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Case reports in autism

Edited by
Marco Colizzi and Fengyu Zhang

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Case reports in autism

Topic editors
Marco Colizzi — University of Udine, Italy
Fengyu Zhang — Global Clinical and Translational Research Institute, United States

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Antonio M. Persico,
University of Modena and Reggio Emilia, Italy

*CORRESPONDENCE
Marco Colizzi
marco.colizzi@uniud.it

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Editorial: Case reports in autism

Marco Colizzi[1]* and Fengyu Zhang[2]

[1]Unit of Psychiatry, Department of Medicine (DAME), University of Udine, Udine, Italy, [2]Global Clinical and Translational Research Institute, Bethesda, MD, United States

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Editorial on the Research Topic
Case reports in autism

Autism is a neurodevelopmental disorder characterized by persistent deficits in social communication and interaction and restricted repetitive patterns of behaviors, interests, and activities (1). It has become an emerging condition that affects 2% of children under eight and throughout adulthood (2), partly due to improved performance of screening and diagnosis and public awareness. However, autism has great complexity and heterogeneity in etiology, clinical manifestations, and biological and behavioral features that cross multiple developmental domains, including physical, cognitive, social-emotional, and sensory, and there are limited options for treatment and intervention (3). Also, it is probably one of the most misunderstood conditions, where efforts are needed to increase comprehension of such a complex phenomenon and dispel myths and misconceptions that may hamper its identification and treatment (4). Case reports and focus groups allow an in-depth examination of individual cases to dissect this complexity and delineate the disease course and progression (4, 5). Even though case reports do not provide the most solid evidence-based indications, they may help perform exploratory analysis or generate intriguing hypotheses for higher-rank investigations in physiological studies and clinical trials (5).

This Research Topic reflects some current challenges and advances in autism. Research reports presented here approach autism for the complex condition that it is (6), thus ranging in their content and trying to offer an overview of the progress that has been made. Also, some evidence about emerging and promising therapeutic interventions is presented.

One of the significant interests in autism research is represented by the possibility of identifying autism as soon as possible, promptly intervening, and possibly modifying its trajectory positively (7). Malachowski et al. compared an infant with autism and a neurotypical infant regarding the early development of fine motor skills and visual attention to objects. Their study revealed how significant differences in such domains may emerge by just three months of age, possibly offering a behavioral marker for early detection of autism.

Another line of research is interested in investigating psychiatric comorbidity and outcomes among autistic children as they grow up (8). Di Luzio et al. presented a case where emerging psychotic symptoms along with late regression posed a diagnostic challenge whether clinicians were facing a very-early onset schizophrenia or autism where social-communicative development and adaptive functioning had been adequate during the first years of life. Authors reflected on the neurodevelopmental continuum paradigm, where autism and psychiatric disorders that emerge later in life can be

conceptualized within a pattern of pathological continuity (9). This is particularly relevant for milder forms of autism and female individuals, whose attempt at camouflaging pathognomonic features of autism may exacerbate psychic distress. Secci et al. described a female adolescent whose undiagnosed autism represented a potential vulnerability for treatment-resistant depression with high suicide risk, possibly through exposure to stressful life events.

Some studies addressed strategies to sustain autistic children in everyday life and in times of difficulty (10). Nair et al. investigated autistic children's preferences regarding colors and lighting to create autistic-friendly interior spaces. Evidence indicated calming or stimulating effects and behavioral changes, depending on hue, saturation, and luminosity, likely driven by atypical sensory processing. The authors emphasized how an autism-friendly built environment may support autistic people's well-being and cognitive function. Arai et al. provided a valuable example of how collecting information on a child's expected behavioral problems from parents and school teachers may be of support during hospital admission for surgery. Such an approach is of paramount importance for at least two main reasons. On the one hand, autistic children present with complex health needs, which make them more prone to any kind of hospital interactions; on the other, autistic children's health management is challenging, as their difficulties render it more difficult to obtain compliance with healthcare pathways.

Following the last point, it is relevant to focus on medical comorbidity and its impact on autism presentation and outcome (11). Milutinovic et al. discussed a case of a child with autism who also presented with a genetic condition, the Coffin-Siris syndrome, that, along with physical abnormalities and dysfunctions, is characterized by neurocognitive and developmental difficulties. Interestingly, the identified heterozygous *de novo* pathogenic variant (class 5) c.1638_1647del in the *ARID1B* gene, which has a causative role in the Coffin-Siris syndrome, is *per se* associated with an autistic phenotype. Hu et al. focused on the *BRSK2* gene, which encodes the brain-specific serine/threonine protein kinase 2, the latter being independently implicated in autism pathophysiology. In such a case, the adolescent presenting with a *de novo* frameshift variant (c.442del, p.L148Cfs*39) suffered from attention-deficit symptoms, auditory hallucinations, and abnormal brain electrical activity mapping, thus revealing a severe form of the disorder. Such evidence urges an in-depth analysis of genetic causes and modifiers of autism (12).

Two studies have opened up novel biological therapies based on comorbid conditions (13). Offutt and Breitschwerdt provided evidence of how treating specific poly-microbial vector-borne infections resulted in overall neuropsychiatric improvement in an autistic adolescent. Interestingly, there was such an improvement that the patient dramatically increased his academic performance, moving from special education needs to grade-level standing without accommodations to college acceptance. The authors questioned whether there was a direct or indirect (i.e., secondary immune consequences) effect of the infections (i.e., bartonellosis and borreliosis) on autism development or, at least, specific phenotypic presentation. Hu et al., based on background supporting the role of the intestinal microbiota in autism, treated a child with fecal microbiota transplantation (FMT) from a healthy donor. FMT into the patient's gastrointestinal tract improved the gut microenvironment, with effects not only for her gastrointestinal symptoms but also for autism core symptoms and overall functioning. The authors called for better-designed clinical trials of FMT and studies of the role of the microbiota in the pathophysiology of autism.

Some studies reported on non-pharmacological treatments, as well as environmental interventions, that may potentially address some unmet needs in the autistic population (14). Colombi et al. reported on the effects of a pre-emptive parent-mediated intervention based on the Infant Start, an adaptation of the Early Start Denver Model (ESDM), in an autistic child followed up during his very first months of life. Beneficial effects were detected on both the child's developmental levels and autistic symptoms. Panesi et al. presented an intervention promoting working memory capacity and executive functions among pre-schooling autistic children by implementing digital apps and analogical playful activities. Interestingly, the child benefited from a nine-week intervention in terms of working memory-related language reception and update, inhibitory control, receptive vocabulary, and playful activities. Such findings highlight the importance of intervening in front of early warning signs of autistic behavior to sustain the child's developmental trajectory. Maggio et al. presented a prospective case series exploring employment perspectives among autistic individuals who benefit from an individual-supported program to enhance placement in a sheltered work environment. Evidence indicated an improvement in working abilities and self-organization, despite patients having severe-to-moderate autism. The authors proposed to implement such intervention to enhance employment in autism with high support needs and co-occurring intellectual disability.

In summary, this Research Topic highlights how case reports could provide information on understudied aspects and emerging biobehavioral underpinnings of a condition, particularly rewarding for those conditions like autism, where the heterogeneity and complexity of phenotypes require the rapid acquisition of new data. We hope that the information summarized here could provide support for further study of new pathophysiological mechanisms and clinical management strategies.

Author contributions

MC: Writing – original draft, Writing – review & editing. FZ: Writing – original draft, Writing – review & editing.

Conflict of interest

MC has been a consultant/advisor to GW Pharma Limited, GW Pharma Italy SRL, and F. Hoffmann-La Roche Limited outside of this work.

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References

1. American Psychiatric Association Publishing. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*. Washington, D.C. (2013).

2. Maenner M, Shaw K, Bakian A. e. a., prevalence and characteristics of autism spectrum disorder among children aged 8 years — Autism and developmental disabilities monitoring network, 11 sites, United States, 2018. *MMWR Surveill Summ* (2021) 70:1–16. doi: 10.15585/mmwr.ss7011a1

3. Masi A, DeMayo MM, Glozier N, Guastella AJ. An overview of autism spectrum disorder, heterogeneity and treatment options. *Neurosci Bull* (2017) 33:183–93. doi: 10.1007/s12264-017-0100-y

4. John RP, Knott FJ, Harvey KN. Myths about autism: An exploratory study using focus groups. *Autism* (2018) 22:845–54. doi: 10.1177/1362361317714990

5. Nayak BK. The significance of case reports in biomedical publication. *Indian J Ophthalmol* (2010) 58:363–4. doi: 10.4103/0301-4738.67038

6. Bradshaw J, Schwichtenberg AJ, Iverson JM. Capturing the complexity of autism: Applying a developmental cascades framework. *Child Dev Perspect* (2022) 16:18–26. doi: 10.1111/cdep.12439

7. Okoye C, Obialo-Ibeawuchi CM, Obajeun OA, Sarwar S, Tawfik C, Waleed SM, et al. Early diagnosis of autism spectrum disorder: A review and analysis of the risks and benefits. *Cureus* (2023) 15:e43226. doi: 10.7759/cureus.43226

8. Antolini G, Colizzi M. Where do neurodevelopmental disorders go? Casting the eye away from childhood towards adulthood. *Healthcare (Basel)* (2023) 11(7):1015. doi: 10.3390/healthcare11071015

9. Bortoletto R, Bassani L, Garzitto M, Lamberti M, Simonati A, Darra F, et al. Risk of psychosis in autism spectrum disorder individuals exposed to psychosocial stressors: A 9-year chart review study. *Autism Res* (2023) 16:2139–49. doi: 10.1002/aur.3042

10. Lam GYH, Sabnis S, Migueliz Valcarlos M, Wolgemuth JR. A critical review of academic literature constructing well-being in autistic adults. *Autism Adulthood* (2021) 3:61–71. doi: 10.1089/aut.2020.0053

11. Bauman ML. Medical comorbidities in autism: challenges to diagnosis and treatment. *Neurotherapeutics* (2010) 7:320–7. doi: 10.1016/j.nurt.2010.06.001

12. Xia L, Ou J, Li K, Guo H, Hu Z, Ba T, et al. Genome-wide association analysis of autism identified multiple loci that have been reported as strong signals for neuropsychiatric disorders. *Autism Res* (2020) 13:382–96. doi: 10.1002/aur.2229

13. Aishworiya R, Valica T, Hagerman R, Restrepo B. An update on psychopharmacological treatment of autism spectrum disorder. *Neurotherapeutics* (2022) 19:248–62. doi: 10.1007/s13311-022-01183-1

14. Carruthers S, Pickles A, Slonims V, Howlin P, Charman T. Beyond intervention into daily life: A systematic review of generalisation following social communication interventions for young children with autism. *Autism Res* (2020) 13:506–22. doi: 10.1002/aur.2264

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EDITED BY
Fengyu Zhang,
Global Clinical and Translational Research Institute, United States

REVIEWED BY
K. Kiruthiga,
Hindustan University, India
Thirumaran Kesavaperumal,
National Institute of Technology, India

*CORRESPONDENCE
Radhakrishnan Shanthi Priya
shanthir1@srmist.edu.in
Xiaowei Zuo
2783369510@qq.com

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A case study on the effect of light and colors in the built environment on autistic children's behavior

Ashwini Sunil Nair[1], Radhakrishnan Shanthi Priya[1]*, Prashanthini Rajagopal[1], Chandramouli Pradeepa[1], Ramalingam Senthil[2], Samiappan Dhanalakshmi[3], Khin Wee Lai[4], Xiang Wu[5] and Xiaowei Zuo[6]*

[1]School of Architecture and Interior Design, SRM Institute of Science and Technology, Chennai, India, [2]Department of Mechanical Engineering, SRM Institute of Science and Technology, Chennai, India, [3]Department of Electronics and Communication Engineering, SRM Institute of Science and Technology, Chennai, India, [4]Department of Biomedical Engineering, Faculty of Engineering, Universiti Malaya, Kuala Lumpur, Malaysia, [5]School of Medical Information and Engineering, Xuzhou Medical University, Xuzhou, China, [6]Department of Psychiatry, The Affiliated Xuzhou Oriental Hospital of Xuzhou Medical University, Xuzhou, Jiangsu, China

Background: The importance of strategies and services by caregivers and family members substantially impact the psychological and emotional wellbeing of autistic children. The rapid research developments in clinical and non-clinical methods benefit the features of autistic children. Among various internal and external factors, the influence of the built environment also impacts the characteristics of autistic children. This study investigates primarily the psychological effect of light and colors on the mood and behavior of autistic children to identify the most favorable and preferred indoor lights and color shades.

Methods: A questionnaire survey was conducted at an autism center among autistic children and their parents. This study included autistic children aged between 6 and 16 (45 males, 42 females, mean age 8.7 years, standard deviation 2.3). Eighty-seven participants were involved in the survey to determine the sensory perceptions, intolerance, preferences, and sensitivities of children with an autism spectrum disorder toward colors and lighting. The margin of error at the statistical analysis's 95% confidence level is $\pm$ 0.481.

Results: As per this case report, the children have various color preferences and respond differently to different shades. Different hues have varying effects on autistic children, with many neutral tones and mellow shades proven to be autistic-friendly with their calming and soothing effect, while bright, bold, and intense colors are refreshing and stimulating. The stimulus of bright-lighting causes behavioral changes in autistic children prone to light sensitivity.

Conclusion: The insights gained from this interaction with parents and caretakers of autistic children could be helpful for designers to incorporate specific autistic-friendly design elements that make productive interior spaces.

A complete understanding of the effect of factors like color and lighting on the learning ability and engagement of autistic children in an indoor environment is essential for designers and clinicians. The main findings of this study could be helpful for a designer and clinicians to address designing an autism-friendly built environment with a color palette and lighting scheme conducive to their wellbeing and to maximize their cognitive functioning.

KEYWORDS

autistic children, cognitive functioning, wall colors, indoor lighting, built environment, behavioral changes

Introduction

A significant instance of pervasive development being witnessed throughout the globe is the complex neurodevelopment condition called autism spectrum disorder (ASD) which impacts behavior, communication, and social interaction (1–4). The scientific community has conducted several research studies in recent years to assess the incidence and prevalence of ASD (5–7). A significant increase in ASD could be globally recognized (8–10). India is a highly populated nation of about 1.3 billion families with children under 15, representing almost many inhabitants per a detailed clinical evaluation (11, 12). More than two million individuals in India have been impacted by autism. This challenging observation has led to user-centric strategies, support and intervention services such as healthcare facilities, education support, and rehabilitation services to facilitate easy interaction and seamless social integration. The need to cater to the unique needs, preferences, requirements and challenges of autistic children has directed the efforts of designers toward considering these essential aspects while designing inclusive and empowering spaces for children on the autism spectrum (13, 14). ASD is characterized by cognition, understanding, social behavior, and emotional expression. People with autism have challenges deciphering emotional expressions, cannot comprehend the emotions of others, avoid eye contact, and have extreme sensitivity to the environment. Such sights or sounds could influence a positive change and behavior (15). Research studies have shown that the ASD group demonstrated greater perceptual and learning characteristics (16–18). Challenging features of executive functioning are commonly observed in people experiencing ASD, with noticeable suppression of cognitive flexibility; such behavioral inflexibility impacts their ability to perform any task (19).

Autistic children tend to perceive and experience their environment differently from others (20, 21). By paying attention to the sensory sensitivities and challenges with visual information processing faced by autistic children, appropriate changes can be incorporated into their indoor environment to turn it into a friendly and accommodative place tailored to their unique needs. Suggestions were made optional but solicited to understand the user's needs before designing an inclusive space for autistic children. This calming environment would encourage their growth and facilitate their learning regarding the visual environment and other influencing factors. The survey method provided valuable insights into the preliminary considerations for designing an engaging and welcoming indoor environment that provides positive sensory experiences and alleviates anxiety.

Any autism-friendly design depends first and foremost on the end-user's unique needs, preferences, and comfort. The design considerations for sensory-friendly spaces must be based on the core aspects of functionality, connectivity and responsiveness following a careful study of the inherent features of the built environment and after gaining a good understanding of the unique perspectives of autistic individuals (22). Design mechanisms must also thoroughly examine essential factors such as imagination, verbal/non-verbal communication, social interaction, sensory issues, behavior, and safety. There continue to be several research studies on the many facets of autism, resulting in various scientific advancements and noteworthy developments. However, evidence shows that many factors remain unknown. Cognitive deficits and motor coordination challenges are common in children with autism. They have a detrimental impact on children's everyday lives and limit their achievements. Due to the increased effort in caring for autistic children and finding ways to cope with their behavioral challenges, parents should be familiar with the environmental impacts (23, 24). Autistic children tend to have a dysfunctional sensory system; this sensory processing disorder is perceived as the biggest challenge to surmount (25, 26). Few but well-chosen articles and publications provide valuable insights into all aspects of one vital concept: the senses.

Information comes through all the senses, which are processed and organized by the brain. Processing sensory information is extremely difficult for autistic children, affecting

their sensory responsiveness and reactions. Human senses are interconnected and cannot be separated, but multisensory integration is challenging for autistic children. The eight sensory systems are visual, auditory, olfactory, gustatory, tactile, proprioceptive, vestibular, and interoception. These are highly central to understanding sensory processing in autism and a sensory integration approach would make them very relevant to investigating visual processing (27–29). Sensory processing disorder is often a comorbid symptom of ASD, but not all children with sensory processing disorder have autism.

According to the literature, sensory difficulties and processing disorders appear to be more prevalent in autistic children and ASD is perceived to be the root cause of their sensory system (30). People with sensory processing disorders are generally classified as hypo and hypersensitive (under and over-responsiveness). The response and reaction of both categories to low and high stimuli in any setting tend to differ based on how they process sensory information. Individuals with autism are frequently more socially aware due to sensory difficulties with seeing, hearing, and feeling. Children with autism do not interact much with others, struggle with sensory overload, have difficulty expressing their feelings, and prefer to live in their private world of self-imposed isolation. Despite social, behavioral and communication challenges and sensory processing challenges, they have a strong understanding of their surroundings, have exceptional memories, are very creative and possess the ability to learn new skills (31). Thus, sensory integration issues can continually make the built environment unpleasant and hostile for many people on the autism spectrum.

Since ASD impairments can fluctuate between moderate and severe with few or mild characteristics and with co-occurring conditions, the abilities, needs and services demand to vary wildly across individuals. However, almost all require therapeutic interventions and support for their lifespan (32). Apart from a functional link with human health, emotions influence individuals' interactions with environmental factors. In the long run, the features arising from misguided attempts to "regularize" the perception of an autistic individual may prompt corrective behavioral responses such as repeated motions and other methods to regain some predictability in sensory inputs. Free and open communication is essential because it affects how one understands, investigates, and evaluates surroundings (33). The emotional responses that arise throughout the relationship between a human and the different ecosystem entities might align with the earlier statement (34). Much clinical evidence is available in the Indian setting on ASD. The active involvement and participation of parents of children and young adults in intervention, integration, and rehabilitation efforts help in gaining a better understanding of autistic behavior, which is essential for all productive experimentation with the goal of better developmental, behavioral, and educational outcomes (35).

Many researchers have investigated the relationship between the five senses and their impact on the surrounding environment with multiple parameters. Investigating the quality and dynamics of early encounters is a difficult task. It usually necessitates observing and integrating multimodal social signals and comprehending how two interactions synchronize for understanding the autistic child's behavior (36, 37). Such understanding can significantly help designers design a supportive, autism-friendly environment and help them innovate in the design considerations of various inclusive spaces. Researchers have experimented, analyzed and briefly explained specific design considerations, elements and components for users on the autistic spectrum. The following design components help to understand the importance and need for a unique, autistic-friendly built environment for preliminary studies.

Space organization

The spatial element is a crucial factor that designers and architects must be aware of when building for people with ASD. This is attributed to the importance of routine, order, regularity, and predictability. Well-defined areas should be placed in a logical sequence based on the regular schedule followed in specific settings regarding spatial sequencing to make it easier for autistic children to navigate these spaces without assistance. A research study was conducted to recommend the setting up of an organized space focusing on accessibility to and inclusivity of autistic children by creating surroundings that were clearly defined, orderly, simple, safe, satisfying, predictable, welcoming, and stable (38–40). Spatial experiences are a method of using spatial knowledge to decode the arrangement of built spaces. A research study provided an overview of the Faison School in the United States. It demonstrated how adaptable and customizable layouts with sensory benefits could benefit autistic children with a sensory processing disorder. Introducing clearly defined strips along corridors is a component of spatial sequence and navigation aids that make indoor spaces reachable, inviting, and comfortable for autistics. The color of those strips is also crucial in the case of spatial navigation and when wayfinding techniques are deployed.

Wayfinding

This technique develops a simple and easy navigational approach by incorporating assistive visual aids such as landmarks, decoration, and color-coding (32). Environmental navigation, orientation, and wayfinding were explored in a research study conducted in a school for autistic children (34). Before the study, the researcher spent time in the

participants' classrooms to become better acquainted with the users' everyday routines and observe their behaviors and interactions during class activities, which helped frame their actions during wayfinding tasks (41, 42). Various metrics were employed in evidence-based research to examine the effects of spatial navigational aids and the setting up of demarcated sensory-friendly zones such as sensory rooms. Children with sensory sensitivities could use it as a safe place to withdraw or shelter when overwhelmed by a sensory overload. A simple navigation system can help visually sensitive autistic users traverse their environment quickly and without fear. Color-coded paths can help them easily navigate from one location to another (43).

Lighting

The importance of good lighting, both natural and artificial, is evident in the way it can transform any space. Lighting has a significant impact on the sensory system of autistic children. Evidence-based research was conducted on an active group of autistic users to determine their responses to lighting, their light sensitivity and possible light modifications that could be implemented for people with sensory challenges (44, 45). The diffusive light effects on the walls were thoroughly studied through windows, floors, ceilings, and furniture. The study analyzed how the users reacted to light in the hallway when the change in hue caused corresponding changes in users' behavior and mood. The study also explored adjustable lighting settings to match the natural circadian cycle of the body closely. Indirect lighting reduces flickering, intensity, and brightness, helping ASD individuals cope with their light sensitivity (38). Artificial lights should ideally be fitted with dimming controls to alter or produce a luminous interior as an indirect light source (13). Before the research observation of the study group of autistic children began each morning, a checklist was implemented to validate the accurate establishment of the route and to verify if the circumstances between the participants were consistent, remarkably everyday sensory stimuli like light and sound. To verify if circumstances between the participants are consistent, particularly considering light and sound, potentially observe autistic children.

Based on the environmental conditions, the responses gathered included the children's reactions to light (amount of illumination) and sound (number of decibels), which were studied to devise ways to help autistic children struggling with sound and light sensitivity. Ideally, the environmental circumstances should be constant for all participants, especially since bright lights and loud sounds can be bothersome sensory overloads to autistic children affecting their functioning and behavior. The restriction of visual stimulation was enforced through dimmer switches provided for all lighting installations to reduce light levels based on the need (46). Students could easily regulate the degree and intensity of light stimulation by switching each light row as needed.

Acoustics

Sound quality is perhaps the most critical component in managing and maintaining autism spectrum conduct on an even keel among all the visual inputs involved in building design (47). Therefore, attempts must be made to reduce the auditory sensitivity of autistic children and prevent sensory overload. An experiential study showed that lowering sound levels and echoes in zones packed with autistic students resulted in improved mental attentiveness, service quality, a better quality of work, and reduced the tempo of compulsive self-stimulating behavior (32). The authors indicated that due to the intolerance of extraneous noise and difficulties in auditory processing, auditory sensitivity measures while planning interior acoustics are essential for building environments housing people with autism. Therefore, architects must avoid excessive ambient noise and effectively manage the acoustic requirements of enclosed spaces to prevent the extra stimulation from a noisy space that could distress autistic children with sound sensitivity in a space.

By identifying and eliminating interfering sensory information under the user's needs and creating a quiet and comfortable environment conducive to productivity, people with autism can enhance their attention, reduce stress, and prevent inappropriate behavior. The authors advised the integration of pink cacophony for privacy and a salutogenic sound design approach in a space with many activities. A lower sound intensity of less than 50 dB is preferable for autistic children and beyond 60 dB makes it inappropriate. It was also recommended that a suitable acoustic environment within an enclosed space by reducing the frequency of the room's resonance for acoustic comfort and soundproofing a room by ensuring good sound absorption.

Colors

Autistic children are sensitive to colors depending on how they perceive them. Most see them with greater intensity than they are. Colors in interior spaces affect their mood, learning, and behavior and must be chosen judiciously (42, 43). Colorful mat boards were chosen in a research study to make color shapes on the floor as the lightweight material was not a potential hazard. It was ensured that their color complimented the aids placed by the door to establish a uniform color pattern. The colored indicators, colored doors, and floor forms enabled traceability and consistency. The study's findings revealed that colorful signs made areas more accessible and easier to navigate for autistic children. Using autism-friendly color palettes such as pastel shades, neutral colors, and muted tones can foster a

soothing sensory experience in an indoor environment. Bold and bright colors must be avoided as they could be over-stimulating and disturbing, which may cause autistic children to become tense and aggressive. Autistic children keenly feel different from others due to a lack of self-confidence and an inability to adapt. The importance of using color therapy to assist and empower autistic children to function without discomfort in a calm environment and in correcting their behavioral abnormalities must be recognized (48).

Investigations are necessary to examine the impact of color indices on learning specific complex tasks. Thus, the variable effect of indices on generalization and persistence is mainly in the case of color formation. Investigations are necessary to examine the psychological impact and effects of color on learning specific complex tasks and cognitive task performance by autistic children. Evidently, with the understanding of the existing scenario and the available data, it seems worth examining the application of color techniques for autistic individuals (49). Using organic material and neutral and relaxing color tones is deemed suitable for an autistic educational environment as they are conducive to learning, increase attention and boost energy levels. Psychological features are practical with selective colors. Red or yellow can be problematic as they can agitate, depress or confuse autistic children causing their withdrawal (13). An uncommon experimental study was conducted to determine if concepts could be taught to autistic children by associating them with color (50). The authors attempted to explain an inclination model simply by associating colors with symmetrical items objects (51–53).

People pick colors linked to things they like and do not prefer the colors they dislike (54). Autistic children generally have atypical color preferences and aversions with complex emotional associations with color (55, 56). Their visual perceptions of color can influence their emotions and behavior (57–60). High contrast choices by participants with ASD may be due to color compulsions and may be attributed to a preference for items in colors they like. A study of participants with ASD found that color preferences and obsessions could be linked to a preferred object, resulting in higher color preference than usual (50).

Safety

Protecting autistic children from harm by providing a safe and secure environment is vital as their sensory processing ability is not developed enough to recognize challenges and handle crises (13). As children with autism often prefer to flee and escape frightening situations, it is necessary to establish standard procedures or safety systems that make it impossible for them to leave any place unnoticed places or amenities. Generally, any place's structure, organization, and design must be ensured that it offers maximum freedom and flexibility, eliminates all problematic situations, addresses safety concerns, and is tailored to the behavioral factors unique to ASD users. Although all possible chances cannot be eliminated, they must be anticipated; safety issues must be duly considered, and safety strategies must be customized, as ASD children are susceptible to many challenges. Integrating primary entry points of safety systems enables the monitoring and tracking of the movement of people. For example, establishing exterior barriers improves safety aspects and facilities better organization, particularly in open spaces and courts. Installing mirrors with rounded corners in restrooms, using reflectors and fixing wider toilets are simple and easy measures that can be adopted to make areas safe, comfortable, easily accessible, and autism-friendly zones.

In most research studies, the preferences and opinions of autistic people are kept for analysis at a later stage. Several studies have highlighted the importance of clear rules, consistent routines, and calm orderliness for the adaptive functioning of individuals with ASD. Such studies are to help them cope with a predictable environment, situation, or setting without unexpected changes and help them to be engaged without being overwhelmed by anxiety (61, 62). As they face language difficulties and communication challenges, schedules and structure are very important as they provide much-needed stability and help improve their wellbeing.

Many behavioral changes are attributed to different colors, and many research studies have attempted to decode the physiological effects of colors observed in autistic people. A study found that the strategic use of color could foster learning and suggested that the materials for learning activities could be chosen based on favorable color perceptions (63). The fixtures and furnishings provided in an enclosed space also play a crucial role in the sensory experiences of an autistic person while transitioning from one space to another. Loud and noisy disturbances are usually not tolerated by autistic individuals as they have auditory sensitivity. These jarring stimulants can serve as triggers and bring about behavior changes ranging from mild to severe. Surveys on autistic users have provided an exceptional understanding of how they perceive space and spatial relations.

Many diverse research studies conducted by various scholars have extensively investigated the fundamental aspects relevant to enabling an autism-friendly environment (50). However, the core concepts of color, light and texture, all fundamental design aspects, must be linked to the essential components of visual and tactile sensory learning. These interconnected factors can provide an enriching experience for autistic individuals when they are integrated. Not many quantitative research studies have explored creating an independent, sensory-friendly environment for autistic individuals. The initial findings of some research studies have indicated that design elements such as color, light, and texture must be studied collectively. Determining the combined influence of color, light, and texture on interior spaces makes them more accommodating for

autistic people with sensory intolerance. The perception of psychological changes, emotional expressions, and behavioral alterations in autistic children could be studied further to enhance their features.

Although several diseases fall under the gambit of ASD, this study focuses on autistic children's visual sensitivity. The understanding of the sensory perceptions of ordinary people is evident. Understanding the sensory perceptions of ASD people are challenging to determine their human psychology toward colors and lights. The novelty of the present study is a non-clinical approach to identifying the favorable visual environment for ASD children using interaction with the parents and caretakers of children with ASD. The indoor domestic environment has been critically investigated to determine if it is conducive to the unique needs and requirements of the children. Many environmental circumstances can affect the behavior, learning, performance, functioning, and wellbeing of autistic children, such as sound, smell, temperature, sense perceptions, communication, and social interactions. This investigative study is limited to the influence and impact of the two crucial sensory factors of light and color on autistic children in addition to space, wayfinding, and acoustics. This case study is primarily aimed at improving the quality of life of children with ASD through architectural aspects of the indoor built environment.

The present study examines the sensory impact of light and color in an indoor environment on autistic children whose senses are generally more heightened than usual. The insights on sensory triggers gained from this study can guide designers and clinicians while designing living spaces and taking steps to reduce stimuli that may lead to behavioral features. Understanding ASD is difficult due to neurological abnormality and a complex behaviorally defined development disorder with multiple contributing factors. With the increasing prevalence of autism worldwide, the need for progressive architectural design standards, guidelines and best practices to improve the built environment, explicitly incorporating sensory sensitivity strategies in interior spaces that cater to autistic requirements, is being keenly felt. There is greater recognition for design's impact in providing a soothing yet engaging environment for children with special needs. The primary objective is to share the fundamental factors to be considered in an indoor space and the tools and techniques that can be deployed to transform it into a calm, supportive, and autism-friendly zone, thereby resolving several adaptive issues for autistic children.

The primary objectives of the present study are as follows:

- Identify the central impairments of sensory intolerance in autism and understand the functional impact of light and color on autistic children.
- To provide a pleasant sensory experience of light and color to make them feel safe and secure within the built environment.
- Investigate the perception of light and color by autistic children and their influence through a comprehensive survey with various parameters.
- The current work is summarized in the following sections. **Section 1** provides the background and needs of the present study. **Section 2** elaborates on the methods adopted in this case study. **Section 3** discusses the results of the case study. **Section 4** describes the discussion of the results. **Section 5** summarizes the significant conclusions and further scope of the research.

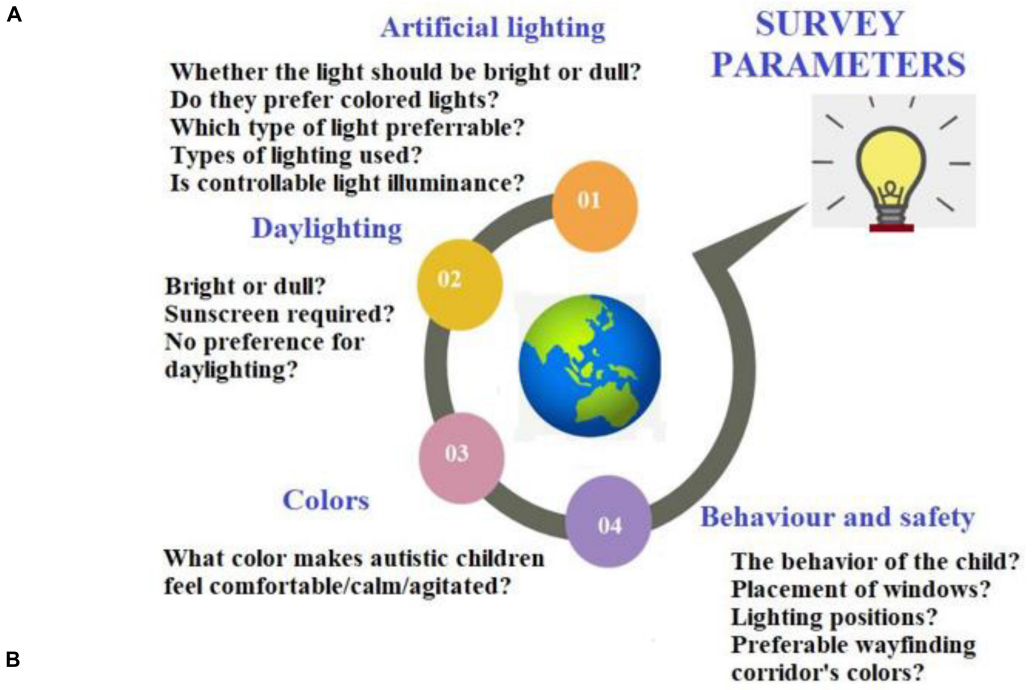
Materials and methods

Data collection

The research commenced with an in-depth literature review carried out in an organized manner to identify the current knowledge and understanding of ASD before framing the questionnaire contents (64–66). The questionnaire survey for the quantitative analysis consisted of forty questions that comprehensively covered the primary design aspects that need to be considered, in terms of light and color perceptions, before designing interior spaces intended for autistic children. The questionnaire was carefully designed in a lucid and straightforward format from the literature (67–73). The questionnaire was fine-tuned further in consultation with the therapists. The questionnaire survey was followed by ranking to indicate the category of the factor under consideration: low (Not at all suitable–one-point scale, suitable–two-point scale)–moderate (neutral–three-point scale), high (Most suitable), not necessarily essential. All the research questions in the questionnaire had this scale as a ranking guide. **Figure 1A** shows the various parameters used for the questionnaire of the present study. **Figure 1B** illustrates the color matrix used to understand user preferences and behavior.

The questionnaire survey was conducted with the parents of autistic children in-person mode. Informed consent was obtained from the participants before the interaction. The data was collected manually from Autism Schools in Northern India. Responses were collected from parents and caretakers of autistic children by conducting a structured interview per the prepared questionnaire. The data collected was then statistically analyzed and interpreted the results. The survey was first conducted with eighty-seven participants, all parents, and caretakers of children with autism.

Prior to commencing the interview, parents were briefed about the purpose of the research study, its envisaged contribution and its importance. The parents and caretakers were notified about the survey's objectives and informed of the importance of the questionnaire survey. The main intention of the questionnaire was to understand the sensory preferences



1	10	19	28	37	46	55	64	73	82	91	100	109	118	127	136	145	154	163
2	11	20	29	38	47	56	65	74	83	92	101	110	119	128	137	146	155	164
3	12	21	30	39	48	57	66	75	84	93	102	111	120	129	138	147	156	165
4	13	22	31	40	49	58	67	76	85	94	103	112	121	130	139	148	157	166
5	14	23	32	41	50	59	68	77	86	95	104	113	122	131	140	149	158	167
6	15	24	33	42	51	60	69	78	87	96	105	114	123	132	141	150	159	168
7	16	25	34	43	52	61	70	79	88	97	106	115	124	133	142	151	160	169
8	17	26	35	44	53	62	71	80	89	98	107	116	125	134	143	152	161	170
9	18	27	36	45	54	63	72	81	90	99	108	117	126	135	144	153	162	171

FIGURE 1
(A) Parameters used for framing the questionnaire of the present study, **(B)** color matrix prepared to understand user preferences and behavior.

of autistic children in an indoor environment regarding light and color factors.

The questionnaire was divided into three sections, details of which are as follows.

- Section A comprises the names of the parents or the therapist/psychologist, the child's age, gender and city of residence.
- Section B includes open-ended questions about artificial and daylight conditions, window position, lighting position, the color of lights, degree of brightness, light color temperature, and favorable behavioral changes that can be brought about by altering lighting conditions.
- Section C presents a color matrix. The child or the parent picks up the color of their choice based on parameters for gauging the children's mood, whether they feel comfortable, uncomfortable, calm, and patient, or disturbed. Colors are chosen for different rooms and preferences are noted to determine autism-friendly colors. Section C also comprises generic questions regarding preferences for sensory dimensions of space and the importance of visual stimuli in providing favorable sensory experiences.

To gain an understanding of the behavior of autistic children, the survey was conducted based on Section A, comprising of age, gender, and city of residence of the

study participants. For this survey, eighty-seven participants were considered, amongst which 45 were male and 42 were female. Section B comprises a comprehensive questionnaire to determine the impact of light on autistic children. Table 1 shows the statistical analysis of the selected participants.

Appendix A provides insights into the section comprising three parts where the focus group is mainly children falling into the age group of 6–16 years, with the overall count being eighty-seven participants. The survey was conducted at autism centers under a professional practitioner's guidance.

Results

The analysis and the questionnaire survey findings are presented in this section with sub-sections for light and color, respectively. The standard deviation of the survey method is 2.3. The margin of error and coefficient of variation at a 95% confidence level is ± 0.85 and 0.27, respectively. This confirms that the results are within the permissible values.

Analysis of light

Figures 2–4 reveal that, in most cases, autistic children did not prefer to have too harsh lights, fluorescent tubes, bright lights, below-eye-level window positions, flickering lights, dark lights, and dark spaces. Children felt flustered in low light conditions and had difficulty perceiving the environment in most cases. Flickering fluorescent lights were to be avoided as they were a stress-producing factor that made the children feel agitated and uncomfortable. Autistic children are extremely sensitive to the sub-visible flicker of direct fluorescent lighting, which can hurt their eyes and cause headaches. Ideally, all lights must be easy to use and come with a control switch so that children can alter the intensity of lighting fixtures, and dim or brighten them, to suit their visual needs. Neutral lighting can calm and soothe children by fostering a relaxing environment. Ideally, lights must be task-specific and based on the circumstances and conditions of the indoor space. Proper lighting design is essential as people with ASD have a heightened response to sensory inputs. According to the survey, direct lighting should be present in rooms, but intense light or glare must be avoided, and natural daylight is preferable in as many places as possible.

Sunscreen can be provided as it can be a convenient option for autistic children who want to block out direct light diffusion. The communication and behavior of the children were observed when they were studying under low light conditions to determine if they were calm and focused or agitated and irritable to identify an autism-friendly lighting arrangement. In most of the cases, it was observed from the survey that the children had difficulty with language activities that involved reading. They struggled with words and quickly got flustered. Autistic children have characteristics with the visual perception of the environment, tend to lose concentration, and have learning difficulties. A combination of factors considered in the study may be needed to better understand their behavior within an enclosed space. This is because autism is a complex spectrum disorder with a broad range of conditions and features that differ vastly from person to person.

TABLE 1 The statistical analysis of the selected population of 87 participants.

Parameter	Values
Arithmetic mean and geometric mean	8.7 and 8.4
Median and mode	9 (both)
Range and count	10 and 87
Smallest and largest	6 and 16
Variance	5.25
Standard deviation	2.29
The margin of error at a 95% confidence level	±0.481

Analysis of colors

When conducting the survey, it was observed that most parents wanted a designated sensory space to provide an immersive sensory experience for their children. A sensory space is a specially designed and personalized therapeutic area with many sensory-friendly objects that autistic children are familiar with, which can be explored with the senses and are in different color palettes and textures. This space is designed to provide a calm and relaxing area for autistic children with sensory processing challenges to slowly habituate themselves to the visual and tactile environment. The survey reveals that it is critical to consider visual aspects at the preliminary design stage to ensure a good balance of visual elements and features in the built environment to make it a safe, secure, accessible, appealing, and comfortable for autistic children. Figure 5 illustrates the color analysis of the survey done using the color matrix.

A color-related questionnaire is handed out to the participants to determine color preferences; it is found that the most suitable colors are pastel, dull, neutral, and muted shades that are not distracting but have a tranquil effect. The chosen color scheme must accommodate visual sensitivity is of prime consideration for autistic children with sensory processing disorder as it can affect their mood, learning ability, and function. The darker shades are deemed to be unsuitable. The least preferred colors cause extreme behavioral changes like agitation, irritability, confusion, distress, anger, and aggressiveness.

The interaction of light and color is observed in this survey as their physiological effects can positively impact an autistic

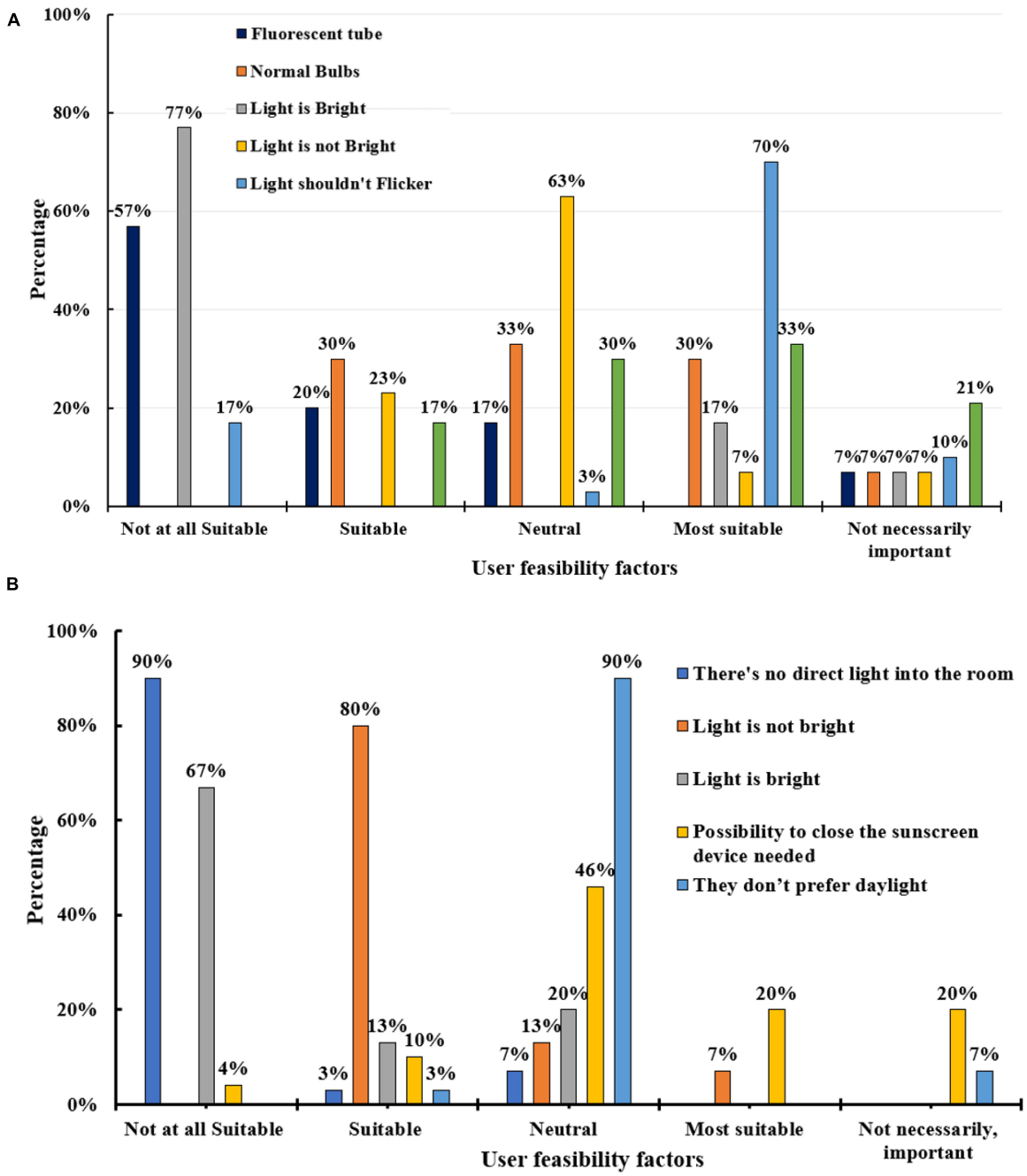


FIGURE 2
(A) Artificial lighting conditions, **(B)** natural light conditions.

child. The variables defined in the table for studying the impact of light create an understanding of whether artificial lights, LED, dimmable, and incandescent bulbs are preferable depending on their effect on the sensitive eyes of autistic children (74–80). The most preferred light position is overhead, as there is no direct eye-level visibility to any artificial lights. Light visibility can be minimal to the user if the lights are flushed in the ceiling or when a false ceiling is provided. The relation of light with color and vice-versa is critical. They do not work in isolation; they work together. Both these factors combine to play an essential role in the built environment. Social contexts and family care are also essential to better servicing autistic children (81–87). Ensuring illumination comfort for autistic children by designing spaces that consider their light sensitivity is essential. The surveys conducted on autistic users offer an exceptional understanding of how they perceive color and react to it with their unusual

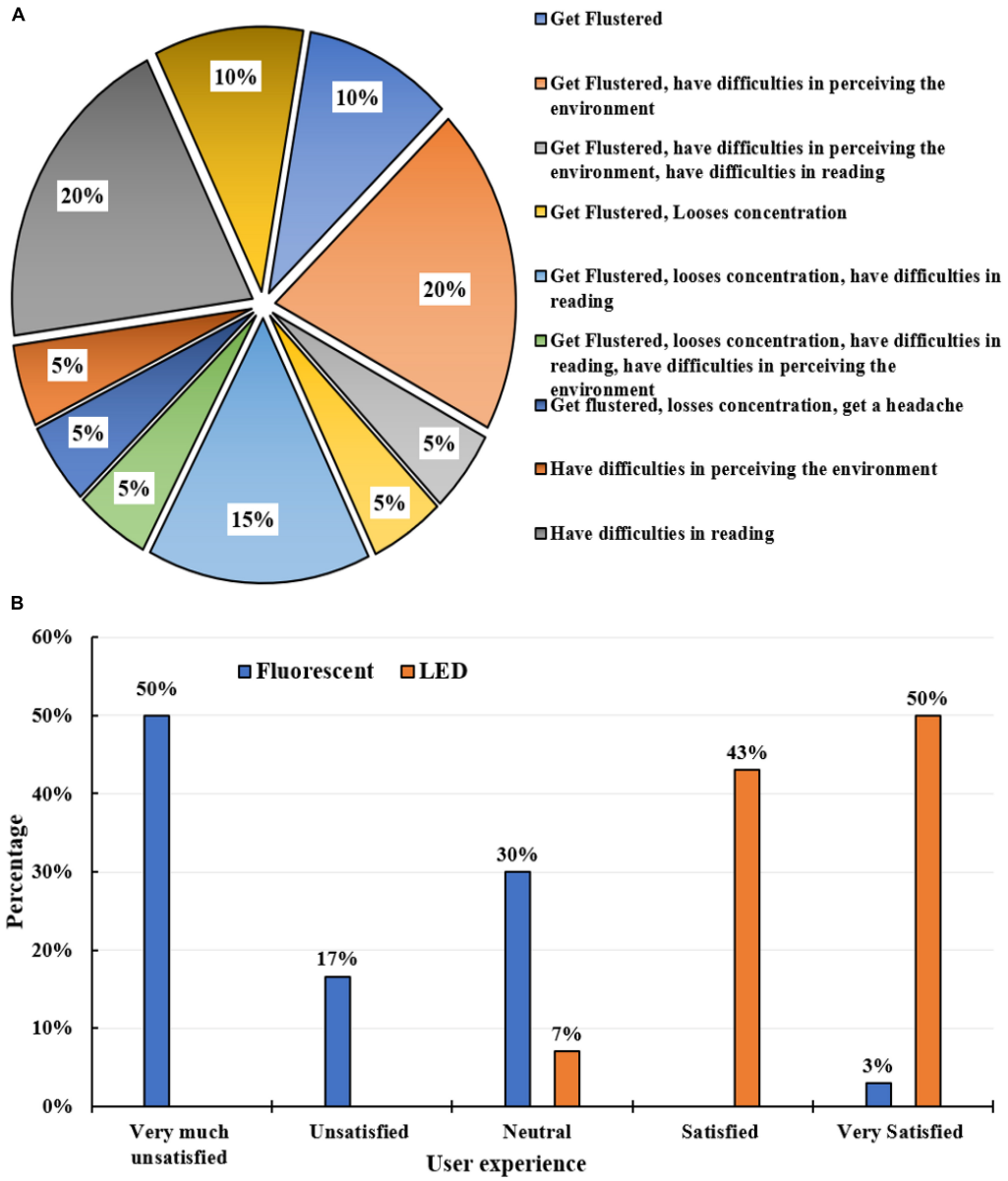


FIGURE 3
(A) The behavior of autistic children under low light conditions, **(B)** preferable light bulb for autistic children.

sensory processing. This study contributes to identifying the initial set of design parameters that must be considered in an indoor environment to meet the needs of autistic children.

Discussion

Impact of lights

On examination of the various lighting conditions, a dark room, darker lights, and more brightness are not preferred. Natural daylight is perceived to be the best lighting for indoor spaces. Fluorescent lamps are suitable if they have the option for the brightness levels to be controlled. Neutral-colored lights are the preferred option. Most participants prefer LED lights over fluorescent lights as the harsh light from the latter tends to cause agitated behavior and extreme distress in autistic children with light sensitivity.

Another component of lighting conditions within enclosed spaces must be considered the light's and window's positions. Autistic children can be oversensitive or under-sensitive to bright lights, which can debilitate their functioning; strategic light and window placements can help minimize the light intensity and provide a calm and relaxed work or play

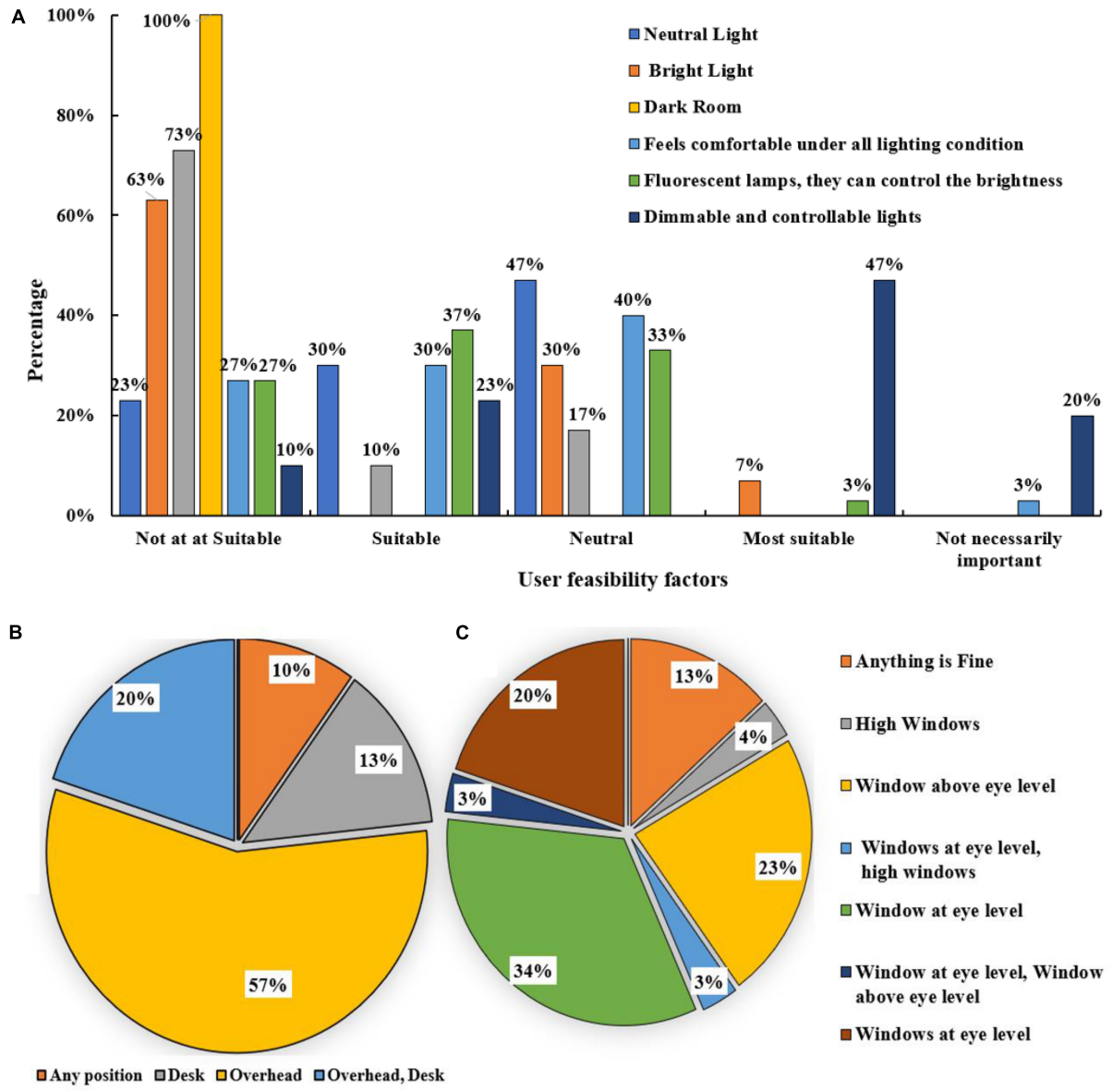


FIGURE 4
(A) Feasibility of autistic children under various lighting conditions, **(B)** preferable position of the light, **(C)** preferable position of window placement.

environment. The overhead lights option is preferable to avoid direct light visibility, and desk lights are another option. It is observed that in most cases, the window is situated at or directly above eye level. Windows at higher levels are not preferred. The study also included the color and temperature of lighting applications while determining the light efficacy factor as they tend to psychologically impact all humans, particularly autistic children with heightened sensory sensitivity. This becomes important as there is a definite connection between lighting and behavior, as evident from behavioral changes noticed in autistic children who become aggressive and flustered if they are not comfortable with the illumination provided by the lighting arrangements. Subtle manipulation of lighting can alter the mood, behavior, and perception of autistic children. Light color, source, quality, direction, and intensity are aspects to be considered in providing an optimally lighted environment that considers the light sensitivity of its inhabitants.

Impacts of colors

A questionnaire survey method investigates the visual aspects that significantly influence a space. According to the

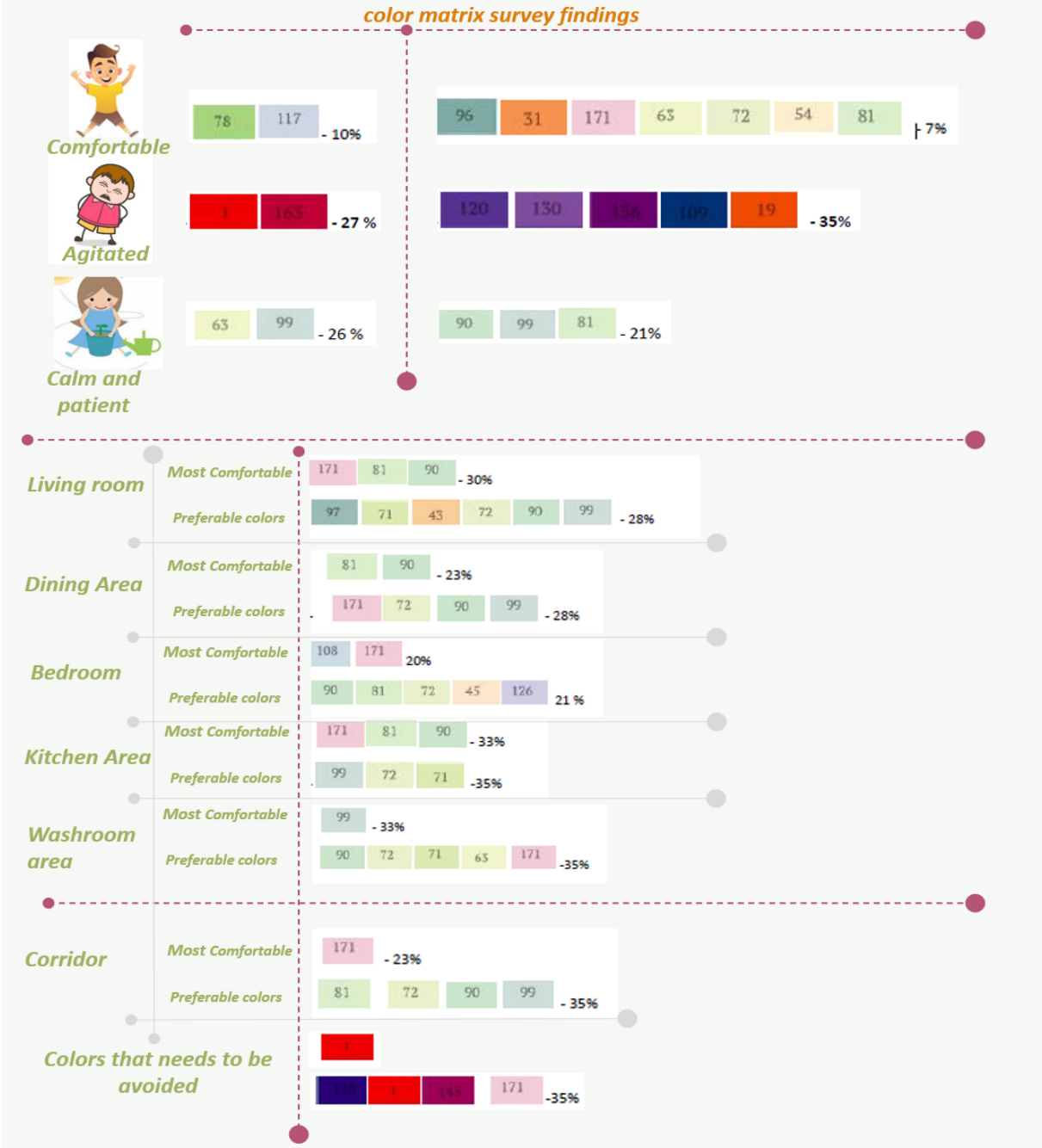


FIGURE 5
Illustration of color analysis from the survey done by the color matrix.

study, it is noted that children have a broad range of color preferences and respond distinctively and differently to various shades showing the importance of using an ASD-friendly color palette. Light, color, and space are essential components of any indoor environment that must be considered when designing for children on the autism spectrum. Architecture, as a profession, uses best design practices to devise customized environments which are engaging spaces that fulfill the specific needs of individuals, help them cope with their surroundings, encourage their independence, and positively impact their performance and behavior. In this regard, with greater recognition of effective space design's impact on individuals with autism, designers and clinicians can consider indoor environmental aspects at the primary level and research the

same issue with other interlinked factors. This study is one kind to facilitate a macroenvironment that can promote clinical services for autistic children. These results help determine the external factors that could enhance the abilities and functioning of autistic children in the built environment.

According to the survey results, light and color are significant variables within a built environment that greatly influence autistic children as they have a sensory processing disorder. Among the selected variables, light and color strongly correlate with the behavior of ASD children when compared to space and wayfinding. The results of the present study are on par with the literature (88–93). Every autistic individual is unique; each person reacts differently to the environment and sensory stimuli besides having individual preferences and aversions. As per the study, they have many color preferences and respond differently to different colors. Colors and light can be effectively deployed to bring about some desired positivity and social and behavioral change. The light sensitivity factor deals with the difficulty of sensory overload and requires further research on light rendering and acoustics. Such architectural aspects of the built environment also favor dealing with the characteristics of autistic children in addition to other clinical and non-clinical methods and techniques.

Limitations of this case study

The number of participants involved in the present study produces substantial input to the architects and clinicians. However, further studies with all stakeholders with more populations and their interactions are necessitated to improve the built environment designs more refined for autistic children. This study is mainly focusing on the non-clinical survey approach. However, the clinical and non-clinical approaches, like measuring heart rate, speech, language skills, emotions, social interactions, other motor, and non-motor skills could produce more appropriate solutions. Further clinical studies are required to expand the demography to improve autistic-friendly built environments and designs to assist the efficiency of the support and services to autistic children. The present study's results are mainly pertinent to design an autistic-friendly built environment on a non-clinical approach using a questionnaire survey. Thus, further non-clinical and clinical studies on several micro factors are required to expand this survey to autistic adults.

Conclusion

The effects of light and color on the behavior of autistic children were investigated using a questionnaire survey. The full involvement of all the users was critical from the commencement to the completion of the survey. The study shows that dialogues were substantially reshaped during the color matrix questionnaire. The findings were obtained through cost-effective non-clinical methods. This was crucial from the start, as most research studies on ASD offer unclear and hypothetical results. Therapists, parents, and children actively participated in the survey sessions and offered valuable insights to designers and clinicians. The therapists and parents are vital users closely involved in meeting the needs and demands of the children under their care. Their experiences with the children offer essential data that helps understand the likes and dislikes of autistic children in the built environment regarding the lights and colors. The major conclusions of the present study are as follows.

- The standard deviation of the survey method is 2.3. The margin of error and coefficient of variation at a 95% confidence level is $\pm$ 0.85 and 0.27, respectively. This confirms that the results are reasonably within acceptable limits.
- The literary assessment and survey were utilized to comprehend the effect of colors and light in any indoor environment for children with autism.
- The lights and colors of indoor environments are the most influencing factors in promoting the harmony of autistic children compared to space and wayfinding.
- Direct lighting and natural daylighting are preferable to intense light or glare in as many places as possible.
- The spaces designed for people with ASD must address how these people perceive the environment and react to space features.
- The study proves that dull and pastel colors and muted lights are more suitable for visually sensitive autistic children.
- Lower sound levels of below 50 dB are autistic-friendly, and beyond 60 dB develops inappropriate behaviors.

Light, color, and space are preliminary considerations of any inhabited environment. There is an increased need to ensure the suitability of light and color provisions in all interior spaces intended for autistic children to make them sensory-friendly. These findings emphasize the need to understand the different parameters associated with autistic users and the benefits of designing an autistic-friendly environment.

Designers should look upon these three variables effectively for comprehensive design and further studies. By recognizing the influence of the sensory environment on autistic behavior, designers should consider these critical variables and adopt a sensory-sensitive approach to design inclusive spaces with optimum comfort. The current findings emphasize the need to understand the different sensory issues and parameters associated with autistic users and the importance of design

considerations required for setting up an accommodative, supportive, neurodiverse, and autistic-friendly environment tailored to their need for positive sensory experiences. Thus, the present analysis and the scope for further research studies could benefit autistic individuals by appropriately analyzing the selective blended clinical and non-clinical techniques.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

AN, RP, and PR contributed to the study's conceptualization, design, and investigation. CP, RS, and SD critically verified the data and analyzed. KL, XW, and XZ contributed to the data analysis and revision of subsequent versions. 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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References

1. Love JS. Sensory spaces: sensory living – studio teaching the design of autism-friendly adult accommodation. *Int J Arch Res Arch IJAR.* (2022) 16:595–619. doi: 10.1108/ARCH-11-2021-0321

2. Roos BA, Mobach M, Heylighen A. How does architecture contribute to reducing behaviours that challenge? A scoping review. *Res Dev Disabil.* (2022) 127:104229. doi: 10.1016/j.ridd.2022.104229

3. Bottema-Beutel K, Kapp SK, Lester JN, Sasson NJ, Hand BN. Avoiding ableist language: suggestions for autism researchers. *Autism Adulthood.* (2021) 3:18–29. doi: 10.1089/aut.2020.0014

4. Amonkar N, Su W, Bhat AN, Srinivasan SM. Effects of creative movement therapies on social communication, behavioral-affective, sensorimotor, cognitive, and functional participation skills of individuals with autism spectrum disorder: a systematic review. *Front Psychiatry.* (2021) 12:722874. doi: 10.3389/fpsyt.2021.722874

5. Schmengler H, Cohen D, Tordjman S, Melchior M. Autism spectrum and other neurodevelopmental disorders in children of immigrants: a brief review of current evidence and implications for clinical practice. *Front Psychiatry.* (2021) 12:566368. doi: 10.3389/fpsyt.2021.566368

6. Siller M, Morgan L, Wedderburn Q, Fuhrmeister S, Rudrabhatla A. Inclusive early childhood education for children with and without autism: progress, barriers, and future directions. *Front Psychiatry.* (2021) 12:754648. doi: 10.3389/fpsyt.2021.754648

7. Su W, Amonkar N, Cleffi C, Srinivasan S, Bhat A. Neural effects of physical activity and movement interventions in individuals with developmental disabilities–a systematic review. *Front Psychiatry.* (2022) 13:794652.

8. Van Schalkwyk GI, Volkmar FR. Autism spectrum disorders: in theory and practice. *Psychoanal Study Child.* (2015) 69:219–41. doi: 10.1080/00797308.2016.11785529

9. Sukiennik R, Marchezan J, Scornavacca F. Challenges on diagnoses and assessments related to autism spectrum disorder in Brazil: a systematic review. *Front Psychiatry.* (2022) 12:598073. doi: 10.3389/fneur.2021.598073

10. Uljarević M, Billingham W, Cooper MN, Condron P, Hardan AY. Examining effectiveness and predictors of treatment response of pivotal response treatment in autism: an umbrella review and a meta-analysis. *Front Psychiatry.* (2022) 12:766150. doi: 10.3389/fpsyt.2021.766150

11. Baio J, Wiggins L, Christensen DL, Maenner MJ, Daniels J. Prevalence of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, united states, 2014. *MMWR Surveillance Summaries.* (2018) 67:1–23. doi: 10.15585/mmwr.ss6706a1

12. Patra S, Kar SK. Autism spectrum disorder in India: a scoping review. *Int Rev Psychiatry.* (2021) 33:81–112. doi: 10.1080/09540261.2020.1761136

13. Altenmüller-Lewis U. Designing schools for students in the spectrum. *Design J.* (2017) 20:S2215–29. doi: 10.1080/14606925.2017.1352738

14. Fabri M, Satterfield D. Special issue on designing with and for users on the autism spectrum. *Int J Hum Comput Int.* (2019) 35:641–2. doi: 10.1080/10447318.2018.1550181

15. Sahuquillo-Leal R, Navalón P, Moreno-Giménez A, Almansa B, Vento M, García-Blanco A. Attentional biases towards emotional scenes in autism spectrum condition: an eye-tracking study. *Res Dev Disabil.* (2022) 120:104124. doi: 10.1016/j.ridd.2021.104124

16. Pastor-Cerezuela G, Fernández-Andrés M-I, Sanz-Cervera P, Marín-Suelves D. The impact of sensory processing on executive and cognitive functions in children with autism spectrum disorder in the school context. *Res Dev Disabil.* (2020) 96:103540. doi: 10.1016/j.ridd.2019.103540

17. Roy RG, Kumar A. The mediating role of parental playfulness on parent–child relationship and competence among parents of children with ASD. *Adv Autism.* (2021) 8:306–18. doi: 10.1108/AIA-02-2021-0010

18. Bitsika V, Heyne DA, Sharpley CF. The inverse association between psychological resilience and emerging school refusal among bullied autistic youth. *Res Dev Disabil.* (2022) 120:104121. doi: 10.1016/j.ridd.2021.104121

19. Juliano AC, Alexander AO, DeLuca J, Genova H. Feasibility of a school-based mindfulness program for improving inhibitory skills in children with autism spectrum disorder. *Res Dev Disabil.* (2020) 101:103641. doi: 10.1016/j.ridd.2020.103641

20. Maslennikova AV, Portnova GV, Martynova OV. Brain oscillatory patterns of affective prosody perception in children with autism spectrum disorder. *Res Autism Spectr Disord.* (2022) 96:101993. doi: 10.1016/j.rasd.2022.101993

21. Shirama A, Stickley A, Kamio Y, Nakai A, Takahashi H. Emotional and behavioral problems in japanese preschool children with motor coordination difficulties: the role of autistic traits. *Eur Child Adolesc Psychiatry.* (2022) 31:979–90. doi: 10.1007/s00787-021-01732-7

22. Black MH, McGarry S, Churchill L, D'Arcy E, Dalgleish J. Considerations of the built environment for autistic individuals: a review of the literature. *Autism.* (2022) 26:2753. doi: 10.1177/13623613221102753

23. Bozkus-Genc G, Sani-Bozkurt S. How parents of children with autism spectrum disorder experience the COVID-19 pandemic: perspectives and insights on the new normal. *Res Dev Disabil.* (2022) 124:104200. doi: 10.1016/j.ridd.2022.104200

24. Logrieco MG, Casula L, Ciuffreda GN, Novello RL, Spinelli M. Risk and protective factors of quality of life for children with autism spectrum disorder and their families during the COVID-19 lockdown. An Italian study. *Res Dev Disabil.* (2022) 120:104130. doi: 10.1016/j.ridd.2021.104130

25. Mallory C, Keehn B. Implications of sensory processing and attentional differences associated with autism in academic settings: an integrative review. *Front Psychiatry.* (2021) 12:695825. doi: 10.3389/fpsyt.2021.695825

26. Lane SJ, Leão MA, Spielmann V. Sleep, sensory Integration/Processing, And Autism: A Scoping review. *Front Psychol.* (2022) 13:877527. doi: 10.3389/fpsyg.2022.877527

27. Chung JCY, Mevorach C, Woodcock KA. Establishing the transdiagnostic contextual pathways of emotional outbursts. *Sci Rep.* (2022) 12:11474. doi: 10.1038/s41598-022-11474-4

28. Page SD, Souders MC, Kral TVE, Chao AM, Pinto-Martin J. Correlates of feeding difficulties among children with autism spectrum disorder: a systematic review. *J Autism Dev Disord.* (2022) 52:255–74. doi: 10.1007/s10803-021-04947-4

29. Schulz SE, Stevenson RA. Convergent validity of behavioural and subjective sensitivity in relation to autistic traits. *J Autism Dev Disord.* (2022) 52:758–70. doi: 10.1007/s10803-021-04974-1

30. Van de Cruys S, Lemmens L, Sapey-Triomphe L, Chetverikov A, Noens I, Wagemans J. Structural and contextual priors affect visual search in children with and without autism. *Autism Res.* (2021) 14:1484–95. doi: 10.1002/aur.2511

31. Zhang S, Wang P, Yang B, Zhong Y, Wang Y. Characteristics of executive function in children with attention deficit/hyperactivity disorder comorbid with high functioning autism. *Natl Med J China.* (2020) 100:2446–51. doi: 10.3760/cma.j.cn112137-20191216-02750

32. Clouse JR, Wood-Nartker J, Rice FA. Designing beyond the americans with disabilities act (ADA): creating an autism-friendly vocational center. *HERD.* (2020) 13:215–29. doi: 10.1177/1937586719888502

33. Seidmann V. On blogs, autistic bloggers, and autistic space. *Inf Commun Soc.* (2021) 24:2277–92. doi: 10.1080/1369118x.2020.1754878

34. Baumers S, Heylighen A. Capturing experience: an autistic approach to designing space. *Design J.* (2015) 18:327–43. doi: 10.1080/14606925.2015.1059599

35. Fearns N, Walker L, Graham K, Gibb N, Service D. User testing of a scottish intercollegiate guideline network public guideline for the parents of children with autism. *BMC Health Serv Res.* (2022) 22:7384. doi: 10.1186/s12913-021-07384-2

36. Ouss L, Palestra G, Saint-Georges C, Leitgel Gille M, Afshar M. Behavior and interaction imaging at 9 months of age predict autism/intellectual disability in high-risk infants with west syndrome. *Trans Psychiatry.* (2020) 10:743. doi: 10.1038/s41398-020-0743-8

37. Fletcher-Watson S, Mcconnell F, Manola E, Mcconachie H. Interventions based on the theory of mind cognitive model for autism spectrum disorder (ASD). *Cochrane Datab Syst Rev.* (2014) 2014:CD008785. doi: 10.1002/14651858.CD008785.pub2

38. Gaines KS, Curry Z, Shroyer J, Amor C, Lock RH. The perceived effects of visual design and features on students with autism spectrum disorder. *J Archit Plann Res.* (2014) 31:282–98.

39. Martin R, Wilkins J. Creating visually appropriate classroom environments for students with autism spectrum disorder. *Interv Sch Clin.* (2022) 57:32–7. doi: 10.1177/10534512211014882

40. Irish JEN. Ten years on: a post-occupancy evaluation of classrooms for pupils with severe autism. *Facilities.* (2022) 40:656–74. doi: 10.1108/F-10-2021-0097

41. Tarver J, Palmer M, Webb S, Scott S, Slonims V, Simonoff E, et al. Child and parent outcomes following parent interventions for child emotional and behavioral problems in autism spectrum disorders: a systematic review and meta-analysis. *Autism.* (2019) 23:1630–44. doi: 10.1177/1362361319830042

42. Franklin A, Sowden P, Burley R, Notman L, Alder E. Color perception in children with autism. *J Autism Dev Disord.* (2008) 38:1837–47. doi: 10.1007/s10803-008-0574-6

43. Tola G, Talu V, Congiu T, Bain P, Lindert J. Built environment design and people with autism spectrum disorder (asd): a scoping review. *Int J Environ Res Public Health.* (2021) 18:1–14. doi: 10.3390/ijerph18063203

44. Boyce PR. Light, lighting and human health. *Light Res Technol.* (2022) 54:101–44. doi: 10.1177/14771535211010267

45. Samiou AI, Doulos LT, Zerefos S. Daylighting and artificial lighting criteria that promote performance and optical comfort in preschool classrooms. *Energy Build.* (2022) 258:111819. doi: 10.1016/j.enbuild.2021.111819

46. Chezan LC, Liu J, Cholewicki JM, Drasgow E, Ding R, Warman A. A psychometric evaluation of the quality of life for children with autism spectrum disorder scale. *J Autism Dev Disord.* (2021) 52:1536–52. doi: 10.1007/s10803-021-05048-y

47. Mayer-Benarous H, Benarous X, Vonthron F, Cohen D. Music therapy for children with autistic spectrum disorder and/or other neurodevelopmental disorders: a systematic review. *Front Psychiatry.* (2021) 12:643234. doi: 10.3389/fpsyt.2021.643234

48. Dhiaba SAT. The impact of colour-drawing in reducing behavioural disorders for autistic children: an applied study on a sample of autistic children. *Int J Innov Creativity Chang.* (2020) 11:144–63.

49. Akande A. Assessing color identification in children with autism. *Early Child Dev Care.* (2000) 164:95–104. doi: 10.1080/0300443001640108

50. Ludlow AK, Heaton P, Hill E, Franklin A. Color obsessions and phobias in autism spectrum disorders: the case of J.G. *Neurocase.* (2014) 20:296–306. doi: 10.1080/13554794.2013.770880

51. Schloss KB, Palmer SE. An ecological framework for temporal and individual differences in color preferences. *Vis Res.* (2017) 141:95–108. doi: 10.1016/j.visres.2017.01.010

52. Schloss KB, Nelson R, Parker L, Heck IA, Palmer SE. Seasonal variations in color preference. *Cogn Sci.* (2017) 41:1589–612. doi: 10.1111/cogs.12429

53. Palmer CJ, Otsuka Y, Clifford CWG. A sparkle in the eye: illumination cues and lightness constancy in the perception of eye contact. *Cognition.* (2020) 205:104419. doi: 10.1016/j.cognition.2020.104419

54. Koegel L, Matos-Freden R, Lang R, Koegel R. Interventions for children with autism spectrum disorders in inclusive school settings. *Cogn Behav Pract.* (2012) 19:401–12. doi: 10.1016/j.cbpra.2010.11.003

55. Paulus FW, Ohmann S, Möhler E, Plener P, Popow C. Emotional dysregulation in children and adolescents with psychiatric disorders. A narrative review. *Front Psychiatry.* (2021) 12:628252. doi: 10.3389/fpsyt.2021.628252

56. Bougeard C, Picarel-Blanchot F, Schmid R, Campbell R, Buitelaar J. Prevalence of autism spectrum disorder and co-morbidities in children and adolescents: a systematic literature review. *Front Psychiatry.* (2021) 12:744709. doi: 10.3389/fpsyt.2021.744709

57. Thompson JIR, Peck CE, Karvelas G, Hartwell CA, Guarnaccia C. Temporal processing as a source of altered visual perception in high autistic tendency. *Neuropsychologia.* (2015) 69:148–53. doi: 10.1016/j.neuropsychologia.2015.01.046

58. Shi F, Sun W, Duan H, Liu X, Hu M, Wang W, et al. Drawing reveals hallmarks of children with autism. *Displays.* (2021) 67:102000. doi: 10.1016/j.displa.2021.102000

59. Faber L, van den Bos N, Houwen S, Schoemaker MM, Rosenblum S. Motor skills, visual perception, and visual-motor integration in children and youth with autism spectrum disorder. *Res Autism Spectr Disord.* (2022) 96:101998. doi: 10.1016/j.rasd.2022.101998

60. Tortelli C, Pomè A, Turi M, Igliozzi R, Burr DC, Binda P. Contextual information modulates pupil size in autistic children. *Front Neurosci.* (2022) 16:752871. doi: 10.3389/fnins.2022.752871

61. Irish JEN. Evidence-based design. *Archnet IJAR.* (2019) 13:25–38. doi: 10.1108/arch-12-2018-0029

62. Gehdu BK, Gray KLH, Cook R. Impaired grouping of ambient facial images in autism. *Sci Rep*. (2022) 12:10630. doi: 10.1038/s41598-022-10630-0

63. Schweizer C, Knorth EJ, Spreen M. Art therapy with children with autism spectrum disorders: a review of clinical case descriptions on 'what works'. *Arts Psychother*. (2014) 41:577–93. doi: 10.1016/j.aip.2014.10.009

64. Bevans KB, Piller A, Pfeiffer B. Psychometric evaluation of the participation and sensory environment questionnaire-home scale (PSEQ-H). *Am J Occup Ther*. (2020) 74:36509. doi: 10.5014/ajot.2020.036509

65. Yamane T. Longitudinal psychometric evaluation of the developmental disorder parenting stressor index with Japanese parents of children with autism. *Autism*. (2021) 25:2034–47. doi: 10.1177/13623613211009349

66. Pratesi CB, Garcia AB, Pratesi R, Gandolfi L, Hecht M, Nakano EY, et al. Quality of life in caregivers of children and adolescents with autistic spectrum disorder: development and validation of the questionnaire. *Brain Sci*. (2021) 11:7. doi: 10.3390/brainsci11070924

67. Xu SQ, Zhu J, Xie Z, Li X. The psychometric properties of the Chinese version of the attitude survey inclusive education-parents. *BMC Psychol*. (2022) 10:808. doi: 10.1186/s40359-022-00808-6

68. Wigham S, Ingham B, Le Couteur A, Wilson C, Ensum I, Parr JR. A survey of autistic adults, relatives and clinical teams in the United Kingdom: and Delphi process consensus statements on optimal autism diagnostic assessment for adults. *Autism*. (2022) 26:1959–72. doi: 10.1177/13623613211073020

69. Tamon H, Itahashi T, Yamaguchi S, Tachibana Y, Fujino J, Igarashi M, et al. Autistic children and adolescents with frequent restricted interest and repetitive behavior showed more difficulty in social cognition during mask-wearing during the COVID-19 pandemic: a multisite survey. *BMC Psychiatry*. (2022) 22:249. doi: 10.1186/s12888-022-04249-8

70. Moroe N, Masuku K, Shirame L. Rehabilitation healthcare professionals' competence and confidence in differentially diagnosing deaf blindness from autism spectrum disorders: a cross-sectional survey in South Africa. *BMC Med Educ*. (2022) 22:3258. doi: 10.1186/s12909-022-03258-1

71. Hellquist A, Tammimies K. Access, utilization, and awareness for clinical genetic testing in autism spectrum disorder in Sweden: a survey study. *Autism*. (2022) 26:1795–804. doi: 10.1177/13623613211066130

72. Wang F, Lao U, Xing Y, Zhou P, Deng W, Wang Y, et al. Parents' knowledge and attitude and behavior toward autism: a survey of Chinese families having children with autism spectrum disorder. *Trans Pediatr*. (2022) 11:1445–57. doi: 10.21037/tp-22-113

73. Bhakta BB, Coleman KJ, Choi KR. Randomized study of survey recruitment strategies for parents of autistic children. *J Pediatr Health Care*. (2022) 36:470–3. doi: 10.1016/j.pedhc.2022.05.008

74. Pulay A, Williamson A. A case study comparing the influence of LED and fluorescent lighting on early childhood student engagement in a classroom setting. *Learn Environ Res*. (2019) 22:13–24. doi: 10.1007/s10984-018-9263-3

75. Pérez-Fuster P, Sevilla J, Herrera G. Enhancing daily living skills in four adults with autism spectrum disorder through an embodied digital technology-mediated intervention. *Res Autism Spectr Disord*. (2019) 58:54–67. doi: 10.1016/j.rasd.2018.08.006

76. Derakhshanrad SA, Piven E. Modification of the training environment to improve functional performance using blacklight conditions: a case study of a child with autism. *Int J Dev Disabil*. (2020) 66:160–8. doi: 10.1080/20473869.2019.1642640

77. Dirix H, Ross V, Brijs K, Vermeiren E, Timmermans C. The appraisal of roadway environment and infrastructure by drivers with autism: a qualitative study. *Trans Res Part F Traffic Psychol Behav*. (2021) 78:280–98. doi: 10.1016/j.trf.2021.01.016

78. Yeoh PSQ, Lai KW, Goh SL, Hasikin K, Hum YC, Tee YK, et al. Emergence of deep learning in knee osteoarthritis diagnosis. *Comput Intell Neurosci*. (2021) 2021:1437. doi: 10.1155/2021/4931437

79. Divan G, Bhavnani S, Leadbitter K, Ellis C, Dasgupta J, Abubakar A, et al. Annual research review: achieving universal health coverage for young children with autism spectrum disorder in low-and middle-income countries: a review of reviews. *J Child Psychol Psychiatry*. (2021) 62:514–35. doi: 10.1111/jcpp.13404

80. Green J, Garg S. Annual research review: the state of autism intervention science: progress, target psychological and biological mechanisms and future prospects. *J Child Psychol Psychiatry*. (2018) 59:424–43. doi: 10.1111/jcpp.12892

81. Teo K, Yong CW, Muhamad F, Mohafez H, Hasikin K, Xia K, et al. The promise for reducing healthcare cost with predictive model: an analysis with quantized evaluation metric on readmission. *J Healthc Eng*. (2021) 2021:138. doi: 10.1155/2021/9208138

82. Sengupta K, Shah H, Ghosh S, Sanghvi D, Mahadik S, Dani A, et al. World health organisation-caregiver skills training (WHO-CST) program: feasibility of delivery by non-specialist providers in real-world urban settings in India. *J Autism Dev Disord*. (2021) 51:1–8. doi: 10.1007/s10803-021-05367-0

83. Dhanalakshmi S, Venkatesh C. Classification of ultrasound carotid artery images using texture features. *Int Rev Comput Softw*. (2013) 8:933–40.

84. Green J, Leadbitter K, Ainsworth J, Bucci S. An integrated early care pathway for autism. *Lancet Child Adolesc Health*. (2022) 6:335–44. doi: 10.1016/S2352-464200037-2

85. Salah BM, Sakher S, Darawsheh SR, Quraann EA, Zaghlool ZDM, Alkhawaldeh MA, et al. Guidance for autistic children in increasing confidence in socializing. *Inf Sci Lett*. (2023) 12:807–12. doi: 10.18576/isl/120222

86. Nagib W, Williams A. Creating "therapeutic landscapes" at home: the experiences of families of children with autism. *Health Place*. (2018) 52:46–54. doi: 10.1016/j.healthplace.2018.05.001

87. Mcallister K, Hadjri K. Inclusion and the special educational needs (SEN) resource base in mainstream schools: physical factors to maximise effectiveness. *Supp Learn*. (2013) 28:57–65. doi: 10.1111/1467-9604.12019

88. Willis KS, Cross E. Investigating the potential of EDA data from biometric wearables to inform inclusive design of the built environment. *Emot Space Soc*. (2022) 45:100906. doi: 10.1016/j.emospa.2022.100906

89. Caniato M, Zaniboni L, Marzi A, Gasparella A. Evaluation of the main sensitivity drivers in relation to indoor comfort for individuals with autism spectrum disorder. Part 1: investigation methodology and general results. *Energy Rep*. (2022) 8:1907–20. doi: 10.1016/j.egyr.2022.01.009

90. Caniato M, Zaniboni L, Marzi A, Gasparella A. Evaluation of the main sensitivity drivers in relation to indoor comfort for individuals with autism spectrum disorder. Part 2: influence of age, co-morbidities, gender and type of respondent on the stress caused by specific environmental stimuli. *Energy Rep*. (2022) 8:2989–3001. doi: 10.1016/j.egyr.2022.01.011

91. Lord C, Risi S, Lambrecht L, Cook EH, Leventhal BL. The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. *J Autism Dev Disord*. (2000) 30:205–23. doi: 10.1023/A:1005592401947

92. Baron-Cohen S, Wheelwright S, Skinner R, Martin J, Clubley E. The autism-spectrum quotient (AQ): evidence from asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *J Autism Dev Disord*. (2001) 31:5–17. doi: 10.1023/A:1005653411471

93. Ma S, Li M, Qiao Y, He H, Luo M. The effective learning of discrete trial teaching: evidence from pre-service teachers of children with autism. *Acta Psych Sin*. (2023) 55:237–256. doi: 10.3724/SP.J.1041.2023.00237

Appendix A

Appendix-1 Questionnaire

- Section A
  - What is the age of child?
  - Which city is the child and family living?
  - What is the gender of the child?

- Section B
  - Impact of light on autistic children.
  - **Parameter 1.0**
    - How suitable is the following artificial lighting conditions for your ward? [Fluorescent tubes].
    - How suitable is the following artificial lighting conditions for your ward? [Normal bulbs].
    - How suitable is the following artificial lighting conditions for your ward? [The light is not bright].
    - How suitable is the following artificial lighting conditions for your ward? [The light is bright].
    - How suitable is the following artificial lighting conditions for your ward? [The light does not flicker].
    - How suitable is the following artificial lighting conditions for your ward? [They can dim the light by themselves (brighter/darker)].
    - How suitable is the following artificial lighting conditions for your ward? [Generally, they do not like artificial lighting].
  - **Parameter 2.0**
    - How suitable is the following natural daylight conditions for your ward? [There is No direct light into the room].
    - How suitable is the following natural daylight conditions for your ward? [The light is not bright].
    - How suitable is the following natural daylight conditions for your ward? [The light is bright].
    - How suitable is the following natural daylight conditions for your ward? [They have the possibility to close the sun screening device].
    - How suitable is the following natural daylight conditions for your ward? [Generally, do not like daylighting].
  - **Parameter 3.0**
    - Select the options that describe how your ward behaves when exposed to low light conditions.
  - **Parameter 4.0**
    - How suitable is the following lighting conditions for your ward? [Neutral Light].
    - How suitable is the following lighting conditions for your ward? [Much of bright light].
    - How suitable is the following lighting conditions for your ward? [Preferably a little bit darker light].
  - **Parameter 5.0**
    - How suitable is the following lighting conditions for your ward? [Totally dark room].
  - **Parameter 6.0**
    - How suitable is the following lighting conditions for your ward? [Feels comfortable under all lighting conditions].
  - **Parameter 7.0**
    - How suitable is the following lighting conditions for your ward? [Fluorescent lamps are also ok, provided they can control the brightness].
    - How suitable is the following lighting conditions for your ward? [Would make all the lights in the house dimmable and controllable].
    - Choose the preferred window option for your ward from the list below.
  - **Parameter 8.0**
    - How satisfied is your ward with the following light bulb? [Fluorescent].
  - **Parameter 9.0**
    - How satisfied is your ward with the following light bulb? [LED].
  - **Parameter 10**
    - Choose the position of the light in any room that your ward prefers.

- Section C
  - Choose three (color numbers; for example, 71, 107, 98) from the given color matrix that makes your ward feel comfortable.
  - Choose three (color numbers) from the color matrix that makes your ward feel uncomfortable.
  - Choose three (color numbers) from the color matrix that causes your ward to become very agitated.
  - Choose three (color numbers) from the color matrix representing your ward's calm and patience.
  - Choose three (color numbers) for the bedroom space from the color matrix above.
  - Choose three (color numbers) for the living room from the color matrix above.
  - Choose three (color numbers) for the kitchen area from the color matrix above.
  - Choose three (color numbers) for the dining area from the color matrix above.
  - Choose three (color numbers) for the washroom area from the color matrix above.
  - Choose three (color numbers) for the corridor area from the color matrix above.
  - Choose three (color numbers) from the color matrix figure given that should be avoided for your ward.
  - Is there a need for sensory space at home for autistic child?
  - Do you feel that the visual aspect is critical for autistic children?
  - Are any specific changes you made to make your ward feel safe and comfortable in your home?
  - Any ideas on what you'd like to include when designing a space for an autistic child?

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EDITED BY
Fengyu Zhang,
Global Clinical and Translational Research Institute, United States

REVIEWED BY
Ramalingam Senthil,
SRM Institute of Science and Technology, India
Camilla Gesi,
ASST Fatebenefratelli Sacco, Italy

*CORRESPONDENCE
Ilaria Secci
✉ ilaria.secci@unito.it

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Case report: Treatment-resistant depression, multiple trauma exposure and suicidality in an adolescent female with previously undiagnosed Autism Spectrum Disorder

Ilaria Secci[1,2]*, Lucie Petigas[2], Alexandra Cuenod[2,3], Paul Klauser[2,4], Carole Kapp[2], Audrey Novatti[2] and Marco Armando[2]

[1]Section of Child and Adolescent Neuropsychiatry, Department of Public Health and Pediatric Sciences, University of Turin, Turin, Italy, [2]Service of Child and Adolescent Psychiatry, Department of Psychiatry, Lausanne University Hospital and the University of Lausanne, Lausanne, Switzerland, [3]Psychiatric Liaison Service, Department of Psychiatry, Lausanne University Hospital, Lausanne, Switzerland, [4]Center for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital and the University of Lausanne, Lausanne, Switzerland

High rates of co-occurring depression are commonly reported in youth with Autism Spectrum Disorder (ASD), especially in individuals without intellectual disability (ID). Depression in ASD undermines adaptive behavior and is associated with a higher risk of suicidality. Females with ASD may be particularly vulnerable due to their greater use of camouflaging strategies. Indeed, in comparison to males, ASD is underdiagnosed in females, despite higher rates of internalizing symptoms and suicidality. Trauma exposure may also play a role in the development of depressive symptoms in this population. Moreover, evidence for effective treatments of depression in autistic youth are lacking, with ASD individuals frequently experiencing low efficacy and side effects. We present the case of an adolescent female with previously undiagnosed ASD without ID, admitted for active suicidal plans and a treatment-resistant depression (TRD), occurred after a COVID-19 lockdown in the context of cumulative exposure to stressful life events. Comprehensive clinical assessments performed at intake confirmed severe depression with suicidality. Intensive psychotherapy and different changes in medications were carried out (SSRI, SNRI, SNRI + NaSSA, SNRI + aripiprazole), all of which were ineffective, with persistent suicidal thoughts, often requiring intensive individual monitoring. The patient was finally successfully treated with lithium augmentation of fluoxetine, with no side effects. During hospitalization she was also evaluated by an ASD specialized center, where a diagnosis of ASD was made according to the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R) scores, as well as to clinical judgment of a senior psychiatrist. The present case report shows that clinicians should not overlook undiagnosed autism as a possible cause of TRD, especially in females without ID, where higher rates of under diagnosis may be in part related to their greater use of camouflage. It also suggests that ASD underdiagnosis and resulting unmet needs may be involved in vulnerability to stressful experiences, depression, and suicidality. Furthermore, it shows the complexity of providing care to TRD in youth with autism, suggesting that an augmentation therapy with lithium, a commonly recommended therapeutic

strategy for refractory depression in typically developing samples, may also be effective in this population.

KEYWORDS

Autism Spectrum Disorder, depression, adolescent, case report, female, lithium, COVID-19, suicidality

Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication and interaction, and by restricted, repetitive patterns of behaviors and /or interests (1). High rates of co-occurring depression are commonly reported in youth with ASD (2, 3), with a lifetime prevalence rate estimated at 20.2% (4). ASD individuals are up to 4 times more likely to develop depressive symptoms than neurotypical subjects, with an increasing trend from adolescence to middle adulthood (5). Depression in ASD undermines adaptive behavior and is associated with a higher risk of suicidality and an increased healthcare burden (3).

A recent body of literature on adolescent and adult samples suggests that females with ASD may experience higher rates of depression and other internalizing symptoms compared to males, including anxiety, suicidality and eating disorders (5–7), although others studies found no sex differences (8, 9). Females with ASD also show higher rates of completed suicide than their male counterpart, in contrast to what is reported in non-ASD samples (i.e., completed suicide more frequent in males) (10). Moreover, evidence suggests that ASD is potentially underdiagnosed in females (11), who are also later diagnosed than their male counterpart and frequently misdiagnosed with other mental disorders, especially personality disorders (12–15). In line with this, some authors suggest that there's a female autism phenotype, including female specific manifestations of autism less likely to be captured by current diagnostic tools (16, 17). Also, females seem to mask more their autistic traits than males, a phenomenon known as camouflage (18), which has been associated to higher rates of distress, depression and suicidality in both adolescents and adults with ASD (19–21). Conversely, an earlier ASD diagnosis has shown a protective effect on depression and self-harm behaviors (22, 23), potentially enabling timely interventions and social support, and reducing the risk of traumatic experiences (24), that have been linked to mood symptoms and suicidality in ASD (25, 26).

Since current evidence is heavily based on male samples, providing information on the female autism phenotype could reduce mis- and missed-diagnosis rates and prevent secondary comorbidities in this population.

Moreover, evidence for efficacious pharmacological interventions is lacking and therapeutic strategies used for neurotypical patients may not be effective in ASD population (27, 28). Some authors suggest considering ASD in case of treatment-resistant depression (TRD) (29), which is defined by the presence of persistent depressive symptoms despite at least two trials of antidepressants at an appropriate dosage and duration. Lithium augmentation is a first-line treatment strategy for TRD in neurotypical samples (30). Moreover, lithium has demonstrated an anti-suicidal effect (31). Despite its potential use, to date, no randomized controlled trials have studied lithium's use in ASD, however, evidence from previous studies suggested a potential efficacy in this population. A preclinical study by Wu et al. (32) found an improvement in anxiety and depressive symptoms in rats with isolation-induced autistic behaviors. Previous chart reviews of youth and adults with ASD suggested a potential efficacy on mood dysregulation and maladaptive behaviors (33, 34). A previous case report showed a completed remission of catatonia and regression in two people with ASD with SHANK3 mutation treated with lithium (35). Epperson et al. (36) reported significant improvements in social relatedness and aggressivity with lithium augmentation of fluvoxamine in a man with ASD. Another case report documented a marked reduction in self-injury and aggressive behavior with lithium augmentation in a depressed adolescent male with intellectual disability (ID) (37). However, to our knowledge, this is the first case report of lithium augmentation efficacy in TRD with suicidality in an adolescent female with ASD, without ID. She was admitted multiple times for chronic suicidal plans and a TRD occurring after COVID-19 lockdown and exposure to traumatic events. Despite different changes in antidepressant treatments, all were ineffective. Eventually, she was diagnosed with ASD during her 4th hospital stay and successfully treated with lithium augmentation, without side effects.

Abbreviations: ASD, Autism Spectrum Disorder; MDD, major depressive disorder; TRD, treatment-resistant depression; NSSI, non-suicidal self-injuries; SSRI, selective serotonin re-uptake inhibitors; SNRI, selective noradrenaline re-uptake inhibitors; NaSSA, noradrenergic and specific serotonergic antidepressants; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ID, intellectual disability; ADOS-2, Autism Diagnostic Observation Schedule; ADI-R, Autism Diagnostic Interview-Revised; HoNOSCA-SR, Health of the Nation Outcome Scale for Children and Adolescents—Self rated.

Case description

Patient information

A. is a 16-year-old girl who was admitted four times in our adolescent psychiatric inpatient unit for depressive symptoms and active suicidal plans. The early development was normal, except for a mild language delay (i.e., she did not speak single words until 2.5 years and had poor speech until 4 years), that benefited from speech therapy. Since early childhood she showed

difficulties in interacting with peers, isolation, peculiar interests (i.e., drawing letters and numbers), and was described by teachers as "being in her world," which was interpreted as a reaction to the sudden death of her father when she was 5 years old. Moreover, she presented poor cognitive flexibility and a marked sense of justice, especially concerning school rules. Her peers frequently bullied her due to this. Also, the school context required her great effort due to her noise sensitivity. During adolescence, she reported a sense of being inadequate in social situations, so that she had to constantly monitor and adjust her reactions to fit into peer contexts. All her activities were organized with a rigid timetable, with a large amount of time dedicated to study and sport training, achieving brilliant sport and school results. Interactions with peers were mostly around these specific interests. Depressive symptoms started during the COVID-19 pandemic lockdown and the interruption of her high-performance sport training due to a sports failure. She presented low mood, fatigue, anhedonia, increased social withdrawal and ruminations about her father's death and the sports failure. She was first referred to an outpatient psychiatric unit, where she was treated with psychotherapy. Despite an initial mild improvement, she was later hospitalized four times for recurrent suicidal plans and diagnosed with major depressive disorder (MDD) according to DSM-5 criteria. During the first three admissions, several changes in medications were carried out: she was first treated with sertraline, up to 200 mg daily, that was then switched to fluoxetine, up to 20 mg daily, that was finally switched to duloxetine, up to 60 mg daily. She was also treated with mirtazapine up to 15 mg daily for her sleep disturbances, with a positive effect. The antidepressant treatments showed only a partial and temporary improvement, with a rapid recrudescence of suicidal plans after each hospitalization. A suspicion of ASD was also hypothesized during her first hospitalization, and the patient was put on a waiting list for outpatient specialized evaluations.

Family history

There was no family history of psychiatric disorders, except a suspicion of autism in her small brother, who had never been investigated.

Clinical findings

At the present hospitalization (i.e., the 4th one), a clinical interview was conducted at intake by a senior psychiatrist, confirming the diagnosis of MDD with active suicidal plans. She was also evaluated by the Prodromal Questionnaire-16 (38), with a score of 6 (cut-off 7) and by the Health of the Nation Outcome Scales for Children and Adolescents, self-rated version (HoNOSCA-SR) (39), suggesting severe depressive symptoms with suicidality (HoNOSCA-SR: *"Have you done anything to injure or harm your-self on purpose"- 4/5; "Have you been feeling in a low or anxious mood, or troubled by fears, obsessions or rituals"- 5/5*). During interviews, she reported depressed mood, guilt, anhedonia, apathy, sleep and appetite disturbances. She struggled to express emotions and her affect was blunted with limited eye contact, neutral facial expressions, and monotone speech. The intelligence quotient was not evaluated due to symptoms severity, however, she demonstrated good cognitive and linguistic competence, as evidenced by her school results and sophisticated vocabulary.

TABLE 1 Scores on the Autism Diagnostic Observation Schedule-2 (ADOS-2) and Autism Diagnostic Interview-Revised (ADI-R), with cut-off values.

Scores and cut-offs on the ADOS-2 and ADI-R subscales		
	Score	Cut-off score
Autism Diagnostic Observation Schedule-2		
Social affect	9	
Restrictive and repetitive behaviors	1	
Total	10	7
Comparison score	Moderate	
Autism Diagnostic Interview-Revised		
Reciprocal social interaction	12	10
Communication	9	8
Restrictive and repetitive behaviors	4	3
Development	5	1

Therapeutic intervention, follow-up, and outcomes

The current hospitalization was complicated by recurrent non-suicidal self-injuries (NSSI) (e.g., self-cutting) and suicidal threats, including an interrupted suicide attempt, requiring intensive individual monitoring during high-risk periods. A. also developed severe food restriction, initially describing it as her only way to die. She subsequently lost significant weight, reaching a body mass index of 16, and ultimately met all diagnostic criteria for anorexia nervosa (DSM-5), necessitating a nasogastric feeding tube.

Concerning pharmacological treatment, duloxetine was initially raised up to 120 mg daily, with no clinical response. Thus, an augmentation treatment, first with mirtazapine (up to 30 mg daily), and then with aripiprazole (up to 15 mg daily), was tried in combination with duloxetine, showing no clinical improvements. Duloxetine was then switched to fluoxetine, augmented up to 40 mg daily (since it had only been previously tried at a low dose), showing no clinical improvements. Lithium was finally added to fluoxetine as an augmentation treatment. Blood tests were conducted periodically to monitor thyroid, parathyroid, and renal function, as well as lithium plasma concentration, to determine the optimal dose and detect possible side effects. The therapeutic dose was 12 mmol daily (corresponding to a lithium plasma level of 0.5 mmol/L), split into two administrations, resulting in a rapid and satisfactory improvement in mood and suicidality, without side effects. A. also showed a parallel improvement in food intake restriction that allowed the removal of the nasogastric tube. During hospitalization, she was evaluated by an ASD specialized center (*Centre Cantonal de l'Autisme)* and diagnosed with ASD based on

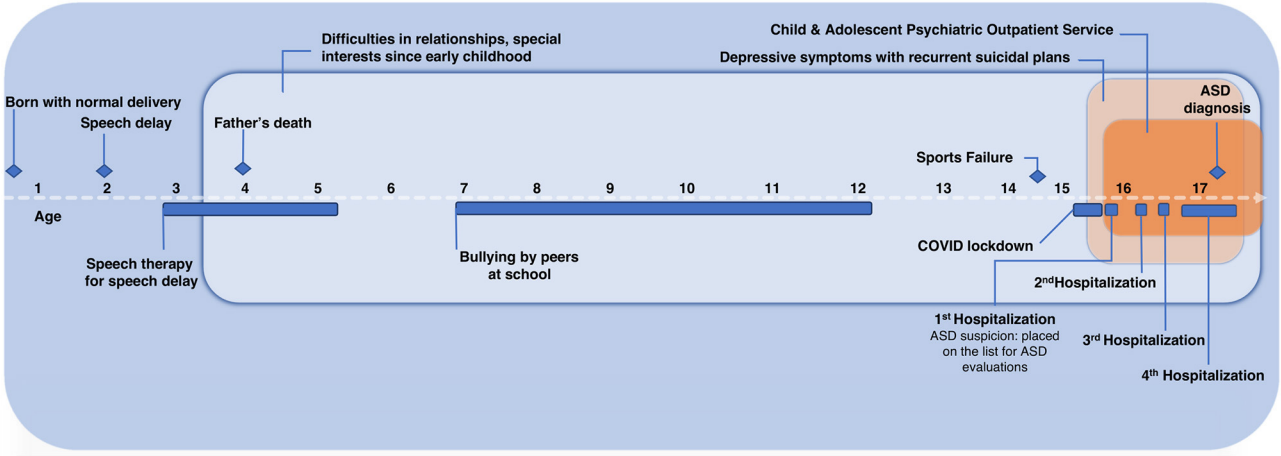

FIGURE 1
Case report timeline with relevant data.

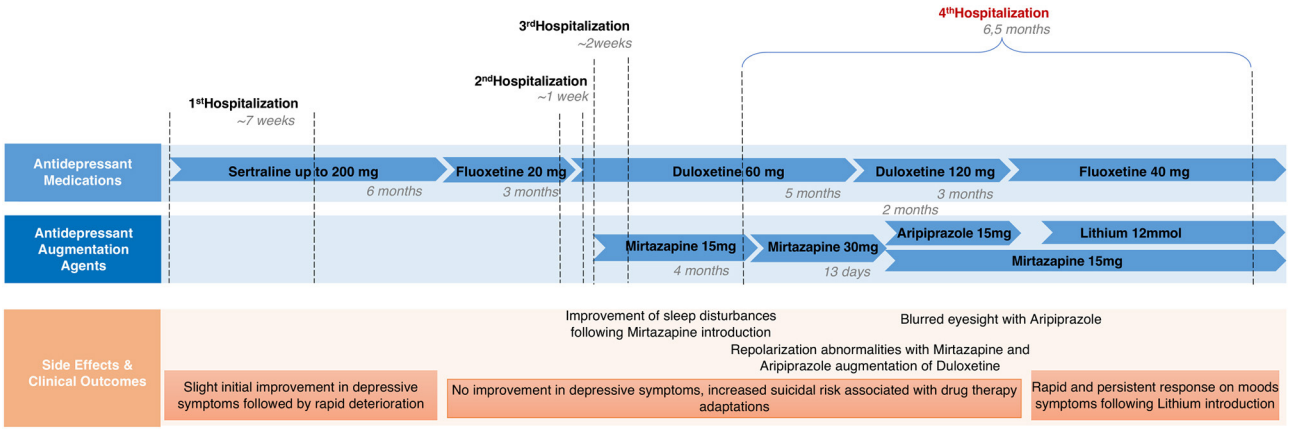

FIGURE 2
Patient's medication history.

ADOS-2 and ADI-R scores (40, 41) (Table 1), as well as the clinical judgment of a senior psychiatrist. A brief psychoeducational intervention followed to help her elaborate the diagnosis. A. also had several ergotherapy sessions focused on recognizing and managing emotions. At hospital discharge, we observed a clinical improvement that was confirmed by the HoNOSCA-SR (with a score of 3/5 as regards to mood and anxiety symptoms, and a score of 3/5 as regards to suicidal thoughts). The patient was addressed to an outpatient clinic for psychological and psychiatric follow-up, as well as to a social skills training group for ASD. Clinically relevant data and medication history are shown in Figures 1, 2.

Discussion

We present the case of a TRD with NSSI, suicidal behaviors and anorexia nervosa in a 16-year-old-girl with comorbid previously undiagnosed ASD, without ID. The strength of our case report is that it highlights the clinical challenges of females with ASD, describing the factors possibly involved in both autism misdiagnosis and in the development of TRD with suicidality. To our knowledge, this is the first case report specifically exploring lithium augmentation's efficacy for TRD with suicidality in an adolescent female with ASD, without ID, suggesting a potential effectiveness. The limitation of our case report is that the evaluations for ASD were performed during hospitalization (albeit together with the improvement of depressive symptoms), therefore, the possible influence of depression on the scores may not be completely excluded. However, ASD suspicions preceded the current patient's hospitalization and the patient's history was thoroughly explored by clinicians with the aid of the ADI-R, a standardized tool providing a developmental perspective.

Our case is in line with the evidence suggesting a greater incidence of depressive symptoms, suicidality and eating disorders in ASD population, especially in females without ID (5, 42). Also, A. showed many typical characteristics of the female autism presentation, including a late ASD diagnosis, being

initially referred for depression and using camouflage to fit in with peers (12, 16, 17). Additionally, she displayed "socially acceptable" repetitive interests (e.g., sport and school performance), consistent with studies indicating that females with ASD exhibit less bizarre interests and externalizing behaviors than their male counterpart, contributing to fewer mental health concerns and missed diagnosis (43, 44). Camouflaging strategies adopted by the patient, described as "constantly monitoring and adjusting her reactions to fit in social contexts," may both have contributed to ASD misrecognition, and represented a risk factor for depression and suicidality, as evidence highlighted that camouflage is a risk factor for a wide range of mental health problems (16, 45). Despite being "exhausting and distressing," qualitative studies in adolescent girls with ASD highlighted that camouflage was aimed at "fitting into" neurotypical contexts and avoiding bullying experiences (46). Traumatic experiences also seem to play a major role in the development of secondary comorbidities in ASD, including depression and suicidality (26, 47). Indeed, evidence show that individuals with ASD reported higher rates of trauma, such as bullying victimization and marginalization, compared to neurotypical peers, especially in females with ASD (48). Furthermore, typical autistic traits, including ruminative thinking, unusual sensory processing and need for predictability, may alter the appraisal of stressful events and hinder coping with changes. This may lead to a wider range of traumatic experiences and a greater impact on mental health (47, 49).

Multiple traumatic events in our patient's history, including sports failure and COVID-19 school closures, preceded the onset of depressive symptoms, and disrupted her routine, highlighting the impact of trauma and COVID-19 pandemic in depression development in ASD samples, as evidenced in previous studies and reports (26, 50–52). Also, COVID-19 lockdown may have exacerbated maladaptive coping strategies, such as ruminations on past traumatic experiences.

In sum, we hypothesize that the delayed diagnosis due to the female-typical ASD presentation, combined with exposure to multiple traumatic events, may have increased the risk of depression and suicidality in our patient. Furthermore, in line with literature findings (22), an earlier ASD diagnosis may have been a protective factor in reducing the patient's exposure to social stressors and in providing appropriate interventions and support. Indeed, evidence-based psychological treatments adapted for autism have shown efficacy for depression (53, 54).

Regarding pharmacological interventions, current evidence for effective treatments for depression in ASD is limited (27, 28). Studies exploring SSRI efficacy in reducing ASD core symptoms suggest that ASD youth may experience more adverse side effects than typically developing peers, especially behavioral activation (55, 56). In general population samples, current treatment guidelines recommend augmentation strategies after the failure of two antidepressants or a partial response with a primary antidepressant (57), with atypical antipsychotics and lithium commonly used as augmentation agents in both adults and adolescents (58, 59). Despite our patient's lack of response to various medications, including SSRI and SNRI monotherapy, as well as aripiprazole or mirtazapine augmentation, she showed improvement in depressive symptoms and suicidality with lithium augmentation. Limited evidence supports lithium's use in ASD, but previous clinical and pre-clinical studies documented its potential efficacy for mood symptoms, catatonia, social relatedness, and maladaptive behaviors in this population (32, 34, 36, 37). Our case also suggests lithium as a potential effective strategy for treating TRD and reducing suicide risk in youth with ASD.

Conclusions

This case report has several clinical implications. First, it provides evidence on the female-typical ASD presentation, which could help recognize ASD in females and prevent secondary comorbidities. Second, it suggests that clinicians should not overlook undiagnosed autism as a possible cause of TRD with suicidality, especially in females without ID. Third, it suggests that an augmentation therapy with lithium, an agent commonly recommended for TRD in neurotypical samples, may also be considered for refractory depression in youth with ASD. Given the high rates of depression and suicidality in ASD and limited evidence for effective interventions, further research is needed to evaluate the efficacy of lithium augmentation strategy for TRD in this population. To address this gap in knowledge, prospective controlled trials with larger samples seem necessary.

Patient perspective

The patient identified with the ASD diagnosis, describing difficulties in understanding other people's feelings or intentions since childhood, expressing relief when we discussed the increased prevalence of bullying among youth with autism. Also, she recognized the benefits of the augmentation therapy with lithium and was satisfied with the psychoeducational intervention that provided her with practical techniques to improve emotions recognition and expression.

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. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

IS contributed to the conceptualization and writing of the manuscript. LP worked with the patient and her family and contributed to the writing. AC, LP, PK, and AN worked with

the patient and her family, contributed to the conceptualization, and supervised the work. CK and MA contributed to the conceptualization and supervised the work. All authors have 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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References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*. Washington, DC: American Psychiatric Pub (2013). doi: 10.1176/appi.books.9780890425596

2. Bougeard C, Picarel-Blanchot F, Schmid R, Campbell R, Buitelaar J. Prevalence of Autism spectrum disorder and co-morbidities in children and adolescents: a systematic literature review. *Front Psychiatry.* (2021) 12:744709. doi: 10.3389/fpsyt.2021.744709

3. Pezzimenti F, Han GT, Vasa RA, Gotham K. Depression in youth with autism spectrum disorder. *Child Adolesc Psychiatr Clin N Am.* (2019) 28:397–409. doi: 10.1016/j.chc.2019.02.009

4. Greenlee JL, Mosley AS, Shui AM, Veenstra-VanderWeele J, Gotham KO. Medical and behavioral correlates of depression history in children and adolescents with autism spectrum disorder. *Pediatrics.* (2016) 137(Suppl. 2):S105–14. doi: 10.1542/peds.2015-2851I

5. Uljarević M, Hedley D, Rose-Foley K, Magiati I, Cai RY, Dissanayake C, et al. Anxiety and depression from adolescence to old age in autism spectrum disorder. *J Autism Dev Disord.* (2020) 50:3155–65. doi: 10.1007/s10803-019-04084-z

6. Schwartzman JM, Williams ZJ, Corbett BA. Diagnostic- and sex-based differences in depression symptoms in autistic and neurotypical early adolescents. *Autism.* (2022) 26:256–69. doi: 10.1177/13623613211025895

7. Westwood H, Tchanturia K. Autism spectrum disorder in anorexia nervosa: an updated literature review. *Curr Psychiatry Rep.* (2017) 19:41. doi: 10.1007/s11920-017-0791-9

8. Gotham K, Brunwasser SM, Lord C. Depressive and anxiety symptom trajectories from school age through young adulthood in samples with autism spectrum disorder and developmental delay. *J Am Acad Child Adolesc Psychiatry.* (2015) 54:369–76.e3. doi: 10.1016/j.jaac.2015.02.005

9. Nasca BC, Lopata C, Donnelly JP, Rodgers JD, Thomeer ML. Sex differences in externalizing and internalizing symptoms of children with ASD. *J Autism Dev Disord.* (2020) 50:3245–52. doi: 10.1007/s10803-019-04132-8

10. Hirvikoski T, Mittendorfer-Rutz E, Boman M, Larsson H, Lichtenstein P, Bölte S. Premature mortality in autism spectrum disorder. *Br J Psychiatry.* (2016) 208:232–8. doi: 10.1192/bjp.bp.114.160192

11. Dworzynski K, Ronald A, Bolton P, Happé F. How different are girls and boys above and below the diagnostic threshold for autism spectrum disorders? *J Am Acad Child Adolesc Psychiatry.* (2012) 51:788–97. doi: 10.1016/j.jaac.2012.05.018

12. Gesi C, Migliarese G, Torriero S, Capellazzi M, Omboni AC, Cerveri G, et al. Gender differences in misdiagnosis and delayed diagnosis among adults with autism spectrum disorder with no language or intellectual disability. *Brain Sci.* (2021) 11:912. doi: 10.3390/brainsci11070912

13. Huang Y, Arnold SRC, Foley K, Lawson LP, Richdale AL, Trollor JN. Factors associated with age at autism diagnosis in a community sample of Australian adults. *Autism Research.* (2021) 14:2677–87. doi: 10.1002/aur.2610

14. Kirby AV, Bakian AV, Zhang Y, Bilder DA, Keeshin BR, Coon H. A 20-year study of suicide death in a statewide autism population. *Autism Res.* (2019) 12:658–66. doi: 10.1002/aur.2076

15. South M, Beck JS, Lundwall R, Christensen M, Cutrer EA, Gabrielsen TP, et al. unrelenting depression and suicidality in women with autistic traits. *J Autism Dev Disord.* (2020) 50:3606–19. doi: 10.1007/s10803-019-04324-2

16. Bargiela S, Steward R, Mandy W. The experiences of late-diagnosed women with autism spectrum conditions: an investigation of the female autism phenotype. *J Autism Dev Disord.* (2016) 46:3281–94. doi: 10.1007/s10803-016-2872-8

17. Hull L, Petrides KV, Mandy W. The female autism phenotype and camouflaging: a narrative review. *Rev J Autism Dev Disord.* (2020) 7:306–17. doi: 10.1007/s40489-020-00197-9

18. Attwood T. *The Complete Guide to Asperger's Syndrome, 1st ed.* London, Philadelphia: Jessica Kingsley Publishers (2006).

19. Bernardin CJ, Mason E, Lewis T, Kanne S. "You must become a chameleon to survive": adolescent experiences of camouflaging. *J Autism Dev Disord.* (2021) 51:4422–35. doi: 10.1007/s10803-021-04912-1

20. Cage E, Troxell-Whitman Z. Understanding the reasons, contexts and costs of camouflaging for autistic adults. *J Autism Dev Disord.* (2019) 49:1899–911. doi: 10.1007/s10803-018-03878-x

21. Cassidy S, Bradley L, Shaw R, Baron-Cohen S. Risk markers for suicidality in autistic adults. *Mol Autism.* (2018) 9:42. doi: 10.1186/s13229-018-0226-4

22. Hosozawa M, Sacker A, Cable N. Timing of diagnosis, depression and self-harm in adolescents with autism spectrum disorder. *Autism.* (2021) 25:70–8. doi: 10.1177/1362361320945540

23. Jadav N, Bal VH. Associations between co-occurring conditions and age of autism diagnosis: implications for mental health training and adult autism research. *Autism Res.* (2022) 15:2112–25. doi: 10.1002/aur.2808

24. Zuckerman K, Lindly OJ, Chavez AE. Timeliness of autism spectrum disorder diagnosis and use of services among U.S. *Element Schl Aged Child Psychiatr Serv.* (2017) 68, 33–40. doi: 10.1176/appi.ps.201500549

25. Holden R, Mueller J, McGowan J, Sanyal J, Kikoler M, Simonoff E, et al. Investigating bullying as a predictor of suicidality in a clinical sample of adolescents with autism spectrum disorder. *Autism Res.* (2020) 13:988–97. doi: 10.1002/aur.2292

26. Taylor JL, Gotham KO. Cumulative life events, traumatic experiences, and psychiatric symptomatology in transition-aged youth with autism spectrum disorder. *J Neurodev Disord.* (2016) 8:28. doi: 10.1186/s11689-016-9160-y

27. Deb S, Roy M, Lee R, Majid M, Limbu B, Santambrogio J, et al. Randomised controlled trials of antidepressant and anti-anxiety medications for people with autism spectrum disorder: systematic review and meta-analysis. *BJPsych Open.* (2021) 7:e179. doi: 10.1192/bjo.2021.1003

28. Menezes M, Harkins C, Robinson MF, Mazurek MO. Treatment of depression in individuals with autism spectrum disorder: a systematic review. *Res Autism Spectr Disord.* (2020) 78:101639. doi: 10.1016/j.rasd.2020.101639

29. White MJ. Treatment-resistant depression: consider autism. *Br J Gen Pract.* (2019) 69:14. doi: 10.3399/bjgp19X700373

30. Bauer M, Adli M, Baethge C, Berghöfer A, Sasse J, Heinz A, et al. (2003). Lithium augmentation therapy in refractory depression: clinical evidence and neurobiological mechanisms. *Can J Psychiatr.* 48:440–8. doi: 10.1177/070674370304800703

31. Smith KA, Cipriani A. Lithium and suicide in mood disorders: updated meta-review of the scientific literature. *Bipolar Disord.* (2017) 19:575–86. doi: 10.1111/bdi.12543

32. Wu X, Bai Y, Tan T, Li H, Xia S, Chang X, et al. Lithium ameliorates autistic-like behaviors induced by neonatal isolation in rats. *Front Behav Neurosci.* (2014) 8:234. doi: 10.3389/fnbeh.2014.00234

33. Siegel M, Beresford CA, Bunker M, Verdi M, Vishnevetsky D, Karlsson C, et al. Preliminary investigation of lithium for mood disorder symptoms in children and adolescents with autism spectrum disorder. *J Child Adolesc Psychopharmacol.* (2014) 24:399–402. doi: 10.1089/cap.2014.0019

34. Mintz M, Hollenberg E. Revisiting lithium: utility for behavioral stabilization in adolescents and adults with autism spectrum disorder. *Psychopharmacol Bull.* (2019)49:28.

35. Serret S, Thümmler S, Dor E, Vesperini S, Santos A, Askenazy F. Lithium as a rescue therapy for regression and catatonia features in two SHANK3 patients with autism spectrum disorder: case reports. *BMC Psychiatry.* (2015) 15:107. doi: 10.1186/s12888-015-0490-1

36. Epperson CN, McDougle CJ, Anand A, Marek GJ, Naylor ST, Volkmar FR, et al. Lithium augmentation of fluvoxamine in autistic disorder: a case report. *J Child Adolesc Psychopharmacol.* (1994) 4:201–7. doi: 10.1089/cap.1994.4.201

37. Clarke D, Baxter M, Perry D, Prasher V. The diagnosis of affective and psychotic disorders in adults with autism: seven case reports. *Autism.* (1999) 3:149–64. doi: 10.1177/1362361399003002005

38. Ising HK, Veling W, Loewy RL, Rietveld MW, Rietdijk J, Dragt S, et al. The validity of the 16-item version of the prodromal questionnaire (PQ-16) to screen for ultra high risk of developing psychosis in the general help-seeking population. *Schizophr Bull.* (2012) 38:1288–96. doi: 10.1093/schbul/sbs068

39. Gowers S, Levine W, Bailey-Rogers S, Shore A, Burhouse E. Use of a routine, self-report outcome measure (HoNOSCA–SR) in two adolescent mental health services. *Br J Psychiatry.* (2002) 180:266–9. doi: 10.1192/bjp.180.3.266

40. Lord C, Rutter M, Goode S, Heemsbergen J, Jordan H, Mawhood L, et al. Austism diagnostic observation schedule: a standardized observation of communicative and social behavior. *J Autism Dev Disord.* (1989) 19:185–212. doi: 10.1007/BF02211841

41. Lord C, Rutter M, Le Couteur A. Autism diagnostic interview-revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord.* (1994) 24:659–85. doi: 10.1007/BF02172145

42. Oswald TM, Winter-Messiers MA, Gibson B, Schmidt AM, Herr CM, Solomon M. Sex differences in internalizing problems during adolescence in autism spectrum disorder. *J Autism Dev Disord.* (2016) 46:624–36. doi: 10.1007/s10803-015-2608-1

43. Lai M-C, Szatmari P. Sex and gender impacts on the behavioural presentation and recognition of autism. *Curr Opin Psychiatry.* (2020) 33:117–23. doi: 10.1097/YCO.0000000000000575

44. Stephenson KG, Norris M, Butter EM. Sex-based differences in autism symptoms in a large, clinically-referred sample of preschool-aged children with ASD. *J Autism Dev Disord.* (2021) 53:624–32. doi: 10.1007/s10803-020-04836-2

45. Leedham A, Thompson AR, Smith R, Freeth M. 'I was exhausted trying to figure it out': the experiences of females receiving an autism diagnosis in middle to late adulthood. *Autism.* (2020) 24:135–46. doi: 10.1177/1362361319853442

46. Halsall J, Clarke C, Crane L. "Camouflaging" by adolescent autistic girls who attend both mainstream and specialist resource classes: perspectives of girls, their mothers and their educators. *Autism.* (2021) 25:2074–86. doi: 10.1177/13623613211012819

47. Dell'Osso L, Carpita B, Cremone IM, Muti D, Diadema E, Barberi FM, et al. The mediating effect of trauma and stressor related symptoms and ruminations on the relationship between autistic traits and mood spectrum. *Psychiatry Res.* (2019) 279:123–9. doi: 10.1016/j.psychres.2018.10.040

48. Haruvi-Lamdan N, Horesh D, Zohar S, Kraus M, Golan O. Autism spectrum disorder and post-traumatic stress disorder: an unexplored co-occurrence of conditions. *Autism.* (2020) 24:884–98. doi: 10.1177/1362361320912143

49. Kerns CM, Lankenau S, Shattuck PT, Robins DL, Newschaffer CJ, Berkowitz SJ. Exploring potential sources of childhood trauma: a qualitative study with autistic adults and caregivers. *Autism.* (2022) 26:1987–98. doi: 10.1177/13623613211070637

50. Carmassi C, Bertelloni CA, Salarpi G, Diadema E, Avella MT, Dell'Oste V, et al. Is there a major role for undetected autism spectrum disorder with childhood trauma in a patient with a diagnosis of bipolar disorder, self-injuring, and multiple comorbidities? *Case Rep Psychiatry.* (2019) 2019:1–6. doi: 10.1155/2019/4703795

51. Lew-Koralewicz A. Psychosocial Functioning and the Educational Experiences of Students with ASD during the COVID-19 Pandemic in Poland. *Int J Environ Res Public Health.* (2022) 19:9468. doi: 10.3390/ijerph19159468

52. Oomen D, Nijhof AD, Wiersema JR. The psychological impact of the COVID-19 pandemic on adults with autism: a survey study across three countries. *Mol Autism.* (2021) 12:21. doi: 10.1186/s13229-021-00424-y

53. Cooper K, Loades ME, Russell A. Adapting psychological therapies for autism. *Res Autism Spectr Disord.* (2018) 45:43–50. doi: 10.1016/j.rasd.2017.11.002

54. Linden A, Best L, Elise F, Roberts D, Branagan A, Tay YBE, et al. Benefits and harms of interventions to improve anxiety, depression, and other mental health outcomes for autistic people: a systematic review and network meta-analysis of randomised controlled trials. *Autism.* (2022) 2022:136236132211179. doi: 10.1177/13623613221117931

55. Persico AM, Ricciardello A, Lamberti M, Turriziani L, Cucinotta F, Brogna C, et al. The pediatric psychopharmacology of autism spectrum disorder: a systematic review - part I: the past and the present. *Progress Neuro Psychopharmacol Biol Psychiatry.* (2021) 110:110326. doi: 10.1016/j.pnpbp.2021.110326

56. Williams K, Brignell A, Randall M, Silove N, Hazell P. Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD). *Cochrane Database Syst Rev.* (2013) 8. doi: 10.1002/14651858.CD004677.pub3

57. Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 3. *Pharmacological Treat Can J Psychiatry.* (2016) 61:540–60. doi: 10.1177/0706743716659417

58. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Azorin J-M, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: acute and long-term treatment of mixed states in bipolar disorder. *World J Biol Psychiatry.* (2018) 19:2–58. doi: 10.1080/15622975.2017.1384850

59. Mullen S. Major depressive disorder in children and adolescents. *Mental Health Clin.* (2018) 8:275–83. doi: 10.9740/mhc.2018.11.275

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EDITED BY
Marco Colizzi,
University of Udine, Italy

REVIEWED BY
Ramalingam Senthil,
SRM Institute of Science and Technology, India
Cheryl Klaiman,
Emory University, United States

*CORRESPONDENCE
Costanza Colombi
✉ costanza.colombi@fsm.unipi.it

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Case report: Preemptive intervention for an infant with early signs of autism spectrum disorder during the first year of life

Costanza Colombi[1]*, Natasha Chericoni[1], Stefania Bargagna[1], Valeria Costanzo[1], Raffaella Devescovi[2], Flavia Lecciso[3], Caterina Pierotti[1], Margherita Prosperi[4] and Annarita Contaldo[1]

[1]Stella Maris Foundation (IRCCS), Calambrone, Italy, [2]Institute for Maternal and Child Health Burlo Garofolo (IRCCS), Trieste, Friuli-Venezia Giulia, Italy, [3]Department of History, Society and Human Studies, University of Salento, Lecce, Apulia, Italy, [4]UFSMIA Valdera-Alta Val di Cecina, Azienda USL Toscana Nord Ovest, Pisa, Tuscany, Italy

Autism spectrum disorder (ASD) includes neurodevelopmental conditions traditionally considered to bring life long disabilities, severely impacting individuals and their families. Very early identification and intervention during the very first phases of life have shown to significantly diminish symptom severity and disability, and improve developmental trajectories. Here we report the case of a young child showing early behavioral signs of ASD during the first months of life, including diminished eye contact, reduced social reciprocity, repetitive movements. The child received a pre-emptive parent mediated intervention based on the Infant Start, an adaptation of the Early Start Denver Model (ESDM), specifically developed for children with ASD signs during the first year of life. The child here described received intervention from 6 to 32months of age, in combination with educational services. Diagnostic evaluations performed at several time points (8, 14, 19, and 32months) showed progressive improvements in his developmental level and ASD symptoms. Our case study supports the possibility of identifying ASD symptoms and providing services as soon as concerns emerge even during the first year of life. Our report, in combination with recent infant identification and intervention studies, suggests the need for very early screening and preemptive intervention to promote optimal outcomes.

KEYWORDS

preemptive intervention, parent mediated intervention, ESDM, autism spectrum disorder, early development

Introduction

Autism spectrum disorder (ASD) includes heterogeneous conditions characterized by immaturities and atypicalities in social communication and by the presence of restricted patterns of behaviors and interests (1). Research on early development suggests that brain and behavioral atypicalities emerge during the first year of life in children later diagnosed with ASD (2, 3). For example, in their study of infants at high and low familial risk for ASD, Jones and Klin (2) showed a decline in eye contact, as measured through eye-tracking technology, between 2 to 6 months of age in infants later diagnosed with ASD. Moreover, Bosl et al. (3)

showed that in infant siblings a diagnosis of ASD could be predicted with high accuracy using EEG measurements as early as 3 months of age.

Importantly, research shows that interventions delivered during the first 2 years of life lead to greater impact on developmental trajectories and symptom severity in comparison to interventions started later (4). In Lombardo et al.'s study (4), children starting intervention during the first 24 months of age demonstrated predictable gains, while it was not the case for children starting intervention later. Moreover, in their recent study, Guthrie et al. (5) showed that children starting a parent-mediated intervention, the Early Social Interaction (ESI) model, at 17 months of age, showed greater gains in receptive/expressive language, social communication, and daily living skills in comparison to children beginning the same intervention at 27 months of age. In order to increase access to intervention as early as possible for young children at high likelihood of receiving a diagnosis of ASD, researchers have developed interventions that can be delivered by teaching strategies to parents. Brian et al. (6), in their large community implemented study, showed that an evidenced-based parent-mediated intervention, the Social ABCs, for toddlers with ASD (age range: 14–34 months) can be delivered within community services. Indeed, parents learned the intervention at fidelity level and toddlers made clinically meaningful gains, suggesting that this approach is feasible and effective and may be proposed to families immediately in response to first signs of ASD. Furthermore, it seems plausible that very early parent-mediated intervention may set children on an accelerated learning trajectory, resulting in fewer resource needs later in development (7).

Research on intervention within the first year of life is very limited, so far only a handful of studies have evaluated the feasibility and the efficacy of parent-mediated intervention for symptomatic infants before 15 months of age. Both Rogers et al. (8) and Whitehouse et al. (9), using, respectively, an adapted version of the Early Start Denver Model [ESDM; Rogers et al. (10)], the Infant Start, and the iBASIS-Video Interaction to Promote Positive Parenting [iBASIS-VIPP; Pickles et al. (11)], showed that symptomatic infants starting intervention before 15 months of age were significantly less likely to have a diagnosis of ASD at 3 years of age and showed more developmental gains in comparison to matched control groups of children who did not receive the intervention. These data are promising as they suggest that by providing intervention during the first phases of life, disability can be reduced and in a portion of individuals the full-blown diagnosis may perhaps even be prevented. However, it is important to note that for the current clinical model of ASD services, the identification of a risk is usually not sufficient, and a diagnosis is necessary to be able to access community intervention, thus only a limited number of children receive intervention within the developmental window most likely to significantly impact outcomes, that is during the first and second year of life.

Our report contributes to the literature on very early intervention, as it describes the clinical presentation and developmental outcomes of a 32-month-old-child who showed early signs of ASD during his first year of life and received a preemptive intervention based on an adapted version of the ESDM, the Infant Start (8), from 6 months of age. To our knowledge this is the first case study to report on an intervention starting so early in life and implemented in a community setting using an evidence-based intervention.

Case description

Due to privacy issues we are not using the real name of the child. Here we will refer to the child as Francesco. Data related to Francesco's medical history and developmental milestones were collected through clinical interviews, video-based observations, and standardized tools administered during clinical assessments at 6, 8, 14, 19, and 32 months.

Based on parent reports, from the first months of life, Francesco showed social and communicative atypicalities including diminished or almost absent eye contact, social orientation, and social smile as well as the presence of stereotyped motor behaviors and restricted interests. In his family there was no history of neurodevelopmental disorders or neurological conditions. The pregnancy proceeded regularly. Francesco was born at the 38th week of gestation without complications and an Apgar score of 8/9. Weight at birth was 3,140 g, length 48.5 cm, and head circumference 33.2 cm. Breastfeeding was suspended at 3 months due to hypogalease. Weaning was carried out successfully and the diet was varied. Sleep–wake rhythm was described as normal. According to parent report, social smiling appeared at about 4 months, but was generally scarce throughout the first year of life. As for posturomotor development, head control was achieved at about 4 months, sitting posture with support at 5½–6 months, complete rolling at 7 months, autonomous sitting posture at 8 months, quadrupedal movement at 9 months, autonomous walking at 14 months. In general, during the first year of life, spontaneous motility and motor initiative were slightly immature and asymmetrical as demonstrated by the prevalent use of the right side of the body. For example, during the 8-month assessment Francesco would reach for objects mainly with his right hand and roll only on his right side. In regard to the stages of language development, babbling emerged at 11 months after the child was specifically stimulated during intervention.

During the first months of life, Francesco's parents consulted with several local professionals who attributed the mother's concerns about her child's social communication development to her own anxiety. Subsequently, Francesco's parents consulted with one of the authors, an expert in early ASD identification and intervention when the child was 6 months of age. Francesco's mother started worrying about his development when he was about 4 months old. She was concerned that Francesco seemed extremely passive. He would be found in his crib awake, without complaining nor trying to attract his parents' attention. Francesco would spend time in the crib by flickering his hands in front of his face. His mother could not make eye contact with him, and only occasionally and partially would he respond to her social smile. Francesco did not orient his gaze toward his parents. He was annoyed when his parents tried to touch him, to pick him up or to caress him. He would get fractious when picked up from the front. He only tolerated being picked up when his back was held against his parents' chest. Francesco was interested in visually inspecting cell phones, televisions or computers even when these devices were turned off. He used almost exclusively the right part of his body. For example, he grabbed objects only with his right hand. Plagiocephaly was present on the right side since birth. He rarely vocalized. His mother had consulted several pediatricians who had not noticed immaturity or atypicalities, but attributed the mother's worries to anxiety. However, when two experts in early detection and treatment of ASD reviewed videos of interaction between Francesco and his mother, they confirmed his mother's concerns. Indeed, even when Francesco was

positioned in front of his mother, he did not orient toward her voice, nor did he establish eye contact with her, rather he remained with his head in a static position toward the left side, as if he had a stiff neck. He laughed without looking at his mother only after having been rocked by her. His mother confirmed that he usually laughed only after physical stimulation, without, however, directing his gaze toward the adult. This behavior is highly atypical, as children easily establish eye contact with the adult from birth and constantly respond to the adult's smile by smiling back from the second month of life. After in presence and online observations, the above clinicians recommended further medical investigation and intervention. However, this time coincided with the beginning of the first COVID-19 Lockdown in Italy (March 2020). Therefore, it was not possible for the family to leave their home and access services. Thus, one of the authors started online parent mediated intervention based on Infant Start (8) and adaptation of the Early Start Denver Model [ESDM; Rogers and Dawson (10)].

The ESDM (10) is an evidence-based intervention validated in the USA [e.g., (12, 13)] and in several other countries around the world including Italy, where it has been implemented also in community settings [e.g., (14, 15)]. The ESDM is an empirically based intervention that fuses a relationship-focused developmental model with principles/practices of Applied Behavior Analysis. It uses a child-centered and responsive interactive style. It is delivered by adults within the context of play and daily routines in which highly precise naturalistic behavioral teaching is embedded, making this a Naturalistic Developmental Behavioral Intervention (NDBI), that is, one the most efficacious interventions for improving outcomes of children with ASD during the first phases of life (16). In Francesco's case, the Infant Start (8), an adapted version of the ESDM for infants, was delivered. The program addressed the five elements of efficacious very early intervention described in Wallace and Rogers (17): (1) parent coaching, (2) frequency and length of intervention, (3) individualized, developmentally appropriate activities, (4) beginning the interventions as early as possible, and (5) increasing parental sensitivity and responsivity to infant cues. The Infant Start focuses on teaching parents strategies to improve atypicalities and immaturities identified in infants at risk for ASD including diminished eye contact, diminished communicative intent/communication, and unusual pattern of object exploration. Thus, Francesco's parents were coached through five foundational intervention themes described in Rogers et al. (8) including: (1) joining into toy play to facilitate attention shifting from object to parent and parallel play, (2) encouraging flexible and varied actions and play to increase number and maturity of schemes used by the child, (3) increasing engagement and interaction to elicit communicative gesture, vocalizations, and integrated communicative behaviors for varied pragmatic intents, (4) developing the foundation of speech to increase the frequency of child vocalizations and shape specific consonant and vowel, (5) maximizing social attention to increase gaze, infant pleasure, and engagement in social interaction.

Diagnostic assessment, details of the therapeutic intervention, follow-up and outcomes

When Francesco was 8 months old, he was admitted to the Division of Child Neurology and Psychiatry of the Institute for Maternal and Child Health – IRCCS "Burlo Garofolo" in Trieste, Italy, a regional public institute for health care and scientific research. The evaluation was conducted by a child neuropsychiatrist expert in ASD and Neurodevelopmental Disorders in the early stages of life. The evaluation, which took place during a three-day hospitalization, included clinical observation, administration of standardized developmental tests [i.e., Griffiths Developmental Scales (18)], and instrumental neurological evaluation. During the evaluation Francesco took little interest in his parents and other adults. When the parents moved away from him, he showed no signs of awareness or dismay. Francesco entertained himself with stereotyped hand movements in front of his face, atypical rotations of his hands and repetitive behaviors with objects. For example, lying on the hospital bed, he repeatedly turned the cap of a bottle without varying his movements and without orienting himself toward the adults near him who were talking and trying to attract his attention. The Griffiths Developmental Scales (18) evidenced a highly immature level of development for Francesco's age, corresponding to an equivalent age of development similar to a 4–5-month-old infant (see Figure 1). So, at 8 months Francesco was highly immature as regards his psychomotor and socio-communicative development. Atypicalities included poor eye contact, lack of response to social smile, poor awareness of the presence or absence of the adult, stereotyped hand movements and repetitive behaviors with objects, which could not be accounted for by sensory deficits such as blindness or deafness. Although Francesco was too young to undergo an ADOS-2 assessment (19), his behaviors met 4 out of 5 critical items on the SACS-R (20, 21), a research screening tool for young children with ASD (risk for ASD is hypothesized when 3 or more critical items are identified). In Francesco's case the critical behaviors identified were: (1) atypical eye contact, (2) reduced reciprocal behaviors, (3) absent imitation behaviors, (4) reduced social smiling. The only critical item that was not met was failure to respond to name. As far as the instrumental tests are concerned, no asymmetries or epileptiform abnormalities were found in resting-state EEG. However, a slight immaturity in the organization of the bioelectric activity of the brain was found during sleep EEG. The MRI showed a mild plagiocephaly as well as a modest enlargement of the subarachnoid CSF spaces, especially in the frontal and vertex areas, in the base cisterns and ventricular cavities. At the audiometric evaluation, hearing appeared in the normal frequency range, and acoustic reflexes were present both ipsi- and contralaterally. The otoacoustic emissions were present bilaterally. At the eye examination visual acuity appeared normal and orthophoria was present for near objects. The child was able both to fix and follow a target. The anterior segment of the eye and the posterior pole were normal. However, an asymmetrical distribution of flash visual evoked potentials (VEPs) was found. Genetic testing for Fragile X Syndrome and SNP array analysis were negative. Francesco was discharged from the Hospital with a diagnostic risk for Autism Spectrum Disorder.

When Francesco was 9 months old, during the month of July, he underwent home intervention with one of the authors, 1–2 times a day for about 20–30 min at a time, based on Infant Start and ESDM strategies. The intervention was provided both directly (therapist – child) and mediated by the parents. During this month Francesco began to pay attention to the adult, to use eye contact both to request objects, to request the continuation of social games, and to share his interest with others. Pointing, used both to request and to share, also emerged. Francesco seemed involved and interested, but strongly

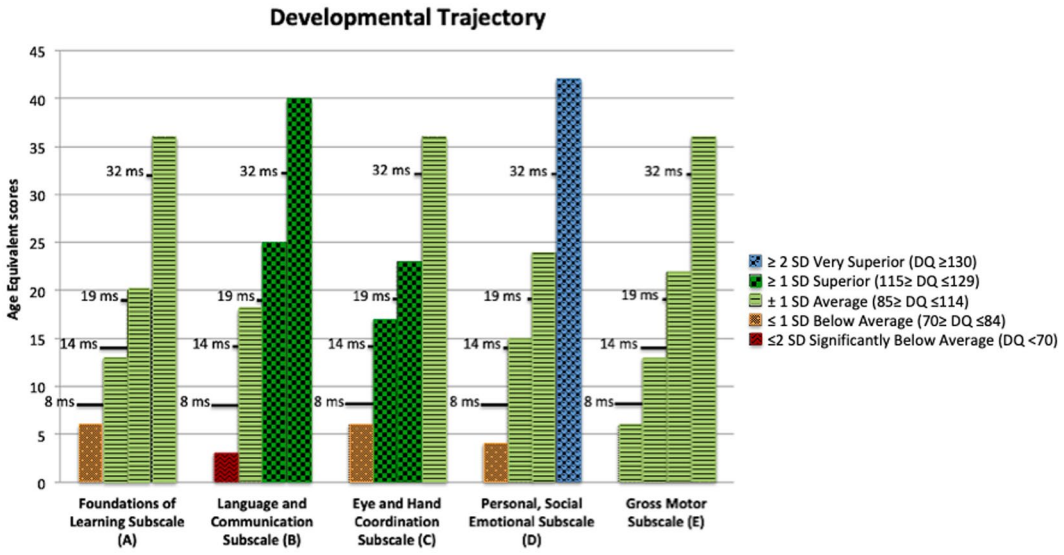

FIGURE 1
Griffiths III age equivalent (AE) scores at 8, 14, 19, 32months of chronological age. The bars, representing the AE score at each evaluation, are colored differently in accordance with the standard deviation of the Developmental Quotient from the norm.

TABLE 1 Intervention program.

	1st year		2nd year	3nd year
	(6–8ms)	(9ms)	(11–20ms)	(23–32ms)
P-ESDM	2 h a week*		1 h a week	
ESDM		30 min twice a day	2 h a week	1 h a week
Nursery School			Half time	Full time
Supervision of School activities			1 h a week	1 h (until December)

Description of frequency of parent mediated intervention (P-ESDM), therapist delivered intervention (ESDM), and nursery school attendance across the years. *Sessions were delivered online.

passive, with little communicative initiative if not stimulated, and little motor initiative. Facial expressions were almost absent. Francesco showed a neutral gaze although he participated in the interaction with the other. It should be noted that Francesco communicated with his gaze and some gestures (e.g., pointing), but did not vocalize during the activities. He kept trying to put his lips together to produce vocalizations but could not produce sounds. This absence of vocalizations and babbling at 10–11 months of life denotes an important immaturity and is highly atypical. The therapist implemented vocalization stimulation strategies by standing in front of Francesco, while he was sitting in his high chair, and reproducing simple vocalizations for the child to imitate. These strategies seemed to have a positive effect on Francesco's vocal development. However, Francesco continued to isolate himself when the adult was not intentionally stimulating him. He could remain in the cot or sitting in the stroller for a long time, even for 20–30 min looking into space without orienting himself toward or looking for other people near him.

In September, after the summer break, when Francesco was 11 months old, the family enrolled in services at the Intervention Centre of the IRCCS Stella Maris Foundation (Pisa). The intervention, based on the ESDM, was carried out by a team of professionals including a child neuropsychiatrist, two psychologists and a neuropsychomotricist (see Table 1 for the detailed scheme of his intervention program). The intervention continued to be supervised by the same therapist who had delivered the Infant Start since the child was 6 months of age. In the meantime, Francesco also started nursery school enrolling in a half day program, with the presence of a special education teacher for all the hours of his attendance. The collaboration with the school, through weekly supervisions conducted by one of the psychologists of the Centre, made it possible to coordinate the health professional intervention (IRCCS Stella Maris) and the educational program. Thus, it was possible to work in a coordinated way with common objectives so that Francesco practiced the skills acquired within 1:1 therapy also in the school context with educators and peers.

Throughout the second year of life, Francesco underwent two global assessments, at the age of 14 and 19 months, which showed he had reached developmental skills within the typical range or above (see Table 2 for an overview of the Griffiths III Scales scores). It is not surprising that he improved in all areas of development, as the ESDM is a global intervention that addresses all developmental areas, including receptive and expressive communication, social interaction, imitation, play, cognition, motor skills, and personal independence. Moreover, at both assessments the ADOS-2 (19), considered "gold standard" for the detection of symptoms attributable to ASD, presented scores below threshold for the disorder with a low severity score index (see Table 2 for an overview of the ADOS-2 scores). However, clinically Francesco still presented some atypicalities including restricted interests, rigidity and occasionally, reduced

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TABLE 2 Developmental quotients (DQ), age equivalent (AE) scores and percentiles (%) for each of the Griffiths III subscales at 8, 14, 19, and 32months of chronological age (CA).

Griffiths III		8ms	14ms	19ms	32ms
Foundations of learning subscale (A)	DQ	79	95	105	113
	AE	6	13	20	36
	%	8	37	63	79
Language and communication subscale (B)	DQ	68	112	120	123
	AE	3	18	25	40
	%	1	79	90	94
Eye and hand coordination subscale (C)	DQ	82	115	125	111
	AE	6	17	23	36
	%	10	84	95	75
Personal, social emotional subscale (D)	DQ	76	104	113	136
	AE	4	15	24	42
	%	5	61	79	>99
Gross motor subscale (E)	DQ	86	90	114	110
	AE	6	13	22	36
	%	16	25	81	75
General quotient	GQ	74	95	117	123
	AE	5	13	23	36
	%	4	37	87	94
ADOS-2					
Module			Toddler	Toddler	Module 2
Social affect			2	4	1
Restricted repetitive behaviors			4	2	1
Total score			6	6	2
Calibrated severity score			3	3	1
VABS-II					
Communication domain			82	108	106
Daily living skills domain			80	99	90
Socialization domain			80	89	101
Motor skills domain			85	92	98
Adaptive behavior composite			79	96	111

reciprocity. Consequently, his intervention program was extended to the following year, but it included fewer hours of individual intervention and more involvement in regular school activities, which Francesco attended full time (see Table 1 for an overview of his intervention program).

Toward the end of the school year, at the age of 32 months, Francesco underwent an additional developmental and diagnostic assessment. The ADOS-2 confirmed scores under the cut-off for ASD (see Table 2). It is worth noting that at this time point, Francesco was able to sustain an ADOS-2 module 2, which is used for children with phrase speech abilities. Indeed, at the assessment with the Griffiths Scales, Francesco performed on the Language and Communication subscale as a child with an equivalent age of 40 months [Developmental Quotient (DQ) 123]. Francesco was able to communicate using complex sentences with advanced grammar markers, such as verbs correctly conjugated in the present, past and future tenses, as well as combining complex sentences using grammar connectors such as "why," "when," and "but." He was able to initiate a conversation or respond taking advantage of the interlocutor's comments by adding content that allowed the other person to expand the exchange, therefore showing an optimal level of reciprocity. He was also able to integrate verbal language with non-verbal communication methods such as eye contact and gestures. The use of gestures appeared particularly advanced too. Francesco could use and understand both conventional and descriptive gestures. His skills were outstanding also at the Personal, Social Emotional Subscale of the Griffiths (Equivalent age of 42 months; DQ 136), where he showed that he was able to assume the perspective of the other person, and to understand some moral principles (e.g., stealing is bad, helping is good). Francesco not only caught up with his peers but also placed himself on the higher percentiles in most areas of development (see Table 2 on the Griffiths III scores). Indeed, he obtained a general development quotient of 123 (the norm is between 85 and 115) with an equivalent age of 36 months, placing his skills at the 94th percentile (i.e., his developmental abilities

were higher than 94% of the children his age). In Figure 1, it is possible to observe how toward the end of his first year of life and in his second year of life immaturities decreased. At first Francesco reached an adequate level for his age (14-month assessment) and subsequently (19 and 32-month assessments) he reached above average linguistic and cognitive abilities. It is noteworthy that not only was his performance during the Griffiths assessment good, but also his adaptive functioning, as reported by parents at the Vineland Adaptive Behavior Scales – 2nd edition Survey Interview Form (22), was adequate for his chronological age (Adaptive Behavior Composite Score: 111), meaning that he was able to generalize the abilities learnt during the intervention and use them also in everyday life.

Conclusion

In this report we described the case of an infant showing early behavioral signs of ASD, who received preemptive intervention from the age of 6 months. Francesco's parents were concerned because his developmental profile not only presented immaturities but also a significant deviation from a typical developmental trajectory. Many of his behaviors were in fact atypical, including intolerance to touch, prolonged visual interests in inanimate objects such as cell phones and TVs, stereotyped hand movements, repetitive behaviors with objects, scarce interest in people including parents, absent or limited use of eye contact to request or share, reduced modulation of facial expressions, and rigidity in maintaining certain body postures. In order to address these concerns Francesco received a parent mediated low intensity intervention based on the Infant Start and the ESDM, in combination with state-funded educational services. Developmental changes were documented longitudinally on behavioral measures including the ADOS-2, the Griffiths-III, and the Vineland Adaptive Behavior Scales at 8, 14, 19, and 32 months by different teams of professionals who were not involved in the intervention program. Based on these measures and clinical judgment, Francesco showed a significant improvement in developmental skills and did not meet criteria for a diagnosis of ASD when formally evaluated at 32 months of age. Although these results cannot be generalized, the perspective of diminishing disability and preventing a diagnosis is in line with previous accounts (8, 9). In this respect, Rogers's et al. (8) pilot study on Infant Start, showed that at 36 months the treated group reported higher gains in DQs and much lower rates of ASD than a similarly symptomatic group who did not enroll in the treatment study at 9 months. Similarly, Whitehouse et al. (9) showed that participation in a preemptive intervention for symptomatic infants starting at 9 months of age led to reduced ASD symptom severity and lowered the odds of an ASD diagnosis at 3 years of age.

Considering the low intensity of specialized services involved in Francesco's treatment and the absence of side effects, in combination with the positive results shown in previous group studies (8, 9), a wider application of such an approach at the community level could be a feasible practice. The current clinical model, which requires a diagnosis before accessing intervention often leads to beginning treatment after the second year of life, when brain plasticity is not at its maximum capacity anymore. Our case report, in line with current research, supports the implementation of universal screening during the first year of life (23, 24) and the use of preemptive intervention to promote optimal outcomes for infants with early social communication atypicalities. Thus, a controlled trial is a fundamental next step for demonstrating the feasibility and efficacy of this model in Italian health services. Not only does preemptive intervention have the potential to improve childhood and adulthood long-term outcomes, but it could also reduce the costs of lifelong services.

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. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

CC and NC drafted the manuscript. NC, AC, VC, RD, and MP assessed Francesco at different time points. CC and CP treated the patient and worked with the family. FL offered consultation during the administration of the intervention. CC contacted the family for approval and coordinated the approval of the final draft. 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.

Publisher's note

References

1. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders. 5th* ed. Arlington, VA: American Psychiatric Publishing (2013).

2. Jones W, Klin A. Attention to eyes is present but in decline in 2-6-month-old infants later diagnosed with autism. *Nature*. (2013) 504:427–31. doi: 10.1038/nature12715

3. Bosl WJ, Tager-Flusberg H, Nelson CA. EEG analytics for early detection of autism Spectrum disorder: a data-driven approach. *Sci Rep*. (2018) 8:6828. doi: 10.1038/s41598-018-24318-x

4. Lombardo MV, Busuoli EM, Schreibman L, Stahmer AC, Pramparo T, Landi I, et al. Pre-treatment clinical and gene expression patterns predict developmental change in early intervention in autism. *Mol Psychiatry*. (2021) 26:7641–51. doi: 10.1038/s41380-021-01239-2

5. Guthrie W, Wetherby AM, Woods J, Schatschneider C, Holland RD, Morgan L, et al. The earlier the better: an RCT of treatment timing effects for toddlers on the autism spectrum. *Autism*. (2023):136236132311591. doi: 10.1177/13623613231159153

6. Brian JA, Drmic I, Roncadin C, Dowds E, Shaver C, Smith IM, et al. Effectiveness of a parent-mediated intervention for toddlers with autism spectrum disorder: evidence from a large community implementation. *Autism*. (2022) 26:1882–97. doi: 10.1177/13623613211068934

7. Landa RJ. Efficacy of early interventions for infants and young children with, and at risk for, autism spectrum disorders. *Int Rev Psychiatry*. (2018) 30:25–39. doi: 10.1080/09540261.2018.1432574

8. Rogers SJ, Vismara L, Wagner AL, McCormick C, Young G, Ozonoff S. Autism treatment in the first year of life: a pilot study of infant start, a parent-implemented intervention for symptomatic infants. *J Autism Dev Disord*. (2014) 44:2981–95. doi: 10.1007/s10803-014-2202-y

9. Whitehouse AJO, Varcin KJ, Pillar S, Billingham W, Alvares GA, Barbaro J, et al. Effect of preemptive intervention on developmental outcomes among infants showing early signs of autism: a randomized clinical trial of outcomes to diagnosis. *JAMA Pediatr*. (2021) 175:e213298. doi: 10.1001/jamapediatrics.2021.3298

10. Rogers SJ, Dawson G. *The early start Denver model for young children with autism: promoting language, learning, and engagement*. New York, NY: Guilford (2010).

11. Pickles A, le Couteur A, Leadbitter K, Salomone E, Cole-Fletcher R, Tobin H, et al. Parent-mediated social communication therapy for young children with autism (PACT): long-term follow-up of a randomised controlled trial. *Lancet*. (2016) 388:2501–9. doi: 10.1016/S0140-6736(16)31229-6

12. Dawson G, Rogers S, Munson J, Smith M, Winter J, Greenson J, et al. Randomized, controlled trial of an intervention for toddlers with autism: the early start Denver model. *Pediatrics*. (2010) 125:e17–23. doi: 10.1542/peds.2009-0958

13. Rogers SJ, Estes A, Lord C, Vismara L, Winter J, Fitzpatrick A, et al. Effects of a brief early start Denver model (ESDM)-based parent intervention on toddlers at risk for autism spectrum disorders: a randomized controlled trial. *J Am Acad Child Adolesc Psychiatry*. (2012) 51:1052–65. doi: 10.1016/j.jaac.2012.08.003

14. Colombi C, Narzisi A, Ruta L, Cigala V, Gagliano A, Pioggia G, et al. Implementation of the early start Denver model in an Italian community. *Autism*. (2018) 22:126–33. doi: 10.1177/1362361316665792

15. Devescovi R, Colonna V, Dissegna A, Bresciani G, Carrozzi M, Colombi C. Feasibility and outcomes of the early start Denver model delivered within the public health system of the Friuli Venezia Giulia Italian region. *Brain Sci*. (2021) 11:1191. doi: 10.3390/brainsci11091191

16. Schreibman L, Dawson G, Stahmer AC, Landa R, Rogers SJ, McGee GG, et al. Naturalistic developmental behavioral interventions: empirically validated treatments for autism spectrum disorder. *J Autism Dev Disord*. (2015) 45:2411–28. doi: 10.1007/s10803-015-2407-8

17. Wallace KS, Rogers SJ. Intervening in infancy: implications for autism spectrum disorders. *J Child Psychol Psychiatry*. (2010) 51:1300–20. doi: 10.1111/j.1469-7610.2010.02308.x

18. Green E, Stroud L, Bloomfield S, Cronje J, Foxcroft C, Hurter K, et al. *Griffths scale of child development*. Florence Italy: Hogrefe (2016).

19. Lord C, Luyster RJ, Gotham K, Guthries W. *The autism diagnostic observation schedule 2 manual*. Florence: Hogrefe (2013).

20. Barbaro J, Dissanayake C. Early markers of autism spectrum disorders in infants and toddlers prospectively identified in the social attention and communication study. *Autism*. (2013) 17:64–86. doi: 10.1177/1362361312442597

21. Barbaro J, Sadka N, Gilbert M, Beattie E, Li X, Ridgway L, et al. Diagnostic accuracy of the social attention and communication surveillance-revised with preschool tool for early autism detection in very Young children. *JAMA Netw Open*. (2022) 5:e2146415. doi: 10.1001/jamanetworkopen.2021.46415

22. Sparrow SS, Cicchetti DV, Balla DA. *Vineland adaptive behavior scales. 2nd* ed. Circle Pines, MN: American Guidance Service (2005).

23. Petrocchi S, Levante A, Lecciso F. Systematic review of level 1 and level 2 screening tools for autism Spectrum disorders in toddlers. *Brain Sci*. (2020) 10:180. doi: 10.3390/brainsci10030180

24. Levante A, Petrocchi S, Lecciso F. The criterion validity of the first year inventory and the quantitative-CHecklist for autism in toddlers: a longitudinal study. *Brain Sci*. (2020) 10:1–25. doi: 10.3390/brainsci10100729

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EDITED BY
Fengyu Zhang,
Global Clinical and Translational Research Institute, United States

REVIEWED BY
Sabrina Panesi,
National Research Council (CNR), Italy
Ramalingam Senthil,
SRM Institute of Science and Technology, India

*CORRESPONDENCE
Lauren G. Malachowski
✉ lmala94@gmail.com

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Case report: An evaluation of early motor skills in an infant later diagnosed with autism

Lauren G. Malachowski*, Margaret-Anne Huntley and Amy Work Needham

Department of Psychology and Human Development, Vanderbilt University, Nashville, TN, United States

Researchers and clinicians are increasingly interested in understanding the etiology of autism spectrum disorder (ASD) and identifying behaviors that can provide opportunities for earlier detection and therefore earlier onset of intervention activities. One promising avenue of research lies in the early development of motor skills. The present study compares the motor and object exploration behaviors of an infant later diagnosed with ASD (T.I.) with the same skills in a control infant (C.I.). There were notable difference in fine motor skills by just 3 months of age, one of the earliest fine motor differences reported in the literature. In line with previous findings, T.I. and C.I. demonstrated different patterns of visual attention as early as 2.5 months of age. At later visits to the lab, T.I. engaged in unique problem-solving behaviors not demonstrated by the experimenter (i.e., emulation). Overall, findings suggest that infants later diagnosed with ASD may show differences in fine motor skills and visual attention to objects from the first months of life.

KEYWORDS

autism, infancy, fine motor skills, visual attention, emulation

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent social and behavioral differences (1). Children with autism spectrum disorder (ASD) typically do not receive formal diagnoses until "core features" (i.e., social communication differences) emerge in toddlerhood (1, 2). However, detection and intervention *before* the onset of these behavioral differences may be especially beneficial for understanding etiological mechanisms and optimizing child outcomes (1–3). Early developments in the motor domain may offer important insight into the etiology of ASD. Given close ties between social skills and motor skills, as well as rapid changes in motor skills during infancy, some researchers have proposed that the earliest signs of ASD are likely to be motor-related (4–6).

In infancy, motor skills like reaching, grasping, and crawling facilitate object exploration, a primary means through which infants collect sensory information and build knowledge about the world (7). From a developmental cascades perspective, these early interactions with objects, and the diverse learning opportunities they provide, accumulate across time to drive developmental change (8–10). In fact, object exploration has been found to predict later cognitive, language, and even social development (11–13). Thus, examining object exploration and associated motor skills in infancy may be particularly useful in the search for early markers of ASD (14).

In line with this developmental cascades framework, recent work has documented differences in motor skills (1, 6, 15–17) and object exploration behaviors (18–20). However, many of these studies focus on mid- to late- infancy (6+ months), and more work is needed to understand emerging differences in the first months of life. Additionally, many previous studies recruit infant samples at elevated likelihood for developing ASD, which may introduce confounding factors that obscure findings (i.e., characteristics of infants at higher likelihood for ASD that are not directly relevant to ASD). Retrospective analyses of infants with confirmed ASD diagnoses can help to eliminate this concern.

The present study is a longitudinal, retrospective case study comparing the exploration and motor behaviors of two infants–one later diagnosed with ASD and one age-matched control–between 2.5 and 24 months of age. Both T.I. and C.I. were male, White, and non-Hispanic. Both of their mothers had graduate degrees. Both infants were born full-term and approximately the same age at each visit. To the authors' knowledge, this study is the first retrospective case study of its kind. The primary aim was to identify potential early motor and object exploration markers to guide future studies on the etiology and development of ASD.

Methods

Diagnosis information was obtained via a brief survey sent to previous participants in an infant research lab. The survey asked parents to report on any diagnoses their child may have received since their last lab visit. One family reported that their child ("T.I." for "target infant") had been diagnosed with ASD and a speech delay. T.I. had previously participated in a longitudinal study in the lab. The original longitudinal study was designed to assess basic developmental processes and did not involve recruitment of infants at elevated likelihood of developmental disorders. A participant from the same longitudinal study was selected as a sex- and age-matched control ("C.I." for "control infant"). C.I.'s parents confirmed the absence of any developmental delays or diagnoses by 3 years of age.

According to T.I.'s mother, T.I. was diagnosed with ASD and speech delay at 19 months of age via the Vineland Adaptive Behavior Scales (21); the Mullen Scales of Early Learning (22); and the Autism Diagnostic Observation (23). The family had the ASD diagnosis confirmed by the state's early intervention system. T.I. had no family history of ASD. When the mother endorsed T.I.'s diagnosis in the survey, T.I. had already begun speech therapy, occupational therapy, physical therapy, and developmental therapy.

As a part of the original study, T.I. and C.I. visited the lab four times at the following ages: 2.5, 3, 8.5, and 24 months (this last visit was post-diagnosis for T.I., and lab members were first made aware of the diagnosis during this visit). See Figure 1 for a visual timeline. Each laboratory session consisted of structured play sessions with the infant sitting on a caregiver's lap at a semicircular table. At the 2.5- and 3-month visits, various age-appropriate objects were placed on the table within reach of the infant for 30- or 60- s intervals. At the 8.5- and 24-month visits, infants were asked to imitate multiple object-related actions, such as building a tower with blocks. All laboratory sessions were filmed with a 4-way video camera system for future coding. Additionally, the Early Motor Questionnaire (EMQ), a parent-report questionnaire assessing children's early motor skills in the context of everyday situations, was administered at 3 and 24 months (24). The EMQ was not administered at every visit due to the close temporal proximity of visits as well as efforts to reduce participant burden. The EMQ assesses gross motor skills (49 items), fine motor skills (48 items), and perception-action skills (31 items). The EMQ has demonstrated concurrent and predictive validity when compared to standardized assessments (e.g., Mullen Scales of Early Learning; 21).

Quantitative and qualitative analyses were conducted to compare T.I. and C.I. on motor and object exploration behaviors. Quantitative analyses of video footage were conducted by coders blind to diagnosis information. A detailed coding scheme was developed based on previous work (13). Using Datavyu video coding software (25), coders marked the onsets and offsets of pre-determined behaviors (looking, touching, mouthing, and rhythmic play). Each behavior was double-coded, and final codes were determined after coders discussed and resolved any discrepancies. Total durations of each behavior were then calculated for each infant and each visit. Quantitative analyses also included scores from the Early Motor Questionnaire completed at 3 and 24 months. T.I.'s scores in the gross motor and fine motor domains were calculated and compared to the mean scores for the entire study sample. The original study sample was comprised of 49 infants (56% female). The racial breakdown of the sample was: 84% White, 8% Asian, 6% Black, and 2% Pacific Islander. This was a highly-educated sample, with 53% of mothers having earned a graduate degree.

Qualitative analyses were conducted by the second author, who was unblinded to diagnosis information. These analyses were conducted by carefully examining the video footage of T.I. and C.I. side-by-side and taking detailed notes regarding observable differences in behavior. These qualitative analyses offer insights into behaviors not specified in the video coding schemes.

Results

Parent-reported gross and fine motor skills

Table 1 displays a comparison of scores on the EMQ between T.I., C.I., and the overall sample mean. T.I.'s gross motor score was similar to both C.I.'s score and the sample mean at the 3-month visit but substantially lower by the 24-month visit. Most notably, T.I.'s 3 month fine motor score (0) was more than 3 standard deviations below the sample mean ($M = 0.67$, $SD = 0.20$). A score of 0 indicates that the infant has not yet demonstrated any of the fine motor behaviors listed on the questionnaire. Examples of fine motor behaviors that other 3-month-old infants demonstrated were: "opens the fingers of each hand spontaneously," "brings hands together near the face, chest, or tummy," and "tightly holds onto a toy placed into his/her hand" (24). T.I.'s mother verbally noted at the 2.5-month visit that T.I. liked to tuck his thumb into the palm of his hand. The experimenter noted on a study documentation form

FIGURE 1
Timeline of lab visits and assessments.

TABLE 1 EMQ score comparison.

	T.I.	C.I.	Full sample
Gross motor 3 months	0.65	0.67	0.71 (0.18)
Fine motor 3 months	0	0.85	0.67 (0.20)
Perception-action 3 months	1.26	1.48	1.21 (0.27)
Gross Motor 24 Months	3.37	3.71	3.80 (0.15)
Fine motor 24 months	2.60	3.33	3.13 (0.31)
Perception-action 24 months	3.29	3.81	3.77 (0.21)

Means are presented with standard deviations in parentheses. The full sample statistics include both T.I. and C.I.'s scores.

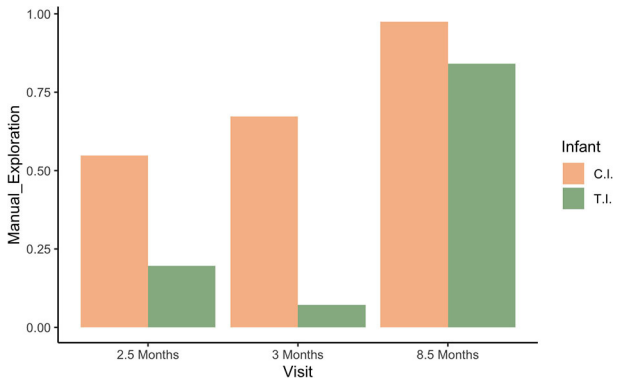

FIGURE 2
Manual object exploration by visit and infant.

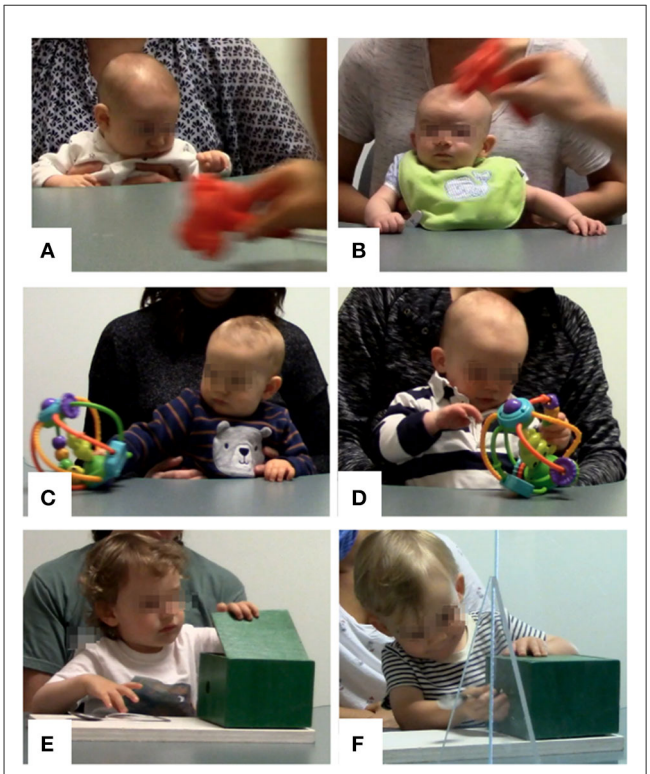

FIGURE 3
(A–F) Images of T.I. and C.I. in the lab.

that she had trouble opening T.I.'s fingers to place a rattle in his hand.

Manual object engagement

Results from video coding (quantitative analyses) revealed that T.I. spent less time manually engaging with presented objects than C.I. at the first three visits (see Figure 2).

At the 8.5-month visit, T.I. engaged in more rhythmic play than C.I. (e.g., repeatedly sliding the activity ball across the table; see Figure 3C). T.I.'s mother noted during the filmed session that T.I. liked to slide his hands and toys across the table at home. In contrast, the **second** author noted that C.I. spent more time manipulating the individual components of the activity ball (see Figure 3D).

Visual attention

At 2.5 and 3 months, T.I. demonstrated a longer latency to visually attend to presented objects compared to C.I., as measured by the number of seconds that passed between the presentation of an object and the onset of the first "look" code. When the experimenter attempted to direct T.I.'s attention to an object, T.I.

often took up to 10 s to visually orient. C.I. did not demonstrate this same behavior and tended to orient quickly to new objects (Figure 3B). The second author noted that T.I. displayed a strong preference for looking down at his hands and at the table's surface (Figure 3A). Compared to C.I., T.I. rarely shifted his attention–looking at his hands, the toy, and the table surface continuously for up to 60 s. At the 8.5-month visit, T.I. no longer looked at his hands, but similarly maintained visual attention to presented objects for periods of up to 60 s. In contrast, C.I. frequently shifted his attention between the toy, his mother, and the experimenter.

Task imitation

At the 8.5-month visit, the experimenter stacked a set of 5 blocks to build a tower and asked the infant to imitate this behavior. Neither infant successfully stacked any blocks. As with the activity ball, T.I. slid the blocks back and forth across the table. The same blocks task was repeated at the 24-month visit. Both C.I. and T.I. successfully built a block tower. C.I. proceeded to knock down the tower, just as the experimenter had demonstrated. In contrast, T.I. accomplished the same goal by removing each block from the tower one at a time to create a straight line of blocks on the table.

A second imitation task at the 24-month visit involved inserting a metal spoon into the side of a lightbox to activate a display of lights. C.I. inserted the spoon into a hole in the side of the lightbox, just as the experimenter demonstrated (see Figure 3F). In contrast, T.I. explored the box itself and discovered that the top of the box could be removed to reveal the lights inside (see Figure 3E). No other child in the study noticed the removable top, which was designed to be discreet (i.e., all painted the same color). T.I. then used his finger, instead of the tool, to activate the light, a solution that was not modeled by the experimenter.

Discussion

Analyses reveal behavioral differences between T.I. and C.I. in four domains: fine motor skill, manual object exploration, visual orientation, and task-imitation. First, T.I.'s parent-reported fine motor skills at both 3 and 24 months were substantially lower than C.I.'s. This aligns with previous work reporting less advanced fine motor skills in 6-month-old infants with a higher familial likelihood for developing ASD (26), perhaps due to atypical organization of the primary motor cortex (4, 27). However, the present study supports and extends these findings by suggesting that these differences in fine motor skill may be detectable as early as 3 months of age. If this finding is replicated in future studies, very young infants' tendencies to open their fingers, grasp objects, and bring their hands to midline should be further investigated as predictors of ASD. If found to reliably predict symptoms of ASD, fine motor items from the Early Motor Questionnaire may be promising targets for early ASD screening.

Second, consistent with previous literature (18), T.I. spent less time than C.I. looking at (28–32) and manually exploring (18) presented objects. The qualitative findings expand upon existing work by identifying more specific potential markers of ASD; namely, visual attention to the hands and nearby surfaces. Because visual attention and learning are closely related, early differences in visual attention behaviors may accumulate to impact learning (1).

Lastly, at 24 months, T.I. reproduced task goals but did not directly imitate the experimenter's actions with blocks and tools. These findings support previous work suggesting that children with ASD tend to engage in less direct imitation than their typically-developing peers (33–35). Instead, children with ASD are more likely to emulate, or reproduce a goal using methods not observed (35).

These findings must be considered in light of the natural limitations of a case study. ASD can present in many different ways. Additionally, infants' individual differences (e.g., temperament) and experiences with objects may shape their object-related behaviors produced in the lab setting. T.I. and C.I. in the present study may have differed on a number of non-ASD related attributes. Thus, replications of the present study's findings are needed before direct application in clinical settings. Additionally, given sex-related differences in ASD presentation and in general motor development, it will be important to assess early motor signs of ASD in female infants as well.

Conclusion

Overall, the present study's findings build on previous literature by identifying potential early-emerging signs of ASD in the motor and object exploration domain. Key findings include differences between T.I. and C.I. in parent-reported fine motor skill by 3 months of age, differences in manual and visual engagement with objects, and differences in task-imitation. Future work should explore fine motor skills (i.e., spontaneous finger movement) as possible indicators of ASD in early infancy.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

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 individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

LM and AN contributed to the conception and design of this study. LM conducted quantitative analyses. M-AH conducted all

qualitative analyses of videos. 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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References

1. Bradshaw J, Schwichtenberg AJ, Iverson JM. Capturing the complexity of autism: applying a developmental cascades framework. *Child Dev Perspect.* (2022) 16:18–26. doi: 10.1111/cdep.12439

2. Finlay-Jones A, Varcin K, Leonard H, Bosco A, Alvares G, Downs J. Very early identification and intervention for infants at risk of neurodevelopmental disorders: a transdiagnostic approach. *Child Dev Perspect.* (2019) 13:97–103. doi: 10.1111/cdep.12319

3. Dickinson A, Daniel M, Marin A, Gaonkar B, Dapretto M, McDonald NM, et al. Multivariate neural connectivity patterns in early infancy predict later autism symptoms. *Biol Psychiatry Cogn Neurosci Neuroimaging.* (2021) 6:59–69. doi: 10.1016/j.bpsc.2020.06.003

4. Nebel MB, Eloyan A, Barber AD, Mostofsky SH. Precentral gyrus functional connectivity signatures of autism. *Front Syst Neurosci.* (2014) 8:80. doi: 10.3389/fnsys.2014.00080

5. Thomas MSC, Knowland VCP, Karmiloff-Smith A. Mechanisms of developmental regression in autism and the broader phenotype: a neural network modeling approach. *Psychol Rev.* (2011) 118:637–54. doi: 10.1037/a0025234

6. West KL. Infant motor development in autism spectrum disorder: a synthesis and meta-analysis. *Child Dev.* (2019) 90:2053–70. doi: 10.1111/cdev.13086

7. Adolph KE, Franchak JM. The development of motor behavior. *WIREs Cognitive Science.* (2017) 8:e1430. doi: 10.1002/wcs.1430

8. Iverson JM. Developmental variability and developmental cascades: lessons from motor and language development in infancy. *Curr Dir Psychol Sci.* (2021) 30:228–35. doi: 10.1177/0963721421993822

9. Malachowski LG, Needham AW. Infants exploring objects: a cascades perspective. In: *Advances in Child Development and Behavior*. Elsevier (2023).

10. Masten AS, Cicchetti D. Developmental cascades. *Dev Psychopathol.* (2010) 22:491–5. doi: 10.1017/S0954579410000222

11. Needham A. Improvements in object exploration skills may facilitate the development of object segregation in early infancy. *J Cogn Dev.* (2000) 1:131–56. doi: 10.1207/S15327647JCD010201

12. Wilson KP, Carter MW, Wiener HL, DeRamus ML, Bulluck JC, Watson LR, et al. Object play in infants with autism spectrum disorder: a longitudinal retrospective video analysis. *Autism Dev Lang Impair.* (2017) 2. doi: 10.1177/2396941517713186

13. Zuccarini M, Guarini A, Savini S, Iverson JM, Aureli T, Alessandroni R, et al. Object exploration in extremely preterm infants between 6 and 9 months and relation to cognitive and language development at 24 months. *Res Dev Disabil.* (2017) 68:140–52. doi: 10.1016/j.ridd.2017.06.002

14. Gernsbacher MA, Sauer EA, Geye HM, Schweigert EK, Hill Goldsmith H. Infant and toddler oral- and manual-motor skills predict later speech fluency in autism. *J Child Psychol Psychiatry.* (2008) 49:43–50. doi: 10.1111/j.1469-7610.2007.01820.x

15. Licari MK, Varcin K, Hudry K, Leonard HC, Alvares GA, Pillar SV, et al. The course and prognostic capability of motor difficulties in infants showing early signs of autism. *Autism Res.* (2021) 14:1759–68. doi: 10.1002/aur.2545

16. Reynolds JE, Whitehouse AJO, Alvares GA, Waddington H, Macaskill E, Licari MK. Characterising the early presentation of motor difficulties in autistic children. *J Autism Dev Disord.* (2022) 52:4739–49. doi: 10.1007/s10803-021-05333-w

17. Posar A, Visconti P. Early motor signs in autism spectrum disorder. *Children.* (2022) 9:294. doi: 10.3390/children9020294

18. Kaur M, Srinivasan SM, Bhat AN. Atypical object exploration in infants at-risk for autism during the first year of life. *Front Psychol.* (2015) 6:798. doi: 10.3389/fpsyg.2015.00798

19. Koterba EA, Leezenbaum NB, Iverson JM. Object exploration at 6 and 9 months in infants with and without risk for autism. *Autism.* (2014) 18:97–105. doi: 10.1177/1362361312464826

20. Micai M, Fulceri F, Caruso A, Guzzetta A, Gila L, Scattoni ML. Early behavioral markers for neurodevelopmental disorders in the first 3 years of life: an overview of systematic reviews. *Neurosci Biobehav Rev.* (2020) 116:183–201. doi: 10.1016/j.neubiorev.2020.06.027

21. Sparrow SS, Cicchetti DV. The Vineland Adaptive Behavior Scales. In: *Major psychological assessment instruments*, Vol 2. Needham Heights, MA, US: Allyn & Bacon (1989). p. 199–231.

22. Akshoomoff N. Use of the mullen scales of early learning for the assessment of young children with autism spectrum disorders. *Child Neuropsychol.* (2006) 12:269–77. doi: 10.1080/09297040500473714

23. Lord C, Risi S, Lambrecht L, Cook EH, Leventhal BL, DiLavore PC, et al. The autism diagnostic observation schedule—generic: a standard measure of social and communication deficits associated with the spectrum of autism. *J Autism Dev Disord.* (2000) 30:205–23. doi: 10.1037/t17256-000

24. Libertus K, Landa RJ. The early motor questionnaire (EMQ): a parental report measure of early motor development. *Infant Behav Dev.* (2013) 36:833–42. doi: 10.1016/j.infbeh.2013.09.007

25. Datavyu Team. *Datavyu: A Video Coding Tool*. New York University (Databrary Project) (2014). Available online at: http://datavyu.org (accessed March, 2023).

26. Libertus K, Sheperd KA, Ross SW, Landa RJ. Limited fine motor and grasping skills in 6-month-old infants at high risk for autism. *Child Dev.* (2014) 85:2218–31. doi: 10.1111/cdev.12262

27. Mostofsky SH, Burgess MP, Gidley Larson JC. Increased motor cortex white matter volume predicts motor impairment in autism. *Brain.* (2007) 130:2117–22. doi: 10.1093/brain/awm129

28. Bradshaw J, Klin A, Evans L, Klaiman C, Saulnier C, McCracken C. Development of attention from birth to 5 months in infants at risk for autism spectrum disorder. *Dev Psychopathol.* (2020) 32:491–501. doi: 10.1017/S0954579419000233

29. Chawarska K, Macari S, Shic F. Decreased spontaneous attention to social scenes in 6-month-old infants later diagnosed with ASD. *Biol Psychiatry.* (2013) 74:195–203. doi: 10.1016/j.biopsych.2012.11.022

30. Di Giorgio E, Frasnelli E, Rosa Salva O, Luisa Scattoni M, Puopolo M, Tosoni D, et al. Difference in visual social predispositions between newborns at low- and high-risk for autism. *Sci Rep.* (2016) 6:26395. doi: 10.1038/srep26395

31. Elsabbagh M, Fernandes J, Jane Webb S, Dawson G, Charman T, Johnson MH. Disengagement of visual attention in infancy is associated with emerging autism in toddlerhood. *Biol Psychiatry.* (2013) 74:189–94. doi: 10.1016/j.biopsych.2012.11.030

32. Zwaigenbaum L, Bryson S, Rogers T, Roberts W, Brian J, Szatmari P. Behavioral manifestations of autism in the first year of life. *Int J Dev Neurosci.* (2005) 23:143–52. doi: 10.1016/j.ijdevneu.2004.05.001

33. Dawson G, Osterling J, Meltzoff AN, Kuhl P. Case study of the development of an infant with autism from birth to two years of age. *J Appl Dev Psychol.* (2000) 21:299–313. doi: 10.1016/S0193-3973(99)00042-8

34. Edwards LA. A meta-analysis of imitation abilities in individuals with autism spectrum disorders. *Autism Research.* (2014) 7:363–80. doi: 10.1002/aur.1379

35. Vivanti G, Trembath D, Dissanayake C. Mechanisms of imitation impairment in autism spectrum disorder. *J Abnorm Child Psychol.* (2014) 42:1395–405. doi: 10.1007/s10802-014-9874-9

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EDITED BY
Marco Colizzi,
University of Udine, Italy

REVIEWED BY
Elisabetta Filomena Buonaguro,
University of Naples Federico II, Italy
Robert Waltereit,
University Medical Center Göttingen, Germany

*CORRESPONDENCE
Silvia Guerrera
✉ silvia.guerrera@opbg.net

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Autism spectrum disorder, very-early onset schizophrenia, and child disintegrative disorder: the challenge of diagnosis. A case-report study

Michelangelo Di Luzio[1], Silvia Guerrera[1]*, Maria Pontillo[1], Maria Rosaria Lala[2], Laura Casula[1], Giovanni Valeri[1] and Stefano Vicari[1,2]

[1]Child and Adolescent Neuropsychiatry Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy, [2]Life Sciences and Public Health Department, Catholic University, Rome, Italy

Background: Autism spectrum disorder (ASD) in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) contains several disorders previously present as distinct diagnoses in the DSM Revised Fourth Edition (DSM-IV-TR). These include child disintegrative disorder (CDD). The latter presents typical features, such as a late regression of developmental acquisitions. However, it also shows symptoms similar to ASD, and psychotic symptoms, such as very-early onset schizophrenia (VEOS), are described in the literature.

Case report: In this case report we deepen the case of P., a child who presents a late regression, at 7 years old, associated with psychotic symptoms in the absence of organic alterations. The child was treated with antipsychotic drug therapy and cognitive behavioral therapy. P. was diagnosed with ASD with acute and late regression associated with psychotic symptoms. During the follow-up, there was a gradual improvement in the clinical conditions. Improvements were possible due to therapeutic intervention (pharmacological and psychotherapeutic) and/or the natural course of the disorder.

Conclusion: The diagnostic difficulty of this case reflects a clinical complexity in which it is not easy to distinguish between neurodevelopmental and psychiatric aspects. Clinical cases such as that of P. emphasize the theme of the neurodevelopment continuum model in which neurodevelopmental and psychiatric disturbances can be considered within a pattern of pathological continuity.

KEYWORDS

child disintegrative disorder, autism spectrum disorder, very-early onset schizophrenia, neurodevelopment, late regression, case report

1. Introduction

The DSM-5 changed the concept of autism from a multicategorical diagnostic system to a single diagnosis based on multiple dimensions. This transition removed diagnostic subcategories within the pervasive developmental disorders (PDD) classification (autistic disorder, Asperger's disorder, pervasive developmental disorder not otherwise specified, Rett's disorder, and childhood disintegrative disorder); hence, the dimensional diagnosis of autism spectrum disorder (ASD) defined as a neurodevelopmental disorder characterized by impairment in

develop of sociolinguistic communication and behavioral skills with associated restricted interests and repetitive behaviors (1). Atypias can be observed early in the development of many children with ASD (1).

In 1908, a group of children were observed exhibiting typical development until the ages of 3 or 4, followed by a sudden and severe decline in cognition and language. This regression was often accompanied by mood dysregulation (2). Heller initially defined this condition as "infantile dementia." Subsequent changes in nomenclature included "disintegrative psychosis" and "pervasive developmental disorder with childhood onset," as described in the International Classification of Diseases, Ninth Revision (ICD-9) (3) and the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III) (4). In the tenth edition of ICD (ICD-10) (5) and the Revised Fourth Edition of the DSM (DSM-IV-TR) (6), the disorder was referred to as disintegrative childhood disorder (CDD). The inclusion criteria for CDD encompass the following: a period of apparently normal development lasting more than 2 years (including age-appropriate verbal and non-verbal communication, social relationships, play, and adaptive behavior); and clinically significant loss of previously acquired skills (between the ages of 2 and 10 years) in at least two areas, such as expressive or receptive language, social skills or adaptive behavior, bowel or bladder control, play, and motor skills. Additionally, abnormalities in functioning must be present in at least two of the following areas: qualitative impairments in social interaction (e.g., impairments in non-verbal behaviors, failure to develop peer relationships, and a lack of social or emotional reciprocity); qualitative impairments in communication (e.g., delay or absence of spoken language, inability to initiate or sustain a conversation, stereotyped and repetitive use of language, and a lack of varied make-believe play); and restricted, repetitive, and stereotyped patterns of behavior, interests, and activities, including motor stereotypies and mannerisms; and a general loss of interest in objects and the environment. Furthermore, the disturbance cannot be better explained by another specific pervasive developmental disorder, schizophrenia, acquired aphasia with epilepsy, elective mutism, or Rett syndrome (6). Over time, several factors have contributed to conflicting conclusions about the nosological validity of CDD, such as its low prevalence (7), the absence of large case–control studies, and the limited differentiation of clinical criteria between CDD and ASD (8). Consequently, owing to ongoing debate and limited literature, CDD was excluded as a distinct diagnostic category in the DSM-5 (2, 8). Various arguments have been presented in favor of validating CDD as a single diagnostic category, including greater male prevalence, onset following a typical developmental period, more pronounced and rapid regression compared with ASD, more significant cognitive impairment than ASD, frequent loss of motor skills and continence (which are rare in ASD), higher frequency of seizures than ASD, and a generally poorer prognosis for individuals with CDD compared with ASD (9).

Similar to autism, in DSM-5, schizophrenia is dimensionally reorganized in a schizophrenia spectrum disorder (SSD). Schizophrenia is a rare neuropsychiatric disorder in childhood, with a prevalence of 0.05% in young people before 13 years of age, and 2% of schizophrenia adult-onset patients report that their psychotic symptoms began before the age of 13 (10). The National Institute of Mental Health (NIMH) has described very-early-onset schizophrenia (VEOS) as a kind of schizophrenia with an onset before the age of 13. VEOS tends to be a more serious disease (10, 11) than adult-onset schizophrenia, presenting after 18 years of age (10). VEOS patients show a more premorbid neurodevelopment difficulty load, in particular with respect to early and adult-onset schizophrenia (11). Genetic conditions, such as 22q11 deletion syndrome, may lead to a greater likelihood of being identified with psychosis (12).

Scientific literature has long since highlighted the frequent psychiatric comorbidity in children and adolescents with ASD. In particular, SSD and other psychotic disorders ranged from 4 to 67% (10, 13–15). In addition to the strong comorbidity, some genetic variants would appear to be common to both disorders (16).

CDD shows to share common features both with ASD and VEOS but at the same time shows important differences with these disorders. CDD and ASD have an impairment in the sociolinguistic communication dimension. Poor investment in social communication and a social withdrawal have been considered overlapping symptoms between ASD and the prodromes of schizophrenia. According to DSM IV-TR criteria for CDD, a decline in acquired developmental skills is expected, with a rapid course between 2 and 10 years of age distinguishing it from ASD cases with a more gradual regression before the age of 2. Moreover, CDD onset is different from the onset in VEOS, as it is generally insidious and occurs after 10 years of age (17, 18). In addition, VEOS does not show a regression in development skills as the main symptomatology, but more a social withdrawal associated with negative symptoms (blurred effects, apathy, and anhedonia) (19). In a recent case study, Di Vara et al. (13), focused on the later onset of loss of previously acquired skills in sociality, communication, bowel/bladder control, and general impairment as more indicative of CDD than ASD or VEOS features. On the other hand, in CDD, the presence of affective symptoms, feelings of oddity, and/or the presence of hallucinations were described in the literature in association with regression (2, 14, 19–26). CDD shares these features with SSD but not with ASD. Finally, CDD and ASD show a high frequency in males, and VEOS shows a similar frequency in males and females (differently from adolescent and adult schizophrenia, which are much more frequent in males) (20, 27, 28). In Table 1, the main differences between CDD, ASD, and VEOS, in terms of onset, gender, and symptomatology, are summarized.

These findings support the neurodevelopmental continuum model, which holds that childhood neurodevelopmental difficulties and psychiatric disorders, in particular those with childhood onset (e.g., VEOS), belong to an etiological and neurodevelopmental continuum, as also shown by genetic studies, and should not be interpreted as different entities (10, 15, 16, 19, 29–31).

In light of the evidence, we report the case of an 8-year-old Caucasian child with a history of neurodevelopment difficulties (speech delay and primary encopresis until 5 years of age) who presented in June 2021, at the age of 7, a sudden regression of neurodevelopmental skills, adaptive abilities, bladder control, and loss of speech associated with hallucinations and unusual thought contents without any apparent organic causes.

2. Case report

P. is the only child of a couple with a referred negative familial history for neuropsychiatric disorders and whose mother's pregnancy

TABLE 1 Differential diagnosis among disorders.

	ASD	CDD	VEOS
Onset	Gradual regression before 2 years	Acute regression after 2 years and before 10 years	Most common, insidious onset after 10 years and before 13 years
Gender	M	M	M ≅ F
Symptoms	Atypical social-communicative development and restricted interests and repetitive behavior	Skills loss in language, social interactions, adaptative behavior, play, motricity, and bladder/bowel control Hallucinations and bizarre thought contents and speech or behaviors with disorganization are described in the literature	"Positive" as hallucinations or delusions "Negative" as social retreat Disorganized behavior or speech

ASD, autism spectrum disorder; CDD, child disintegrative disorder; F, female; M, male; VEOS, very early-onset schizophrenia.

concluded at 37 gestational weeks by cesarean section due to an abnormal intrauterine position. The couple denied any suffering at birth and reported a birth weight of 3,700 g. Autonomous walking was reported to be reached at approximately 16 months. A delay in language skills was reported that required speech therapy with partial benefit and persistent phonetic-phonological errors. These difficulties in expressive language have been reported to cause a state of social anxiety in the patient. Sphincterial control was also reached late, with reported encopresis until the age of 5 years. Abnormalities in bladder control were not reported. In the remote pathological history, a *Salmonella Typhi* infection at age 3 years required hospitalization. Simple motor (involving the neck) and vocal (cough) tics were reported previously, which spontaneously remitted.

The onset of symptoms was reported at 7 years of age, at the end of May 2021. P. showed social closing and a tendency for muteness, which the parents attributed to a stressful period (returning to school after Covid-19 lockdown, bullying episodes, and the use of a video game featuring adult content). Two weeks later abnormal thought contents appeared as thought insertion, with some features of auditory and visual hallucinatory symptoms (he claimed his mother was speaking in his head and joking with him, and he reported he was frightened by some monsters on his village roads and square). These symptoms were self-limited and lasted a few days. He also reported body-related symptoms, such as aspecific abdominal pain and the presence of a "thing in abdomen which might be removed." General conditions were normal at a pediatric check-up.

In September 2021, after the summer holidays, symptoms quickly worsened with the development of a passive attitude, an absence of social interaction, a loss of speech, repetitive stereotyped movements, a tendency to orally explore objects, emotional and behavioral dysregulation and episodes of disruptive rage at school, anxiety, and fear. Positive affectivity was always been reported. A neuropsychiatric control was performed in another hospital in his region of residence, in October 2021, completed by brain magnetic resonance imaging (MRI) and an electroencephalogram (EEG) while he slept, which report normal findings. Antipsychotic therapy was started with risperidone associated with cognitive behavioral therapy (CBT). Urinary incontinence, with regression in bladder control, occurred between November 2021 and May 2022. However, incontinence is described in the literature as a side effect of risperidone (32), although in this case incontinence disappeared despite the continuation of risperidone at the same dosage.

He first visited the Child and Adolescent Psychiatry Unit, Bambino Gesù Children's Hospital, IRCCS, in July 2022. During Summer 2022, there was an improvement in the clinical status, with a slight social opening and the demise of disruptive rage; therefore, a decalage of risperidone was started until 0.75 mg/die.

We have known P. since September 2022, when he attended the Child and Adolescent Psychiatry Unit, Bambino Gesù Children's Hospital, IRCCS, for hospital day care. On this occasion, a psychiatric visit took place. P. presented with a passive attitude and loss of speech and was disorganized when exploring the surrounding environment and prone to putting objects in his mouth as a sort of oral exploration and display of disinterest in social interaction. There was no evidence of a deviation of mood or apparent signs of a manic, depressive, or dysphoric mood. His behavior showed no depressive or manic features (e.g., slow or accelerated movements) but was rather incongruous and disorganized, with fixed, non-contextual, smiling, and motor stereotypes visible. Eye contact was present but not well-modulated for social communication. At the end of hospital day care in September 2022, risperidone was replaced with olanzapine at a maximum dose of 5 mg/die. Additionally, he received an indication to intensify CBT and add speech therapy (both twice a week).

At the follow-up control with a second psychiatric visit in November 2022, he appeared to show better compliance toward the clinicians but with little improvement in social and communicative opening; however, non-contextual smiling, disorganized behavior, and a less severe mutism persisted (he said only a few words upon request). The contact of gaze was always present, and the affectivity was preserved. Play persisted in a stereotypical way, as did the oral exploration of objects of interest and possible abdominal pain complaints experienced with anxiety; however, motor stereotypes were reduced. Parents reported a sporadic episode of possible visual hallucinations in which P. was scared by the presence of an "unknown man" in his house. We conducted a comprehensive medical assessment to exclude neurological, infectious, autoimmune, or metabolic causes, as indicated in the scientific literature for the onset of a serious alteration of behavior with atypical manifestations and possible psychotic symptoms in childhood (19, 33). The assessment was conducted after hospitalization and further instances of hospital day care in January and February, 2023. On this occasion, brain MRI and EEG were repeated, and metabolic screening and spinal tap in search of inflammatory indexes, autoimmunity, and neurotropic viruses were performed. Moreover, to further explore neurodevelopmental, psychiatric, psychosocial, and familial aspects, a comprehensive assessment combining neuropsychological and psychopathological evaluations, along with social and familial observations, was conducted. The results of the multidisciplinary evaluation are reported below:

2.1. Neurophysiological and neuroradiological assessment

An EEG was performed, recording awake activity, with the presence of spindle-like short bursts of theta rhythm on the frontal regions, of non-specific significance. An EEG was repeated with non-specific findings of a diffuse fast rhythm. Brain MRI (T1 and T2 weighted), diffusion-weighted imaging (DWI), and magnetization-prepared rapid acquisition gradient echo (MPRAGE) were conducted. The MRI showed no altered cerebral tissue signal, no altered diffusivity at DWI, normal morpho-volumetry of the ventricular system, and a median line structure in axis. In general, no pathological findings were found with the EEG and MRI.

2.2. Biochemical and instrumental assessment

A metabolic screening was performed with an indication to perform in-depth metabolic blood and genetic testing. A lumbar puncture and serum analysis did not show the presence of neuroinflammation of any origin (autoimmune, metabolic, or infective). There was an isolated presence of anti-cardiolipine IgM antibodies of non-specific significance and high levels of glycated hemoglobin without diabetes in his serum. Metabolic screening was negative. The genetic visit did not find any signs or symptoms that suggested a genetic disease. Screening for celiac disease was performed and produced a negative result. As there was a referred history of constipation, to exclude an organic cause for abdominal pain, an abdomen ultrasound was undertaken and showed no pathological findings.

2.3. Neuropsychological and psychopathological assessment

The Leiter International Performance Scale, Third Edition (Leiter-3) (31), was used for the neurodevelopmental assessment. Leiter-3 is a tool for assessing non-verbal cognitive level, memory, and attention skills, which was designed to be administered to individuals without language difficulties and provides a non-verbal intelligence quotient (NVIQ). In our case, a non-verbal NVIQ of 74 was obtained (borderline score). The adaptive behavior profile was assessed using the Adaptive Behavior Assessment System, Second Edition (ABAS-II) (34). The TABAS-II is a parent-report questionnaire that measures a child's skills related to development, behavior, and cognitive abilities, from which a below-average General Adaptive Composite emerged. Regarding autism symptomatology, we used the two main "gold standard" tools, performed by a well-trained clinician. The presence of autism symptoms in the past and in the present were deepened through The Autism Diagnostic Interview Revised (ADI-R) (35) and the Autism Diagnostic Observation Schedule-Second Edition (ADOS-2) (36). The ADI-R is a structured clinical caregiver interview that provides historical information, mainly for the time period between 4 and 5 years of age, as well as current information focusing on ASD-related symptoms. The ADI-R results did not suggest ASD during preschool age. However, from the age of 7, the ADI-R scores exceeded the cut-off for all subscales. Indeed, parents referred to the presence of a significant regression in language abilities, social interaction skills, and sphincter control. Qualitative abnormalities in reciprocal social interaction, stereotyped language, atypical oral object exploration, and hand stereotypies were reported. Current ASD symptoms were also confirmed through the administration of ADOS-2, a semi-structured direct assessment of communication, social interaction, and play with, or the imaginative use of, materials for individuals with suspected autism. Module 1, used for children who do not use phrase speech consistently, was performed. The ADOS 2 Calibrated Severity Score result suggested a moderate level of ASD symptom severity. Regarding psychopathological assessment, we used the Schedule for Affective Disorders and Schizophrenia for School-Aged Children Present and Lifetime Version DSM-5 (K-SADS-PL) (37), a semi-structured interview based on DSM-5 criteria that investigates the present or life-time occurrence of psychiatric symptoms in adolescent or child subjects. The K-SADS-PL interview was administered only to parents when there was a lack of cooperation from their child. The parents exposed the child's social fears and phobias, such as a fear of sleeping alone, people dying, falling, and being hurt, since the age of 3 or 4 years old. Parents reported several possible environmental stressors that may have contributed to the onset of symptomatology. These included recent exposure to a traumatic video game during playtime, characterized by expressing the concept of death and past experiences of bullying during early childhood, where schoolmates used to tease him with verbal jokes, and the initial years of primary school, as well as the impact of the SARS-CoV-2 pandemic and subsequent lockdown, during which he spent his time in social isolation playing video games. From the age of 7, parents reported the presence of apathy, loss of interest in the environment, limited use of facial expressions, social withdrawal, some bizarre thoughts such as a "fear that his mother might play tricks on him," visual hallucinations of "frightening monsters standing on the village square," enuresis episodes, and the presence of some vocal tics and simple motor tics involving the eyes, arms, and shoulders. During the interview, there were no suggestions of symptoms related to major depressive disorder or manic or hypomanic episodes. P. did not manifest sadness, negative thoughts, inappetence, or self-harm. On the other hand, he never showed grandiosity, dangerous behavior, or a reduced need for sleep. Furthermore, the description of the symptomatology did not align with a relapsing–remitting pattern as with mood disorders but instead demonstrated a continuous and progressive decline in functional abilities without any signs of recovery to premorbid functioning. There were no clear symptoms indicative of post-traumatic stress disorder or adjustment disorder that emerged during the interview. The Children's Global Assessment Scale (CGAS), which evaluates the influence of psychiatric symptoms on the subject's functioning, showed a moderate degree of impairment of functioning in most social areas. Table 2 summarizes the main assessment findings.

To rule out any potential trauma or familial abuse as a cause, we deepened psychosocial aspects through anamnestic data and conducted a thorough observation of the family context, involving experts in relational systemic psychology. The child's father was a freelance worker, and his mother was a housewife. There were no economic problems and the family appeared to belong to the middle class. There were no signs of familial psychological or physical abuse. Both parents demonstrated a high level of attentiveness and sensitivity towards their son's needs and emotions. P.'s family had the emotional and material support of the grandparents, who played an active and affectionate role in the patient's daily life.

TABLE 2 Assessment findings.

Neurophysiological and neuroradiological assessment	Biochemical and instrumental assessment	Neuropsychological and psychopathological assessment
EEG in awake activity: (Nov. 2022) Presence of spindle-like short bursts of theta rhythm on the frontal regions, of non-specific significance (Jan. 2023) Non-specific findings of diffuse fast rhythms.	Serum analysis: Normal findings, no evidence of autoimmunity except for the presence of anti-cardiolipine IgM antibodies of non-specific significance and high levels of glycated hemoglobin without diabetes	Leiter-3: NVIQ of 74 (borderline score)
MRI (T1 e T2, FLAIR, DWI e MPRAGE): No altered signal of cerebral tissues, no altered diffusivity at DWI. Normal morfovolumetry of the ventricular system Median line structure in axis	Metabolic screening: no evidence of metabolic disease	ABAS-II: below-average General Adaptive Composite (GAC)
	Lumbar puncture: no evidence of neuroinflammation	ADI-R: not suggestive for ASD at preschool age Scores exceed the cutoff for all its subscales after the age of 7
	Celiac screening: no pathological findings	ADOS-2, module 1: Calibrated Severity Score (CSS) result was suggestive of a moderate level of ASD symptom severity
	Eco-abdomen: no pathological findings	K-SADS-PL (only parents): fear and phobias since 3–4 years of age From age of 7: feelings of apathy, loss of interest in the environment, limited use of facial expressions, social withdrawal, some bizarre thoughts such as "fear that his mother might play tricks on him," visual hallucinations of "frightening monsters standing on the village square," enuresis episodes, and the presence of some vocal tics and simple motor tics
		CGAS: a moderate degree of impairment in functioning in most social areas
		Psychosocial assessment and familial observation: no evidence of trauma emerged

ABAS-II, Adaptive Behavior Assessment System, Second; ADI-R, Autism Diagnostic Interview Revised; ADOS-2, Autism Diagnostic Observation Schedule-Second Edition; CGAS, Children's Global Assessment Scale; DWI, diffusion weighted imaging; EEG, electroencephalogram; Leiter-3, Leiter International Performance Scale, Third Edition; Jan., January; Nov., November; MPRAGE, magnetization-prepared rapid acquisition gradient echo; MRI, magnetic resonance imaging; NVIQ, non-verbal intelligence quotient; K-SADS-PL, Schedule for Affective Disorders and Schizophrenia for School-Aged Children Present and Lifetime Version DSM-5.

In conclusion, a descriptive diagnosis of autism spectrum disorder with an acute and late regression in association with psychotic symptoms and a loss of primary autonomies was performed for P. This description seems similar to the inclusion criteria for CDD and more complete than the simple diagnosis of ASD or VEOS. Notably, no loss of acquired social-relational communication skills emerged in the child's developmental history until the age of 7. In addition, during the first meeting, the parents showed videotapes of the child at age 4 that featured communicative initiative, social reciprocity, and shared play with peers and adults. The child also showed a social smile by using verbal language to relate to peers. Finally, the ADI-R results did not suggest preschool ASD, as previously reported. In terms of psychotic symptoms, bizarre thoughts and visual hallucinations were not associated with a history of hyperreactivity or hyporeactivity to sensory input, either before or after the individual episodes. Therefore, we have framed these individual episodes as possible hallucinations associated with abnormal thought contents, as reported in the K-SADS-PL interview. However, the challenge lies in elucidating the nature of such symptoms definitively, as the absence of language and socio-communicative impairments hinder the exploration of thought content and the presence of hallucinations. Furthermore, the potential psychotic symptoms, particularly unusual thought contents, manifested throughout different phases of the disorder albeit not in a continuous manner. Moreover, the onset of psychotic symptoms is very rare before the age of 13 and atypical before 10 years old (17, 18). A diagnosis of an affective disorder was excluded based on the findings from the K-SADS-PL assessment, clinical observation, and anamnesis; in fact, there were no clear indications of mood disturbances or a return to the premorbid level of functioning. In particular, symptoms such as apathy, reduced interest in the environment, reduced use of facial expressions, and social withdrawal seem to belong more to a negative symptomatology (i.e., blunted affectivity) rather than a depressive symptomatology. Moreover, anxiety seems to be a consequence of the remaining symptomatology rather than the underlying cause. The psychosocial and familial assessment did not reveal any specific traumatic events or child abuse, and the previously mentioned potential stressors (bullying, video game, and COVID-19 lockdown) did not account for the severity and persistence of the symptoms observed. Furthermore, the K-SADS-PL assessment did not yield any suggestive elements for a diagnosis of post-traumatic stress disorder or adjustment disorder. A longitudinal investigation of the case may provide further answers. However, we must consider what previously explained that CDD diagnosis, despite being suggested as a separate entity, is placed in a continuum with the other two conditions.

The therapies adopted in these cases are both pharmacological and psychotherapeutic or educational. In our case, we opted for a CBT intervention for socio-communicative and behavioral regression and the use of antipsychotic treatment for psychotic symptomatology and behavioral dysregulation. Risperidone was suspended for partial effectiveness and suspected sedation and replaced with olanzapine, as the latter has been used for hyperactivity and behavioral problems in childhood disintegrative disorder and is considered a good option for second-line therapy in VEOS after risperidone to control psychotic symptoms (23, 38–42). P. showed good compliance with the assessment and the therapies administrated. The improvements achieved have made it possible to continue with this type of therapy.

From November 2022 (18 months after the onset of symptoms) until the current time, P. showed a slight and slow but continuous improvement in speech and social interaction with fewer stereotypic movements, diminished anxiety, and sporadic psychotic symptoms. However, up until now, P. has not exhibited a return to a premorbid level of functioning. Our research group continues to monitor P. with follow-up appointments approximately every 3 months. A summarized timeline of the assessments is shown in Figure 1.

3. Discussion

The case report primarily focuses on the process of differential diagnosis and then on results and reflections derived from this process. To exclude potential neurological, infectious, autoimmune, or metabolic causes, several assessments were necessary. It is well-documented in the scientific literature that when there is a significant change in behavior with potential atypical psychotic manifestations it is important to exclude any other non-psychiatric causes (e.g., encephalitis or a brain tumor) (19, 33). Therefore, the patient underwent brain MRI, EEG, metabolic screening, and a spinal tap to investigate inflammatory markers, autoimmunity, and neurotropic viruses. These screenings yielded negative results, ruling out other medical causes for the patient's symptomatology. To delve deeper into the neuropsychiatric and psychosocial aspects, comprehensive neuropsychological and psychopathological evaluations were conducted, along with social and familial observations. This assessment was necessary to evaluate the presence of neurodevelopmental disorders such as ASD, psychiatric disorders including mood disorders and SSD, and psychosocial causes such as

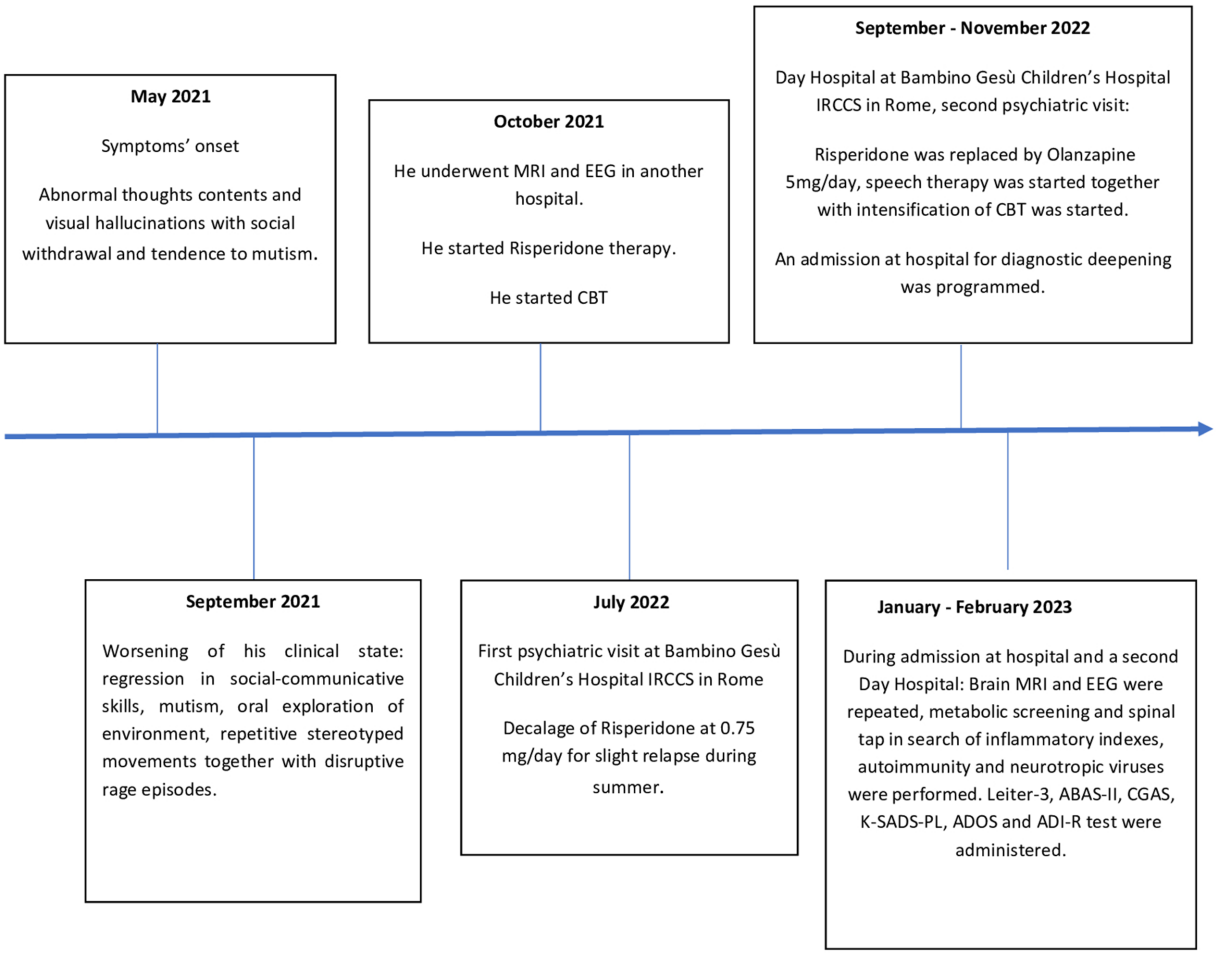

FIGURE 1
Timeline of assesments. ABAS-II, Adaptive Behavior Assessment System, Second; ADI-R, Autism Diagnostic Interview Revised; ADOS-2, Autism Diagnostic Observation Schedule-Second Edition; CBT, cognitive behavioral therapy; CGAS, Children's Global Assessment Scale; EEG, electroencephalogram; Leiter-3, Leiter International Performance Scale, Third Edition; MRI, magnetic resonance imaging; K-SADS-PL, Schedule for Affective Disorders and Schizophrenia for School-Aged Children Present and Lifetime Version DSM-5.

trauma or child abuse episodes. We excluded the presence of mood disorders, anxiety disorders, post-traumatic stress disorder, and adjustment disorder.

The first recommended intervention in childhood, especially when there is suspicion of a neurodevelopmental disorder such as ASD, is cognitive-behavioral psychotherapy. However, owing to the severity of the symptoms, particularly the psychotic symptoms and behavioral dysregulation, we opted for the integration of pharmacotherapy into the treatment plan. Research has shown that an integrated approach combining pharmacological and psychotherapeutic interventions is more effective than using either intervention alone (43, 44).

As our evaluations did not indicate the presence of traumatic or psychosocial causes, we did not deem it necessary to involve other interventions, such as social services evaluations or family psychotherapy. Additionally, as no indications of affective disorders emerged from the assessment, we did not use antidepressant or mood stabilizer medications.

The case of P. allows us to approach the issue of the differential diagnosis between CDD, VEOS, and ASD. This clinical presentation, like other similar (13, 22, 23, 25) presents many difficulties with regard to diagnosis and thus treatment. Albeit it shows a symptomatology of impaired communication and social interaction as framed in ASD. However, it appears clear that the child has achieved up to the age of 7 years an adequate social-communicative development and adaptive functioning in the absence of stereotypies or repetitive behaviors. Moreover, P. shows a positive psychotic symptomatology and disorganized behavior that could identify him as VEOS, although the onset was atypical depending on the age, and the psychotic symptomatology did not appear clear and explorable due to the muteness and socio-communicative closure of the child. The case of P. does not appear to align with the typical characteristics of ASD due to the late onset of a severe and rapid socio-communicative regression accompanied by symptoms of bizarre behavior suggestive of psychosis. Similarly, it does not fit the profile of VEOS due to the absence of clear and well-defined psychotic symptoms and the extremely early onset of such symptoms. Consequently, the disorder that encompasses the various characteristics of this case seems to be CDD, which demonstrates a delayed onset of socio-communicative regression along with possible psychotic symptoms, even in childhood. However, even this diagnosis does not appear to fully capture the complexity of the case, leading us to opt for a descriptive diagnosis of autism spectrum disorder with acute and late regression, in association with psychotic symptoms and a loss of primary autonomies. It seems that the symptomatology has common features among the three disorders. Each of the three diagnostic entities (ASD, VEOS, and CDD) possess identifiable and relevant characteristics, yet none of them alone provides a comprehensive picture of the clinical case.

It would be useful to think about a common spectrum disorder inserted within a psychopathological continuum between ASD and SSD, especially in those children with late-onset regression (after 4 years) and psychotic manifestations: a condition in which nuanced elements of the neurodevelopmental disorder can signal a subsequent regression in a frank autistic and psychotic-like symptomatology, even after the completion of normal evolutionary stages.

The DSM-5 is a commendable classification system for psychiatric pathologies, and its new dimensional approach enhances the ability to assess conditions that do not fit neatly into specific categories. However, this task is not always straightforward. For instance, cases like the one illustrated in this report demonstrate how certain conditions can manifest as a bridge between psychopathological dimensions. Consequently, we believe, as elucidated in the text, that it is crucial to improve the diagnostic tools in a similar way to the DSM-5, considering the continuum of pathological dimensions between neurodevelopmental and psychiatric conditions. The emphasis of this paradigm should be placed on integrating these diverse conditions rather than categorizing them in opposition to one another.

The study has several strengths, including the unique and distinctive nature of the described symptoms, the early age of onset, and the comprehensive assessment that was conducted. However, one main limitation of the study was the need for further evaluation over time to observe any potential changes in the symptomatology. This longitudinal approach is crucial for reaching a definitive diagnosis and gaining a deeper understanding of the case.

The Case Report was written following the CARE guidelines (the CARE guideline checklist is provided in the Supplementary Materials, Supplementary Figure S1). We did not provide the patient perspective as the patient had serious socio-communicative and language alterations.

As a take-home message, we want to highlight that our diagnostic difficulty reflects a clinical reality in which we cannot easily distinguish between neurodevelopmental and psychiatric aspects. Therefore, any assessment and treatment should be tailored to age, the level of neurodevelopment, and the "symptom stage." Perhaps to better emphasize the psychopathological continuity and improve the communication of diagnosis to parents, it would be useful to conceptualize a new spectrum dimension for this nosological entity given the current division between ASD and VEOS and the previous separate diagnosis of CDD. Further studies are necessary to better understand the clinical features, causes, and efficacious treatments in this clinical manifestation.

Data availability statement

The datasets presented in this article are not readily available because patient privacy and security are protected, according to the ethical rules of our institutions and their restriction on data sharing. Requests to access the datasets should be directed to michelangelo.diluzio@opbg.net.

Ethics statement

The studies involving human participants were reviewed and approved by Children Hospital Bambino Gesù. Ethic Committee Name: Approval Code: 243_OPBG_2021 Approval Date: 27 October 2021. 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 individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

MD, ML, and SG: conceptualization. MD, SG, and ML: writing—original draft preparation. LC and MP: writing—review and editing.

MP, GV, and SV: supervision. All authors have read and agreed to the published version of the manuscript.

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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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1212687/full#supplementary-material

References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders. 5th* ed. Arlington, VA: American Psychiatric Publishing (2013).

2. Westphal A, Schelinski S, Volkmar F, Pelphrey K. Revisiting regression in autism: Heller's dementia infantilis. Includes a translation of Über dementia Infantilis. *J Autism Dev Disord.* (2013) 43:265–71. doi: 10.1007/s10803-012-1559-z

3. National Center for Health Statistics and the Health Care Financing Administration. Official authorized addendum for the international classification of diseases, ninth revision, clinical modification. ICD-9-CM. *J Am Med Rec Assoc.* (1988) 59:1–34.3.

4. American Psychiatric Association. *Diagnosticand Statistical Manual of Mental Disorders. 3rd* ed. Washington DC: American Psychiatric Publishing (1980).

5. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems: Tenth Revision. 2nd* ed World Health Organization (2004) Available at: https://apps.who.int/iris/handle/10665/42980.

6. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders. 4th* ed. Washington DC: American Psychiatric Association (2010).

7. Fombonne E. Epidemiology of autistic disorder andother pervasive developmental disorders. *J Clin Psychiatry.* (2005) 66 Suppl 10:3–8.

8. American Psychiatric Association. *DSM-5 Autism Spectrum Disorder Fact Sheet.* Washington, DC: American Psychiatric Association (2013).

9. Rosman NP. Childhood disintegrative disorder: part of the autism spectrum? *Dev Med Child Neurol.* (2019) 61:503. doi: 10.1111/dmcn.14181

10. Pontillo M, Averna R, Tata MC, Chieppa F, Pucciarini ML, Vicari S. Neurodevelopmental trajectories and clinical profiles in a sample of children and adolescents with early- and very-early-onset schizophrenia. *Front Psych.* (2021) 12:662093. doi: 10.3389/fpsyt.2021.662093

11. Nicolson R, Lenane M, Singaracharlu S, Malaspina D, Giedd JN, Hamburger SD, et al. Premorbid speech and language impairments in childhood-onset schizophrenia: association with risk factors. *Am J Psychiatry.* (2000) 157:794–800. doi: 10.1176/appi.ajp.157.5.794

12. International 22q11.2 Brain and Behavior ConsortiumDavies RW, Fiksinski AM, Breetvelt EJ, Williams NM, Hooper SR, et al. Using common genetic variation to examine phenotypic expression and risk prediction in 22q11.2 deletion syndrome. *Nat Med.* (2020) 26:1912–8. doi: 10.1038/s41591-020-1103-1

13. Di Vara S, Guerrera S, Valeri G, Vicari S. Later onset of childhood disintegrative disorder (CDD): a case report. *Neurocase.* (2022) 28:369–74. doi: 10.1080/13554794.2022.2130804

14. Sullivan S, Rai D, Golding J, Zammit S, Steer C. The association between autism spectrum disorder and psychotic experiences in the Avon longitudinal study of parents and children (ALSPAC) birth cohort. *J Am Acad Child Adolesc Psychiatry.* (2013) 52:806–814.e2. doi: 10.1016/j.jaac.2013.05.010

15. Hossain MM, Khan N, Sultana A, Ma P, McKyer ELJ, Ahmed HU, et al. Prevalence of comorbid psychiatric disorders among people with autism spectrum disorder: an umbrella review of systematic reviews and meta-analyses. *Psychiatry Res.* (2020) 287:112922. doi: 10.1016/j.psychres.2020.112922

16. Sawant NS, Parkar S, Kulkarni P. Childhood disintegrative disorder misdiagnosed as childhood-onset schizophrenia. *S Afr J Psychiatry.* (2014) 20:2. doi: 10.4102/sajpsychiatry.v20i3.518

17. Werry JS. Child and adolescent (early onset) schizophrenia: a review in light of DSM-III-R. *J Autism Dev Disord.* (1992) 22:601–24. doi: 10.1007/BF01046330

18. Masi G, Mucci M, Pari C. Children with schizophrenia: clinical picture and pharmacological treatment. *CNS Drugs.* (2006) 20:841–66. doi: 10.2165/00023210-200620100-00005

19. Driver DI, Thomas S, Gogtay N, Rapoport JL. Childhood-onset schizophrenia and early-onset schizophrenia Spectrum disorders: an update. *Child Adolesc Psychiatr Clin N Am.* (2020) 29:71–90. doi: 10.1016/j.chc.2019.08.017

20. Mouridsen SE. Childhood disintegrative disorder. *Brain Develop.* (2003) 25:225–8. doi: 10.1016/s0387-7604(02)00228-0

21. Volkmar FR, Rutter M. Childhood disintegrative disorder: results of the DSM-IV autism field trial. *J Am Acad Child Adolesc Psychiatry.* (1995) 34:1092–5. doi: 10.1097/00004583-199508000-00020

22. Agarwal V, Sitholey P, Mohan I. Childhood disintegrative disorder, an atypical presentation: a case report. *J Autism Dev Disord.* (2005) 35:873–4. doi: 10.1007/s10803-005-0033-6

23. Mehra C, Sil A, Hedderly T, Kyriakopoulos M, Lim M, Turnbull J, et al. Childhood disintegrative disorder and autism spectrum disorder: a systematic review. *Dev Med Child Neurol.* (2019) 61:523–34. doi: 10.1111/dmcn.14126

24. Jaydeokar S, Bal G, Shah N. Childhood disintegrative disorder: a case report. *Indian J Psychiatry.* (1997) 39:85., 21584052

25. Ellis MJ, Larsen K, Havighurst SS. Childhood disintegrative disorder (CDD): symptomatology of the Norwegian patient population and Parents' experiences of patient regression. *J Autism Dev Disord.* (2022) 52:1495–506. doi: 10.1007/s10803-021-05023-7

26. Hulse WC, Heller T. Dementia infantilis. *J Nerv Ment Dis.* (1954) 119:471–7. doi: 10.1097/00005053-195406000-00001

27. Seminog O, Hoang U, Goldacre M, James A. National record-linkage study of hospital admissions for schizophrenia in childhood and adolescence in England. *Eur Child Adolesc Psychiatry.* (2022) 31:1943–51. doi: 10.1007/s00787-021-01817-3

28. Fombonne E. The prevalence of autism. *Am J Med.* (2003) 289:87–9l. doi: 10.1001/jama.289.1.87

29. Morris-Rosendahl DJ, Crocq MA. Neurodevelopmental disorders-the history and future of a diagnostic concept. *Dialogues Clin Neurosci.* (2020) 22:65–72. doi: 10.31887/DCNS.2020.22.1/macrocq

30. Owen MJ, O'Donovan MC. Schizophrenia and the neurodevelopmental continuum: evidence from genomics. *World Psychiatry.* (2017) 16:227–35. doi: 10.1002/wps.20440

31. Roid GH, Miller LJ, Pomplun M, Koch C. *Leiter International Performance Scale. 3rd* ed. Los Angeles: Western Psychological Services (2013).

32. Kumazaki H, Watanabe K, Imasaka Y, Iwata K, Tomoda A, Mimura M. Risperidone-associated urinary incontinence in patients with autistic disorder with mental retardation. *J Clin Psychopharmacol.* (2014) 34:624–6. doi: 10.1097/JCP.0000000000000197

33. Giannitelli M, Consoli A, Raffin M, Jardri R, Levinson DF, Cohen D, et al. An overview of medical risk factors for childhood psychosis: implications for research and treatment. *Schizophr Res.* (2018) 192:39–49. doi: 10.1016/j.schres.2017.05.011

34. Harrison PL, Oakland T. ABAS-II assessment methods In: R Ferri, A Orsini and M Rea, editors. *Adaptive Behavior Assessment system-II.* Cambridge, MA: Academic Press (2008). 37–49.

35. Lord C, Rutter M, LeCouteur A. Autism diagnostic interview-revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive

developmental disorders. *J Autism Dev Disord*. (1994) 24:659–85. doi: 10.1007/BF02172145

36. Lord C, Rutter M, DiLavore PC, Risi S, Gotham K, Bishop S. Autism diagnostic observation schedule—Second edition (ADOS-2) In: C Colombi, R Tancredi, A Persico and A Faggioli, editors. *Los Angeles: Western Psychological Service Italian Edition*. Hogrefe Editore: Firenze (2012)

37. Sogos C, Di Noia SP, Fioriello F. *K-SADS-PL DSM-5: Intervista Diagnostica per la Valutazione dei Disturbi Psicopatologici in Bambini e Adolescenti*. Trento, Italy: Erikson (2019).

38. Masi G, Liboni F. Management of schizophrenia in children and adolescents: focus on pharmacotherapy. *Drugs*. (2011) 71:179–208. doi: 10.2165/11585350-000000000-00000

39. Barnard L, Young AH, Pearson J, Geddes J, O'Brien G. A systematic review of the use of atypical antipsychotics in autism. *J Psychopharmacol*. (2002) 16:93–101. doi: 10.1177/026988110201600113

40. Hollander E, Wasserman S, Swanson EN, Chaplin W, Schapiro ML, Zagursky K, et al. A double-blind placebo-controlled pilot study of olanzapine in childhood/adolescent pervasive developmental disorder. *J Child Adolesc Psychopharmacol*. (2006) 16:541–8. doi: 10.1089/cap.2006.16.541

41. Stavrakaki C, Antochi R, Emery PC. Olanzapine in the treatment of pervasive developmental disorders: a case series analysis. *J Psychiatry Neurosci*. (2004) 29:57–60.

42. Kemner C, Willemsen-Swinkels SH, de Jonge M, Tuynman-Qua H, van Engeland H. Open-label study of olanzapine in children with pervasive developmental disorder. *J Clin Psychopharmacol*. (2002) 22:455–60. doi: 10.1097/00004714-200210000-00003

43. Morrison AP, Pyle M, Maughan D, Johns L, Freeman D, Broome MR, et al. Antipsychotic medication versus psychological intervention versus a combination of both in adolescents with first-episode psychosis (MAPS): a multicentre, three-arm, randomised controlled pilot and feasibility study. *Lancet Psychiatry*. (2020) 7:788–800. doi: 10.1016/S2215-0366(20)30248-0

44. Pyle M, Broome MR, Joyce E, MacLennan G, Norrie J, Freeman D, et al. Study protocol for a randomised controlled trial of CBT vs antipsychotics vs both in 14-18-year-olds: managing adolescent first episode psychosis: a feasibility study (MAPS). *Trials*. (2019) 20:395. doi: 10.1186/s13063-019-3506-1

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EDITED BY
Fengyu Zhang,
Global Clinical and Translational Research Institute, United States

REVIEWED BY
Liu Yueying,
Affiliated Hospital of Jiangnan University, China
Ennio Avolio,
University of Calabria, Italy

*CORRESPONDENCE
Sainan Shu
✉ shusainan@163.com
Yan Hao
✉ haoyaner@163.com

†These authors have contributed equally to this work

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Fecal microbiota transplantation in a child with severe ASD comorbidities of gastrointestinal dysfunctions—a case report

Cong Hu[1†], Tianyi He[1†], Biao Zou[2†], Heli Li[1], Jinzhu Zhao[1], Chen Hu[1], Jinru Cui[1], Zhihua Huang[2], Sainan Shu[1*] and Yan Hao[1*]

[1]Division of Child Healthcare, Department of Pediatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, [2]Department of Pediatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Autism spectrum disorder (ASD) is a neurodevelopmental disorder defined by social communication impairments and restricted, repetitive behaviors. In addition to behavioral interventions and psychotherapies, and pharmacological interventions, in-depth studies of intestinal microbiota in ASD has obvious abnormalities which may effectively influenced in ASD. Several attempts have been made to indicate that microbiota can reduce the occurrence of ASD effectively. Fecal microbiota transplantation (FMT) is a type of biological therapy that involves the transplant of intestinal microbiota from healthy donors into the patient's gastrointestinal tract to improve the gut microenvironment. In this case report, we describe a case of child ASD treated by FMT. The patient have poor response to long-term behavioral interventions. After five rounds of FMT, clinical core symptoms of ASD and gastrointestinal(GI) symptoms were significantly altered. Moreover, the multiple levels of functional development of child were also significantly ameliorated. We found that FMT changed the composition of the intestinal microbiota as well as the metabolites, intestinal inflammatory manifestations, and these changes were consistent with the patient's symptoms. This report suggests further FMT studies in ASD could be worth pursuing, and more studies are needed to validate the effectiveness of FMT in ASD and its mechanisms.

KEYWORDS

fecal microbiota transplantation (FMT), autism (ASD), gastrointestinal dysfunctions, metagenomic sequencing, case report

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder defined by social communication impairments and restricted, repetitive behaviors (1). The worldwide prevalence of ASD has increased, across all 11 Autism and Developmental Disabilities Monitoring (ADDM) sites in the United States, 1/36 have been estimated to have ASD 8 years old children reported by the American Centers for Disease Control and Prevention (CDC) in 2020, and incidence and median age varied widely from site to site, causing a great economic and social burden. And in recent years, the incidence rate is still gradually increasing (2). The prevalence of ASD in children aged 6–12 years in China is 0.7%, and the overall number of cases exceeds 10 million (3). From a pathogenesis perspective, ASD may be caused by a combined interaction of abnormal genetic factors, exposure

to adverse environmental factors, leading to neurological abnormalities (4). However, there is no effective and specific treatment for ASD, the current treatment of ASD mainly focuses on various forms of educational intervention training. But it is not enough for severe ASD to get a significant improvement in core symptoms (5). Therefore, new approaches for ASD treatment are still being explored.

Children with ASD often experience one or more comorbidities, including attention deficits and hyperactivity, intellectual disability, language delay, and GI dysfunction (5). One of the most significant comorbidities in patients with ASD is GI dysfunction. It is worth noting that between 23 and 70% of patients present with associated symptoms (6). Many individuals with ASD experience significant GI dysfunctions, including altered bowel habits and chronic abdominal pain, which often coincide with their neurological alterations (7). Researchers have shown that there is a strong correlation between the severity of ASD and GI symptoms (8). The fecal microbial imbalance has been extensively studied in recent years. Microbial dysbiosis has been widely recognized as a critical factor in the development of various diseases, including neuroimmune and neurobehavioral conditions (9). Detailed examination of microbiota showed that there is a strong connection between the microbial imbalance in children and ASD development. The gut microbiome has played a crucial role in the bidirectional gut-brain axis that integrates the gut and central nervous system (CNS) activities (10). For example, the gut microbiome could affect the nerves of the brain in different ways, including the neuroendocrine, immune system, and metabolites produced by intestinal bacteria and barrier system, finally changing the behaviors (10, 11). The microbiota-gut-brain (MGB) axis has been extensively studied in animal models, and it is clear that alterations in the composition of microbiota influenced neurological and behavioral outcomes. There are some studies suggested that microbial intervention could improving ASD-associated symptoms, such as antibiotics (12), and FMT (13, 14), and probiotics (15, 16). Fecal microbiota from ASD patients could induce ASD-like behavior in mice, and intervention with the microbiota could improve symptoms (17). Therefore, changing the gut microbiota of children with ASD may be an effective means of improving the symptoms of autism spectrum disorders.

Fecal microbiota transplantation (FMT) is a direct treatment method that attempts to restore healthy microbiota composition and function to patients by transplanting feces from a healthy donor into their gastrointestinal tract. FMT also benefits the intestinal barrier, altering the inflammatory response, regulating immunity, and treating some specific intra-intestinal and extra-intestinal diseases (18). However, only a few studies have been published on FMT treated for ASD, and the direct association between microbiome and ASD is still limited. Given the successful observation that FMT can successfully alleviate ASD, this case reports a case of FMT in a child with severe symptoms who did not respond to continuously many years of comprehensive behavioral interventions.

2. Materials and methods

2.1. Patient case

We present a case study of a 7-year-old female child who began to say the first words at the age of 1 year and 5 months, could speak simple sentences at the age of 2, and showed obvious regression of language ability at the age of 2 years and 6 months, and showed the phenomenon of not responding to people and not looking at people. The ABC scale was examined in the hospital at the age of 2 years and 10 months, the score was 71, and the patient was clinically diagnosed with ASD. At the age of 4, she stopped talking, did not play with other children, and exhibited apparently stereotypical behaviors such as repeatedly tapping objects and laughing pointlessly. There is an obvious phenomenon of picky eating in eating habits. The Chromosome examination and tandem mass spectrometry showed no abnormality. At the age of 6, there were squinting eyes, waving hands, screaming, tapping hands on the head, and other meaningless behaviors. Later, at the age of 7, she was continuing rehabilitation training after the ASD diagnosis by DSM-5 and ADOS-2 in our hospital in 2020, but the effect was unsatisfactory. Due to the COVID-19 epidemic, training is often spaced out, which has had a significant impact on the treatment of children. In June 2020, parents agreed to implement FMT and conducted a comprehensive evaluation in our hospital, including Autism Behavior Scale (ABC), Pediatric Autism Assessment Scale (CARS), Social Response Scale (SRS), Checklist for Autism in Toddlers-23 (CHAT-23), Autism Treatment Assessment Scale (ATEC), and the Children Neuropsychological and Behavioral Scale-Revision 2016 (CNBS-R2016).

2.2. Ethical approval

This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The Committee of Tongji Medical College of Huazhong University of Science and Technology [(2020) (S290)], approved the study. We gained written informed consent from the minor(s)' legal guardian, for any potentially identifiable images or data in the publication.

2.3. FMT procedure

2.3.1. Fecal microbiota preparation

We selected healthy donors of the same age as the patient, because the species and abundance of fecal bacteria would change with age (19). Fresh feces were collected from the donor, quickly placed in anaerobic bags, and transported to the fecal bacteria transplantation operation room, and the transplantation was completed within 1–2 h. Extraction of fecal bacteria transplant suspension: each gram of healthy feces was diluted with 5 mL of normal saline, mixed thoroughly, filtered with three layers of sterile gauze twice to obtain fresh fecal bacteria solution, and 30–50 mL of sterile injection was extracted. Excess part could be frozen and stored at −80°C after adding glycerol to the fecal bacterial solution.

2.3.2. Fecal microbiota transplant

The patient was given 40 mg/kg/day vancomycin orally for 14 days for colon cleansing before transplantation (oral administration was taken in four divided doses a day). The transplant period was divided into five rounds, each round was separated by a rest period of 1 week and lasted for 3 months in total. For the first time, a colonoscopy was performed to examine the entire colon and distal ileum after standard bowel preparation(fasting for 8 h, water prohibition for 4 h, taking compound polyethylene glycol electrolyte powder). The fecal fluid was perfused from the end of the ileum through an electronic colonoscope, and the fecal fluid was 5 mL/kg each time (80 mL of bacterial solution was used).

By transplanting the fluid at the proximal end, the fluid moves distally with the intestinal peristalsis, which will bring the fluid in full contact with the colonic mucosa. After the transplantation, the child slept for 30 min. The rest of the treatment was injected into the child's digestive tract by enema. After each transplant, the evaluation was performed by ABC, CARS, ATEC, SRS, and CNBS-R2016 (Figure 1).

2.4. Microbiological and metabolomics studies

Collect 3–5 g of fecal samples each time in the sterile sampling box, stored at the −80°C. Total DNA was extracted from the stool samples. PCR amplification by using TransGen AP221-02:TransStart Fastpfu DNA Polymerase, and ABI GeneAmp® 9700 was used. The PCR products were detected and quantified using the QuantiFluor™-ST Blue fluorescence quantification system (Promega). Miseq sequencing was performed using the TruSeqTM DNA Sample Prep Kit. The PE reads obtained by Misseq sequencing were first spliced according to the overlap relationship, and the sequence quality was qualitatively controlled and filtered. OTU clustering analysis and species classification analysis were performed after the samples were distinguished. Taxonomic analysis of OTU representative sequences with 97% similar levels was performed by the Ribosomal Database Project (RDP) Classifier, a naïve Bayesian classifier in the http://www.drive5.com. The function of the flora is annotated via http://picrust.github.io/picrust/. The sample diversity was estimated by Bray–Curtis dissimilarity in PcoA， and the data illustration was processed by http://www.ehbio.com/ImageGP/.

3. Results

3.1. Variation in autism assessment scale data

At the end of all five transplant rounds, the scores of the CARS, ATEC, and SRS gradually decreased, especially after the cleansing phase of vancomycin. The overall ABC score showed a downward trend with some fluctuations (Figure 2A). CHAT-23 is done by the guardian and professional, judging the playing habits and behaviors; the behavior and response to some stimuli, the total score reflects the severity of the illness. The number of positive CHAT-23 items has decreased significantly since one round of treatment (Figure 2B). The total score of SRS reflects the severity of impaired social ability in ASD patients and can be refined into Social perception, social cognition, social communication, and social motivation, a total of four aspects. It can be found that the SRS scores of children will fluctuate slightly after FMT, but the overall downward trend will be obvious after the end of treatment, which indicates the improvement of children's social ability (Figure 2C). The ATEC scale includes the core symptoms and developmental levels of children with ASD, and its Health/Physiology part can also reflect the diet and sleep problems of children with ASD to some extent (20). Multiple part scores of ATEC decreased after treatment. All of the data indicate that the social behavior of his child has improved significantly after FMT treatment (Figure 2D).

3.2. Changes in child development scale data

Children Neuropsychological and Behavioral Scale-Revision 2016 is a widely used developmental assessment tool for children aged 0–6 years in China (21). In the CNBS-R2016 assessment of this child, we can find significant progress in multiple areas after treatment, including gross motor, adaptive behavior, language, and personal-social. Although the scores are still lower than that of typical children (the score should be higher than 85). Besides, the score value decreased significantly in the warning behavior which indicates the severity of ASD. The decrease in the warning behavior score reflected the improvement of the children's ASD social disorder and stereotyped behavior (Figure 3). There are some details in the different areas. In the Gross motor and Fine motor, movement coordination has improved compared to the previous period, manifested in walking and running, and jumping. Before treatment, she was mainly held by my mother or grandmother, and rarely walks on the ground. After

FIGURE 1
Timeline with relevant timepoints from the episode of study and evaluation.

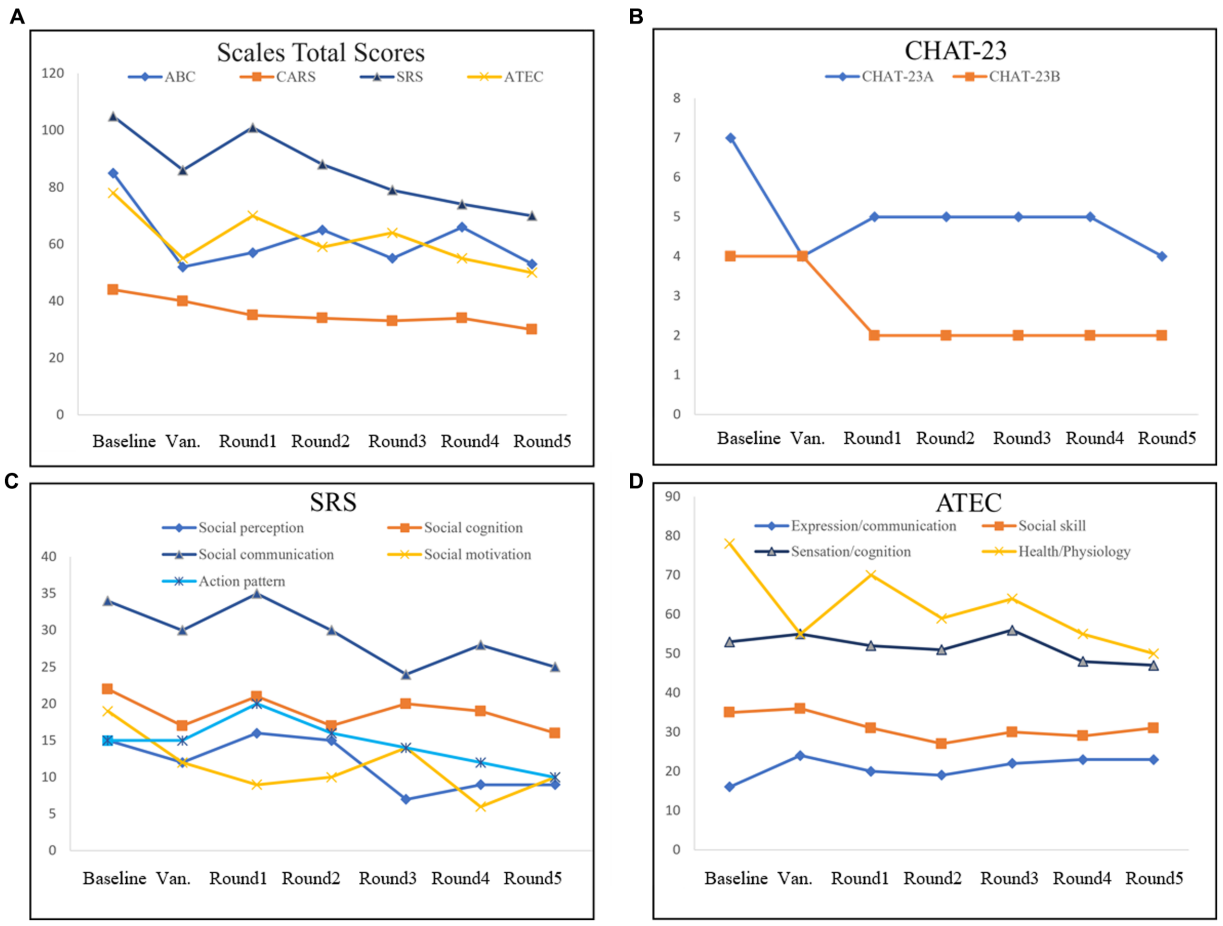

FIGURE 2
Evaluation of the scales in FMT. The Scales Total Scores **(A)**, including Autism Behavior Scale (ABC), Autism Assessment Scale (CARS), Social Response Scale (SRS), and Autism treatment evaluation checklist (ATEC). Positive items in Checklist for Autism in Toddlers-23 (CHAT-23; **B**). Evaluation checklist details in SRS **(C)**. Evaluation checklist details in ATEC **(D)**.

treatment, she could walk or run when going out. In terms of language, children begin to speak the language on the fifth day of the bowel clearing period, calling them "Mom" once a day, and gradually increasing in time. Gradually started to say "No." During the second transplant period, she could say some simple nouns. During round 3, she would like to say simple sentences "Mom, love you." At the end of the treatment, she is not only willing to call her mother every day, and constantly say "I love you," but also occasionally use "I want" to express her needs. In addition, body language has also become meaningful, with movements such as shaking/nodding/waving her hands consistent with the oral expressive meanings. In addition to language development, children have significantly increased emotional communication and begin to observe and respond to parental expressions, such as consolation. Those data and clinical manifestations support that there is a significant improvement in multiple functional areas of the child after FMT treatment.

3.3. Changes in intestinal structure

Before FMT, the patient underwent electronic gastroscopy and colonoscopy, and it was found that the end of the ileum was scattered with granular hyperplasia, and the rectum was scattered with shallow ulcers covered with white moss. Pathological findings showed chronic ileus and multiple granulomas with unclear boundaries in the mucosa. Immunohistochemical staining was performed for CD68 (focal +), CD163 (scattered +), and S-100 (scattered +). After fecal bacteria transplantation, only a few granular hyperplasias were observed at the end of the ileum. The other intestinal mucosa was smooth, and the rectal ulcer was healed under the microscope (Figure 4).

3.4. Changes in the composition of the microbiota

To explore the changes in the child's flora after treatment, we analyzed the composition and metabolic function through microbiota analysis. Before FMT, the intestinal microbiota diversity and proportion of Bacteroides were significantly lower than that of the donor. After FMT, the abundance of Bacteroides increased significantly, as did Ruminococcus. On the contrary, Bifidobacterium, Anaerostipes, Streptococcus, and Faecalibacterium showed significant declines after transplantation (Figure 5). Furthermore, the production capacity of short-chain fatty acids

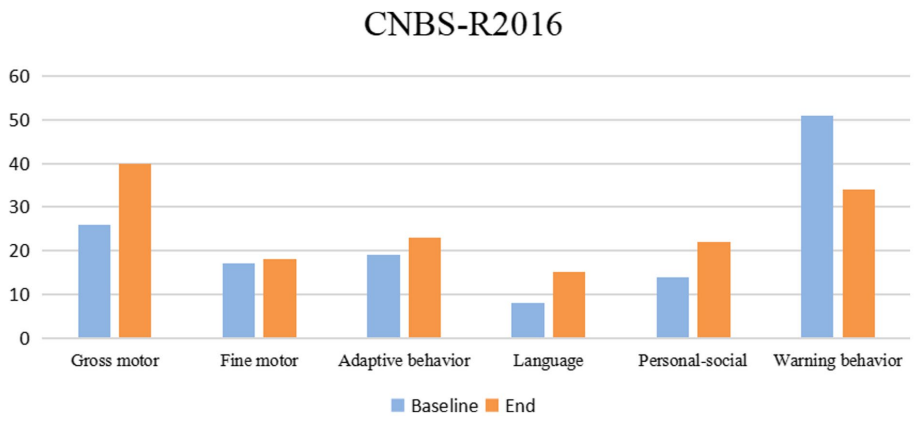

FIGURE 3
Children's Neuropsychological and Behavioral Scale—2016 Revision (CNBS-R2016) scores of case before and after FMT treatment.

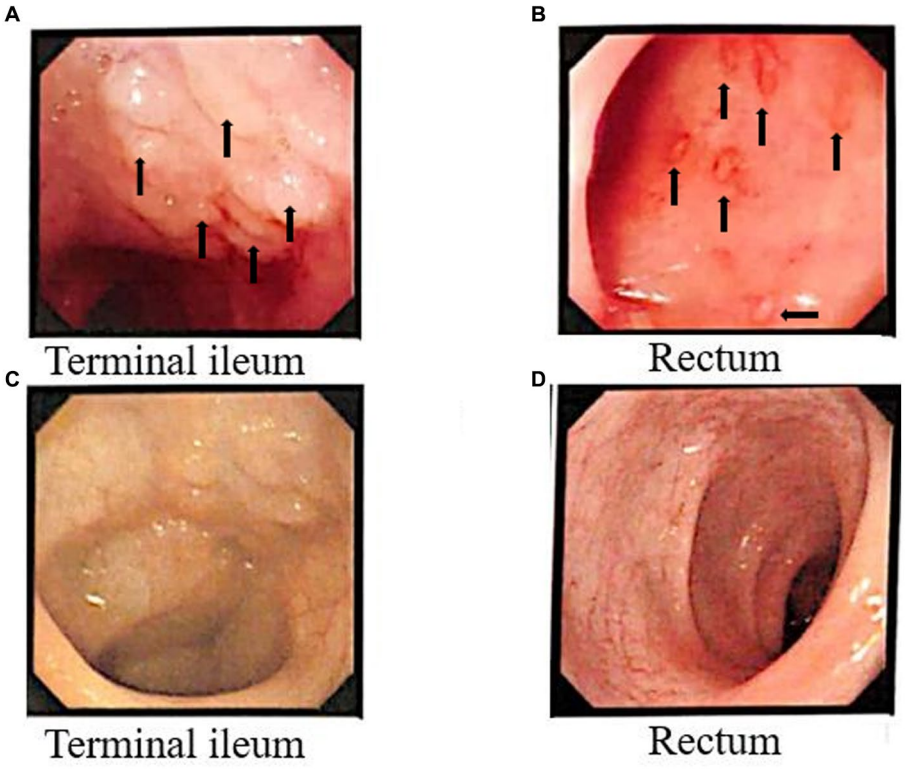

FIGURE 4
Colonoscopy results before and after FMT. Before FMT, the arrows indicate multiple granulomatous changes in the Terminal ileum **(A)**, and in the rectum **(B)** the arrows indicate bleeding sites accompanied by inflammatory changes. Terminal ileum **(C)** and rectal **(D)** surface results after FMT.

(SCFAs) was weak (Table 1), which is important for behavioral development (6). After FMT, the diversity of the flora was significantly improved, as we can see the diversity scores increased from 22 to 92, and the diversity of flora composition was closer to the donor (Figure 6). Surprisingly, the proportion of the Bacteroides was significantly increased, which may be a bacterium that plays an important role (Figure 5). The FMT also improved the production capacity of SCFAs from weak (0%) to normal (20%). In addition, the dietary bias of the children was similar to the donor (Table 1).

4. Discussion and conclusion

This study confirmed that the child with ASD Autism co-exists with GI symptoms and has made significant progress in multiple abilities after FMT treatment. In clinical observation, it could be found that the improvement in eating and defecation appears the earliest, in the intestinal clearing period of antibiotics. At the end of the transplant she could eat out. The change in behavior associated with vancomycin is similar to previous studies, suggesting the

importance of vancomycin in FMT (22). There were some improvements observed in the initial 1–2 treatment round in eye contact, olfactory abnormalities, and partially stereotyped behaviors. Social ability and emotional changes mainly partly appropriate emotional expression. In terms of motor and self-care ability, children can jump on both feet from the one round to the 4–5 treatment round, which is rarely held by their parents, and is more willing to walk or run by herself. In terms of language, she could call her mom from the first round, moving forward to say "Mom, I love you" in the third round. Before each transplant round, the subjects showed no abnormalities in serum, urine, or stool routine tests, with no severe rash, vomiting, diarrhea, abdominal pain, fever, abdominal distension, and emotional problems. Above all, this case report suggests that FMT can improve the social viability of autistic children and improve living quality.

Next, to explore the changes in the flora of children after treatment, Chen et al. found that FMT alleviated behavioral abnormalities and chemokine defects in mouse models of ASD by performing gut microbiota transplantation in a mouse model of ASD induced by maternal immune activation(MIA). In addition, some key unique taxa in the composition of the ASD gut microbiome have also changed (17). FMT from donors of children with autism led to colonization of ASD-like microbiota and autistic behavior. These alterations are closely associated with the expression levels of proinflammatory factors IL-1β, IL-6 in the brain and intestine (23). Elaine et al. (24) using oral treatment of MIA offspring with the human commensal *Bacteroides fragilis* corrects gut permeability, alters the microbial composition, and ameliorates defects in communicative, stereotypic, anxiety-like, and sensorimotor behaviors. Ruminococcus are mucosa-associated bacteria linked with gastrointestinal disease, which have been confirmed that altered in ASD patients (25). In the mice models, bifidobacteria could play a role in the pathogenesis of ASD by modifying the correction of oxidative stress, and restoration of depleted GABA (26). We are pleased to be able to find alterations in these flora in the treatment, unfortunately, the abundance changes may be biased because this case involved only one patient. Those results are consistent with the change in *Bacteroides fragilis* abundance in this case. There is another research that indicates that gut microbiota from individuals with ASD is sufficient to promote altered behaviors in Mice. Furthermore, treating an ASD mouse model with candidate microbial metabolites which includes taurine and 5AV improves behavioral abnormalities and modulates neuronal excitability in the brain (27). Daniel et al. (28) determined that SCFAs, microbial-derived bacterial fermentation products, could regulate microglia homeostasis and play an important role in the onset of autism. In this case, the ability of the microbiota to produce SCFAs, particularly butyric acid, was significantly increased after FMT, which may be an important cause of induced behavior change. This also suggests that behavioral improvement led by SCFAs may be a potential new therapeutic direction in ASD. Significant analysis and discussion were presented by Yap et.al about the relationship between this microbiome and diet,

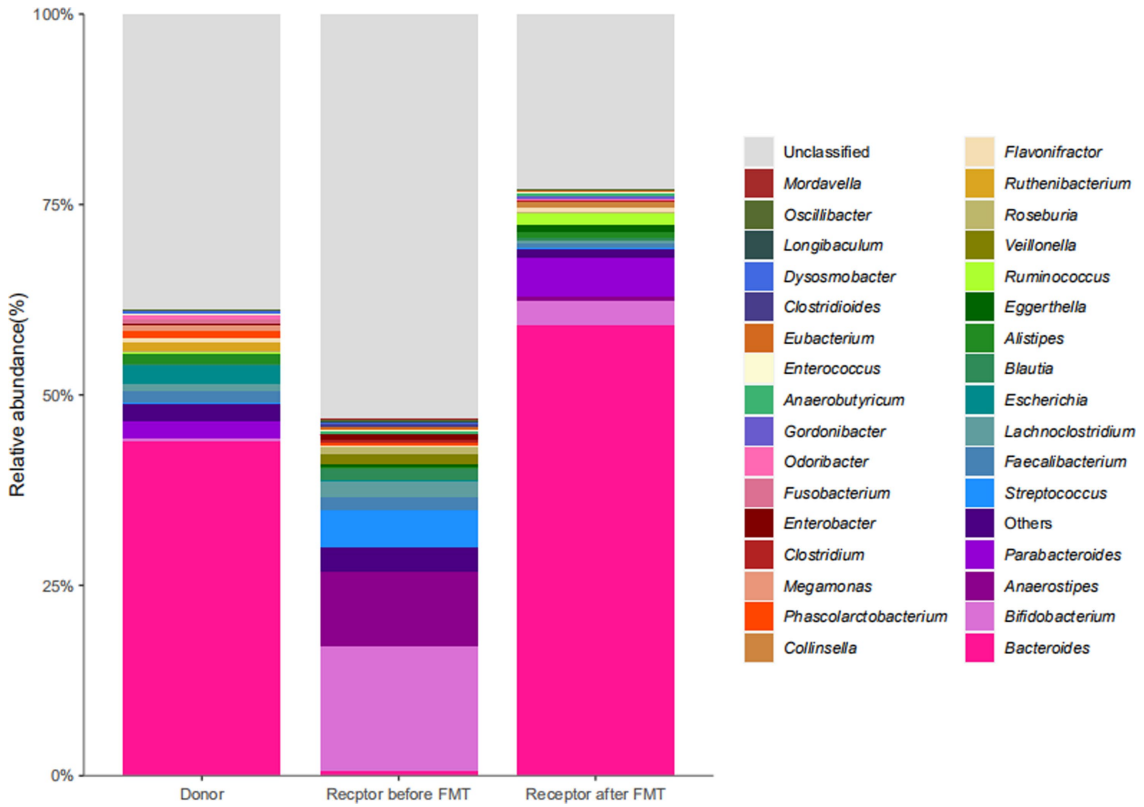

FIGURE 5
Metabolite profiles before and after fecal microbiota transplantation.

TABLE 1 Characteristics of flora and diet.

	Donor	Pre-transplant recipients	Post-transplant recipients
Diversity of flora	High (78 points)	Normal (22 points)	High (92 points)
Production capacity of SCFAs	Normal	Weak	Normal
Production capacity of butyric acid	Normal (35%)	Weak (0%)	Normal (20%)
Dietary bias	High in protein and meat	High fiber	High in protein and meat

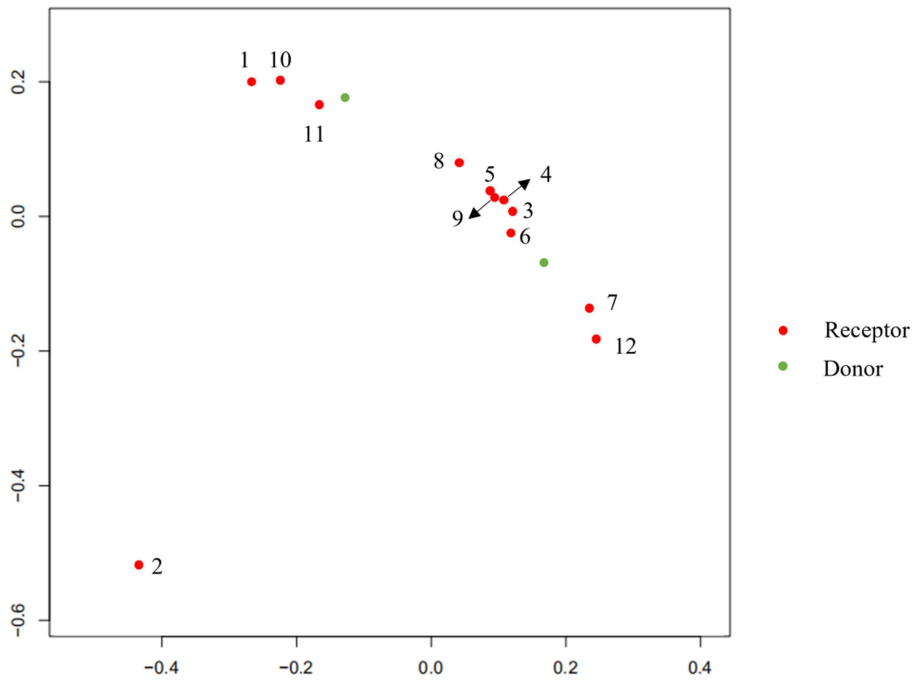

FIGURE 6
PCA analysis at different periods of transplantation in Doner and Receptor.

who hold an idea that microbiome differences in ASD may reflect dietary preferences that relate to diagnostic features (29). Dan et al. revealed some different neurotransmitters which are associated with certain specific bacteria in normal individuals and ASD. The neurotransmitters include serotonin, dopamine, histidine, and GABA which play a critical role in neurological development (30). These substances may pass through the leaky gut and blood–brain barrier, and eventually the effects on the functional brain areas associated with ASD. For example, social cognition of ASD has been shown to be altered in cerebellar gray matter (31). To sum up, factors caused by changes in the flora, such as immunity, metabolites, and neurotransmitters, may collectively influence the etiology of ASD by exacerbating the severity of symptoms.

In conclusion, the treatment effect of this case is very satisfying to patients and doctors, however, there are still some deficiencies and reflections. Firstly, the clinical trials of FMT for ASD are still inadequate, especially, the long-term effects of this treatment have not been adequately clarified. Secondly, FMT offers a new dawn for the treatment of ASD, but the direct contribution of the microbiota to the pathophysiology and behavioral outcomes of ASD still needs to be further explored.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by The Committee of Tongji Medical College of Huazhong University of Science and Technology [(2020) (S290)], approved the study. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal

guardians/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

CoH and TH wrote the first draft of the manuscript and coordinated and supervised data collection. BZ and ZH performed all FMT. JZ, ChH, HL, SS, and YH substantially contributed significantly to the design of the experiment and critically reviewed and revised manuscripts. 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.

Publisher's note

References

1. Battle DE. Diagnostic and statistical manual of mental disorders (DSM). *Codas*. (2013) 25:191–2. doi: 10.1590/s2317-17822013000200017

2. Maenner MJ, Warren Z, Williams AR, Amoakohene E, Bakian AV, Bilder DA, et al. Prevalence and characteristics of autism Spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2020. *MMWR Surveill Summ*. (2023) 72:1–14. doi: 10.15585/mmwr.ss7202a1

3. Lord C, Brugha TS, Charman T, Cusack J, Dumas G, Frazier T, et al. Autism spectrum disorder. *Nat Rev Dis Primers*. (2020) 6:5. doi: 10.1038/s41572-019-0138-4

4. Bai D, Yip B, Windham GC, Sourander A, Francis R, Yoffe R, et al. Association of genetic and environmental factors with autism in a 5-country cohort. *JAMA Psychiat*. (2019) 76:1035–43. doi: 10.1001/jamapsychiatry.2019.1411

5. Hirota T, King BH. Autism Spectrum disorder: a review. *JAMA*. (2023) 329:157–68. doi: 10.1001/jama.2022.23661

6. Abdel-Haq R, Schlachetzki J, Glass CK, Mazmanian SK. Microbiome-microglia connections via the gut-brain axis. *J Exp Med*. (2019) 216:41–59. doi: 10.1084/jem.20180794

7. Horvath K, Perman JA. Autistic disorder and gastrointestinal disease. *Curr Opin Pediatr*. (2002) 14:583–7. doi: 10.1097/00008480-200210000-00004

8. Adams JB, Audhya T, McDonough-Means S, Rubin RA, Quig D, Geis E, et al. Nutritional and metabolic status of children with autism vs. neurotypical children, and the association with autism severity. *Nutr Metab (Lond)*. (2011) 8:34. doi: 10.1186/1743-7075-8-34

9. Davoli-Ferreira M, Thomson CA, McCoy KD. Microbiota and microglia interactions in ASD. *Front Immunol*. (2021) 12:676255. doi: 10.3389/fimmu.2021.676255

10. Wang Y, Kasper LH. The role of microbiome in central nervous system disorders. *Brain Behav Immun*. (2014) 38:1–12. doi: 10.1016/j.bbi.2013.12.015

11. Sorboni SG, Moghaddam HS, Jafarzadeh-Esfehani R, Soleimanpour S. A comprehensive review on the role of the gut microbiome in human neurological disorders. *Clin Microbiol Rev*. (2022) 35:e0033820. doi: 10.1128/CMR.00338-20

12. Finegold SM, Molitoris D, Song Y, Liu C, Vaisanen ML, Bolte E, et al. Gastrointestinal microflora studies in late-onset autism. *Clin Infect Dis*. (2002) 35:S6–S16. doi: 10.1086/341914

13. Li N, Chen H, Cheng Y, Xu F, Ruan G, Ying S, et al. Fecal microbiota transplantation relieves gastrointestinal and autism symptoms by improving the gut microbiota in an open-label study. *Front Cell Infect Microbiol*. (2021) 11:759435. doi: 10.3389/fcimb.2021.759435

14. Kang DW, Adams JB, Gregory AC, Borody T, Chittick L, Fasano A, et al. Microbiota transfer therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study. *Microbiome*. (2017) 5:10. doi: 10.1186/s40168-016-0225-7

15. Liu YW, Liong MT, Chung YE, Huang HY, Peng WS, Cheng YF, et al. Effects of *Lactobacillus plantarum* PS128 on children with autism Spectrum disorder in Taiwan: a randomized, double-blind, placebo-controlled trial. *Nutrients*. (2019) 11:820. doi: 10.3390/nu11040820

16. Wang Y, Li N, Yang JJ, Zhao DM, Chen B, Zhang GQ, et al. Probiotics and fructo-oligosaccharide intervention modulate the microbiota-gut brain axis to improve autism spectrum reducing also the hyper-serotonergic state and the dopamine metabolism disorder. *Pharmacol Res*. (2020) 157:104784. doi: 10.1016/j.phrs.2020.104784

17. Chen K, Fu Y, Wang Y, Liao L, Xu H, Zhang A, et al. Therapeutic effects of the in vitro cultured human gut microbiota as transplants on altering gut microbiota and improving symptoms associated with autism Spectrum disorder. *Microb Ecol*. (2020) 80:475–86. doi: 10.1007/s00248-020-01494-w

18. Adams JB, Borody TJ, Kang DW, Khoruts A, Krajmalnik-Brown R, Sadowsky MJ. Microbiota transplant therapy and autism: lessons for the clinic. *Expert Rev Gastroenterol Hepatol*. (2019) 13:1033–7. doi: 10.1080/17474124.2019.1687293

19. Kelly CR, Kahn S, Kashyap P, Laine L, Rubin D, Atreja A, et al. Update on fecal microbiota transplantation 2015: indications, methodologies, mechanisms, and outlook. *Gastroenterology*. (2015) 149:223–37. doi: 10.1053/j.gastro.2015.05.008

20. Magiati I, Moss J, Yates R, Charman T, Howlin P. Is the autism treatment evaluation checklist a useful tool for monitoring progress in children with autism spectrum disorders. *J Intellect Disabil Res*. (2011) 55:302–12. doi: 10.1111/j.1365-2788.2010.01359.x

21. Chen S, Zhao J, Hu X, Tang L, Li J, Wu D, et al. Children neuropsychological and behavioral scale-revision 2016 in the early detection of autism spectrum disorder. *Front Psychol*. (2022) 13:893226. doi: 10.3389/fpsyt.2022.893226

22. Sandler RH, Finegold SM, Bolte ER, Buchanan CP, Maxwell AP, Väisänen ML, et al. Short-term benefit from oral vancomycin treatment of regressive-onset autism. *J Child Neurol*. (2000) 15:429–35. doi: 10.1177/088307380001500701

23. Avolio E, Olivito I, Rosina E, Romano L, Angelone T, De Bartolo A, et al. Modifications of behavior and inflammation in mice following transplant with fecal microbiota from children with autism. *Neuroscience*. (2022) 498:174–89. doi: 10.1016/j.neuroscience.2022.06.038

24. Hsiao EY, McBride SW, Hsien S, Sharon G, Hyde ER, McCue T, et al. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cells*. (2013) 155:1451–63. doi: 10.1016/j.cell.2013.11.024

25. Wang L, Christophersen CT, Sorich MJ, Gerber JP, Angley MT, Conlon MA. Increased abundance of Sutterella spp. and Ruminococcus torques in feces of children with autism spectrum disorder, Mol. *Autism*. (2013) 4:42. doi: 10.1186/2040-2392-4-42

26. Bin-Khattaf RM, Alonazi MA, Al-Dbass AM, Almnaizel AT, Aloudah HS, Soliman DA, et al. Probiotic ameliorating effects of altered GABA/glutamate signaling in a rodent model of autism. *Meta*. (2022) 12:720. doi: 10.3390/metabo12080720

27. Sharon G, Cruz NJ, Kang DW, Gandal MJ, Wang B, Kim YM, et al. Human gut microbiota from autism Spectrum disorder promote behavioral symptoms in mice. *Cells*. (2019) 177:1600–1618.e17. doi: 10.1016/j.cell.2019.05.004

28. Erny D, Hrabě de Angelis AL, Jaitin D, Wieghofer P, Staszewski O, David E, et al. Host microbiota constantly control maturation and function of microglia in the CNS. *Nat Neurosci*. (2015) 18:965–77. doi: 10.1038/nn.4030

29. Yap CX, Henders AK, Alvares GA, Wood DLA, Krause L, Tyson GW, et al. Autism-related dietary preferences mediate autism-gut microbiome associations. *Cells*. (2021) 184:5916–5931.e17. doi: 10.1016/j.cell.2021.10.015

30. Dan Z, Mao X, Liu Q, Guo M, Zhuang Y, Liu Z, et al. Altered gut microbial profile is associated with abnormal metabolism activity of autism Spectrum disorder. *Gut Microbes*. (2020) 11:1246–67. doi: 10.1080/19490976.2020.1747329

31. Olivito G, Siciliano L, Clausi S, Lupo M, Baiocco R, Gragnani A, et al. The cerebellum gets social: evidence from an exploratory study of cerebellar. *Neurodev Psychiatr Disord Biomed*. (2023) 11:309. doi: 10.3390/biomedicines11020309

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EDITED BY
Juehua Yu,
The First Affiliated Hospital of Kunming Medical University, China

REVIEWED BY
Beibei Wu,
University of California, Los Angeles, United States
Jian Zhou,
Baylor College of Medicine, United States

*CORRESPONDENCE
Amy Offutt
✉ droffutt@amyoffuttmd.com

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Case report: Substantial improvement of autism spectrum disorder in a child with learning disabilities in conjunction with treatment for poly-microbial vector borne infections

Amy Offutt[1]* and Edward B. Breitschwerdt[2]

[1]Heart and Soul Integrative Health, Marble Falls, TX, United States, [2]Intracellular Pathogens Research Laboratory, Department of Clinical Sciences, and the Comparative Medicine Institute, College of Veterinary Medicine, North Carolina State University, Raleigh, NC, United States

Poly-microbial vector-borne infections may have contributed to neuropsychiatric symptoms in a boy diagnosed with autism spectrum disorder. Targeted antimicrobial treatment resulted in substantial improvement in cognitive (such as learning disabilities, focus, concentration) and neurobehavioral (such as oppositional, defiant, anti-social, disordered mood, immaturity, tics) symptoms.

KEYWORDS

tics, infections, *Bartonella*, Lyme, PANS, OCD, autism, ADHD

Introduction

Autism, or autism spectrum disorder (ASD), is a common and increasingly diagnosed entity among children in the United States (1). This complex neurodevelopmental disorder manifests with atypical social communication skills, and interactions consisting of restrictive, repetitive patterns of behavior. CDC's MMWR data reports an ASD prevalence of 1 in 36 children in 2020 in the United States (2). Ratajczak proposed that this disorder is a consequence of genetic defects, with or without inflammation of the brain (3). Based upon the diverse and wide range of clinical histories in these children, he also postulated that inflammation could be the result of placental defects, blood–brain barrier immaturity, an abnormal maternal immune response *in utero*, prematurity, encephalitis, or toxic environmental exposures (3).

Considering the medical complexity associated with the wide array of clinical presentations, there is a substantial need for additional research into the causes of ASD neuropsychiatric conditions. A case published in 2019 reported significant improvement in a 14-year-old boy diagnosed with Pediatric Acute Onset Neuropsychiatric Symptoms (PANS), who was treated for infection with *Bartonella henselae* (4). Antimicrobial treatments directed at this bacterial pathogen resulted in a gradual return to baseline activities, resolution of his Bartonella-associated cutaneous lesions, and discontinuation of all psychiatric medications. We now describe a case involving a boy with developmental delays from an early age that was presumed to be associated with a congenital brain anomaly. Shifts in the constellation of his symptoms resulted in a high level of clinical suspicion for potential underlying infectious etiologies (5). In conjunction with the administration of antimicrobial therapy, the boy experienced a positive clinical response, including being moved from a long-term special education classroom setting

to an age appropriate and grade level general classroom setting, based on standardized testing and school performance, in conjunction with dramatic improvement in cognitive functions, and ultimately acceptance to a 4-year college. In addition to these cognitive improvements, several other non-cognitive symptoms also significantly improved. This case report provides further support to the growing body of literature indicating that infectious triggers may contribute to neuropsychiatric disorders, including those in children who phenotypically present as academically challenged, or meet the criteria for autism spectrum disorder.

Background

A 14 year-old boy was examined at the request of his mother, who accompanied him to the appointment. She provided a detailed medical, developmental, and educational history. During this initial visit, his mother reported that their entire family had been challenged for many years by her son's neuropsychiatric issues that included a diagnosis of autism spectrum disorder. This patient's mother had taken him to several other physicians seeking an explanation for the fluctuating nature of his neuropsychiatric symptoms. Before his birth, *in utero* ultrasound showed cerebellar hypoplasia, for which prognostically his future neurological function was unknown. At 6-months of age, the boy developed a neck-roll-like tic; at 8 months he began to crawl; and at 10 months fell down the stairs but did not sustain any injuries. He had some developmental delays, including first walking at 18 months of age. He struggled to fall asleep at night, and developed unusual behaviors, including atypical physical movements (flapping, falling out of chairs, requiring assistance with coordinated movements involving heights like navigating open stairs). When he was noted to have impulsivity and learning difficulties, attention deficit hyperactivity disorder (ADHD) was diagnosed at 5 years of age, after which he was given educational accommodations in school. Although his mother reported that she believed that he could have received a diagnosis of autism by the usual criteria, the description used to acquire educational accommodations was described by those evaluating him in his elementary school years as "other impairments." However, the mother did not advocate strongly for a diagnosis of autism at that time because her son was already getting accommodations. As he grew older, swimming, riding a bike, and playing catch were very difficult activities, but were marginally achieved. He was diagnosed with pediatric acute onset neuropsychiatric syndrome at age 10. In June 2019, at 14 years of age, he was diagnosed as autistic and a pediatric neurologist (Children's Medical Center of Dallas, Dallas TX) also diagnosed autoimmune encephalitis. On Module 4 of the ADOS-2 administered by his school in 2019, the patient's communication score was 9 and his reciprocal social interaction score was 8, for a combined score of 17, which meets the ADOS-2 classification of Autism. The Autism Diagnostic Observation Schedule, Second Edition (ADOS-2), Module 4 is considered a "gold-standard" instrument for diagnosing autism spectrum disorder (ASD). Although ADOS-2 screening has a high degree of sensitivity, it also has low specificity due to a high rate of false positives among adults with psychosis. (6). Following approval of insurance coverage, he was treated with intravenous immunoglobulin in November 2019, after which his mother reported improvement in most of his symptoms. However, in January 2020, behavioral challenges increased, including the boy running away from home.

When this patient was presented to our practice (AO), his mother reported multiple symptoms, both past and present. The mother had maintained detailed notes about his day-to-day mental, physical and emotional status, including how he responded to various medical and behavioral interventions. She reported that the boy would have a flare of various behavioral issues during times when antibiotics were administered for streptococcal pharyngitis and borreliosis. During his 14-year history, multiple therapeutics and lifestyle interventions had been attempted to manage his symptoms, including, among others, amantadine, doxycycline, minocycline, amoxicillin, amoxicillin/clavulanate, clindamycin, IV ozone, gluten-free diet and a dairy-free diet. Following the introduction of a drug, most therapeutics, particularly antibiotics, were quickly discontinued due to intolerable side effects and flaring of behavioral symptoms.

Reading comprehension testing was low, placing him in special education with accommodations. His mother reported that he had recently failed the STAAR test, which is state-wide standardized testing administered by his school district. His social skills had continued to regress and he had developed an affinity for constantly playing video games. Defiant behavior had increased. His mother noticed that he had an increased craving for sugar and that eating foods that contain refined sugar seemed to make his symptoms even more intense. Obsessive and compulsive symptoms, which were part of his pediatric acute-onset neuropsychiatric syndrome, were quite prominent. His habit of eating a wide variety of foods when younger had transitioned to a state of food aversions and "picky" eating. Based upon vision assessment, prism lenses had been recommended, but he refused to wear glasses.

The mother also reported that his behavior tended to improve when he was given ibuprofen, administered most afternoons. He was currently taking hydroxyzine to help with sleep initiation, but he stated that he did not have trouble sleeping. He indicated that he was annoyed with his mother and felt depressed when she would not let him eat dairy foods. He had multiple episodes prior to and after the presentation during which he had behavioral outbursts and ran away from home multiple times. Child protective services were even brought in during one of these episodes because he made false claims after a running away incident. His mother was also quite concerned about his nutrition and low weight, just over 100 pounds. Historically, the patient did not have a known tick bite or any other specific environmental exposures, even though he lived in a midwestern state where vector-borne diseases are common.

From birth, his mother had chronic inflammatory symptoms that prompted her to suspect the possibility of a congenital infection. His mother's symptoms included childhood onset anxiety, bedwetting, emotional lability, dysautonomia, migraine headaches, joint pains, numbness in her digits, Graves' disease at 32 years old, and a 6-month eating disorder as a teenager. She had multiple tick bites around ages 7 to 8, but she believed that she had been exposed even earlier based on her family's recollection of her childhood behaviors. She noted that she was having problems with mood and anxiety as early as age 3.

The boy's historical symptoms, up to the time of presentation, are summarized in a graphic timeline (Figure 1).

Physical examination findings at initial presentation

Vital Signs: Blood Pressure (R arm): 100/62.
Weight: 101.6lbs.

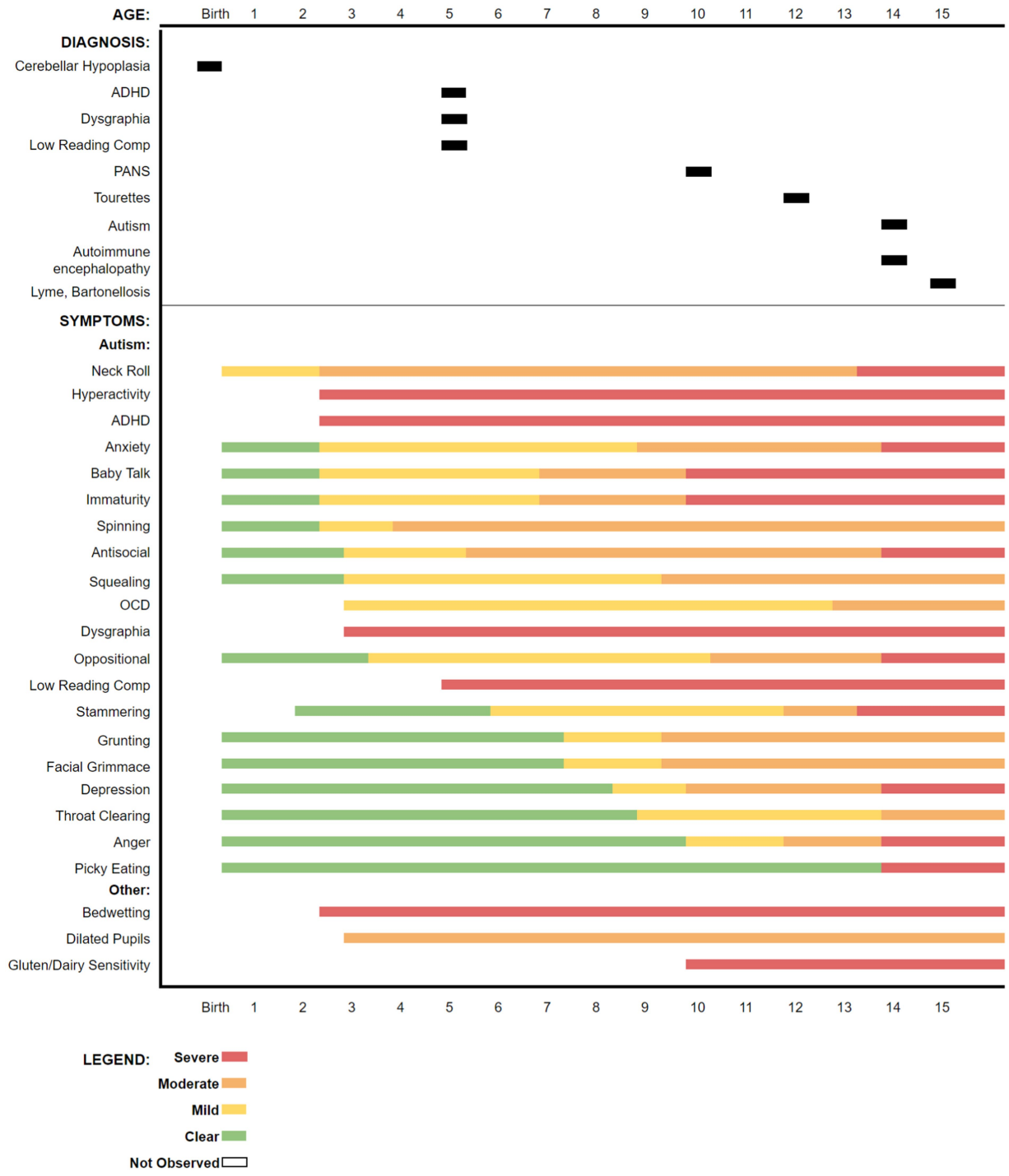

FIGURE 1
Timeline for diagnoses and symptom onset over the child's lifetime as reported by the mother up to the time of initiating treatment for borreliosis at 15 years-old, approximately 9 months after presentation. Some symptoms were not recognized by the parents until the boy attended school.

Pertinent Findings: Generally thin habitus. The neuropsychiatric exam revealed slow, somewhat irregular speech cadence, frequently interruptive during conversation, diffuse, mildly reduced neuromuscular tone noted with gait generally intact, slightly depressed mood (negative outlook). Cardiovascular, pulmonary, and dermatologic exams were unremarkable.

Patient laboratory data

Upon presentation, detailed medical records, including laboratory reports, were reviewed. Autoimmune, genetic, immunological, infectious disease, nutritional, and research testing results (7) are summarized in Table 1 in association with

TABLE 1 Laboratory report results, reference ranges, and laboratory interpretation extracted from patient records and research testing.

Age 10:
IGeneX Laboratory:
Borrelia burgdorferi, IFA titer= 1:40 (reference range <40 negative, 40 equivocal, >=80 positive)
Borrelia burgdorferi IgG and IgM = negative
Bartonella henselae IgG and IgM = negative
Babesia microti IgM = negative, IgG = 1: 40 (may or may not suggest active infection)
Babesia duncani IgG / IgM = negative
Babesia FISH = negative
Cunningham Panel, (Moleculera Laboratory):
Anti-tubulin = 1000 (upper limit of normal range, 0 - 1000)
Four other measured parameters were within normal limits.
LabCorp:
Anti-DNase B Strep Antibodies = 1020 U/ml (reference range 0 - 170)
Antistreptolysin O Antibodies - 620.8 IU/ml (reference range 0 - 200)
Beta Strep Gp A Culture = negative
Nutritional deficiencies = thiamin, riboflavin, magnesium
Comprehensive Stool Profile = Dientamoeba fragilis, dysbiosis
Multiple IgE elevations - cat dander, dog dander, shrimp, cockroach
Elevated IgG subclass 4 (164, range 1 - 121)
MTHFR C677T single mutation
Age 14:
Mayo Clinic Laboratories:
Autoimmune Encephalopathy, GAD65 Ab, Assay, S: 0.14 nmol/L (reference range <=0.02)
Age 16 (after treatment with disulfiram, minocycline, and rifampin):
Vibrant America Lab *Borrelia burgdorferi* and *Bartonella henselae* testing
VlsE1 IgM elevated (IgG normal)
C6 peptide = IgM elevated (IgG normal)
p18 (DpbB) = IgM elevated
P45 = IgG elevated
Crude extract B31 = IgM elevated
Crude extract 297 = IgM elevated
Overall laboratory interpretation for Lyme disease serological testing: NEGATIVE
• *Borrelia afzelli* BmpA = IgG elevated
• *Borrelia garinii* DbpA = IgG elevated
• *Borrelia spielmanii* DbpA = IgM elevated
• *Bartonella henselae* SucB = IgG elevated
Age 17:
In August 2022, the patient and his mother entered a research study entitled Detection of *Bartonella* Species in the Blood of Healthy and Sick People (North Carolina State University [NCSU] Institutional Review Board approval, IRB 1960). Both study participants provided three blood and serum collections, obtained on alternate days, and gave permission for testing for *Babesia, Bartonella* and *Borrelia* species. Previously described serology and enrichment blood culture qPCR and droplet digital PCR (ddPCR) assays were used for testing (7).
Research Testing, (North Carolina State University Intracellular Pathogens Research Laboratory). *Bartonella* IFA serology: Patient
• *Bartonella vinsonii* subsp. *berkhoffii* Genotype I < 1:16
• *Bartonella vinsonii* subsp. *berkhoffii* Genotype II < 1:16
• *Bartonella henselae* < 1:16
• *Bartonella koelerae* < 1:16
• *Bartonella quintana* < 1:16

(Continued)

TABLE 1 (Continued)

Patient's mother

- *Bartonella vinsonii* subsp. *berkhoffii* Genotype I < 1:16
- *Bartonella vinsonii* subsp. *berkhoffii* Genotype II < 1:16
- *Bartonella henselae* < 1:16
- *Bartonella koelerae* < 1:16
- *Bartonella quintana* < 1:16

Interpretation: Patient and patient's mother seronegative to all five IFA antigens

qPCR and ddPCR testing was performed on blood, serum, 7, 14, and 21-day enrichment blood culture samples (24 independent DNA extractions per individual tested) for the patient and patient's mother.

qPCR and Droplet Digital PCR (ddPCR) Testing Results:

Patient

- qPCR
  - *Babesia* = Negative
  - *Bartonella* = Negative
  - *Borrelia* = Negative
- ddPCR
  - *Babesia* = Negative
  - *Bartonella* = *Bartonella quintana* (DNA amplified and sequenced from a 21-day enrichment blood culture
  - *Borrelia* = one ddPCR+ droplet in 4/24 samples tested, unable to confirm by DNA sequencing

Patient's mother

- qPCR
  - *Babesia* = Negative
  - *Bartonella* = Negative
  - *Borrelia* = Negative
- ddPCR
  - *Babesia* = Negative
  - *Bartonella* = *Bartonella koehlerae* (DNA amplified and sequenced from a 21-day enrichment blood culture
  - *Borrelia* = one ddPCR+ droplet in 3/24 samples tested, unable to confirm by DNA sequencing

the time of testing, including the interpretation provided by the testing laboratory.

In summary, prior to presentation to our practice, this 14-year-old boy had been diagnosed with cerebellar hypoplasia (*in utero*), ADHD (onset age 5 years), PANS (onset during elementary school, but not officially diagnosed until 10 years-old), autism (symptoms onset during elementary school, but not officially diagnosed until 14 years-old), and autoimmune encephalopathy (diagnosed at age 14 years). After our medical evaluation, partially treated Lyme disease (borreliosis), with chronic neurocognitive effects, and congenital systemic bartonellosis were tentatively diagnosed.

Assessment and treatment plan

Based upon the boy's historical symptoms, prior laboratory testing results, and previous intolerance to multiple therapeutics, treatment initially targeted borreliosis and then bartonellosis. Disulfiram was initiated because the drug had not been tried previously, had somewhat predictable and manageable side effects, and prior therapeutic agents had not been well tolerated. Also, recent *in vitro* data and patient studies supported the potential efficacy of disulfiram for treating borreliosis (8–17). A graphic representation of symptom tracking in conjunction with the administration of disulfiram and the other subsequently administered antibiotics is provided in Figure 2. As was done prior to antibiotic administration, symptoms, carefully monitored and documented in writing by his mother, were used to generate figures for both pre-and post-antibiotic treatment periods.

During treatment, certain interventions including changes in antibiotics, resulted in abrupt or, sometimes, more gradual changes in symptoms. As the patient's symptoms would plateau, a transition to a new therapeutic regimen was implemented, gradually administering individual or combinations of multiple different antimicrobial agents, including disulfiram, rifampin, minocycline, rifabutin, clarithromycin, and methylene blue (18–20). Supportive measures including probiotics, antioxidants, and anti-inflammatories were administered throughout the course of care. Again, patient responses during the time course of treatment are summarized in the bar graph (Figure 2).

Treatment outcome

This patient had a cadre of symptoms documented by his mother with all being present to some extent just prior to or at the time of initiation of antibiotic treatment. Oppositional behavior and anger improved almost immediately after the initiation of disulfiram and

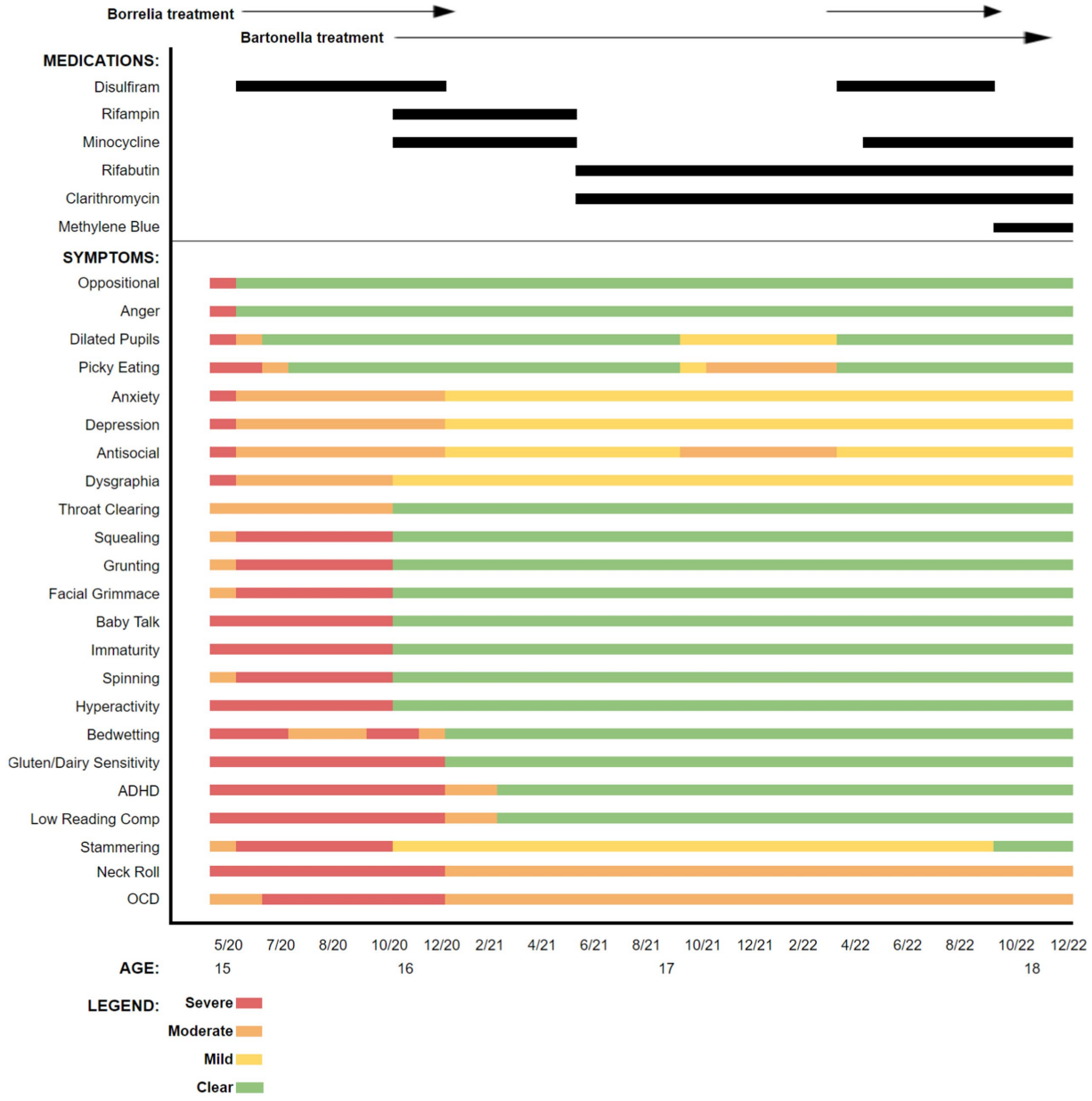

FIGURE 2
Symptoms reported at the time of presentation to our practice and following initiation of each antibiotic or antibiotic combination. Symptoms and clinical signs were assessed by the mother as mild, moderate, severe, or cleared.

these symptoms remained clear throughout the treatment period. Other symptoms initially persisted but lessened in severity. Still other symptoms, including squealing, grunting, grimacing, and stammering worsened when disulfiram was introduced. However, because of noticeable improvement in some of the other symptoms, antibiotics were continued despite the worsening of other symptoms. As is demonstrated in the graphic representation, several antimicrobials were selected, and some were only utilized once, while others were initiated, discontinued, and reinstated, based on clinical responses. Shortly after treatment was initiated, the patient's appetite improved resulting in a 35 pound weight gain over the first 6 months, potentially addressing prior concerns about his overall nutritional status.

As of December 2022, many of the boy's chronic symptoms had resolved or improved. One of the most noticeable improvements by his parents, his teachers, and school administrative staff was that his academic testing transitioned from the special education level to tenth grade level, as he no longer required the special accommodations that had been provided at his school. His IQ testing increased by 7 points and his English STAAR testing scores increased by 27 percentage points, placing him in the 46th percentile for 10th grade (Table 2). Also, after initiation of antimicrobial drug administration in June 2020, he experienced substantial improvement in structured educational testing scores for reading and mathematics (Table 2). With these significant improvements, his special education placement ended, and he transitioned to a regular classroom setting where he was able to maintain adequate academic performance through high school graduation. In addition, there was a sudden and noted improvement in his social skills, progress that had not been noted by school officials since kindergarten. He has been able to take a college entrance examination resulting in acceptance to a 4-year university.

TABLE 2 Results of academic assessments included structured IQ testing administered by the school neuropsychologist, as well as standardized educational assessments. After antimicrobials were administered to treat Bartonellosis and Borreliosis, based upon WISC testing, the patient's IQ rose 7 points between 2012 and 2021. NOTE: The higher KABC II NU score in 2016 should not be directly compared to the WISC and WAIS testing scores due to the difference in testing approach. The KABC II NU testing methodology differs by measuring intelligence without the Short-term Memory and Processing Speed components that are often depressed in students with autism, ADHD, or emotional disturbances. Results of standardized educational assessments for reading and mathematics for grades 3 through 11 show an increase in English performance by 27 percentage points and an increase in math performance by 9 percentage points after treatment. Antimicrobial drug administration was initiated in June 2020.

IQ SCORES				
WISC IV* 2012 (2nd grade)	KABC II NU** 2016 (6th grade)	WISC V/ CTOPP for Auditory Processing*** 2018 (8th grade)	WAIS IV**** 2021 (11th grade)	
88	97	89	95	
STRUCTURED EDUCATIONAL ASSESSMENTS				
	ENGLISH		MATH	
Grade (Year)	Percentile	Comments	Percentile	Comments
Missouri Assessment Program (MAP)				
3rd (2014)		Basic		Basic
4th (2015)		Below Basic		Basic
5th (2016)		Below Basic		Below Basic
6th (2017)		Basic		Basic
7th (2018)		Basic		Proficient
Texas STAAR Assessment				
8th (2019)	19	Did not meet grade level	49	Approaches grade level
10th (2021)	46	Approaches grade level		*Not administered*
Measures of Academic Performance (MAP)				
11th (2022)		*Not administered*	58	Grade level

*WISC: Wechsler Intelligence Scale for Children.
**KABC II NU: Kaufman Assessment Battery for Children 2 Normative Update.
***WISC V/ CTOPP for Auditory Processing: Wechsler Intelligence Scale for Children V/Comprehensive Test of Phonological Processing.
****WAIS: Wechsler Adult Intelligence Scale.
Below Basic: Does not show understanding of the content expected at this grade level.
Basic: Demonstrates a partial understanding of the content expected at this grade level.
Proficient: Demonstrates understanding of the content expected at this grade level.

This accomplishment was not something that his family or educators would have anticipated before May of 2020.

As of December 2022, the patient has maintained improvements as noted in the symptom timeline, but he is unable to discontinue antimicrobials without a noticeable recurrence of several of his symptoms. This affects his quality of life significantly, and therefore, we have opted to continue antimicrobial coverage while considering additional strategies.

Discussion

Autism spectrum disorders are increasing in prevalence and are negatively impactful on many families and individual communities throughout the United States. The CDC estimates that 1 in 36 children in the United States were diagnosed with an autism spectrum disorder in 2020 (2). The estimated annual cost for children's autism spectrum disorder care is between $61 and $66 billion, while the annual adult services cost is estimated to be between $175 and $196 billion (21). A strategic therapeutic approach that significantly addresses the burdens placed on these families, their communities and society in general has been elusive. Despite substantial research efforts and an ever-increasing need to better understand the cause(s) of ASD, effective therapeutic interventions have focused on modifying or controlling abnormal behaviors. With the current medical philosophy that these disorders are largely caused by genetic abnormalities, the extent to which infectious agents might be contributory has been minimally explored on a clinical or research basis. It stands to reason that exposure to infectious agents or neurotoxins, either *in utero* or later during the early developmental years, might result in mutations or alternatively impact disease expression in genetically predisposed individuals. Agents that induce persistent, stealth intravascular or central nervous system infections would potentially negate the effectiveness of symptomatic therapies.

This patient had a well-defined embryonic abnormality diagnosed *in utero*, clearly complicating the developmental assessment of his physical and mental capabilities. Based upon symptomatology he was diagnosed and treated medically for over a decade as an "impaired" child, up to the time of our initial evaluation. Test results in this patient supported exposure to one or more vector borne pathogens, a serological diagnosis of bartonellosis and borreliosis, and the borderline presence of anti-neuronal antibodies, which can occur in association with vector borne and other non-vector borne infections (22). Therefore, a decision was made to treat with antimicrobial agents targeting a potential infectious etiology, with secondary auto-antibody formation. His response to this therapeutic approach included improvement or elimination of a substantial number of neuropsychiatric symptoms and significant improvement in his academic status, placing

him at grade level without accommodations and eligible for more advanced educational planning. Lacking the benefit of clinical trials or previously defined treatment protocols, antibiotics targeting two vector borne genera were administered for an extended period, while carefully monitoring various symptomatic responses and safety parameters. Despite having stable or progressive symptoms for potentially his entire life, the response to treatment suggested that neither the cerebellar hypoplasia, inherited genetic defects, or autoimmunity were singularly causative. Strikingly, normalization of some symptoms supported the possibility that there had been no permanent CNS damage, although the onset and duration of the putative infections remains unknown. Although very much incompletely studied, perinatal transmission of both *Bartonella* and *Borrelia* species have been suspected (23, 24). Ongoing antimicrobial coverage was required at the time of writing this case report due to recurrence of all symptoms to one degree or another with the exception of oppositional behavior and anger with discontinuation, potentially related to ongoing infection with Borrelia and *Bartonella quintana*. Treatments with single or combinations of several antimicrobial drugs were accompanied by substantial improvements in neurological symptoms; however, research testing in August, 2022, documented the presence of *B. quintana* and potentially Borrelia spp. DNA in blood and enrichment blood cultures by ddPCR and qPCR/DNA sequencing testing in the patient and his mother. Our interpretation is that the treatments utilized suppressed, but did not eliminate these infections in the patient, indicating the need for future studies that use sequential testing with advanced direct detection modalities to assess treatment response. Nonetheless, until further documented efficacious therapeutic options are available, and with close monitoring for safety and tolerability, benefits from improved quality of life outweigh the risks of long-term antibiotic administration.

We propose that a risk/benefit analysis in most patients diagnosed with autism spectrum disorder would warrant evaluation and treatment for potential chronic infectious triggers. Incorporation of diagnostic modalities that detect pathogen antigens or DNA will allow for increased support for a causative role for specific organisms in association with patient symptoms. More research is obviously needed, but if this type of clinical and microbiological approach were to be further explored, the result could dramatically impact future clinical practice. Documenting the presence of an infectious etiology in blood or cerebrospinal fluid could provide an even more meaningful, positive impact in the lives of so many who are suffering with limited therapeutic options. The fact that this patient was treated as a teen also indicates that these infections may persist, well beyond any acute exposures, or occurring *in utero*, or during the perinatal period. Therefore, treating earlier in life may result in improvements in academic performance, improved social development, and a better chance at full adult independence, which would represent a significantly altered outcome for many people. Currently, borreliosis and bartonellosis are infections that are rarely considered in the evaluation and treatment of patients with neuropsychiatric presentations, but this case and others point to the possibility that chronic persistent infections may contribute to the presence and severity of symptoms in children and young adults with neuropsychiatric symptoms. Although an autoimmune or immunomodulatory component is suspected, more research is clearly needed to further delineate if it is the infection itself or the secondary immune consequences of the infection that may contribute to this phenotypic presentation of neuropsychiatric disease.

Conclusion

This teenage boy had a drastic improvement in his neuropsychiatric symptoms and in his academic standing, moving from special education services with accommodations to grade level academic standing without accommodations, to college acceptance. Progressive symptomatic improvement occurred only following targeted administration of antimicrobial agents directed at suspected, underlying, chronic infectious pathogens, namely the causative agents of bartonellosis and borreliosis. Further research is clearly needed to define if or the extent to which occult infections can contribute to neuropsychiatric illness, such as ASD.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The patient and his parents provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Research testing at North Carolina State University was conducted as a component of a study entitled: Detection of *Bartonella* Species in the Blood of Healthy and Sick People (NCSU Institutional Review Board approval, IRB 1960).

Author contributions

AO was the primary physician providing medical care, was in charge of the diagnostic testing, therapy plan, patient follow-up, and drafted the manuscript. EB conducted further microbial diagnostic testing on the patient and co-wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

AO was employed by Heart and Soul Integrative Health.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Hyman SL, Levy SE, Myers SM. Identification, evaluation, and management of children with autism spectrum disorder. *Pediatrics*. (2020) 145:e20193447. doi: 10.1542/peds.2019-3447

2. Maenner MJ, Warren Z, Williams AR, Amoakohene E, Bakian AV, Bilder DA, et al. Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States. *MMWR Surveill Summ*. (2020) 72:1–14. doi: 10.15585/mmwr.ss7202a1

3. Ratajczak HV. Theoretical aspects of autism: causes--a review. *J Immunotoxicol*. (2011) 8:68–79. doi: 10.3109/1547691X.2010.545086

4. Breitschwerdt EB, Greenberg R, Maggi RG, Mozayeni BR, Lewis A, Bradley JM. *Bartonella henselae* Bloodstream Infection in a Boy With Pediatric Acute-Onset Neuropsychiatric Syndrome. *J Cent Nerv Syst Dis*. (2019) 11:1179573519832014. doi: 10.1177/1179573519832014

5. Bransfield RC, Kuhn M. Autism and Lyme Disease. *JAMA*. (2013) 310:856–7. doi: 10.1001/jama.2013.194747

6. Maddox BB, Brodkin ES, Calkins ME, Shea K, Mullan K, Hostager J, et al. The Accuracy of the ADOS-2 in Identifying Autism among Adults with Complex Psychiatric Conditions. *J Autism Dev Disord*. (2017) 47:2703–9. doi: 10.1007/s10803-017-3188-z

7. Maggi R, Breitschwerdt EB, Qurollo B, Miller JC. Development of a Multiplex Droplet Digital PCR Assay for the Detection of Babesia, Bartonella, and Borrelia Species. *Pathogens*. (2021) 10:1462. doi: 10.3390/pathogens10111462

8. Alvarez-Manzo HS, Zhang Y, Shi W, Zhang Y. Evaluation of Disulfiram Drug Combinations and Identification of Other More Effective Combinations against Stationary Phase *Borrelia burgdorferi*. *Antibiotics*. (2020) 9:542. doi: 10.3390/antibiotics9090542

9. Feng J, Weitner M, Shi W, Zhang S, Sullivan D, Zhang Y. Identification of Additional Anti-Persister Activity against *Borrelia burgdorferi* from an FDA Drug Library. *Antibiotics*. (2015) 4:397–410. doi: 10.3390/antibiotics4030397

10. Feng J, Zhang S, Shi W, Zubcevik N, Miklossy J, Zhang Y. Selective Essential Oils from Spice or Culinary Herbs Have High Activity against Stationary Phase and Biofilm *Borrelia burgdorferi*. *Front Med*. (2017) 4:169. doi: 10.3389/fmed.2017.00169

11. Feng J, Shi W, Miklossy J, Tauxe GM, McMeniman CJ, Zhang Y. Identification of Essential Oils with Strong Activity against Stationary Phase *Borrelia burgdorferi*. *Antibiotics*. (2018) 7:89. doi: 10.3390/antibiotics7040089

12. Feng J, Leone J, Schweig S, Zhang Y. Evaluation of Natural and Botanical Medicines for Activity Against Growing and Non-growing Forms of *B. burgdorferi*. *Front Med*. (2020) 7:6. doi: 10.3389/fmed.2020.00006

13. Gao J, Gong Z, Montesano D, Glazer E, Liegner K. "Repurposing" Disulfiram in the Treatment of Lyme Disease and Babesiosis: Retrospective Review of First 3 Years' Experience in One Medical Practice. *Antibiotics*. (2020) 9:868. doi: 10.3390/antibiotics9120868

14. Liegner KB. Disulfiram (Tetraethylthiuram Disulfide) in the Treatment of Lyme Disease and Babesiosis: Report of Experience in Three Cases. *Antibiotics*. (2019) 8:72. doi: 10.3390/antibiotics8020072

15. Pothineni VR, Wagh D, Babar MM, Inayathullah M, Solow-Cordero D, Kim KM, et al. Identification of new drug candidates against *Borrelia burgdorferi* using high-throughput screening. *Drug Des Devel Ther*. (2016) 10:1307–22. doi: 10.2147/DDDT.S101486

16. Potula HSK, Shahryari J, Inayathullah M, Malkovskiy AV, Kim KM, Rajadas J. Repurposing Disulfiram (Tetraethylthiuram Disulfide) as a Potential Drug Candidate against *Borrelia burgdorferi* In Vitro and In Vivo. *Antibiotics*. (2020) 9:633. doi: 10.3390/antibiotics9090633

17. Sharma B, Brown AV, Matluck NE, Hu LT, Lewis K. *Borrelia burgdorferi*, the Causative Agent of Lyme Disease, Forms Drug-Tolerant Persister Cells. *Antimicrob Agents Chemother*. (2015) 59:4616–24. doi: 10.1128/AAC.00864-15

18. Li T, Feng J, Xiao S, Shi W, Sullivan D, Zhang Y. Identification of FDA-Approved Drugs with Activity against Stationary Phase *Bartonella henselae*. *Antibiotics*. (2019) 8:50. doi: 10.3390/antibiotics8020050

19. Xiao M, Jacob L, Sunjya S, Ying Z. Botanical Medicines With Activity Against Stationary Phase *Bartonella henselae*. *Infect Microbes Dis*. (2021) 3:158–67. doi: 10.1097/IM9.0000000000000069

20. Zheng X, Ma X, Li T, Shi W, Zhang Y. Effect of different drugs and drug combinations on killing stationary phase and biofilms recovered cells of *Bartonella henselae* in vitro. *BMC Microbiol*. (2020) 20:87. doi: 10.1186/s12866-020-01777-9

21. Autism Speaks. Autism statistics and facts. (2023). Available at: https://www.autismspeaks.org/autism-statistics-asd (Accessed 10 April 2023).

22. Fallon BA, Strobino B, Reim S, Stoner J, Cunningham MW. Anti-lysoganglioside and other anti-neuronal autoantibodies in post-treatment Lyme Disease and Erythema Migrans after repeat infection. *Brain Behav Immun Health*. (2020) 2:100015. doi: 10.1016/j.bbih.2019.100015

23. Breitschwerdt EB, Maggi RG, Farmer P, Mascarelli PE. Molecular evidence of perinatal transmission of *Bartonella vinsonii* subsp. berkhoffii and *Bartonella henselae* to a child. *J Clin Microbiol*. (2010) 48:2289–93. doi: 10.1128/JCM.00326-10

24. Middelveen MJ, Burke J, Sapi E, Bandoski C, Filush KR, Wang Y, et al. Culture and identification of Borrelia spirochetes in human vaginal and seminal secretions. *F1000Res*. (2014) 3:309. doi: 10.12688/f1000research.5778.3

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EDITED BY
Fengyu Zhang,
Global Clinical and Translational Research Institute, United States

REVIEWED BY
Aislinn Joanmarie Williams,
The University of Iowa, United States
Jun Li,
Peking University Sixth Hospital, Peking University, China

*CORRESPONDENCE
Lixin Yang
✉ lx.yang@siat.ac.cn
Xuerong Luo
✉ luoxuerong@csu.edu.cn

†These authors have contributed equally to this work

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Case report: A novel frameshift mutation in BRSK2 causes autism in a 16-year old Chinese boy

Yu Hu[1,2†], Miao Li[1,2†], Yanmei Shen[3†], Tianyun Wang[4,5,6,7], Qiwei Liu[1,2,8], Zhonghua Lu[1,2], Hong Wang[1,2], Xuerong Luo[3*] and Lixin Yang[1,2*]

[1]The Brain Cognition and Brain Disease Institute, Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, Shenzhen, China, [2]Shenzhen-Hong Kong Institute of Brain Science-Shenzhen Fundamental Research Institutions, Shenzhen, China, [3]Department of Psychiatry, National Clinical Research Center for Mental Disorders, The Second Xiangya Hospital of Central South University, Changsha, Hunan, China, [4]Department of Medical Genetics, Center for Medical Genetics, School of Basic Medical Sciences, Peking University Health Science Center, Beijing, China, [5]Neuroscience Research Institute, Peking University, Beijing, China, [6]Key Laboratory for Neuroscience, Ministry of Education of China and National Health Commission of China, Beijing, China, [7]Autism Research Center, Peking University Health Science Center, Beijing, China, [8]State Key Laboratory of Primate Biomedical Research, Institute of Primate Translational Medicine, Kunming University of Science and Technology, Kunming, China

Serine/threonine protein kinases are involved in axon formation and neuronal polarization and have recently been implicated in autism spectrum disorder (ASD) and neurodevelopmental disorders (NDD). Here, we focus on BRSK2, which encodes brain-specific serine/threonine protein kinase 2. Although previous studies have reported 19 unrelated patients with BRSK2 pathogenic variation, only 15 of 19 patients have detailed clinical data. Therefore, more case reports are needed to enrich the phenotype associated with BRSK2 mutations. In this study, we report a novel *de novo* frameshift variant (c.442del, p.L148Cfs*39) identified by exome sequencing in a 16 year-old Chinese boy with ASD. The proband presented with attention-deficit, auditory hallucinations, limb tremor, and abnormal brain electrical activity mapping. This study expands the phenotypic spectrum of BRSK2-related cases and reveals the highly variable severity of disorders associated with BRSK2.

KEYWORDS

BRSK2, autism, *de novo* mutation, exome sequence, clinical phenotype

Introduction

Children with autism spectrum disorder (ASD, also known as autism) share some symptoms, such as differences in social communication, and stereotyped, repetitive, or restricted behaviors or interests, based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) (1). The male-to-female ratio of patients with ASD is 4.2 (2). In addition, the prevalence of autism continues to increase, with serious implications for affected families and society.

Autism has a strong and diverse genetic background. Recent large cohort studies revealed that *BRSK2* has strong statistical support and is a genome-wide significant risk gene for ASD (3). Brain selective kinase 2 (BRSK2) is a serine/threonine protein kinase that belongs to the AMPK-related protein kinase family, which also includes BRSK1 and 11 other kinases (4). BRSK2 was found to be selectively expressed in the mouse brain, and exhibited the highest expression in the brain among various human organs (5). Recent studies using KO mice

suggested that BRSK1 and BRSK2 are essential for the development of polarity of forebrain neurons, which realizes distinct properties of axons and dendrites (6). In addition, BRSK2 mutations have been reported to be associated with ASD and neurodevelopmental disorders (NDD) (3). However, detailed clinical courses have not been described in many cases of BRSK2 mutations.

In this study, clinical exome sequencing was performed on an ASD patient and his family members, and the results revealed the presence of c.442del, p.L148Cfs*39, which is a *de novo* BRSK2 pathogenic mutation, in this proband. Notably, the patient exhibited acousma and abnormal EEG. This study expands the phenotypic spectrum associated with BRSK2 mutations.

Materials and methods

Psychological assessment

The Autism Diagnostic Observation Scale-Second Edition (ADOS) was used in autism clinical judgment. This scale is one of the most frequently used research tools, which has a standardized structure (7). Scale for assessment of negative symptoms (SANS) has 24 items which was used to measure the severity of negative symptoms in schizophrenia. Its score ranges between 0-120. Scale for assessment of positive symptoms (SAPS) has 35 items and its score ranges between 0 and 165 (8). The Wechsler Intelligence Scale for Children-Fifth Edition (WISC-V) is a valuable IQ test tool for assessing cognitive abilities in children between the ages of 6 and 16 years old (9).

EEG recording and data analysis

The EEG recording were obtained with 16-electrode Stellate Harmonie EEG systems (Natus Medical Incorporated). The EEG signals were preprocessed using a 0.1–100 Hz band-pass filter and the data was analyzed using Harmonie software (Stellate HARMONIR 7.0).

Sample preparation and DNA extraction

Peripheral blood of the proband and his family members was sampled by using EDTA tubes at The Second Xiangya Hospital of Central South University. DNA extraction was achieved by utilizing a DNA Blood Midi/Mini kit (Qiagen, Germany), and DNA concentrations were measured by utilizing a DNA Assay Kit (Qubit®, Life Technologies, USA).

Exome sequencing and variant prioritization

Exome sequencing of genomic DNA samples of the patient and his family members was executed using the Nonaseq 6000 platform (Illumina, USA). An exome library was developed by utilizing xGen Exome Research Panel V1.0 (Integrated DNA Technologies, USA). The raw paired-end reads were aligned to hg38/GRCh38, which serves as a reference genome, with BWA Enrichment. The Genome Analysis Tool Kit (GATK) was used to call variants. ANNOVAR was employed for annotation of Variant Call Format (VCF) acquired previously. The Human Genome Mutation Database (HGMD) and 1,000 Genomes Project were applied to characterize the detected variants. All variants were categorized based on mutation, location, and frequency. The threshold of low frequency filter was minor allele frequency (MAF) < 0.05. The synonymous SNVs and unannotated variants were discarded, and only SNVs observed in splice sites or exons were further investigated. Missense variants were predicted by utilizing the bioinformatics mutation prediction software programs (SIFT). The variations were categorized into groups of benign, likely benign, uncertain significance, likely pathogenic, and pathogenic by using American College of Medical Genetics and Genomics (ACMG). The AlphaFold tool was used to model and visualize the mutant and wild-type protein structures.

Sanger sequencing

The BRSK2 mutation was confirmed by Sanger sequencing of exon5, as well as its flanking intron regions (NM_001256627.2) of the proband and his family members. DNA amplification was achieved by utilizing PCR with gene-specific primers, and purification of the PCR products was achieved by utilizing a PCR Purification Kit (Qiagen, Germany). Additionally, Sanger sequencing using the ABI 3730xl DNA Analyzer (Applied Biosystems, USA) was executed on the purified PCR products to confirm BRSK2 mutation, and the results were investigated by utilizing SnapGene V.4.1.9 (SnapGene, USA).

Results

Clinical description

The patient was a 16-year-old boy who is the first child of a healthy, non-consanguineous couple. There was no family history of neurodevelopmental disorders. He was born at 39 weeks gestation with the following auxological parameters: length 50 cm and weight 3,900 g. The mother reported that the proband began crawling at 8 months, walking independently at the age of 1 year, saying single words at the age of 2 years, and saying simple sentences at 30 months. Meanwhile, eye contact with the patient exhibited no problems, and sphincter control was obtained at 24 months. At the age of 5 years, the proband was still unable to perform fine motor tasks, such as tying shoelaces, but interaction with peers was normal. The patient entered school at the age of 6, but exhibited severe difficulties in learning Chinese and inattention. The mother reported that the boy had auditory hallucinations and giggled involuntarily at the age of 11. The boy told his mother that he heard a male teacher talking to him and telling him to do things. This patient was first diagnosed with mental retardation in the Children's hospital in Tianjin at the age of 11. After 2 years of functional training and rehabilitation exercises, there was no significant improvement. However, the patient was found to have limb tremors at the age of 13. Although the proband did not have

any dietary changes, he had a sleep disorder. He was too agitated to fall asleep for 2 days every month. The Wechsler Intelligence Scale for Children, Fifth Edition (WISC-V) was used to test the patient's level of intellectual functions. His full-scale intelligence quotient (FSIQ) score was 38, which was below 70, and he was considered to have moderate intellectual disability. The Autism Diagnostic Observation Schedule (ADOS) score and the autism cut-off score of the proband were 18 and 10, respectively. The scale for the Assessment of Positive Symptoms (SAPS) and the scale for the Assessment of Negative Symptoms (SANS) were also used to assess the patient's schizophrenia symptoms. The scores of SAPS and SANS were 10 and 40, respectively, both below the cut-off score of 50. Based on these assessment results, the boy was second diagnosed with autistic spectrum disorder at Xiangya Hospital at the age of 13. The MRI results of his brain were normal, while the EEG results showed abnormal changes in brain electrical activity mapping (BEAM). The power of the theta band increased in the patient compared to typically developing (TD) boy of the same age (see Figure 1). Although the BEAM of this patient was altered, his mother reported that he never had a seizure.

Through literature review, we identified 19 cases with BRSK2 pathogenic mutations. Fifteen of the 19 cases reported partial clinical data. All cases with partial clinincal data were diagnosed with autism and presented with speech delay (100%, 15/15). Three of the 15 cases were female, and their age ranged from 3 to 19 years at first report. Twelve of the 15 cases presented with motor delay (80%, 12/15). In addition, some were reported to have sleep disorders (20%, 3/15), feeding problems (13.34%, 2/15), epilepsy (13.34%, 2/15), and schizophrenia (6.67%, 1/15). Details are presented in Supplementary Table S1.

Genetic analysis

Exome sequencing was performed on the proband and his family members. The mean depth of coverage was 20X. The mapping rates of all samples exceeded 98%. The analysis revealed the presence of c.442del, p.L148Cfs*39, which is a *de novo* frameshift variant in exon 5 of BRSK2 gene on chromosome 11 (Figure 2A). Sanger sequencing demonstrated that the heterozygous variant was present in the proband, but not in his parents or his sister (Figure 2B). This C-deletion mutation in BRSK2 leads to a premature translation termination codon and a 187 amino acid truncated protein (Figure 2C). This *de novo* frameshift deletion was identified for the first time in this study and is not present in the SPARK or SFARI gene databases (Figure 2D) (one sequence deletion, two non-sense variants, six frameshift variants, six missense variants, and six splice-site variants).

Discussion

This study reports a novel pathogenic BRSK2 variant in an ASD patient. The proband presented with speech delays, attention-deficit, and acousma. Exome sequencing demonstrated the presence of c.442del, p.L148Cfs*39, which is a *de novo* frameshift variant predicted to be deleterious. Previous publications have reported 19 non-sense, splice alteration, frameshift, and deleterious missense variations in BRSK2. These mutations were likely responsible for the phenotypes of these patients with or without ASD (3, 10–16). We compared the reported clinical phenotypes caused by the mutations located in the same catalytic domain. There were four missense mutations, three splice alterations, two non-sense mutations and one single-base deletion in the same domain. Three of the four missense mutations were all G to A variations, but they caused different symptoms, including intermittent horizontal nystagmus, sleep disorder and undescended testis. One splice alteration caused mild gait ataxia and tremor in a female patient. This symptom is similar to the limb tremor of the patient in our study. Although facial features have been reported in some probands, no consistent set of features was observed in our case. Previous publications indicated the heterogeneity among different mutation sites. Hence, more detailed case reports are necessary to expand the phenotypic spectrum associated with BRSK2 mutations. In this study, abnormal brain electrical activity mapping and acousma were reported for the first time in an ASD patient with BRSK2 mutation. Although the patient's theta band power was altered, he never had seizures. In previous studies, Pablo Billeke and his group assessed the electroencephalographic activity of ASD and TD subjects during a working memory task. They found that impaired theta modulation correlated with autistic symptoms (17), which is consistent with our findings. It has been suggested that the alteration of the theta band may be related to the physiopathology of ASD.

BRSK2, also known as SAD-A, is located at 11p15.5 and encodes 736 amino acids. The protein comprises multiple domains, including a proline-rich domain (aa 424-468), a kinase-associated domain (KA1; aa 530-653), a protein kinase (aa 19-270), and a ubiquitin-associated domain (UBA; aa 297-339) (18). BRSK2 is highly conserved in evolution and exclusively expressed in the vertebrate brain (14). In fact, BRSK2 is involved in axonogenesis and cortical neuron polarization (4, 6, 19, 20). Previous studies have reported that BRSK2 interacts with NDD-associated genes such as autism and developmental delay (DD) and/or intellectual disability (ID). BRSK2 can phosphorylate TSC2 and suppress mTORC1 activity (21, 22). As a component of the TSC signaling pathway, TSC2 regulates cell size and growth. The TSC signaling pathway is associated with autophagy during early axonal growth. Also, BRSK2 interacts with PTEN, which is associated with various developmental disorders (e.g., autism). PTEN knockout mice exhibit neuronal structure malformation and autistic features caused by aberrant TSC-mTORC1 signaling (23, 24). A previous publication reported that single mutant BRSK1 or BRSK2 mice were healthy and fertile, but BRSK1 and BRSK2 double knockout mice showed perinatal lethality with a severe defects in axon differentiation and died within 2 h after birth (4). Conversely, another study demonstrated that on a C57BL/6N background, BRSK2 is essential for cortical development. The BRKS2 knockout mice died within a few days after birth (10). Meanwhile, BRSK2-mutant zebrafish exhibited ASD-like features (e.g., developmental delay, social impairment) (4, 14).

BRSK1, also known as SAD-B, is the homolog of BRSK2. BRSK1 acts as a multifunctional regulator, by phosphorylating its downstream proteins it is involved in many biological processes. BRSK1 can phosphorylateγ-tubulin to regulate centrosome duplication, and phosphorylate CAST to control active zone

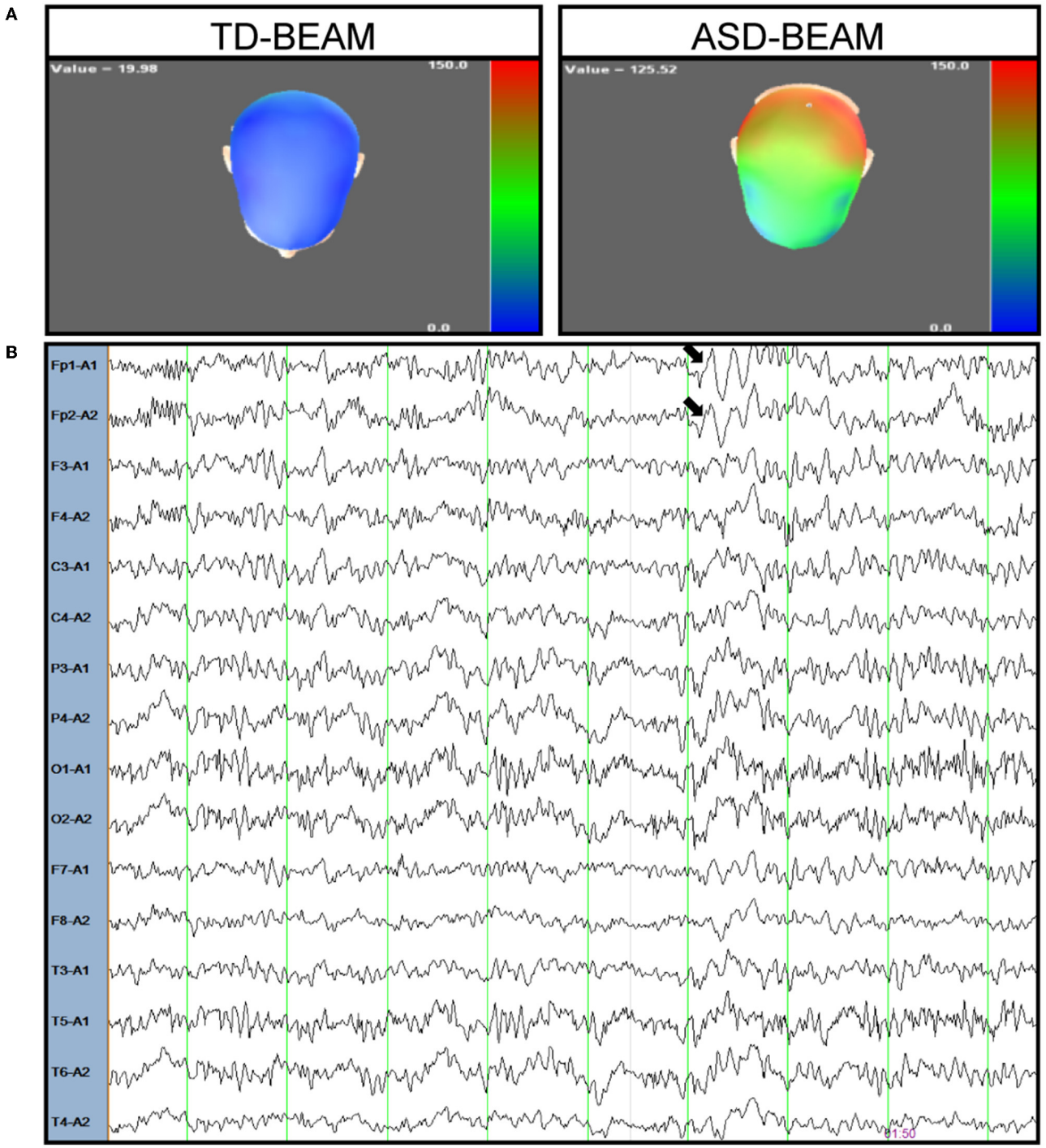

FIGURE 1
Electroencephalogram of the patient. **(A)** The power of theta band was observed increased in the patient (right) compared to a typical developing boy (left), colors depicted represent power (μV2) within theta bands across regions. Blue areas correspond to the lower power for theta band and the red areas correspond to higher power. **(B)** A representative EEG trace recorded from the patient during resting condition. The arrow marks the increase in the theta band in frontal brain region.

vesicle recycling for synaptic depression (25, 26). Furthermore, BRSK1 knockout mice showed impaired contextual fear learning. BRSK1 plays a critical role in controlling vesicle release properties and regulating hippocampal function in the mature brain (27). However, when we queried the SFARI Gene database, which tracks the ever-expanding genetic risk factors of autism, surprisingly, we found that BRSK1 has not yet been included among the autism risk genes. Although the evidence suggests that BRSK1 and BRSK2 play a key roles in cortical and neurodevelopmental processes, the functional compensation between BRSK1 and BRSK2 has not been

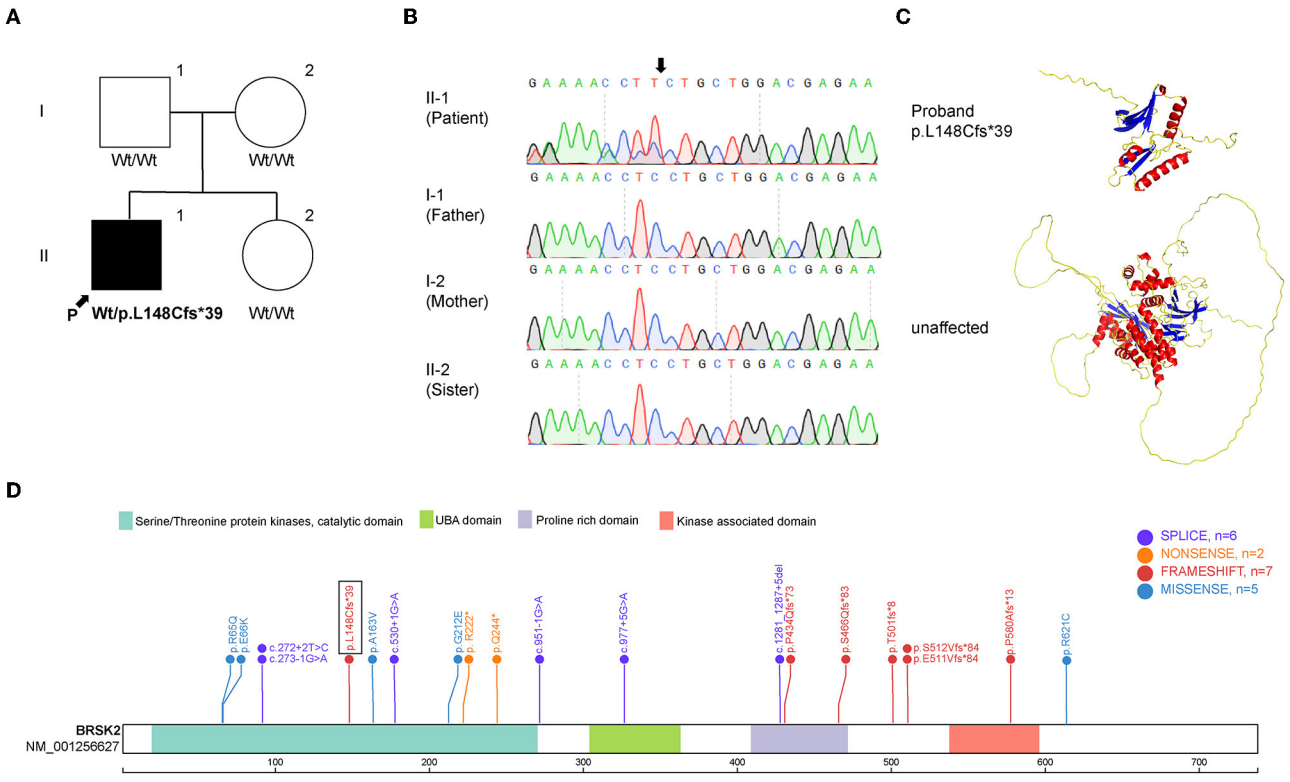

FIGURE 2
Mutation analysis of BRSK2. **(A)** Pedigree of the family described in this report. **(B)** Sequences around the BRSK2 mutation in the patient and his family. The patient carries a C deletion, which leads to a loss function variant, and his family carrier normal sequence. **(C)** The computational modeling of wild type and mutant BRSK2 in human. **(D)** Genomic structure of BRSK2 mutations reported previously are shown and the mutation found in this study is shown in a box.

sufficiently studied. Hence, more work is needed to investigate the function of BRSK1 and BRSK2.

In conclusion, we report a pathogenic *de novo* BRSK2 mutation in an ASD patient, and our findings expand the phenotypic spectrum associated with BRSK2 mutations.

Data availability statement

The datasets for this article are not publicly available due to concerns regarding participant/patient anonymity. Requests to access the datasets should be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board, Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences. 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 individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

LY and TW developed the writing plan and drafted the manuscript. XL and YS performed the autism clinical evaluation. YH, ML, HW, and QL performed the experiments. ZL, LY, and QL developed the figures. LY reviewed and approved the final manuscript. All authors have read and agreed to published version of the manuscript.

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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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Supplementary material

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References

1. DaWalt LS, Taylor JL, Movaghar A, Hong J, Kim B, Brilliant M, et al. Health profiles of adults with autism spectrum disorder: differences between women and men. *Autism Res.* (2021) 14:1896–904. doi: 10.1002/aur.2563

2. Zeidan J, Fombonne E, Scorah J, Ibrahim A, Durkin MS, Saxena S, et al. Global prevalence of autism: a systematic review update. *Autism Res.* (2022) 15:778–90. doi: 10.1002/aur.2696

3. Zhou X, Feliciano P, Shu C, Wang T, Astrovskaya I, Hall JB, et al. Integrating *de novo* and inherited variants in 42,607 autism cases identifies mutations in new moderate-risk genes. *Nat Genet.* (2022) 54:1305–19. doi: 10.1038/s41588-022-01148-2

4. Kishi M, Pan YA, Crump JG, Sanes JR. Mammalian SAD kinases are required for neuronal polarization. *Science*. (2005) 307:929–32. doi: 10.1126/science.1107403

5. Nakanishi M, Higashi Y, Sanes JR, Shimada S, Ugawa S, Pan YA, et al. Isozyme-specific role of SAD-A in neuronal migration during development of cerebral cortex. *Cerebral Cortex.* (2019) 29:3738–51. doi: 10.1093/cercor/bhy253

6. Dhumale P, Menon S, Chiang J, Puschel AW. The loss of the kinases SadA and SadB results in early neuronal apoptosis and a reduced number of progenitors. *PLoS ONE.* (2018) 13:e0196698. doi: 10.1371/journal.pone.0196698

7. Frigaux A, Evrard R, Lighezzolo-Alnot J. ADI-R and ADOS and the differential diagnosis of autism spectrum disorders: Interests, limits and openings. *Encephale.* (2019) 45:441–8. doi: 10.1016/j.encep.2019.07.002

8. Samiei M, Hedayati K, Mirabzadeh Ardekani A, Dolatshahi B, Daneshmand R, Samadi R. Obsessive-compulsive disorder in hospitalized patients with schizophrenia. *Basic Clin Neurosci.* (2016) 7:323–30. doi: 10.15412/J.BCN.03070405

9. Na SD, Burns TG. Wechsler intelligence scale for children-V: test review. *Appl Neuropsychol Child.* (2016) 5:156–60. doi: 10.1080/21622965.2015.1015337

10. Hiatt SM, Thompson ML, Prokop JW, Lawlor JMJ, Gray DE, Bebin EM, et al. Deleterious variation in BRSK2 associates with a neurodevelopmental disorder. *Am J Hum Genet.* (2019) 104:701–8. doi: 10.1016/j.ajhg.2019.02.002

11. Iossifov I, O'Roak BJ, Sanders SJ, Ronemus M, Krumm N, Levy D, et al. The contribution of de novo coding mutations to autism spectrum disorder. *Nature.* (2014) 515:216–21. doi: 10.1038/nature13908

12. Feliciano P, Zhou X, Astrovskaya I, Turner TN, Wang T, Brueggeman L, et al. Exome sequencing of 457 autism families recruited online provides evidence for autism risk genes. *NPJ Genom Med.* (2019) 4:19. doi: 10.1038/s41525-019-0093-8

13. De Rubeis R, He X, Goldberg AP, Poultney CS, Samocha K, Cicek AE, et al. Synaptic, transcriptional and chromatin genes disrupted in autism. *Nature*. (2014) 515:209–15. doi: 10.1038/nature13772

14. Deng J, Wang Y, Hu M, Lin J, Li Q, Liu C, et al. Deleterious variation in BR serine/threonine kinase 2 classified a subtype of autism. *Front Mol Neurosci.* (2022) 15:904935. doi: 10.3389/fnmol.2022.904935

15. Woodbury-Smith M, Lamoureux S, Begum G, Nassir N, Akter H, O'Rielly DD, et al. Mutational landscape of autism spectrum disorder brain tissue. *Genes.* (2022) 13. doi: 10.3390/genes13020207

16. Mahjani B, De Rubeis SC, Gustavsson M, Mulhern M, Xu X, et al. Prevalence and phenotypic impact of rare potentially damaging variants in autism spectrum disorder. *Mol Autism*. (2021) 12:65. doi: 10.1186/s13229-021-00465-3

17. Larrain-Valenzuela J, Zamorano F, Soto-Icaza P, Carrasco X, Herrera C, Daiber F, et al. Theta and alpha oscillation impairments in autistic spectrum disorder reflect working memory deficit. *Sci Rep.* (2017) 7:14328. doi: 10.1038/s41598-017-14744-8

18. Guo Z, Tang W, Yuan J, Chen X, Wan B, Gu X, et al. BRSK2 is activated by cyclic AMP-dependent protein kinase A through phosphorylation at Thr260. *Biochem Biophys Res Commun.* (2006) 347:867–71. doi: 10.1016/j.bbrc.2006.06.178

19. Lilley BN, Krishnaswamy A, Wang Z, Kishi M, Frank E, Sanes JR, et al. Kinases control the maturation of nerve terminals in the mammalian peripheral and central nervous systems. *Proc Natl Acad Sci USA.* (2014) 111:1138–43. doi: 10.1073/pnas.1321990111

20. Fogarty S, Hardie DG. C-terminal phosphorylation of LKB1 is not required for regulation of AMP-activated protein kinase, BRSK1, BRSK2, or cell cycle arrest. *J Biol Chem.* (2009) 284:77–84. doi: 10.1074/jbc.M806152200

21. Tamir TY, Bowman BM, Agajanian MJ, Goldfarb D, Schrank TP, Stohrer T, et al. Gain-of-function genetic screen of the kinome reveals BRSK2 as an inhibitor of the NRF2 transcription factor. *J Cell Sci.* (2020) 133. doi: 10.1242/jcs.241356

22. Saiyin H, Na N, Han X, Fang Y, Wu Y, et al. BRSK2 induced by nutrient deprivation promotes Akt activity in pancreatic cancer via downregulation of mTOR activity. *Oncotarget.* (2017) 8:44669–81. doi: 10.18632/oncotarget.17965

23. Bright NJ, Carling D, Thornton C. Investigating the regulation of brain-specific kinases 1 and 2 by phosphorylation. *J Biol Chem.* (2008) 283:14946–54. doi: 10.1074/jbc.M710381200

24. Nie J, Han X, Shi Y. SAD-A and AMPK kinases: the "yin and yang" regulators of mTORC1 signaling in pancreatic beta cells. *Cell Cycle.* (2013) 12:3366–9. doi: 10.4161/cc.26496

25. Alvarado-Kristensson M, Rodriguez MJ, Silio V, Valpuesta JM, Carrera AC, SADB. phosphorylation of gamma-tubulin regulates centrosome duplication. *Nat Cell Biol.* (2009) 11:1081–92. doi: 10.1038/ncb1921

26. Mochida S, Hida Y, Tanifuji S, Hagiwara A, Hamada S, Abe M, et al. SAD-B Phosphorylation of CAST controls active zone vesicle recycling for synaptic depression. *Cell Rep.* (2016) 16:2901–13. doi: 10.1016/j.celrep.2016.08.020

27. Ayako Watabe M, Masashi N, Akari H, Yamato H, Megumi T, Ohtsuka T. SAD-B kinase regulates pre-synaptic vesicular dynamics at hippocampal Schaffer collateral synapses and affects contextual fear memory. *J Neurochem.* (2016) 136:36–47. doi: 10.1111/jnc.13379

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EDITED BY
Fengyu Zhang,
Global Clinical and Translational Research Institute, United States

REVIEWED BY
Mara L. Cordeiro,
Faculdades Pequeno Principe, Brazil
Branko Aleksic,
Nagoya University, Japan
Maja Drobnič Radobuljac,
University of Ljubljana, Slovenia
Hojka Gregoric Kumperscak,
Maribor University Medical Centre, Slovenia
Megan Thomas,
Dalhousie University, Canada

*CORRESPONDENCE
Roberto Grujicic
robertogrujicic@gmail.com

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Autism spectrum disorder and Coffin–Siris syndrome—Case report

Luka Milutinovic[1], Roberto Grujicic[1]*, Vanja Mandic Maravic[2], Ivana Joksic[3], Natasa Ljubomirovic[1] and Milica Pejovic Milovancevic[1]

[1]Clinical Department for Children and Adolescents, Institute of Mental Health, Belgrade, Serbia, [2]Day Hospital for Psychotic Disorders, Institute of Mental Health, Belgrade, Serbia, [3]Clinic for Gynecology and Obstetrics "Narodni Front", Belgrade, Serbia

Introduction: Autism spectrum disorders (ASDs) are a group of developmental disorders characterized by deficits in social communicative skills and the occurrence of repetitive and/or stereotyped behaviors. Coffin–Siris syndrome (CSS) is classically characterized by aplasia or hypoplasia of the distal phalanx or nail of the fifth and additional digits, developmental or cognitive delay of varying degrees, distinctive facial features, hypotonia, hirsutism/hypertrichosis, and sparse scalp hair. In this study, we present a detailed description of autistic traits in a boy diagnosed with CSS and further discuss their genetic backgrounds.

Case description: An 8-year-old boy with ASD, congenital anomalies, and neurological problems had been diagnosed with Coffin–Siris syndrome after genetic testing. Genetic testing revealed a heterozygous *de novo* pathogenic variant (class 5) c.1638_1647del in the *ARID1B* gene that is causative of Coffin–Siris syndrome but also other intellectual disability (ID)-related disorders, including autism. Tests that preceded the diagnoses, as well as congenital anomalies and developmental issues, were further described in an attempt to better present his phenotype.

Conclusion: Both autism and *ARID1B*-related disorders are on a spectrum. This report points out the importance and necessity of further research regarding the genetic backgrounds of these disorders to understand their complex etiology.

KEYWORDS

autism spectrum disorders, Coffin–Siris syndrome, *ARID1B*, developmental disorders, neurodevelopment

1. Introduction

Autism spectrum disorders (ASDs) are a group of developmental disorders with increasing prevalence worldwide. In 2018, one in 44 children aged 8 years was estimated to have ASD (1). The core characteristics of ASD are difficulties in social communication and the occurrence of repetitive and/or stereotyped behaviors. Common ASD-associated impairments include intellectual disability (ID) (currently estimated to occur in ~30% of cases) and attention deficit (occurring in ~30–40% of cases, though estimates outside this range are common), as well as sensory hypo- and/or hypersensitivity, gastrointestinal problems, immune system deficits, anxiety, depression, sleep disturbances (2), motor-skills delays, and a range of other co-occurring conditions (3).

Genetic variation accounts for a major proportion of the liability for ASD. Up to 5–10% of cases can be linked to a known genetic cause via monogenic syndromes (such as Fragile X syndrome, tuberous sclerosis, and Timothy syndrome) (4). Twin studies show that the heritability of ASD is ∼50%, given that the concordance of ASD in monozygotic twins ranges from 37 to 95%, depending on the study design and the diagnostic criteria used. The importance of genetics in ASD susceptibility is also reflected by the recent success of microarray and whole-exome sequencing studies, which have established the role of *de novo* copy-number variants (CNVs) and *de novo* protein-disrupting single-nucleotide variants (SNVs) in ASD pathogenesis. Similar contributions have been identified in individuals with ID without ASD (5).

Coffin–Siris syndrome (CSS) is classically characterized by aplasia or hypoplasia of the distal phalanx or nail of the fifth and additional digits, developmental or cognitive delay of varying degrees, distinctive facial features, hypotonia, hirsutism/hypertrichosis, and sparse scalp hair (6).

ARID1B-related disorder (*ARID1B*-RD) constitutes a clinical continuum, from ID with or without non-specific dysmorphic features to classic Coffin–Siris syndrome (7). Heterozygous pathogenic gene variants and cytogenetic abnormalities involving *ARID1B* are considered to be the leading cause of Coffin–Siris syndrome, being found in 68–83% of cases (8, 9). More than 170 unique pathogenic or likely pathogenic variants in *ARID1B* have been reported in ClinVar, most of them *de novo* truncating variants, leading to gene haploinsufficiency (10). What is striking is the considerable clinical variability associated with reduced levels of ARID1B. One review identified the major features associated with ARID1B haploinsufficiency as ID, speech delay, prominent facial features, and hypertrichosis (9). Currently, there is no clear genotype–phenotype correlation, suggesting the involvement of other phenotypic modifiers.

ARID1B is a member of the switch/sucrose non-fermenting (SWI/SNF) chromatin remodeling complex (BAF complex in mammals) and is highly expressed in the brain and embryonic stem cells. It uses an ATP-dependent mechanism to modify the structure of chromatin and change its accessibility to transcription factors. In mammals, these complexes are assembled from subunits encoded by 29 genes, making their composition very diverse (11).

The importance of the BAF complex in human neuronal development and cancer occurrence has emerged through the recent discoveries that mutations in their subunit genes and related genes are implicated in several ID syndromes: CSS, non-syndromic ID (*ARID1B*-MIM: 614556, *ARID1A*-MIM: 603024, *SMARCA4*, BRG1 MIM: 603254, *SMARCB1*-SNF5-MIM: 601607, *SMARCE1*-MIM: 603111, SMARCC2-MIM, *DPF2* MIM: 601671), Nicolaides–Baraitser syndrome (NCBRS, *SMARCA2*-MIM: 600014), sporadic autism, schizophrenia, and amyotrophic lateral sclerosis, as well as in sporadic cancers/cancer-predisposing syndromes (12). Some authors suggest that these disorders caused by mutations in BAF subunit genes represent a clinical continuum with non-syndromic ID and mild CSS on one end of the spectrum and NCBRS on the severe end of the spectrum, suggesting the term SWI/SNF-related intellectual disability disorders (SSRIDDs) (13). Noteworthy, besides mutations in the *ARID1B* gene, Coffin–Siris syndrome can be caused by variants in additional genes, including *ARID1A*, *ARID1B*, *ARID2*, *DPF2*, *PHF6*, *SMARCA2*, *SMARCA4*, *SMARCB1*, *SMARCC2*, *SMARCE1*, *SOX4*, and *SOX11* (6).

Switches between BAF subunits play an important role in cell fate determination. Recently, it was suggested that two switches between *ARID1A-BAF* and *ARID1B-BAF* in pluripotent stem cells are needed for proper development: first, for differentiation toward the neuroectodermal lineage (*ARID1A* to *ARID1B*) and second for (*ARID1B*-BAF to *ARID1A*-BAF) neuroectodermal sphere differentiation into neural crest cells. Mainly, it was found that the role of the *ARID1B*-BAF subunit is to repress pluripotency enhancers (NANOG/SOX2 networks) during neural crest cell formation, thus enabling exit from pluripotency and lineage commitment. In *ARID1B* haploinsufficient cells, this process is impaired, leading to impaired *ARID1A* subunit activity and dysregulation of neuroectoderm specification, which can explain both neurocognitive and craniofacial characteristic features of CSS (14). Similarly, its haploinsufficiency partially impairs the function of *BRG1*-associated factor complexes, including *BAF155* or *BAF170*. This leads to the dysregulation of C-MYC expression, delaying the cell cycle entry of developmentally arrested cells, such as neural progenitors (15).

This study aims to present a detailed description of ASD manifestations in a boy diagnosed with CSS. Detailed analysis of ASD features in CSS might lead to specific signs that might orient clinicians toward keeping genetic disorders in mind when diagnosing ASD.

2. Case description

An 8-year-old boy with developmental disabilities, autistic traits, and neurological problems was diagnosed with Coffin–Siris syndrome after genetic testing in February 2021. He was the first child in his family. Pregnancy was complicated by gestational diabetes, which was treated with a diet. Delivery at term was performed with vacuum extraction. The Apgar score was 9/10, body weight was 3.6 kilograms (P50–P75), and body length was 52 centimeters (P75–P90). He was breastfed for the first 7 months. He had a cow's milk protein allergy, which made him use an adapted milk formula. At 18 months, he started walking without any support, and at 3 years, his walk became more stable. At 4 and 6 months of age, he obtained bladder and bowel control.

He had three surgeries (at 14 months—cryptorchidism, 20 months—strabismus, and 4 years—adenoidectomy). He had febrile convulsions since he was 2 years and 4 months old for which he had taken medication, sodium valproate. EEG measured bitemporal focal changes that were more pronounced on the left side of his slow baseline activity. The development of his language and speech skills was the first cause of parental concern. The delay in this particular domain occurred at the age of 2. This is when they initiated their first referral to the attending physician.

He was examined by an otorhinolaryngologist for problems with speech and for not responding to commands when he was 2 years and 1 month old. Brainstem-evoked response audiometry (BERA) testing had been performed, and there were no pathological findings. He was assessed by a child psychiatrist on suspicion of autism 1 month later and diagnosed with delayed psychomotor development. Both mother and father denied any

family history of significant hereditary disorders. He was referred to our Institution for detailed diagnostic exploration when he was 5 years old.

Physical examination showed that stature and head circumference were age-appropriate. Other findings included facial dysmorphia and macrostomia with small, widely spaced teeth, long eyelashes, downslanted palpebral fissures, lower placed hairline with thick and coarse hair, pronounced and descended lower lip, single palmar crease on one hand, and fifth digit distal phalangeal hypoplasia on his feet, as well as a protosystolic heart murmur. According to his parents, diagnostic imaging did not reveal any congenital structural anomalies of the brain or abdomen.

On psychiatric examination, it was noted that the child was well-nourished, active, and curious. A greeting gesture was noted. Eye contact was brief. He immediately approached the toy boxes and spent some time with each of them. Contact with the boy was successfully achieved through playing with toys. He accepted organized play (driving a teddy bear with a toy car). He did not develop any functional speech. Stereotypical movements were not observed. He was clumsy, poorly coordinated, and his sense of spatial orientation was insufficient. It was stated that he participated in organized play, but only briefly. He enjoyed the company of children and tried to interact with them. He particularly enjoyed activities that include motor skills: climbing, jumping, and running. He did not eat with a fork and a knife and did not drink from a glass on his own. He could take off his shoes without any assistance.

A speech therapist examination showed that contact through toys and other objects was achieved with difficulties. Contact through voice and words was not made. He was not turning his head toward the examiner when he was called by his name. Motor skills in total were underdeveloped for his age. Movement of the upper and lower extremities was uncoordinated. His body was often bent forward, which could be attributed to his poor eyesight. Play routines were simple, with very little imagination. He solved the wooden puzzle with animals, letters, and terms without deepening his interaction with the examiner. He played alone and did not show any interest in playing with others. He did not speak. He used two words in the form of syllables with the goal of expressing his needs. Contrary to the psychiatrist's initial assessment, the greeting gesture was confirmed to be absent. He was constantly moving, walking around with toys in his hands, and had difficulty focusing on activities outside of his scope of interest.

His score for general adaptive behavior was 58 on the Vineland II Adaptive Behavior scale. A delay in psychomotor development with significant difficulties in communication (underdeveloped

TABLE 1 ADOS-2 scoresheet.

Social affect (SA)	
Communication	
Frequency of spontaneous vocalization directed to others	2
Pointing	1
Gestures	2
Reciprocal social interaction	
Unusual eye contact	2
Facial expressions directed at others	1
Integration of gaze and other behaviors during social overtures	2
Shared enjoyment in interaction	1
Showing	2
Spontaneous initiation of joint attention	2
Response to joint attention	1
Quality of social overtures	2
Restricted and repetitive behavior (RRB)	
Restricted and repetitive behaviors	
Stereotyped/idiosyncratic use of words or phrases	0
Unusual sensory interest in play material/person	2
Hand and finger and other complex mannerisms	0
Unusually repetitive interests or stereotyped behaviors	2
Overall total (SA + RRB)	22

TABLE 2 Comparison of cases with ASD and CSS and their mutations.

Cases	Characteristics	Mutations in CSS
Our case	Not responding when called by name. Brief participation in organized play, play routines were simple with very little imagination. He played alone and did not show any interest in playing with others. He did not speak. He used two words in the form of syllables with the goal of expressing his needs. A greeting gesture was absent. Difficulty focusing on activities outside of his scope of interest. Poor sense of coordination and spatial orientation. In summary, our case was presented with underdeveloped speech, difficulties in comprehension, socialization, and motor skills.	*ARID1B*
Seda Gulcu et al. (17)	Very little social interaction, restricted facial expression. Limited eye contact, failure to look when called, the absence of focus of interest, unwillingness to point to any desired object, lack interest in his peers, and "flapping" motions when excited.	*ARID1B*
Hersh et al. (18)	Delayed speech development. Only vocalizations heard during the evaluation were lip-trilling sounds. Only interaction with the examiner was pushing his hand toward an object she wished to obtain. Non-existent eye contact, self-occupying behavior. Functional play was not observed.	Genetic tests were not performed
Krause and Rose (19)	The patient was described as having difficulties with expressive speech and speech impairment (despite this, verbal abilities were a relative strength in his cognitive profile), diverted eye contact, restricted interests and stereotypical behaviors, inappropriate social gestures, idiosyncratic and pedantic speech, and restricted affect.	Genetic tests were not performed

speech and difficulties in comprehension), socialization, and motor skills was noted. The childhood autism rating scale (CARS) was used for psychometric assessment. A score of 29 (borderline value) was noted.

The comprehensive and multidisciplinary team assessment led to the conclusion that his developmental difficulties were significant. There were autistic traits, developmental delay, and neurological problems (seizures). He was formally diagnosed as having ASD by a child psychiatrist with supporting evidence from the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule 2 (ADOS-2). The ADI-R scores were as follows: Total A−21; Total non-verbal B−11; Total C−8; and Total D−5. His total score on Module 1 of ADOS-2 was 22 (Table 1), which was beyond the cutoff criteria for autism. The detailed family history revealed that there were no developmental, neurological, or psychiatric disorders in the family.

Since the boy presented with ASD, congenital anomalies, and specific features, genetic testing was performed. Karyotype, Fragile X syndrome testing, chromosomal microarray analysis, and urine metabolite screening did not detect any genetic abnormalities. However, the Trio whole-exome sequencing showed a heterozygous *de novo* variant in the *ARID1B* gene (NM_001371656.1):c.1638_1647del that was classified as pathogenic (class 5 according to ACMG/AAP criteria). This is a frameshift variant leading to non-sense-mediated decay of mRNA. Heterozygous loss of function variants in this gene are causative of Coffin–Siris syndrome.

The boy had attended several different stimulation treatments during the past few years, including logopedic, psychomotor re-education, and sports activities, which have resulted in improvements in several domains. The comprehension of speech and articulation of syllables have improved. He got better at verbalizing his needs. He has a personal assistant and is attending second-grade school for children with special needs, but is attending math classes under a regular program. Aside from verbalization, his other biggest difficulty is graphomotorics. Verbalization still includes only several words. He is of adequate behavior at home. He still needs support and stimulation with his everyday activities, including dressing up, tying his shoes, eating, and maintaining his personal hygiene.

3. Discussion

In this study, we presented a detailed description of a patient who had typical clinical manifestations of CSS (dysmorphic features, strabismus, cryptorchism, hypertrichosis, and seizures) (7) and the core clinical features of ASD. A large study by van der Slujis (10) found that among 79 patients with *ARID1B* mutations and features of CSS, 66.7% had ASD. A study that examined the abilities of 12 children with CSS found that symptoms of pervasive developmental disorders (PDDs) were found in almost half of the CSS patients (16). We compared the features and mutations of these cases with ours, as shown in Table 2.

When it comes to clinical characteristics of ASD symptoms in our case, the most severe symptoms were seen in the disturbance of reciprocal social interaction (eye contact, imaginative play with peers, and lack of need to share pleasure with others) and qualitative communication disturbances (pointing to show interest and nodding). For the restrictive, repetitive, and stereotyped behaviors, the boy showed a lower presence and severity of symptoms, and mostly for stereotyped and repetitive hand and finger mannerisms. It would be potentially beneficial to explore whether there might be a specific clinical phenotype in children with ASD as part of CSS.

ARID1B (MIM135900), besides being a disease-causing gene in CSS, is a prevalent underlying genetic cause of ID (0.5–1%) and ASD (15). Analysis of rare coding variation in 3,871 ASD cases and 9,937 ancestry-matched or paternal controls identified *ARID1B* (20) as a strong candidate to be an ASD risk gene based on a combination of *de novo* mutational evidence and the absence or very low frequency of mutations in controls (21). The deletion of 10 bp found in our patient is located in exon 2 of the ARID1B gene; however, the location of the pathogenic variant does not appear to correlate with the severity of the phenotype (22). The pathogenic gene variant found in our patient was published by Tsurusaki et al. (23), but no detailed description of the patient's characteristics was given.

Recently, models of *ARID1B* heterozygous mutant mice reportedly expressed social behavior impairment, altered vocalization, motor abnormalities, and neuroanatomical anomalies, including agenesis of the corpus callosum (24). A recent morphometric analysis reveals that children with ASD usually have a smaller corpus callosum compared to neurotypical children of the same ethnicity (25).

Many neurodevelopmental disorders exhibit improper inhibitory interneuron development, resulting in excitatory/inhibitory imbalance, including ASD (26, 27). One study showed that *ARID1B* haploinsufficient mice exhibit a reduction and abnormal distribution of interneurons as well as abnormal inhibitory synaptic activity in the cerebral cortex (28). It was also found that *ARID1B* haploinsufficiency in parvalbumin- or somatostatin-expressing interneurons lead to distinct ASD-like and ID-like behaviors (29).

Finally, *ARID1B* belongs to a group of genes that encode key regulators of chromatin remodeling, altering translation within neurons and at synapses. A better understanding of pathways such as this one might lead to a more specific, core autistic symptom-oriented treatment (30). Furthermore, due to the identification of the specific syndrome underlying the symptoms the boy presented with, we were able to advise the parents on future regular somatic checkups, such as the evaluation of growth, endocrinological, and vision and hearing evaluation (22).

The limitation of this study is that it is focused on a single clinical case and, therefore, provides little basis for generalizing results to a wider population. However, it highlights the importance of genetic testing for ASD patients in order to determine the possible underlying cause of this complex condition, which can lead to better understanding and acceptance.

4. Conclusion

ARID1B-related disorder, such as autism, is on a spectrum (22). Similarities between the two can be explained by the

fact that mutations in both disorders are related to genes associated with neuronal communication, synapse development, and chromatin remodeling/transcription regulation. This points out the importance and necessity of further research regarding the genetic background of these disorders in order to understand their complex etiology. Furthermore, this study could serve as a reminder for clinicians to always be aware of genetic syndromes hiding behind the common ASD diagnosis. Genetic consultation can help identify genetic syndromes and other frequent comorbidities in ASD. Knowing the underlying cause of ASD can be very beneficial for parents and families of children with ASD.

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 approval was not required for the study involving human samples in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

LM participated in the literature review, writing the manuscript, and data collection. RG participated in writing the manuscript, literature review and preparation, revising the manuscript, and testing the patient. VMM participated in revising the manuscript and data collection. IJ participated in revising the manuscript and contributed genetic expertise. NL participated in revising the final version of the manuscript and literature research. MPM recruited the patient, obtained informed consent, revised the manuscript, and supervised the research. All authors contributed to the article and approved the submitted version.

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.

Publisher's note

References

1. Maenner MJ, Shaw KA, Bakian A V, Bilder DA, Durkin MS, Esler A, et al. Prevalence and characteristics of autism spectrum disorder among children aged 8 years — autism and developmental disabilities monitoring network, 11 sites, United States, 2018. *MMWR Surveill Summ.* (2021) 70:1–16. doi: 10.15585/MMWR.SS7011A1

2. Lyall K, Croen L, Daniels J, Fallin MD, Ladd-Acosta C, Lee BK, et al. The changing epidemiology of autism spectrum disorders. *Annu Rev Public Health.* (2017) 38:81–102. doi: 10.1146/annurev-publhealth-031816-044318

3. MacDonald M, Ross S, McIntyre LL, Tepfer A. Relations of early motor skills on age and socialization, communication, and daily living in young children with developmental disabilities. *Adapt Phys Act Q.* (2017) 34:179–94. doi: 10.1123/apaq.2015-0091

4. Devlin B, Scherer SW. Genetic architecture in autism spectrum disorder. *Curr Opin Genet Dev.* (2012) 22:229–37. doi: 10.1016/j.gde.2012.03.002

5. Leppa VMM, Kravitz SNN, Martin CLL, Andrieux J, Le Caignec C, Martin-Coignard D, et al. Rare inherited and *de novo* CNVs reveal complex contributions to ASD risk in multiplex families. *Am J Hum Genet.* (2016) 99:540–54. doi: 10.1016/j.ajhg.2016.06.036

6. Vergano SS, Santen G, Wieczorek D, Wollnik B, Matsumoto N, Deardorff MA. Coffin-Siris Syndrome - GeneReviews® - NCBI Bookshelf. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, et al., editors. Seattle, WA: University of Washington, Seattle (1993–2020). Available online at: https://www.ncbi.nlm.nih.gov/books/NBK131811/ (accessed October 6, 2021).

7. Vergano SA, Sluijs PJ van der, Santen G. *ARID1B-Related Disorder. GeneReviews®*. (2019). Available online at: https://www.ncbi.nlm.nih.gov/books/NBK541502/ (accessed October 6, 2021).

8. Santen GWE, Aten E, Vulto-van Silfhout AT, Pottinger C, van Bon BWM, van Minderhout IJHM, et al. Coffin-siris syndrome and the BAF complex: Genotype-phenotype study in 63 patients. *Hum Mutat.* (2013) 34:1519–28. doi: 10.1002/humu.22394

9. Santen GWE, Clayton-Smith J, Adachi-Fukuda M, AlKindy A, Baban A, Berry K, et al. The ARID1B phenotype: what we have learned so far. *Am J Med Genet Part C Semin Med Genet.* (2014) 166:276–89. doi: 10.1002/ajmg.c.31414

10. van der Sluijs PJ, Jansen S, Vergano SA, Adachi-Fukuda M, Alanay Y, AlKindy A, et al. The ARID1B spectrum in 143 patients: from nonsyndromic intellectual disability to Coffin–Siris syndrome. *Genet Med.* (2019) 21:1295–307.

11. Pagliaroli L, Trizzino M. The evolutionary conserved SWI/SNF subunits ARID1A and ARID1B are key modulators of pluripotency and cell-fate determination. *Front Cell Dev Biol.* (2021) 9:449. doi: 10.3389/fcell.2021.643361

12. Kosho T, Miyake N, Carey JC. Coffin-Siris syndrome and related disorders involving components of the BAF (mSWI/SNF) complex: historical review and recent advances using next generation sequencing. *Am J Med Genet Part C Semin Med Genet.* (2014) 166:241–51. doi: 10.1002/ajmg.c.31415

13. Bögershausen N, Wollnik B. Mutational landscapes and phenotypic spectrum of SWI/SNF-related intellectual disability disorders. *Front Mol Neurosci.* (2018) 11:252. doi: 10.3389/fnmol.2018.00252

14. Pagliaroli L, Porazzi P, Curtis AT, Scopa C, Mikkers HMM, Freund C, et al. Inability to switch from ARID1A-BAF to ARID1B-BAF impairs exit from pluripotency and commitment towards neural crest formation in ARID1B-related neurodevelopmental disorders. *Nat Commun.* (2021) 12:1–16. doi: 10.1038/s41467-021-26810-x

15. Demily C, Duwime C, Lopez C, Hemimou C, Poisson A, Plasse J, et al. Corpus callosum metrics predict severity of visuospatial and neuromotor dysfunctions in ARID1B mutations with Coffin–Siris syndrome. *Psychiatr Genet.* (2019) 29:237–42. doi: 10.1097/YPG.0000000000000225

16. Swillen A, Glorieux N, Peeters M, Fryns J-P. The Coffin-Siris syndrome: data on mental development, language, behavior and social skills in 12 children. *Clin Genet.* (1995) 48:177–82. doi: 10.1111/j.1399-0004.1995.tb04084.x

17. Seda Gulcu N, Karayagmurlu A, Gulcu NS. ARID1B gene mutation in a patient with Coffin-Siris syndrome and autism spectrum disorder. *Dusunen Adam J Psychiatry Neurol Sci.* (2019) 32:355–8. doi: 10.14744/DAJPNS.2019.00051

18. Hersh JH, Bloom AS, Weisskopf B. Childhood autism in a female with coffin siris syndrome. *J Dev Behav Pediatr.* (1982) 3:249–52. doi: 10.1097/00004703-198212000-00016

19. Krause KA, Rose AM. Analysis of functioning in a 12-year-old boy with Coffin-Siris Syndrome. *J Clin Case Rep.* (2018) 1:1016.

20. De Rubeis S, He X, Goldberg AP, Poultney CS, Samocha K, Cicek AE, et al. Synaptic, transcriptional and chromatin genes disrupted in autism. *Nature.* (2014) 515:209–15. doi: 10.1038/nature13772

21. Iossifov I, Levy D, Allen J, Ye K, Ronemus M, Lee YH, et al. Low load for disruptive mutations in autism genes and their biased transmission. *Proc Natl Acad Sci USA.* (2015) 112:E5600–7. doi: 10.1073/pnas.1516376112

22. van der Sluijs PJ, Jansen S, Vergano SA, Adachi-Fukuda M, Alanay Y, AlKindy A, et al. The ARID1B spectrum in 143 patients: from nonsyndromic intellectual disability to Coffin–Siris syndrome. *Genet Med.* (2019) 21:1295–307. doi: 10.1038/S41436-018-0330-Z

23. Tsurusaki Y, Okamoto N, Ohashi H, Mizuno S, Matsumoto N, Makita Y, et al. Coffin-Siris syndrome is a SWI/SNF complex disorder. *Clin Genet.* (2014) 85:548–54. doi: 10.1111/cge.12225

24. Celen C, Chuang JC, Luo X, Nijem N, Walker AK, Chen F, et al. Arid1b haploinsufficient mice reveal neuropsychiatric phenotypes and reversible causes of growth impairment. *Elife.* (2017) 6:1–22. doi: 10.7554/eLife.25730.030

25. Allouh MZ, Al Barbarawi MM, Ali HA, Mustafa AG, Alomari SO. Morphometric analysis of the corpus callosum according to age and sex in middle Eastern Arabs: racial comparisons and clinical correlations to autism spectrum disorder. *Front Syst Neurosci.* (2020) 14:30. doi: 10.3389/fnsys.2020.00030

26. Ramamoorthi K, Lin Y. The contribution of GABAergic dysfunction to neurodevelopmental disorders. *Trends Mol Med.* (2011) 17:452–62. doi: 10.1016/j.molmed.2011.03.003

27. Nelson SB, Valakh V. Excitatory/inhibitory balance and circuit homeostasis in autism spectrum disorders. *Neuron.* (2015) 87:684–98. doi: 10.1016/j.neuron.2015.07.033

28. Jung EM, Moffat JJ, Liu J, Dravid SM, Gurumurthy CB, Kim WY. Arid1b haploinsufficiency disrupts cortical interneuron development and mouse behavior. *Nat Neurosci.* (2017) 20:1694–707. doi: 10.1038/s41593-017-0013-0

29. Smith AL, Jung EM, Jeon BT, Kim WY. Arid1b haploinsufficiency in parvalbumin- or somatostatin-expressing interneurons leads to distinct ASD-like and ID-like behavior. *Sci Rep.* (2020) 10:1–13. doi: 10.1038/s41598-020-64066-5

30. Fernandez BA, Scherer SW. Syndromic autism spectrum disorders: Moving from a clinically defined to a molecularly defined approach. *Dialog Clin Neurosci.* (2017) 19:353–71. doi: 10.31887/DCNS.2017.19.4/sscherer

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EDITED BY
Marco Colizzi,
University of Udine, Italy

REVIEWED BY
Domenico De Berardis,
ASL 4, Italy
Leila Kashani Vahid,
Azad University,
Science and Research Branch, Iran

*CORRESPONDENCE
Sabrina Panesi
✉ panesi.sabrina@gmail.com

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Case Report: A playful digital-analogical rehabilitative intervention to enhance working memory capacity and executive functions in a pre-school child with autism

Sabrina Panesi[1]*, Marina Dotti[2] and Lucia Ferlino[1]

[1]Institute for Educational Technology of the CNR, Genoa, Italy, [2]David Chiossone Onlus, Genoa, Italy

Background: Autism Spectrum Disorder (ASD) is often associated with deficits in Working Memory Capacity (WMC) and Executive Functions (EFs), as early as the first years of life. Research has shown that, even young children with ASD, WMC and EF deficits can be effectively addressed through interventions employing digital and/or analogical tools. Early intervention is important because executive dysfunction can negatively impact on the quality of life, both of children and their families. However, very few studies have been carried out involving intervention with pre-schoolers with ASD. To fill this gap, we developed an intervention that promotes pre-schoolers' WMC and EFs by employing both digital apps and analogical playful activities. This study reports on the feasibility of this intervention, which was carried out in a rehabilitative context.

Methods: A male pre-schooler diagnosed with ASD was engaged in a total of 17 intervention sessions, all held in a clinical context, over a nine-week period. Outcomes were measured using a battery of pre- and post-treatment tasks focusing on WMC, EFs and receptive language. The clinician who administered the intervention made written observations and noted any improvements in the child's performance emerging from the digital and analogical activities.

Results: The pre- and post-test scores for the cognitive tasks revealed qualitative improvements in the following cognitive domains: (a) WMC in the language receptive domain; (b) updating in WMC; (c) inhibition, specifically concerning control of motor response; (d) receptive vocabulary. Furthermore, when monitoring the child's performance, the clinician noted improvement in almost all the playful activities. Particularly notable improvements were observed in interaction with the apps, which the child appeared to find very motivating.

Conclusion: This study supports feasibility of a playful digital-analogical intervention conducted by a clinician in a rehabilitation context to promote cognitive abilities in pre-schoolers with ASD. Further studies are needed to establish whether the intervention's effectiveness can be generalized to a broad sample of children with ASD.

KEYWORDS

case report, working memory, executive functions, rehabilitative intervention, Autism Spectrum Disorder, preschool, app

Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by impairments in social interaction, communication and sometimes stereotyped behavior [DSM-5; (1)]. Individuals with ASD constitute a heterogeneous group, with significant symptom variability, the presence/absence of comorbidities, including psychiatric comorbidities (2), impaired empathy in both cognitive and affective dimensions (3), and various types of cognitive difficulties (4).

In terms of cognitive abilities, ASD is often associated with deficit in working memory capacity (WMC) and Executive Functions (EFs). The term "Working Memory Capacity" (WMC) refers to a limited capacity system that allows information to be temporarily stored and manipulated (5). Miyake et al. (6) argue that WMC may rely on EFs, defined as a family of adaptive, goal-directed, top-down mental control processes (e.g., (7)). Further investigation (6, 8) has revealed that EFs comprise three main components: *inhibition,* the ability to suppress task-irrelevant cognitive processing and ignore salient yet irrelevant information; *shifting*, the ability to switch between different operations or levels of processing; and *updating,* the ability to encode, retain and monitor incoming information in working memory.

Recent literature reviews and meta-analyses reveal that, compared to individuals with typical development, those with ASD have impairments in WMC (9), inhibitory control (10), and cognitive flexibility (11). The construct of updating remains under-investigated, especially in the preschool period (12, 13). What's more, the findings from the few studies that explore this EF component in autism have proven to be inconsistent (9).

Impaired WMC and EFs in individuals with ASD has a negative impact on self-regulation and daily functioning, especially concerning autonomy. Hence, it is important to enhance these components through cognitive interventions [e.g., (4)] administered as early as the first years of life.

Both digital and analogical-based interventions can be adopted to promote WMC and EFs in individuals with ASD. In a meta-analysis, Grynszpan et al. (14) highlighted the effectiveness of technology-based training for children with ASD. They establish that children find this type of training enjoyable and safe; it constitutes a secure environment in which errors have minimal consequences and therefore trigger less social anxiety and shame (15). Similarly, the meta-analysis performed by Pasqualotto et al. (4) analyses computerized and non-computerized training. They report growing evidence for the overall effectiveness of cognitive training as a tool to enhance WMC and EFs, particularly when activities are computer based.

It's worth noting that most of the studies in these meta-analyses regard school-age children or older. Despite the importance of cognitive development at preschool age (16, 17), very few studies focus on rehabilitative intervention to enhance WMC and EFs in the early years of life (4). Furthermore, in the majority of cases, studies on WMC and EFs interventions involving pre-schoolers with autism propose activities that do not entail use of digital technologies [e.g., (18, 19)]. Cai et al. (18) propose a 12-week mini-basketball training program for 18 pre-schoolers with autism; following the intervention, the subjects exhibited significantly better performance in working memory and regulation as compared to a control group. A recent study conducted by Zhang et al. (19) sought to investigate the impact of a three-game intervention on EFs involving different groups of pre-schoolers with autism. Twenty-four pre-schoolers with autism were selected and divided into three groups; these groups took part in an eight-week programme of, respectively, sports games, pretend play, and comprehensive games. The authors found that the children involved in the sports games group and in the pretend play group significantly improved working memory and cognitive flexibility and comprehensive game group improved the working memory and cognitive flexibility, and the improvement of inhibitory control has reached a marginal significant level; furthermore, the intervention effect of comprehensive games was better than that of single sports games or pretends play.

To the best of our knowledge, only one study has been conducted that proposes an intervention featuring use of digital materials (20). This involved 24 children of preschool age. Specifically, the authors proposed an intervention in which a computer-based puzzle game named "Tatka" was employed; this was accompanied by a set of home-based tasks designed to enhance set-shifting ability. When comparing outcomes from pre- and post-test phases and from a repetitive behavior task, the authors found a significant change in both cognitive and behavioral flexibility. Furthermore, the result was to some extent sustained for about a month after the treatment.

So there is a clear paucity of available research on promotion of WMC and EFs in pre-school children with ASD using a variety of means, including digital applications. To fill this gap, the authors of this paper have conducted a study in which a playful digital-analogical rehabilitative intervention was conducted with a pre-school child with ASD. The study in question was carried out as part of the ShareFUN project.[1] This follows the authors' previous research (21), which has demonstrated that the integration of digital and analogical materials in interventions for preschool children could yield added value; this is because the two forms offer different affordances in clinical intervention contexts (22). For the digital activities, we opted for educational apps because they are low cost, familiar, and intuitive for pre-schoolers to use (23). What's more, they have been proven to be fun to use, and motivating (24).

Case description

For the intervention, one male child with ASD was selected from a group of ASD children attending a rehabilitation centre. This child met all the predefined inclusion criteria: (a) diagnosis of ASD; (b) age range 3–5 years old; (c) mild or moderate intellectual disability[2]; (d) deficit in WMC and EFs[3]; (e) the family's willingness to participate in

1 The ShareFUN project (www.sharefun.it) entailed various interventions designed to enhance WMC and EFs in children with neurodevelopmental disorders and/or from low Social Economic Status (SES) backgrounds.

2 The intellectual disability level was set at mild or moderate because this type of intervention is too difficult for pre-schoolers with a high level of intellectual disability to understand or follow.

3 In the selection phase, we consulted clinicians who had carried out various activities with the chosen subject. They reported that he had difficulty performing various activities that entail memorizing information, paying attention to tasks, and controlling behaviour. We also consulted the mother, who reported the same information as the clinicians. We invited the mother to complete an observation survey, BRIEF-P (25), for screening purposes. The mother reported that her son found it particularly difficult to perform activities involving WMC and inhibition.

this study. To protect the participant's identity, an assumed name (Francesco) was assigned, and all identifying information was removed from the study material. Francesco was 42 months old when his involvement in the study commenced.

Family background and history

Francesco's mother is a 29 year-old freelancer with a degree in communication sciences, while his father is a 28 year-old bar worker with a high school diploma. Francesco lives with his mother; his father had left the family and was not a party to Francesco's clinical evaluation because he did not agree with the need for undertaking a diagnostic process (he did however provide the proxy to be able to carry out the diagnosis). Francesco's maternal grandparents support the mother in carrying for him. The paternal family has a history of epilepsy and dyslexia, while the maternal family had a history of thyroid pathologies.

Francesco was born at the due date (spontaneous delivery) following a normal pregnancy: birth weight 3.34 kg, height 41 cm, good adaptation to extra-uterine life (Apgar not available). His mother opted for formula feeding and he had no difficulty in weaning.

Currently no sphincter control; regular sleep–wake rhythm.

Motor development: sitting independently at 7–8 months, walking autonomous at 15 months.

Language development: babbling at 9 months, first words at 28 months (during the diagnostic assessment period Francesco produced about 60 words, mainly in echolalia, and did not make standard hand gestures, e.g., when greeting.

At 16 months he started nursery school. At that time he also started psychomotor and speech therapy treatment.

Diagnostic assessment

At 31 months, Francesco received a diagnosis of neurodevelopmental disorders, specifically ASD.

Adaptation to the evaluation context took place without particular difficulties. Spontaneous relational initiative was mostly directed toward the mother, whom the child sought above all for requesting purposes. Eye contact was not always appropriate. Francesco also had behavioral rigidity and performed ritual behaviors. Assessment with the Griffith-III developmental scale [Association for Research in Infant and Child Development (26)] revealed an immature level of development (limit area). Adaptive behavior assessment performed via VABS-II interview with the mother (27) showed a globally adaptive level in line with age group (Adaptive Behavior Composite Score = 97). The profile was homogeneous but at the same time some difficulties emerged: "Communication" = 80 and "Motor Skills" = 81 levels are considered below the norm and "Daily Living Skills" = 87 and "Socialization" = 86 levels are in the lower limits of the norm. Assessment with the ADOS-2 (28) returned a score above the cut-off for ASD. To investigate language competence, the MacArthur questionnaire (29) was administered. This revealed the following results: (i) "producing gestures" and "receptive syntax" as for a 17 month-old child; (ii) receptive vocabulary as for a 20 month-old child; (iii) expressive vocabulary as for a 23 month-old child. The Child Behavior Checklist [CBCL; (30)] filled in by the mother to detect any behavioral problems revealed a borderline level for deficit in the "Attention" area. The RBS-R questionnaire (31) to investigate repetitive behaviors did not reveal significant results but at the time of diagnostic evaluation, the mother reported the presence of some repetitive behaviors (opening and closing doors, turning switches on and off) and rituals (closing the school gate). The questionnaire Toddler Sensory Profile 2 (32) showed atypical levels in the "Seeking," "Visual processing," and "Movement" scales. The EDQ questionnaire (33) for detecting precocious development did not reveal developmental regression.

In summary, Francesco received a diagnosis of neurodevelopmental disorders, specifically ASD. His clinical profile revealed global immaturity in development, difficulty in the socio-communicative domain, atypia in the "interest" area, language disorder in both expressive and receptive domains, and motor hyperactivity.

Materials and methods

Procedure

Initially, two CNR-ITD researchers working jointly with a staff clinician from the rehabilitation center analyzed the inclusion criteria and selected Francesco as a suitable child with ASD diagnosis to involve in this study. As Francesco was a pre-school child, we chose a play-based rehabilitative intervention. Furthermore, considering the child's specific deficit, all the activities we proposed were designed to promote WMC and EFs; these involved interaction with both analogue and digital materials, a feature intended to maintain Francesco's level of engagement. Furthermore, considering Francesco's nature in the socio-relational domain, we opted for a rehabilitative intervention that featured interaction between child and clinician.

Before commencing the treatment, one of the researchers trained the clinician in how to administer the designated cognitive tasks and conduct the rehabilitative intervention.

In the baseline phase, the clinician administered a series of cognitive tasks (see "Measures"). Subsequently, Francesco underwent 17 rehabilitative sessions, held twice a week for 9 weeks. Over this period, the clinician recorded the rehabilitation activity scores and noted qualitative observations. In the post-test phase, the clinician re-administered the cognitive tasks (Figure 1).

The case notes, observations, activity scores, and pre- and post-test results were all analyzed to assess the impact of the rehabilitative intervention and possible variables contributing to change.

Rehabilitative intervention

As mentioned, the proposed intervention adopted a play-based approach in order to engage Francesco and maintain his motivation to collaborate.

The main aim of the opening session was to present the intervention to the child. The clinician proposed a doggerel to introduce the intervention program, using a sheep puppet and a visual agenda to explain the activities. During this session, the clinician established a pact with Francesco and designated a set of behavioral rules.

Francesco subsequently underwent rehabilitative sessions of three different kinds (sessions A-B-C); these were repeated five times each

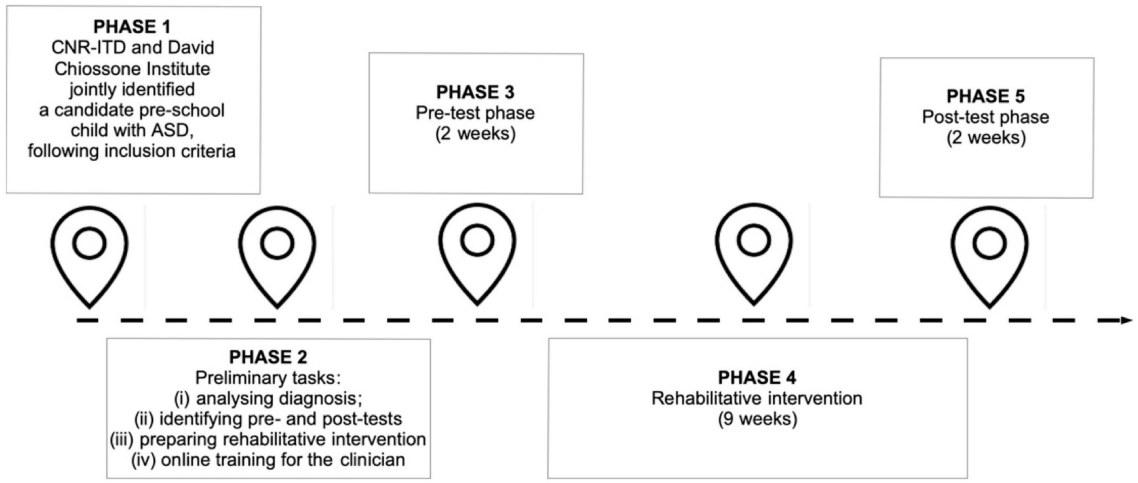

FIGURE 1
Timeline.

for a total of 15 sessions lasting 45 min each. To track Francesco's progress in automation and/or improvement in the targeted cognitive skills, the clinician annotated activity performance scores on a registration sheet.

Each session followed the same core phase structure: (1) familiarization; (2) cognitive training; and (3) metacognition (for details, see Supplementary material).

In the familiarization phase, the clinician introduced Francesco to the daily activities using the Sheep Puppet Companion, proposing the doggerel and showing the main activities of the day using the visual agenda.

The cognitive training phase comprised four mini-games, two of which were analogue and two digital. Specifically, this phase was split in two sections. The first involved two playful memory games (a specially-created analogical game and an educational digital app game) to enhance short-term memory and WMC. These were followed by playful EF games, once again involving a specially-created analogical game and an educational app game. The predetermined game order (first analogical then digital) was adopted as Francesco considered playing with the app[4] to be a reward. The decision to adopt the four short (3–5 min) mini-games, involving both analogue and digital materials, was driven by the intention to maintain interest, motivation and attention.

In the last phase, the clinician engaged Francesco in a metacognitive activity in which they reflected jointly about the strategies used in the games. In this phase, a set of visual strategy cards was employed.

In the last session, Francesco reflected with the clinician about all the activities undertaken. This included reflection about the strategies Francesco had used (metacognition). He then received a diploma of merit (prize) and a party was held involving the clinician, Francesco and his mother.

4 For details about the educational apps used in the rehabilitative intervention, see Supplementary material.

Measures

To investigate the effects of the proposed playful analogical-digital rehabilitative intervention, various cognitive measures were adopted during the pre- and post-phases.

Mr Cucumber (34) – task for assessing WMC in the visuo-spatial domain. The silhouette of an extra-terrestrial figure was displayed for 5 s with one or more colored stickers attached. Following each display (game item), the child had to show the position/s of the sticker/s on a separate bare silhouette. The game had eight levels (from 1 to 8 stickers appearing in each) and each level comprised three silhouette-display items. One point was given for each level at which the child got at least two of the three items correct, and an extra third of a point was assigned when response to all three items was correct (range: 0–8).

Backward Word Span [BWS; (35)] – task for assessing WMC in the verbal domain. The child was required to repeat lists of words (ranging from 2 to 7 words) in reverse order. Three list-items were presented at each level. One point was given for each level at which the subject got at least two of the three items correct, and an extra third of a point was assigned when response to all three items was correct (range: 0–7).

Direction Following Task [DFT; (36)] – task for assessing WMC in the receptive language domain. This task required the subject to follow oral directions of increasing complexity. There were three levels, with five items presented at each level. The score was calculated following Morra et al. (37) and the adapted version for pre-schoolers [(17); range: 0–3].

Day/Night Stroop (38) – task for assessing the ability to inhibit an inappropriately verbal response and to activate an alternative. In the first phase, the subject was required to say "day" when shown a white card with a yellow sun, and "night" for a black card with a moon and stars. In the second phase, the subject was required to invert the card/word association. There were 16 items for each phase (range: 0–32).

Simon Says (39) – task for assessing motor inhibition. In the first game, the child is instructed to perform an action only when the verbal cue "Simon says" is pronounced immediately before the corresponding command is given (activation trial), and to refrain

from carrying out that action if the cue is *not* pronounced first (inhibition trial). In the second phase of the game, an additional difficulty factor is added, namely the examiner performs each action regardless of whether the "Simon says" cue is pronounced or not. There were 10 items per phase. For each item, two points were given for the correct response, one point was given when the child self-corrected and inhibited his behavior, zero point was given when the child is wrong (range: 0–40).

Circle drawing (40) – task for assessing the ability to control ongoing motor response. It involves using a cardboard square with an 8.5 cm circle drawn on and a small arrow indicating the starting point. In baseline condition, the child moved a doll around the circle, and in a second condition had to repeat this with a toy snail, moving it as slowly as possible. The score was calculated as the proportion of the slowdown to the total time in both conditions using the following formula (T2 − T1)/(T1 + T2).

Dimensional Change Card Sort [DCCS; (41)] – task for assessing complex shifting. The child was shown a deck of cards with two variants – shape (rabbit, boat, etc.) and color. During the pre-switch phase, the child sorted the cards according to shape (6 items), and in the post-switch phase according to color (6 items). In the third phase, the experimenter explained that if a card had a black border, then the child had to sort according to shape, and if not, according to color (12 items). The pre-switch and post-switch phases were scored one point if at least five responses out of six were correct, and the border phase was scored one point if at least nine out of 12 were correct (range: 0–3).

Magic House (42) – task for assessing the constant monitoring and addition or deletion of working memory contents (updating). For each item, the child was shown three, four or five toy animals, which were placed sequentially in a cardboard house. He was then required to recall the last two animals placed in the house. There were nine items, each scored from 0 to 2 points (range: 0–18).

Peabody Picture Vocabulary Test, third version [PPVT-III; Italian version: (43)] – task for assessing receptive vocabulary. The experimenter read a word, and the child was asked to select the corresponding picture from a set of four. If the child gave eight correct responses before the first error, a 'basal' was established. The task then continued until the child reached an error rate of six out of the last eight items (ceiling). The score was the sum of correct responses; the items before the basal were considered correct (range: 0–175).

Results

The child was able to perform all the proposed digital and analogical activities, indicating the intervention's feasibility. He participated in both types of activity with interest and enthusiasm, demonstrating a preference for the apps.

We transformed the raw scores from each activity into z-points. Figure 2 presents a visual representation of Francesco's performance changes during the intervention. This shows qualitative improvements in almost all activities, especially those with apps. His progress in all sessions represents positive consolidation of abilities and achievement of the intervention goals.

In addition, comparison of pre- and post-assessments revealed some qualitative improvements. Concerning WMC, a small improvement in the DFT was found (from one to two correct responses at Level 1).

As to inhibition, the Circle Drawing task revealed an important finding: if we analyze only time, it seems that Francesco's performance declined, passing from performance between the twenty-fifth and fiftieth percentile to performance under the fifth percentile (44). However, when considering accuracy, we observe that in the post-test phase he did not make any errors. So, Francesco's performance declined in terms of time but improved in accuracy. A small inhibition improvement was also detected in the Simon Says task (from 16 to 20). Another small improvement was also detected in the updating task, Magic House (from 8 to 9): in the pre-test phase, Francesco obtained a score between the tenth and twenty-fifth percentile, while in the post-test phase between the twenty-fifth and fiftieth percentile (42). Finally, a qualitative improvement was also detected in the receptive language task, PPVT-III (from 7 to 17). In line with Stella et al. (43), in the pre-test phase Francesco had a weighted score of 67 and in the post-test phase a weighted score of 73.

In those tasks in which the child achieved better scores in the post-test phase, we also utilized the Jacobson and Truax (45) approach to reliable clinical change including calculation of the Reliable Change Index (RCI >1.96) using previous data sets to obtain the standard deviation and α coefficient. The RCI is a statistic that determines the magnitude-of-change score necessary for a given measure to be considered statistically reliable.

For the Simon Says activity, the RCI was calculated using the SD (7.39) and α coefficients (0.82) from a large sample of pre-schoolers (46).

The RCI for the DFT score was computed using the SD (1.08) and α coefficients (0.84) for the total score from a large sample of pre-schoolers (17).

The RCI for the total score of the Magic House activity was computed using the SD (2.12) and α coefficients (0.72) for the total score from a large sample of pre-schoolers (42). Specifically, SD regarded a subsample of children from 36 to 48 months old.

For the PPVT-III, the RCI was calculated using the SD (21.20) and α coefficients (0.96) from a large sample of pre-schoolers (47).

Although qualitative changes emerged from pre- and post-test assessment, significantly reliable improvements were not noted in Simon Says (RCI = 0.90), Magic House (RCI = 0.63), DFT (RCI = −0.54) or PPVT-III (RCI = 1.67), even if the last one approached statistical significance (Table 1).

Discussion

This study provides preliminary support for the feasibility of a new playful digital-analogical rehabilitative intervention for children with ASD, starting from pre-school age. The experience gained within this study gave us direct and concrete understanding of some key positive and critical aspects.

Key positive aspects of the intervention

On the positive side, the intervention set-up was well suited to the study's objectives; the tablet proved to be a very attractive device for promoting interest, motivation and attention. Indeed, while Francesco was very happy to carry out both the digital and analogical activities, he preferred those with the educational apps. During these activities,

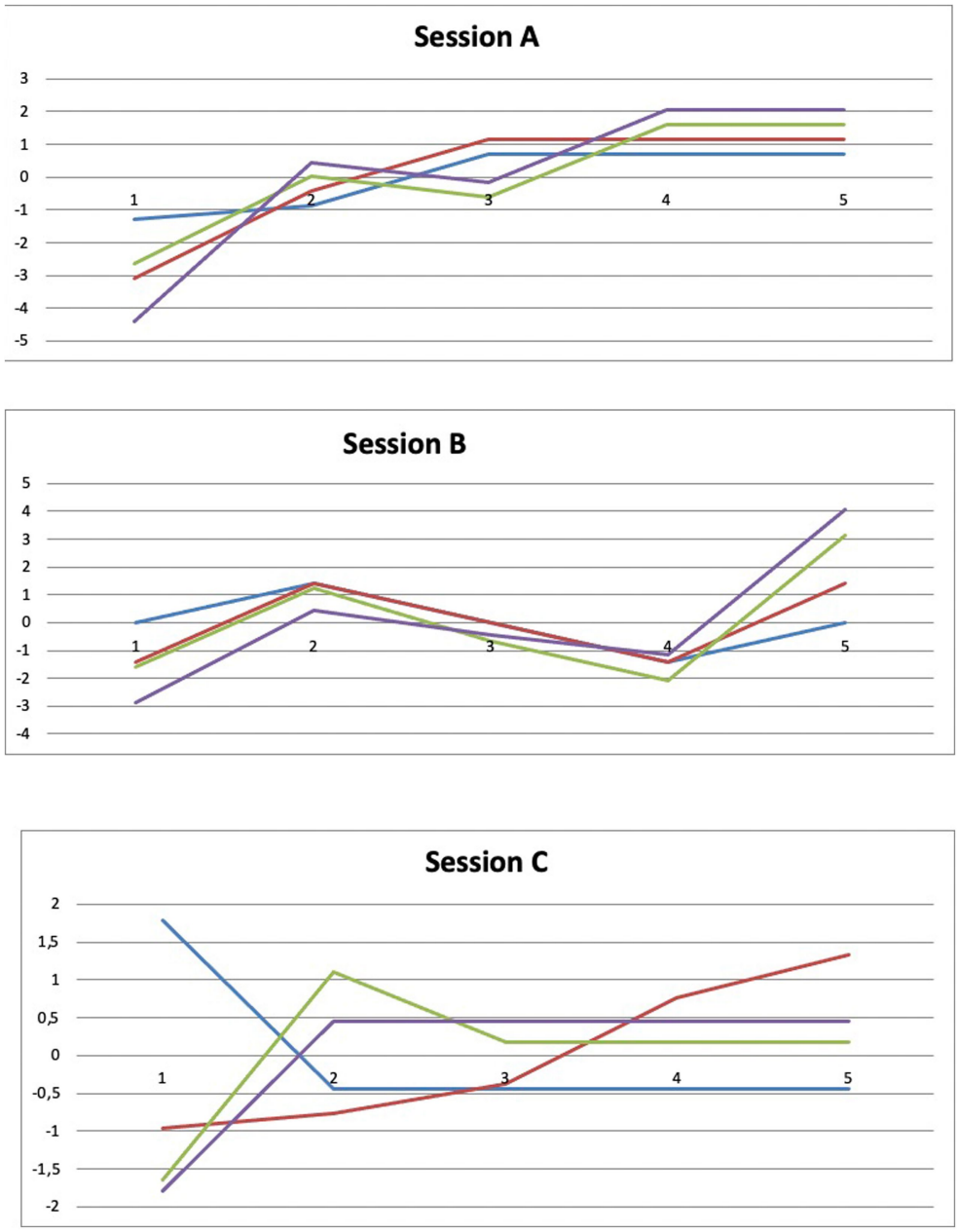

FIGURE 2
Changes in activity performance through the rehabilitative intervention (z-points). Blu lines: performance in analogue memory games; Red lines: performance in digital memory games; Green lines: performance in analogue EFs games; Violet lines: performance in digital EFs games.

he showed greater motivation and stronger improvement across the various sessions than in the analogue activities. This is consistent with findings reported in the literature, which suggest that pre-school digital-native children are very attracted and motivated by apps, a means they find very familiar and intuitive (24). Furthermore, the study findings also confirmed the capacity of educational apps to enhance WMC and EFs in an intervention program (21, 48). This is also in line with studies involving children with ASD, which highlight the added value of using digital technologies during the intervention (14), in particular when seeking to enhance cognitive abilities such as WMC and EFs (4). Overall, Francesco was able to tackle all the activities, both analogue and digital, and improved in performance. These findings underline the feasibility of the playful digital-analogical rehabilitative intervention proposed.

Analysis of pre- and post-assessments reveals qualitative enhancements in some cognitive domains. Specifically, a small improvement emerged in WMC. Concerning inhibition, we note enhanced accuracy in two tasks requiring inhibition in the motor domain; however, improved accuracy in the Circle Tracing task was offset by slower times. One very important finding regards improvement in Francesco's updating ability, an EF construct that remains both under-investigated and controversial where pre-schoolers are concerned (12), especially with ASD (9). These qualitative changes were not confirmed by the statistical analysis.

TABLE 1 Pre- and post-assessment scores and RCI index.

Measure	Pre	Post	+ improved; = no change; – worse	RCI index
Mr Cucumber	1	1	=	
BWS	1	1	=	
DFT	0.33	0.66	+	−0.54
Day/Night Stroop	31	27	–	
Simon Says	16	20	+	0.90
Circle Drawing Time	0.12	−0.31	–	
Circle Drawing Accuracy*	It goes around randomly leaving and reentering the circle	No error	+	
DCCS	2	2	=	
Magic House	8	9	+	0.63
PPVT-III	7	17	+	1.67

*For the circle drawing time data are available to compare findings with the normative sample [see (44)] but not for accuracy. We reported here data about accuracy as qualitative information.

This result could indicate that the intervention does lead to improvement, but to achieve significant improvement the intervention would need to continue over a longer time span.

The intervention not only seems to yield small qualitative improvements in WMC and EFs (the cognitive abilities directly enhanced), but also in language in the receptive domain, where it approaches statistical significance. This finding demonstrates that, when pursuing enhancement of WMC and EFs, interventions can also boost language capabilities, which, in the pre-school period, are related to WMC and EFs (49).

Furthermore, it is worth noting that the intervention featured opportunities for metacognitive reflection. This gave Francesco the chance to reflect jointly with the clinician about the strategies he adopted to undertake the various activities. This reflection was conducted using visual strategy cards, and this could have heightened awareness of his specific cognitive style and how it impacts on his daily functioning.

Limitations and further research

The findings reported in this study need to be considered in the light of the inherent limitations of a case study. Further studies on larger samples are needed to gain more comprehensive evaluation of the feasibility and generalizability of this intervention with children with ASD. Future studies with ASD children should seek to include both an experimental group that undergoes the intervention and a control group that does not. This is ambitious due to the heterogeneity of children with ASD. However, given that the playful digital-analogical rehabilitative intervention is customizable, it would be possible to investigate whether it could also be proposed to children along the spectrum of the autism. Another important aspect to be considered is that the pre-school child in the study only managed to pass the first levels of the proposed activities. This could mean that these activities are overly challenging for pre-school children. Therefore, we believe that it would be more appropriate to engage school-age children with ASD who have a medium or high cognitive level. Consequently, further research is needed to explore the actual feasibility and effectiveness of the intervention with school-age children with ASD as well.

Suggestions for clinical practice

The present case study provides some suggestions for clinical practice. First, in order to improve WMC and EFs in children with ASD, it's important to propose activities with a number of key characteristics so as to engage the subject and maintain motivation. Specifically, they need to be playful in nature, brief in duration, feature levels of progressively increasing difficulty, and involve interaction with a variety of materials, both analogue and digital. In this last case, it's preferable to propose analogue activities first and then move on to digital activities, which may be perceived by the child as a kind of reward. Furthermore, it's important to use mainly visual materials, since this is the preferential channel for most children with ASD, many of whom speak little or even not at all.

Furthermore, it's worth noting that in this case study the subject did obtain qualitative improvements – as revealed by results from the pre- and post-test phases - but only in some cases did those improvements approach statistical significance. With this in mind, it is advisable that future research should propose longer interventions as children probably need more experience with a greater number of activities in order to enhance WMC and EFs. Finally, where possible, parental involvement is important as children's motivation is boosted when they know they can show their progress to their parents at the end of the intervention.

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 approval was not required for the study involving human samples in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

SP: conceptualization, methodology, investigation, data curation, formal analysis, and writing—original draft. MD: collecting information about the patient's condition and data curation. LF: project administration, Funding acquisition, supervision, and writing—review. 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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1205340/full#supplementary-material

References

1. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders. 5th* ed. Washington, DC, USA: American Psychiatric Association (2013).

2. De Berardis D, De Filippis S, Masi G, Vicari S, Zuddas A. A neurodevelopment approach for a transitional model of early onset schizophrenia. *Brain Sci*. (2021) 11:275. doi: 10.3390/brainsci11020275

3. Mazza M, Pino MC, Mariano M, Tempesta D, Ferrara M, De Berardis D, et al. Affective and cognitive empathy in adolescents with autism spectrum disorder. *Front Hum Neurosci*. (2014) 8:791. doi: 10.3389/fnhum.2014.00791

4. Pasqualotto A, Mazzoni N, Bentenuto A, Mulè A, Benso F, Venuti P. Effects of cognitive training programs on executive function in children and adolescents with autism spectrum disorder: a systematic review. *Brain Sci*. (2021) 11:1280. doi: 10.3390/brainsci11101280

5. Giofrè D, Mammarella IC, Cornoldi C. The structure of working memory and how it relates to intelligence in children. *Intelligence*. (2013) 41:396–406. doi: 10.1016/j.intell.2013.06.006

6. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The unity and diversity of executive functions and their contributions to complex Frontal Lobe tasks: a latent variable analysis. *Cogn Psychol*. (2000) 41:49–100. doi: 10.1006/cogp.1999.0734

7. Burgess PW, Simons JS. Theories of frontal lobe executive function: clinical applications In: PW Halligan and DT Wade, editors. *Effectiveness of rehabilitation for cognitive deficits*. Oxford: Oxford University Press (2005). 211–32. doi: 10.1093/acprof:oso/9780198526544.003.0018

8. Miyake A, Friedman NP. The nature and organization of individual differences in executive functions: four general conclusions. *Curr Dir Psychol Sci*. (2012) 21:8–14. doi: 10.1177/0963721411429458

9. Wang Y, Zhang YB, Liu LL, Cui JF, Wang J, Shum DH, et al. A meta-analysis of working memory impairments in autism spectrum disorders. *Neuropsychol Rev*. (2017) 27:46–61. doi: 10.1007/s11065-016-9336-y

10. Tonizzi I, Giofrè D, Usai MC. Inhibitory control in autism spectrum disorders: meta-analyses on indirect and direct measures. *J Autism Dev Disord*. (2022) 52:4949–65. doi: 10.1007/s10803-021-05353-6

11. Leung RC, Zakzanis KK. Brief report: cognitive flexibility in autism spectrum disorders: a quantitative review. *J Autism Dev Disord*. (2014) 44:2628–45. doi: 10.1007/s10803-014-2136-4

12. Morra S, Panesi S, Traverso L, Usai MC. Which tasks measure what? Reflections on executive function development and a commentary on Podjarny, Kamawar, and Andrews (2017). *J Exp Child Psychol*. (2018) 167:246–58. doi: 10.1016/j.jecp.2017.11.004

13. Panesi S, Bandettini A, Traverso L, Morra S. On the relation between the development of working memory updating and working memory capacity in preschoolers. *J Intelligence*. (2022) 10:5. doi: 10.3390/jintelligence10010005

14. Grynszpan O, Weiss PL, Perez-Diaz F, Gal E. Innovative technology-based interventions for autism spectrum disorders: a meta-analysis. *Autism*. (2014) 18:346–61. doi: 10.1177/1362361313476767

15. Kapp K. *The gamification of learning and instruction: Game-based methods and strategies for training and education; Pfeiffer*. San Francisco, CA, USA: (2012).

16. Garon N, Bryson SE, Smith IM. Executive function in preschoolers: a review using an integrative framework. *Psychol Bull*. (2008) 134:31–60. doi: 10.1037/0033-2909.134.1.31

17. Panesi S, Morra S. Executive functions and mental attentional capacity in preschoolers. *J Cogn Dev*. (2020) 21:72–91. doi: 10.1080/15248372.2019.1685525

18. Cai KL, Wang JG, Liu ZM, Zhu LN, Xiong X, Klich S, et al. Mini-basketball training program improves physical fitness and social communication in preschool children with autism spectrum disorders. *J Hum Kinet*. (2020) 73:267–78. doi: 10.2478/hukin-2020-0007

19. Zhang Y, Tian H, Tao Y, Li Y, Wang D, Qin L. A study on the effects of three game intervention programs on executive functions of preschool autistic children. *Int J Develop Disabilit*. (2023):1–11. doi: 10.1080/20473869.2023.2215606

20. Saniee S, Pouretemad HR, Zardkhaneh SA. Developing set-shifting improvement tasks (SSIT) for children with high-functioning autism. *J Intellect Disabil Res*. (2019) 63:1207–20. doi: 10.1111/jir.12633

21. Panesi S, Ferlino L. A digital-analogical intervention program following a play-based approach for preschoolers: the effects on executive functions and ADHD symptoms in a pilot study. *Int J Inf Educ Technol*. (2023) 13:604–13. doi: 10.18178/ijiet.2023.13.4.1844

22. Panesi S., Ferlino L.. Enhancing executive functions in preschoolers: technologies yes or not? *Proceedings of 18th international conference on cognition and exploratory learning in the digital age (CELDA 2021)*, October 13–15 pp. 367–369 (2021)

23. Dini S, Ferlino L. La conoscenza tra le dita Dei bambini. Imparare e giocare a tempo di app. [Knowledge at their fingertips: kids' learning and playing in the app age]. *TD Tecnologie Didattiche*. (2016) 24:147–55.

24. Hirsh-Pasek K, Zosh JM, Golinkoff RM, Gray JH, Robb MB, Kaufman J. Putting education in "educational" apps: lessons from the science of learning. *Psychol Sci Public Interest*. (2015) 16:3–34. doi: 10.1177/1529100615569721

25. Gioia GA, Andrwes K, Isquith PK. *Behavior rating inventory of executive function-preschool version (BRIEF-P)*. Odessa, FL: Psychological Assessment Resources (1996).

26. Association for Research in Infant and Child Development. *Parent questionnaire: Griffiths III*. Oxford, UK: Hogrefe Ltd. (2020).

27. Sparrow SS, Cicchetti D, Balla DA. *Vineland adaptive behavior scales, second edition (Vineland-II)* Database record APA PsycTests (2005).

28. Lord C, Rutter M, DiLavore PC, Risi S. *Autism diagnostic observation schedule: ADOS manual*. Torrance, CA: Western Psychological Corporation (2008).

29. Fenson L, Marchman VA, Thal DJ, Dale PS, Reznick JS, Bates E. *MacArthur-Bates communicative development inventories, second edition (CDIs) [database record]*. Washington, DC: APA PsycTests (2006).

30. Achenbach TM, Edelbrock C. *Manual for the child behavior checklist and revised child behavior profile*. Burlington, VT: Author (1983).

31. Lam KSL, Aman MG. The repetitive behavior scale-revised: independent validation in individuals with autism spectrum disorders. *J Autism Dev Disord*. (2007) 37:855–66. doi: 10.1007/s10803-006-0213-z

32. Dunn W. *Sensory profile 2*. Bloomington, MN, USA: Psych Corporation (2014).

33. Ozonoff S, Williams BJ, Landa R. Parental report of the early development of children with regressive autism: the delays-plus-regression phenotype. *Autism*. (2005) 9:461–86. doi: 10.1177/1362361305057880

34. Case R. *Intellectual development: birth to adulthood*. Orlando, FL: Academic Press (1985).

35. Morra S. Issues in working memory measurement: testing for M capacity. *Int. Soc. Study Behav. Develop.* (1994) 17:143–59. doi: 10.1177/0165025494017001

36. Pascual-Leone J, Johnson J. A dialectical constructivist view of developmental intelli- gence In: O Wilhelm and R Engle, editors. *Handbook of understanding and masuring intelligence*. Thousand Oaks, CA: Sage (2005). 177–201.

37. Morra S, Camba R, Calvini G, Bracco F. Italians do it better? M-capacity measurement and cross-linguistic differences in the direction following task (DFT). *J. Appl. Psycholing.* (2013) 13:9–24.

38. Gerstadt CL, Hong YL, Diamond A. The relationship between cognition and action: performance of children 3 1/2-7 years old on a Stroop-like day- night test. *Cognition*. (1994) 53:129–53. doi: 10.1016/0010-0277(94)90068-x

39. Marshall PJ, Drew AR. What makes Simon Says so difficult for young children? *J Exp Child Psychol*. (2014) 126:112–9. doi: 10.1016/j.jecp.2014.03.011

40. Bachorowski JA, Newman JP. Impulsivity in adults: motor inhibition and time-interval estimation. *Personal Individ Differ*. (1985) 6:133–6. doi: 10.1016/0191-8869(85)90041-8

41. Zelazo PD. The dimensional change card sort (DCCS): a method of assessing executive function in children. *Nat Protoc*. (2006) 1:297–301. doi: 10.1038/nprot.2006.46

42. Panesi S, Morra S. La Casetta Magica. un nuovo strumento per indagare l' aggiornamento (updating) della memoria di lavoro in eta` prescolare [The Magic House. A new measure of updating for pre-schoolers]. *Psicol Clin Svilupp*. (2017) 21:443–62. doi: 10.1449/88502

43. Stella G, Pizzoli C, Tressoldi PE. *Peabody test di vocabolario recettivo [Peabody picture vocabulary test]*. Torino: Omega (2000).

44. Usai MC, Viterbori P, Gandolfi E, Traverso L. *FE-PS 2–6: Batteria per la valutazione delle funzioni esecutive in età prescolare* Edizioni Centro Studi Erickson (2017).

45. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *J Consult Clin Psychol*. (1991) 59:12–9. doi: 10.1037/0022-006X.59.1.12

46. Bandettini A, Traverso L, Panesi S, Morra S. The relationship between working memory, updating and inhibition in preschool children. *Jean Piaget Soc.*. 1-3 June, Madrid. (2023)

47. Traverso L, Viterbori P, Gandolfi E, Zanobini M, Usai MC. The contribution of inhibitory control to early literacy skills in 4-to 5-year-old children. *Early Child Res Q*. (2022) 59:265–86. doi: 10.1016/j.ecresq.2021.11.010

48. Panesi S, Ferlino L. Using apps in formal education to improve executive functions in preschoolers. *International Proceedings of the International Conference on Innovation, Documentation and Education INNODOCT 2019*. (2019):189–19.

49. Panesi S, Morra S. The relation between drawing and language in preschoolers: the role of working memory and executive functions. *Cogn Dev*. (2022) 61:101142. doi: 10.1016/j.cogdev.2021.101142

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EDITED BY
Fengyu Zhang,
Global Clinical and Translational Research Institute, United States

REVIEWED BY
Anna Ceraso,
University of Brescia, Italy
Aseel Al-Jadiri,
Seton Hall University, United States
Romain Coutelle,
Hôpitaux Universitaires de Strasbourg, France

*CORRESPONDENCE
Francesca Cucinotta
✉ francesca.cucinotta@irccsme.it

†These authors have contributed equally to this work

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An individual-supported program to enhance placement in a sheltered work environment of autistic individuals mostly with intellectual disability: a prospective observational case series in an Italian community service

Roberta Maggio[1†], Laura Turriziani[1,2†], Caterina Campestre[1], Marcella Di Cara[3], Emanuela Tripodi[3], Caterina Impallomeni[3], Angelo Quartarone[3], Claudio Passantino[1] and Francesca Cucinotta[3*]

[1]Center for Autism "Dopo di noi", Barcellona Pozzo di Gotto, Messina, Italy, [2]Unit of Child Neurology and Psychiatry, Department of Human Pathology of the Adult and Developmental Age, "Gaetano Barresi" University of Messina, Messina, Italy, [3]IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy

Introduction: Autism spectrum disorder is a lifelong neurodevelopmental disorder. The profile of functioning in autistic people is very heterogeneous, and it is necessary to take into account individual characteristics to better support integration in the workplace. However, unemployment rates are higher for autistic people than for other types of disabilities. We present a prospective case series to explore the feasibility and efficacy of an individual-supported program to enhance placement in a sheltered work environment delivered by an Italian community day care center.

Methods: Autistic subjects, aged from 12 to 31 years, participated in an individual-supported program regarding employment in sheltered art workshops, integrated into the regular activity of a semi-residential center three times a week for 1 year. Their feasibility retention rate and time worked per session were registered; moreover, working methods efficacy and self-organization improvement were tracked by the Likert-based rating system. Secondary outcome measures span functional levels, challenge behaviors, and sensory problems.

Results: All the individuals presented a good adaptation to the environment, with a significant increase in time worked per session. After 1 year, the intervention allowed an increase in tasks completed in an assigned complex job and an improvement in self-organization within the work schedule in a group of subjects consisting mainly of severe-to-moderate levels of autism severity (86.6%). Finally, we observed a significant increase in independent functioning areas of the TEACCH transitional assessment profile. Challenge behaviors and sensory problems were also recorded.

Conclusion: This case series supports the idea that individual-supported programs for placement in sheltered job environments delivered by community day care centers could be feasible and effective for ASD with higher levels of severity and co-occurring intellectual disability. Further targeted studies based on community models and accessible methods need to be planned to define the effectiveness of the intervention and promote improved practice at the community level with a better social impact.

KEYWORDS

autism spectrum disorder, intellectual disability, employment, vocational/labor participation, transitional age, adolescents, adult

1. Introduction

Autism spectrum disorder (ASD) is an early onset, pervasive, and lifelong neurodevelopmental disorder (1). After the first diagnosis, psychosocial and behavioral interventions are needed to ameliorate core symptoms and to improve specific skills, such as joint attention, language, and social engagement (2, 3). Thereafter, in adolescence and adulthood, the treatment is focused on social skills (4–6), emotional and behavioral problems (7, 8), managing the co-occurring mental health conditions (9–11) and promoting independence, personal autonomy, and self-employment (12–14). However, many autistic adolescents or young adults do not receive adequate support for attaining and maintaining employment (15). Indeed, over the transition period from school to work, only 25% of autistic individuals got paid work (16). Specifically, 80% of autistic adults are estimated to be jobless worldwide (17), and recent reports affirm that unemployment rates are higher for autistic people than for other types of disabilities (18, 19). Conversely, it has been recorded that people with autism who receive vocational rehabilitation services have a higher rate of competitive employment (37%). Social inclusion labs offer training and dignity to young people with ASD, but it is estimated that only 1.1% have received them, making the unemployment rate higher (20). Therefore, it should be considered the use of integrated vocational rehabilitation and high school employment transition programs, especially some components of these interventions, such as vocational counseling and intensive employment support services (21). Thus, outcomes for autistic adults have frequently been described as poor, although there is variability based on individual characteristics including intelligence quotient (IQ), ASD severity, socio-economic status, and parental support (22). Autistic subjects often experience difficulties with social interactions, problem-solving in social situations, and troubles with changing routines, based on their neuropsychological profile, which could cause problems and loss of work (23). Indeed, the profile of functioning in autistic people is very heterogeneous, and it is necessary to take into account individual characteristics to better support integration in the workplace (24). Often, autistic people show intellectual disability (ID) (25) and psychiatric comorbidities (26–28). A recent study showed that ∼31% of 8-year-old children with ASD presented a co-occurring intellectual impairment (intelligence quotient <70) (29). The Centers for Disease Control and Prevention confirmed this percentage and reported that ∼33% of autistic children were estimated to have ID (30). Despite this high prevalence, autistic individuals with intellectual disability are often excluded or routinely under-recruited in studies regarding interventions to improve vocational integration with a consequent lack of data (31).

Usually, existing employment options include sheltered employment, supported employment, and competitive employment (32). The majority of the studies have evaluated inclusion programs in sheltered workshops, which allow autistic adults to obtain a job more easily (33). Most of these programs start by identifying the individual's strengths and interests, aiming to find the right job position, and finally providing the necessary support and strategies to improve adjustment, social cognition, and independence (34–36). However, the systematic review of Walsh et al. (37) highlighted the paucity of research that addresses sheltered employment despite the great opportunity that it represents for autistic people. Among the experiences reported in the literature, the Adult Life-Skills Program of the Princeton Child Development Institute (PCDI) begins preparation well before the age of 21 years, and the areas in which intervention is provided concern fundamental skills (care self, language, social skills, leisure skills, community skills, and work skills) (14). Another college-to-career transition intervention program, PEERS® for Careers, has shown promise in addressing the multi-faceted needs of autistic people in the workplace. Autistic pre-adults have been able to learn employment-related social skills (38). However, among the critical issues encountered, difficulties in the social aspects of work are reported, especially in communication with supervisors or colleagues (39).

In Italy, there are several projects for the job placement of autistic people. Most of them provide individual paths based on specific characteristics. The main activities involve farm-related chores (Cascina Rossago, residential farm community, Pavia; European Therapeutic Center, Florence) (40), catering works (A.L.I. Project, Ascot srl, Florence; PizzAut Onlus, Milan), and artistic pathways (Fondazione Bambini e Autismo Onlus, Pordenone). In Modica, where in Sicily, a project was implemented leading to the creation of a B & B run by young adults with neurodiversity, including ASD (La Casa di Toti onlus).

We present a prospective case series that evaluated the feasibility and effectiveness of a 1-year individual-support program

for autistic people, both adolescents and adults, in a Musiva Art Laboratory. Within the workshop, autistic people were involved in the production and promotion of artworks. The lab was integrated into an Italian community service, in the province of Messina, in Barcellona Pozzo di Gotto, operated by the Social Coop "Progetto Dopo di Noi." The principal aim was to improve placement in a sheltered work environment, teaching functional skills and self-directed actions to autistic young adults who have heterogeneous profiles and a wide range of intellectual functioning.

2. Materials and methods

2.1. Participants and ethics

Subjects were consecutively enrolled and treated at the specialized Autism "Progetto Dopo di Noi" in Barcelona P.G., Italy, and evaluated at the IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, from January 2021 to January 2023. The local Ethics Committee approved the study (IRCCSME 39/2017). Researchers provided clear and concise study information to most participants even using supportive tools based on each subject's functioning to maximize participation in decision-making. Written informed consent was obtained from participants or from both parents according to the terms established by law. All procedures comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration. The inclusion criteria were fulfilling DSM-5 diagnostic criteria for autism spectrum disorder (1), age between 12 and 35 years old, and minimal communication ability (verbal speech or augmentative and alternative communication, AAC). Participants were excluded if they presented severe aggressive behaviors or severe hypersensitivity to the work materials (i.e., clay, glass, painting, or glue).

2.2. Measures and design

At the time of recruitment, all subjects undergo a complete diagnostic assessment including neuropsychological and behavioral testing. IQ was determined using the Leiter International Performance Scale—third edition (41). Autistic behaviors were assessed using the Autism Diagnostic Observation Scales—second edition (ADOS-2) (42). Adaptive functioning was evaluated using the Vineland Adaptive Behavior Scales—second edition (VABS-II) (43).

Feasibility was evaluated in terms of engagement and participation in the educational programs and demonstrated through analysis of service utilization and retention rate. In addition, we measured compliance by registering the time in minutes that each participant worked per session.

To evaluate preliminary efficacy, we documented specific target behaviors through task analysis and data collection methods by two independently trained therapists. The average inter-observer agreement (IOA) across all participants was 93.6%. Specifically, we evaluated (A) work chain procedure (as the number of tasks executed) and (B) self-organization and autonomy in the work processes using both a six-point Likert-based rating system that focuses on specific skills; for more details (see Supplementary Table S1).

Secondary outcome measures included the TEACCH Transitional Assessment Profile (TTAP) (44): the TTAP is designed to provide assessment data for transition planning from school age to adolescence and adulthood, it is a criterion-referenced test designed for autistic individuals who have mild-to-severe intellectual disabilities and are over 12 years of age. We used the Direct Observation Scale of the TTAP in this study. The TTAP test items cover the six functional areas of vocational skills (VS), vocational behaviors (VB), independent functioning (IF), leisure skills, functional communication, and interpersonal behavior. Based on the observation in specific assessment tasks, the psychologist rated participants' performance on a three-point scale consisting of pass (P), emerging (E), or fail. Each scale consists of twelve sub-items, which indicate different functional levels. As outcome measures of the ISP, we take into account only the VS, VB, and IF subscales. Participants were evaluated before (T0) and after (T1) the completion of the intervention program, by the same blinded expert child psychologist and psychiatrist. Furthermore, each subject based on tactile hypersensitivity was gradually exposed to the material used in the art laboratory (clay, paint, or glass); to measure material tolerability, data were taken at the time of manipulation in the absence of problem behaviors or signs of distress. In addition, we measured challenging behaviors (i.e., hetero-directed aggression, self-injurious behavior, or throwing and destroying objects) through the frequency/event and rate recording method, which implicates counting and recording the number of times a behavior happens within each work session by two independent trained therapists (45, 46).

To analyze differences at the two time points, we adopted repeated measures ANOVA, using severity level as a covariate. To account for assumptions of violation of repeated measures ANOVA, we used the Greenhouse–Geisser degrees of freedom correction strategy.

2.3. Intervention

The people participated in an individual-supported program regarding employment in sheltered art workshops, integrated into the regular activity of a semi-residential center for autistic adolescents and young adults, three times a week for 1 year. The essential goal of ISP was to increase compliance with work rules and the cooperative work method (work chain). Simultaneous to the professional goals, we aimed to improve independence and self-organization and to develop new skills and their ability to adapt to the work environment.

The standardized ISP was based on the TEACCH approach (34) adapted within the applied behavior-analytic framework; the structure and strategies used for the ISP are elucidated in Supplementary Table S2. The work program was set up after an initial assessment of the functional skills (TTAP) of each participant. Autistic individuals have been included in the laboratory, involving them in the production and promotion of their artistic projects. The work programs were carried out by a qualified group of therapists and art teachers. Each session was

organized through a structured environment program based on the TEACCH method, aimed at hiring in the laboratory as employees (47). Environment and individual activities were organized to optimize learning and avoid frustration. Participants, through an individualized program, experienced an increase in structure to promote independence by adult guidance/suggestions from the organization of the physical environment (e.g., settled tables with well-divided materials in the same position, minimizing possible distractions in a manner consistent with the people's needs), activity systems (e.g., predictable arrangement of activities by the use of visual schedules of work routines; basic left-to-right-to-finished routines across work routines), visually structured activities (e.g., materials designed to specifically target or explicitly teach skills), well-established routines (e.g., visual countdown), and positive behavior management (48). In addition, applied behavior analysis (ABA) principles were used, which include different procedures that can be well combined as well as the use of the visual prompt and subsequently of the fading. Furthermore, chaining has been used to promote autonomy and job skill learning: a stimulus-response chain is a sequence of discriminative stimuli (SD) and responses (R) of which each R, except the last, provides the SD for the next ones, while the last one is typically followed by a reinforce (49).

Based on the individual ability of each person, the main method to be used to teach a stimulus–response chain was chosen, namely:

- The entire presentation of the task (through this modality, the subject tries every time all the steps from the beginning to the end of the sequence, only then he will carry out the whole task until he reaches a certain mastery in each step).
- Retrograde chaining (gradually building the chain in the opposite direction to that in which it is normally done; that is, first the last step is established, then the penultimate is taught and concatenated with the last, then the antepenultimate is concatenated with the other two, and so on, continuing back to the beginning of the chain).
- Forward chaining (the initial step in the chain is taught first and then the second step is taught; these are chained together, moving on to the first three steps, and so on until the entire sequence is learned).

3. Result

In total, we enrolled fifteen autistic people, aged from 12 to 31 years (with mean age 22.5 ± 5.3 years), with a percentage of adolescent subjects of 21.1%. Three were female subjects, and 12 were male subjects, with M:F = 4:1 ratio. All the subjects fulfilled the autistic cutoff value in ADOS2; among those, eight (53.3%) presented an autism severity level 3, five (33.3%) presented level 2, and two (13.3%) presented level 1, which accompanied intellectual disability (IQ level ≤ 70) in 10 subjects (66.7%). The mean adaptive behavior composite score was 90.1 at VABS-II, see global demographic details in Table 1. Specifically, three individuals (20.0%) displayed severe language impairment, while five (33.3%) and seven (46.7%) individuals had moderate and mild impairment, respectively. Challenging behaviors were exhibited more frequently

TABLE 1 Demographic and clinical characteristics of the entire sample.

	N	Mean ± SEM or %	Range
Age in years	$N = 15$	22.5 ± 5.3	12–31
Sex			
Male	12	80%	
Female	3	20%	
M:F ratio	4:1		
ASD severity			
Level 1	2	13.3%	
Level 2	5	33.3%	
Level 3	8	53.3%	
I.Q.			
>70	5	33.3%	
≤70	10	66.7%	
VABS-II score			
Communication	15	22.25	20–29
Daily living skills	15	28.75	20–39
Socialization	15	22	20–28
Adaptive behavior composite score	15	90.1	50–153
ADOS-2			
On the autism spectrum	0	0%	
Autistic	15	100%	

IQ, intelligence quotient; VABS-II, Vineland Adaptive Behavior Scales II edition; ADOS-2, Autism Diagnostic Observation Schedule-second edition.

by seven (46.7%) subjects, and five subjects (33.3%) presented psychiatric comorbidity, represented by obsessive-compulsive disorder ($N = 3$, 60.0%), anxiety disorder ($N = 1$, 20.0%), major depressive disorder ($N = 1$, 20.0%); Supplementary Table S3 shows whole clinical and behavioral features of each person. Regarding engagement and participation, the retention rate of autistic people who completed 1 year of ISP was 100%. All the individuals presented a good adaptation to the environment. Specifically, we found a significant increase in time worked per session ($F = 4.73$, $p = 0.048$; Figure 1). After 1 year of ISP, the number of tasks completed in the work chain procedure increased significantly for all kinds of subjects ($F = 6.33$, $p = 0.026$; Figure 2A); furthermore, the number of tasks completed independently increased although not in a statistically significant way: for most participants, task engagement and self-organization were maintained even without the job coach's control (Figure 2B). During the work period in the art lab, some individuals showed such involvement that they were able to create entire works of art by themselves (Supplementary Figure S1). Moreover, we analyzed the passed items (P) in TTAP functional areas of vocational skills, vocational behaviors, and independent functioning. Among those, by repeated measures-ANOVA, we observed a significant increase in the IF subscale at T1 ($F = 22.29$, $p < 0.001$; Figure 3A) as well as significant interaction with the severity level ($F = 9.43$, $p = 0.009$).

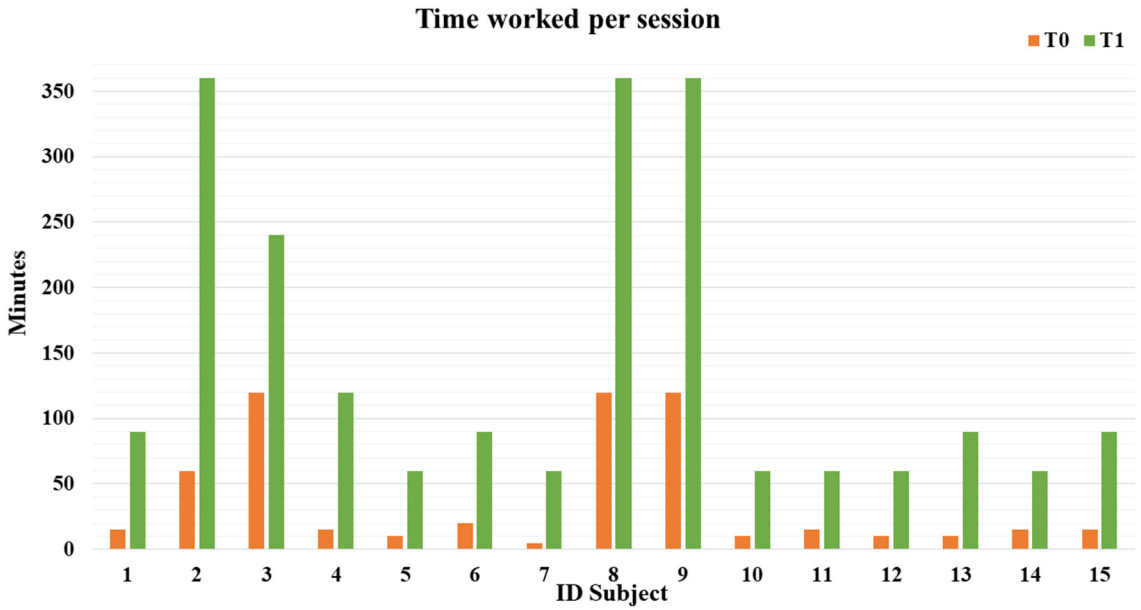

FIGURE 1
Time worked per session for each subject at T0 (baseline) and T1 (1 year later).

The same trend was verified in IF emerging items too ($F = 21.41$, $p < 0.001$) as well as significant interaction with severity level ($F = 15.29$, $p = 0.002$). There were no significant improvements in the VS and VB areas (Figures 3B, C). At baseline, most subjects showed mild tactile hypersensitivity to manipulation. During the art lab, each subject was gradually exposed to and worked with different materials (clay, glass, paint, and glue) that had different sensory characteristics. In particular, eight subjects (ID 1, 2, 3, 4, 6, 8, 9, and 15) presented a great improvement and were then able to manipulate the material for a longer time, without presenting signs of stress (Figure 4). Finally, 11 subjects presented problematic behaviors at the beginning of ISP, reduced over time or completely resolved for three individuals.

4. Conclusion

In this prospective observational case series, we described 15 autistic individuals who participated in an individual-support program integrated into the rehabilitative activities of an Italian semi-residential center for autistic adolescents and young adults. The group consisted of ASDs of different severity, with a greater presence of moderate and severe levels; furthermore, 66.7% of them presented a cognitive disability, accompanied by impairment in adaptive function. The ISP aimed to teach functional skills and self-directed actions usefully to employment in sheltered art workshops. Established on individual needs, the ISP program was based on the TEACCH approach in combination with applied behavior-analytic principles. This study mainly focused on (a) feasibility and engagement documented through retention rate and time in minutes that each participant worked per session; (b) working methods efficacy and self-organization improvement tracked by the Likert-based rating system; (c) changes in the level of functioning through TTAP (VS, VB, and IF areas); (d) management of challenging behaviors by registered the frequency/event and rate recording method; and (e) tolerance to tactile sensory stimuli through the time in minutes of material manipulation in the absence of signs of distress. Collectively, this case series demonstrated the feasibility of integrating professional ISP into a semi-residential Italian center, documented by the full participation in the educational programs, and the growing time in minutes that each participant worked per session. Moreover, the intervention allowed an increase of tasks completed in an assigned complex job and an improvement in self-organization and autonomy within the work schedule in a group of people consisting mainly of severe-to-moderate levels of autism severity (86.6%). This achievement was accompanied by an improvement in the IF areas, both in passed and emergent items.

By looking at the improvement trend, even though the sample size is too small to draw absolute conclusions, the time worked per session and the tolerance to work materials appear to be the variables that, at baseline, guide a better result and a greater enhancement, independently by the autism severity level and the intellectual functioning (Supplementary Figure S2). These considerations may suggest what has already been stated in the literature: a greater correspondence between professional aptitude and occupational placement may improve engagement, learning, and behavioral development (50, 51). The degree of intellectual disability influences outcomes in adulthood (52), but it is clear that this is not the only factor, and the impact of other variables, including personal preference, needs to be evaluated (37). Although these results cannot be generally applicable, this report supports the idea that individual-supported programs could be effective in preparing autistic subjects with higher levels of severity and co-occurring intellectual disability for placement in sheltered job environments, in line with previous studies (53).

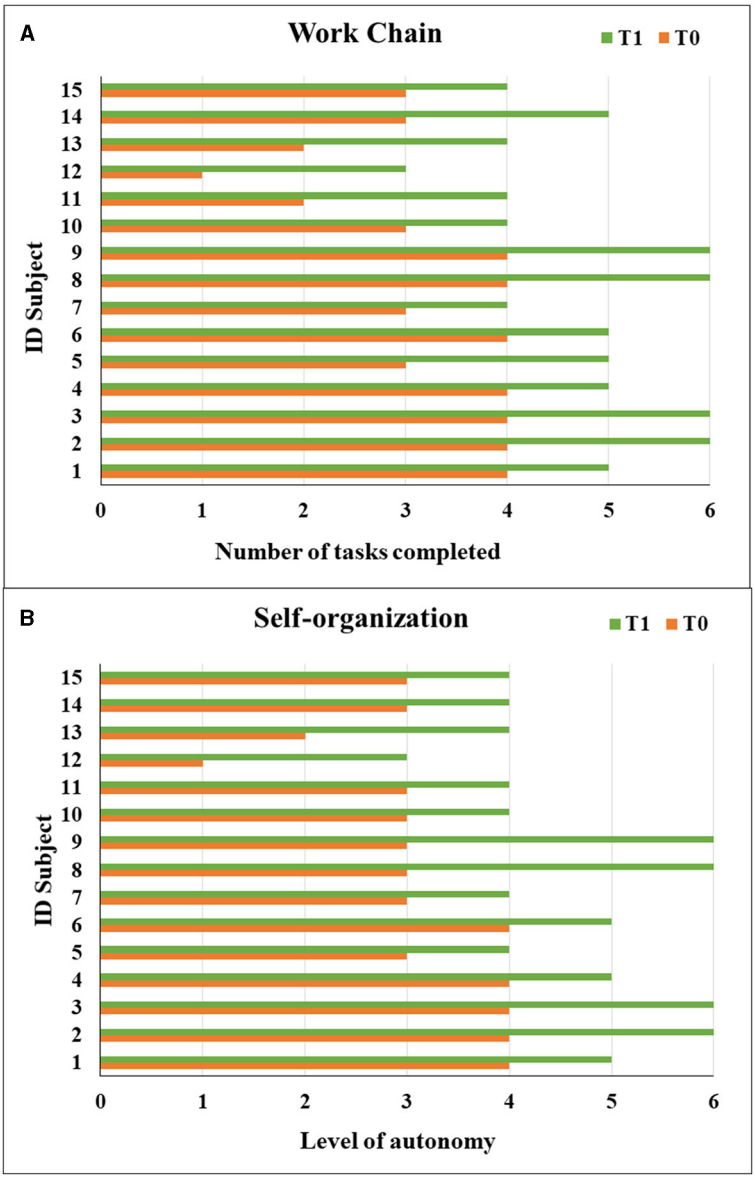

FIGURE 2
Tasks completed in the work chain procedure from each subject at T0 and T1 **(A)**. Self-organization and independence in work sessions for each subject at T0 and T1 **(B)**.

It will be favorable to consider it as part of the usual activities planned by daily community rehabilitation centers, especially since it should be designed for the most levels of ASD severity and intellectual disability to increase skills or vocational dispositions that will help them in adaptive functioning and increase their community participation (54–56). It is also useful to promote the job placement of adults with autism, with or without intellectual disabilities, to organize comprehensible timed sequential programs that promote choice and autonomy, and an individualized work schedule and a well-defined role must be considered, to provide participants with the necessary adjustment phase (57). Many autistic people display unique skills that may be valuable to specific employment, such as attention to detail and tolerance for repetition (58, 59). The feasibility of an individual-supported program to enhance placement in a sheltered work environment in the Italian community is supported by other experiences on the national territory. The implementation of publicly funded employment services is critical in view of the rapid increase of adults with autism in need of employment support. A recent study conducted a survey for autistic adults to improve the understanding of current services experienced in different countries of the European Union (60). The responders globally preferred autism-specific support services; however, autistic adults living in Italy reported more often that they had tried to get a service and failed (residential, employment, and education services). It seems worthwhile to suggest that the Italian Public Health System continue to allocate resources for the training of health professionals and to promote and facilitate greater community involvement for autistic people, including through integrated vocational pathways in daycare centers. One of the main limitations of this study is the number of subjects

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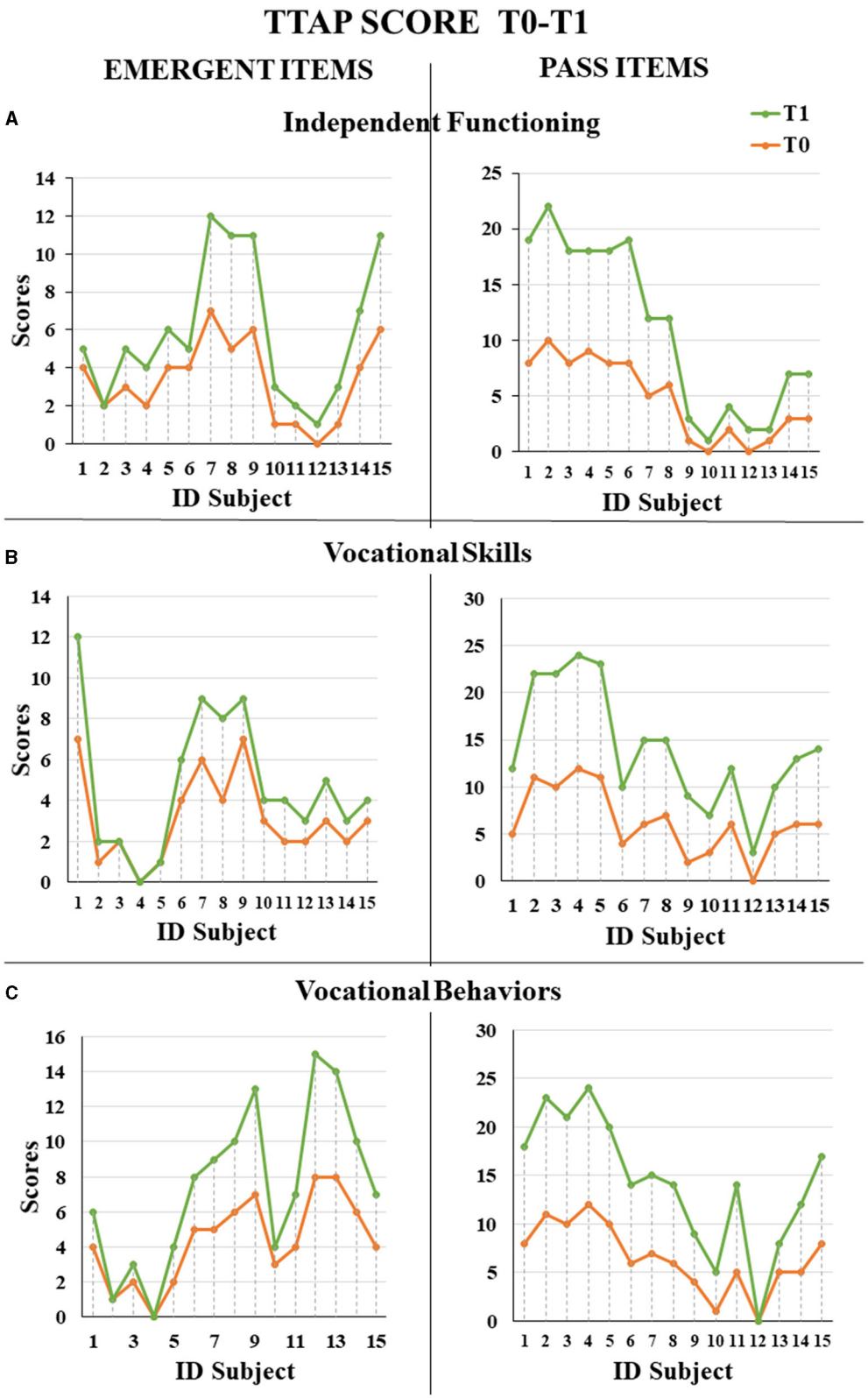

FIGURE 3
TTAP emergent and pass scores for each subject at T0 and T1 **(A)** Independent functioning scores; **(B)** Vocational skills score; **(C)** Vocational behaviors score.

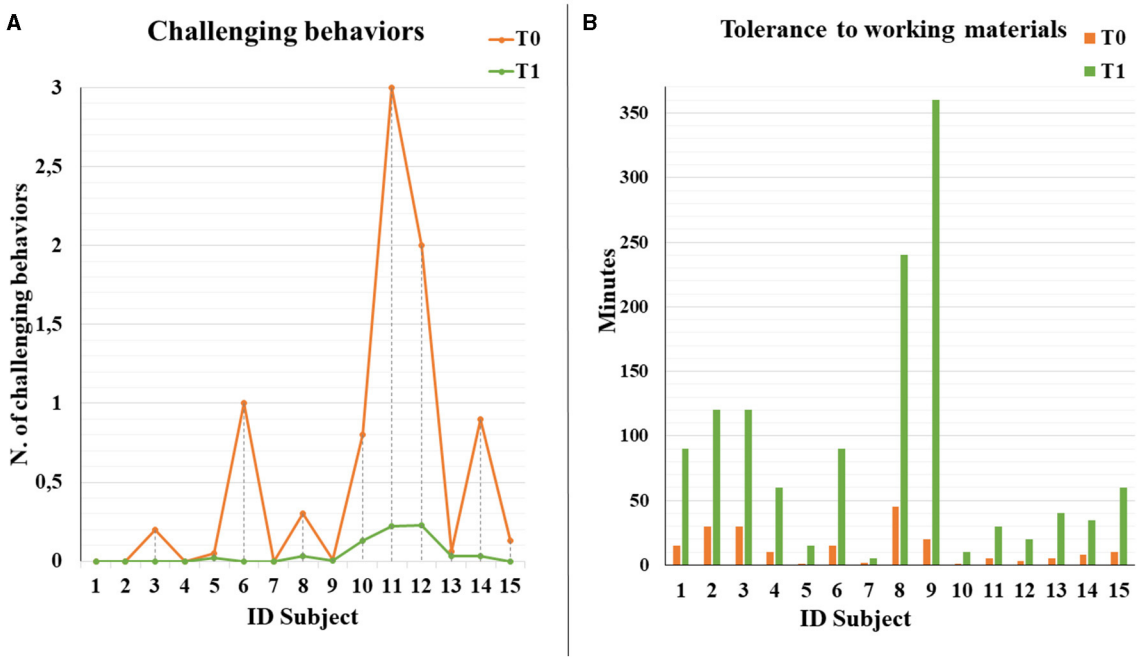

FIGURE 4
Challenging behavior rates recorded for each subject at T0 and T1 **(A)**. Time spent to work with the material then initially was poorly tolerated for each subject at T0 and T1 **(B)**.

reported, therefore, further studies with bigger sample sizes have to be conducted in order to corroborate our results. Thus, this small sample cannot be representative of the ASD population; however, including all consecutive autistic individuals reduces the chances of bias and increases the validity for generalizing the results. In addition, the sample size in our study is relatively small in statistical terms, which limits the conclusions that can be drawn from these data. A second important limitation was that we only measured participation and engagement in educational programs, in terms of service usage and retention rate. We missed an important occasion to collect and take into account participants' and their parents' point of view in a standardized way. Gathering different perspectives who share their lived experiences of services is very important in developing a service (61); it would have been desirable to devise a more participatory approach from the outset, with the inclusion of the autistic perspective (62). Finally, we did not have a control group to compare outcomes and feasibility. However, this would be a beginning step: we believe that these case series could help health professionals to stake on their individuals, and, given our results, it seems useful to propose that the rehabilitation centers and semi-residential services plan individual-supported programs to enhance placement in a sheltered work environment for qualifying inclusive and personalized emancipation paths of autistic young. In moving forward, it seems necessary that the social inclusion efforts favor the maturation and growth of the individual through qualified and specific paths of development of skills that allow to achieve a degree of personal, social, and work autonomy, appropriate to everyone's potential (63). There is a need to identify better strategies to guide the choice of goals within the adolescent transition (64) and to build a better exchange of community and work-place supports: adults with disabilities often aspire to start and maintain real jobs (65), and an individual-supported program may offer the means for achieving this goal. Research related to transition and employment in autism needs more development, filling the gap of evidence-informed approaches guiding service delivery (66). Further research is needed to define how to address the heterogeneity of ASD concerning professional support and to better clarify the key elements of community-based support models related to autistic individuals in adulthood. In addition to community studies on the short-term work of autistic people, it would also be appropriate to implement research on subjects in need of long-term work services, identifying the favorable prognostic neuropsychological characteristics.

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 humans were approved by Comitato Etico IRCCS Sicilia—Sezione Centro Neurolesi Bonino-Pulejo. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

RM, LT, and CC participated in the study design and coordination, provided clinical oversight for data collection and interpretation, and drafted the manuscript. AQ and FC conceptualized the study and supervised the manuscript. MDC participated in data collection and processing, contributed to the literature review, and helped draft the manuscript. FC performed statistical analysis of the data. ET and CI contributed to the literature review and helped draft the manuscript. CP supervised the coordination of the study. All authors have read and agreed to the published version of the manuscript.

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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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1225236/full#supplementary-material

References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Washington, DC: American Psychiatric Association (2013). doi: 10.1176/appi.books.9780890425596

2. Fuller EA, Oliver K, Vejnoska SF, Rogers SJ. The effects of the early start Denver model for children with autism spectrum disorder: a meta-analysis. *Brain Sci.* (2020) 10:368. doi: 10.3390/brainsci10060368

3. Reichow B, Hume K, Barton EE, Boyd BA. Early intensive behavioral intervention (EIBI) for young children with autism spectrum disorders (ASD). *Cochrane Database Syst Rev.* (2018) 5:CD009260. doi: 10.1002/14651858.CD009260.pub3

4. Laugeson EA, Frankel F, Gantman A, Dillon AR, Mogil C. Evidence-based social skills training for adolescents with autism spectrum disorders: the UCLA PEERS program. *J Autism Dev Disord.* (2012) 42:1025–36. doi: 10.1007/s10803-011-1339-1

5. Reichow B, Servili C, Yasamy MT, Barbui C, Saxena S. Non-specialist psychosocial interventions for children and adolescents with intellectual disability or lower-functioning autism spectrum disorders: a systematic review. *PLoS Med.* (2013) 10:e1001572. doi: 10.1371/journal.pmed.1001572

6. Laugeson EA, Frankel F. *Social Skills for Teenagers with Developmental and Autism Spectrum Disorders: The PEERS Treatment Manual.* London: Routledge (2011). doi: 10.4324/9780203867686

7. Tarver J, Palmer M, Webb S, Scott S, Slonims V, Simonoff E, et al. Child and parent outcomes following parent interventions for child emotional and behavioral problems in autism spectrum disorders: a systematic review and meta-analysis. *Autism.* (2019) 23:1630–44. doi: 10.1177/1362361319830042

8. Bearss K, Johnson C, Smith T, Lecavalier L, Swiezy N, Aman M, et al. Effect of parent training vs parent education on behavioral problems in children with autism spectrum disorder: a randomized clinical trial. *JAMA.* (2015) 313:1524–33. doi: 10.1001/jama.2015.3150

9. Hume K, Steinbrenner J.R, Odom S.L, Morin K.L, Nowell S.W, Tomaszewski B, et al. Evidence-based practices for children, youth, and young adults with autism: third generation review. *J Autism Dev Disord.* (2021) 51:4013–32. doi: 10.1007/s10803-020-04844-2

10. Keefer A, Kreiser NL, Singh V, Blakeley-Smith A, Reaven J, Vasa RA. Exploring relationships between negative cognitions and anxiety symptoms in youth with autism spectrum disorder. *Behav Ther.* (2018) 49:730–40. doi: 10.1016/j.beth.2017.12.002

11. Linden A, Best L, Elise F, Roberts D, Branagan A, Tay YBE, et al. Benefits and harms of interventions to improve anxiety, depression, and other mental health outcomes for autistic people: a systematic review and network meta-analysis of randomised controlled trials. *Autism.* (2023) 27:7–30. doi: 10.1177/13623613221117931

12. Lord C, Brugha TS, Charman T, Cusack J, Dumas G, Frazier T, et al. Autism spectrum disorder. *Nature Rev Dis Primers.* (2020) 6:5. doi: 10.1038/s41572-019-0138-4

13. Bishop-Fitzpatrick L, Minshew NJ, Eack SM. A systematic review of psychosocial interventions for adults with autism spectrum disorders. *J Autism Dev Disord.* (2014) 43:687–94. doi: 10.1007/s10803-012-1615-8

14. McClannahan LE, MacDuff GS, Krantz PJ. Behavior analysis and intervention for adults with autism. *Behav Modif.* (2002) 26:9–26. doi: 10.1177/0145445502026001002

15. Shattuck PT, Wagner M, Narendorf S, Sterzing P, Hensley M. Post-high school service use among young adults with an autism spectrum disorder. *Arch Pediatr Adolesc Med.* (2011) 165:141–6. doi: 10.1001/archpediatrics.2010.279

16. Roux AM, Garfeld T, Shattuck PT. Employment policy and autism: analysis of state Workforce Innovation and Opportunity Act (WIOA) implementation plans. *J Vocat Rehabil.* (2019) 51:285–98. doi: 10.3233/JVR-191046

17. Ki-moon B. *Secretary-general Invites Business to Commit to Hiring People with Autism, as he Launches 'Call to Action' Initiative on World Day* (2015). Retrieved June (2015) 8:2018.

18. Sparkes I, Riley E, Cook B, Machuel P. *Office for National Statistics. Outcomes for Disabled People in the UK: 2020* (2021). Available online at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/disability/articles/outcomesfordisabledpeopleintheuk/2021

19. Shattuck PT, Narendorf SC, Cooper B, Sterzing PR, Wagner M, Taylor JL. (2012). Postsecondary education and employment among youth with an autism spectrum disorder. *Pediatrics.* (2012) 129:1042–9. doi: 10.1542/peds.2011-2864

20. Roux AM, Miller KK, Tao S, Rast JE, Ventimiglia J, Shattuck PT, et al. Unrealized cross-system opportunities to improve employment and employment-related services among autistic individuals. *Milbank Q.* (2023) 37526044 doi: 10.1111/1468-0009.12666

21. Schall C, Wehman P, Avellone L, Taylor JP. Competitive integrated employment for youth and adults with autism: findings from a scoping review. *Child Adolesc Psychiatr Clin.* (2020) 29:373–97. doi: 10.1016/j.chc.2019.12.001

22. Scott M, Milbourn B, Falkmer M, Black M, Bölte S, Halladay A, et al. Factors impacting employment for people with autism spectrum disorder: a scoping review. *Autism.* (2019) 23:869–901. doi: 10.1177/1362361318787789

23. Lindsay S, Osten V, Rezai M, Bui S. Disclosure and workplace accommodations for people with autism: a systematic review. *Disabil Rehabil.* (2021) 43:597–610. doi: 10.1080/09638288.2019.1635658

24. Müller E, Schuler A, Burton BA, Yates GB. Meeting the vocational support needs of individuals with Asperger syndrome and other autism spectrum disabilities. *J Vocat Rehabil.* (2003) 18:163–75.

25. Fombonne E. Epidemiology of autistic disorder and other pervasive developmental disorders. *J Clin Psychiatry.* (2005) 66:3. doi: 10.1002/9780470939345.ch2

26. Van Steensel FJ, Bogels SM, Perrin S. Anxiety disorders in children and adolescents with autistic spectrum disorders: a meta-analysis. *Clin Child Fam Psychol Rev.* (2011) 14:302–17. doi: 10.1007/s10567-011-0097-0

27. Risi S, Lord C, Gotham K, Corsello C, Chrysler C, Szatmari P, et al. Combining information from multiple sources in the diagnosis of autism spectrum disorders. *J Am Acad Child Adolesc Psychiatry.* (2006) 45:1094–103. doi: 10.1097/01.chi.0000227880.42780.0e

28. Persico AM, Cucinotta F, Ricciardello A, Turriziani L, Chen B. Chapter 3: Autisms. Comprehensive developmental neuroscience. *Neurodev Disord.* (2020) 35–77. doi: 10.1016/B978-0-12-814409-1.00003-3

29. Shenouda J, Barrett E, Davidow AL, Sidwell K, Lescott C, Halperin W, et al. Prevalence and disparities in the detection of autism without intellectual disability. *Pediatrics.* (2023) 151:e2022056594. doi: 10.1542/peds.2022-056594

30. Zeidan J, Fombonne E, Scorah J, Ibrahim A, Durkin MS, Saxena S, et al. Global prevalence of autism: a systematic review update. *Autism Res.* (2022) 15:778–90. doi: 10.1002/aur.2696

31. Russell G, Mandy W, Elliott D, White R, Pittwood T, Ford T. Selection bias on intellectual ability in autism research: a cross-sectional review and meta-analysis. *Mol Autism.* (2019) 10:1–10. doi: 10.1186/s13229-019-0260-x

32. Gottlieb A, Myhill WN, Blanck P. Employment of people with disabilities. *International Encyclopedia of Rehabilitation.* (2010).

33. Taylor JL, Seltzer MM. Employment and post-secondary educational activities for young adults with autism spectrum disorders during the transition to adulthood. *J Autism Dev Disord.* (2011) 41:566–74. doi: 10.1007/s10803-010-1070-3

34. Keel JH, Mesibov GB, Woods AV. TEACCH-supported employment program. *J Autism Dev Disord.* (1997) 27:3–9. doi: 10.1023/A:1025813020229

35. Howlin P. Outcomes in autism spectrum disorders. In: Volkmar FR, Paul R, Klin A, Cohen D, editors. *Handbook of Autism and Pervasive Developmental Disorders*, Volume 1. Hoboken, NJ: John Wiley & Sons, Inc. (2005) 1:201–20. doi: 10.1002/9780470939345.ch7

36. Mesibov GB, Shea V, Schopler E. *The TEACCH Approach to Autism Spectrum Disorders*. New York, NY: Springer Science & Business Media. (2005). doi: 10.1007/978-0-306-48647-0

37. Walsh L, Lydon S, Healy O. Employment and vocational skills among individuals with autism spectrum disorder: predictors, impact, and interventions. *Rev J Autism Dev Disord.* (2014) 1:266–75. doi: 10.1007/s40489-014-0024-7

38. Moody CT, Factor RS, Gulsrud AC, Grantz CJ, Tsai K, Jolliffe M, et al. A pilot study of PEERS® for careers: a comprehensive employment-focused social skills intervention for autistic young adults in the United States. *Res Dev Disabil.* (2022) 128:104287. doi: 10.1016/j.ridd.2022.104287

39. Hendricks D. Employment and adults with autism spectrum disorders: challenges and strategies for success. *J Vocat Rehabil.* (2010) 32:125–34. doi: 10.3233/JVR-2010-0502

40. Fusar-Poli L, Brondino N, Orsi P, Provenzani U, De Micheli A. Ucelli di Nemi S, et al. Long-term outcome of a cohort of adults with autism and intellectual disability: a pilot prospective study. *Res Dev Disabil.* (2017) 60:223–31. doi: 10.1016/j.ridd.2016.10.014

41. Roid G, Miller L, Pomplun M, Koch C. *Leiter International Performance Scale*, 3rd ed. Wood Dale, IL: Stoelting (2013).

42. Lord C, Rutter M, DiLavore PC, Risi S, Gotham K, Bishop S. *Autism Diagnostic Observation Scales-—2nd edition (ADOS-2)*. Torrance, CA: Western Psychological Services (2012).

43. Sparrow SS, Cicchetti DV, Balla DA. *Vineland Adaptive Behavior Scales: Second edition (Vineland II), Survey Interview Form/Caregiver Rating Form*. Coushatta, LA: Pearson Assessments (2005). doi: 10.1037/t15164-000

44. Mesibov G, Thomas JB, Chapman SM. and Schopler E. *TEACCH Transition Assessment Profile,* 2nd ed. Austin, TX: Pro-ed (2007).

45. Inoue M. Assessments and interventions to address challenging behavior in individuals with intellectual disability and autism spectrum disorder in Japan: a consolidated review. *Yonago Acta Med.* (2019) 62:169–81. doi: 10.33160/yam.2019.06.001

46. Gardenier NC, MacDonald R, Green G. Comparison of direct observational methods for measuring stereotypic behavior in children with autism spectrum disorders. *Res Dev Disabil.* (2004) 25:99–118. doi: 10.1016/j.ridd.2003.05.004

47. Siu AMH, Lin Z, Chung J. An evaluation of the TEACCH approach for teaching functional skills to adults with autism spectrum disorders and intellectual disabilities. *Res Dev Disabil.* (2019) 90:14–21. doi: 10.1016/j.ridd.2019.04.006

48. Van Bourgondien ME, Reichle NC, Schopler E. Effects of a model treatment approach on adults with autism. *J Autism Dev Disord.* (2003) 33:131–40. doi: 10.1023/A:1022931224934

49. Friman PC. Cooper, Heron, and Heward's applied behavior analysis: checkered flag for students and professors, yellow flag for the field. *J Appl Behav Anal.* (2010) 43:161–74. doi: 10.1901/jaba.2010.43-161

50. Taylor JL, Smith LE, Mailick MR. Engagement in vocational activities promotes behavioral development for adults with autism spectrum disorders. *J Autism Dev Disord.* (2014) 44:1447–60. doi: 10.1007/s10803-013-2010-9

51. LaRue RH, Maraventano JC, Budge JL, Frischmann T. Matching vocational aptitude and employment choice for adolescents and adults with ASD. *Behav Anal Pract.* (2019) 13:618–30. doi: 10.1007/s40617-019-00398-7

52. McCauley JB, Pickles A, Huerta M, Lord C. Defining positive outcomes in more and less cognitively able autistic adults. *Autism Res.* (2020) 13:1548–60. doi: 10.1002/aur.2359

53. Hedley D, Uljarević M, Cameron L, Halder S, Richdale A, Dissanayake C. Employment programmes and interventions targeting adults with autism spectrum disorder: a systematic review of the literature. *Autism.* (2017) 21:929–41. doi: 10.1177/1362361316661855

54. National Institute for Health and Care Excellence (NICE). *Autism Spectrum Disorder in Adults: Diagnosis and Management.* (2012). Available online at: https://www.nice.org.uk/guidance/cg142 (accessed June 14, 2021).

55. National Institute for Health and Care Excellence (NICE). *Autism Spectrum Disorder in Adults: Diagnosis and Management*. London (2021). ISBN-13:978-1-4731-2039-6.

56. *Advisory Committee on Increasing Competitive Integrated Employment for Individuals with Disabilities Final Report*. (2016). Final Report. Available online at: https://www.dol.gov/odep/topics/pdf/ACICIEID_Final_Report_9-8-16.pdf (accessed September 15, 2016).

57. García-Villamisar D, Hughes C. Supported employment improves cognitive performance in adults with autism. *J Intellect Disabil Res.* (2007) 51(Pt 2):142–50. doi: 10.1111/j.1365-2788.2006.00854.x

58. Cope R, Remington A. The strengths and abilities of autistic people in the workplace. *Autism Adulthood.* (2022) 4:22–31. doi: 10.1089/aut.2021.0037

59. Russell G, Kapp SK, Elliott D, Elphick C, Gwernan-Jones R, Owens C. Mapping the autistic advantage from the accounts of adults diagnosed with autism: a qualitative study. *Autism Adulthood.* (2019) 1:124–33. doi: 10.1089/aut.2018.0035

60. Micai M, Fulceri F, Salvitti T, Romano G, Poustka L, Diehm R, et al. Autistic adult services availability, preferences, and user experiences: results from the autism spectrum disorder in the European Union Survey. *Front Psychiatry.* (2022) 13:919234. doi: 10.3389/fpsyt.2022.919234

61. Burke M, Taylor JL. To better meet the needs of autistic people, we need to rethink how we measure services. *Autism.* (2023) 27:873–5. doi: 10.1177/13623613231164495

62. Pukki H, Bettin J, Outlaw AG, Hennessy J, Brook K, Dekker M, et al. Autistic Perspectives on the Future of Clinical Autism Research. *Autism Adulthood.* (2022) 4:93–101. doi: 10.1089/aut.2022.0017

63. Revell G, Inge KJ, Mank D, Wehman P. *The Impact of Supported Employment for People with Significant Disabilities: Preliminary Findings from the National Supported Employment Consortium. Virginia Commonwealth University. School of Education. Rehabilitation Research and Training Center, National Supported Employment Consortium (U.S.). Edit Virginia Commonwealth University Rehabilitation Research & Training Center on Workplace Supports*. University of Illinois at Urbana-Champaign (1999).

64. Cavagnola R, Alzani L, Carnevali D, Chiodelli G, Corti S, Fioriti F, et al. Neurodevelopmental disorders and development of project of life in a lifespan perspective: between habilitation and quality of life. *Ann Ist Super Sanita.* (2020) 56:230–40. doi: 10.4415/ANN_20_02_13

65. Garcia-Villamisar D, Wehman P, Navarro M. Changes in the quality of autistic people's life that work in supported and sheltered employment. A 5 years follow-up study. *J Vocat Rehabil.* (2002) 17:309–12.

66. Nicholas DB, Hodgetts S, Zwaigenbaum L, Smith LE, Shattuck P, Parr JR, et al. Research needs and priorities for transition and employment in autism: considerations reflected in a "Special Interest Group" at the International Meeting for Autism Research. *Autism Res.* (2017) 10:15–24. doi: 10.1002/aur.1683

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EDITED BY
Fengyu Zhang,
Global Clinical and Translational Research Institute, United States

REVIEWED BY
Spencer Wade,
New York University, United States
Wenn Lawson,
Curtin University, Australia

*CORRESPONDENCE
Tohru Okanishi
✉ okanishipediatrics@gmail.com

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Successful perioperative preparation of a child with autism spectrum disorder in collaboration with his school for special needs education: a case report

Yuto Arai, Tohru Okanishi*, Yuko Nakamura and Yoshihiro Maegaki

Division of Child Neurology, Department of Brain and Neurosciences, Faculty of Medicine, Tottori University, Yonago, Japan

Introduction: The incidence of autism spectrum disorder (ASD) in children is greater than 1%. Children with ASD show an increased rate of hospital contact for several reasons. Perioperative preparation for children with ASD can be challenging; therefore, obtaining information from patients' families prior to surgery is important. However, no previous reports have described the collection of information from educational facilities.

Case report: A 12 years-old male patient with ASD was referred for surgery for traumatic dislocation of the left knee joint. Before admission, we obtained valuable information from his parents regarding expected behavioral problems and coping strategies during hospitalization and from his teachers at his school for special needs education. In particular, the information obtained from teachers was specific and practical. Consequently, we could effectively conduct perioperative management based on his specific autistic characteristics.

Conclusion: We report a pediatric case of ASD in which favorable perioperative management was successfully achieved by collecting information before admission from family members as well as teachers at the patient's school for special needs education. This management may help in future hospital admissions for children with autism.

KEYWORDS

autism spectrum disorder, unique behavior, perioperative management, parents, school for special need education, school information, school cooperation

Introduction

The estimated prevalence of autism spectrum disorders (ASD) in children and adolescents is approximately 1.5% (1). Children with ASD are more likely to experience medical complexities than their typically developing peers and more frequently utilize the healthcare system (2). Children with ASD also have an increased rate of hospital contact for multiple reasons (3) and an increased risk of adverse events during hospitalization or procedures (4).

Perioperative preparation for children with ASD can be challenging because of their unique individual needs and behavioral differences (5). However, data on perioperative preparation for children with ASD are limited (6), and little is known about the optimal management approaches for patients who require surgical intervention (7). Previous studies have shown that healthcare providers should obtain the necessary information for preparation from the patient's family members prior to the child's arrival at the hospital (4, 5). On the other hand, the individual coping methods employed for children with ASD at schools for special needs education, which are employed by non-family members, may be easier to apply for medical staff, who are also not family members and are likely to be more practical for the perioperative preparation of children with ASD. However, there have been no reports on the application of coping methods used in education for the preparation of children with ASD.

Herein, we report a case of pediatric ASD in which favorable perioperative management was successfully achieved by collecting information before admission from family members as well as the teachers at the patient's school for special needs education.

Case report

A male patient was referred for surgery for a traumatic dislocation of the left knee joint. The patient was 12 years old with a history of Pitt-Hopkins syndrome (identification of *TCF4* gene mutation). He had underlying ASD and severe intellectual disability (Intelligence Quotient: 31). The patient was treated with aripiprazole (2 mg/day) and as-needed risperidone for irritability associated with ASD. His family consisted of his father, mother, and a 14 years-old brother. He was in the sixth grade at a school for special needs education and had been in a welfare facility for disabled children since the first grade of elementary school. He spent weekdays in the welfare facility and weekends at home. At the age of seven, he fell from a height and was diagnosed with traumatic dislocation of the left knee joint, which was treated conservatively with a brace, considering the difficulty in perioperative management. However, his gait gradually deteriorated, and he experienced frequent falls. Therefore, his family strongly desired surgical intervention, and he was referred to our hospital.

Before admission, we obtained information about the children's autistic symptoms from his parents and teachers. We obtained information directly from his parents as an outpatient first, and then obtained information from his teachers through online meetings and patient referral documents. The collected information was summarized according to a previously reported protocol (4) (Table 1). In addition, his teachers explained about the picture cards that they typically used (Figure 1). Based on this information, we made the following decisions: (i) the patient was to be admitted in principle with his mother, (ii) when his mother had to go out for some reason, the medical staff would take care of the patient based on the information gathered before hospitalization as summarized in Table 1.

TABLE 1 Summary of information from parents and schools and preparation at the hospital.

Type of behavior	Inputs from family	Inputs from school	Preparations at the hospital
Persistent deficits in social communication	• He does no harm to other people	• He requests by crane phenomenon • He clap his hand twice when he wants to ask • When he refuses, sits still	• Sharing with the medical staff how he makes his wishes known
Restrictive and repetitive interests, behaviors, and activities	• He calms down with a music box and planetarium in the darkroom	• He likes to repeatedly turn cup containers and lids • When putting on clothes, spread them out in the order in which he will be worn • Say "Goshigoshi" when washing his face • When washing the body, indicate body parts to wash every 10 s • Prepare bread by cutting it into sticks	• Used cup containers and lids to comfort • Tried not to break his routine • No whole-body restraint band was used (only fixation of affected lower limb) • Selected a private room that could be darkened with curtains • Used appropriate voice while providing instructions for brushing and washing
Associated mental health problems	• He rocks back and forth when he is in a good mood • When he gets angry, he yells and bites his own hand		• Trying to understand his emotions at an early stage
Sensory hypersensitivity	• He'll want to pull IV line out • If the room is too small, he will run away	• He hates when we try to clean his eyes • He hates wearing a mask	• Removed IV line as soon as possible • Tried to avoid things that he hated
Intellectual impairment	• He can understand "stand up" and "sit down," but not "do not move"	• Minimizing words and guiding with card instructions is effective	• Used simple clear language • Used the picture cards given by his school as needed
Epilepsy	• He experiences breath-holding seizures when he gets excited		• Used the music box and planetarium to calm him down • Placed his room near the nurse station to account for the possibility of seizures
IV: intravenous line			

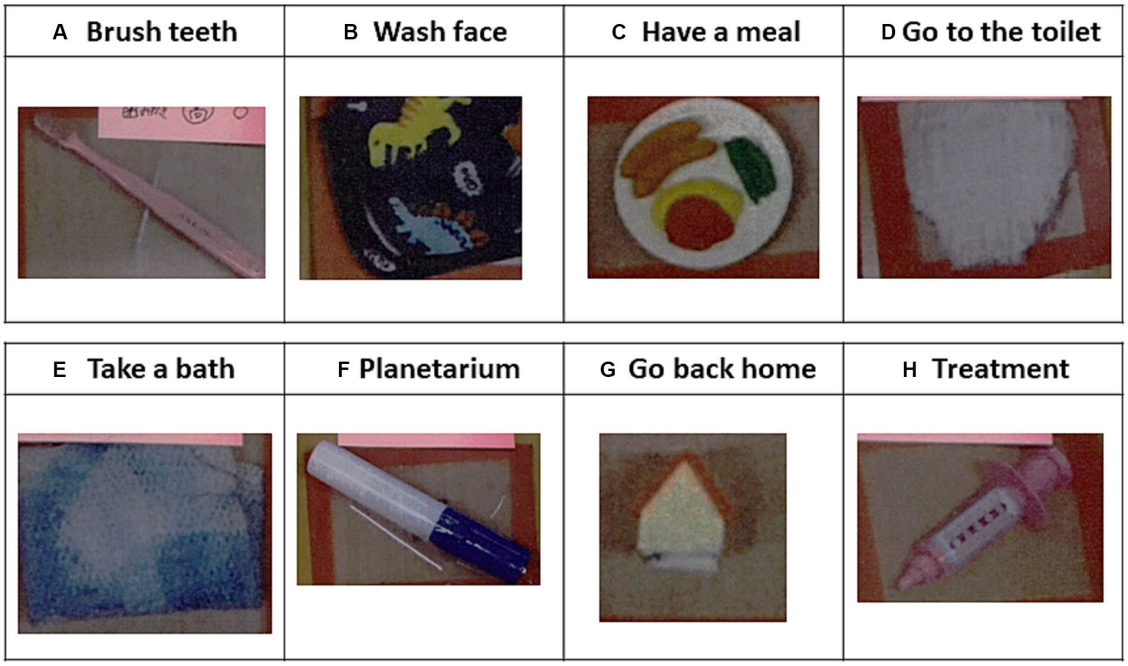

FIGURE 1
Examples of picture cards used in the school for special needs education. The cards were obtained before admission from the patient's teachers. Picture cards of **(A)** a toothbrush for brushing teeth, **(B)** a towel for washing the face, **(C)** a cooking plate for eating food, **(D)** a diaper for going to the toilet, **(E)** a pajama for taking a bath, **(F)** a glowing pen for playing with a planetarium, **(G)** a toy house for going home, and **(H)** a toy injection for indicating upcoming medical procedures.

After admission, surgery was performed the following day as scheduled. For analgesic management, continuous intravenous fentanyl injection was administered until the second postoperative day, after which the line was removed and followed by regular oral administration of acetaminophen and diclofenac suppository insertion as needed. Under this analgesic management protocol, the patient was kept calm except on the first day when he cried for pain. He was also emotionally stable with only environmental adjustments based on prehospital information, and he never needed risperidone. The postoperative course was uneventful, and the patient was transferred to a rehabilitation hospital as scheduled. We explained our management methods to the hospital.

Discussion

We performed perioperative preparation for the treatment of traumatic dislocation of the knee joint in a pediatric patient with ASD patient. Preparations were performed to ensure favorable perioperative management by collecting information before admission from the patient's parents and the teachers at his school for special needs education.

Children with ASD who undergo surgery require individualized supportive strategies and a multi-faceted approach to ensure optimal care (8). A lack of understanding and knowledge of ASD among healthcare providers is one of the factors interfering with patient access to appropriate services (9). Therefore, previous reports have emphasized the importance of collecting information about autistic characteristics from parents before hospitalization (5). However, no reports to date have emphasized the importance of collecting information from schools for special needs education.

Schools for special needs education serve children with comparatively severe disabilities. In these schools, children learn through a special curriculum while being surrounded by a sufficient number of teachers and various facilities and equipment that meet their needs (10). According to a Japanese survey of schools for special needs education conducted by Nishimura et al. (11), 45.3% of the children in these schools were medically diagnosed with ASD. Moreover, all of these schools had a curriculum for ASD, and the learning environment was devised for children with ASD. Therefore, ASD care at schools for special needs education may be established through education and individual trial and error. We have previously shown that interpersonal communication between children with ASD and the doctors and staff promotes positive emotions and reduces medical examination-related anxiety among these patients (12). For medical staff, who were not family members, the individualized communication methods employed by schoolteachers, who were also not family members, may be more specific, objective, and easier to apply to medical situations. In fact, we obtained a lot of concrete information from the school in this case (Table 1). Thus, information obtained from schools for special needs education may be useful for preparation of children with ASD.

Our report has a limitation. Because the patient's school for special needs education is located nearby his welfare facility, there is a possibility that the information obtained from his school partially includes information from his welfare facility.

In conclusion, we present a case of successful perioperative management in a pediatric patient with ASD. We collected information available for preparation not only from family members but also from teachers at the patient's school for special needs

education. Thus, comprehensive information from the patient's family and the educational environment may facilitate the process of preparing for perioperative management of pediatric patients with ASD.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Ethical committee of Tottori University Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

TO was responsible for the organization and coordination of the trial. YA was the chief investigator responsible for data analysis. YN and YM designed the trial. YA, TO, YN, and YM contributed to the writing of the final manuscript and met the ICMJE authorship criteria. 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.

Publisher's note

References

1. Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators, Centers for Disease Control and Prevention (CDC). Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2010. *MMWR Surveill Summ*. (2014) 63:1–21.

2. Kohane IS, McMurry A, Weber G, MacFadden D, Rappaport L, Kunkel L, et al. The co-morbidity burden of children and young adults with autism spectrum disorders. *PLoS One*. (2012) 7:e33224. doi: 10.1371/journal.pone.0033224

3. Atladóttir HO, Schendel DE, Lauritsen MB, Henriksen TB, Parner ET. Patterns of contact with hospital for children with an autism spectrum disorder: a Danish register-based study. *J Autism Dev Disord*. (2012) 42:1717–28. doi: 10.1007/s10803-011-1416-5

4. Taghizadeh N, Davidson A, Williams K, Story D. Autism spectrum disorder (ASD) and its perioperative management. *Paediatr Anaesth*. (2015) 25:1076–84. doi: 10.1111/pan.12732

5. Thompson DG, Tielsch-Goddard A. Improving management of patients with autism spectrum disorder having scheduled surgery: optimizing practice. *J Pediatr Health Care*. (2014) 28:394–403. doi: 10.1016/j.pedhc.2013.09.007

6. Elliott AB, Holley AL, Ross AC, Soleta AO, Koh JL. A prospective study comparing perioperative anxiety and posthospital behavior in children with autism spectrum disorder vs typically developing children undergoing outpatient surgery. *Paediatr Anaesth*. (2018) 28:142–8. doi: 10.1111/pan.13298

7. Selvey P, Stypulkowski K, Waisbren S. Surgical management of the patient living with autism. *Surg Open Sci*. (2019) 1:90–6. doi: 10.1016/j.sopen.2019.06.006

8. Taghizadeh N, Heard G, Davidson A, Williams K, Story D. The experiences of children with autism spectrum disorder, their caregivers and health care providers during day procedure: a mixed methods study. *Paediatr Anaesth*. (2019) 29:927–37. doi: 10.1111/pan.13689

9. Wharton S, Hames A, Milner H. The accessibility of general NHS services for children with disabilities. *Child Care Health Dev*. (2005) 31:275–82. doi: 10.1111/j.1365-2214.2005.00497.x

10. Ministry of Education, Culture, Sports, Science and Technology, Japan (2016). Available at: https://www.mext.go.jp/en/policy/education/elsec/title02/detail02/1373858.htm

11. Nishimura T, Yanagisawa A, Murai K, Lee H. Research for understanding the actual conditions of children with autism enrolled in schools for special needs education (for intellectual disabilities) and their instruction -investigation of teaching based on educational continuity between departments. *NISE Bull*. (2017) 16:4. In Japanese

12. Inoue N, Okanishi T, Inoue M, Maegaki Y. Psychological preparations affecting the emotions of children with developmental disorders toward hospitals. *Yonago Acta Med*. (2021) 64:92–7. doi: 10.33160/yam.2021.02.012

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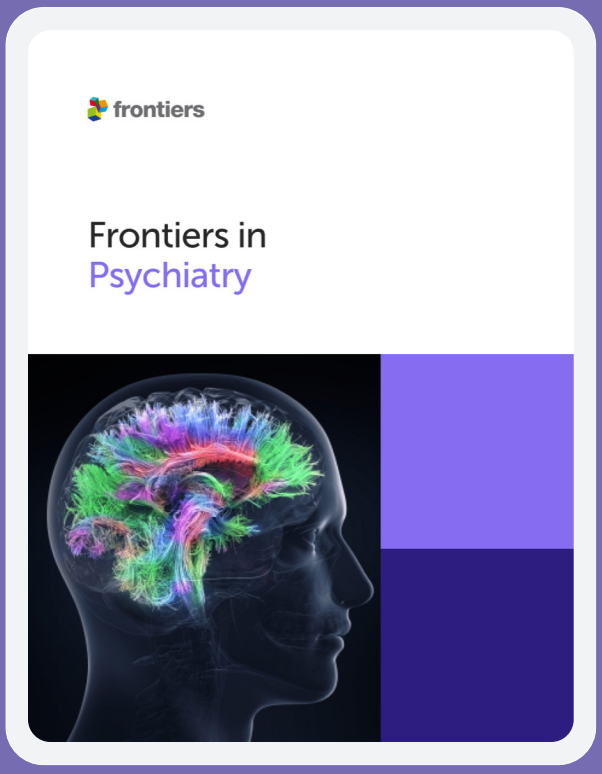

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