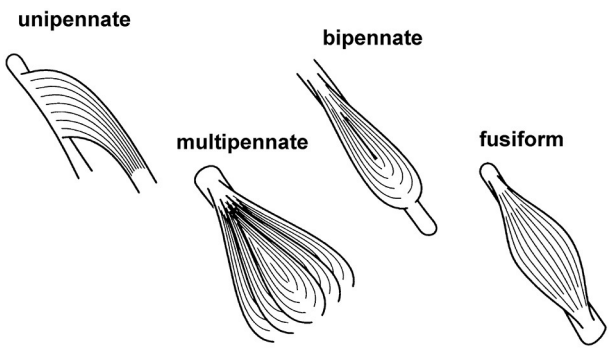

FIGURE 9 | Schematic figure of different structural arrangements of fibers relative to the long axis of the muscle. See text for further explanation and definition.

Mechanisms of Contraction

Prior to the 1950s, muscle contraction was thought to occur through the shortening of the A-band region containing the myosin filaments in sarcomeres. However, in 1954, Andrew Huxley and Hugh Huxley (not related) arrived independently at the conclusion that muscle shortening and lengthening was not caused by myosin shortening but by the relative sliding of the actin to the myosin filaments. This discovery has been named the "sliding filament" theory (32, 33). Three years later, Andrew Huxley proposed the first mathematical model of how the relative sliding of these two myofilaments may occur; the cross-bridge theory (34). Despite many refinements and improvements of the cross-bridge theory in the past half century, much of the initial model has been retained to this day and is still used in many applications of muscle modeling and muscle function. In simple words, the cross-bridge theory might be summarized as follows: The myosin filaments have protrusions (cross-bridges) that attach cyclically to specific attachment sites on the actin filaments, and when attached, they pull the actin past the myosin filaments, thereby producing shortening and force. The energy for these processes is provided by adenosine-triphosphate (ATP) that is hydrolyzed into adenosine-diphosphate (ADP) and a free phosphate: one ATP per cross bridge cycle.

Muscle contractions are categorized into three conceptual groups, depending on the length change of the muscle during contraction. When a muscle is contracting and its length remains the same, the contraction is called isometric. When a muscle is shortening during contraction, thereby overcoming the external resistance and producing positive mechanical work, the contraction is called concentric, and when a muscle is actively producing force, but the external forces are greater than those produced by the muscle, and thus the muscle is elongated while activated, the contraction is referred to as an eccentric contraction. These contractile conditions are insofar important as they determine the forces that are (maximally) available to a muscle. For example, a muscle that is shortening (concentric contraction) has a reduced capacity to produce force compared to a muscle that is being stretched at the same rate (eccentric contraction) (35).

Mechanical Properties of Skeletal Muscle

In most textbooks of muscle mechanics and physiology, authors refer to two basic mechanical properties: the force–length and the force–velocity relationship. However, there is a distinct third property of skeletal muscle: the history-dependent property, which manifests itself as the residual force enhancement and residual force depression property.

The force–length relationship of skeletal muscles describes the maximal, active, steady-state, isometric force that a muscle can exert as a function of its length (36). Over a century ago, scientists were aware that the maximal force capacity of a muscle depended on its length (37). However, an understanding of the mechanisms underlying the force–length relationship only became available after the introduction of the sliding filament theory, when scientists proposed that the force potential of a muscle needs to be proportional to the amount of overlap that exists between the actin and myosin filaments in a sarcomere, and the amount of this overlap, of course, depends on the length of a muscle (38) (**Figure 10**).

The force–velocity relationship describes the maximal, active, steady-state force of a muscle at optimal length (the length where a muscle produces the maximal isometric force) as a function of its rate of change in length (typically referred to as the speed/velocity of shortening) (36) (**Figure 11**). Thus, it describes how the maximal steady-state force of a muscle decreases with increasing speeds of shortening. Fast twitch fibers can shorten faster than slow twitch fibers, and muscles with long fibers have a greater capacity to shorten fast than muscles with short fibers. The eccentric part of the force–velocity relationship is much less well defined than the concentric part, and is left out of this discussion here, but can be found in many textbooks of muscle mechanics and physiology (39).

Residual force enhancement (rFE) and residual force depression (rFD) are two properties of skeletal muscle contraction that have been observed consistently for all skeletal muscles for more than half a century (40). rFE is the extra steady-state isometric force that is obtained when a muscle is actively stretched, compared to the corresponding (same length and same activation) purely isometric force (41) (**Figure 12**). rFD is the loss in steady-state isometric force observed following shortening of an active muscle compared to the corresponding (same length and same activation) purely isometric reference contraction (42) (**Figure 12**).

Residual force enhancement increases with increasing stretch magnitudes, is independent of the stretch speed, is not associated with a change in muscle stiffness (compared to isometric reference contractions), and can be abolished instantaneously by deactivating the muscle. It has been demonstrated that rFE is associated with the engagement of a passive structural element in skeletal muscle (43), and there is increasing evidence that this passive element is the structural, filamentous sarcomere protein titin (44–47).

Titin is a spring-like molecule that tethers the thick myosin filaments to the Z-line and is the primary determinant of myofibril stiffness (**Figure 3**) (48). The working hypothesis for titin's role in rFE is (i) that titin binds calcium upon activation, thereby increasing its spring stiffness by reinforcing molecular bonds that unfold when sarcomeres, and thus, titin are stretched, and (ii) that when a muscle undergoes an eccentric action (i.e., it is actively stretched), titin binds to actin so that its proximal segment cannot be elongated and its free spring length (the unbound distal segment) becomes shorter and thus stiffer (48–50).

HOW IS CEREBRAL PALSY MUSCLE MECHANICALLY DIFFERENT?

CP muscle differs structurally, biologically, and mechanically from those of age-matched typically developing children (TDC). The primary function of skeletal muscles is to produce force and movement, and there is good evidence that spastic muscles in children with CP are reduced in these functions compared to TDC. There are at least four mechanical/structural reasons for the reduced active force potential of spastic skeletal muscles in children with CP:

(i) reduced muscle size,
(ii) reduced contractile tissue,
(iii) over-stretched sarcomeres, and
(iv) loss of sarcomeric titin.

Reduced Muscle Size

Muscle size is typically decreased in spastic muscles of children with CP compared to muscles in appropriate controls. Noble et al. (12) found an average muscle volume deficit of 27.9% in nine lower limb muscles of 19 independently ambulant children with spastic CP compared to typically developing children. Matthiasdottir et al. (51) found an average of 43% reduced fascicle length in 11 children with CP (ambulant and nonambulant) compared to 14 typically developing children, 6 of which were sex-matched twin siblings. However, physiological cross-sectional area, rather than muscle volume, is a direct indicator of maximal force capacity. Since physiological cross-sectional area can be estimated as volume divided by optimal fascicle length, and since fascicle lengths also tend to be reduced in children with CP, physiological cross-sectional area might not be as compromised as the reduced muscle volumes might suggest.

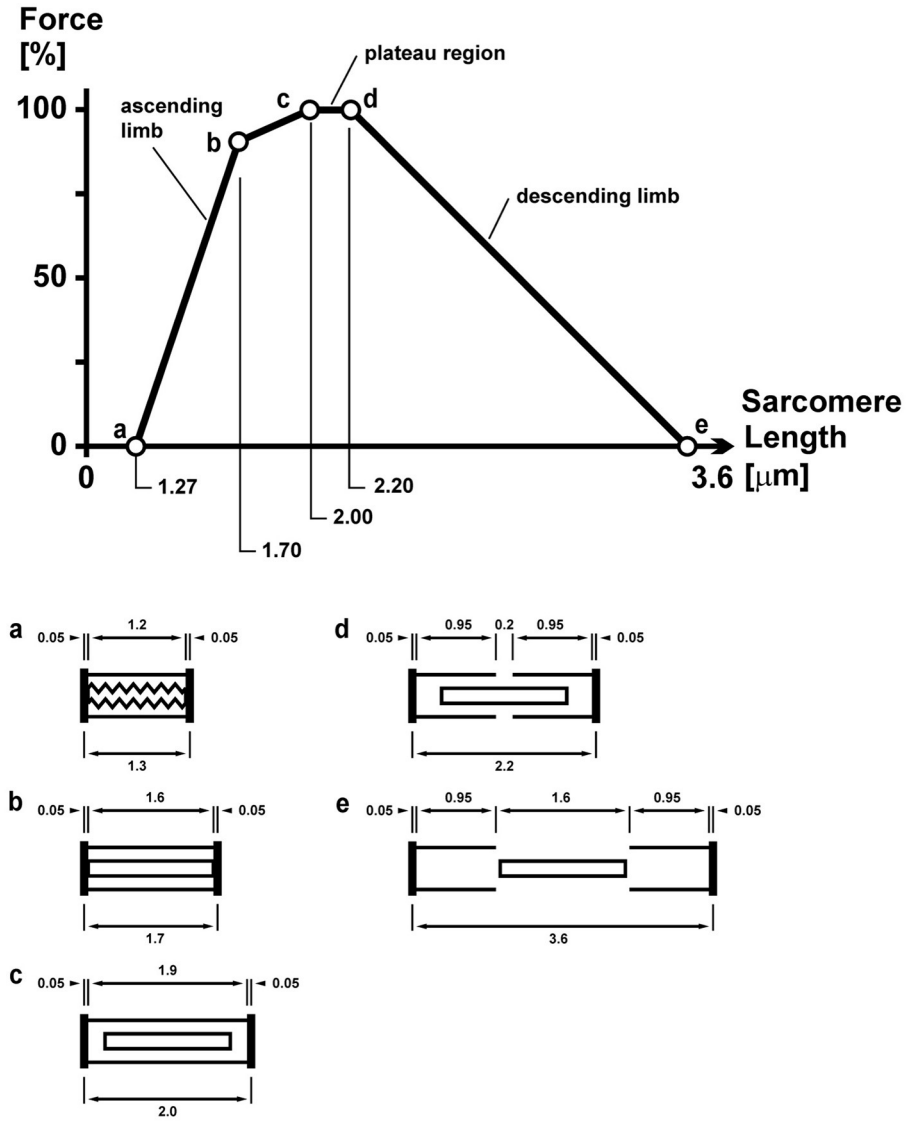

FIGURE 10 | Sarcomere force–length relationship of a frog skeletal muscle as first described by Gordon et al. (38). The so-called plateau and descending limb regions are well explained by the sarcomere lengths (shown schematically below for lengths c, d, and e) and the corresponding overlap between the contractile filaments actin and myosin. The overlap between these filaments determines the number of possible cross-bridge interactions and thus the maximal, isometric force capacity.

Reduced Contractile Tissue

There are two basic mechanisms by which the amount of contractile tissue per unit of muscle cross-sectional area can be reduced: (i) through fibrosis (i.e., increased intramuscular connective tissue) (52) and (ii) by replacement of connective tissue by other tissues, primarily fat in the context of cerebral palsy (53).

Several authors have reported increased connective tissue in CP. Booth et al. (14) reported a significant increase in the hydroxyproline content (a proxy measure of collagen content) of vastus lateralis in children with spastic CP compared to TDC. deBruin et al. (54) reported increased connective tissue content in the perimysium with the flexor carpi ulnaris of children with CP (54). Lieber and Fridén (55) also reported increases in connective tissue in the CP muscle, but this was not consistent across all muscle groups. Furthermore, and somewhat surprising, the authors found that connective tissue content was only related weakly to passive forces in the muscles when compared at corresponding sarcomere length.

Replacement of contractile tissue in the CP muscle by fat has been shown to be prevalent, both in higher functioning and more severely affected children (53, 56). Noble et al. (57) studied 10 young adults with CP and GMFCS levels 1–3 and compared intramuscular and intermuscular fat content to a control group of typically developing young adults. They found a significant increase in intra- and intermuscular

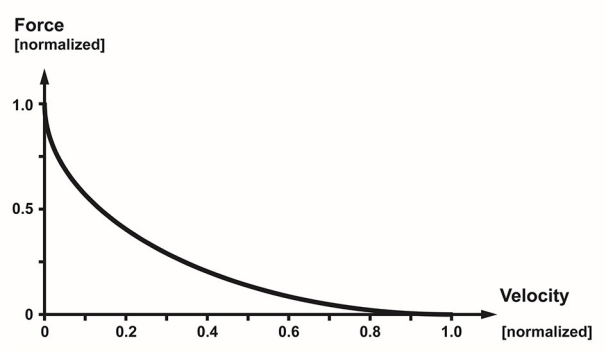

FIGURE 11 | Normalized force–velocity relationship of a skeletal muscle showing the well-known hyperbolic relationship between the maximal, steady-state force of a muscle as a function of its speed of shortening.

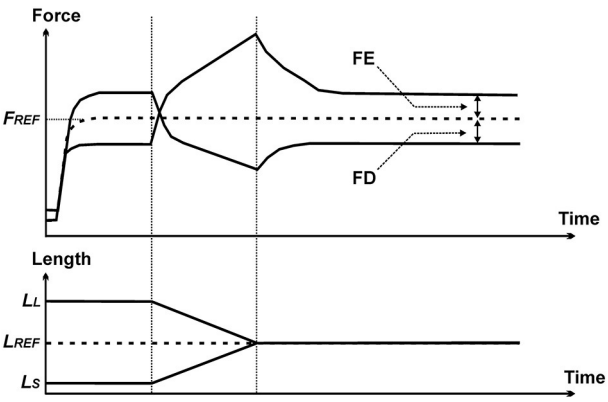

FIGURE 12 | Force–time (top panel) and length–time (bottom panel) history of the contractile properties that produce residual force enhancement (FE) and residual force depression (FD). The dashed line labeled F_{REF} represents the force obtained in an isometric reference contraction. Force enhancement represents the increase in steady-state isometric force (relative to F_{REF}) of a muscle following active stretching, and force depression is the decrease in steady-state isometric force (relative to F_{REF}) following active shortening.

fat content in a variety of muscles in the patients with CP compared to control, even in the absence of recent treatments with botulinum toxin (BoNT-A), casting or surgical interventions. However, consistent longitudinal data on muscular fat invasion in patients with CP are not available. Interestingly, BoNT-A injection has been shown to significantly increase the amount of intramuscular fat, replacing atrophied contractile tissue, which may potentially compound the already compromised natural state of the CP muscle when used for the treatment of spasticity (58). This will be discussed in more detail below.

Overstretched Sarcomeres

Human myofilament lengths are 1.65 μm for myosin and 1.27 μm for actin (31), resulting in an optimal sarcomere length for maximal force capacity between 2.64 and 2.81 μm (30, 59, 60). When sarcomere length in muscles are either shorter than 2.64 μm or longer than 2.81 μm, force capacity is reduced rapidly. Lieber et al. performed a series of studies measuring the *in vivo* sarcomere length in patients with spastic cerebral palsy and found consistent sarcomere lengths within the functional range of 3.5–4.0 μm, reducing the force capacity of these muscles to about 17–48% of maximum (30, 31). Similarly, we found average sarcomere lengths of 3.6 μm in the adductor longus of children with spastic CP compared to 2.6 μm in typically developing children (15). This increase in sarcomere length would be associated with a loss of ∼55% in isometric force in the spastic adductor longus compared to control.

Interestingly, overstretched sarcomeres in children with cerebral palsy are often associated with reports of decreased fiber/fascicle lengths, thereby indicating a reduction in the number of serial sarcomeres in the fibers and myofibrils of children with cerebral palsy. A reduction in sarcomere number, in turn, is associated with a smaller excursion of the muscle and a greater absolute sarcomeric shortening speed for a given speed of muscle contraction. Both these factors would contribute to a further reduction in force generating capacity of the CP muscle (61). From a purely mechanical point of view, a reduction in serial sarcomeres, with the associated increase in sarcomere length and faster shortening speed, is likely the greatest contributor to force loss (i.e., weakness) in children with CP. Therefore, targeting interventions that might prevent the loss of serial sarcomeres in these patients would likely have the greatest effect on retaining/re-establishing the functional capacity of children with cerebral palsy.

Loss of Sarcomeric Titin

The sarcomeric protein titin has been associated with many crucial functions in skeletal muscle sarcomeres: passive force (62), myosin and sarcomere stabilization (63), residual force enhancement (43, 64), passive force enhancement (46, 65), reduced energetic cost for muscle contraction (35, 66), and force transmission (67). There has been speculation that titin isoforms might be altered in children with CP, thus possibly contributing to the increased passive forces seen in biopsy samples from spastic muscles compared to healthy control muscles. However, these speculations have not been supported by recent evidence (15, 55). Paradoxically, in contrast to the increased passive forces observed in whole muscles, fascicles, and fibers (55), we found that passive forces in single, isolated myofibril preparations were reduced by 50% compared to control in adductor longus from children with CP undergoing hip adductor release surgery (15). This decrease in passive force was not associated, as we had initially speculated, with a change in the titin isoform, but was associated with a 50% decrease in the amount of titin in sarcomeres of the spastic muscle. Instead of the normal six titin molecules per half myosin filament (6:1 ratio), we found that, in these biopsies, the ratio of titin to half myosin was in the vicinity of 3:1. It has been shown previously that a decrease in the amount of titin per myosin is directly, and proportionally, associated with a corresponding decrease in active force (68). Therefore, we assume that the loss of titin in the spastic muscle of

children with cerebral palsy is also associated with a loss of active force production, but this requires further investigation.

SATELLITE CELLS AND EPIGENETIC ABNORMALITIES

Satellite Cells Are Reduced

In addition to the mechanical/structural aspects detailed above, disordered muscle growth and regeneration may be causative factors associated with the decreased muscle volumes seen in children with CP. Normal growth and healthy regeneration of muscle requires satellite cells, progenitor cells responsible for the production of myocytes, and thus contractile muscle tissue (69). Even though muscle size and fascicle lengths are often found to be smaller in CP compared to the muscle from TDC, from a functional point of view, the reduced number of serial sarcomeres in fibers and myofibrils is likely of primary importance.

Unfortunately, serial sarcomere adaptation and longitudinal muscle growth are much less studied and understood than parallel sarcomere adaptation and circumferential muscle growth. It is well accepted, however, that muscle stretching (70), increased muscle excursion (71), and long-term muscle length changes (72–75) are potent stimulators for sarcomerogenesis (i.e., serial sarcomere adaptation) in healthy skeletal muscle. However, even aggressive muscle stretching through physiotherapy and joint fixation has not been shown to promote normal longitudinal growth and sarcomerogenesis in the CP muscle, suggesting an intrinsic reason for the lack of response to mechanical stimuli.

One such reason may be related to satellite cell function. Lieber et al. found that CP muscles have a reduced number of satellite cells and, given their known role in myofiber development, suggested that this reduction might be causative for decreased longitudinal muscle growth (13, 76, 77). However, there is no direct evidence that the reduced number of satellite cells is the cause of the inhibited sarcomerogenesis or merely a by-product. Similarly, it is not known if the reduction in satellite cells is specific to the CP muscle or if muscles not directly affected by the brain lesion (i.e., non-spastic) also have a reduced number of satellite cells (personal communication with R. Lieber, August 2019). If satellite cells were also reduced in nonspastic muscles, then likely they would not be the reason for impaired growth of spastic muscles. If, however, nonspastic muscles in children with cerebral palsy had a normal satellite cell concentration, then it would be strong evidence for a direct and local involvement of the satellite cells in the inhibition of muscle growth. This knowledge could then be used as a primary target strategy for local intervention with the aim to promote normal sarcomerogenesis in spastic muscles of children with cerebral palsy.

Epigenetics: The Role of DNA Methylation

DNA methylation, whereby gene expression is modulated through the addition or subtraction of methyl groups, has become an area of increasing interest in CP, particularly with respect to impaired muscle growth and sarcomerogenesis (78). It has been hypothesized that epigenetic mechanisms, most notably DNA methylation, play a significant role in regulating the response of skeletal muscle in CP, determining the initiation, and/or severity, of contracture (79). Tissues with high metabolic demand and need for increased synthesis, such as skeletal muscle, typically have hypomethylated DNA translating to increased DNA transcription and vice versa (17, 80). These epigenetic changes have been further hypothesized to be imprinted at the time of the inciting insult in CP (11, 16). The literature supporting this theory is emerging but still indeterminate.

In an interesting study from Sweden, CP muscle samples from the biceps brachii determined that DNA methylation of the ribosomal DNA (rDNA) promotor responsible for ribosome biosynthesis—a function crucially important for muscle growth—was increased in more severely affected children (by GMFCS) and with more severe contractures (17). The study, however, did not find a difference in rDNA promotor methylation between CP and TDC subjects.

In another comparative study investigating the role of DNA methylation in the erector spinae muscles of CP and TDC children undergoing scoliosis surgery, significant differences in methylation patterns were found, suggesting an influence of this mechanism in skeletal muscle pathology in CP (81). Using machine learning techniques, this same research group demonstrated significantly different DNA methylation patterns in peripheral blood, reliably detecting CP from non-CP (16).

Investigating the impact of epigenetic changes on satellite cell-derived myoblasts in CP vs. TDC hamstring muscles, Domenighetti et al. (76) showed that, in addition to having a decreased capacity to form and fuse myotubes, the signaling pathway responsible for regulating myotube formation was correspondingly downregulated in children with CP. Accordingly, the promotor region of this pathway (integrin-β 1D) was found to be hypermethylated, with improved myotube formation following application of a demethylating agent. The authors proposed that DNA hypermethylation of myoblast gene promotor regions were responsible for the decreased myofiber formation (and thus muscle growth) observed in the CP muscle. They also suggested that this "epigenetic memory" has likely been imprinted very early in development, preceding the development of muscle contracture.

Although in the early stages of investigation, the role of epigenetics in CP muscle development seems to have merit, this may provide an explanation, or at least part of, as to why growth is compromised in this population.

PATHOPHYSIOLOGY OF SPASTIC MUSCLE CONTRACTURE TREATMENT

Botulinum Toxin and Skeletal Muscle Adaptations

BoNT-A is a frequently used treatment modality aimed at reducing spasticity in children with cerebral palsy, with early basic science research purporting increased muscle growth (i.e., decreased muscle contracture) following intramuscular injection in a spastic mouse model (82, 83). The clinical effects of this treatment have been extensively described (84). However,

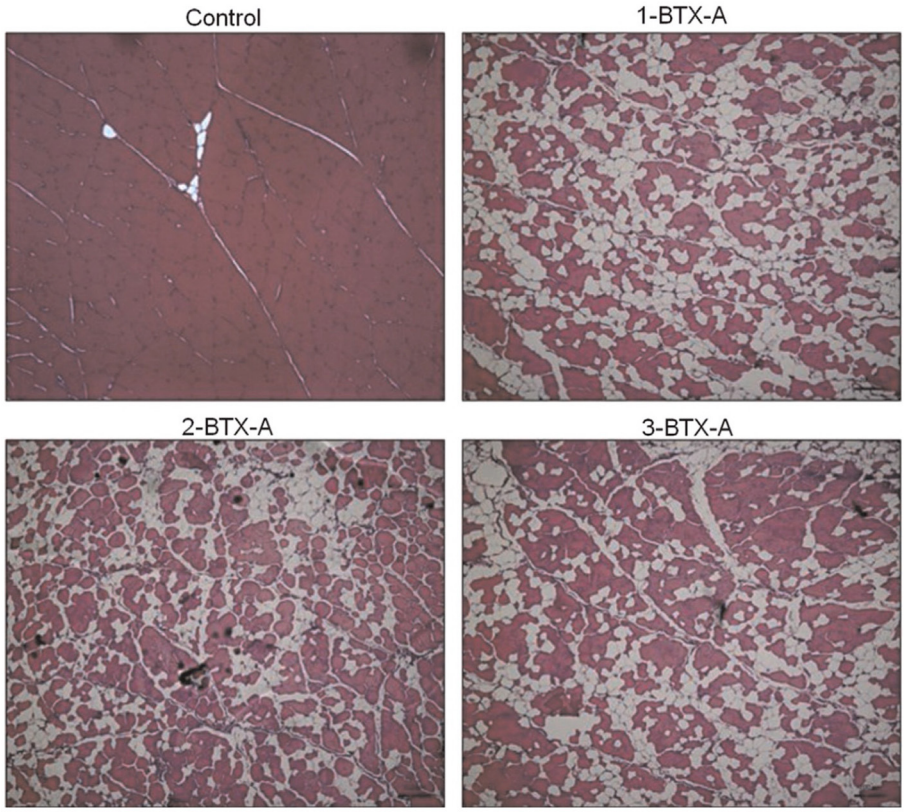

FIGURE 13 | Exemplar histology slides of muscles injected with Botulinum toxin type-A (BoNT-A). Control tissue that was injected with a corresponding volume of saline (Control), muscle receiving one BTXA injection evaluated 6 months following injection (1-BTX-A), muscle receiving two BTXA injections separated by 3 months and evaluated 6 months post the second injection (2-BTX-A), and muscle injected three times with BTXA, separated by 3 months and evaluated 6 months following the third and last injection. The red staining shows the contractile material of the muscle. The white, thin lines (especially visible in the Control slide) are representative of the collagen matrix structure, and the white extended areas (especially visible in the BoNT-A injected muscles) represent intramuscular fat. The average percentage of contractile tissue in these muscles were 96.9 ± 2.0% (Control), 59.2 ± 6.0% (1-BTX-A), 62.5 ± 6.1% (2-BTX-A), and 59.9 ± 11.8% (3-BTX-A), respectively.

relatively less attention has been paid to the short- and long-term effects of BoNT-A into the injected, target muscles and the potential side effects in noninjected, nontarget muscles. In a series of animal studies, we found that BoNT-A injections caused dramatic reductions in target muscle size and strength and were associated with greater intramuscular fat infiltration (85). Muscle strength was also reduced in adjacent, nontarget muscles, as was muscle size, strength, and substantial fibrosis in contralateral, noninjected muscles (52). Furthermore, a single, clinically relevant amount of BoNT-A injection has been shown to reduce muscle size in humans for up to a year (86) and produce a 50% decrease in strength and a decrease in contractile material with a corresponding amount of fat infiltration in rabbit knee extensor muscles after a 6 months recovery period (**Figure 13**) (57, 87). In addition, mRNA expression levels for the matrix molecules (responsible for fibrosis) collagens I and III, the anabolic growth factors insulin-like growth factor-1 (IGF-1) and transforming growth factor beta (TGFß), and muscle-specific atrophy marker MuRF1 were significantly elevated in the BoNT-A-injected animals compared to values in control group rabbits (57).

Human histological studies investigating the impact of BoNT-A on the CP skeletal muscle morphology are sparse at present, but two imaging studies deserve mention. In a study of 15 children with spastic diplegic CP receiving BoNT-A injections into the gastrocnemius, Williams et al. (88) used magnetic resonance (MR) imaging to measure calf muscle volumes 2 weeks before and 5 weeks after injection. In addition to a 5% decrease in gastrocnemius volume post-injection, they identified a concomitant 4% increase in soleus volume and suggested that this adjacent muscle hypertrophy may be compensatory. Another study by Schless et al. (89), applying ultrasound to the medial gastrocnemius, demonstrated decreased volume and increased connective tissue in children with CP compared to TDC, effects that were further exacerbated post BoNT-A injection.

In summary, BoNT-A injections in preclinical animal models have been shown to produce substantial and long-lasting muscle atrophy, muscle weakness, fat infiltration, fibrosis, inflammation, and degenerative molecular profiles that occur not only in target muscles but also in muscles close to the target injection site (within hours) and far removed from the injection site. More

human, preferably histological, studies are needed to confirm these effects in the CP muscle.

Surgical Management of Muscle Contracture

Surgical lengthening of muscle contractures is a long standing and widely accepted means to improve both muscle length and function in children with CP (90). Despite this history, there are few studies that specifically look at the effects of surgery on sarcomere length or function. On a more macroscopic scale, Shortland et al. (91) observed a post-operative reduction in both fascicle length and pennation angle in the medial gastrocnemius of children with spastic diplegic CP using ultrasound.

Also using ultrasound following postsurgical lengthening of semitendinosus (by tendon Z-plasty), Haberfehlner et al. (92) observed a 30% decrease in muscle belly length and an 80% increase in tendon length, implying a shortening of fascicles with a concomitant reduction in sarcomeres in series, despite improvements in knee joint kinematics. As discussed in previous sections, this would lead to a relative increase in sarcomere shortening during contraction and less ability to generate force. The authors suggested utilizing surgical strategies that maintained muscle belly length and cross-sectional area to help improve treatment outcomes.

Clearly, there is room for more studies investigating the role of surgery in CP muscle function, in particular with respect to its effects on the sarcomere.

Other Treatments

The literature investigating muscle histopathology in CP after nonoperative treatments such as serial casting and physical therapy (PT) is currently sparse. Serial casting is a commonly used modality for the treatment of static muscle contracture in CP, based in early animal work that showed increased sarcomere addition following chronic stretch (93). In further animal work investigating soleus during stretch immobilization, sarcomere addition was not impaired in a satellite cell-depleted mouse model, despite demonstrating decreased muscle cross-sectional area (CSA) and increased extracellular matrix (ECM) connective tissue (94). The authors suggested that, although satellite cells likely play a role in the maintenance of the ECM and muscle volume, impaired sarcomerogenesis was not affected by the loss of these cells. Extrapolating these results to the use of serial casting in CP, it would seem that the increased length achieved is secondary to tendon length increases, rather than by sarcomere addition, and may be at the expense of muscle atrophy and ECM increase (95).

Ankle foot orthoses (AFOs) are commonly used in CP and other neuromuscular disorders, especially at night, to impose a chronic stretch to the gastrocnemius with the goal to improve muscle length and/or prevent static contracture. In the only clinical study investigating the impact of AFOs in CP, Hösl, and colleagues demonstrated decreases in fascicle length—which they suggested to be caused by reduced sarcomere addition—and little change in belly or tendon length (96).

The impact of PT, specifically passive stretching, on changes in CP muscle morphology at the fiber and myofibrillar levels is lacking at this point (97).

CONCLUSIONS

Although research into the pathophysiology of the CP muscle is increasing, there are still many unanswered questions, particularly with respect to the development of fixed muscle contractures, reduced muscle growth, and weakness. The evidence to date, both from human and animal studies, would suggest that there are many factors at play, including satellite cell dysfunction, decreased myotube formation, increased fibrofatty tissue replacement, and overlong sarcomeres with reduced titin, possibly regulated by epigenetic instructions imprinted at the time of brain insult. Therapeutic measures, including BoNT-A and surgical lengthening, may serve to exacerbate muscle weakness in CP, with a dose-dependent effect. Additional studies investigating other treatments for spasticity reduction (e.g., selective dorsal rhizotomy), as well as properties of CP muscle with motor types other than spastic, are required to help complete the picture. Consideration of what is currently known about CP muscle pathophysiology by the treating clinician is important to help determine the most appropriate interventions for these children.

AUTHOR CONTRIBUTIONS

JH developed the initial review outline and wrote the clinically-based sections of the manuscript and also reviewed, edited, and formatted the final manuscript. WH revised the review outline and wrote the basic science-based sections of the manuscript and also reviewed, edited, and formatted the final manuscript. Both authors contributed to the article and approved the submitted version.

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Muscle Characteristics in Pediatric Hereditary Spastic Paraplegia vs. Bilateral Spastic Cerebral Palsy: An Exploratory Study

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Hereditary spastic paraplegia (HSP) is a neurological, genetic disorder that predominantly presents with lower limb spasticity and muscle weakness. Pediatric pure HSP types with infancy or childhood symptom onset resemble in clinical presentation to children with bilateral spastic cerebral palsy (SCP). Hence, treatment approaches in these patient groups are analogous. Altered muscle characteristics, including reduced medial gastrocnemius (MG) muscle growth and hyperreflexia have been quantified in children with SCP, using 3D-freehand ultrasound (3DfUS) and instrumented assessments of hyperreflexia, respectively. However, these muscle data have not yet been studied in children with HSP. Therefore, we aimed to explore these MG muscle characteristics in HSP and to test the hypothesis that these data differ from those of children with SCP and typically developing (TD) children. A total of 41 children were retrospectively enrolled including (1) nine children with HSP (ages of 9–17 years with gross motor function levels I and II), (2) 17 age-and severity-matched SCP children, and (3) 15 age-matched typically developing children (TD). Clinically, children with HSP showed significantly increased presence and severity of ankle clonus compared with SCP ($p = 0.009$). Compared with TD, both HSP and SCP had significantly smaller MG muscle volume normalized to body mass ($p \leq 0.001$). Hyperreflexia did not significantly differ between the HSP and SCP group. In addition to the observed pathological muscle activity for both the low-velocity and the change in high-velocity and low-velocity stretches in the two groups, children with HSP tended to present higher muscle activity in response to increased stretch velocity compared with those with SCP. This exploratory study is the first to reveal MG muscle volume deficits in children with HSP. Moreover, high-velocity-dependent hyperreflexia and ankle clonus is observed in children with HSP. Instrumented impairment assessments suggested similar altered MG muscle characteristics in pure HSP type with pediatric onset compared to bilateral SCP. This finding needs to be confirmed in larger sample sizes. Hence, the study results might indicate analogous treatment approaches in these two patient groups.

Keywords: hereditary spastic paraplegia, cerebral palsy, instrumented impairment assessments, ultrasound, muscle morphology, muscle volume, hyperreflexia, spasticity

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INTRODUCTION

Hereditary spastic paraplegia (HSP) is described as a genetic, heterogeneous disorder leading to axonal degeneration of the spinal pathways and mostly classified in either pure or complex (i.e., additional symptoms rather than pyramidal signs) types (1, 2). In children with the pure HSP type presenting symptoms already from infancy or childhood, bilateral spasticity and muscle weakness in the lower limbs contribute to gait deviations (3, 4). This predominant clinical picture is similarly observed in children with bilateral spastic cerebral palsy (SCP) (2, 4). Hence, the symptomatic treatment management in HSP is often analogous to the common treatment in SCP. Conservative treatment includes orthotic management and regular physiotherapy, which incorporates strengthening, stretching, and gait rehabilitation. This approach is commonly combined with spasticity management [i.e., oral medication, intrathecal baclofen therapy, and/or intramuscular botulinum neurotoxin (BTX) injections; (5–7)].

Caused by upper motor neuron lesions in the developing brain, children with SCP present with neuromotor symptoms already within the first 2 years of life. Therefore, these children have an atypical development resulting in altered muscle function and pathological gait (5). In the last decade, there has been growing research interest in the muscle morphology of children with SCP, with studies showing evidence for decreased muscle volume (MV) and muscle belly length of the medial gastrocnemius (MG) muscle in comparison with typically developing (TD) children (8). The calf muscle is most often selected as a target muscle because of its pathological involvement in the clinical presentation and consequently functional importance (9). Muscle morphology is considered related to muscle function in the sense that decreased MV has been indicated as one of the major contributors to muscle weakness (10, 11). Moreover, altered MG muscle morphology combined with the manifestation of lower limb spasticity has been observed already from early ages (12, 13).

Muscle imaging using 3D-freehand ultrasound (3DfUS) is a reliable and valid method to determine macroscopic alterations of muscle morphology in children with SCP (14–16). In addition, instrumented assessment of hyperreflexia provides reliable, objective parameters to evaluate the stretch of hyperreflexia by combining surface electromyography (sEMG) signals with joint motion analysis during manually applied muscle stretches at low and high velocity (17, 18). This quantitative approach enables the assessment of the neural component of muscle hyper-resistance, which is further indicated as hyperreflexia (19). Moreover, using such instrumentation, different muscle activation patterns in reaction to increased stretch velocity have been reported (20). Treatment response may differ between these phenotypes, highlighting the importance to use instrumented impairment assessment for treatment guidance (21, 22).

In more than half of the children who are clinically suspected of having HSP, the genetic diagnosis is not confirmed by means of whole exome sequencing or HSP gene panels (23). The latter considers the pathogenic mutations in the spastic paraplegia genes (SPG) known to date (24). Moreover, since the clinical picture is often suggestive of SCP, other markers for a good differential diagnosis are a priority (2). Previous research has already pointed out possible indications for the HSP condition based on the gait deviations, whereby these results could contribute to the diagnostic process of children with HSP (25, 26). In the same sense, an objective and quantitative investigation of both hyperreflexia and potential alterations in muscle morphology in children with HSP might help to differentiate them from SCP.

Whereas, the clinical presentation indicates an overlap in children with HSP and SCP, it is unclear if similarities are also presented in terms of muscle characteristics. These insights might help to distinguish HSP and SCP and, thus, potentially provide markers for more accurate diagnosis, which may support the treatment management in the HSP population and optimize treatment plans toward delineated patient-specific approaches. However, to date, muscle characteristics in children with HSP have not yet been studied.

Therefore, the first aim of this retrospective study is to explore the MG muscle characteristics in children with HSP using instrumented impairment assessments. Second, we tested the hypothesis that the muscle morphology and hyperreflexia in children with HSP differ from those of children with SCP.

MATERIALS AND METHODS

Participants

This study retrospectively selected 41 participants who were recruited via the Clinical Motion Analysis Laboratory in collaboration with the pediatric–orthopedic department of the University Hospitals Leuven. Children underwent one or more assessments including clinical examination, 3DfUS and instrumented assessment of hyperreflexia. Written informed consent was signed by all parents of the children. The study assessments were performed as part of different ongoing research projects and were approved by the Ethical Committee of the University Hospitals Leuven and KU Leuven (S56977 and S59945).

In the previous described research projects, children with a genetically confirmed diagnosis of HSP were eligible for inclusion. In the absence of a genetic diagnosis after performing extensive genetic workup, a clinical HSP diagnosis was made by qualified professionals based on (a) neurological findings, such as spasticity and weakness in the plantar flexor muscles, (b) the age of onset, and if available, (c) a positive family history of gait disturbances, and (d) normal neuro-imaging, electromyography measures, and metabolic investigations [**Supplementary Table 1**; (1, 2, 27)]. The latter is performed to ensure the exclusion of other disorders (2, 28). As a result, from the population of children with HSP who received regular clinical follow-up between May 2017 and July 2020 at the University Hospitals Leuven, 17 patients were assessed as part of ongoing research projects (S56977 and S59945).

For this retrospective study, the following inclusion criteria for children with either clinically or genetically confirmed HSP were applied: (a) aged between 8 and 17 years; (b) level I or II on the gross motor function classification system (GMFCS);

(c) uncomplicated or pure type of HSP; (d) no BTX injections in the previous 6 months; (e) no orthopedic surgery in the previous 2 years; (f) no history of soft-tissue musculoskeletal- or neurosurgery (e.g., selective dorsal rhizotomy), and (g) no intrathecal baclofen pump. This resulted in a group of nine children with HSP, including six boys and three girls. Mutations in SP-designated genes were confirmed in four patients (two children with SPG3A, one with SPG4, and one with SPG56). For the other five participants, genetic analysis could not indicate mutations in the SP-designated genes. The flowchart of the HSP patient selection and inclusion process is presented in **Figure 1**.

Based on the age, GMFCS levels and gender of this HSP group, a cohort of children with bilateral SCP were group matched. These children were selected from a retrospective database (S59945) that was established during an ongoing research project on muscle characteristics in children with SCP. To aim for a maximum number of children that were eligible from the retrospective database, group matching was performed per available assessment. As a result, 15 children with SCP were included with 3DfUS data, and nine children with SCP were included with hyperreflexia data. Seven children with SCP were measured for both assessments. **Supplementary Figure 1** gives a schematic overview of the study samples per assessment. To confirm the diagnosis of bilateral SCP, these children showed abnormal neuro-imaging and the clinical presentation of plantar flexor muscle spasticity.

The muscle morphology of these two patient groups was compared with a reference group of 15 TD children, which was retrospectively included based on the available 3DfUS data in the Clinical Motion Analysis Laboratory database (S59945). This cohort was group matched following the age and gender of the HSP group. No reference of instrumently assessed hyperreflexia data were used for the TD group, since the muscle activation during passive muscle stretches in TD children is negligible (17).

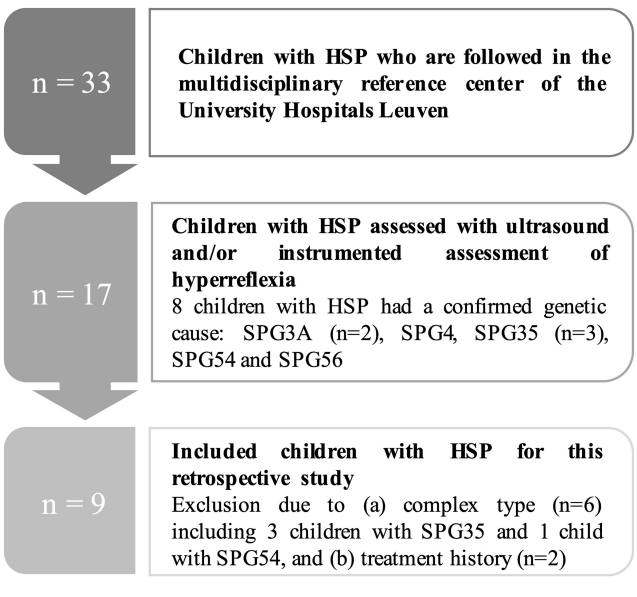

FIGURE 1 | Flowchart of the patient selection process for the children with hereditary spastic paraplegia (HSP). *N*, number.

Data Collection and Processing

Assessments were carried out by the different experienced examiners who were involved in the research projects, whereas all data processing was performed by the same experienced researcher (ND). As defined by the clinical examination, the most affected leg was measured in the children with HSP and SCP, whereas a random leg was selected in the TD children. Anthropometric data including body mass, body length, and leg lengths were measured. The latter was measured from the lower border of the anterior superior iliac spine to the lower border of the medial malleolus.

Clinical Assessments

Clinical examination was performed including the passive range of motion to maximal ankle dorsiflexion (ROM), plantarflexor spasticity assessed with the Modified Ashworth Scale (MAS) and Modified Tardieu Angle (MTA), and plantarflexor strength using the Medical Research Council grade scale (29–31). ROM, MAS, and MTA were measured with the knee extended. The presence and severity of the clonus was clinically graded based on how quickly a rhythmic, oscillating reflex appears, and disappears while stretching the ankle towards the dorsiflexion position. The clonus grading is as follows: 0, no clonus; 1, clonus after multiple stretches; 2, quick clonus, quick stop; 3, quick clonus, slow stop, and 4, quick clonus, no stop. Clinical scores including the Functional Mobility Scale (FMS), walking ability, self-selected gait speed, presence of pain during gait, and bladder and bowel function were retained from the clinical assessments, which were performed at the time of or within 1 year of the study assessment, as part of the routine clinical follow-up. The FMS describes the functional mobility by scoring the walking ability over three distances (i.e., 5–50–500 m) on a six-point scale for which lower scores indicate more need for assistance (32).

3D-Freehand Ultrasound

To aim for a comfortable and resting joint position, the children were positioned in prone with a triangular cushion placed under the lower leg whereby the ankle was placed over the edge of this cushion. This resting position provided ∼25° of knee flexion and 30° of plantar flexion. Muscle morphology was assessed using 3DfUS, combining a 2D ultrasound system and motion-tracking system of three fixed optical cameras, with the same instrumentation settings as described by Schless et al. (33). US images of the MG muscle were acquired in a transverse orientation, starting from the medial femoral condyle to the distal end of the calcaneus. Both data collection and processing were completed using STRADWIN software (version 6.0; Mechanical Engineering, Cambridge University, Cambridge, UK). The following processing guidelines to assign landmarks in the transverse plane were applied: (a) MG muscle origin was defined as the most superficial part of the medial femoral condyle, (b) the muscle–tendon junction (MTJ) was defined as the first image after the last image with visible muscle belly mass,

and (c) the first image of the calcaneus bone was defined as the tendon insertion. Data processing started with segmenting the created 3D-reconstruction by manually outlining the cross-sectional areas along the inside of the muscle borders starting from the defined origin to the last image before the MTJ. A linear interpolation between the outlined borders was applied to compute the MV (in ml). In addition, MV was normalized to body mass (ml/kg). Muscle belly lengths (ML) were defined from the origin to the MTJ, and the tendon lengths (TL) were defined from the MTJ to the tendon insertion. The distance between the muscle origin and insertion was specified as the muscle–tendon unit complex length (MTUL). The same assessor assigned the landmarks twice, and the average of the length scores was calculated. ML, TL, and MTUL data were reported in millimeter (mm). Both ML and MTU L were normalized for leg length (i.e., nML and nMTUL) and therefore expressed as percentages.

Instrumented Assessment of Hyperreflexia

A previously described measurement protocol was applied in which muscle activation and joint motion analysis data were simultaneously collected during manually applied ankle rotations to stretch the MG muscle at low (LV) and high (HV) velocity (17). Muscle activity was registered using sEMG data (Zerowire, Cometa, Milan, IT) whereby circular Ag/Ag Cl electrodes (diameter 2 cm) were attached on the MG and tibialis anterior muscle bellies following the SENIAM guidelines (34). Inertial measurement units were placed on the shank and foot to analyze the ankle joint motions. Participants were assessed in supine position on an examination table, while the lower leg rested on a support to avoid contact of the MG muscle sEMG sensors with the table. The foot was fixated in a custom-made orthotic with an attached force sensor. Data of the latter were not reported in the current study. While holding on the force sensor with the shank in a fixed position, the examiner manually rotated the ankle from maximal plantarflexion to maximal dorsiflexion position. Four passive rotations over the full ankle ROM were performed at LV (i.e., in 5 s) and then four rotations were repeated at HV (i.e., performed as fast as possible). During each velocity trial, the participants were asked to remain relaxed, and a rest period of 7 s between the four repetitions was taken to minimize post-activation depression.

Offline data processing was performed using a custom-made Matlab software (Mathworks, R2017b). Data quality checks for velocity consistency and quality of the EMG signals were performed as described by Bar-On et al. (17). ROM and the maximum angular velocity (V_{max}) were calculated and averaged over the repetitions per velocity trial. Hyperreflexia parameters were based on the registered MG muscle activity whereby first, the raw sEMG data were filtered, and second, root-mean square (RMS)-EMG (μV) was calculated, as previously described for both steps (17). Hyperreflexia was defined as the average RMS-EMG over the duration of the maximal velocity zone. This time zone was restricted to 200 ms prior to Vmax up to 90% of the full ROM. In addition, this hyperreflexia parameter was normalized to the peak RMS-EMG value of the obtained maximum voluntary isometric contractions (MVIC) and expressed as percentage. Both non-normalized and normalized hyperreflexia parameters were averaged over the stretch repetitions for the LV trial as well as for the change between the high and low velocity trials (change HV–LV). The latter is important to investigate the velocity-dependent nature of muscle hyperreflexia. In addition, visualization of normalized sEMG data across the LV and HV stretches over the ROM were used to classify responses according to previously described muscle activation patterns (i.e., velocity- or length-dependent pattern). More details on the definition of hyperreflexia parameters and muscle activation patterns can be found in earlier publications (17, 20).

Statistical Analysis

Statistical analyses were performed using SPSS (IBM SPPS Statistics version 27), and graphs were designed in GraphPad Prism 9 and Matlab software. Normality of the data was both visually checked and tested with the Shapiro–Wilk test. Due to the small sample size and non-normally distributed data, descriptive statistics included median and interquartile ranges and non-parametric test were applied. Independent-sample Kruskal–Wallis test was carried out to explore differences in mean ranks of age, anthropometric data, and muscle morphology between the three groups. Group differences were tested with *post-hoc* Mann–Whitney *U* (MWU) test. Bonferroni adjustment for multiple testing was applied after these *post-hoc* MWU analyses ($p < 0.017$). Comparisons of the clinical examination data, performance, and hyperreflexia parameters between the HSP and SCP groups were performed with MWU analyses, whereby the level of significance was set at $p < 0.05$.

RESULTS

Participant characteristics and anthropometric data of the nine children in the HSP group were compared to (a) data of 15 participants in the SCP group and 15 participants of the TD group defined by 3DfUS, and (b) data of nine participants in the SCP group, defined by instrumented assessment of hyperreflexia (**Table 1**). No differences were found between the groups for age, body mass, body length, and leg length. Results of the clinical examination for ankle ROM, spasticity, and muscle strength did not differ significantly between the HSP group ($n = 8$, missing data for one child) and all children with SCP ($n = 17$) (**Table 2**). For the HSP group ($n = 8$), only one child had low MAS-scores (MAS 1+) and seven children had high MAS-scores (four MAS of 2; three MAS of 3), whereas in the SCP group ($n = 17$), 10 children had low MAS-scores (two MAS 1 and eight MAS 1+) and seven children had high MAS-scores (two MAS 2; five MAS 3). The ankle clonus scores differed significantly between the HSP and the total SCP group ($p < 0.009$). Specifically, only one child with HSP did not present a clonus, whereas the majority of children with SCP (i.e., 11 out of 17) had no clonus. All children in the HSP and SCP groups had regular physiotherapy with a median of 120 min per week and 100 min per week, respectively. One third of the HSP children frequently used day orthoses, whereas 10 out of the 17 children with SCP used orthoses during the day. For both groups, more than 50% of the children were never administered with BTX injections (**Supplementary Table 2**). The HSP and SCP cohort presented

TABLE 1 | Participant characteristics and anthropometric data in the HSP, SCP, and TD group.

	HSP*† ($n = 9$)	SCP* ($n = 15$)	SCP† ($n = 9$)	TD* ($n = 15$)	p*	p†
Age (y)	12.9 (5.5)	11.3 (5.8)	11.2 (5.9)	13.8 (5.6)	0.935	0.340
GMFCS level (n)	I = 4, II = 5	I = 7, II = 8	I = 4, II = 5	NA		
Gender (G/B)	3/6	6/9	3/6	6/9		
Body mass (kg)	47.0 (18.6)	44.5 (27.5)	38.5 (2.6)	50.4 (25.3)	0.652	0.136
Body length (cm)	159.5 (27.6)	149.0 (25.6)	146.6 (27.6)	164.5 (32.4)	0.491	0.387
Leg length (cm)	83.5 (12.7)	75.7 (16.4)	75.5 (16.3)	86.2 (18.2)	0.201	0.436

*Data are shown as median (interquartile range). * and † indicated the different group comparisons. HSP, hereditary spastic paraplegia; SCP, spastic cerebral palsy; TD, typically developing; n, number; y, years; GMFCS, gross motor function classification system; NA, not applicable; G, girl; B, boy.*

TABLE 2 | Median (minimum and maximum values) of all clinical examination results in the HSP and SCP group.

	HSP ($n = 8$)	SCP ($n = 17$)	HSP-SCP, p
ROM (°)	5 (−5; 10)	5 (−5; 15)	1.00
MAS	2 (1.5; 3)	1.5 (1; 3)	0.140
MTA (°)	−13 (−30; 5)	−10 (−30; 0)	0.636
MRC	4 (3; 4)	3 (2; 5)	0.549
Clonus	2 (0; 4)	0 (0; 2)	0.009

Missing data of one child in the HSP group. HSP, hereditary spastic paraplegia; SCP, spastic cerebral palsy; n, number; ROM, range of motion to maximal ankle dorsiflexion; MAS, Modified Ashworth Scale; MTA, Modified Tardieu Angle; MRC, Medical Research Council.

with median FMS scores of 6-6-5 and 6-5-5, respectively. More than half of the children in both groups were able to walk for more than 3,000 m, whereas the self-selected walking speed was slightly or even moderately reduced. Especially in the SCP group, 12 children out of 17 presented with a walking speed of more than 10 s over a 10-m distance. Pain during gait was reported by only two and three children in the HSP and SCP groups, respectively (**Supplementary Table 3**).

Compared with the TD reference group, both children with HSP and SCP differed significantly in the MG muscle volume normalized to the body mass ($p \leq 0.001$) with the greatest deficits in the SCP group, namely, 32%. *Post-hoc* MWU test revealed only a significantly smaller absolute MV in the children with SCP compared with TD children ($p = 0.004$; **Supplementary Figure 2**). Muscle lengths were not significantly different between the three groups, although normalized muscle belly lengths (i.e., ML/MTUL and nML) tended to be lower in both patient groups compared with the TD group, with more alterations in the SCP group (**Table 3**).

Ankle joint rotations during HV stretch were performed over a median ROM of 50.7° (15.1) and 52.8° (18.4) with median maximal velocity of 81.1°/s (88.4) and 122.9°/s (45.6) in the HSP and SCP groups, respectively. The between-group differences in ankle joint rotations were not significant. Both non-normalized and normalized hyperreflexia parameters for LV and for the change between HV and LV were not significantly different between the HSP and SCP groups (**Table 4**). Higher hyperreflexia values, especially for change in HV–LV, tended to be present in the HSP group, compared with the SCP group. Eight children with HSP were categorized in a pure high-velocity-dependent pattern, whereas this pattern was observed in only six children with SCP. Additionally, muscle activity in one child of the HSP and three children of the SCP group was categorized as mixed high-velocity-dependent activation pattern. **Figure 2** shows an example joint motion and muscle activation data during the instrumented assessment of hyperreflexia in a child with HSP and age-matched child with bilateral SCP.

DISCUSSION

The purpose of this exploratory study was to investigate whether the MG exhibits muscle-related differences in two patient groups who are known to present with similar clinical impairments, despite their different etiology. To date, HSP is unexplored in terms of muscle morphology and instrumented assessment of hyperreflexia. In this study, only children presenting the pure or uncomplicated HSP type (i.e., solely pyramidal signs) with a pediatric onset were retrospectively included. This restriction minimized the possibility of a progressive disease course as seen in complicated and late onset HSP types (35). In the HSP group of this study, the mean age of symptom onset was 2.7 years, ranging from 2 months to 9 years old (**Supplementary Table 1**). The confirmed gene mutations in three of the four patients are described as the most common cause of autosomal dominant HSP. The mutations in these SPG3A and SPG4 cases and their HSP-associated proteins atlastin-1 and spastin, respectively, result in dysfunctional axonal transport with consequently corticospinal motor neuron degeneration (2, 36–38). Moreover, children with SPG3A and SPG4 are known to present similarities in upper motor neuron signs that are commonly observed in children with bilateral SCP (39). In line with the current literature, the included child with the SPG56 subtype, which is described as recessive–autosomal HSP, is presenting as pure form with an early onset [i.e., at the age of 2 years; (40, 41)]. The involved gene mutation results in altered mitochondrial architecture and function (42). To further ensure differences in etiology between the two groups, only children with SCP showing clear, abnormal neuro-imaging findings (e.g., periventricular leukomalacia) were included (43). In the current study, the results

TABLE 3 | Median (and IQR) of medial gastrocnemius muscle morphology outcomes in the HSP, SCP, and TD group.

	HSP ($n = 9$)	SCP ($n = 15$)	TD ($n = 15$)	p	HSP-SCP, p	HSP-TD, p	SCP-TD, p
MV (ml)	80.0 (51.7)	73.0 (29.1)	127.3 (60.4)	0.017	1.00	0.084	0.004
nMV (ml/kg)	1.8 (0.4)	1.7 (0.7)	2.6 (0.4)	0.001	1.00	0.001	0.001
ML (mm)	199.6 (36.7)	185.3 (30.1)	213.5 (51.5)	0.078			
TL (mm)	170.2 (49.2)	173.1 (39.3)	169.8 (39.7)	0.978			
MTUL (mm)	390.2 (73.4)	363.8 (51.4)	388.3 (87.7)	0.237			
ML/MTUL (%)	54.0 (1.0)	53.0 (4.0)	57 (1.0)	0.141			
nML (%)	24.7 (3.9)	24.4 (2.5)	26.1 (4.2)	0.101			
nMTUL (%)	45.9 (2.5)	45.9 (3.0)	46.4 (1.2)	0.683			

HSP, hereditary spastic paraplegia; SCP, spastic cerebral palsy; TD, typically developing; n, number; MV, muscle volume; nMV, muscle volume normalized to body mass; ML, muscle belly length; TL, tendon length; MTUL, muscle-tendon unit complex length; nML, ML normalized to leg length; nMTUL, MTUL normalized to leg length.

TABLE 4 | Median (and IQR) of performance- and hyperreflexia-parameters in the HSP and SCP group.

	HSP ($n = 9$)	SCP ($n = 9$)	HSP-SCP, p
ROM, LV (°)	50.7 (15.1)	52.8 (18.4)	0.796
ROM, HV (°)	49.6 (12.4)	52.0 (22.4)	1.00
$V_{max,}$ LV (°/s)	17.4 (7.6)	20.5 (12.3)	0.666
$V_{max,}$ HV (°/s)	81.1 (88.4)	122.9 (45.6)	0.387
MVIC (mV)	0.2 (0.1)	0.2 (0.2)	0.666
RMS-EMG, LV (μV)	1.0 (0.9)	1.1 (2.1)	0.546
Norm. RMS-EMG, LV (%)	1.0 (1.0)	0.5 (2.3)	0.340
RMS-EMG, HV-LV (μV)	9.1 (9.6)	4.5 (7.2)	0.113
Norm. RMS-EMG, HV-LV (%)	7.9 (9.6)	3.7 (7.3)	0.222

HSP, hereditary spastic paraplegia; SCP, spastic cerebral palsy; n, number; ROM, range of motion; LV, low velocity; HV, high velocity; V_{max}, maximal angular velocity; MVIC, maximal voluntary isometric contraction; Norm., normalized.

of the clinical examination showed comparable levels of ankle mobility, spasticity, and muscle strength between both patient groups. However, the ankle clonus score was significantly higher in children with HSP compared with those with SCP, indicating increased presence and severity with mostly a quick clonus appearance with either slow or no stop (**Supplementary Table 4**).

Muscle Morphology

Altered MG muscle morphology in children with HSP was demonstrated by significantly smaller MV normalized to body mass of 30%, compared to TD. Furthermore, no significant differences were observed between the HSP and SCP groups, which indicate similarities in altered MG muscle morphology. Although the children in the SCP group tended to be lower in body mass and shorter in length than the children in the HSP group, normalization to this anthropometric data did not reveal significant differences in muscle volumes, nor in muscle lengths between both groups. However, a trend towards longer muscle belly lengths normalized to leg length was observed in the HSP group compared with the SCP group.

In agreement with previous research, muscle volumes in children with SCP were significantly smaller than the muscle volumes of the TD reference group (8). In the current study, average muscle volume deficits of 21% in the HSP group and 35% in the SCP group were observed when compared with the TD data. Interestingly, these differences are larger than the previously reported minimal detectable changes of 9.9% for MG muscle volumes (15). In the same sense, Noble et al. previously reported deficits of 38% in MG muscle volume for children with bilateral CP, with the same age ranges (i.e., older than 9 years) and similar levels of ambulatory ability [i.e., GMFCS levels I and II; (44)]. No significant differences were found with respect to the muscle lengths. Nonetheless, in comparison with data of the TD peers, absolute muscle belly lengths were 4 and 12% shorter in the HSP and SCP groups, respectively. These results were in line with previous research reporting 10% shorter muscle lengths in the paretic limb of children with unilateral SCP compared with data of TD children (45). However, only limited 3D ultrasound data of MG muscle lengths in children older than age 12 years have been reported so far (9). In conclusion, altered muscle volumes were observed in children with HSP and showed similarities to the muscle alterations in children with SCP.

Hyperreflexia

Hyperreflexia parameters were not significantly different between the HSP and SCP groups. Pathological muscle activity with increasing stretch velocity was observed in both patient groups, with a tendency of more hyperreflexia in the HSP group. This velocity-dependent hyperreflexia was confirmed by the results of the classification in hyperreflexia muscle activation patterns. Most of the children with HSP were classified with pure high-velocity-dependent muscle activation pattern. The amount of normalized EMG over increased velocity (i.e., EMG-change HV–LV) during MG muscle stretches was comparable to previous reported MG data. Specifically, the SCP group showed a median EMG-change of 3.96% (7.26) when comparing muscle activity at HV to LV stretches, which is in line with previously reported median scores of 2.57% (3.25) of children with the same spasticity scores (MAS 1.5) (17). The children in the HSP group presented MAS scores of 2 and normalized EMG-change of 7.88%. Previous research reported similar EMG change scores (median of 7.25%) in a cohort of children with SCP presenting MAS scores of 2.3 (17).

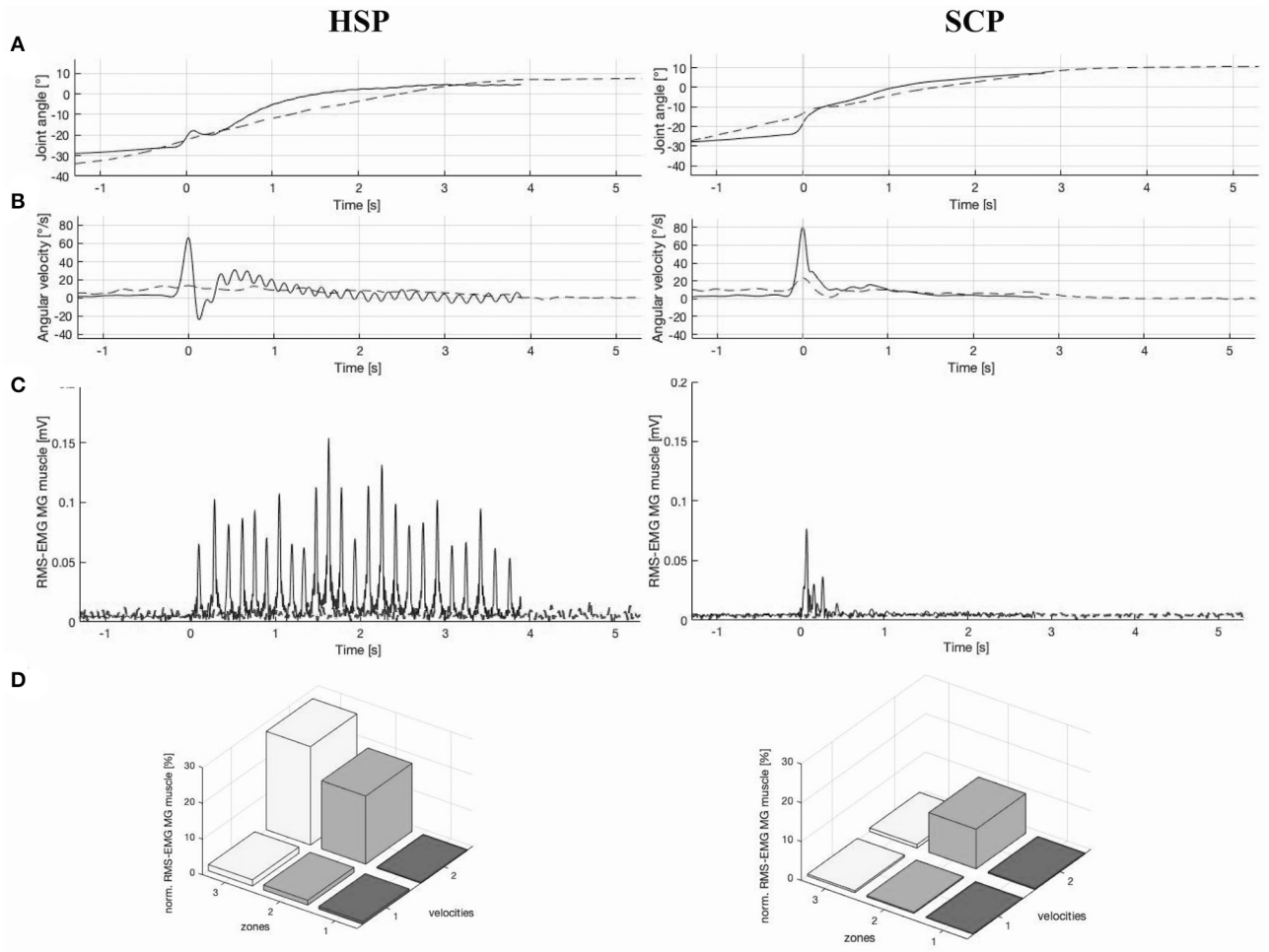

FIGURE 2 | Example illustration of **(A)** ankle joint angle vs. time graph, **(B)** ankle angular velocity vs. time graph, **(C)** root-mean square-electromyography (RMS-EMG) vs. time graph, and **(D)** 3D bar graph of average normalized RMS-EMG across three position zones and the two velocities of the medial gastrocnemius (MG) muscle, in a child with hereditary spastic paraplegia (HSP) and an age-matched child with spastic cerebral palsy (SCP) (20). Graphs **(A–C)** presented both a slow (dashed line) and high (continuous line) velocity stretch, whereby 0 s represent the time at the maximal velocity. In addition, the RMS-EMG vs. time graph **(C)** for the child with HSP indicates a clear ankle clonus, with 24 oscillations over a time period of 4 s. For the SCP case, this graph **(C)** indicates a catch during the high velocity stretch. In graph **(D)**, the position zones indicate 10–90% of range of motion (ROM) divided in three equal parts. Velocity 1 and velocity 2 represent the low-velocity and high-velocity muscle stretches, respectively. High-velocity-dependent activation patterns are presented in both the HSP and SCP case.

Clinical Implications

The objective instrumented investigation of MG muscle characteristics in the HSP group may help to gain more insight in the clinical impairments of children with HSP and to reveal potential markers for accurate differential diagnosis to SCP. In line with the findings of Harding et al., our results suggest the potential predominance of hyperreflexia rather than muscle weakness with the latter indirectly indicated based on the muscle volume results (1). Smaller muscle volumes are likely to generate less active force and are consequently indicative for decreased muscle strengths (46, 47). In the HSP group, muscle volumes tended to be less altered in comparison with the SCP group. This observation was combined with a tendency of higher hyperreflexia values, suggesting the predominance of spasticity in HSP. Yet, this trend needs to be confirmed in larger study samples.

Noticeably, it is important to investigate hyperreflexia using an objective instrumented assessment while performing quantitative analysis of the neurophysiological muscle response during passive muscle stretches in order to describe the neural contributor of hyper-resistance. Manual clinical examinations, such as MAS and MTA, are unable to discriminate among neural or non-neural contributors (19, 22, 48). The observed tendency of more hyperreflexia in the HSP group in comparison with rather similar MAS and MTA scores between the HSP and SCP groups confirms this statement.

The occurrence of clonus (i.e., repetitive oscillatory muscle contractions following stretch) is described as an upper motor neuron lesion sign and is generally presented in combination

with hyperreflexia (49, 50). In an additional exploration, normalized RMS-EMG graphs of the high velocity stretches were visually inspected for the number of oscillations over the time period for which a minimal RMS-EMG activity was observed. **Figure 2** represents an HSP case with a clear clonus, indicating 24 oscillations over a time period of 4 s. Both the results of the clinical examination scores for clonus and number of oscillations over time are presented per participant in **Supplementary Table 4**. The presence of clonus in particular in the HSP group is equally observed according to these two approaches. Moreover, in the children with HSP showing clinically a quick clonus with no stop, an increasing number of oscillations was suggested in comparison with children with a quick stop. In contrast, in the SCP group, only three children showed a clonus in the clinical examination, whereas the phenomenon was confirmed by EMG data for only two children with SCP. However, more research should be conducted to provide valid and reliable methods to quantify clonus with the described assessment of hyperreflexia in both children with HSP and SCP. In the context of the current study, hyperreflexia and clonus can be suggested as clinical markers to distinguish the two disorders.

Treatment approaches in children with HSP are symptomatic and generally aimed to reduce muscle spasticity. Treatment management mainly involves physiotherapy and tone-reducing medication. However, a recent review highlighted the lack of high-level studies, like randomized control trials, that provide sufficient evidence to promote these treatments in children with HSP (6). Yet, the hyperreflexia data of the current study might indicate tone reduction as an important treatment goal in children with HSP. Despite limited data on the effectiveness of BTX injections on focal spasticity and function in children with HSP (6, 7), the presence of high-velocity-dependent phenotypes indicates the potential positive outcomes of BTX treatment. Indeed, in children with SCP, previous research on the effect of BTX demonstrated more pronounced decreases in muscle tone in children with high-velocity-dependent muscle activation patterns compared with length-dependent muscle activation patterns (21). Apart from daily orthotic management and regular physiotherapy as the general treatment approach, the use of BTX is widely applied as tone-reducing treatment in children with bilateral SCP (51). Since the muscle characteristics were found to be similar, it is reasonable to recommend analogous treatment approaches in children with HSP and SCP.

Limitations and Future Perspectives

It should be noted that some limitations are present in the current study. The main drawback of this retrospective study is the small sample size, which compromises the power of the statistical tests and may prevent generalization of the observations. Due to the nature of the single-center, retrospective study design, we were limited to the available datasets for each subgroup. In addition, specific inclusion criteria for both the HSP and SCP groups were applied, aiming to reduce the clinical heterogeneous presentation. Despite these efforts, the muscle data presented high variability, although normalization to anthropometric data successfully decreased this heterogeneity. This finding suggests that children of the different cohorts should be matched for anthropometric data rather than for age. Notably, HSP is a rare disease with an estimated prevalence of 1:10,000, and not all case were genetically confirmed (52). The restriction to only include pure HSP types enlarges the rareness of the disease. Future studies should aim for a prospective case-control design and could be carried out as a multi-center study to increase the size of the dataset.

This study only addressed the MG muscle. The restriction to the MG as muscle of interest was fixed due to (a) the available muscle-specific datasets and (b) the ability to compare our results with previous publications. Hamstring muscle spasticity and weakness have been described as clinical impairments in HSP (4, 35). Since muscle activation patterns were found to be muscle specific, future studies should investigate these muscle-specific characteristics. In the current study, the observed high-velocity-dependent pattern of the MG muscle confirmed this previously reported MG-specific pattern (20).

Furthermore, the current study focused on the neurophysiological response to passive muscle stretch. Future studies should further explore the specific contribution of both neural and non-neural components of the hyper-resistance against passive muscle stretch using instrumented assessments in children with HSP. In addition, these assessments should be used to consider the effectiveness of frequently applied tone-reducing treatment approaches in children with HSP.

CONCLUSION

This is the first study that explored the MG muscle characteristics in children with HSP using instrumented impairment assessments. Muscle volume deficits, high-velocity hyperreflexia, and ankle clonus were presented in children with HSP. In general, instrumented assessments of the altered muscle morphology and hyperreflexia suggested similar MG muscle-related impairments in pediatric pure HSP types with pediatric onset and in children with bilateral SCP. Hence, the use of analogous treatment approaches might be supported by the study results. Due to the limited statistical power caused by the limitations in sample size, the study results should be confirmed in larger cohorts.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of the University Hospitals Leuven and KU Leuven (S56977 and S59945). Written informed consent was provided by the participants' parents/legal guardians.

AUTHOR CONTRIBUTIONS

This study was designed by ND, LB-O, EO, KD, and AV. ND, BH, and NP contributed to the data collection of the retrospective database. EO and AV evaluated the eligibility of the participants. ND was responsible for the data processing and conducted all presented analyses. ND, LB-O, KD, and AV contributed to the interpretation of the results and were involved in the critical revision and editing of the manuscript that was written by ND. All authors approved the final version of the manuscript and agreed to be accountable for the content of the work. All authors have had complete access to the study data throughout the study.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.635032/full#supplementary-material

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frontiers in Neurology

ORIGINAL RESEARCH
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Parents and Caregivers Satisfaction After Palliative Treatment of Spastic Hip Dislocation in Cerebral Palsy

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Objectives: Pain appearance is one the most common complication of spastic hip disease in children with cerebral palsy (CP). It determines child and caregiver quality of life and life priorities. Reconstruction hip surgery should be considered as a treatment of choice. Some clinical conditions give the inability to perform such a procedure. In our paper, we would like to present four palliative methods of spastic hip dislocation treatment in children with CP.

Material: We analyzed four groups of patients treated because of hip pain. Inclusion criteria were pain appearance (visual analog scale-11 or numeric rating scale-11) and hip joint dislocation (migration percentage >80%). All patients were admitted to our department between 2008 and 2018. In the first group, patients were treated only by steroid injections to hip joints; in the second group, patients were recruits after hip interposition arthroplasty with shoulder spacer; in the third group, they were patients after valgus subtrochanteric osteotomy (Schanz); and in the fourth group, these were patients after proximal femoral resection (Castle procedure). The minimal follow-up time was 2 years. The first group consisted of 15 patients (15 hips) with a mean age of 15.5 (8–17) years; the second group, 20 patients (24 hips) with a mean age of 14.2 (9–22.6) years; the third group, 22 patients (24 hips) with a mean age of 13.5 (7–20.5) years; and the fourth group, 10 patients (15 hips) with a mean age of 12.9 (7–17.6) years.

Methods: Radiological evaluation was based on a standardized anteroposterior X-ray of the hip joints. Pain severity before surgery and at the last follow-up time was measured by visual analog scale-11. Parents or caregivers were asked about their child's pain during sitting, perineal care, and rest. During the visit, all caregivers were asked about treatment satisfaction (no 0 to max 10) and if they would decide again for the same surgery.

Results: In all groups of patients, we observed a decrease in pain complaints. The observed reduction of pain in the first group was from 7.88 (4–10) to 3.08 (0–8) ($p = 0.05$), but results of injection were observed only for 4 months (2–8), and it has to be repeated (average: two times). In the second group, level of pain was reduced from 4.93 (1–10) to 0.93 (0–5) ($p < 0.001$); in the third group, from 6.22 (3–10) to 0.59 (0–6) ($p < 0.001$); and in the fourth group, pain reduces from 5.43 (2–10) to 2.13 (0–5) ($p < 0.001$). Observed changes concerned mostly sitting position and perineal care. The

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complication rate was in the second group, 6 of 24 cases of extraarticular ossification; in the third group, 2 of 24 cases with extraarticular ossification, two cases of revision surgery. In the fourth group, two cases needed another femoral resection. In the first group, five patients died during follow-up time, so they were excluded from the study. In the steroid injection group, parents' treatment evaluation was 6.83 (0–10), and only in three cases that they would resign from the treatment. In the hip interposition arthroplasty group, caregivers' evaluation was 7.41 (0–10), and in five cases, parents did not accept the surgery. In the Schanz osteotomy group, parents' evaluation was 5.9 (0–10), and in eight cases, caregivers would not repeat surgery. In the proximal femoral resection group, satisfaction was the highest, 8.3 (3–10), and only two parents would not decide for surgery again.

Conclusion: All procedures can be considered as palliative treatment options for pain complain in a spastic hip joint dislocation in children with CP. Steroid injections to the hip joint need to be repeated, and with the follow-up time, it becomes less effective. Steroid injection seems to be the treatment of choice for patients with general anesthesia contraindications. Interposition arthroplasty of the hip joint seems to give better final results, but the highest parents' satisfaction surprisingly was observed in the proximal femoral resection group, but differences were not statistically significant.

Keywords: pain, spastic hip dislocation, salvage procedures, cerebral palsy, palliative treatment

INTRODUCTION

Spastic hip dislocation is the second most common orthopedic manifestation of cerebral palsy (CP) after equinus deformity of the foot (1). All the hip pathologies potentially found in children with CP are collectively described as a spastic hip disease (SHD) (2). The severity of this medical issue is strongly connected with patients' functional level described by the Gross Motor Function Classification System (GMFCS) (3). Because one of the most severe complications of SHD is a complete hip dislocation (migration percentage >80%), the classification system also provides a prognostic value. The hip subluxation in GMFCS level I is reported to be below 1%, whereas GMFCS levels IV and V have a subluxation risk of 70–90%, defined as migration percentage above 33% (4). Hip dislocation among non-ambulators can lead to chronic pain, sitting imbalance, pelvic obliquity, and scoliosis (1, 5–8). Parents or caregivers often complain about problems with hygiene and perineal care. The medical professionals should regard "Proreactive" soft tissue release or "reactive" hip reconstruction procedures such as open reduction and femoral varus derotation with shortening osteotomy or pelvic Dega osteotomy as the treatment of choice (9, 10). When the struggle to prevent hip dislocation is lost, chronic pain and permanent dislocation can be managed with palliative salvage procedures such as Schanz osteotomy (SO), Girdlestone, Castle resection, McHale procedure, or finally proximal femur prosthetic interposition arthroplasty (PFIA) (11–14). There exist many papers describing salvage treatment options for children with CP, but the literature is quite scant in comparative studies (15–17). Our main interest is to find an optimal treatment method for chronic painful spastic hip dislocation. Thus, the purpose of this study is to compare parents' or caregivers' satisfaction with treatment and to assess the treatment results in terms of reported pain due to spastic hip dislocation.

METHODS AND OPERATIVE TECHNIQUE

A retrospective analysis of all patients with painful hip dislocation treated in our department in the years 2008 to 2018 was performed. We identified a total of 312 patients, of which 167 had palliative treatment (primary or secondary). To this group, we applied inclusion criteria such as diagnosis of CP, GMFCS level IV or V, hip pain, and at least 2 years of follow-up. Excluding cases with any previous hip reconstruction procedures has yielded a total of 67 patients who fall under one of the four therapeutic groups: steroid injections (SIs), Castle hip resection (HR), Schanz femoral valgus osteotomy (SO), and PFIA. All groups are described in **Table 1**.

The pain was assessed before surgery and at the last follow-up either with a self-report (providing sufficient child's communication skills) or with a parent or caregiver report, which was the case most often. The pain severity was recorded during the child's rest (lying position), perineal care, and sitting using a visual analog scale (VAS)-11 or numeric rating scale (NRS)-11, depending on the child's communication skills. The satisfaction of parents/caregivers with treatment was also recorded at each follow-up using a modified VAS—Satisfaction or NRS-11 (no 0 – max 10). Also, parents were surveyed whether given a choice again they would have decided for the same surgical treatment option once again on the operating

TABLE 1 | Description of the groups.

	Steroid injection group (SI)	Femoral head resection group (HR)	Shanz osteotomy group (SO)	Proximal femoral interposition arthroplasty group (PIFA)
Patients/Hip Joints	15/15	10/15	22/24	20/24
Age	15.5 years (8–17)	12.9 years (7–17)	13.5 years (7–20)	14.2 years (9–22)
GMFCS IV Patients/Hip Joints	0	0	8/9	2/3
GMFCS V Patients/Hip Joints	15/15	10/15	14/15	18/21
Male/Female	9 (9 hips)/6 (6 hips)	5 (8 hips) – 5 (7 hips)	14 (15 hip)/8 (9 hips)	12 (14 hips) – 8 (10 hips)

site. Statistical analysis was performed using Statistica 12 and PQ stat software. To assess the statistical differences between groups, the Student's *t*-test and chi-square test were used to compare two groups, and analysis of variance was used when comparing more than two groups. Correlation between parameters was evaluated by Pearson's correlation coefficient (rs). Differences were considered significant with $p < 0.05$. Due to the selected group of patients and collected data, the choices of statistical tests were fully approved and correct.

The SI group included patients who could not be operated (general medical condition, no consent for the proposed treatment) and obtained at least 2 SIs (Betamethasone), minimum 3 months apart. The SI was performed during contrast arthrography in the operation theater under fluoroscopic guidance. The HR group underwent a proximal femoral resection at the level of the ischial tuberosity according to Castle procedure with the femoral end cap made of bone cement. The acetabulum was covered by a double-layered hip joint capsule. The post-surgery hip traction for 2–4 weeks was applied to every patient. The SO group underwent a subtrochanteric osteotomy, according to Shanz, with an average value of valgus correction of 60°. The primary decision behind all cases from the SO group was to perform an inspection of the hip. Only the intraoperative evaluation of the femoral head shape with the joint cartilage was providing grounds for SO in place of hip reconstruction. The osteotomy was stabilized with locking or a blade plate without cast immobilization but with the use of abduction splint post-surgery.

Regarding PFIA, the final decisions were taken before surgery. The resection was performed under the same level as in Castle procedure, but to protect soft tissues and acetabulum, we used a temporary shoulder spacer Tecres® Spacer-S, which was fixed with bone cement. This implant has the smallest endoprosthesis stem that can be used (**Figures 1** and **2**). Furthermore, the size of the stem can be further slimmed to fit the femoral intramedullary canal. Before spacer implantation, two holes are drilled in the proximal end of the femur for better and more stable fixation of the spacer in the femur with the bone cement. During surgery, almost a complete resection of the joint capsule is performed. The acetabulum is covered by the double-layered fold sutured from fascia and muscles, i.e., gluteal, adductors, and iliopsoas.

RESULTS

A decline in pain complaints in all four therapeutic groups was observed. The average pain in the SI group declined from 7.88 (range = 4–10) to 3.08 (range = 0–8) ($p < 0.001$). The analgesic effect was observed for an average of 4 months (range = 2–8), and the treatment was repeated at least once (twice on average). The PFIA, SO, and HR groups recorded a pain relief from 4.93 (1–10) to 0.93 (0–5), 6.22 (3–10) to 0.59 (0–6), and 5.42 (2–10) to 2.13 (0–5) in the NRS score, respectively ($p < 0.001$; **Figure 3**). The pain score was reduced comparably in all the three activities during which it was recorded, i.e., lying position, perineal care, and sitting position. The reduction difference was statistically significant in all cases except patients after proximal femoral resection, where the change in pain at the lying position was not statistically significant ($p = 0.15$). There were no differences between patients that were GMFCS levels IV and V in the SO or the PIFA groups.

The extent of pain relief correlates strongly with age, i.e., the older the patient, the smaller the reduction in pain, at sitting ($p = 0.04$, $rs = -0.24$) and perineal hygiene ($p = 0.01$, $rs = -0.29$) in particular.

The treatment satisfaction scores reported by the parents or caregivers were 6.83 (0–10), 7.41 (0–10), 5.9 (0–10), and 8.3 (3–10) for the SI, PFIA, SO, and HR groups, respectively (**Figures 1**, **3**). The proportions of parents or caregivers who would not have consented to the surgery again were 3/15, 5/20, 8/22, and 2/10, respectively (**Figure 4**).

Expectedly, the extent of pain relief correlates with the degree of satisfaction of parents with the treatment. Patients after PFIA had a significant pain difference during all three activities (lying, perineal care, and sitting) that correlated well with the parent/caregiver satisfaction (respectively: $p = 0.002$, $rs = 0.58$; $p = 0.01$, $rs = 0.49$; $p = 0.001$, $rs = 0.62$; **Figures 2**, **5**). By the same token, the decrease of pain was strongly associated with the parents' acceptance expressed by the willingness to repeat

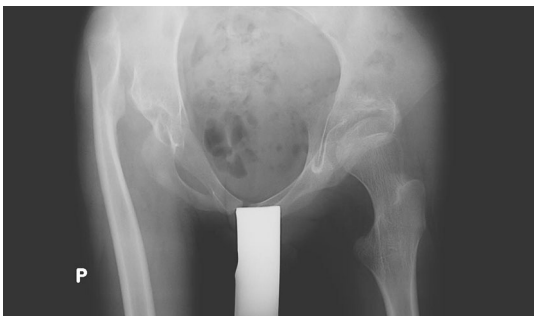

FIGURE 1 | 17 y old, male, treated because painful hip dislocation.

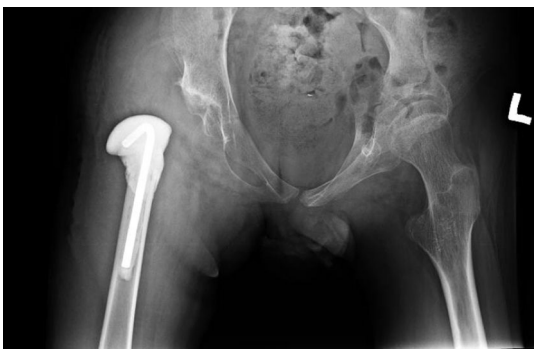

FIGURE 2 | Patient after PFIA – right side.

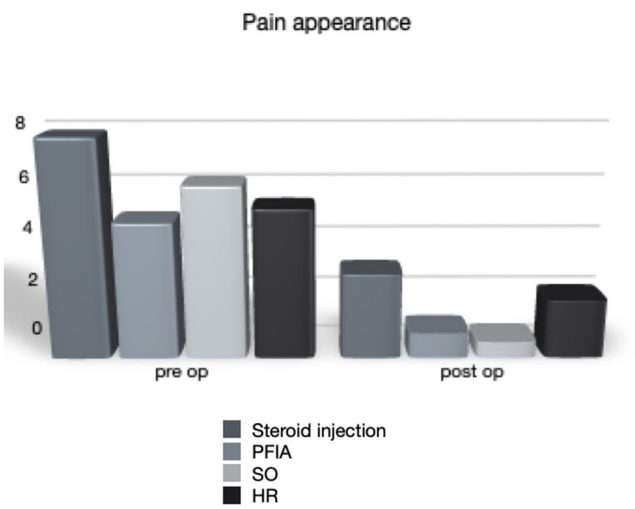

FIGURE 3 | Pain appearance before and after the treatment.

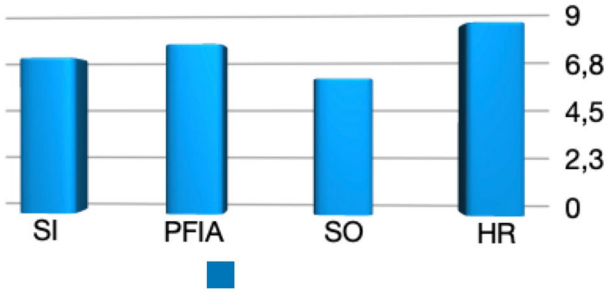

FIGURE 4 | Parents or Caregivers treatment satisfaction.

the surgical treatment, especially for the group of patients after PFIA ($p = 0.004$).

In the SI group, five patients have died during the follow-up period, resulting in exclusion from the study. In the PFIA group, a total of six hips had a quite typical complication of extraarticular ossification in contrast to only two hips after Schanz valgus osteotomy that shared the same sequela. Also, two patients required revision surgery in both the SO and HR groups because of hardware failure and femoral stump migration, respectively.

DISCUSSION

Global pain complaints can be observed in 22–75% of non-ambulatory children with CP with great neurological impairment in particular. Children with GMFCS levels IV and V are at the highest risk of developing painful progressive hip displacement. The natural history of SHD shows that only 50% of dislocated hip joints are painful. Why the rest is pain-free remains elusive (1, 18). Because communication problems are often seen in such patients, parents, or caregivers who take care of a severely handicapped child are in the best position to observe and interpret the child's behavioral or idiosyncratic signals in reaction to pain. Indeed, many authors focus mainly on the parent-reported pain suffered by the child as a proper source of information (19–21).

Hip reconstruction surgery should always be considered as a treatment of choice for SHD (10). This procedure includes soft tissue release, derotation varus shortening femoral osteotomy, and transiliac pelvic osteotomy providing no degenerative cartilage changes. Non-ambulatory patients with a chronic spastic hip dislocation who develop pain due to joint cartilage lesion should be offered a rather palliative treatment (15, 16, 20, 22–25). Among salvage treatment options, there is no preferred surgical procedure. Many are described, including proximal femoral resection, valgus osteotomy, McHale procedure, PFIA, and total hip replacement (26, 27). It has been reported that almost all salvage hip procedures may bring pain relief, and they are almost equally effective at reducing the level of pain (15, 25). Some considerations have to be listed when a decision about surgery is to be taken. Proximal femoral resection is a relatively short and simple procedure, but patients will require traction treatment, and the lower extremity will lose its weight-bearing potential (11, 17, 19, 23). Femoral proximal stump migration is a consequence often seen in a proximal femoral resection. Heterotropic ossification and hardware failure are the most

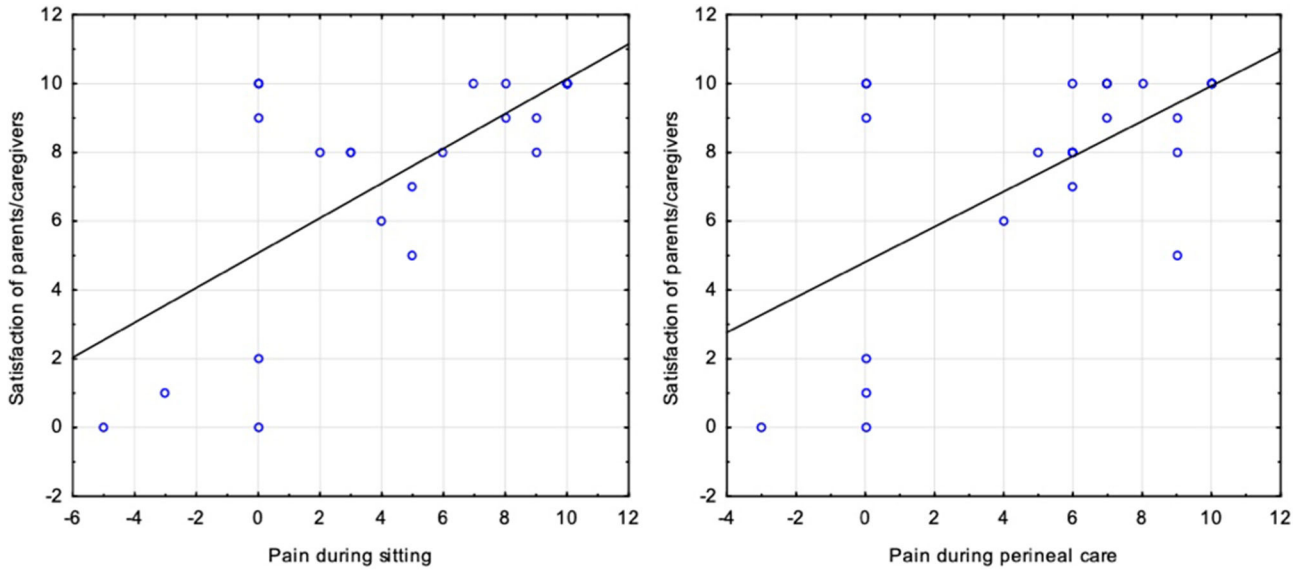

FIGURE 5 | Correlation between Pain and Parents satisfaction.

commonly observed problems after Schantz valgus osteotomy, but patients retain the possibility for assisted standing with partial weight-bearing after surgery (24, 28).

Total hip replacement is an option for ambulatory CP patients, but complex bony deformities, severe osteoporosis, and a pelvic obliquity may constitute a relative contraindication. In CP patients with GMFCS levels IV and V, the total hip endoprosthesis is rather avoided (15, 26, 27).

Hip arthrodesis is a method that is least recommended for its high rate of post-operative complications. It was proved that children with CP after hip fusion had impaired bone healing and discomfort in regular life due to a constrained hip position (15).

According to Sliverio et al., PFIA is a preferred salvage option for painful spastic hip dislocation in children with CP whose conditions improved after surgery. The risk connected with PFIA is acceptable and comparable with the other salvage procedures (21). The results of our study lend support to PFIA being widely accepted by the parents and bringing a well-documented patient improvement. Patel et al. pointed that proximal femoral resection provides a pain-free movable articulation (19). However, during longer follow-up time, symptoms may recur and will probably be connected with proximal femoral end migration. Patel suggests that an interposition myopathy may function as a mechanical barrier, which helps to stop the migration of the proximal femur and allow for articulation with the iliac wing (19). Furthermore, PFIA is regarded as the best palliative treatment option in the paper of Wright et al. (20). Also, there is a consensus of all authors suggesting that post-operative traction treatment is only needed after proximal femoral resection (15, 19). Chan et al. compared femoral resection, valgus osteotomy, and arthroplasty in light of patient ability for weight-bearing. They assumed that patients and parents are willing to maintain the possibility to weight-bearing post-operatively if they were able to do it preoperatively. They declined the procedure of proximal femoral resection (22). Godfrey described a modified McHale procedure and believes it is the most effective and efficient operative treatment technique for painful SHD (23). In contrast to pointing out a single procedure, Kolman et al. recommend all palliative hip procedures except hip arthrodesis, which has a very high rate of post-operative problems (16). They also point out that every palliative procedure has a potential complication: femoral head resection—femur migration; heterotypic ossification and Valgus osteotomy—problems with implants; and PFIA—revision surgery and fracture of long bones. Interestingly, there are no papers describing SI as a method of hip pain treatment, in contrast with the common use of this method in clinical practice. Our study shows a decrease in pain after hip joint SI. It has time-limited effectiveness (2–6 months) but may be suitable for painful non-operative patients. In our opinion, it is the first paper describing the effectiveness of serial hip intraarticular SIs in children with SHD, and on the basis of our material, we can recommend this treatment option for this selective group of patients.

Our study shows that the decision about surgery in chronic spastic hip dislocation is not straightforward. Steroid injection to the hip joint is generally a simple procedure but needs to be repeated. It seems to be the treatment of choice for patients with short life expectancy or with general contraindications. Interposition arthroplasty seems to give better long-term results than other procedures. Surprisingly, the highest parents' satisfaction was observed in the proximal femoral resection group, but the differences were not statistically significant ($p > 0.05$). Based on the literature and our experience, we recommend PFIA as a surgical treatment for chronic spastic painful hip dislocation in children with CP with GMFCS levels IV and V. The optimal salvage procedure for GMFCS level IV remains

undefined, as PIFA has a potential cost of losing the ability for assisted standing.

One fact that we could not find in other papers was a correlation between the age of the patient and the level of pain complaints. Older patients are more willing to have severe pain complaints. Probably, it is due to a period because the child has a diagnosis of spastic hip dislocation, and finally, a decision about surgery was made. Duration of dislocation may lead to cartilage lesions and sensitization of pain receptors around the hip joint, which is obviously caused by direct and indirect inflammatory factors (18). It also implicates the final result of the treatment because older patients get a smaller reduction of pain after applied treatment.

Reduction of pain is the main goal of chronic spastic hip dislocation treatment. Many authors had proved that palliative treatment leads to a decrease in pain complaints. Very often, it is only described if the pain was or not before and after surgery (20–22). Patel et al., in a paper describing proximal femoral resection, get a reduction of pain from 7.8 to 2.8 according to VAS (19). Our results for that group of patients were comparable, from 5.42 to 2.13. Results for the other three groups are similar to the other researchers (15, 16, 19–24).

STUDY LIMITATION

Because patients did not get preventive or reconstructive hip surgery, their general health condition and communication skills were quite poor and non-homogenous in pain status. Consequently, most of the pain assessments were parent/caregiver reports in place of self-reports, which results in all sorts of potential bias and limitations to comparison. The experience of our orthopedic team is based on more than 50% of all cases treated because of the neuromuscular condition, but presented results are not statistically significant, so we cannot recommend one easy and simple solution for chronic painful spastic hip dislocation.

CONCLUSION

All procedures presented in our paper can be considered as palliative treatment options for chronic painful spastic hip dislocation in children with CP. Steroid injection to the hip joint is a generally simple procedure but needs to be repeated. Steroid injection seems to be the treatment of choice for patients with general anesthesia contraindications. Interposition arthroplasty of the hip joint seems to give better final results, but differences were not statistically significant ($P > 0.05$). On the basis of the literature and our experience, we recommend PFIA as a surgical treatment of chronic spastic painful hip dislocation in children with CP with GMFCS level V.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Bioethical Committee University of Medical Sciences in Poznan, Poland. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

AK, JK, MD, MR, and MJ contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript. All authors contributed to the article and approved the submitted version.

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Development of Lower Extremity Strength in Ambulatory Children With Bilateral Spastic Cerebral Palsy in Comparison With Typically Developing Controls Using Absolute and Normalized to Body Weight Force Values

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This cross-sectional study aimed to examine the development of lower limb voluntary strength in 160 ambulatory patients with bilateral spastic cerebral palsy (CP) (106 diplegics/54 quadriplegics) and 86 typically developing (TD) controls, aged 7–16 years. Handheld dynamometry was used to measure isometric strength of seven muscle groups (hip adductors and abductors, hip extensors and flexors, knee extensors and flexors, and ankle dorsiflexors); absolute force (AF) values in pounds were collected, which were then normalized to body weight (NF). AF values increased with increasing age ($p < 0.001$ for all muscle groups), whereas NF values decreased through adolescence ($p < 0.001$ for all muscle groups except for hip abduction where $p = 0.022$), indicating that increases in weight through adolescence led to decreases in relative force. Both AF and NF values were significantly greater in TD subjects when compared with children with CP in all muscle and all age groups ($p < 0.001$). Diplegics and quadriplegics demonstrated consistently lower force values than TD subjects for all muscle groups, except for the hip extensors where TD children had similar values with diplegics ($p = 0.726$) but higher than quadriplegics ($p = 0.001$). Diplegic patients also exhibited higher values than quadriplegics in all muscles, except for the knee extensors where their difference was only indicative ($p = 0.056$). The conversion of CP subjects' force values as a percentage of the TD subjects' mean value revealed a pattern of significant muscle strength imbalance between the CP antagonist muscles, documented from the following deficit differences for the CP muscle couples: (hip extensors 13%) / (hip flexors 32%), (adductors 27%) / (abductors 52%), and (knee extensors 37%) / (knee flexors 53%). This pattern was evident in all age groups. Similarly, significant force deficiencies were identified in GMFCS III/IV patients when compared with TD children and GMFCS I/II

patients. In this study, we demonstrated that children and adolescents with bilateral CP exhibited lower strength values in lower limb muscles when compared with their TD counterparts. This difference was more prevalent in quadriplegic patients and those with a more severe impairment. An important pattern of muscle strength imbalance between the antagonist muscles of the CP subjects was revealed.

Keywords: strength, cerebral palsy, lower limb, diplegia, quadriplegia, children and adolescents

INTRODUCTION

Muscle weakness is a major component of cerebral palsy (CP) which contributes to functional disability. Lower limb strength has been correlated with gait deficits and pathological walking patterns (1, 2), while its relationship to joint kinetics has been further described (3, 4). Children with spastic CP (diplegia and hemiplegia) have been found to be weaker than typically developing (TD) children in several studies (3, 5, 6). Muscle weakness is evident even in ambulatory children with mild CP; severe loss of strength has been documented in non-ambulating children with severe CP (7). In a comparison of knee and ankle spasticity and strength in 60 children with spastic diplegia with controls, more distal than proximal involvement in the lower extremities was also demonstrated (6). Stackhouse et al. found that children with spastic diplegic CP (7–13 years) produced 56 and 73% less knee extensor and ankle plantar–flexor force, respectively, compared with participants without disabilities (8). While the aforementioned studies demonstrated weakness in isolated muscle groups, Thompson et al. examined the degree and distribution of weakness in multiple muscles (six muscle groups) in 50 ambulant children with spastic diplegia at Gross Motor Function Classification System (GMFCS) levels I to III and compared them with 15 control children of similar age (9). All muscle groups were significantly weaker in children with CP than in healthy controls ($p < 0.05$) except for the hip extensors. Strength ranged from 43 to 90% of control values depending on the muscle group, with the knee extensors being the relatively weakest group of all. There was significant reduction in strength in all muscle groups with increasing walking difficulty from GMFCS level I to level III. The greatest difference in strength between independent walkers and those dependent on walking aids was in the hip abductors and knee extensors at 30°, which are key muscle groups in sagittal and coronal plane walking stability. In 2014, Davids et al. (10), prospectively examined case series of 255 diplegic children aged 8–19 years. They demonstrated that while the strength of lower extremities increased significantly for the entire group, strength normalized for weight significantly declined with age without important differences among GMFCS levels (10). There was a 90% chance for independent ambulation (GMFCS levels I and II) when strength normalized for weight was 49% predicted relative to TD children.

The ultimate goal of the studies that describe the degree and distribution of weakness in CP was to determine treatment goals and interventions that may result in strength gains and functional improvements; this has proven difficult to accomplish (11). On the contrary, even though about 50–80% of individuals with CP are able to ambulate in some way, there is loss of ambulatory skills in some with age, particularly in those at GMFCS levels III and IV (12, 13); this may be related to the pattern and evolution of muscle weakness they exhibit. Recent evidence as to this matter remains controversial and suggests that muscle strengthening may not result in functional improvements (14). However, in a pragmatic setting, the clinician, the patient, and the family have to explore interventions that are likely to conserve the ability to ambulate and the current level of motor function or alternatively devote time and energy toward directions that may improve participation even with deteriorating motor skills. For this reason, the exploration of muscle strength parameters that evolve with age particularly in different muscle groups remains of interest.

The goals of this study were to compare the pattern of changes in muscle strength between ambulatory patients with bilateral spastic CP and TD subjects between the ages of 7 and 16 years, and also, to examine if specific differences exist in patients with GMFCS levels III/IV as opposed to independent walkers (GMFCS levels I/II). Measuring muscle strength differences in patient groups of different ages and severity of involvement was expected, among other factors, to determine realistic rehabilitation goals and quantitative monitoring of interventions.

METHODS

In order to study the development of force in different ages, the subjects were divided into five age groups from ages 7–16 with a 2-year interval. TD controls were volunteers attending a private school close to our laboratory. They were all informed that their data would be used for research. The measurement protocol was approved by the private school administration, and there was a collaboration with physical education teachers during the measurements.

The patients with CP were selected from patients referred to our center for gait analysis on the basis of their age and their ability to follow (intellectually and behaviorally) the gait analysis protocol. We excluded children who had had orthopedic surgery or botulinum toxin injections in any muscle group, over the preceding year. All CP subjects or their parents signed an informed consent form to allow the use of their data in research. All patients had BSCP and were further categorized into patients with spastic diplegia or patients with spastic quadriparesis or quadriplegia. GMFCS scale categorization of the patients was also applied to identify muscle groups that were significantly weaker in patients who walked with the use of assistive devices (group B:

GMFCS levels III and IV) than in patients who were able to walk independently (group A: levels I and II).

The force data measurements were collected using a Hoggan microFET2 digital handheld dynamometer. The positioning of the patient and the dynamometer application were standardized as shown in **Figure 1**. The same examiner performed all measurements in normal subjects and patients. The following seven muscle groups were assessed: hip adductors, hip abductors, hip extensors, hip flexors, knee extensors, knee flexors, and ankle dorsiflexors. Ankle plantar flexors were not included in the study because of the documented difficulties for reliable measurement with the handheld dynamometer (15, 16). All subjects performed three consecutive muscle force measurements with a resting interval of at least 20 s among trials for each muscle group (17, 18). For each trial, the subject was instructed to contract maximally ("as possible") against the dynamometer for 3 s while encouragement was given by the assessor (measurement type: "make test"), and the maximal dynamometer reading during the 3-s effort was recorded. In cases of subjects where muscle force exceeded the examiner's resistance, an assistant was used to increase the resistance acting over the hand of the examiner. Measurements that could not be performed due to inability of the patients with CP to exhibit resistance were registered and reported as not applicable (N/A) and were inserted as 0 for the analysis. Absolute force (AF) values were registered from the dynamometer and expressed in pounds and then pounds were converted to kilograms (conversion factor 0.45359237). However, absolute strength values may not reflect functional muscle strength due to differences in body weight. Normalized force (NF) values were calculated by dividing AF with body weight and were included in the analysis, to account for these body weight differences. The three measurements for each limb, six measurements in total for each muscle group, were collected and averaged (total measurements = 10332). We chose to analyze the mean value of the three efforts for each muscle group instead of the maximal one (peak value) to take into account the performance variability usually observed in children with CP (18, 19).

CP patients' mean muscle force values were also converted to percentages of the respective TD control mean values. The difference from 100% of the above values was used to define the muscle force deficit that the CP subjects exhibited compared with the TD controls in each muscle group. These deficit values were also used for comparison between the couples of the following antagonist muscle groups: (a) hip extensors/hip flexors, (b) hip adductors/hip abductors, and (c) knee extensors/knee flexors. Equal values indicated a balanced deficit between antagonists, while increased difference indicated disproportional deficit and increased imbalance.

Statistical Analysis

Demographic data, GMFCS level, and force measurements were available for all study participants. Continuous data were tested for normality using the Kolmogorov–Smirnov test. Normally distributed continuous variables were expressed as mean values (± standard deviation) whereas non-normal data were expressed as median values (range). Categorical data were presented as frequencies and/or percentages. Comparisons across patient groups (typical development, diplegia, quadriplegia) of demographic characteristics, represented as continuous variables, were based on one-way ANOVA if variables were normally distributed (height) and on Kruskal–Wallis test when this was not the case (age, weight). Distribution of gender was recorded for all the participant groups (typical development, diplegia, quadriplegia) and percentages were compared across groups with the chi exact test.

In order to identify factors predicting missing/invalid force measurement values, we performed logistic regression analysis. Factors tested in the univariate analysis were age (categorized in five 2-year groups: 7–8, 9–10, 11–12, 13–14, and 15–16 years), sex (male vs. female), type of the involvement (typical development, diplegia, quadriplegia), and severity of the impairment (GMFCS I–II vs. GMFCS III–IV). Those that were significant or with a $p \leq 0.200$ were inserted in the multivariate analysis. $p < 0.05$ was set as the significance level.

Comparisons of force values across groups (typical development, diplegia, quadriplegia) were based on one-way ANOVA, except for the ankle dorsiflector force values which were not normally distributed and were compared with the Kruskal–Wallis test. *Post hoc* analyses were performed: Bonferroni correction followed ANOVA; after the Kruskal–Wallis test, we performed pairwise comparisons with the Mann–Whitney *U* test, followed again by Bonferroni correction. Comparisons of force values between the two GMFCS groups (I/II vs. III/IV) were based on *t* tests for all muscles tested, except for ankle dorsiflector force values which were not normally distributed and were compared with the Mann–Whitney *U* test. Stata 13 was used for all analyses.

RESULTS

Subject Description

A total of 246 children and adolescents (160 with cerebral palsy and 86 TD subjects) were included in the present study. Participants with cerebral palsy were further categorized into two subgroups: 106 were diplegic (66.25%) and 54 quadriplegic ambulatory (33.75%).

Table 1 displays the demographic characteristics of patients and controls. Participants of the two groups were similar in terms of age and sex, but they differed in weight and height. TD participants were heavier than diplegic ($p = 0.009$) and quadriplegic children ($p = 0.036$) and taller than them ($p = 0.024$ and $p = 0.021$, respectively). On the other hand, diplegic, and quadriplegic patients had similar weights and heights ($p = 0.784$ and $p = 1.000$, respectively). When these characteristics were analyzed separately for boys and girls, we discovered that the abovementioned differences were attributed to boys rather than girls. That is, TD and patient girls seemed to have similar weights and heights ($p = 0.285$ and $p = 0.149$, respectively), whereas TD boys were heavier and taller than patient boys ($p = 0.036$ and $p = 0.032$, respectively). **Figure 2** displays the changes of weight and height of TD and patients with age.

The distribution of patients in the GMFCS levels were as follows: six patients, all diplegics in GMFCS level I; 115 in level

FIGURE 1 | Subject's position and dynamometer application for each muscle group measured.

TABLE 1 | Demographic and somatometric characteristics of CP patients and TD children.

	Diplegia ($n = 106$)	**Quadriplegia ($n = 54$)**	**TD Children ($n = 86$)**	***p***
Age (years)[a]	10 (7–16)	11 (7–16)	11 (7–15)	0.714*
Sex (M/F)	58/48	31/23	42/44	0.566
Weight (kg)[a]	35 (20–84)	38.5 (16–59)	42 (22–101)	0.019*
Height (cm)[b]	141 ± 15	140 ± 16	147 ± 15	0.008**

[a]*Median values (range).*
[b]*Mean values (SD).*
**Comparison across groups with Kruskal–Wallis test.*
***Comparison across groups with one-way ANOVA.*

II (86 diplegics/29 quadriplegics); 17 in level III (7 diplegics/10 quadriplegics); and 22 in level IV (7 diplegics/15 quadriplegics).

Measurement Success

In total, 3,444 muscles were finally tested: 2,240 of these were in CP patients. In 256 muscles, measurements were marked as N/A since no attempt of the three performed measurements were valid: in 120 cases, the problem was bilateral; in 10 cases, only the right limb was involved; and in six cases, only the left limb was involved. Only subjects with CP showed N/A values in various muscle groups ($n = 59$). Therefore, 7.4% of the force measurements of the patients were invalid due to the inability of the subjects to perform the tests. In the seven muscle groups tested in the patients with CP, a successful measurement rate of 72–97% was found (**Figure 3A**). Knee flexion and ankle dorsiflexion showed lower successful measurement rates of 79 and 72%, respectively. Concerning movement that caused difficulty, in 52 cases, it involved the hip (flexion: 10, extension: 7, adduction: 15, abduction: 20); in 39 cases, it involved the knee (flexion: 34, extension: 5); and in 45 cases, the ankle (dorsiflexion). In three patients, one attempt for knee extension ($n = 1$) and hip abduction ($n = 2$) measurement was not valid. However, the other two attempts produced force measurements and the whole measurement was considered valid.

From the successful measurement rates of the two CP groups, across age groups (**Figure 3B**), it can be observed that for all age groups, except the one of 13–14 years, diplegic subjects showed higher successful measurement rates than quadriplegics. Also, quadriplegic subjects showed substantially higher rates of N/A in younger rather than older age groups. The univariate logistic regression analysis performed to identify patients' characteristics that may be associated with a higher rate of N/A measurements demonstrated that patients with N/A measurements were similar to those with no such results in terms of age ($p = 0.5382$) and sex ($p = 0.982$). On the other hand, quadriplegic patients and those with a more serious involvement (GMFCS III–IV) were more likely to have N/A measurements when compared with diplegics ($p < 0.001$) and those patients with GMFCS I–II ($p < 0.001$). After multivariate logistic regression analysis, quadriplegic children and those with more serious involvement still had more invalid measurements ($p = 0.002$ and $p = 0.022$, respectively).

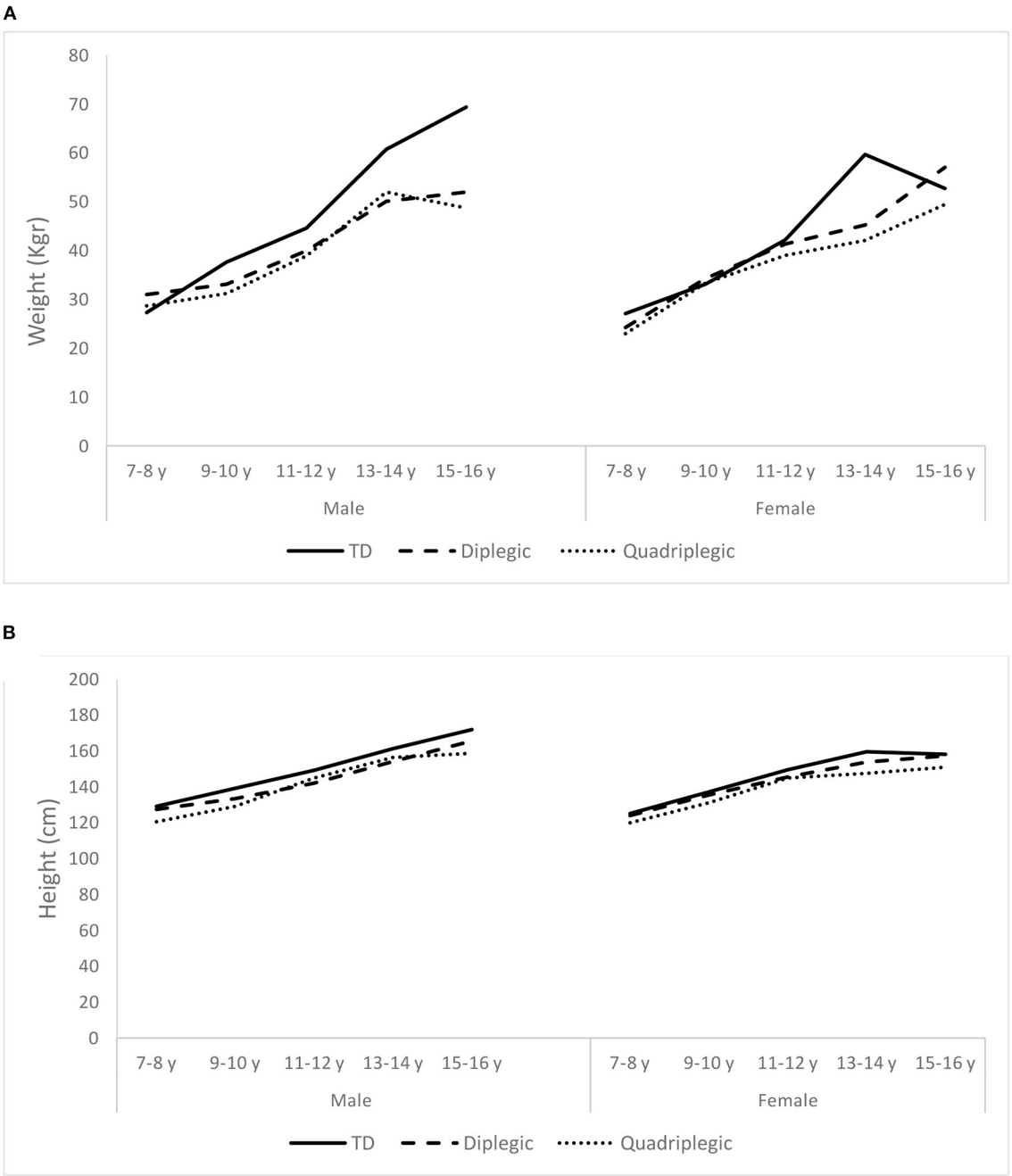

FIGURE 2 | Average weight **(A)** and height **(B)** of the Typically Developing children (TD) and the two patient groups (Diplegic and Quadriplegic), for boys and girls.

Force Results

As demonstrated in the AF graphs (**Figure 4**), AF values showed a positive (upward) slope, with increasing age. TD children's AF graphs showed a progressive increase in all muscle groups. For TD boys, this increase presented a steep slope especially after 13–14 years. In TD girls, this steep increase was still present, but it was demonstrated earlier (9–10 or 11–12 years of age) for hip flexors, hip extensors, knee flexion, and knee extension and at same age as boys for hip adductors and abductors. For ankle dorsiflexion, we could not display such a pattern. CP patients, of both sexes, had distinguishably lower AF values for most muscle groups. A lower difference between diplegic patients and TD children was presented in hip extension (for girls) and hip adduction (for boys and girls), especially during childhood and to a lesser extent into adolescence. CP children, especially diplegic patients, also demonstrated some steep increases, though with greater variations.

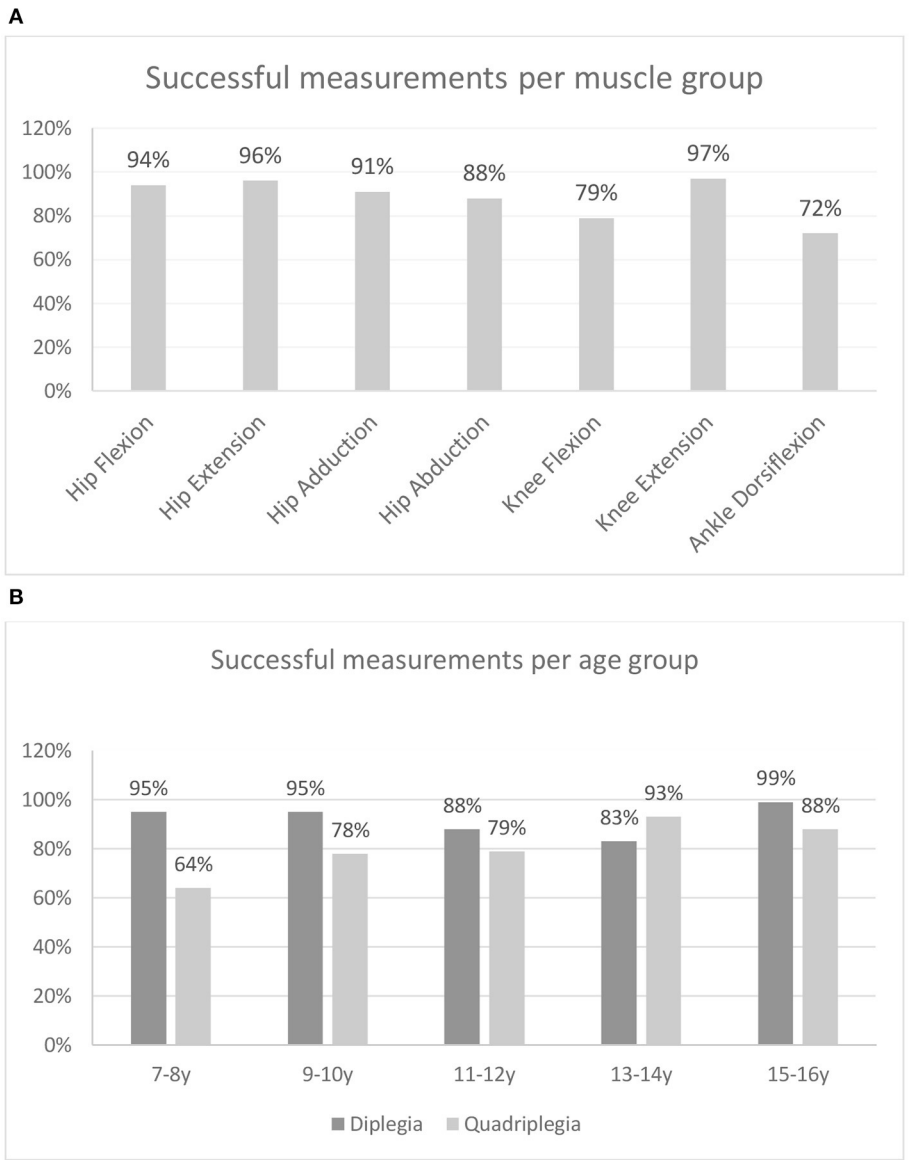

FIGURE 3 | Percentage of successful measurements **(A)** per muscle group and **(B)** per age group for patients with bilateral spastic CP.

On the contrary, NF values showed a negative (downward) slope. TD children demonstrated a notable decrease at the 13–14 year age group in all measured muscles and for both boys and girls, followed by a sudden increase thereafter (**Figure 4**). In CP patients, this pattern was not so evident. For diplegic patients, the secondary increase was observed mostly in males. Quadriplegic patients had more varying patterns. As demonstrated in the graphs, bigger differences between TD and diplegic–quadriplegic patients were observed for hip abduction, knee flexion and extension, and ankle dorsiflexion and hip flexion to a lesser degree. For hip extension and hip adduction, NF values especially between TD and diplegic patients were not distinguishable.

Table 2 displays mean force measurements for CP patients and TD children for all muscle groups tested. Hip flexor values were found significantly lower in both diplegic and quadriplegic patients than in TD subjects ($p < 0.001$ for both comparisons), and quadriplegic patients also had lower values than diplegic patients ($p < 0.001$). Furthermore, hip extensor values were also different in the compared groups. In this muscle group, however, TD subjects had similar values with diplegic patients ($p = 0.726$) but higher values than quadriplegics ($p = 0.001$). For this muscle group, force values were also different between quadriplegic and diplegic patients ($p = 0.001$). In hip adduction, the pattern followed that of hip flexion with all participant groups differing from each other (diplegic–TD: $p = 0.002$,

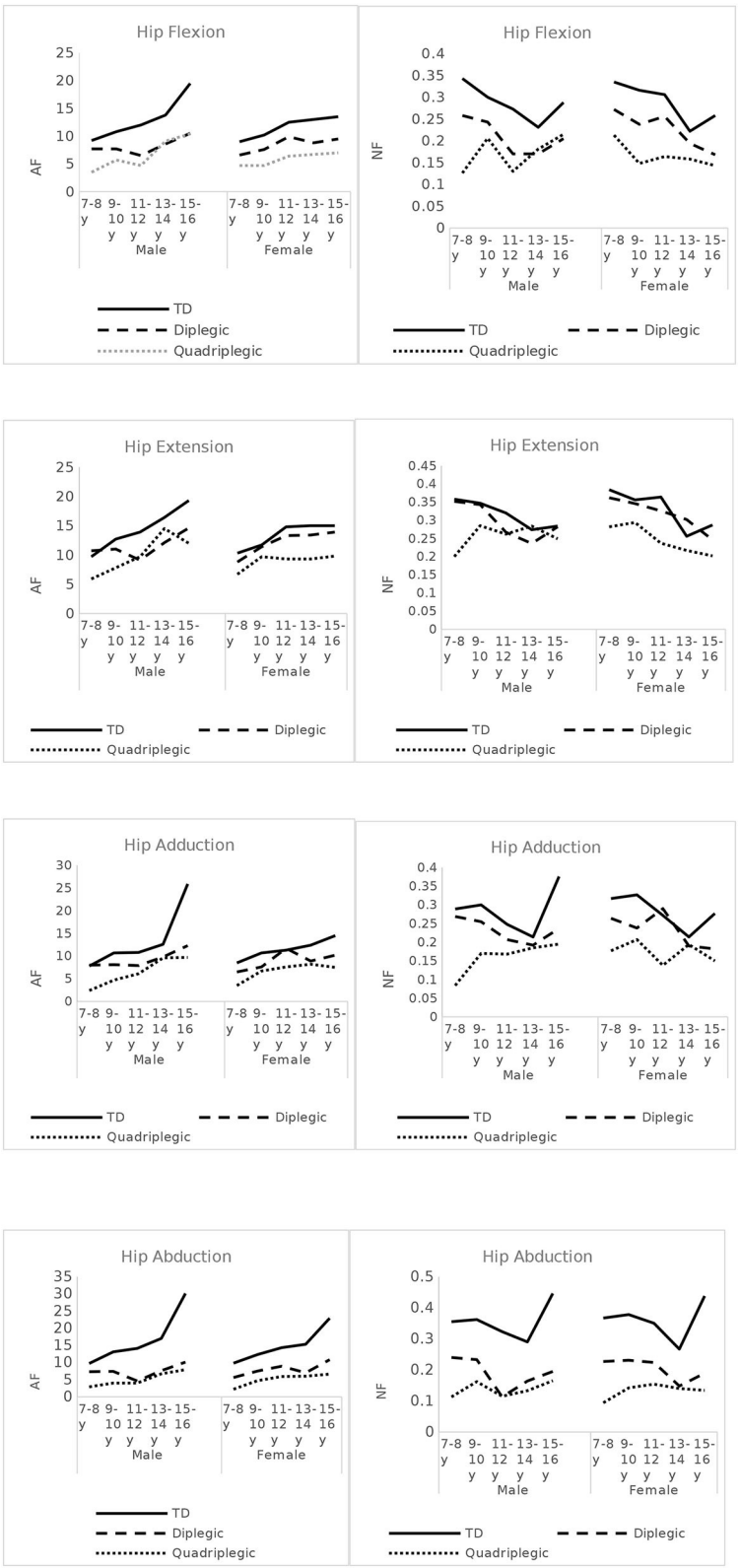

FIGURE 4 | Continued

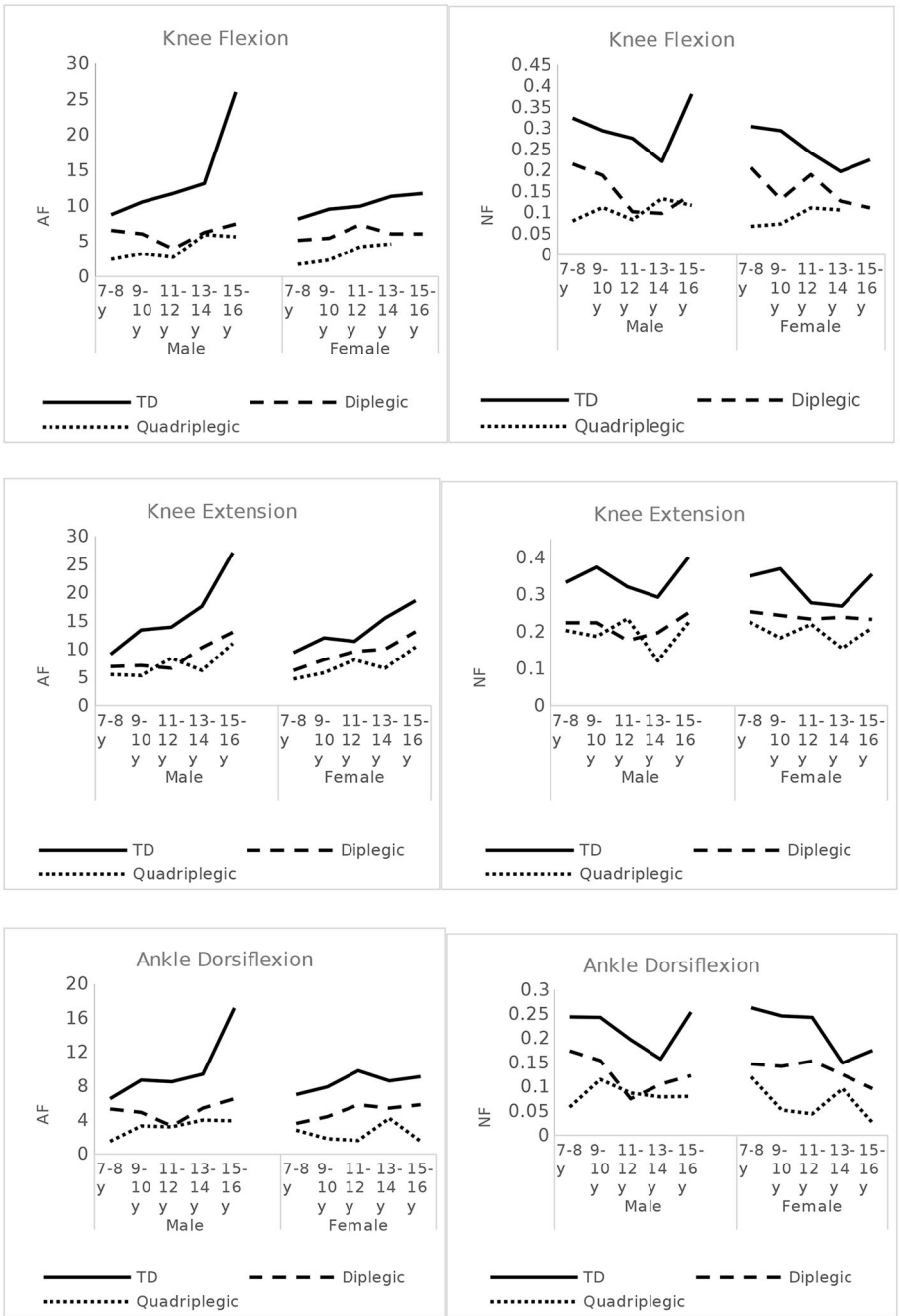

FIGURE 4 | Absolute Force (AF) and Normalized Force (NF) - Force per Kg- values across age-groups, for all muscles tested, in CP patients and TD children.

quadriplegic–TD: $p < 0.001$, diplegic–quadriplegic: $p < 0.001$). For hip abduction and knee flexion, that was also the case ($p < 0.001$, for all group comparisons). Concerning knee extension, both patient groups differed from TD subjects ($p < 0.001$ for both comparisons), but the difference between quadriplegic and diplegic patients was indicative ($p = 0.056$). Similarly, for ankle dorsiflexion, all groups differed from each other ($p < 0.001$ for all comparisons).

GMFCS Group A vs. Group B

The results showed consistently significantly lower values of force profile in all muscle groups of group B than group A, with the

exception of knee extension where the difference was marginally significant (**Table 3**).

Muscle Force Deficit Analysis

Figure 5A demonstrates the deficit of the CP patients compared with the TD controls and **Figure 5B** shows the respective GMFCS groups A and B data. Our data revealed significant deficiencies in hip abductors (52%), in knee flexion (53%), and in ankle dorsiflexion (50%) for CP patients and lower values for knee extension (47%), hip flexion (32%), hip adduction (73%), and hip extension (13). For GMFCS group A, values ranged from 94 to 58% of the TD values, and for group B, values ranged lower in all muscle groups from 76 to 30%. The analysis of the antagonist muscle group couples revealed a large deficit imbalance between (adductors 27%) / (abductors 52%) and (knee extensors 37%) / (knee flexors 53%), and a smaller imbalance for the (hip extensors 13%) / (hip flexors 32%) couple. This pattern was evident in all age groups (**Figure 4**). Similarly, significant force deficiencies were identified in GMFCS III/IV patients as compared with TD children and GMFCS I/II patients.

DISCUSSION

In this cross-sectional study, we examined the age-dependent evolution of voluntary lower limb muscle strength in 160 patients with bilateral spastic CP, aged 7–16 years. When we compared their strength performance with typical developing children and adolescents of the same age, we were able to demonstrate that CP patients exhibited lower strength values in lower limb muscles when compared with their TD counterparts, with deficits being more pronounced in patients with quadriplegia and those with a more severe impairment (GMFCS levels III/IV vs. I/II). Furthermore, an important pattern of muscle strength imbalance between the antagonist muscles of the CP subjects was revealed.

Muscle weakness associated with the spastic form of CP has been studied extensively. Previous studies have linked insufficient force generation to decreased central activation or neuronal drive (5, 8, 20, 21), inappropriate co-activation of antagonist muscle groups (5, 8, 20), secondary myopathy (22–24), and altered muscle physiology (differing muscle force–frequency relationship and fatigue properties) (8), with considerable variation concerning the muscles involved and with a particular pattern of muscle weakness underlying the same type of gait (5, 6, 8, 9). Greater strength deficits in the lower extremities were recorded in distal muscles, when compared with the proximal ones (5, 6, 8, 20, 25) and in faster rather than slower speeds of movement (26). Similar motor deficits in distal muscles have been observed through adulthood, when they probably cause the compensatory trunkal–posture mechanisms (e.g., Trendelenburg sign) usually presented in adults with CP (27, 28).

The reliability for isometric force measurements of lower extremity muscles using handheld dynamometry in CP has been demonstrated (18, 29, 30). However, consensus is lacking with regard to standardization of the testing procedure (e.g., position of the child, method of assessment, with/without stabilization, peak/mean force, contraction time, intervals between measurement session, etc.) (19).

In our study, the slope of force development with age using absolute strength values moved in a positive direction (upwards), while it moved negatively (downwards) for normalized values, indicating that increases in BW through adolescence led to decreases in relative force in the tested muscles. Recently, in a prospective case series of 255 subjects (8–19 years old) with diplegic CP and in accordance with our results, it has been demonstrated, unlike absolute force values and weight that increase with age, that total lower extremity strength normalized to weight declines with increasing age (between 8 and 19 years), with a similar rate in young children and adolescents (10). As opposed to children with CP, TD participants in our study demonstrated a drop in the 13–14 age group in NF values, in all measured muscle groups. This coincides with a rather abrupt increase in BW; hence, this may be attributed to a possible increase of fat vs. muscle in their body composition (31) or to a relative lack of exercise as opposed to children with CP who were continuously enrolled in physiotherapy programs.

When comparing lower extremity strength in patients and TD controls of the same age, we demonstrated that in the majority of the muscles tested, CP patients exhibited significantly lower force measurements than their TD counterparts, and diplegic patients exhibited lower measurements than quadriplegics, with one exception: in hip extension, TD children and diplegic patients had similar values, higher though than quadriplegics. Reduced strength in all lower limb muscles tested has been reported previously (5, 32, 33). In accordance with our results, Thompson et al. also found that hip extensors preserved their strength in CP patients when compared with controls (9). They attributed this difference from other studies on the supine lying position that they chose (similar to our testing position), which is considered gravity neutral.

The force deficit was calculated for the whole group of CP patients. The average force deficit was 13–53%, with quadriplegics exhibiting larger deficits than diplegics (5–50% for the diplegics and 22–65% for the quadriplegics). At the muscle level, hip flexors and extensors, hip adductors, and knee extensors maintained forces nearer to TD controls (>60% TD), while hip abductors, knee flexors, and ankle dorsiflexors exhibited greater deficits (<50% TD). These results are in close approximation to the result of Dallmeijer et al. (32). In that study, mean strength values of children with CP and in the different GMFCS levels were compared with those of TD children, and it was reported that force measurements in knee extensors were reduced to 56–68% of values in TD children; in knee flexors, these were reduced to 36–68%; in hip abductors, to 47–76%; in hip flexors, to 63–82%; and in ankle plantar flexors, to 37–57% (32). Thompson et al. also reported similar deficits (43–90%), depending on the muscle group tested (9). In fact, our results were very similar to these authors for hip extensors and abductors, fairly close for the flexors and knee extensors, and different for the knee flexors, possibly due to a different measuring method. The knee extensors measured at 30° of flexion were relatively the weakest muscle group (9). Similarly, Stackhouse et al. found that children with spastic diplegic CP produced 56 and 73% less knee extensor and ankle plantar–flexor force, respectively, compared with participants without disabilities (8).

TABLE 2 | Comparison of normalized to weight force measurements in CP patients and TD children.

	Diplegic patients (*n* = 106)	Quadriplegic patients (*n* = 54)	TD children (*n* = 86)	*p*
Hip flexion[a]	0.222 (±0.085)	0.168 (±0.083)	0.285 (±0.072)	<0.001*
Hip extension[a]	0.309 (±0.094)	0.254 (±0.105)	0.324 (±0.073)	<0.001*
Hip adduction[a]	0.235 (±0.091)	0.171 (±0.091)	0.279 (±0.073)	<0.001*
Hip abduction[a]	0.202 (±0.086)	0.132 (±0.084)	0.348 (±0.091)	<0.001*
Knee flexion[a]	0.160 (±0.092)	0.095 (±0.076)	0.270 (±0.079)	<0.001*
Knee extension[a]	0.226 (±0.081)	0.192 (±0.093)	0.331 (±0.086)	<0.001*
Ankle dorsiflexion[b]	0.143 (0–0.355)	0.093 (0–0.248)	0.202 (0–0.445)	<0.001**

[a]*Mean values (SD).*
[b]*Median values (range).*
**Comparison across groups with one-way ANOVA.*
***Comparison across groups with Kruskal–Wallis test.*

TABLE 3 | Comparison of normalized to weight force data between patients with Gross Motor Function Classification System (GMFCS) I–II and patients with GMFCS III–IV.

	GMFCS I–II (*n* = 121)	GMFCS III–IV (*n* = 39)	*p*
Hip flexion[a]	0.223 (±0.081)	0.145 (±0.014)	<0.001*
Hip extension[a]	0.305 (±0.094)	0.246 (±0.111)	0.001*
Hip adduction[a]	0.227 (±0.091)	0.171 (±0.099)	0.001*
Hip abduction[a]	0.202 (±0.081)	0.105 (±0.083)	<0.001*
Knee flexion[a]	0.157 (±0.087)	0.080 (±0.084)	<0.001*
Knee extension[a]	0.222 (±0.083)	0.190 (±0.095)	0.041*
Ankle dorsiflexion[b]	0.133 (0–0.355)	0.091 (0–0.197)	0.001**

[a]*Mean values (SD).*
[b]*Median values (range).*
**Comparison across groups with t test.*
***Comparison across groups with Mann–Whitney U test.*

In our study, we also emphasized the distinct patterns of force development across age groups, for each pair of antagonist muscle groups. The imbalance in the NF values between the hip adductors and abductors was due to the fact that the former exhibited force close to TD values while the latter exhibited significantly lower values across all ages (**Figure 4**). A similar imbalance was noted between hip extensors and flexors where the former had values not significantly different from values in TD subjects while the latter were significantly lower in CP than in TD subjects. At the knee, both extensors and flexors had significantly reduced group forces compared with TD subjects; yet, the knee extensors tended to maintain force while the deficit for knee flexors was greater. These findings are relevant to the fact that our patients were able to stand and ambulate since one of the main mechanisms of maintaining erect posture during gait is the ability to extend the hip and knee (34). Remarkably, these imbalances were present in all age groups, indicating that the pattern of muscle involvement was constant independent of age and subject since this was a cross-sectional study and not a longitudinal one. These findings suggest that muscle imbalances are inherent to CP from an early stage and do not develop with age.

Important deficits were recorded in GMFCS III–IV patients when compared with controls (25%–70%), while GMFCS I–II patients performed better (58–94%). When we compared the strength in GMFCS levels I/II and III/IV to TD children, a uniform pattern emerged, with all patients exhibiting the best performance in hip extensors, closely followed by hip adductors, and the worst in knee flexors, hip abduction, and ankle dorsiflexion. We also demonstrated consistently lower values of force profile in all muscle groups of patients at GMFCS levels III/IV when compared with GMFCS levels I/II. There was a significant deficiency (<55% TD) in hip abductors, knee flexors, and ankle dorsiflexors for GMFCS levels III/IV compared with GMFCS levels I/II. Most previous studies investigating the relationship of lower limb strength and motor impairment (gross motor function) have demonstrated similar results, indicating that muscle strength affects walking ability (7, 9, 32). Thompson et al. depicted that with worsening ambulatory level from GMFCS levels I–III, strength values decreased in all muscle groups, while joint contractures increased. The greatest strength reduction between independent (GMFCS level I) and dependent walkers (GMFCS level III) was in the hip abductors (61%) and knee extensors at 30° (45%) (9). In their study, Dallmeijer et al. also reported that CP children with GMFCS level I had significantly higher strength values than GMFCS levels II and/or III for all muscle groups, except for knee extensors. The latter showed no differences between GMFCS levels (32). These results partly differ from our study, but our method of assessment in this muscle group and the calculation of normalized strength were different (9). Furthermore, the participation of patients with GMFCS level IV in our study may provide another explanation for that, since knee flexors have an important role in predicting mobility capacity or gait (32, 35), but those patients already had a severe walking impairment. In contrast to these studies presenting an association between lower limb force and walking performance, in a study of 24 children and adolescents (aged 5.3–19.6 years) with spastic CP, the authors failed to demonstrate similar force differences across GMFCS levels (36). However, in this study, researchers used a fixed handheld dynamometer and included patients with both unilateral and bilateral involvement, which may have affected their results.

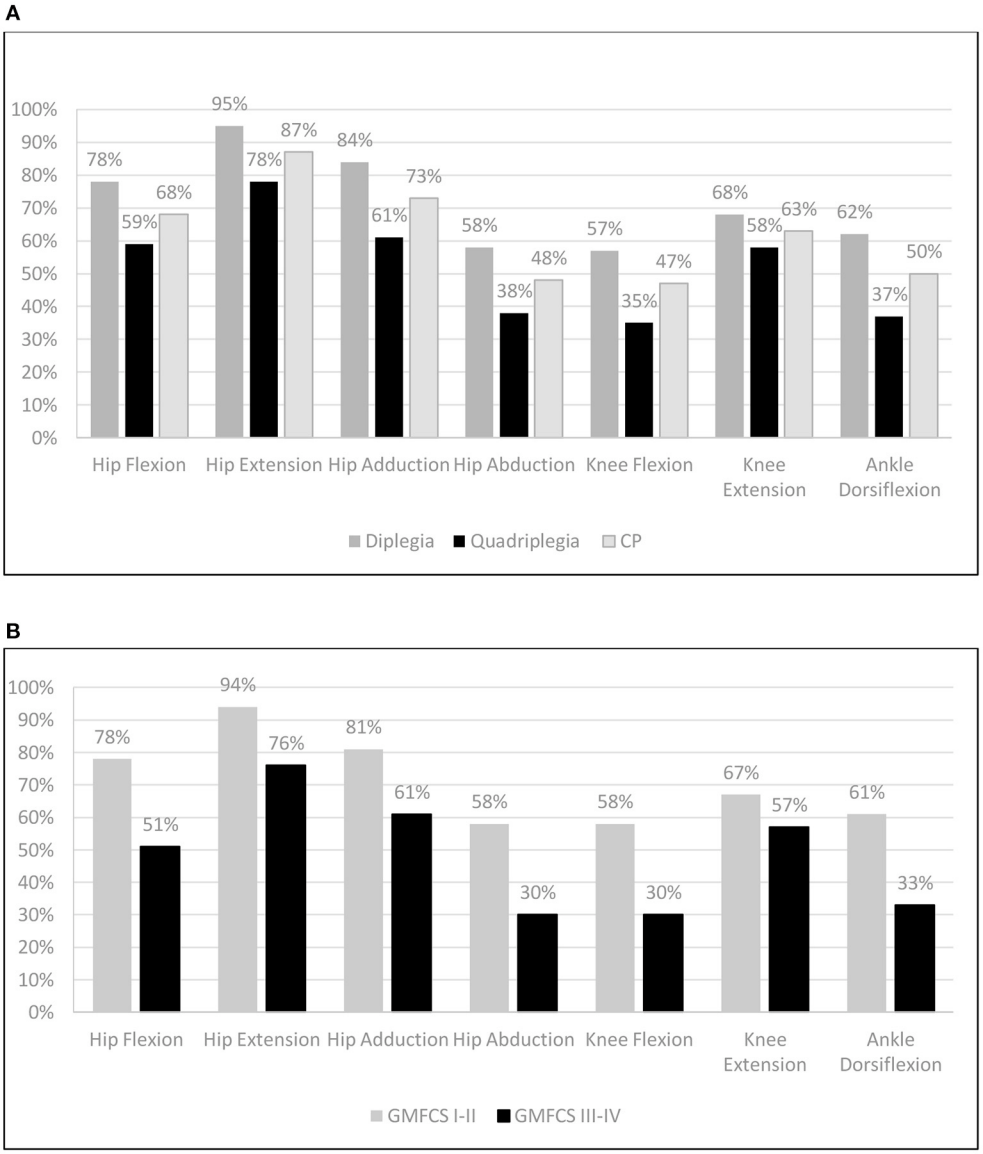

FIGURE 5 | Mean muscle group force as percentage (%) compared to Typically Developing children: **(A)** per CP group and **(B)** per GMFCS group (Independent & Dependent) walkers.

The finding that, in children at GMFCS levels III/IV, the best performance was at the hip extensors, and that the strength of knee extensors was among the best preserved compared to controls, partly explain the fact that these patients were ambulatory up to the age of 16 years, as strength in hip and knee extensors better predicts their ability to walk, more so than spasticity (37). Recently, Davids et al. demonstrated that there is a 90% chance for independent ambulation (GMFCS levels I and II) when strength normalized for weight was 49% predicted relative to TD children, a 75% chance of independent ambulation when it was 33% predicted relative to TD children, and a 50% chance of independent ambulation when it was 16% predicted relative to TD children (10).

The major limitation of the our study was its cross-sectional design, which did not account for the effect of time and training on changes of weight, muscle mass, and force values. Secondly, our study group was fairly imbalanced: independent walkers were more represented, something that could influence the results. Another limitation of the study was the fact that while measuring CP patients' muscle forces, coactivation of the antagonist muscles occurred which may lead to underestimation of the strength of muscle measured (38). Finally, the accurate assessment of extremity muscle strength in children with CP was challenging due to a range of confounding variables, related both to patient's ability and motivation and to technical measurement issues, such as equipment used and testing protocol.

In conclusion, this study confirmed that NF in TD children was significantly greater than in children with CP in all muscle and age groups, with the greatest differences in the 15–16-year-old group. In CP, a constant pattern of significant muscle strength imbalance between antagonist muscles across all ages was identified, indicating that this muscle strength imbalance in CP was present from an early age and did not change significantly during development. Hip flexors, knee flexors, and ankle dorsiflexors were found significantly weaker than adductors and extensors. Lastly, a significant deficiency in hip abductors, knee flexors, hip flexors, and ankle dorsiflexors was identified in GMFCS III/IV when compared with TD and children in GMFCS levels I/II.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

ND: conceptualization, data collection, methodology-research design, resources, and assessment writing—original draft preparation. EN: formal analysis, research design, and writing—original draft preparation: MT: data collection, methodology, resources, and assessment. GG: resources and assessment. AP: conceptualization, methodology, writing—reviewing and editing, supervision. DP: data collection, methodology-research design, resources, and assessment. All authors contributed to the article and approved the submitted version.

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New Ethical Issues in Cerebral Palsy

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Current societal and technological changes have added to the ethical issues faced by people with cerebral palsy. These include new representations of disability, and the current International Classification of Functioning, Disability, and Health, changes in legislation and international conventions, as well as applications of possibilities offered by robotics, brain–computer interface devices, muscles and brain stimulation techniques, wearable sensors, artificial intelligence, genetics, and more for diagnostic, therapeutic, or other purposes. These developments have changed the way we approach diagnosis, set goals for intervention, and create new opportunities. This review examines those influences on clinical practice from an ethical perspective and highlights how a principled approach to clinical bioethics can help the clinician to address ethical dilemmas that occur in practice. It also points to implications of those changes on research priorities.

Keywords: cerebral palsy, bioethics, machine learning, human enhancement, disability, ICF

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INTRODUCTION

A widely used definition of cerebral palsy describes the condition as a group of permanent disorders of the development of movement and posture, causing activity limitation [as defined within the framework of the International Classification of Functioning, Disability, and Health (ICF), https://apps.who.int/iris/bitstream/handle/10665/42407/9241545429.pdf], which are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain, with the motor disorders being often accompanied by disturbances of sensation, perception, cognition, communication, and behavior, by epilepsy, and by secondary musculoskeletal problems (1). As a complex neurodevelopmental disorder, cerebral palsy presents with a number of ethical challenges across the lifespan. Many of these are in continuing evolution as a result of current societal and cultural changes. Some are general but have a profound impact on individuals with cerebral palsy; others concern them more specifically. Enhanced longevity, for example, is gradually making it obvious that cerebral palsy is not restricted to the pediatric age group [it never was! (2)]. This is the result of improvement in medical management, and it is also calls for attention for specific medical issues (3). In addition, this evolution calls for the reorganization of service in order to adequately address the needs of many adults with cerebral palsy, as well as profound changes in societal perspectives. Societal change has been slow, however, so that a number of issues to which individuals with cerebral palsy are confronted incur ethical dilemmas that often go unrecognized or unaddressed, such as those relating to transition from school age to adulthood (4), the notion of personhood and social participation in adults with developmental disability (5, 6), and aging (7, 8). This leads to disenfranchisement of many individuals with cerebral palsy.

This brief overview examines how technological advances and societal changes influence clinical practice in cerebral palsy from an ethical perspective and highlight how a principled approach to

clinical bioethics can help the clinician to address ethical dilemmas that occur in practice. It also points to future research priorities that those changes appear to call for.

TECHNOLOGICAL ISSUES

Dramatic technological advances, some of them potentially empowering, pose ethical questions in cerebral palsy. First of all, access to technological possibilities is typically associated with the risk of a technological imperative that would imply that "if something can be done, then it must be done." However, it would be simplistic and inappropriate to feel compelled to use any technological possibilities for diagnostic, therapeutic, or other purposes just because they are available. When considering new possibilities, it is decisive to discuss their utility and implications with the patient and family with regard to factors that would be anticipated to interact with the experience of new results. It may be useful to review a few examples and examine how they potentially impact the lives of people with cerebral palsy and even the very concept of cerebral palsy.

New technologies can make diagnosis more accurate than previously. This rekindles ethical issues associated with making diagnoses. Clinicians strive to make diagnoses that will be helpful in improving the person's health and well-being. A diagnosis helps rationalize the observed features and provide prognostic projections. It contributes the person's self-concept, i.e., how one would answer the question "Who am I," calling for attention in order not to reduce the person to his or her diagnosis and minimizing the risk of stigma. Critically, a diagnosis enables access to appropriate services. The dimension of helpfulness of the diagnosis is more relevant ethically than its accuracy, though the latter contributes to the former. As cerebral palsy is essentially a descriptive diagnosis, the search for causal factors is important, as etiology may have implications for the person and his or her family. Next-generation sequencing is among the technologies that are emerging to their full potential in this respect. Its application to the exome and whole genome has clarified the etiology of cerebral palsy in an increasing number of cases. Development in genetic testing also calls for refinement in the accuracy of the clinical evaluation, challenging the conception that technology is making clinical skills redundant. The results of a recent study illustrate how difficult this remains (10). The study involved pediatric neurologists, rehabilitation physicians, and other movement disorder specialists viewing the same videos of individuals with cerebral palsy in order to identify the presence and evaluate the severity of the core movement disorders that are characteristic of the condition, namely spasticity, dystonia or choreo-athetosis, and ataxia. However, unacceptably high levels of disagreement were found both within and between observers, which suggests that we must very much improve the way we look at and talk about motor features in cerebral palsy if we are to make sense of the diagnostic concept to help patients appropriately. Further progress in genetic evaluation of cerebral palsy also requires a stronger consensus on how cerebral palsy should be defined (11). Insights gained into the understanding of etiological factors, thanks to the results of genetic testing, offer a renewed opportunity to reflect on the usefulness of the construct of cerebral palsy, which to date remains essentially clinical. Based on clinical and research experience, the concept of cerebral palsy remains arguably useful in order to promote development and functioning, and support family well-being in a life-course perspective (2).

Next-generation sequencing has also expanded knowledge about genetic conditions associated with consistent phenotypes, which is relevant to the diagnosis process (9). Additional ethical implications of these development include those that have been explored in genetic counseling. They span across a variety of topics like testing (and carrier testing), predictive value (particularly if testing is performed very early in life), antenatal diagnosis, screening, therapeutic avenues, access to service, and communication.

Information processing of the outcomes of this type of technology increasingly relies on artificial intelligence and machine learning, which depend critically on the quality and relevance of data that are used by algorithms. An example focusing on DNA methylation patterns (not sequencing) showed how this might also be used for predicting the occurrence of cerebral palsy (12). Indeed, artificial intelligence and machine learning support a range of other technological developments for which we can anticipate ethical discussion relating to cerebral palsy (13). In a not-so-distant future, artificial intelligence may allow reliable objective characterization of clinical presentations (14), possibly fed by wearable sensor technology (15, 16). As previously demonstrated in other populations, machine learning can now recognize a range of relevant physical activity behaviors in individuals with cerebral palsy with great accuracy (17). This progress may bring about clinical improvement to patients, but ethical attention will be required to avoid inappropriate surveillance of people (as continuing monitoring is likely to be unnecessary), to avoid excessive normalization (based on the incorrect assumption that it is better for an individual to have recorded values within the normative range), and to solve issues of mediation and substitutions (i.e., the tension between the use of technological devices and human relationships).

Ethical reflection is also required when it comes to addressing challenges to preservation of self-identity that may arise with new advances in robotics and brain–machine interfaces that will increasingly include artificial intelligence. Robotic exoskeletons, neural-control interface devices, transcutaneous electric stimulation of muscles, and brain stimulation techniques are currently being used in research and are starting to be applied in clinical practice. Future refinements of those technologies may prove transformative for users. They could thus amount to providing "human enhancement" in cerebral palsy through applications ranging from functional electric stimulation to patient–robot interaction and neural implants. As with other applications of human enhancement, progress should be considered within a clear ethical frame of reference (18).

Another critical issue with human enhancement, as with all technological advances and indeed all interventions and services, concerns accessibility in a context of social and economic inequality. An even more fundamental ethical question, which is not specific to technology either, is to appreciate to what extent

improved functioning effectively leads to improved quality of life. We must accept that it is not necessarily so in cerebral palsy (and other conditions) because the quality of life is essentially based on individual experience, so the assumption that intervention impacts the well-being of a person remains to be proven systematically based on individual situations.

SOCIETAL ISSUES

Another area of change that comes with ethical questions affects society itself. There has been increasing societal interest for development and children in general (admittedly mostly as consumers in a market economy, with specific ethical problems). The knowledge of cerebral palsy, and even of the term, is still extremely limited in the general population compared to much rarer conditions. It is not entirely clear why; it is possible that opportunities for self-projections offered by communication media play a role, e.g., "this could happen to me" is less of a theme than in the case of acquired conditions, "how would I deal with my own intellect and emotions" may be more appealing in conditions with intact cognitive functioning (which, of course, also occurs in many people with cerebral palsy). Yet, access to information and communication resources has dramatically increased over the last decades, and this may lead to better awareness of cerebral palsy in society. Access to such resources also has ethical implications, and it has contributed to changing the nature of the relationship between health professionals and families, with more ethical implications.

Changing societal perspectives have been incorporated into national legislation in many countries in the last 30 years and in international treaties, most famously the United Nations Convention on the Rights of Persons with Disabilities, which aims to promote and protect the rights and dignity of disabled persons, including respect for the evolving capacities of children with disabilities and respect for their right to preserve their identity, and ensure that disabled persons enjoy full equality under the law. This is important to underline in a context in which legal institutions are often maligned in clinical care, as they actually play a critical role in shaping societal values and can sometimes even offer support for the ethical decision-making. However, legal institutions can also perpetuate bias. Sadly, recent warfare, natural disasters, and health crises including various stages during the COVID-19 pandemic have provided repeated examples of barriers and deprioritization faced by persons with disabilities as a result of political decision and lack of adequate societal response. This is not acceptable; it can, however, be corrected preemptively by raising awareness of the individual and collective human rights to equal access to services and equal treatment of all people with respect and dignity.

Hopefully, this change is underway as there has been a crucial evolution in the cultural perception of disability, which is at long last becoming less negative and more nuanced than in the past. The perspective is gradually moving from an exclusive focus on deficiencies toward functioning, opportunities, and personal expectations. In many settings, the word "handicap" has fallen into disfavor—not all, though, e.g., the term "polyhandicap" has even been coined in France to refer to the condition of people presenting with multiple disabilities that include severe intellectual and motor impairment attributed to the same causal factors (19). The framework of the ICF suggested 20 years ago has been exerting increasing influence on the understanding of health and disability, the setting of goals, and the organization of service. Beyond the opposition between the medical and the social models of disability, the ICF provides a holistic model of functioning and disability that integrates those models together. In contrast with the medical model, which overlooked the role of social forces in enhancing disability, and the social model, which ignored the significance of health problems, the ICF captures a comprehensive range of determinants of disability (20). In addition, the ICF recognizes participation as a specific dimension in one's health condition with direct relevance to one's experience, values, and sense of purpose (21). The ICF follows a universalistic approach that regards disability as a human trait rather than "something that happens to some people" (20). Therefore, it has been recognized to have an intrinsic ethical significance arising from this standpoint and essentially the interactional framework (20). Nevertheless, some pervasive cognitive biases that are still widely prevalent underlie the persistence of a metaphysical model of disability that implies victimization of disabled people (22). This complicates ethical issues. Individuals with those biases tend to have more negative views about people with disabilities and experience more discomfort in dealing with them, contributing to ethical problems relating to social marginalization and exclusion (23).

It is important to recognize cultural disparities and remaining barriers that still limit the disenfranchisement of many disabled individuals worldwide. Socioeconomic factors have been highlighted, including on a global scale. Whereas, 85% of disabled children are estimated to live in low- and middle-income countries (LMIC), <5% of them have access to basic rehabilitative and support services, and they are at higher risk for discrimination, neglect, and abuse. Primary and secondary prevention strategies for cerebral palsy are absent or insufficient (24), and the needs of most children with cerebral palsy, particularly those in rural settings, are not met, as illustrated by low school attendance, care-seeking, and access to assistive devices (25, 26). Lack of stimulation and rehabilitation likely hamper self-care skills, communication, and mobility. Many of those children with cerebral palsy face additional challenges owing to exacerbation of the interplay between disability and culture by poverty, e.g., lack of access to medical services precludes management of pain and epilepsy; and limited knowledge on nutrition compounded by poor food insecurity may result in malnutrition and increased morbidity (26). Local awareness of the prominent importance of functional needs and quality of life has been documented, and action should be taken to support it effectively (27).

AN ETHICAL APPROACH

Awareness for the ethical issues associated with cerebral palsy is rising in persons with lived experience, health care professionals, and, to a lesser extent, policy makers and the wider public. It is often considered that an understanding of bioethics is part and

parcel of good clinical practice. This can be most evident when dealing with issues directly involving the clinicians' knowledge or skills, partnership with parents or professional team members, communication, and trust. Bioethical practice makes a link between professionalism and humanism, with an emphasis on integrity, humility, respect, empathy, and generosity. Indeed, these attitudes should promote the emergence of ethical decisions in clinical practice, firmly anchored within the interaction with individuals with cerebral palsy and their family. At times, this can be a difficult exercise. As a starting point, it is helpful to realize that while the field of ethics is concerned with questions of morality, a distinction can be made between "common morality" and the ethical reasoning that is at stake here: common morality relates to everyday moral behaviors and decisions that are based on fairly intuitive processes, but what we are concerned with under the banner of ethics aims to resolve perplexing, often difficult moral problems using explicit strategies.

In practical terms, the first step is often to recognize an issue as raising an ethical problem. This may not be obvious if we do not consider the medical, psychological, and social consequences of decision, or if we do not realize that alternative choices are possible. All these choices are potential "solutions" to the ethical problem. It is also useful to consider carefully who are involved in the situation and what their interests are in order to clarify what is at stake and for whom. Ethical questioning and deliberation are the key parts of the exercise and arguably the most important to good clinical practice. They help address challenges and engage in a constructive dialogue with patients and their family, leading to formulating a coherent argument about which of the potential solutions we can reasonably work toward. A number of approaches have been described to that effect. An example is the application of four bioethical principles that were suggested by Beauchamp and Childress (28), as these have proved particularly useful to address ethical dilemmas that occur in the context of cerebral palsy (29). These principles do not impose attitudes or provide ready-made solutions for the resolution of ethical problems, but they can help to organize reflections and support a constructive dialogue. The four principles are respect for autonomy, beneficence, non-maleficence, and justice. When using them, one should rely on an appropriate evidence base. For example, delineating beneficence or non-maleficence or justice in a given situation should not be performed based on intuition or solely on common sense when evidence is available. For some situations, however, the evidence base is currently found wanting. This is in part due to the heterogeneity encountered in cerebral palsy, which has not been comprehensively addressed in research. The condition affects people of all ages and functioning profiles in infinitely different settings across the globe, with much variation in diagnostic and intervention needs. Currently available studies disproportionately include children and young people in Gross Motor Function Classification System levels I to III and often lack controls or long-term outcome measure, resulting in poor quality findings that may be difficult to interpret and generalize. Evaluation of some critical aspects, e.g., economic issues relating to diagnostic and interventional strategies, functional effects in "real life," and quality of life outcomes, is often lacking. Moreover, owing to their novelty, new approaches have often not lent themselves to useful enough studies. This makes the attraction to new technologies challenging, especially when they are presented with dramatic promises (sometimes even for a cure) by their proponent, and these seem to be supported by anecdotal reports and (social) media hype. The lack of knowledge we have on so many aspects of cerebral palsy calls for particular care in dealing with uncertainty—and points to the importance of promoting good quality research for the benefit of people with cerebral palsy.

The bioethical principle of autonomy describes the patient's right to make his or her own choices. This must be supported by informed consent, which is obtained following person-adapted communication, e.g., avoiding technical jargon. Communication can be very challenging for many people with cerebral palsy (30). This can lead to situations in which the patient's needs remain unmet and hamper his or her autonomy in making decisions. As a consequence, individuals with cerebral palsy can feel that their opinions, perceptions, desires, or rights are neglected (31). An example of topic for which there has been progress but remains much to achieve is reproductive health (32). In many people with cerebral palsy, particularly in children, the right for autonomy is exerted by a third who represents the patients, often the persons who take decisions on their behalf. Parents typically play this role with the assumption that they seek their child's best interest, informed and supported by the professionals (33, 34) (there are rare exceptions when it is questioned whether the decisions they take are in the child's best interest). During adolescence, there is a risk of parental overprotection, which may at times interfere with the normal process of development of individual autonomy and decision-making capacity (31). In this context, health professionals should facilitate the young person's personal autonomy, even when they do not express the need for this.

The principle of beneficence literally means "do good." In practice, it refers to doing more good than harm. It is not identical to the principle of non-maleficence, which is taken into account separately. The latter is allegedly inspired by the age-old Hippocratic Oath, though the oft-cited (Latin) formula *primum non nocere* meaning "First, do no harm" is not explicitly mentioned in the Oath that suggests that it may be better not to do something, or even to do nothing, than risk causing more harm than good. The principle of non-maleficence also emphasizes the patient's interest, in particular his or her quality of life. A common challenge to both of the beneficence and maleficence principles occurs when caregivers desire to try unproven interventions for cerebral palsy, e.g., hyperbaric oxygen or stem cell therapy (35). One important aspect when addressing this challenge is to make sure they have sufficiently sound information to make informed decisions about risks and benefits. As clinicians, we can also inform them about other interventions as well as opportunities for participating in current or future clinical research—not forgetting the ethical implications of clinical research in children and disabled people, with regard to vulnerability, decision-making, consent, power relationship, and precedence of the patient's inalienable right to the best available management!

The fourth biomedical principle is justice. Contrary to the other three principles, which have a focus on the individual as most of what we are aware that we do in routine clinical

practice, the principle of justice concerns the health system in which we organize the management of the patient. It is a complex principle to handle, but it must be considered on an individual basis when addressing ethical dilemmas. The principle of justice implies, for example, fair distribution of care by the health professional as well as by the health system. This raises complex discussions, particularly when it involves management of scarce resources—including in resource-rich settings: how much time should a patient be accorded in a clinic, how much therapy, how do we deal with expensive service or intervention, etc.? With regard to cerebral palsy, two perspectives of justice have been identified, one emphasizing equality among individuals and the other fairness (36). This principle has also been used to guide policies. The principle of justice understood as equality has an individualistic orientation: it sees health as an individual good and cerebral palsy as a problem for the individual, requiring from the health system that it organizes service to address individual needs. The approach is typical for settings entrenched in liberalism, e.g., the United States. The other perspective, which is characteristic of countries that favor a welfare state with a strong social security system, e.g., Belgium, equates this principle with fairness, theorizing health as a collective good, which would imply that cerebral palsy is a problem for the community (including the potential problem of exclusion of individuals from the community), so that the health system should provide service for individuals as members of a community and society as a whole should strive to provide those individuals with fair or equal opportunities. However, comparison of outcomes according to different systems remains difficult to interpret (36).

It should help the developers of future disability policies to let themselves guided by the ethical principle of justice through the challenges they will face as disability policy will become increasingly entangled with other policies, including those that relate to employment and retirement. Employment of people with cerebral palsy in Gross Motor Function Classification System I–III levels without intellectual impairment is currently low compared with the general population (the other groups of people with cerebral palsy are at high risk for unemployment), but it appears to remain stable (37). With the relative increase in less physically demanding jobs, employment can be expected to increase provided enablement is enhanced through vocational interventions aiming at balancing personal capabilities, helping with an ergonomic workplace, and other environmental support. Disability policy in a number of European countries at least is shifting toward social investment in human capital and access to the labor market (38). To remain ethical, this evolution should not be done to the detriment of social protection. Future research should monitor those aspects and evaluate the effect on the well-being of people with cerebral palsy.

CONCLUSION

In conclusion, technological and societal changes are associated with some novel ethical issues for people with cerebral palsy, but these can be addressed within the same context of ethical reasoning that is an integral part of ongoing clinical practice. This exercise is entrenched in clinical encounters, in which individual situations may give rise to multiple realities and singular "truths"—and these are not necessarily expected to coincide. Emphasis should be placed on the relevance of a narrative approach that supports a constructive dialogue with the individual with cerebral palsy and the family. Once an ethical dilemma is identified, it can be analyzed using the principles of respect for autonomy, beneficence, non-maleficence, and justice (as both equality and fairness) as guides, bearing in mind that there is no hierarchy of value between these principles, and they do not offer readily available solutions but facilitate a process of shared reflection (29). This approach is mostly pragmatic. It is based on careful observation of signs, facts, and empirical data in a context that is often endowed with incomplete knowledge, requiring conjecture and situational judgment. This approach is not specific to cerebral palsy; it is applied widely in health care. One must recognize that it does not prevent uncertainty from occurring, but the clinician must still aim for the best in every case while running the risk of failure. This type of bioethical reasoning works well to clarify general attitudes with respect to clinical situations, but it is particularly useful for specific decision-making, emphasizing the concept of shared decision-making. Given the enormity of what we do not know, shared decision-making makes allowances for the fact that beneficence and non-maleficence are difficult to assess in many situations. Best practices or guidelines to implement shared decision-making in routine clinical practice with people with cerebral palsy are yet to be developed. Meanwhile, ethical practice remains a process that takes time and may require successive counseling sessions, each demanding appropriate management of current priorities, so the actual resolution of difficult questions should not be expected to be immediate. As in so many areas of cerebral palsy, an increase in the quality of research is necessary. To ensure relevance, future research must involve people with lived experience of cerebral palsy (patients, parents, siblings) when conceiving studies, collecting results, and analyzing findings. Individualized goal setting and realization, well-being, and social determinants are particularly important research priorities, and so are the lifelong and global perspective, not overlooking areas that have been identified as requiring specific attention in low- and middle-income countries, such as ICF domains of activity, participation, and environmental factors, interventions aiming to modify the environment and increasing participation (39). There is a great need for sound qualitative research exploring the perspectives of people with cerebral palsy and for the evaluation of knowledge translation strategies.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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BRIEF RESEARCH REPORT
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Genetic Testing Contributes to Diagnosis in Cerebral Palsy: Aicardi-Goutières Syndrome as an Example

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Cerebral palsy (CP) is a non-progressive neurodevelopmental disorder characterized by motor impairments, often accompanied by co-morbidities such as intellectual disability, epilepsy, visual and hearing impairment and speech and language deficits. Despite the established role of hypoxic–ischemic injury in some CP cases, several studies suggest that birth asphyxia is actually an uncommon cause, accounting for <10% of CP cases. For children with CP in the absence of traditional risk factors, a genetic basis to their condition is increasingly suspected. Several recent studies indeed confirm copy number variants and single gene mutations with large genetic heterogeneity as an etiology in children with CP. Here, we report three patients with spastic cerebral palsy and a genetically confirmed diagnosis of Aicardi-Goutières syndrome (AGS), with highly variable phenotypes ranging from clinically suggestive to non-specific symptomatology. Our findings suggest that AGS may be a rather common cause of CP, that frequently remains undiagnosed without additional genetic testing, as in only one case a clinical suspicion of AGS was raised. Our data show that a diagnosis of AGS must be considered in cases with spastic CP, even in the absence of characteristic brain abnormalities. Importantly, a genetic diagnosis of AGS may have significant therapeutic consequences, as targeted therapies are being developed for type 1 interferonopathies, the group of diseases to which AGS belongs. Our findings demonstrate the importance of next generation sequencing in CP patients without an identifiable cause, since targeted diagnostic testing is hampered by the often non-specific presentation.

Keywords: cerebral palsy, aicardi goutières syndrome, next generation sequencing, genetic testing, genetic diagnosis

INTRODUCTION

Aicardi-Goutières syndrome (AGS) is a rare hereditary inflammatory disorder which usually presents in early infancy with systemic and central nervous manifestations caused by the inappropriate induction of a type I interferon-mediated immune response (1). To date, mutations in seven genes have been identified to cause AGS, namely *TREX1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, *ADAR1*, and *IFIH1*. AGS is part of the type 1 interferonopathies. The type 1 interferon-mediated antiviral response is usually triggered by viral infections (2). In case of Aicardi-Goutières syndrome, it is hypothesized that self-nucleic acids are no longer recognized as such, leading to an inappropriate immune response with an overactive type 1 interferon signaling, even in the absence of a viral infection. Suggestive features include cerebrospinal fluid (CSF) lymphocytosis and the neuroradiological findings of calcifications of the basal ganglia and leukoencephalopathy. Neurological manifestations include progressive microcephaly, spasticity, epilepsy and developmental delay, while systemic manifestations include hepatosplenomegaly, skin rash and chilblain lesions, glaucoma and systemic lupus erythematosus-like manifestations. Although the majority of patients present with this "classical" phenotype, several studies report a broader spectrum of disease presentation, progression and outcome, with even static or slowly progressive forms presenting as cerebral palsy (CP) (3–5). Due to this clinical heterogeneity, the actual prevalence of AGS is not known.

Cerebral palsy (CP) is a clinical descriptive term that defines a heterogeneous group of non-progressive neurodevelopmental disorders of motor impairment, which co-occur with a wide range of medical conditions such as intellectual disability (ID), speech and language deficits, autism, epilepsy and visual and/or hearing impairment. CP is caused by a cerebral anomaly/dysfunction that develops during pregnancy, birth or infancy (before the age of 2 years). With a prevalence of 1.5–2.5 per 1,000 live births in high-income countries and an estimated prevalence of up to 3.6 per 1,000 children in low-income countries (6), CP is the most common cause of physical disability in childhood (7) with an important impact on the quality of life of patients and on society. Historically, inadequate oxygen delivery to the brain during birth was thought to be the leading cause of CP, but large population-based controlled studies have shown birth asphyxia to be a rather uncommon cause accounting for <10% of CP cases (8). This recent insight has led to an increased interest in genetic studies to elucidate its additional causes. However, compared to other neurodevelopmental disorders, i.e., ID and autism, large genetic studies in CP are still underrepresented (2).

Triggered by these findings, we started to perform genetic testing in our cohort of patients with a clinical diagnosis of CP in order to identify underlying molecular diagnosis. Testing involves SNP microarray to exclude pathogenic copy number variants followed by whole exome sequencing with *in silico* filtering of variants in around 200 genes associated with CP or "CP-mimics." The latter is defined as a neurodevelopmental disorder that initially presents with a CP phenotype, but with a differing natural history and prognosis (9, 10). A full list of the genes included in our CP panel with their associated disorder, inheritance pattern and clinical characteristics is available in the supplements (**Supplementary Table 1**). While our study is ongoing, we already present three cases from our CP cohort with a genetically confirmed diagnosis of Aicardi-Goutières syndrome (AGS); phenotypes ranged from clearly suggestive for the disorder to non-specific findings like spastic diplegia/quadriplegia, developmental delay and non-pathognomonic brain MRI findings.

With these three cases, we want to illustrate the added value of genetic testing in CP, as this may lead to unexpected diagnoses that may alter treatment options. Moreover, a molecular diagnosis in CP patients aids in the counseling of patients and their families, as it helps them understand the cause of the condition and improves the testing possibilities in future family planning.

METHODS

In all three cases, Single Nucleotide Polymorphism (SNP) array was performed using an Illumina HumanCytoSNP-12 v2.1 beadchip on an iScan system, following manufacturer's protocols. CNV analysis was done using GenomeStudio software (Illumina) and CNV WebStore, version 2.0 as previously described (11).

Whole exome sequencing (WES) of DNA obtained from blood lymphocytes of the index case and both parents was performed on an Illumina HiSeq4000 instrument after enrichment with the Agilent SureSelect Human All Exon V5 kit. Data analysis was performed using an in-house developed pipeline following GATK Best Practice Guidelines, followed by variant annotation and filtering using VariantDB (12). We analyzed a gene panel consisting of 200 genes associated with CP and CP mimics.

In one case (case 1), sequencing of the coding exons and exon/intron boundaries of *TREX1* (NM_007248.5), *RNASEH2A/B/C* (NM_006397.2, NM_001142279.2, NM_032193.4), *ADAR1* (NM_001193495.2), *SAMHD1* (NM_001363729.2) and *IFIH1* (NM_022168.4) was performed using a targeted next-generation sequencing panel for AGS (by courtesy of Yanick Crow, Laboratory of Neurogenetics and Neuroinflammation, Paris Descartes University, Sorbonne-Paris-Cité, INSERM UMR 1163, Institut Imagine, Paris, France). In addition, Multiplex Amplicon Quantification (MAQ) analysis of exon 5 of *SAMHD1* was performed.

CASE REPORTS

Our first case is a girl referred because of delayed motor development and gait difficulties at the age of 2 years. She is the first child of healthy, non-consanguineous parents of Caucasian origin with a normal family history. Pregnancy and birth were uneventful. Neurological examination at the time of referral demonstrated cerebral palsy with spastic diparesis; brain MRI showed non-specific, periventricular leukomalacia.

At the age of 8 years, she was diagnosed with attention deficit hyperactivity disorder and developed skin lesions on hands and toes during cold months, most likely chilblain lesions. This was supported by analysis of a skin biopsy, demonstrating a perivascular inflammation and immunofluorescence pattern suggestive for the presence of a lupus band. Brain Magnetic Resonance Imaging (MRI) at the age of 10 years demonstrated periventricular and frontoparietal white matter abnormalities suggestive of sequels of cortical and white matter infarctions and limited parietal cortical atrophy (**Figure 1A**). MR angiography displayed images compatible with moyamoya disease at the distal left internal carotid artery and the proximal right middle cerebral artery (**Figure 1B**). Ophthalmological investigations were normal. RNA analysis of blood showed an increase of interferon-related gene expression, compatible with a diagnosis of AGS. Blood analysis also showed persistently mildly increased aspartate aminotransferase (AST)/alanine aminotransferase (ALT) as well as presence of antinuclear antibodies (anti-DFS70) with normal complement.

The chilblain lesions were initially treated with a combination of a calcium antagonist and hydroxychloroquine, with little improvement. After the molecular confirmation of the AGS diagnosis, a switch to a Janus Kinase (JAK) inhibitor demonstrated good results, with normalization of AST/ALT and reduction of chilblains.

The second case is a girl referred at the age of 9 years because of developmental delay that was only noted after an episode of fever of unknown origin at the age of 10 months. The girl is the third child of healthy parents of North-African origin, who are first-degree cousins. The mother had two early miscarriages. No other relatives presented with neurological problems.

At initial presentation, a quadriplegia of mixed spastic and dyskinetic type was noted, more pronounced on the right side of her body. Mild intellectual disability and speech deficit were observed. During winter, she developed skin lesions on her feet which were initially attributed to pressure lesions from splints, but were later classified as chilblain lesions (**Figure 2**).

MRI of the brain showed posterior thinning of the corpus callosum without other abnormalities (**Figure 1C**). Ophthalmological evaluation was normal. At the age of 9 years, a bilateral femur-osteotomia was performed because of recurrent bilaterally occurring hip luxations. At the age of 13 years, she underwent a combined hamstring release with open hip reduction and pelvic girdle osteotomia.

Currently, at the age of 15, she can roll over independently and sit with support. Speech is limited to single words and short sentences. She developed a scoliosis and joint contractures, treated with a corset, wrist splints and baclofen. Chilblain

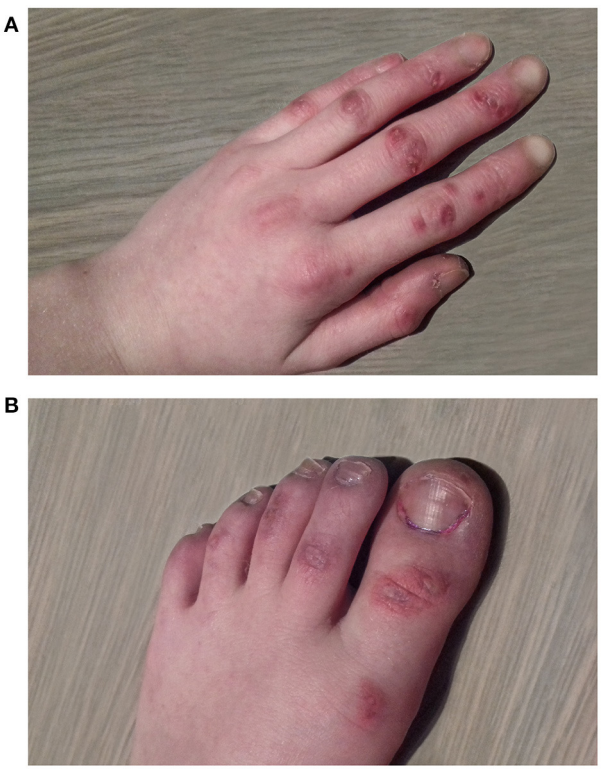

FIGURE 2 | Chilblain lesions appearing in winter time on hands **(A)** and feet **(B)** of patient 2.

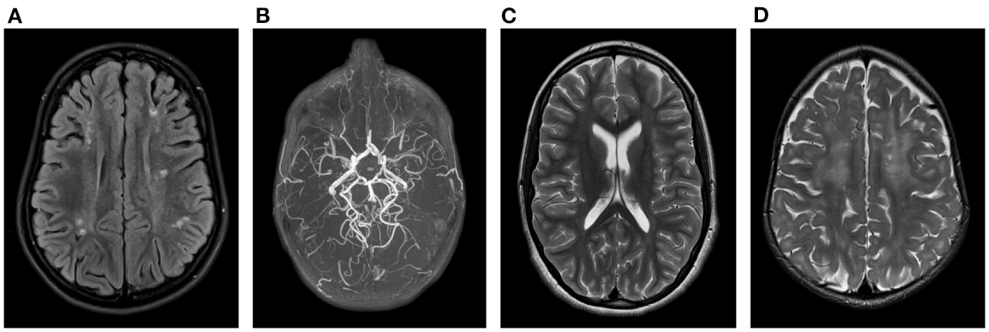

FIGURE 1 | Brain MRI findings in our AGS patients: **(A)** Periventricular and frontoparietal lesions suggestive of cortical and white matter infarctions associated with **(B)** moyamoya disease at the distal left internal carotid artery and the proximal right middle cerebral artery on MR angiography in patient 1. **(C)** Isolated posterior thinning of the corpus callosum in patient 2. **(D)** Bilateral frontal periventricular microcysts and diffuse white matter hyperintensities in patient 3.

lesions are treated with a topical corticosteroid cream with good response.

The third case is a girl referred at the age of 1½ years because of developmental delay. She is the fourth child of healthy, apparently unrelated parents of Moroccan descent. Pregnancy and birth were uneventful. At first referral, a spastic diparesis with hypertonia of both legs was noted. She had recurrent fever episodes, and parents noted a temporary relapse during these episodes, with a decrease in babbling and an increase in feeding difficulties that later resolved. At the age of 1 year, she had one episode suggestive of an epileptic seizure, but a subsequent electroencephalogram was normal. Brain MRI identified bilateral frontal periventricular cysts (**Figure 1D**). Metabolic investigations showed elevated lactic acid and hyperammonaemia, that both had normalized at a second evaluation. Because of the findings on brain MRI and the elevated lactic acid, genetic testing for mitochondrial disorders, both on mitochondrial and nuclear DNA, was performed, but turned out normal. Ophthalmological evaluation was normal. Currently, at the age of 2 years, she starts to sit without support and is able to take little steps with support of both hands. Speech is limited to some words. Neurological examination confirmed a spastic diplegic cerebral palsy with hyperreflexia. No chilblain lesions are noticed.

The clinical findings of our cases are summarized in **Table 1**.

RESULTS

SNP array did not reveal clinically relevant copy number variants in any of the cases.

In the first case, analysis of a panel for AGS showed compound heterozygosity for two pathogenic variants in the *SAMHD1* gene. Initially, only a paternally inherited c.109G>T (p.Glu37*) variant was identified and confirmed by Sanger sequencing. Further interrogation of the read depth suggested a possible deletion of exon 5 of the *SAMHD1*-gene, that was confirmed by MAQ analysis and was maternally inherited. Both variants are absent from GnomAD (https://gnomad.broadinstitute.org/). Truncating variants and intragenic *SAMHD1* exon deletions have previously been described as pathogenic (13–15).

In cases 2 and 3, WES demonstrated the same homozygous c.529G>A (p.Ala177Thr) variant in the a*RNASEH2B* gene. Heterozygous carriership for the mutation was confirmed in the parents. This variant was already reported as pathogenic in the literature (16, 17).

DISCUSSION

We describe three patients with a clinical diagnosis of spastic cerebral palsy in whom genetic testing contributed to a molecular diagnosis of Aicardi-Goutières syndrome. Based on the clinical findings in our cases, an AGS diagnosis was suspected in only one (case 1). The other two cases were identified by WES, a technology that has only recently been implemented in our routine diagnostics for CP patients. The identification of two AGS cases in approximately 100 CP cases that have been analyzed by WES at our genetic center to date suggests that AGS may be a rather common cause of CP that can remain undiagnosed without thorough genetic testing, although we acknowledge that the small sample size of our CP cohort can cause a bias in the interpretation of these data.

Our first case presented with cerebrovascular abnormalities with cortical and white matter infarctions associated with moyamoya disease. The latter is an important complication specific for *SAMHD1*-related AGS and is not seen in the other subtypes (18). Consequently, we were not surprised that a targeted AGS panel consisting of the seven genes currently known to be associated with AGS demonstrated compound heterozygosity for a *SAMHD1* non-sense mutation and a single exon deletion.

The homozygous c.529G>A (p.Ala177Thr) variant in *RNASEH2B* identified in the second and third case is a recurrent pathogenic mutation that was already reported in several cases of AGS that presented with a more non-specific phenotype, including two adult-onset cases with cerebral calcifications and chilblains, one case with chilblain lesions only and three cases presenting with spastic di/quadriplegia and preserved intellect. This, together with the non-specific phenotype of spastic CP in our two cases, may suggest a potential genotype-phenotype correlation with a tendency toward non-specific clinical features. However, a classic infantile AGS presentation was also present in two cases (16, 17).

The highly variable and sometimes rather non-specific phenotype of AGS hampers a swift diagnosis and probably results in underdiagnosis of the condition. A recent study of interferon-related gene expression in seven patients with sine causa spastic-dystonic tetraparesis led to the diagnosis of AGS in one patient by the demonstration of a "type 1 interferon signature," a specific expression pattern of IFN-related genes identified in type 1-interferonopathies (19, 20). While an analysis of interferon-related gene expression may indeed be useful, we suggest performing genetic testing by whole exome sequencing as a first-tier strategy in CP diagnostics due to the wide differential diagnostic considerations in CP. Determining the type 1 interferon signature may be of added value in case of the identification of variants of unknown significance, or in cases highly suggestive of AGS but in which genetic testing fails to identify a pathogenic variant in one of the currently known AGS genes. One drawback of WES is that certain variant types, i.e., CNVs, or potentially relevant intronic/promoter/regulatory variants can remain undetected, rendering it possible that a genetic diagnosis is missed, while the interferon signature in these cases can still point to the diagnosis of AGS.

The importance of a genetic diagnosis of AGS cannot be overestimated: it aids in the counseling of patients and their families, offers opportunities for family planning and has therapeutic consequences, as targeted therapies for type 1 interferonopathies are emerging. Several treatment strategies modulating components of the transducing pathway of the interferon response are under study, including reverse transcriptase inhibitors (RTIs) and Janus kinase (JAK) inhibition, although further testing is needed to prove their efficacy and study their long-term effects (21, 22).

TABLE 1 | Summary of genetic and clinical findings of our AGS cases.

	Case 1	Case 2	Case 3
Affected gene	*SAMHD1*	*RNASEH2B*	*RNASEH2B*
Pathogenic variant	c.109G>T (p.Glu37*)(HET)/deletion exon 5 (HET)	c.529G>A (p.Ala177Thr)(HOM)	c.529G>A (p.Ala177Thr)(HOM)
Sex	F	F	F
History of consanguinity	–	+	–
Age at last examination	12 y, 1 m	15 y, 8 m	3 y, 6 m
Age at presentation	1 y, 10 m	8 y, 8 m	2 y, 1 m
Age at diagnosis	10 y, 3 m	14 y, 9 m	3 y, 2 m
Motor delay	+	+	+
Speech delay	+	+	–
Intellectual disability	+	+	+
Seizures	–	–	?
Chilblain lesions	+	+	–
Head circumference (cm)	46.5 (p20)	52 (p50)	48.3 (p50)
Neurological findings	Spastic diplegia ADHD	Spastic and dyskinetic quadriplegia	Spastic diplegia
Ophthalmological findings	–	–	–
Other findings	Eczema	–	–
Brain MRI	Bilateral white matter abnormalities, parietal cortical atrophy and signs of Moyamoya disease	Posterior thinning corpus callosum	Periventricular microcysts and white matter abnormalities

HET, heterozygous; HOM, homozygous; F, female; y, years; m, months.

Although this report focuses on AGS patients, we want to stress the importance of genetic testing in all CP patients, since a definite diagnosis in this cohort can easily be missed solely based on the often non-specific clinical presentations.

As previously stated, large genetic studies in CP are only just emerging, but they all point to an important contribution of genetic causes (8). The first publication on the benefit of early (genetic) diagnosis dates from 2014; Leach et al. summarized several inborn errors of metabolism that can present as CP mimics, of which several are amendable to treatment (9). 1 year later, clinically relevant copy number variants (CNVs) were demonstrated in 9.6% (11/115) of CP cases (23). An additional study by Zarrei et al. in 2018 demonstrated a frequent occurrence of *de novo* CNVs in the hemiplegic CP subtype (7.2%) compared to controls (1%) (24). Also in 2015, the first WES study in a cohort of 201 CP cases demonstrated an important contribution of single nucleotide variants (SNVs), with a diagnostic yield of 14% (25). Another study in 2018 even reached a diagnostic yield of 65% using WES in 50 individuals with atypical CP; however, this study also included promising candidate genes whose role in CP has not been validated (26). A study in 2019, using a gene panel of 112 genes consisting of a combination of known disease genes and candidate genes classified as intolerant to variation, found genetic variants of possible clinical relevance in 10% of the CP cohort (27). While the genetic causes are heterogeneous, this study identified six recurrent genes that contributed to at least 4% of disease burden in CP: *COL4A1*, *TUBA1A*, *AGAP1*, *L1CAM*, *MAOB* and *KIF1A* (27).

Based on these findings, the Center of Medical Genetics in Antwerp started routinely offering SNP-array followed by trio-bases WES with analysis of a targeted gene panel consisting of around 200 genes associated with CP or CP mimics (**Supplementary Table 1**) in all CP cases without evident traditional risk factors as of 2019. The full results of the genetic findings in our CP cohort will be published in an additional manuscript. Due to the continuous increase in genes associated with a CP phenotype, the drawback of our approach using a selected gene panel is that pathogenic variants in genes only recently associated with CP or genes associated with neurodevelopmental disorders in which CP is only a rare presentation can be missed. A phenotype-driven genome-wide analysis may therefore be offered in the absence of pathogenic CNVs or pathogenic variant in the targeted panel. An advantage of using a targeted gene panel is that the chance of incidental findings is low.

The genetic heterogeneity associated with CP has triggered a discussion regarding the validity of CP as a clinical diagnosis. This topic was recently addressed by MacLennon et al., stating that CP is a neurodevelopmental disorder diagnosed based on clinical signs, not etiology (28). The authors present several important arguments to keep CP as a clinical diagnosis instead of replacing it with the molecularly identified disorder, including social and financial support systems that are present for CP patients, access to services, utility and accuracy of CP registries and community understanding of the term CP (28). We fully agree that the diagnosis of CP should not be altered, but it should warrant additional genetic testing to enable genetic subclassifications of CP, for example "CP caused by a pathogenic *COL4A1* variant." Subclassifying CP based on genetic causes improves genetic counseling of families e.g., regarding future family planning and contributes to an improved and overall more personalized treatment and follow-up of CP patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are publicly available. This data can be found here: https://www.ncbi.nlm.nih.gov/clinvar/, accession numbers SUB9038630: SCV001478409, SUB9149334: SCV001481865.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

This work was realized with the collaboration of all authors. DB contributed by designing and conceptualizing the study and drafting of the manuscript for intellectual content. CDC contributed by designing and conceptualizing the study and drafting of the manuscript for intellectual content. CD contributed by playing a major role in the acquisition of clinical data. BO contributed by playing a major role in the acquisition of clinical data and in the revision of the manuscript for intellectual content. JD contributed by playing a major role in the acquisition of clinical data. ER contributed by the generation and interpretation of the genomic data. KJ contributed by the interpretation of the data and by revision of the manuscript for intellectual content. MM designed and conceptualized the study, analyzed and interpreted the data and drafted the manuscript for intellectual contentment. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.617813/full#supplementary-material

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Trends in Prevalence and Severity of Pre/Perinatal Cerebral Palsy Among Children Born Preterm From 2004 to 2010: A SCPE Collaboration Study

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Aim: To report on prevalence of cerebral palsy (CP), severity rates, and types of brain lesions in children born preterm 2004 to 2010 by gestational age groups.

Methods: Data from 12 population-based registries of the Surveillance of Cerebral Palsy in Europe network were used. Children with CP were eligible if they were born preterm (<37 weeks of gestational age) between 2004 and 2010, and were at least 4 years at time of registration. Severity was assessed using the impairment index. The findings of postnatal brain imaging were classified according to the predominant pathogenic pattern. Prevalences were estimated per 1,000 live births with exact 95% confidence intervals within each stratum of gestational age: ≤27, 28–31, 32–36 weeks. Time trends of both overall prevalence and prevalence of severe CP were investigated using multilevel negative binomial regression models.

Results: The sample comprised 2,273 children. 25.8% were born from multiple pregnancies. About 2-thirds had a bilateral spastic CP. 43.5% of children born ≤27 weeks had a high impairment index compared to 37.0 and 38.5% in the two other groups. Overall prevalence significantly decreased (incidence rate ratio per year: 0.96 [0.92–1.00[) in children born 32–36 weeks. We showed a decrease until 2009 for children

born 28–31 weeks but an increase in 2010 again, and a steady prevalence (incidence rate ratio per year = 0.97 [0.92–1.02] for those born ≤27 weeks. The prevalence of the most severely affected children with CP revealed a similar but not significant trend to the overall prevalence in the corresponding GA groups. Predominant white matter injuries were more frequent in children born <32 weeks: 81.5% (≤27 weeks) and 86.4% (28–31 weeks), compared to 63.6% for children born 32–36 weeks.

Conclusion: Prevalence of CP in preterm born children continues to decrease in Europe excepting the extremely immature children, with the most severely affected children showing a similar trend.

Keywords: cerebral palsy, preterm birth, prevalence, severity, brain imaging

INTRODUCTION

Cerebral palsy (CP) is a group of disorders of various etiologies that have movement and posture disturbances in common. The clinical picture includes a wide range of deficits of varying severity that have a significant impact on daily lives, and that persist through the lifespan (1). CP occurs as a result of abnormal brain development or damage to the developing brain. The increasing use of early magnetic resonance imaging (MRI) allows a better comprehension of the underlying pathophysiological mechanisms (2, 3). Children born preterm (PT) i.e. before 37 completed weeks of gestation are at increased risk of developing CP, and the risk increases with higher immaturity at delivery (4, 5). Meta-analyses of studies that addressed the relationship between length of gestation and prevalence of CP for the generations born 1985 to 2002/2004 showed that children born at 32–36, 28–31, and ≤27 weeks were, respectively, 5–6, 32–54, and 60–130 times more likely to have CP than full-term children (6, 7). These findings are in line with a considerable number of studies demonstrating that children born extremely preterm (EPT, ≤27 weeks) presented neurodevelopmental disabilities with higher incidence and severity than term-born children (8–14).

Over decades it has been commented on CP prevalence is unchanging. Only slowly have reports about decreasing prevalence come to recognition. First this was reported in children with low birthweight (LBW, <2,500 g) in Sweden and Germany (15). In children born in the late 80ies and after, a decrease in prevalence was reported among those with moderately LBW (MLBW, 1,500–2,499 g) in Europe (16, 17) and Australia (18). Also in children with very low birthweight (VLBW, 1,000–1,499 g), prevalence decreased starting in the 80ies in Europe (16, 19) and about one decade later in Australia (18, 20). This decrease in prevalence then also led to a decrease concerning the overall prevalence of CP (16, 18, 20–25). However, it remains unclear whether this downward trend benefits children with extremely low birthweight (ELBW, <1,000 g).

Among children born preterm, there is also limited knowledge on severity of CP across GA groups (6). In studies examining long-term trends, there is some evidence that the prevalence of severe forms has decreased over time in children born PT or with a LBW with an increasing rate of ambulant children and fewer concomitant disabilities reported (16, 18). However, in children who were born EPT or with ELBW, the severity rates seemed to remain steady over the studied periods (16), and declining trends were only observed in associated intellectual impairment (18).

Most children with CP who were born very preterm (VPT) have neuroimaging evidence of predominant white matter injury (26). Standardizing terminology and classification allows to heighten the knowledge of the nature of brain lesions at population's level. A very first analysis using the MRI Classification System (MRICS) developed and validated by the Surveillance of Cerebral Palsy in Europe (SCPE) collaboration (27) showed a very clear lesional pattern in children born VPT with 80% having predominant white matter lesions (such as periventricular leucomalacia or sequelae of hemorrhage). Data also suggested that this proportion increases with decreasing GA at birth (28).

Harmonized and reliable population-based data on children with CP from population-based registries from across Europe are routinely collected as part of the SCPE network. These have the advantage of providing a consistent and clear definition of the condition, a detailed clinical description with severity standardly described by functional scores, and a classification for MRI findings. The aim of this study was to use 2004 to 2010 birth cohorts to report on prevalence of CP, severity rates, and types of brain lesions in children born preterm overall and stratified by GA groups.

Abbreviations: BW, Birth weight; CI, confidence interval; CP, cerebral palsy; ELBW, extremely low birthweight; EPT, extremely preterm; GA, gestational age; GMFCS, Gross Motor Function Classification System; IQ, intelligence quotient; IRR, incidence rate ratio; LBW, low birthweight; MLBW, moderately low birthweight; MPT, moderately preterm; MRI, Magnetic resonance imaging; MRICS, Magnetic resonance imaging classification system; NNS, neonatal survivors; PT, Preterm; PVL, periventricular leukomalacia; SCPE, Surveillance of Cerebral Palsy in Europe; VLBW, very low birthweight; VPT, very preterm.

MATERIALS AND METHODS

Source of Data

We used data from population-based registries participating in the SCPE network, covering either a part or their whole country (https://eu-rd-platform.jrc.ec.europa.eu/scpe). These registries

TABLE 1 | Number of children with cerebral palsy born preterm (<37 weeks gestation) between 2004 and 2010 and corresponding live births, and total annual live births, by registry.

Location of the registry	Birth-years available	Total annual live births[†]	*n* live births <37 WG	*n* children with CP <37 WG
C05, Northern Ireland, UK	2004–2010	24,032	11,876	122
C06, Western Sweden	2004–2010	25,122	9,822	127
C07, Counties of Dublin, Kildare and Wicklow, Ireland	2004–2008; 2010	25,184	8,398	136
C12, Denmark (Faroe Island and Greenland excluded)	2004–2007	64,714	17,493	188
C15, Norway	2004–2010	59,831	28,006	316
C19, Slovenia	2004–2009	19,675	8,557	100
C21, Portugal	2004–2006; 2008–2010	105,014	48,611	366
C22, Riga, Latvia	2004–2008	7,349	1,816	19
C23, South West Hungary	2004–2010	8,562	6,127	46
C27, Belgium	2004–2010	75,586	42,072	353
C28, Croatia	2004–2010	36,387	14,162	252
C31, Attica (Athens Metropolitan area), Greece	2004–2010	41,118	27,138	248
Total			224,078	2,273

WG, weeks gestation.
[†] *Average of the total annual number of live births over the study period.*

provide yearly pseudonymized data on children with CP to the SCPE central database. Population data (live births and neonatal mortality the same year in the same catchment area) are available from the census or any official data population source. The SCPE central database is stored and managed by the European Commission Joint Research Center, Health in Society Unit, Directorate Health, Consumers and Reference Materials, Ispra (Italy). Definitions, classifications, data collection and harmonization methods have been reported elsewhere (29–32).

Population Studied

Children with CP were eligible for this study if they were born preterm (<37 weeks GA) between 2004 and 2010 (2010 was the most recent year validated at European level), had a pre/perinatal CP according to SCPE definition (30) (children with CP of post neonatal origin, i.e., a recognized brain damaging event that is unrelated to factors in the ante-, peri-, or neonatal periods, were excluded), and were at least 4 years old at time of registration. Children included in the analyses were born from mothers living in the catchment areas at the time of birth. Registries were eligible if the number of live births <37 weeks' gestation stratified by GA groups (EPT, ≤27 weeks; VPT, 28–31 weeks; moderately preterm, MPT, 32–36 weeks) were available for the geographical areas covered. Centers with <5,000 average annual livebirths between 2004 and 2010 were not considered. Within each registry, birth years with more than 25% missing data on GA on children with CP were excluded.

Study Variables

The following characteristics were collected. Perinatal data included mother's age at birth (in years), multiple birth (singletons vs. twins or higher multiple), cesarean delivery (yes/no), GA in completed weeks, sex. CP subtype was classified according to the predominant neurological clinical findings into spastic CP (bilateral or unilateral), dyskinetic CP, and ataxic CP or unknown (https://eu-rd-platform.jrc.ec.europa.eu/scpe/data-collection/cp-subtypes_en). The severity of motor impairment was assessed using the Gross Motor Function Classification System (GMFCS) (33). GMFCS levels were grouped into 3 categories, I-II (ability to walk), III (walk with aids), and IV-V (wheelchair). The following co-morbidities were also considered: moderate to severe intellectual disability (based either on a formal intelligence quotient (IQ) testing or on a clinical estimate corresponding to an IQ < 50), severe visual impairment (blind or no useful vision in both eyes), severe hearing impairment (bilateral hearing loss >70 dB), active epilepsy (history of unprovoked seizures, still on treatment at age of registration). Severity was characterized using several options. First, we reported separately the percentage of children affected by moderate to severe intellectual disability, severe visual impairment, or active epilepsy. Second, children were classified according to their impairment index (34) into highly impaired (GMFCS IV-V and/or IQ < 50, whatever existence and severity of other impairments), lowly impaired (GMFCS I-II and IQ > 70, without any visual or hearing impairment, and no epilepsy), moderately impaired corresponding to all other conditions. We also recorded data on brain MRI performed post-neonatally and classified the findings according to the MRICS based on the predominant pathogenic pattern into maldevelopments, predominant white matter injury, predominant gray matter injury, miscellaneous, and normal (27).

Analysis

All the analyses were stratified according to GA groups: ≤27, 28–31, 32–36 weeks. Maternal and perinatal characteristics, CP subtype, and impairments were described using counts and percentages calculated on non-missing data. They were compared between GA groups using chi-square tests. Prevalences

TABLE 2 | Characteristics of children with cerebral palsy born 2004–2010, by gestational age groups, $n = 2,273$.

	EPT ≤27 WG $n = 499$	VPT 28–31 WG $n = 868$	MPT 32–36 WG $n = 906$	*p*-value (chi-square)
Maternal age at birth, in years, *n* (%)				0.416
<20	21 (5.6)	28 (4.1)	23 (3.2)	
20–29	158 (42.1)	288 (41.8)	295 (40.7)	
30–34	107 (28.5)	213 (30.9)	243 (33.6)	
35–39	70 (18.7)	122 (17.7)	135 (18.6)	
>39	19 (5.1)	38 (5.5)	28 (3.9)	
Missing, *n*	124	179	182	
Multiple birth, *n* (%)	143 (29.3)	240 (28.1)	192 (21.7)	0.001
Missing, *n*	11	13	23	
Cesarean delivery, *n* (%)	231 (53.1)	489 (62.9)	488 (59.3)	0.004
Missing, *n*	64	91	83	
Sex, male, *n* (%)	307 (61.5)	527 (60.7)	518 (57.2)	0.182
CP-subtype, *n* (%)				<0.001
Bilateral spastic	326 (65.5)	617 (71.1)	533 (58.9)	
Unilateral spastic	110 (22.1)	204 (23.5)	284 (31.4)	
Dyskinetic	23 (4.6)	27 (3.1)	48 (5.3)	
Other forms/unable to classify	39 (7.8)	20 (2.3)	40 (4.4)	
Missing, *n*	1	0	1	
GMFCS, *n* (%)				0.054
I-II, able to walk	264 (55.2)	480 (56.5)	546 (62.3)	
III, walk with aids	67 (14.0)	118 (13.9)	96 (10.9)	
IV-V, wheelchair	147 (30.8)	251 (29.6)	235 (26.8)	
Missing, *n*	21	19	29	
Moderate to severe intellectual disability (IQ<50), *n* (%)	139 (32.1)	171 (22.3)	228 (28.5)	0.001
Missing, *n*	66	102	105	
Severe visual impairment, *n* (%)	53 (12.3)	61 (7.8)	65 (8.1)	0.019
Missing, *n*	68	88	103	
Severe hearing impairment, *n* (%)	24 (5.7)	26 (3.6)	27 (3.6)	0.162
Missing, *n*	78	147	160	
Active epilepsy, *n* (%)	110 (25.6)	148 (18.8)	232 (28.2)	<0.001
Missing, *n*	70	80	83	
Impairment index[a], *n* (%)				0.003
High	202 (43.5)	294 (37.0)	316 (38.5)	
Moderate	171 (38.3)	313 (39.4)	351 (42.8)	
Low	73 (16.4)	188 (23.6)	154 (18.8)	
Missing, *n*	53	73	85	

EPT, extremely preterm; VPT, very preterm; MPT, moderately preterm; CP, Cerebral Palsy; WG, weeks gestation; GMFCS, Gross Function Classification System; IQ, Intellectual quotient.
[a]Impairment index: high (GMFCS IV-V and/or IQ<50 intellectual impairment, with or without one or more of the following impairments: severe visual impairment, severe hearing impairment, and active epilepsy; low (GMFCS I-II and IQ>70, without visual or hearing impairment, no epilepsy); moderate impairment (all other conditions).

were estimated per 1,000 live births and presented with exact 95% confidence intervals (CI).

We examined the overall prevalence time trend of CP and severe CP using negative binomial regression models considering the number of children with CP by registry and by year as the dependent variable and the number of live births per year in each registry as offset term. The model incorporated a random intercept that was specific to each registry, allowing

the average level of prevalence over the period to vary between registries. The linearity of the average trend was tested by comparing a model with year of birth as a continuous variable and a more general model where the time trend was smoothed using restricted cubic splines with 3 knots (thus allowing a change in slope every 3-year period) (35). Between registries random variations around the average time trend were then tested by adding a random slope (random slope allows each registry time trend to deviate from the overall time trend) to the regression model. Three covariance matrixes were examined: unstructured, exchangeable, and independent which made different assumptions about variances and covariances of the random effects. We concluded that the average time trend differed between registries if one of these models better fitted the data than the random intercept model. All comparisons were based on the Akaike information criterion (AIC) values. A sensitivity analysis excluding observations (i.e., birth cohort in a given registry) with more than 10% of missing GA was carried out.

Analyses were performed using STATA software (version 14.0 Stata Corp., College Station TX, USA).

RESULTS

Among the 18 registries that contributed to the SCPE database for birth years 2004–2010, 12 had adequate size and denominators by GA available. After exclusion of birth years (at registry's level, median of 4.4% of missing GA by birth year and by registry), and cases (at child's level) with missing GA, the study sample comprised 2,273 individuals with pre/perinatal CP born <37 weeks (**Table 1**). In total, 22.0, 38.2, and 39.9% were born EPT, VPT, and MPT, respectively. Their characteristics are presented in **Table 2** according to GA groups. In total, 25.8% were born from multiple pregnancies. About 2-thirds had a bilateral spastic CP. The proportion of those with unilateral spastic CP slightly increased from 22.1% in children born EPT to 31.4% in those born MPT. The distribution of GMFCS categories significantly differed between children born EPT and MPT. The proportion of children unable to walk even with aids (GMFCS IV-V) increased with decreasing GA at birth. Associated impairments were most frequent in children born EPT: 32.1% with IQ < 50, 12.3% with severe visual impairment, as compared to other GA groups, except for active epilepsy, most frequent in children born MPT. Whatever GA group, the proportion of children with associated impairments increased with increasing loss of gross motor function (**Supplementary Table 1**). The distribution of impairment index significantly differed across GA groups. Overall, 43.5% born EPT had a severe phenotype (high impairment index) compared to 37.0 and 38.5% in the two other groups.

The birth prevalence of CP among preterm born children varied from 7.5 per 1,000 live births in Portugal to 17.8 per 1,000 live births in Croatia. The overall prevalence and the prevalence of severe CP per birth year and GA group are given in **Supplementary Table 2**. **Figure 1** shows time trends according to GA groups over the period considered. In children born MPT, prevalence significantly decreased linearly from 2004 to 2010 with a mean decrease of 4% per year (Incidence rate ratio (IRR) per year = 0.96 [0.92–1.00[, *p*-value 0.034). The AICs of the model indicated that a random intercept model better fitted the data compared to a random effect (random intercept and random slope) model, thus indicating that there was no significant heterogeneity between registries in the time trend. In children born VPT, the shape of time trend best fitted with a restricted cubic splines model with 3 knots, which showed a decrease until 2009 only, with no significant differences between

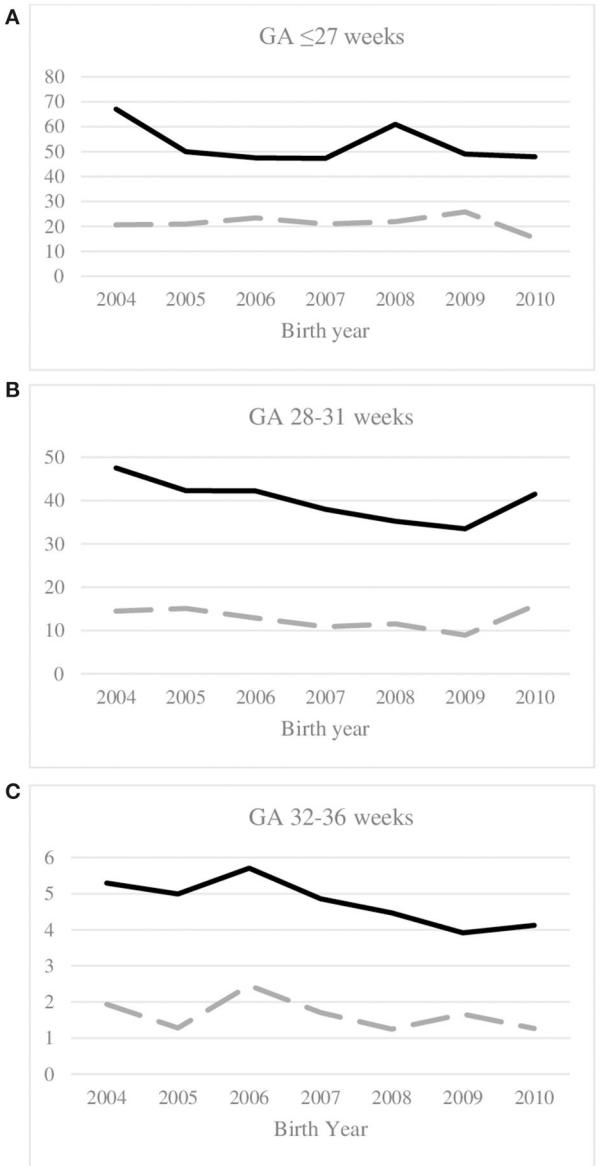

FIGURE 1 | Time trends of overall prevalence of CP (full line) and prevalence of serve CP (dotted line) per 1,000 live births, and gestational age group: **(A)** ≤27 weeks, **(B)** 28–31 weeks, **(C)** 32–36 weeks; birth years 2004–2010. Severe CP is defined as GMFCS IV-V and/or IQ < 50 (high impairment index). GMFCS, Gross motor function classification system; IQ, intellectual quotient.

centers. For those born EPT, we observed a steady prevalence rate over the period (IRR per year = 0.97 [0.92–1.02]). No center effect was found. Results indicated that the shape of the evolution of the prevalence of severe forms of CP (with GMFCS IV-V and/or IQ < 50) was similar to that of the overall prevalence of the corresponding GA group. The overall trend of severe CP was not significant (IRR = 0.96 [0.89–1.02]) in children born MPT, but variations in trends were observed between centers. In children born VPT, time trends of severe CP did not differ between centers, and overall no time effect was observed. In those born EPT, time effect for the prevalence of severe CP was found linear and not significant, with no differences between centers. Very similar results were observed in sensitivity analyzes whatever the cut-off of missing GA used.

The brain lesions issued from post-neonatal MRI are shown in **Table 3** according to GA groups. Overall, about 50% of MRI findings were available, the availability increasing from 22 to 65% over the study period. A higher availability of MRI results was observed among CP cases with severe visual impairment (58 vs. 49% among those with no severe visual impairment) or with active epilepsy (57 vs. 47%, respectively). Predominant white matter injuries were the most common lesional patterns in all GA groups, and were more frequent in children born <32 weeks: 81.5% (≤27 weeks) and 86.4% (28–31 weeks), compared to 63.6% for children born 32–36 weeks. The proportion of children with predominant gray matter injuries increased with increasing GA, from 5.4% for those born EPT to 14.2% for those born MPT. Normal imaging related to 5.6% of children born preterm.

DISCUSSION

Key Findings

Our study showed that among children born preterm, only those who were born 32–36 weeks GA demonstrated a decline both in overall prevalence (significant) and prevalence of severe CP (not significant), the latter showing variations between centers. A declining trend has continued for children born 28–31 weeks between 2004 and 2009 in Europe, while children born before 28 weeks remain a matter of specific concern with a high prevalence (47.9, p. 1,000 live-births for those born in 2010), steady over the period; nearly half of them had a severe phenotype. As expected, white matter injury was the most prevalent pattern of brain lesions, with 84.6% of children born <32 weeks GA showing such brain lesions.

Strengths and Limitations

The extended availability of GA in census data used for denominators now allows to document and compare patterns and trends of CP prevalence across GA groups from population-based CP registries. However, in this study we still could not investigate all geographical areas covered by a registry in Europe because of the unavailability of denominators by GA, thus reducing the number of children available for analyses. Besides, we must acknowledge missing values on GA but in a low proportion of children with CP, 7.6% overall. Thus, 2,273 children with CP were included in the analyses allowing precise estimates. Our analysis concentrated on the most recent period and was based on seven time points even if a long history of surveillance exists in some regions. These registries share the same definitions and classifications. Moreover, stable methodology over years limited methodological errors and provided confidence in the study findings. The rigor in data acquisition and ascertainment couldn't exclude variations in the completeness of registration between registries. Parental consent is sometimes required thereby resulting in underestimation of CP prevalence in several regions. Although completeness could have varied amongst centers, under-reporting of the most severely affected children with CP is unlikely. We, therefore, considered that changes in the prevalence of severe CP have not been affected by selection bias. All trends have to be interpreted with some caution, especially in the VPT and EPT groups because of small numbers and because points' estimates at the end of the study period have to be confirmed with additional birth years. We also observed some heterogeneity between registries in the distribution of GA in a ratio of nearly 3–1 (data not shown) that must be interpreted in line of care practices and mortality especially in EPT neonates (36) in each region. Not all registries contributed data to all the study years. We used multilevel negative binomial regression models to take into consideration such patterns and make it possible to let the average level of and temporal trend in the prevalence vary between registries. The GA-stratified analyses allowed to demonstrate specific patterns in each GA group.

Interpretation

Our results confirmed the significant declining trend (mean linear decrease of 4% per year over the period 2004–2010) from 1983 and onwards in Europe in children born MPT or with a moderately LBW (1,500 and 2,499 g) (16, 17), consistent with reports from the Australian state of Victoria (18). Investigating a shorter period (1995–2009), Galea et al. showed a different pattern with no evidence of declining prevalence, but the prevalence rates per 1,000 LB were lower than ours for the corresponding birth years (2004–2009) except in Western Australia (20). Among children born VPT, a decrease was found until 2009. Of concern is the increase thereafter with a peak for those born in 2010, who recorded the highest rate (41.5, p. 1,000 LB) since birth year 2006. We have to note that the two centers not included in the analysis for birth years 2009–2010 (data not available, C12 and C22) showed a downward trend over the previous period 2004–2008. Therefore, higher prevalence in 2010 in the VPT group is more likely to be due to a bias linked to a reduced number of centers in the analyses rather than a true increase. However, a similar evolution was found in Western Australia (20). Both estimates were found higher to that reported in Northern Alberta, Canada (29.5 per 1,000 LB) for children with CP born VPT in 2008–2010 (25), but close to the pooled prevalence (45, p. 1,000) estimated in the meta-analysis of Pascal et al. (5). In the French population-based cohort EPIPAGE2, CP was diagnosed in 44 per 1,000 children born 27–31 weeks' gestation in 2011 (37). In this study, the median age of 24 months corrected age at diagnosis thereby should lead to an expected even higher prevalence at the age of 4–5 years, commonly considered in population-based registries.

TABLE 3 | Post neonatal brain MRI findings according to gestational age groups, 2,273 preterm born children with CP, birth years 2004 to 2010.

MRICS *n* (%)	EPT ≤27 WG *n* = 499	VPT 28–31 WG*n* = 868	MPT 32–36 WG *n* = 906
(A) Maldevelopments	7 (3.2)	7 (1.8)	33 (7.1)
(B) Predominant white matter injury	181 (81.5)	342 (86.4)	297 (63.6)
(C) Predominant gray matter injury	12 (5.4)	23 (5.8)	67 (14.3)
(D) Miscellaneous	10 (4.5)	10 (2.5)	35 (7.5)
(E) Normal	12 (5.4)	14 (3.5)	35 (7.5)
Missing	277	472	439

EPT, extremely preterm; VPT, very preterm; MPT, moderately preterm; WG, weeks gestation; MRICS, Magnetic Resonance Imaging Classification System.

Much attention has been given to those born before 28 weeks. In this numerically small group, reported figures and trends not only depend on the range of birth cohorts under consideration but also on the size of the populations studied. Large random variations probably affected the precision of our estimates, and some caution should be taken when interpreting the results. In the literature, various patterns of trends in CP prevalence were reported in this group. Most studies first reported an increasing prevalence until the mid-1990ies (16, 18, 38) followed by a steady (16) or downwards trend (18, 20, 38). Studies investigating the most recent period (2007 and onwards) (5, 20, 24, 25, 37, 39) mentioned highly heterogeneous prevalences from 27.2 p. 1,000 in Northern Alberta (25) to 100 p. 1,000 [meta-analysis, (5)]. In our study, the prevalence for those born EPT was in the lower range, approximatively 47–49 p. 1,000 LB from 2005 (except a peak in 2008). In this group, survival rates still highly vary especially in children born 22–23 weeks and must be taken into consideration. Thus, prevalences expressed per 1,000 neonatal survivors (NNS) are likely to be higher than prevalences per 1,000 livebirths, and should be preferred when comparing studies or periods in the most immature group of infants. In our study, the differences in the prevalences per 1,000 LB and per 1,000 NNS remained stable over the study period in regions where NNS par GA groups were available as denominators (10 centers, data not shown), with the exception of 2010 that showed a lower neonatal mortality.

A key issue was to investigate whether the most severely affected children with CP also showed a reduced prevalence thereby benefited to the same extent from optimum care for vulnerable preterm infants. No universal agreement has been reached so far to describe the severity of the condition so that substantial variation exists between studies. Information mostly focused on a combination of gross motor function loss and intellectual impairment. Incorporating various associated impairments and their severity might better reflect the overall limitations (34, 40) but possibly limits comparisons between studies. Horber and coll. reported that the proportion of those with a high impairment index did not significantly vary in children who were born PT or with a low BW between 1990 to 2006, and was very similar when considering BW or GA categories (35–39%) (34). In our study, the proportion of children with severe CP defined as non-ambulant children or children with moderate to severe intellectual disability (which corresponds to a high impairment index) slightly increased across the GA groups with 38.5% with severe phenotype among children born 32–36 weeks, up to 43.5% for those born ≤27 weeks, consistent with other studies (18, 20, 21). Our results also indicated that the prevalence of the most severely affected children with CP revealed a similar trend to the overall prevalence in the corresponding GA groups, in line with the observations previously reported by our group (16). Despite no significant time effects were found, possibly related to both the limited number of time-points and the size of sub-populations available for analyses thus reducing the chance of detecting an effect, the similarity in trends should encourage future research to focus on understanding the cumulative effect of severe associated impairments beyond to severe motor impairment.

Cerebral white matter injury is the predominant form of brain injury associated with premature birth (41). However, a large heterogeneity in the distribution of brain lesions in children born PT, and especially in the proportions of children with white matter injuries (31–71%) has been first reported in the review by Reid et al. (42). The SCPE working group has developed a MRI classification system (MRICS) for children with CP which proved highly reliable (27) and a process of regular training and feed-back is ongoing in SCPE. Using the SCPE database, Horber and coll. recently published that more than 80% of the children born <32 weeks GA had predominant white matter injury (28). Children born <32 weeks had fewer maldevelopments, a lesser proportion of gray matter injuries and consequently a greater proportion of predominant white matter injuries than children born MPT (32–36 weeks). Nagy and coll. confirmed that the distribution of brain lesions was highly correlated to perinatal data (43). As these injuries arise in the period when children are born, the decrease of prevalence in CP indicates that its major lesional cause, periventricular leukomalacia (PVL) in its severe, cystic form is decreasing. This is in line with the observation of a significant decline in the incidence of c-PVL reported in hospital based studies (44, 45), also reviewed by de Vries et al. (46). In our study, the distribution of MRI findings was comparable in children born ≤27 and 28–31 weeks, which gives hope that in the long run, also in the first group not only their mortality but also prevalence of CP will decrease.

In conclusion, in this large European study based on population-based data from CP registries, we focused on children with CP born preterm and reported a comprehensive overview of the prevalence, severity, and brain lesions according to GA groups. This paper provides evidence that a decline in prevalence

of CP for those born 32–36 weeks has continued in Europe, and also for those born between 28 and 31 weeks until 2009. Trends related to the most severe phenotypes showed a similar pattern to that of overall prevalence in the corresponding GA groups.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The analyses were based exclusively on pseudonymized register data compiled at European level in the SCPE database. The study did not require contact with the registered persons. Therefore, ethical review and approval were not required for this study. Each participating register has its own ethical approval that follows the legislative rules of its country. In particular procedures have been performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent from the patients/ participants or patients/participants legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

CA, MD-A, DK, and IK-M designed the study. VE performed the data analysis. CA drafted the manuscript. All authors interpreted the data, contributed to revisions, and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.624884/full#supplementary-material

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The Contribution of Decreased Muscle Size to Muscle Weakness in Children With Spastic Cerebral Palsy

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Muscle weakness is a common clinical symptom in children with spastic cerebral palsy (SCP). It is caused by impaired neural ability and altered intrinsic capacity of the muscles. To define the contribution of decreased muscle size to muscle weakness, two cohorts were recruited in this cross-sectional investigation: 53 children with SCP [median age, 8.2 (IQR, 4.1) years, 19/34 uni/bilateral] and 31 children with a typical development (TD) [median age, 9.7 (IQR, 2.9) years]. Muscle volume (MV) and muscle belly length for m. rectus femoris, semitendinosus, gastrocnemius medialis, and tibialis anterior were defined from three-dimensional freehand ultrasound acquisitions. A fixed dynamometer was used to assess maximal voluntary isometric contractions for knee extension, knee flexion, plantar flexion, and dorsiflexion from which maximal joint torque (MJT) was calculated. Selective motor control (SMC) was assessed on a 5-point scale for the children with SCP. First, the anthropometrics, strength, and muscle size parameters were compared between the cohorts. Significant differences for all muscle size and strength parameters were found ($p \leq 0.003$), except for joint torque per MV for the plantar flexors. Secondly, the associations of anthropometrics, muscle size, gross motor function classification system (GMFCS) level, and SMC with MJT were investigated using univariate and stepwise multiple linear regressions. The associations of MJT with growth-related parameters like age, weight, and height appeared strongest in the TD cohort, whereas for the SCP cohort, these associations were accompanied by associations with SMC and GMFCS. The stepwise regression models resulted in ranges of explained variance in MJT from 29.3 to 66.3% in the TD cohort and from 16.8 to 60.1% in the SCP cohort. Finally, the MJT deficit observed in the SCP cohort was further investigated using the TD regression equations to estimate norm MJT based on height and potential MJT based on MV. From the total MJT deficit, 22.6–57.3% could be explained by deficits in MV. This investigation confirmed the disproportional decrease in muscle size and muscle strength around the knee and ankle joint in children with SCP, but also highlighted the large variability in the contribution of muscle size to muscle weakness.

Keywords: cerebral palsy, muscle weakness, muscle size, ultrasound, muscle volume, selective motor control

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INTRODUCTION

Cerebral palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. It is the most common cause of childhood-onset physical disability (1). Spastic CP (SCP) is the largest subcategory, affecting between 70 and 80% of children with CP (2). Children with SCP present with physical impairments like abnormal gait and gross motor function, which can deteriorate gradually. These physical impairments are associated with limitations in daily life activities and restrictions in societal participation. They are primarily caused by neural impairments including spasticity, decreased selected motor control (SMC), and poor postural stability. Additionally, the neural impairments can lead to secondary non-neural musculoskeletal impairments like altered intrinsic muscle structure, muscle contractures, and bony deformities (3).

Another consistent clinical finding in children with SCP is muscle weakness (4–7), defined as an inability to produce or maintain an anticipated level of force (8). When studying mechanisms underlying physical disability, higher associations with gross motor function have been reported for strength and selectivity than for spasticity (9–13). In ambulant children with SCP, lower extremity muscle strength deficits have been identified, ranging from 15 to 80%, with larger deficits reported for less functional children (4, 5, 14). Moreover, the increase in strength during growth is lower than in typically developing (TD) children and suggested to be insufficient in relation to increases in body mass (15, 16).

However, muscle weakness cannot be categorized as just a neural or just a musculoskeletal impairment. Both the neural ability to selectively activate the muscle and the intrinsic capacity of the muscle influence strength production (6, 7). Furthermore, the assessment of strength in children with SCP can also be influenced by cognitive, attentional, or motivational difficulties (17). The primary cause of muscle weakness in children with SCP is impaired neural function due to damage to the descending pathways of the central nervous system (7). The central damage impacts the ability to maximally activate the agonists and the degree of cocontraction of antagonists (6, 7, 18, 19). Secondarily, muscle weakness is caused by intrinsic muscle property alterations involving decreases in muscle size, deteriorated muscle integrity, and potentially also changes in fascicle arrangement (17, 20–22).

Improved access to muscle imaging techniques in clinical research has led to a great increase in the number of studies quantifying intrinsic muscle properties in children with SCP (23). Lower limb muscle volume (MV) reduction ranging from 18 to 50% has been documented (6, 24–31). Similar reductions have been described based on two-dimensional ultrasound (US) measures of muscle size like muscle thickness and cross-sectional area (CSA) (6, 17, 29, 32, 33). These deficits in muscle size present as early as the age of 15 months (27, 34, 35) and increase into later childhood and adolescence (36). Comparable to muscle weakness, muscle size is also related to the level of functionality, with larger reductions seen in less functional children (25, 26, 29, 37–39). However, large variability has been reported between subjects and between different muscles, often with distal predominance of MV reduction (25, 28).

The physiological CSA (pCSA) of a muscle is the ratio of MV to fascicle length. This value represents the number of fascicles in parallel. It is therefore directly related to the force-generating capacity of a muscle. Since pCSA and muscle size show a strong association with muscle strength in TD populations (40, 41), it can serve as a proxy measure of potential strength in children with SCP. It is likely that decreased MV and shorter or similar fascicle lengths result in decreased pCSA in children with SCP (29, 42). However, as discussed above, the decrease in muscle strength is larger than the reduction in MV. While investigating the muscle size–strength relationship, Reid et al. (20) found a weaker association between knee flexors and extensors MV and anatomical CSA (aCSA) and joint torque in comparison to TD children. Elder et al. (6) found a reduction in specific tension, defined as the ratio of joint torque and aCSA, for both the plantar and dorsiflexors in SCP. The disproportional decrease in muscle strength could be related to other properties such as impaired neural control (6, 7).

Most focal treatments for children with SCP, like strength training, casting, and botulinum neurotoxin-A injections, are administered at the muscular level (43, 44). Knowing the contribution of decreased muscle size to muscle weakness is of importance in choosing the appropriate treatment options. The muscle size–strength relationship in children with SCP has been evaluated both at the knee and the ankle, but in different, possibly not equivalent, ways (6, 20). Additionally, in investigations about the factors underpinning gross motor function, parameters of muscle size have been combined with neuromotor symptoms like SMC and indirect estimates of muscle quality (12, 24). Evaluating the muscle size–strength relationship at the knee and ankle joint in one cohort of children with SCP, using data of TD children as a reference, as well as including SMC, could improve our understanding of the neural and non-neural contributions to muscle weakness in this population.

The first aim of this investigation was to describe the deficits in muscle strength, muscle size, and their ratio for knee flexors and extensors, plantar, and dorsiflexors in children with SCP. Secondly, the muscle size–strength relationship was defined, combined with the influence of age, anthropometric measures, functional level, and SMC following a multiple linear regression approach. Finally, the contribution of muscle weakness due to decreased muscle size to the total deficit in muscle strength was defined for the four investigated joint movements.

MATERIALS AND METHODS

Participants

This investigation included a convenience sample of 84 participants, 53 with SCP (19 unilateral and 34 bilateral) and a control group of 31 TD children, who were recruited at the Clinical Motion Analysis Laboratory at the University Hospitals Leuven, Belgium. Inclusion criteria for the SCP cohort were a confirmed diagnosis of SCP, age between 5 and 12 years, and

gross motor function classification system (GMFCS) level I–III (45). Botulinum neurotoxin-A injections 6 months prior to the assessments, lower limb bony surgical interventions 2 years prior to the assessments, and history of lower limb muscular surgeries at any time point were defined as exclusion criteria. In case of insufficient cooperation during testing or insufficient understanding of the test procedures, the participant was also excluded. TD children were recruited *via* hospital co-workers and students within the same age range of 5–12 years and could not have any known neurological or orthopedic lower limb problems. All data were collected as part of an ongoing project that was approved by the local Ethical Committee of the University Hospitals Leuven (S59945) and Ghent (EC/2017/0526). Written informed consent was obtained from all parents or caregivers.

Data Collection and Analysis

Participant Characteristics and Anthropometrics

The clinical and anthropometric features of the participants are summarized in **Table 1**. The most affected leg was assessed in the participants with SCP, according to the clinical reports and the most recent clinical exam results for muscle spasticity (Modified Ashworth Scale and Modified Tardieu angle) and strength (Medical Research Council grade scale) at the knee and ankle (46–48). If the clinical examination indicated no difference, the assessed leg for study was chosen at random by flipping a coin. In the TD cohort, the assessed leg was identified in the same way. Age, weight, and height were recorded for each participant. A clinical classification of SMC assessed in standard manual muscle testing position, graded on a 5-point scale between 0 and 2, was used for knee extension (KE), knee flexion (KF), plantar flexion (PF), and dorsiflexion (DF) [adapted from the method described by Gage et al. (49)].

Three-Dimensional Freehand Ultrasonography

Three-dimensional freehand ultrasonography (3DfUS) acquisitions were performed by combining a conventional two-dimensional B-mode ultrasonography device (Telemed-Echoblaster 128 Ext-1Z, with a 5.9-cm 10-MHz linear US transducer, Telemed Ltd., Vilnius, Lithuania) with a motion tracking system (Optitrack V120:Trio, NaturalPoint Inc., Corvallis, Oregon, USA) (50). According to a previously described technique, four markers were attached to the US probe and tracked by the motion tracking system, resulting in the synchronized position and orientation of every acquired two-dimensional US image (50).

Both data collection and processing were performed using STRADWIN software (version 6.0; Mechanical Engineering, Cambridge University, Cambridge, UK) for four lower limb muscles: m. rectus femoris (RF), m. semitendinosus (ST), m. tibialis anterior (TA), and m. gastrocnemius medialis (MG). The reliability of 3DfUS has been confirmed for the plantar flexor muscles (50–52), as well as for the processing of the TA, RF, and ST (53). MV (in milliliters) was estimated by drawing equally spaced transverse plane segmentations along the inside of the muscle border for ∼5% of all acquired images, followed by an automatic linear interpolation. The reconstructed muscle was visually inspected, and additional images were segmented to improve the interpolated shape if needed. Muscle length (ML) (in millimeters) was determined as the linear distance between muscle origin and distal muscle tendon junction. MV was normalized to body mass (nMV; ml/kg) and ML, to subject height (nML; mm/cm), enabling comparisons between cohorts. More details about the measurement and processing protocol can be found in **Supplementary File 1**.

Isometric Strength Assessments

Maximum voluntary isometric contractions (MVIC) were collected for KE, KF, PF, and DF with a fixed dynamometer (MicroFet 2, Hogan Health Industries, West Jordan, Utah, USA) in a previously described, custom-designed chair (5). The procedure is further explained in **Supplementary File 2**. Custom-written MATLAB scripts were used to determine the peak force (in Newton) of each MVIC, from which average maximal joint torque (MJT; Nm) and normalized joint torque (nMJT; Nm/kg) were calculated over the three MVIC trials (5).

Statistical Analysis

Data were analyzed using SPSS (Version 26, SPSS Inc., Chicago, Illinois, USA). A ratio of strength to muscle size was calculated for every joint movement by dividing the MJT by the corresponding MV. Percentage differences in muscle strength and muscle size between TD and SCP were calculated as shown below, where M represents the median of the specified parameter:

$$\%Diff = \left(\frac{M_{SCP} - M_{TD}}{M_{TD}}\right) * 100\% \quad (1)$$

A negative percentage indicated a deficit in the SCP group in comparison to the TD group. Normality of the data distribution was evaluated using the Shapiro–Wilk test, histograms, and QQ plots. Since most parameters were not normally distributed, all descriptive statistics are presented as median (interquartile range). Bonferroni corrections were applied for multiple testing and specified beneath each table.

To investigate the first aim, differences between the TD and SCP cohort were assessed using a Student's *t*-test (after confirming equality of variances) or the Mann–Whitney *U*-test.

For the second aim, linear associations between anthropometric measures (normalized) MV and ML, SMC, GMFCS, and (n)MJT were explored by univariate linear regression. Standardized residuals (≥3 standard deviations) were used to remove outliers, and normal distribution of residuals and heteroscedasticity were checked. Correlation coefficients were classified as negligible ($r < 0.300$), low ($r = 0.300$–0.499), moderate ($r = 0.500$–0.699), high ($r = 0.700$–0.899), or very high ($r \geq 0.900$) (54), and differences in correlation coefficients between TD and SCP were defined by Fisher *Z*-scores. Based on the linear association with (n)MJT and the interassociations of potential independent variables within the categories anthropometrics (age, weight, and height), muscle morphology (MV and ML), and clinical scales (SMC and GMFCS), one parameter was selected per category to be used in the multivariate analyses. Multiple linear regression models were built using a backward approach (enter $p \leq 0.05$, remove $p \geq 0.10$). A first

TABLE 1 | Participant characteristics.

	Typically developing ($n = 31$)		Spastic cerebral palsy ($n = 53$)		Comparison	
	Median	**IQR**	**Median**	**IQR**	***T*-test**	**MWU**
Age (yrs)	9.7	2.9	8.2	4.1		0.064
Weight (kg)	29.2	9.1	27.3	13.6		0.407
Height (cm)	138.6	17.5	130.4	19.3	0.021	
	Frequencies		**Frequencies**			
Sex (F/M)	16/15		22/31			
Involvement (uni/bi)	NA		19/34			
GMFCS (I/II/III)	NA		32/12/9			
SMC (2/1.5/1/0.5/0) ($n = 52$)						
Knee extension	NA		33/13/6/0/0			
Knee flexion	NA		24/15/7//0/1			
Plantar flexion	NA		18/15/7/4/4			
Dorsiflexion	NA		23/20/9/6/1			

Comparison of anthropometric parameters between TD children and children with spastic cerebral palsy. Significant p-value ≤ 0.017 (p = 0.05/3). n, number; IQR, inter quartile range; MWU, Mann-Whitney U test; F, female; M, male; NA, not applicable; GMFCS, gross motor function classification system; SMC, selective motor control.

model included the same parameters for both cohorts from the categories anthropometrics and muscle morphology. In a second model for the SCP cohort, the additional explained variance by a clinical scale was explored. Standardized residuals and Cook's distance value were used to diagnose and remove outliers. Final models were assessed for normal distribution of residuals, multicollinearity, and heteroscedasticity.

For the third aim, the MJT deficit observed in the SCP cohort was further investigated using the TD regression equations. The regression equation of MV with MJT defined in the TD cohort was used to estimate potential muscle strength in children with SCP ($MJT_{potential}$) based on their MV. The regression equation for MJT based on an anthropometric variable was used to estimate the expected norm value of muscle strength for children with SCP (MJT_{norm}). Muscle strength profiles based on the relative contribution of decrease in MV ($MJT_{deficitMV}$) and the other factors ($MJT_{deficitother}$) to muscle weakness were calculated as a percentage of the total strength deficit (**Figure 2A**).

There were some missing data due to 3DfUS reconstructions that could not be analyzed, MVICs that could not be assessed, and missing information about SMC. For the univariate linear regressions, the participant with missing data was excluded for all analyses of the specific joint movement. An overview of missing data is added in **Supplementary Table 1**.

RESULTS

Like in the Methods section, the results are structured in the order of the three aims. First, the descriptive results and deficits of SCP children in comparison to TD children are described and reported in **Tables 1**, **2**. Thereafter, the linear associations and multiple regression models are discussed and presented in **Figure 1** and **Tables 3**, **4**. Finally, the contributions to muscle weakness are explored and reported in **Figure 2**.

Deficits

Descriptive results of participant characteristics are shown in **Table 1**. There were no significant differences in age, weight, and height between the SCP and TD groups. **Table 2** describes the differences in muscle morphology and strength parameters between the TD children and children with SCP. Both MV and nMV for all four muscles were significantly decreased in the SCP cohort ($p \leq 0.002$). For nMV, the median deficits ranged between 19.7% for the ST and 43.5% for the TA. Similarly, both ML and nML were significantly decreased in the SCP cohort for all four muscles except for nML of the RF, which was close to significance ($p \leq 0.011$). Differences in median nML ranged from 4.6% for the RF to 11.3% for the MG. Similar to the alterations in muscle morphology, both MJT and nMJT were significantly decreased for all four joint movements ($p < 0.001$). Normalized MJT showed median decreases ranging from 47.1% for PF to 71.7% for DF. The ratio of joint torque over muscle size was also significantly decreased for KE, KF, and DF, with median deficits of 40.3–54.0% ($p < 0.001$), but PF showed a lower, non-significant deficit of 18.1% ($p = 0.071$).

Relationships

The univariate associations of anthropometric parameters, muscle morphology, GMFCS, and SMC with MJT, as well as with nMJT, are depicted in **Table 3**. In the TD cohort, all anthropometric and muscle morphology parameters showed significant moderate to high associations with MJT of KE, KF, and DF ($r = 0.537$–0.849, $p \leq 0.003$). For PF, only age and height showed significant moderate associations ($r = 0.502$–0.556, $p \leq 0.008$). Associations of PF with weight and MV were close to significance but low ($r = 0.449$–0.463, $p \leq 0.019$). Similarly,

TABLE 2 | Comparisons of muscle morphology and maximal joint torque.

	Typically developing			Spastic cerebral palsy			Comparison		
	n	Median	IQR	*n*	Median	IQR	*T*-test	MWU	%
Muscle volume (ml)									
Rectus femoris	31	96.0	32.0	53	64.9	33.2		<0.001*	−32.7
Semitendinosus	29	68.8	31.3	48	48.8	30.6		0.002*	−30.4
Medial gastrocnemius	27	68.5	29.1	49	40.0	26.4		<0.001*	−41.6
Tibialis anterior	28	48.6	28.7	49	25.5	12.6		<0.001*	−47.6
Normalzied MV (ml/kg)									
Rectus femoris	31	3.17	0.61	53	2.30	0.63	<0.001*		−27.5
Semitendinosus	29	2.24	0.75	48	1.80	0.36	<0.001*		−19.7
Medial gastrocnemius	27	2.44	0.41	49	1.49	0.76		<0.001*	−38.9
Tibialis anterior	28	1.60	0.49	49	0.90	0.25		<0.001*	−43.5
Muscle length (mm)									
Rectus femoris	31	256.8	47.1	53	224.5	47.5	0.003*		−12.6
Semitendinosus	29	244.1	50.8	48	221.0	46.7	<0.001*		−9.5
Medial gastrocnemius	27	185.5	39.6	49	146.1	39.9		<0.001*	−21.3
Tibialis anterior	28	242.9	58.0	49	198.2	43.7		<0.001*	−18.4
Normalized muscle length (mm/cm)									
Rectus femoris	31	1.84	0.23	53	1.75	0.16		0.011	−4.6
Semitendinosus	29	1.81	0.28	48	1.68	0.21	0.001*		−7.2
Medial gastrocnemius	27	1.35	0.15	49	1.19	0.24		<0.001*	−11.3
Tibialis anterior	28	1.74	0.23	49	1.58	0.20	<0.001*		−9.1
Maximal joint torque (Nm)									
Knee extensors	31	31.0	35.5	53	13.3	18.4		<0.001*	−57.1
Knee flexors	29	22.5	11.9	48	6.7	10.4		<0.001*	−70.2
Plantar flexors	27	12.5	8.3	49	7.0	5.2		<0.001*	−44.0
Dorsiflexors	28	9.9	6.0	49	2.3	2.0		<0.001*	−77.2
Normalized maximal joint torque (Nm/kg)									
Knee extensors	31	1.11	0.63	53	0.54	0.53		<0.001*	−51.8
Knee flexors	29	0.74	0.49	48	0.28	0.30		<0.001*	−62.4
Plantar flexors	27	0.42	0.21	49	0.22	0.24		<0.001*	−47.1
Dorsiflexors	28	0.31	0.16	49	0.09	0.07		<0.001*	−71.7
Joint torque/muscle size (Nm/ml)									
Knee extensors	31	0.40	0.19	53	0.24	0.20		<0.001*	−40.3
Knee flexors	29	0.31	0.16	48	0.14	0.17		<0.001*	−54.0
Plantar flexors	27	0.19	0.10	49	0.15	0.13		0.071	−18.1
Dorsiflexors	28	0.19	0.11	49	0.09	0.06	<0.001*		−51.2

*Comparisons of muscle morphology parameters and MJT between TD children and children with SCP. *Significant difference at $p \leq 0.007$ ($p = 0.05/7$). n, number; IQR, interquartile range; MWU, Mann–Whitney U-test.*

in the SCP cohort, associations of anthropometrics and muscle morphology with MJT were significant for KE and KF, with coefficients ranging from low to high ($r = 0.437$–0.746, $p \leq 0.007$). For DF, height, MV, and ML were significant, whereas age and weight were close to significance ($r = 0.353$–0.639, $p \leq 0.013$). Only MV and ML were significant for PF with low associations ($r = 0.413$–0.431, $p \leq 0.003$). GMFCS level showed a low significant association with KE MJT and a low, close to significant association with KF ($r = -0.340$–0.469, $p \leq 0.018$), but negligible non-significant associations with PF and DF MJT ($r = -0.251$, $p \leq 0.082$). SMC was moderately significantly correlated with KE and PF MJT ($r = 0.450$–0.480, $p = 0.001$), close to significant for KF ($r = 0.337$, $p = 0.021$), and there was no association with DF MJT. Fisher's *Z*-scores did not demonstrate significant differences between the reported relationships for children with and without SCP, except for KE with weight ($Z = 2.442$) and age with DF MJT ($Z = 1.764$).

To eliminate the influence of growth on the associations with MJT, the univariate analyses were also performed with normalized parameters (nMJT, nMV, and nML). In the TD cohort, only the association of weight and height with KE nMJT remained significant ($r = 0.486$–0.528, $p \leq 0.006$). However, in the SCP cohort, nMV associated significantly with nMJT of KE, PF, and DF ($r = 0.401$–0.608, $p \leq 0.004$), and nML

with KE nMJT ($r = 0.454$, $p = 0.001$). GMFCS showed low to moderate significant associations with KE and KF nMJT ($r = -0.504$ to -0.414, $p \leq 0.003$), and SMC showed low to moderate significant associations with KE, KF, and PF ($r = 0.442$–0.528, and $p \leq 0.002$).

Based on the univariate associations with MJT (**Table 3**) and the interassociations between predictors within each category (**Supplementary Table 2**), the following parameters were selected: height within the category anthropometrics, MV within muscle morphology, and SMC within clinical scales. The results of the multiple linear regression models for MJT in both cohorts are presented in **Table 4**. The models in the TD cohort (**Table 4A**) included height, MV, or both parameters. All regression models were significant ($p \leq 0.002$), and explained variance ranged from 29.3% for PF to 66.3% for KE. The results in the SCP cohort for MJT (**Table 4B**) were also all significant ($p \leq 0.002$), and in the first model, with the same independent variables as in the TD cohort, only MV was included per joint movement. Explained variance ranged from 16.8% for PF to 54.8% for KE. In the second model, also SMC was entered into the model. The model for DF MJT did not change, whereas SMC was included for KE, KF, and PF MJT. The regression coefficients increased accordingly, explaining an additional 5.3–11.1% of the variance compared to the first model (**Table 4B**). The multiple linear regression models in the SCP cohort for nMJT had explained variances ranging from 21.0 to 41.9% and were all significant ($p \leq 0.002$) (**Table 4C**). The included parameters were SMC, nMV, or both.

Contributions to Muscle Weakness

Although the correlation coefficients of MV with MJT were similar between TD and SCP, the regression coefficients or slopes of this relationship tended to be lower in the SCP cohort for all joint movements, except for KF. However, there was a large difference in the regression constant for KF (**Figure 1**). The children with SCP are largely located at the bottom-left quadrant of the graphs, pointing toward lower MV with even lower MJT than what would be potential for the MV.

Figure 2 and **Supplementary Table 3** show the relative deficits in MJT divided into the part caused by the decrease in MV ($MJT_{deficitMV}$) and the part resulting from other factors, like decreased neural control or alterations in muscle composition ($MJT_{deficitother}$). $MJT_{deficittotal}$ as a percentage of MJT_{norm} ranged from 44.7% for PF to 73.3% for DF. The contribution of $MJT_{deficitMV}$ was largest for KE with 57.3%, followed by PF (47.7%), DF (39.3%), and KF (22.6%). The muscle strength profiles for every participant are depicted in **Supplementary Figure 1**, indicating the absolute values of $MJT_{measured}$, $MJT_{deficitMV}$, and $MJT_{deficitother}$. **Supplementary Figure 1** shows that the contribution of decreased MV to muscle weakness is not constant, as it changes with increasing MJT. At the younger ages, there were some children who did not have a deficit based on MV, especially for KF, and KF and DF showed an almost constant and large contribution of other factors to the $MJT_{deficittotal}$. However, the contribution of a deficit in MV appeared to increase with growth and therefore with increasing MJT_{norm}. **Supplementary Figure 1** specifically highlights the high heterogeneity, not only between joint movements but also between subjects.

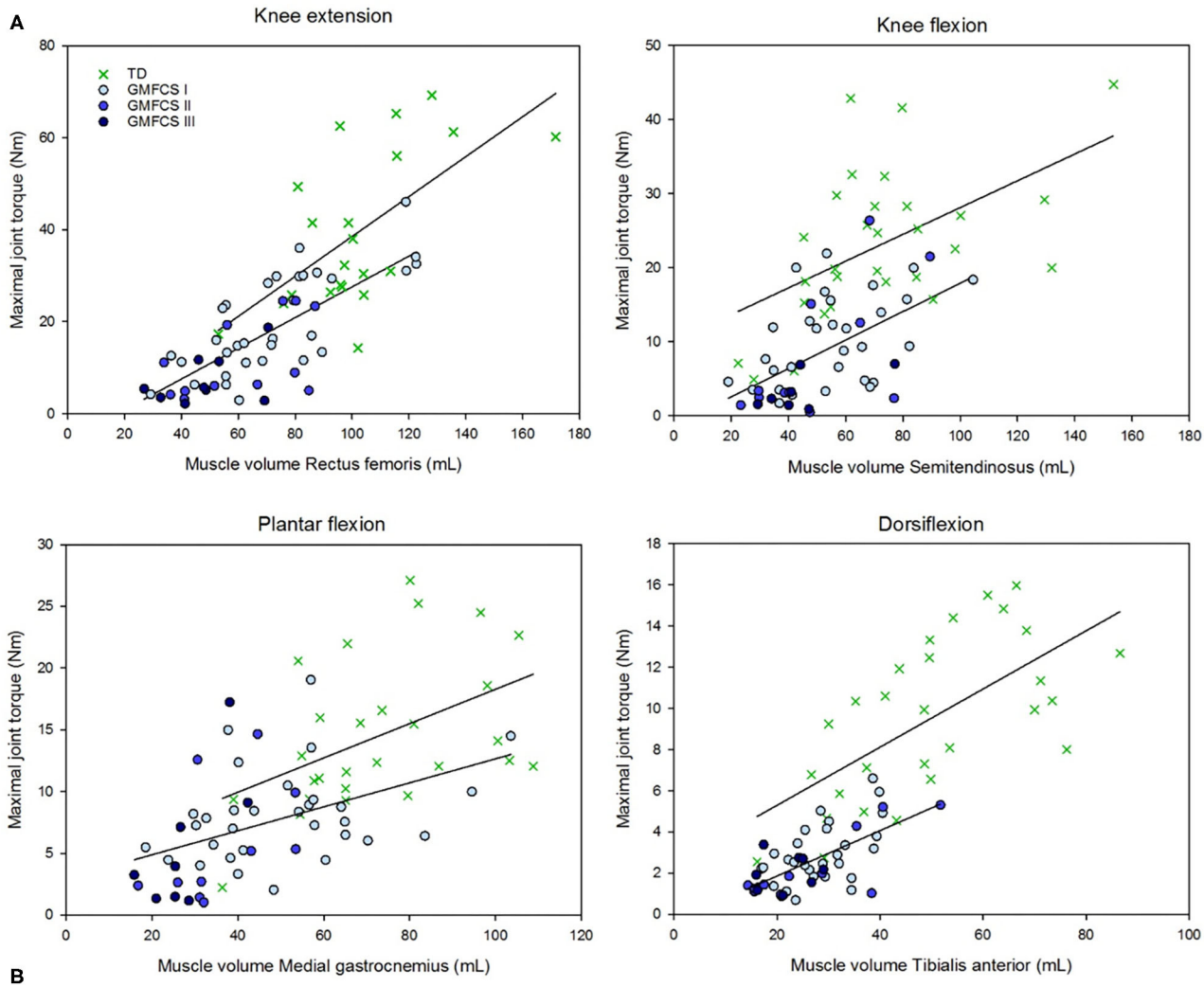
DISCUSSION

Deficits

The first aim of this investigation was to define the deficits in muscle strength, muscle size, and their ratio for KF, KE, PF, and DF in children with SCP. The children with SCP demonstrated significant deficits in MV compared to their TD peers, for all assessed muscles (**Table 2**). Since the TD cohort appeared slightly older (**Table 1**), MV was also normalized to body weight, but the differences remained. The deficits in nMV, ranging from 19.7 to 43.5%, were consistent with earlier results in literature (6, 24, 25, 28, 30). The differences in deficits in proximal and distal muscles were also in line with previous findings, with the proximal muscles showing ∼70% MV of the TD cohort values and the distal muscles showing 50–60% MV of the values of TD children (25, 28). Similarly, ML and nML were significantly decreased, with deficits in nML ranging from 4.6 to 11.3%. The decreases in muscle size parameters were accompanied with significant decreases in muscle strength, ranging from 47.1 to 71.7% for the nMJT (**Table 2**). These deficits are consistent with earlier reported deficits in muscle strength in children with CP (4, 5, 15). In the current investigation, KE and KF were similarly weakened, whereas DF was far more affected than PF. This difference between DF and PF torque could be partly explained by the different impact of the ankle joint angle at which the strength was assessed, which was in neutral (90°). This joint angle might already have induced a stretch on the plantar flexors, which the dorsiflexor muscles first must overcome.

The disproportionality in the deficits in muscle strength and size in children with SCP was a first confirmation of an altered muscle size–strength relationship. This was further confirmed in the ratio of torque over size, which was significantly lower in the SCP group in comparison to the TD group for three of the four muscle groups. Both KE and KF, as well as DF, showed deficits in strength per muscle size of 40.3–54.0%. Only PF was an exception, where the relative decrease in MV was almost equal to the relative decrease in MJT, resulting in a similar muscle strength-to-size ratio in the two cohorts. In the investigation by Elder et al. (6), the specific tension defined as torque over the whole muscle group CSA of both PF and DF was significantly reduced. However, they also found a few cases where torque was proportional to the CSA. The results for PF in the current investigation are in line with results by O'Brien et al. (55), who found that muscle activation capacity did not strongly predict ankle PF weakness in high-functioning adults with SCP, suggesting that muscle size may contribute more to weakness than neural voluntary activation. However, it should also be noted that PF is probably the joint movement where compensation from more proximal joints is most challenging to be avoided in the fixated position used in this investigation, as is also visible in some of the relatively high $MJT_{measured}$ bars in **Supplementary Figure 1**. Despite the heterogeneity between the current and previous study results, these findings confirm that

A



B

Dependent variable	N (outliers)	Constant			Regression coefficient			R^2	
		Value	SE	p-value	Value	SE	p-value	Value	p-value
Typically developing cohort									
Knee extension	31 (0)	-11.179	7.566	0.15	0.527	0.072	<0.001	0.648	<0.001
Knee flexion	29 (0)	10.021	4.258	0.026	0.181	0.055	0.003	0.262	0.003
Plantar flexion	27 (1)	4.386	4.012	0.285	0.139	0.053	0.015	0.183	0.015
Dorsiflexion	28 (2)	2.470	1.729	0.165	0.141	0.033	<0.001	0.393	<0.001
Spastic cerebral palsy cohort									
Knee extension	53 (0)	-6.609	2.984	0.031	0.341	0.043	<0.001	0.557	<0.001
Knee flexion	48 (1)	-1.292	2.442	0.599	0.192	0.044	<0.001	0.281	<0.001
Plantar flexion	49 (0)	2.645	1.504	0.085	0.105	0.032	0.002	0.168	0.002
Dorsiflexion	49 (2)	-0.334	0.544	0.542	0.110	0.019	<0.001	0.396	<0.001

FIGURE 1 | Relationship between muscle volume and maximal joint torque for four lower limb joint movements in children with a typical development (TD) and with spastic cerebral palsy with gross motor function classification scale (GMFCS) levels I to III. **(B)** Regression formula parameters for the estimation of maximal joint torque based on muscle volume as shown in **(A)**. SE, standardized error. The outliers indicate the cases that were removed based upon the standardized residuals or Cook's distance.

TABLE 3 | Associations with maximal joint torque.

	Typically developing				Spastic cerebral palsy			
	KE (31)	**KF (29)**	**PF (27)**	**DF (28)**	**KE (53)**	**KF (48)**	**PF (49)**	**DF (49)**
Maximal joint torque								
Age (yrs)	0.706	0.680	0.502	0.668$^{\Delta}$	0.528	0.437	0.250	0.353$^{\Delta}$
p-value	<0.001*	<0.001*	0.008*	<0.001*	<0.001*	0.002*	0.083	0.013
Weight (kg)	0.849$^{\Delta}$	0.615	0.449	0.595	0.589$^{\Delta}$	0.578	0.198	0.377
p-value	<0.001*	<0.001*	0.019	0.001*	<0.001*	<0.001*	0.172	0.008
Height (cm)	0.749	0.729	0.566	0.605	0.646	0.516	0.302	0.422
p-value	<0.001*	<0.001*	0.002*	0.001*	<0.001*	<0.001*	0.035	0.003*
Muscle volume (ml)	0.805	0.537	0.463	0.645	0.746	0.544	0.431	0.639
p-value	<0.001*	0.003*	0.015	<0.001*	<0.001*	<0.001*	0.002*	<0.001*
Muscle length (mm)	0.586	0.605	0.221	0.539	0.697	0.483	0.413	0.449
p-value	0.001*	0.001*	0.268	0.001*	<0.001*	0.001*	0.003*	0.001*
GMFCS			/		−0.469	−0.340	−0.251	−0.251
p-value					<0.001*	0.018	0.082	0.082
Selective motor control			/		0.450	0.337	0.480	0.209
p-value					0.001*	0.021	0.001*	0.154
Normalized maximal joint torque								
Age (yrs)	0.451	0.244	0.130	0.330	0.291	0.217	−0.069	0.015
p-value	0.011	0.201	0.517	0.086	0.034	0.139	0.637	0.921
Weight (kg)	0.486	0.034	0.004	0.140	0.214	0.244	−0.211	−0.159
p-value	.006*	0.861	0.984	0.476	0.123	0.095	0.145	0.274
Height (cm)	0.528	0.278	0.182	0.239	0.331	0.248	−0.064	−0.014
p-value	0.002*	0.144	0.362	0.220	0.016	0.090	0.664	0.926
Normalized muscle volume (ml/kg)	0.396	0.161	0.100	0.317	0.529	0.160	0.401	0.608
p-value	0.027	0.404	0.621	0.101	<0.001*	0.276	0.004*	<0.001*
Normalized muscle length (mm/cm)	0.020	0.052	0.307	0.395	0.454	0.157	0.243	0.188
p-value	0.915	0.793	0.119	0.038	0.001*	0.287	0.093	0.196
GMFCS			/		−0.504	−0.414	−0.232	−0.191
p-value					<0.001*	0.003*	0.108	0.188
Selective motor control			/		0.528	0.442	0.520	0.290
p-value					<0.001*	0.002*	<0.001*	0.046

*Univariate associations of anthropometrics, morphology and clinical parameters with MJT. *Significant correlation coefficient $p \leq 0.01$ ($p = 0.05/5$) in the TD cohort and $p \leq 0.007$ ($p = 0.05/7$) in the SCP cohort. $^{\Delta}$Significant difference between the correlation coefficient in the two cohorts ($p \leq 0.05$). The colors indicate the strength of the relationship: dark gray, high; middle gray, moderate; light gray, low; MJT, Maximal joint torque; KE, knee extension; KF, knee flexion; PF, plantar flexion; DF, dorsiflexion; GMFCS, gross motor function classification system.*

most of the muscles in children with SCP are undersized, but even more underpowered, producing less force per unit muscle tissue.

Relationships

The second aim of the current study was to define the muscle size–strength relationship, as well as associations of anthropometric measures, GMFCS level, and SMC with muscle strength. The correlation coefficients of anthropometric parameters with MJT (**Table 3**) were similar between TD and SCP (17, 34, 35, 56). While the coefficients appeared a little lower in the SCP cohort, the only significantly different associations were for KE with weight ($Z = 2.442$) and for DF MJT with age ($Z = 1.764$). Similarly, the associations of muscle morphology parameters with MJT were comparable between the cohorts. This is in contrast with previous results by Reid et al. where correlation coefficients of MV with KE and KF isometric MJT were significantly lower in the SCP cohort. However, in the same investigation, they found no differences in the correlation coefficient of MV with the isokinetic joint torque or joint work (20).

Different conclusions could be drawn when MJT was normalized to body weight (**Table 3**). In the TD cohort, all correlation coefficients became non-significant, with an exception for KE nMJT with weight and height. These findings suggest that the variance in MJT is largely influenced by growth-related parameters in this young, prepubertal TD cohort. In contrast to the TD group, the RF, MG, and TA nMV, as well as RF nML remained significantly associated with nMJT in the SCP cohort. These results confirmed that (muscular) growth is not the only crucial factor contributing to strength in children with SCP. This conclusion is further supported by the observed significant associations of SMC with MJT of KE and PF and nMJT of KE,

TABLE 4 | Regressions best fit.

Dependent variable	Independent variables	Adjusted R^2	*p*-value	Part correlations	Tolerance	VIF
A. Maximal joint torque in typically developing children						
Knee extension	Height	0.663	<0.001*	0.232	0.248	4.038
	RF MV			0.194	0.248	4.038
Knee flexion	Height	0.514	<0.001*	0.729	–	–
Plantar flexion	Height	0.293	0.002*	0.566	–	–
Dorsiflexion	TA MV	0.393	<0.001*	0.645	–	–
B. Maximal joint torque in spastic cerebral palsy						
Knee extension model 1	RF MV	0.548	<0.001*	0.746	–	–
Knee extension model 2	RF MV	0.601	<0.001*	0.644	0.888	1.127
	SMC KE			0.208	0.888	1.127
Knee flexion model 1	ST MV	0.281	<0.001*	0.544	–	–
Knee flexion model 2	ST MV	0.366	<0.001*	0.529	0.988	1.012
	SMC KF			0.276	0.988	1.012
Plantar flexion model 1	MG MV	0.168	0.002*	0.431	–	–
Plantar flexion model 2	MG MV	0.279	<0.001*	0.280	0.882	1.113
	SMC PF			0.355	0.882	1.113
Dorsiflexion model 1/2	TA MV	0.396	<0.001*	0.639	–	–
C. Normalized maximal joint torque in spastic cerebral palsy						
Knee extension	Height	0.419	<0.001*	0.206	0.947	1.056
	RF nMV			0.312	0.788	1.269
	SMC KE			0.326	0.825	1.213
Knee flexion	Height	0.210	0.002*	0.222	0.994	1.006
	SMC KF			0.432	0.994	1.006
Plantar flexion	SMC PF	0.254	<0.001*	0.520	–	–
Dorsiflexion	TA nMV	0.355	<0.001*	0.607	–	–

*Backward multiple linear regression model for maximal joint torque in typically developing children (A) and for maximal joint torque and normalized maximal joint torque in children with spastic cerebral palsy (SCP) (B,C). *indicates a significant regression coefficient ($p \leq 0.0125$; $p = 0.05/4$). Model 1 for the SCP cohort included height and muscle volume. Selective motor control was added in model 2. VIF, variance inflation factor; RF, rectus femoris; MV, muscle volume; TA, tibialis anterior; SMC, selective motor control; KE, knee extension; ST, semitendinosus; KF, knee flexion; MG, medial gastrocnemius; PF, plantarflexion; nMV, normalized muscle volume.*

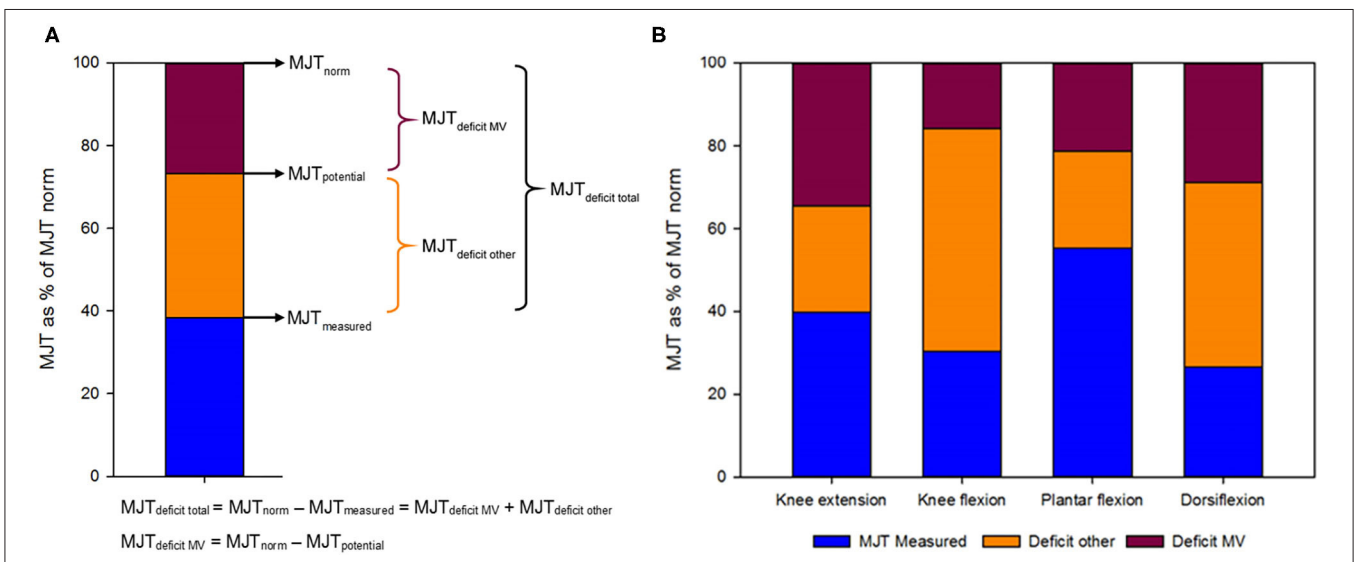


FIGURE 2 | (A) Fictive example of the calculation of the different maximal joint torques (MJT) that were measured or estimated as a percentage of the expected score in typically developing children, their relative representation and their corresponding deficits. $MJT_{potential}$ was based on muscle volume and the relationship with MJT in the typically developing cohort. The MJT_{norm} was based on the relationship of MJT with height in the typically developing cohort. The blue part indicates the relative $MJT_{measured}$. The red part indicates the relative $MJT_{deficit\ MV}$, i.e., the deficit in strength that is proportional to the deficit in muscle volume. The orange part of the graph indicates the relative $MJT_{deficit\ other}$, representing the deficit in MJT that comes from other factors than the decrease in muscle volume. **(B)** Representation of the measured MJT and deficits relative to the expected score in typically developing children for four lower limb joint movements.

KF, and PF, as well as GMFCS with MJT of KE and with nMJT of KE and KF. Earlier investigations found a similar influence of GMFCS level on both isometric and functional strength (4, 5, 14, 57). However, these results point toward the need for further research on the correct normalization parameters for muscle size and strength parameters in healthy and disabled pediatric populations. There was no significant negative association of nMJT with age in the CP cohort, indicating that the previously reported decrease in normalized muscle strength with age was not yet present in our group (16). This is presumably due to study differences in the age range of the cohort, which was 5–12 years in the current investigation in comparison to 8–19 years in the investigation by Davids et al.

In the multiple regression models for MJT in the TD group, height, MV, or both were included (**Table 4A**). Age, height, and weight as well as MV and ML showed high collinearity with each other (**Supplementary Table 2**), upon which only one parameter per category was chosen. The total explained variance of the TD models for MJT ranged from 29.3 to 66.3%. This is lower than previous results for KE MJT from Moreau et al. (17), where muscle thickness of the vastus lateralis and age resulted in an explained variance of 91%. Yet, the latter study was performed in a small study sample ($N = 12$) with a much wider age range (7–20 years) than the current study sample. The first multiple regression model of MJT in the SCP cohort included MV for all four joint movements, resulting in explained variances ranging from 16.8 to 54.8% (**Table 4B**). Adding SMC to the model increased the explained variance for KE, KF, and PF by 5.3–11.1%, resulting in a range of 27.9–60.1% explained variance. Likewise, SMC was included in the models for nMJT for KE, KF, and PF (**Table 4C**). SMC has, to our knowledge, not yet been related to isometric strength. However, SMC as assessed in this investigation has been found to be significantly related to gait parameters around the ankle (24). Moreover, both the Gross Motor Function Measure and overall gait deviation have been found significantly associated with another selectivity score, i.e., the Selective Control Assessment of the Lower Extremity (SCALE) (12, 13).

Contributions to Muscle Weakness

The final aim of this investigation was to define the contribution of decreased muscle size to the deficits in muscle strength. The group results for the four joint movements indicated that the patterns in the proportion of muscle weakness explained by decreased MV and by other factors are muscle specific (**Figure 2** and **Supplementary Table 3**). The part explained by MV, i.e., the difference between the MJT_{norm} based on growth and the $MJT_{potential}$ based on MV, ranged between 22.6% for KF and 57.3% for KE. The part explained by other factors, i.e., the difference between the measured MJT and $MJT_{potential}$, ranged from 42.7% for KE to 77.4% for KF. The weakness in KE and PF presented with approximately equal distributions of MV deficits and remaining factors, whereas KF and DF muscle weakness seemed predominantly caused by other factors. This variability between joint movements can potentially be partially explained by the differences in architectural types of the investigated muscles (like the fascicle arrangement), as well as by the differences in neural control and common treatment at the muscular level. Additionally, muscle weakness, as well as the contributing factors to muscle weakness, largely varied between participants (**Supplementary Figure 1**). This may be caused by participant-specific characteristics, like cognitive ability and motivation, as well as by the treatment history with, among others, the focus of regular physiotherapy, the use of orthoses, and the number of botulinum neurotoxin-A injections (44, 58, 59).

There may be several additional underlying mechanisms, the "other factors," causing the disproportional decrease in muscle strength. A simple, clinical measure of SMC was used to represent the neural component in this investigation and found to have moderately significant associations with MJT of KE, KF, and PF (**Table 3**). The lack of studies evaluating the associations of SMC with isometric muscle strength in previous investigations made it difficult to compare results. However, various underlying neurological factors influencing muscle strength have been identified like reduced central drive, impaired reciprocal inhibition, and disorganized motor unit recruitment (6, 7). Moreover, it should be noted that there is also individual variation in neural control of muscle activation in the healthy population (60), which was confirmed by the wide spread of the TD data around the regression line in **Figure 1**. Furthermore, the assessment of strength can also be influenced by cognition, attention, or motivation (17). So far, previous studies on the role of muscle selectivity, using the SCALE outcome (61), only reported the total limb score without description of the individual scores. Moreover, the SCALE evaluates both directions of movement around one joint in one score (e.g., KF and KE), instead of separately per motion direction, as applied in the current study.

Next to the alterations in neural control, additional muscular changes may also be considered as underlying mechanism of the decreased muscle strength. Muscle architecture parameters, such as the pennation angle and fascicle length, are related to the pCSA and, therefore, to maximal strength. Yet, previous investigations found inconsistent outcomes for fascicle length in participants with SCP (23, 29). Additionally, the ML–force relationship, also known as the torque–angle relationship, is considered to be altered in children with SCP, resulting in measurements being performed at different points of the length–force curve in the TD cohort vs. the SCP cohort (62, 63). Earlier research also indicated alterations in the proportion of contractile tissue relative to non-contractile (fibrotic and fatty) tissue in children with SCP. It is likely that this reduced proportion of contractile tissue in the already reduced MV in children with SCP, compared to their TD peers, also contributes to the observed muscle weakness (21, 22, 64). Yet, individual variation in muscle tissue composition has been determined in the healthy population (65). Future investigations are needed to further delineate and understand the contributions of these "other factors" to muscle weakness in SCP, with a systematic focus on the neuromuscular control, the muscle architecture, the length–force relationship, and the intrinsic muscle composition. Since muscle strength is an important parameter for gross motor function and maintaining ambulation, further research into the

underlying components of muscle weakness is encouraged (15, 16, 36).

Clinical Implications

The muscle strength profile resulting from the combined assessment of muscle strength and muscle morphology gives an indication of the contribution of muscle size deficits to muscle weakness. This could be used to optimize training prescriptions either aiming at enhancing neural drive or inducing muscle hypertrophy. However, for both underlying mechanisms of muscle weakness, the influence of training is not always consistent (44, 66, 67). The muscle strength profile could potentially provide a predictive value on the outcomes of certain types of strength or active movement training in children with SCP. Knowing the contribution of muscle size to muscle weakness could also be used to define if other, potentially atrophy-inducing, treatments like botulinum neurotoxin-A or lower leg casting (68–71) are appropriate for a patient or a specific muscle group.

Impaired muscle growth and muscle size deficits are also underlying causes for muscle contractures in children with SCP (72, 73). Muscle contractures can be defined as unique muscular adaptations that increase the passive stiffness of the muscle, resulting in limited mobility of the joints without active force production of the muscle (74). Reduced muscle growth, as already observed from the age of 15 months (34), may result in reduced ML and muscle–tendon unit length relative to bone length. Although shortened fascicle lengths, related to the number of sarcomeres in series, can be a possible reason for decreased ML (75), this has not been confirmed in every investigation (76). However, in pennate muscles, both the length and the diameter of the fascicle contribute to ML (77). Consequently, reduced MV resulting from reduced muscle fiber diameter, and related to the number of sarcomeres in parallel, can influence longitudinal muscle growth (77, 78). The contribution of reduced muscle diameter to reduced ML depends on the morphology of the muscle and fascicle arrangement. Future studies should define the impact of muscle size deficits on muscle contractures and define the influence of common interventions like stretching and casting.

Limitations and Future Perspectives

There were some limitations to this investigation that should be considered when interpreting the results. First, there was an unequal distribution of GMFCS levels, with a multitude of children classified as GMFCS level I. This was influenced by the selected inclusion criteria related to previous treatment history and the ability to cognitively understand the test procedures, since orthopedic surgeries and cognitive problems are more common in children with higher GMFCS levels (79–82). This investigation had a cross-sectional design limited to prepubertal children. Future investigations should consider longitudinal follow-up to define the alterations of muscle size, strength, and their ratios during growth and aging, as well as the effect of interventions to prevent or improve muscle weakness. This might also uncover the timing of neural and musculoskeletal onset as causes of muscle weakness. Finally, this investigation applied some simplifications. The morphology was only assessed for one muscle per joint movement. Previous investigations showed that all muscles of the lower limb in children with SCP are affected. However, there is heterogeneity, and not all muscles are affected to the same extent (25, 28, 83). Moreover, a subjective clinical classification of SMC was included. Further research into the underlying neural components of muscle weakness is encouraged.

CONCLUSION

This investigation confirmed the disproportional decreases in muscle size and muscle strength around the knee and ankle joint of children with SCP in comparison to TD children. Furthermore, associations of strength with growth-related parameters like age, weight, and height were strongest in the TD cohort, whereas these were also present but accompanied by associations with SMC and GMFCS in the SCP cohort. The correlation coefficients of the muscle size–strength relationship were similar, whereas the regression coefficient was decreased in the SCP cohort, indicating that only part of the muscle weakness can be attributed to smaller MVs. However, there was a lot of heterogeneity between the proportion of muscle weakness that was attributed to deficits in muscle size both between joint movements and between subjects. Future studies should investigate what other mechanisms underlie muscle weakness, as well as how muscle weakness and its components are influenced by treatment, growth, and aging.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of the University Hospitals Leuven and Ghent. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

This study was designed by BH, KD, CV, PC, MD, and LB-O. BH, NP, IV, and NDB contributed to the data collection. AV and GM were involved in patient recruitment. BH was responsible for the data processing, with help from IV in the MATLAB coding and conducted all presented analyses. BH and KD contributed to the interpretation of the results and were involved in the critical revision and editing of the manuscript that was written by BH. All authors approved the final version of the manuscript and agreed to be accountable for the content of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.692582/full#supplementary-material

Supplementary Figure 1 | Display of the measured and estimated maximal joint torques (MJT)s per participant. The blue bar indicates the $MJT_{measured}$, the red part is the deficit to MJT_{norm} due to decreased muscle volume (MV,) and the orange part of the graph indicates the deficit in MJT that comes from other factors than the decrease in MV. A negative red bar indicates an $MJT_{potential}$ based on MV that is larger than expected from growth. A negative orange bar indicates an $MJT_{measured}$ that is larger than expected based on MV. For all four joint movements, the bars on the x-axis are ranked from smallest to tallest child (in height), resulting in the same order of children for all four graphs.

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