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Movement disorders – case report collection 2022

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CASE REPORT
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Case Report: Migraine-Induced Dystonia of the Lower Extremities

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Migraine is a highly prevalent neurological disorder characterized by recurrent, unilateral, or bilateral throbbing severe headaches. Currently, there are extremely rare cases of migraine-induced dystonia. A 52-year-old woman was admitted for intractable migraine for about 5 days and walking difficulties for 1 day. The symptom of an inability to walk appeared on the fourth day of the headache attack lasting for 1 day and resolved on its own as the headache subsided. The same symptoms appeared once 6 years ago. Neurological examination, brain Magnetic resonance imaging (MRI), laboratory tests of blood and cerebrospinal fluid (CSF) were normal. The contrast transcranial Doppler echocardiography (cTCD) revealed a latent and massive right-to-left shunt (RLS) after the release of the Valsalva maneuver. The patient was diagnosed with migraine-induced dystonia of the lower limbs. Oral ibuprofen and flunarizine and avoidance of increased chest pressure maneuvers were used for treatment and prevention. During the 6-month follow-up, the patient was free of headaches and walking difficulties. Our study reported a rare case of migraine-induced dystonia of the lower extremities.

Keywords: migraine, dystonia, movement disorder, patent foramen ovale, case report

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INTRODUCTION

Migraine is the second most common neurological disease worldwide, with an annual incidence of up to 15% in the general population (1). Migraine is frequently characterized by recurrent, unilateral, or bilateral throbbing, severe headache. Dystonia is a movement disorder manifesting as abnormal movements or postures, or both, caused by continuous or intermittent muscle contractions, and the movements and postures are frequently repetitive with an annual incidence of 15–30 per 100,000 in the general population (2). There have been some reports of patients suffering from migraine and dystonia simultaneously (3, 4). However, reports of migraine-induced dystonia are particularly rare, and the mechanisms involved are unclear so far (5).

Here, we report a rare case of a patient with migraine-induced dystonia of the lower extremities manifested by the inability to walk. The dystonia symptoms resolved spontaneously with migraine resolution. Auxiliary examination revealed that she had a patent foramen ovale and a potentially large right-to-left shunt. The same symptoms appeared twice in 6 years. We also make reasonable guesses about possible etiologies.

CASE DESCRIPTION

History

A 52-year-old woman without a family history of migraine and dystonia was admitted to our department due to intractable migraine for about 5 days and walking difficulties for 1 day. She has had a history of headaches for over 20 years with one or two attacks per year described as a

throbbing or swelling pain in the occipital region or even the whole brain with an intensity of 6 to 9/10. There was no significant aura before the attack. The headache attack was accompanied by numbness and coldness of the painful area and stiffness of the neck, and nausea and vomiting without photophobia or phonophobia. At worst, she could not take in any food or medicine because of vomiting. The headache usually lasted for 5–6 days and could last up to 15 days, and was slightly relieved by ibuprofen and flunarizine. On the fourth day of this attack, she suddenly suffered an inability to walk lasting for 1 day. She could stand on her own without any dizziness. However, every time she tried to start walking, she felt stiffness in both lower extremities and was unable to step and walk, but could only maintain an upright position. And, it did not change with prolonged standing time. In addition, no movement other than walking was affected. When she was lying down, the movement of both lower extremities was not restricted and she could raise and lower her legs and move them in any direction at will. The same symptom happened once 6 years ago, and it resolved on its own after lasting for 1 h.

Examinations and Imaging Findings

The physical examination and vital signs were unremarkable, and the neurologic examination was normal. The patient showed a task-specific lower limbs dystonia, characterized by the appearance of sustained dystonic extension of both knees induced by stepping or walking attempts. Magnetic resonance imaging (MRI) scan of the brain showed no significant abnormalities (**Figure 1**). The patient underwent a lumbar puncture, the cerebrospinal fluid (CSF) pressure was 125 mm H_2O (normal range: 80–180 mmH_2O), and the biochemistry and cytology of the CSF were negative. Her blood tests were regular, including routine blood work, liver function, kidney function, ions, D-dimer, and markers of myocardial damage. The contrast transcranial doppler echocardiography (cTCD) showed a latent and massive right-to-left shunt (RLS), that was, more than 25 microbubbles were detected using insonation of the left middle cerebral artery (LMCA) after the release of the Valsalva maneuver (**Figure 2**). No microbubble was seen in the resting state. Right heart contrast echocardiography confirmed the result. Her echocardiography revealed no abnormalities in the structure and function of the heart at rest.

Diagnosis and Treatment

Finally, the patient was diagnosed with migraine and dystonia of the lower extremities induced by it. The cTCD and right heart contrast echocardiography suggested that she had a patent foramen ovale (PFO). Transesophageal echocardiography (TEE) was required to clarify her heart condition further. The patient's headache lasted for 12 days and was relieved with oral ibuprofen (two capsules per day) and flunarizine (10 mg per day). The symptom of the inability to walk cleared spontaneously staying for 1 day, and she was capable of walking slowly and awkwardly during the consultation. Other than medicines for headaches, no additional treatment was given, similar to the situations 6 years ago. Considering the presence of PFO, we recommended she avoid actions that would increase chest pressure, such as diving, violent coughing, and strenuous exercise, which would be of considerable benefit for preventing her headaches. At a follow-up 6 months after the attack, the patient had no episodes of headache and walking difficulty. Unfortunately, owing to financial problems, the patient did not undergo a relevant genetic test, making it difficult to explore the etiology of her condition further.

DISCUSSION

In this case, we demonstrate a patient presenting with migraine combined with dystonia triggered by it, with the dystonia manifesting as a walking impediment. Migraine contains three main types: migraine with aura, migraine without aura, and chronic migraine. There is a strong association between migraine and PFO. The prevalence of PFO accounts for 46.3–88% of migraineurs with aura and 16.2–34.9% of migraineurs without aura (6). Recent studies suggest that PFO may trigger migraine and is positively correlated with attack frequency but are not significantly related to attack symptoms (7). Previous studies have confirmed that suffering from migraine can affect patients' gait and balance. Akdal et al. (8) discovered that migraineurs without manifesting vertigo had more incredible sway velocity when standing, more significant offset center of gravity (COG) alignment, wider step width, and slower speed. Machado Maciel et al. (9) found migraineurs experienced longer step width with increasing light and sound levels. However, in our case, the patient's twice walking disability within 6 years both occurred during the attack of migraine without dizziness and balance impairment and with normal motor and sensory examinations at rest, suggesting that the symptom was migraine-induced-dystonia of lower extremities.

The classification of dystonia is based on two main clinical features: the age of onset, distribution of symptoms, concomitant symptoms, and etiology (2). Combining the patient's medical history, we considered the patient's dystonia of the lower extremities as a task-specific walking dystonia. No significant geste antagoniste or sensory trick was found in the patient's description and examination. Kemp et al. (10) previously reported a case of delayed dystonia of the left leg secondary to traumatic brain injury, with some resemblance to our case. This patient presented with a persistent extension of the left knee and was task-specific, appearing only when he walked forward. Previous studies have revealed that focal task-specific lower extremity dystonia is associated with prolonged vigorous repetitive activity. Katz et al. (11) reported seven patients with task-specific lower extremity dystonia who had multiple exercise triggers. Their motor triggers included prolonged bicycling, hiking, long-distance running, and drumming. In addition, task-specific dystonia usually progresses continuously. This reminds us of the patient in this case, who has been persistently walking briskly 20,000 steps per day, about 14 km per week, for more than a decade. The duration of her two migraine-induced dystonic episodes that occurred within 6 years became longer, from an hour to a day, although the symptoms were the same on both occasions. Dystonia was elicited by walking attempt, in a

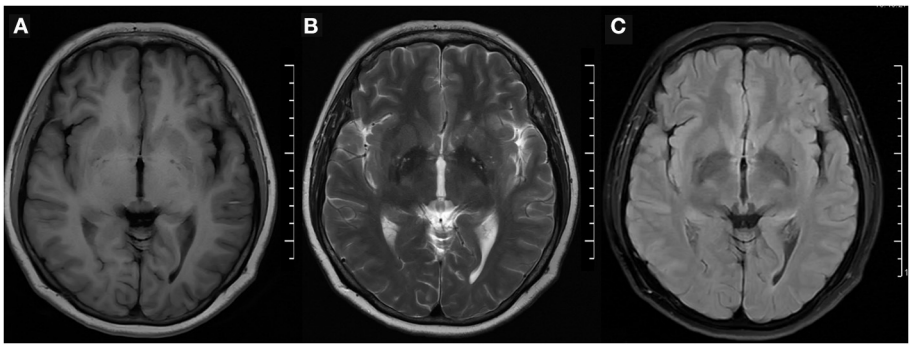

FIGURE 1 | Brain MRI. **(A)** T1-weighted, **(B)** T2-weighted, and **(C)** fluid-attenuated inversion recovery (FLAIR) imaging were normal. MRI, magnetic resonance imaging.

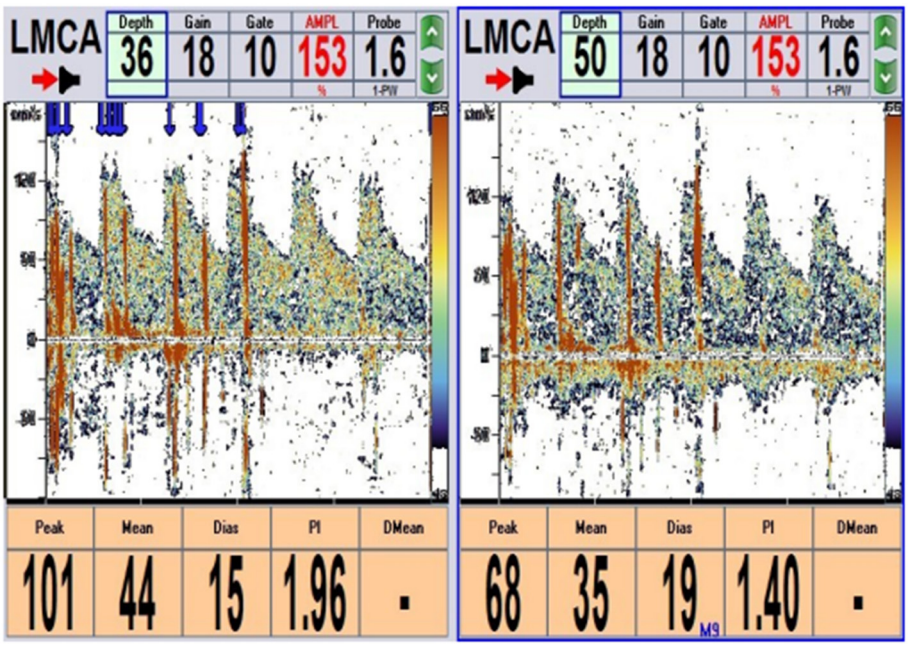

FIGURE 2 | cTCD: More than 25 microbubbles were detected after 2 s of Valsalva maneuver detecting from the left middle cerebral artery (LMCA) (single-channel and double depth) (blue arrow). cTCD, contrast transcranial Doppler echocardiography.

task-specific manner. However, we found no significant geste antagoniste or sensory tricks, which may need to be detected in her subsequent episodes and long-term follow-up.

During the diagnosis of walking disability in the patient, we are not inclined to consider functional movement disorders or extrapyramidal symptoms caused by medication side effects as a diagnosis. Patients with functional movement disorders are often associated with anxiety and depression, and a higher proportion of patients have suffered psychological trauma (12, 13). The patient in this case had not experienced significant previous trauma, and her Hamilton Anxiety and Depression Scale test results did not indicate a tendency to suffer from anxiety or depression. Since the patient was capable of walking when she arrived at the hospital, we did not perform suggestive therapy on her. Studies have found that long-term oral administration of flunarizine significantly increases the risk of movement disorders in a dose-dependent manner, including dystonia, parkinsonism, akathisia, tremor, and tardive dyskinesia (14). The patient in our case did not take flunarizine to prevent migraine. She usually took ibuprofen (two capsules per day) and flunarizine (10 mg per day) orally to relieve her headache when it occurred. Furthermore, due to severe nausea and vomiting and even inability to take her medication during the first 2–3 days of the migraine attack, she usually took oral flunarizine for no more than 5 days during the course. Actually, ibuprofen was the more effective and more often chosen medication for her in most conditions. In addition, the patient's presentation differs from that of paroxysmal kinedigenic dystonia (PKD). PKD has a usual episode duration of <1 min, and the reported presentations of PKD do not cover walking disorders like this patient's

(15). As a result, combining the patient's medical history and clinical manifestations, the final diagnosis was migraine-induced dystonia of the lower extremities.

Prior researches have reported several patients with migraine combined with dystonia and the relevant genetic mutation in these patients. Dale et al. (3) and Cuenca-León et al. (16) reported patients with benign paroxysmal torticollis (BPT) and hemiplegic migraine (HM) accompanied by *PRRT2* and *CACNA1A* gene mutation respectively. Gardiner et al. (17) reported individuals with PKD and migraine accompanied by *PRRT2* gene mutation. Weber et al. (4) and Gardiner et al. reported patients with paroxysmal exertion-induced dyskinesia (PED) and migraine accompanied by *GLUT1* and *SLC2A1* gene mutation respectively. In these cases, the dystonia usually manifests as abnormal movements, and there was no specific association between migraine and dystonia episodes. To our knowledge, only one study mentioned a patient with PED caused by migraine whose dystonia symptoms presented as face contraction with dysarthria, preceded the onset of migraine, and resolved with the relief of migraine (5). In our case, there was a definite association between the patient's two episodes of dystonia and migraine attacks, which occurred in the duration of migraine and disappeared with the reduction of the headache. Moreover, the dystonia presented as walking difficulties of the lower extremities, which was not previously documented.

The specific mechanisms of migraine and dystonia are not well identified so far. Cortical spreading depression (CSD) plays a vital role in the pathophysiology of both migraine and task-specific dystonia (18, 19). However, CDS is not specific and may also be an accompanying phenomenon in the disease process (20). Previously reported channel genes associated with migraine include *CACNA1A*, *ATP1A2*, *ATP1A3*, *ATP1A4*, *SCN1A*, *PRRT2*,

TABLE 1 | Main phenotypic pleiotropy in genes associated with migraine and dystonia.

Genes	Migraine	Dystonia	Other phenotypes
KCNA1 (OMIM * 176260)	Migraine	Myokymia syndrome	Episodic ataxia-1 (EA1) Epilepsy
CACNA1A (OMIM * 601011)	Familiar hemiplegic migraine-1 (FHM1)	Benign paroxysmal torticollis (BPT) Blepharospasm (BSP)	Episodic ataxia-2 (EA2) Spinocerebellar ataxia Epilepsy Epilepsic encephalopathy
ATP1A3 (OMIM * 182350)	Hemiplegic migraine (HM)	Rapid-onset dystonia-parkinsonism (RDP) (Dystonia-12)	Alternating hemiplegia of childhood CAPOS syndrome Developmental and epileptic encephalopathy
PRRT2 (OMIM * 614386)	Familiar hemiplegic migraine-2 (FHM2)	Benign paroxysmal torticollis (BPT) Paroxysmal kinedigenic dystonia (PKD)	Episodic ataxia (EA) Epilepsy Epilepsic encephalopathy
SLC2A1 (OMIM * 138140)	Hemiplegic migraine (HM)	Paroxysmal exertion-induced dyskinesia (PED) Paroxysmal nonkinesigenic dyskinesia (PNKD)	GLUT1 deficiency syndrome (GLUT1DS) Epilepsy Epilepsic encephalopathy
SCN1A (OMIM * 182389)	Familiar hemiplegic migraine-3 (FHM3)	Dystonia	Dravet syndrome Febrile seizures, familial, 3A Generalized epilepsy with febrile seizures plus, type 2 Developmental and epileptic encephalopathy 6B, non-Dravet
PNKD (OMIM * 609023)	Hemiplegic migraine (HM)	Paroxysmal nonkinesigenic dyskinesia (PNKD)	–
ATP1A2 (OMIM * 182340)	Familiar hemiplegic migraine-2 (FHM2) Familial basilar	–	Alternating hemiplegia of childhood Developmental and epileptic encephalopathy Fetal akinesia, respiratory insufficiency, microcephaly, polymicrogyria, and dysmorphic facies
ATP1A4 (OMIM * 607321)	Familiar hemiplegic migraine (FHM)	–	–
SCN8A (OMIM * 600702)	–	Myoclonus, familial, 2	Cognitive impairment with or without cerebellar ataxia Developmental and epileptic encephalopathy Seizures, benign familial infantile

PNKD, *SLC2A1*, *SLC1A3* and *SLC4A4* (21, 22). Different types of myotonia correspond to different pathogenic genes, such as the TOR1A gene mutation in DYT1, the *TUBB4A* gene mutation in DYT4, and the *GNAL* gene mutation in DYT25 (2). Among them, channel genes associated with paroxysmal dystonia include *PRRT2, PNKD, ATP1A3, SLC2A1,* and *SCN8A* (23). It is obvious that migraine and dystonia possess some genetic regulatory mechanisms in common. Given the mutation concerning genes, channel impairment may be an intrinsic mechanism commonly shared by both (24). Gene mutation results in disruption of neurotransmitter release, which in turn impairs synaptic release. The *ATP1A2* and *ATP1A3* genes, which are different isoforms encoding the Na+/K+-ATPase (NKA) alpha subunit, are associated with FHM2 (*ATP1A2*), childhood alternating hemiplegia (*ATP1A2/A3*), RDP (*ATP1A3*), cerebellar ataxia-reflex loss-progressive optic atrophy (*ATP1A3*), and recurrent encephalopathy with cerebellar ataxia (*ATP1A3*), respectively (25). The *ATP1A4* mutation is a novel gene mutation that was detected associated with FHM (22). *PRRT2* mutations lead to dysregulation of transmembrane calcium and sodium channels, resulting in diseases such as FHM2 and PKD (17). Mutations in *SCN1A*, which encodes the pore-forming a1 subunit of the neuronal voltage-gated sodium channel Nav1.1, are likely to cause neurological disorders such as FHM and HM in patients (21). Mutations in *PNKD* disrupt neurotransmitter regulation, which in turn is implicated in HM and PNKD (26). The possibility of phenotypic pleiotropy of genes associated with migraine and dystonia (**Table 1**), meanwhile, cannot be excluded. However, the significant temporal association between migraine and dystonia and the uniqueness of the dystonia manifestation in this case should still be acknowledged.

Management of migraine-induced dystonia is primarily focused on migraine prevention and treatment. Current randomized controlled studies revealed an unremarkable effect of PFO closure on migraineurs (27). A further genetic test is required, even though it has a limited impact on the patient's treatment, it may play a profound role in expanding our understanding of the underlying mechanisms of migraine and dystonia. Further follow-up is required as well.

CONCLUSION

In conclusion, our study suggests a rare case of migraine-induced dystonia of the lower extremities, which broadens our insight into migraine and dystonia. To date, only one case has been reported previously, and there are some discrepancies with our case. Further fundamental analyses are needed to explore the potential mechanisms.

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/s.

ETHICS STATEMENT

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

TJ and HM carried out the patient information acquisition and manuscript preparation and drafted the manuscript and prepared the figure and table. YX and BM checked the literature and developed the idea of the study. YC and ZL revised the manuscript and gave the final approval. HM contributed to the conception and design of the manuscript. All authors read the approved and final manuscript.

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Case Report: A Novel CACNA1A Mutation Caused Flunarizine-Responsive Type 2 Episodic Ataxia and Hemiplegic Migraine With Abnormal MRI of Cerebral White Matter

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Yuan X, Zheng Y, Gao F, Sun W, Wang Z and Zhao G (2022) Case Report: A Novel CACNA1A Mutation Caused Flunarizine-Responsive Type 2 Episodic Ataxia and Hemiplegic Migraine With Abnormal MRI of Cerebral White Matter. Front. Neurol. 13:899813. doi: 10.3389/fneur.2022.899813

Episodic ataxia type 2 (EA2) is one autosomal-dominant neurological disorder characterized by debilitating attacks of ataxia. It is mainly caused by loss-of-function mutations of the CACNA1A gene, which encodes the pore-forming α1A subunit of $Ca_V2.1$ (P/Q type voltage-gated calcium channel). Sporadic hemiplegic migraine (SHM) is another rare disease involving CACNA1A variants, which seldom coexists with EA2. Here we report a novel pathogenic mutation in CACNA1A (c.3836dupA, exon 23, p.Y1279X) of a 16-year-old female, who complained about paroxysmal dizziness, headache, and unsteady gait. Her brain MRI revealed a slightly atrophic cerebellum and numerous asymptomatic hyperintense lesions of the cerebral white matter. The diagnosis of EA2 combined with SHM was made. Administration of 5-mg flunarizine once daily at night effectively reduced the attacks and attenuated her symptoms for a month.

Keywords: episodic ataxia type 2, CACNA1A, MRI, flunarizine, case report, hemiplegic migraine

INTRODUCTION

The primary function subunit of the P/Q type voltage-gated calcium channel, commonly known as Cav2.1, is coded by CACNA1A (chromosome 19p13) (1). This complex gene contains 47 exons with abundant alternative splicing loci. $Ca_V2.1$ is distributed unevenly throughout the central nervous system and is predominantly expressed in cerebellar Purkinje and granular cells. This channel primarily mediates the neurotransmitter release and regulates other crucial activities, such as cell survival (2, 3). Mutations in different sites of CACNA1A lead to various neurological disorders, collectively referred to as $Ca_V2.1$ channelopathies. A wide disease spectrum has been observed, among which three classic phenotypes have been recognized, episodic ataxia type 2 (EA2), familial hemiplegic migraine type 1 (FHM1), and spinocerebellar ataxia type 6 (SCA6). Genetically, EA2 is primarily associated with loss-of-function variants of CACNA1A, whereas FHM1 is primarily associated with gain-of-function mutants, while SCA6 has an expanded CAG repeat in CACNA1A (4). Clinically, EA2 is characterized by adolescent-onset episodes of ataxia, dizziness, and nausea lasting hours to days, which can be accompanied by other cerebellar, brain stem, or cortical symptoms. SCA6 often shows a progressive cerebellar syndrome with a usual onset at middle age. FHM1 is a rare subtype of migraine characterized by aura symptoms, episodic

movement weakness, migraine headaches, and a positive family history. Although most sporadic HM (SHM) cases did not show any $Ca_v2.1$ mutant, it differs from FHM only in family history, suggesting the involvement of CACNA1A in SHM (5, 6). EA2 and HM can coexist within the same family (7, 8) and even in the same patient (9). The similarity of symptoms and signs makes the diagnosis of these disorders difficult, highlighting that genetic testing is necessary (4, 10). Brain MRI of EA2 patients typically reveals cerebellar atrophy or no notable findings, with cerebral white matter appearing to be rarely affected (11). However, in patients with SHM, reversible subcortical hyperintensities on images are relatively common (12). It has been reported that flunarizine is useful in treating certain CACNA1A-related disorders, such as HM, but its efficacy in EA2 remains largely unknown (9, 10). Here we describe a case of concurrent EA2 and SHM caused by a novel nonsense mutant of CACNA1A, with a slightly atrophic cerebellum, hyperintense lesions of cerebral white matter, and a favorable response to flunarizine.

CASE PRESENTATION

A 16-year-old female visited our clinic for increasingly frequent attacks of vertigo and nausea along with gait instability. There was no related family history, such as migraines, epilepsy, or ataxia. The patient had a history of pneumonia at the age of 6 months but no history of other illnesses. She was born full-term and appeared normal in the physical, motor, social, language, and cognitive development. She is now in the third year of high school with good grades but gets relatively insufficient sleep of 5 h a day. Nevertheless, she thinks the study pressure is acceptable. The attacks could date back to a decade ago when she first experienced transient dizziness that resulted in a minor fall for no obvious reason or trigger. She recalled that she had blurred vision for a few seconds but had no other accompanying symptoms at that time. No medical attention was sought. After 2 years, the dizziness recurred leading to a distal radius fracture with no clear inducement and no other abnormalities, which was regarded as an accident, and thus neurological consultation was not provided. Episodes occurred several times at a low but increasing frequency over the next 4 years progressively. At the age of 12 years, the symptoms became non-negligible and affected her life greatly, which manifested as monthly attacks of vertigo and unsteady gaits lasting 10–20 min, accompanied by irritability, photophobia, and phonophobia. Nausea, vomiting, and slurred speech also appeared with the attacks sometimes. Between episodes, she was asymptomatic except for a slight headache. Before each episode, a moderate headache on the left side appeared for a few seconds, with no flash or other auras seen. Notable triggers included lack of sleep and strenuous exercise (such as, running 800–1,200 m). It appeared that posture and menstruation were not associated with triggering the attack. There was no tinnitus, ear fullness, diplopia, loss of consciousness, convulsions, or upper limb dysfunction during the attack. Progressively, her condition continued to deteriorate and reached 2 or 3 episodes a day, each lasting 1–2 h in the months before the visit to our clinic. In severe cases, the weakness of lower limbs or rotation of vision (according to the patient's descriptions) forced her to sit down. She once took Yangxue Qingnao granules (a type of Chinese medicine that treats headache and dizziness) and betahistine mesylate, but her condition did not improve so she interrupted the therapy. No other symptoms occurred within the 4 years before this visit. The slight headache during the interictal period had not changed.

A physical examination was conducted during the interictal period and found no special abnormal signs of the nervous system and general condition. The patient was conscious and had fluent speech, normal memory, and normal higher cortical functioning. No nystagmus was observed. Cranial nerve tests were unremarkable. Sensations of touch, pain, temperature, vibration, and position were symmetrical and normal. The muscle strength of four limbs was five with moderate muscle tension. Tendon reflexes could be elicited symmetrically. The finger-to-nose test and heel-to-shin test were accurate. Pathological responses were negative. We failed to perform an ictal examination directly since this family lived more than 1,600 km away from our hospital and were unable to stay here for too long. We got the video recordings during an attack at home instead. The patient displayed an unsteady and broad-based gait, accurate heel-to-shin test, and absence of nystagmus (**Supplementary Video**). Laboratory tests of hematology, biochemistry and the homocysteine level were normal. A lumbar puncture was not performed. Magnetic resonance imaging (MRI) of the head revealed multiple patchy lesions in the centrum semiovale, and white matter of the bilateral frontoparietal temporal lobe, with T1 hypointensity (**Figure 1A**), T2 hyperintensity (**Figure 1B**), and normal in diffusion-weighted imaging (DWI) sequence (**Figure 1C**). The cerebellum was slightly atrophic (**Figure 1D**). There was no obvious change in the MRI findings compared with 1 year ago. Interictal electronystagmography showed normal recordings while electroencephalogram detected a small amount of asymmetric complex delta waves scattered in the bilateral temporal regions without other abnormal waveforms. To exclude heart and cerebrovascular diseases, we carried out electrocardiogram (ECG), echocardiography, transcranial Doppler ultrasonography, and head MRI angiography. Whole exome next-generation sequencing was conducted afterward considering the possibility of hereditary channelopathies. A novel, heterozygous mutation in the CACNA1A gene (c.3836dupA, exon 23, and p.Y1279X) leading to a premature stop codon was discovered. Further validation of Sanger sequencing for her healthy parents revealed no mutant at the same locus, indicating the identified mutation *de novo* (**Figure 2**). According to the recommendations of the American college of medical genetics and genomics and the association for molecular pathology, this mutation is pathogenic (PVS1 + PS2 + PM2) (13), clarifying the diagnosis of EA2 and SHM.

Carbamazepine (0.1 g bid) was prescribed first for symptomatic therapy before the result of the gene test but was discontinued 2 days later due to the increased attacks after initiation. She failed to start acetazolamide because this drug was unavailable in our institution or pharmacies and was hard to obtain routinely. Flunarizine of 5 mg once daily at bedtime was

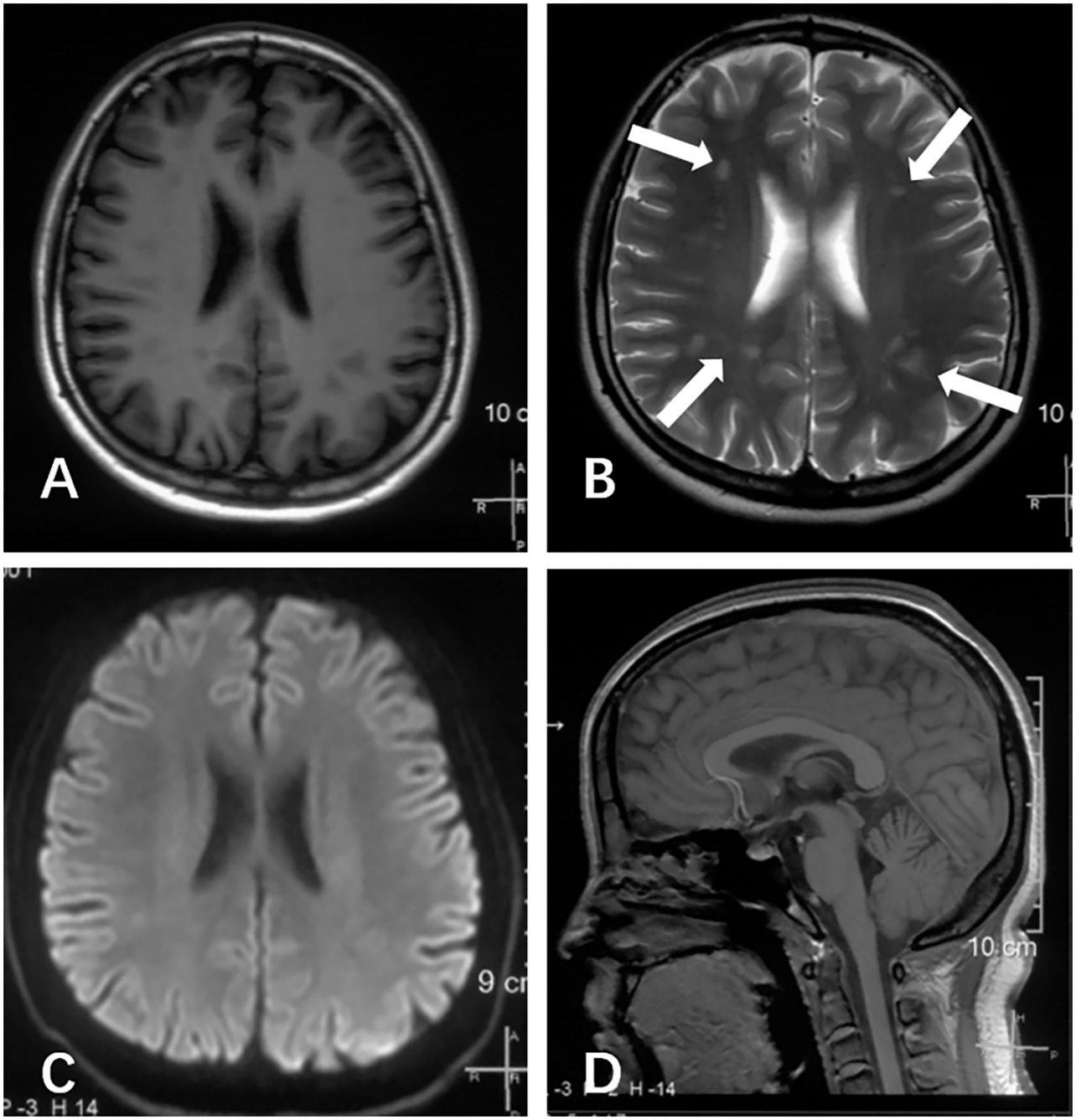

FIGURE 1 | Brain MRI scans of this patient, performed at age of 16 years during the interictal period. **(A)** Axial T1 image revealed several hypointense lesions of the centrum semiovale and white matter of the bilateral frontoparietal temporal lobe. **(B)** Axial T2 image revealed several hyperintense lesions at the same locations (arrows). **(C)** The axial diffusion-weighted imaging (DWI) image appeared normal. **(D)** Sagittal T1 image demonstrated slightly cerebellum atrophy.

administered instead and effectively ameliorated her condition in a month. According to her description, the frequency decreased from 2 or 3 episodes a day to once a month, the attack duration declined from 1 or 2 h to 30 min, interictal and ictal headache almost disappeared, and the symptoms of episodes of dizziness, nausea, and gait instability were significantly relieved. Our patient has not taken triptans or other pain-killing medications because the headache she felt was not that disturbing. The timeline of the clinical course is presented in **Figure 3**.

DISCUSSION

Our patient had the typical manifestations of episodic dizziness and ataxia accompanied by nausea, vomiting, and slurred speech.

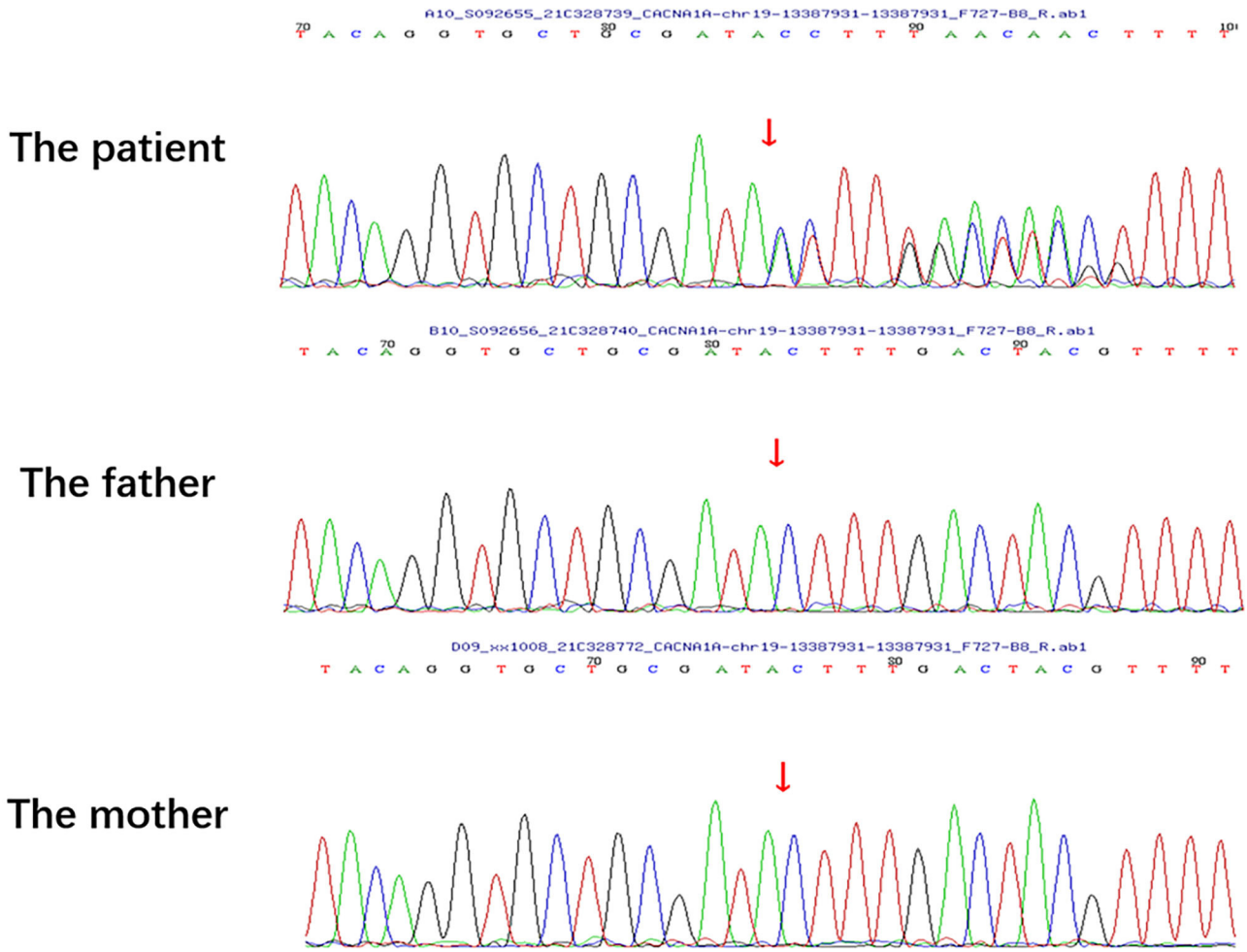

FIGURE 2 | Sanger sequencing of the patient and her healthy parents. No mutation was detected in the parents at the same locus of the patient's pathogenic variant.

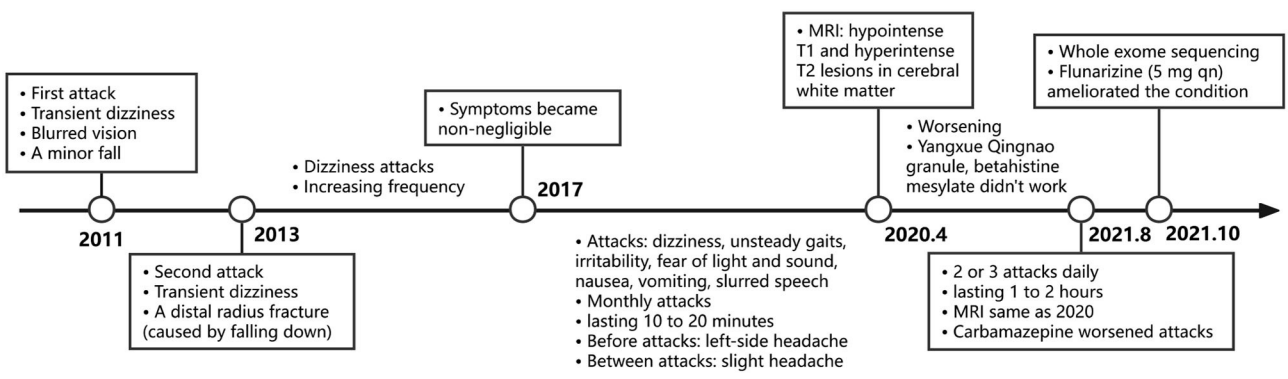

FIGURE 3 | Timeline of the clinical course.

Her MRI presentation was distinctive but lacked specificity (discussed later), while other examinations appeared normal. Next-generation sequencing revealed one truncating mutant of CACNA1A and pointed to the diagnosis of EA2 at first. However, some symptoms atypical in EA2 but common in SHM, such as irritability, the fleeting unilateral headache just before episodes, as well as the photophobia, and phonophobia during an attack, led us to consider the coexistence of SHM. This supposition

was further supported by her adequate response to the classic migraine prevention drug flunarizine and the hyperintense cerebral white matter, which is known in patients with migraine. However, the headaches coming before other symptoms and lasting for a very short time during an attack seemed not to meet the diagnostic criteria ICHD3 (6). Clear identification of CACNA1A-related diseases could be difficult even after getting the gene results. Huge variations and some degree of overlaps have been observed in the presentations of EA2 and HM cases (7, 14). EA2 and HM symptoms did occur in different individuals with the same CACNA1A mutant (7, 8) and even in a single patient (9). The concurrence of these two diseases might cause confusing episodes of ataxia, dizziness, and headaches in our patient. Notably, her manifestations also overlapped immensely with vestibular migraine (VM), which is the most common cause of episodic vertigo and is also characterized by headache, photophobia, and phonophobia. Differentiating EA2 from this disease based on clinical presentation alone could be quite confusing. According to the ICHD3 criteria, VM is a diagnosis of exclusion (15). EA2 and SHM seemed to be a better explanation here given the signature gene CACNA1A. Nonetheless, VM cannot be completely ruled out. The exclusive procedures in previous studies might prevent the identification of candidate genes since VM would be left out whenever a proven gene related to another disease was detected. CACNA1A could be one of the pathogenic genes of VM or not. Additionally, the young age of our patient and her satisfactory response to flunarizine were suspicious. Some children experiencing benign paroxysmal vertigo later develop VM (16). Long-term follow-up is required.

The majority of reported EA2 cases were caused by truncating mutations of CACNA1A, while the pathogenic role of this gene in SHM1 is not that clear (6, 11). Here, the new nonsense mutation in exon 23 of CACNA1A forces translation to terminate at the domain III of $Ca_v2.1$ (2, 3), leading to incomplete channels with probably weakened conductance of Ca^{2+} (17). Neurotransmission in the cerebellum and the pace-making of Purkinje cells could get impaired given their dependency on $Ca_v2.1$ (1, 2, 4). Moreover, the lower inflow through $Ca_v2.1$ eminently stimulates other Ca^{2+} currents into neurons, particularly the L type (17). The overall Ca^{2+} influx increases, as a result, engendering further cytotoxicity, excessive glutamate in the synaptic gap, and the increased susceptibility to cortical spreading depression (CSD) (5, 18). Interestingly, the C-terminus is cleaved from the full-length α_{1A} subunit followed by entry into the nucleus. This translocation process appears uniquely vital for the survival of Purkinje cells but is absent in the case of a truncated protein with no C-terminus, resulting in the deterioration of cerebellar neurons (2, 3). Nonetheless, the above theories are far from adequately explaining the clinical manifestations. The mechanisms underlying $Ca_v2.1$ channelopathies remain poorly understood at present.

Our patient displayed a slightly atrophic cerebellum on images, consistent with the MRI of most CACNA1A-mutant patients, which partially resulted from the degeneration and death of Purkinje cells mentioned above. Abnormal signals of cerebral white matter exhibited in our case have not been described in EA2 but have occasionally appeared in SHM cases with or without CACNA1A mutations (12). Hyperintense lesions on T2 have also been observed in other $Ca_v2.1$ channelopathies, including an infant boy with severe encephalopathy (19) and a family with FHM (20). We suspected that the lesions showed in our patient were caused by microangiopathy-related demyelination, considering the patchy locations and the modes of hypointense T1 and hyperintense T2 (21). Possible pathological evidence came from the ultrastructural examination of biopsy samples in the above-mentioned FHM family, which revealed microangiopathy in skin and muscle (20). Oligodendrocyte progenitor cells, responsible for myelin-forming, were reported to selectively deteriorate in the corpus callosum when $Ca_v1.2$ was deleted, implying the essential involvement of voltage-gated calcium channels in myelination (22). Intriguingly, nerve bundles from the corpus callosum are the main component of the centrum semiovale, one of the abnormal regions of our patient. In models of brain injury, the loss-of-function mutant $Ca_v2.1$ demonstrated suppression of astrocyte activation, which is involved in remyelination failure (23). Thus, we proposed that the myelin loss derived from $Ca_v2.1$-defect-caused microangiopathy brings about the aforementioned abnormal signals. CSD in SHM, which activates the release of vasoactive neuropeptides and triggers inflammation may also account for the image (5). Nevertheless, the relationship between lesions of superficial white matter and $Ca_v1.2$ as one L-type channel is still unknown. We cannot rule out the possibility that these abnormal signals have nothing to do with EA2, given no change in MRI over the year while the condition worsened, the absence of any symptoms related to white matter abnormalities, and the lack of earlier images. Further observations in clinical practice are needed.

The majority of patients with $Ca_v2.1$ channelopathy underwent progressively worsening conditions without proper intervention and were severely affected by the attacks (4), indicating the importance of prompt detection, correct diagnosis, and use of appropriate drugs. Acetazolamide is recommended to treat EA2 and SCA6 for relieving symptoms and slowing disease deterioration; 4-aminopyridine, a potassium channel blocker inhibiting Ca^{2+} inflow indirectly, has shown favorable effects in some EA2 cases (4, 11). However, in our case, neither was readily available while flunarizine was accessible and much cheaper. Flunarizine protects the neurons from ionic overload efficiently by inhibiting the L-type calcium and voltage-gated sodium channels (18). Recent guidelines for HM suggest oral flunarizine at 10 mg/day but this recommendation was largely based on studies in adults with no focus on CACNA1A-caused HM (5, 6). Instead, previous CACNA1A-related cases showing the efficacy of flunarizine were both at the daily dose of 5 mg, involving one FHM1 family and noteworthily, a woman suffering from episodic ataxia and HM (9, 10). A study summarizing 11 years' experience in treating childhood migraine found flunarizine effective in HM at an initial dose of 5 mg daily. Escalation to 7.5 or 10 mg/day took place only when there was an insufficient response to the starting dose (24). It is worth noting that flunarizine may act differently in patients with the same mutation, and several side effects (such as, drowsiness, weight gain, depressive, or extrapyramidal syndromes) could arise in long-term applications

(9). Follow-up for the possible progression of cerebellar atrophy and timely treatment modification are needed. Diagnosis of $Ca_v2.1$ channelopathies is largely facilitated by molecular approaches. Treatments with higher efficacy and fewer side effects demand further investigations. Rehabilitation of impaired neurologic functions and genetic counseling for the families of such patients also represent topics that should not be ignored in the future.

In conclusion, $Ca_v2.1$ channelopathies should be considered when a teenager presents with episodic dizziness, unsteady gait, and headache. The possibility of pluralism should be assessed when a single phenotype cannot display all clinical manifestations. Patients with CACNA1A-related diseases could display cerebellum atrophy or multiple patchy abnormal signals of cerebral white matter on MRI. Flunarizine could serve as one choice in such cases. More studies are needed to confirm the efficacy and possible adverse effects of long-term use. Continuing follow-up is necessary to timely stop progressive damage to the central nervous system.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of ethical and privacy restrictions. Requests to access the datasets should be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board and Ethics Committee at Peking University First Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

XY prepared the original draft. YZ contributed with the acquisition of data and revising the manuscript. FG, WS, and ZW revised the manuscript. GZ reviewed and edited the final manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.899813/full#supplementary-material

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CASE REPORT
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Development of Unilateral Peri-Lead Edema Into Large Cystic Cavitation After Deep Brain Stimulation: A Case Report

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Background and Importance: Deep brain stimulation (DBS) has been approved to treat a variety of movement disorders, including Parkinson's disease (PD), essential tremor, and dystonia. Following the DBS surgery, some perioperative and even delayed complications due to intracranial and hardware-related events could occur, which may be life-threatening and require immediate remedial measures.

Clinical Presentation: We report a case of an older woman with advanced PD who developed the unique complication of unilateral cyst formation at the tip of the DBS electrode after undergoing bilateral placement of subthalamic nucleus DBS. After a period of controlled motor symptoms, the patient showed new neurological deficits related to right peri-lead edema. However, the new neurological symptoms regressed quickly over several days with stereotactic implantation of a puncture needle to drain the cyst fluid without removing the affected lead.

Conclusion: The occurrence of an intraparenchymal cyst following DBS surgery is a rare but life-threatening complication that could relate to edema around the electrodes or cerebrospinal fluid tracking. Stereotactic aspiration makes the intracranial cyst regress safely and effectively and ensures that the electrode is in the optimal position of the target nucleus to achieve an effective DBS surgery.

Keywords: Parkinson's disease, deep brain stimulation, peri-lead edema, intraparenchymal cyst, subthalamic nucleus

BACKGROUND AND IMPORTANCE

Deep brain stimulation (DBS) surgery is associated with a variety of complications ranging from intracranial adverse events to hardware malfunction (1, 2). Although DBS surgery is minimally invasive, it can cause immediate and severe complications like stroke or intracranial hemorrhage, occurring in ∼1–2% of post-operative patients (3, 4). Furthermore, DBS requires chronic implantation of hardware leading to hardware-related complications such as infections (6.1%), migration or misplacement of leads (5.1%), lead fractures (5.0%), and skin erosion (1.3%) (5, 6). These complications lead to a decline in the quality of life in patients, and the previous benefits of DBS could be entirely lost (7). In this case report, we described a patient with Parkinson's

disease (PD) who developed new neurological deficits 2–5 months following the DBS surgery due to peri-lead edema progressing into large cystic cavitation, revealed by imaging (8). We also reviewed the literature to discuss the potential etiologies and proposed some coping strategies for rare complications (9). We considered two possible explanations for intracranial cyst formation: (i) post-operative peri-electrode edema progressing into large cystic cavitation and (ii) cerebrospinal fluid (CSF) at the puncture point of the cerebral cortex flowing along the electrode toward the electrode tip (10). Given the rarity of this complication, there was no expert consensus on treatment. However, previous case reports reported conservative treatment with steroids, and cyst regression occurred along with clinical improvement (11). In addition, removing the affected lead or stereotactic cyst aspiration could be a potential supplementary treatment.

CLINICAL PRESENTATION

We presented a case of a 60-year-old right-hand dominant illiterate female patient who was diagnosed with PD approximately 12 years before undergoing DBS surgery. The patient had no history of chronic diseases like hypertension and diabetes, and no behavioral or cognitive complaints were reported. At first, the patient presented only with tremors on the right upper limb and a significant increase in muscle tone, which significantly improved with levodopa and dopamine agonists. At this time, the patient took half a tablet of Medopa (a tablet of Medopa including levodopa 200 mg and benserazide 50 mg,TID). However, the dosage and type of medicine were changed to one tablet of Madopa (QID) and pramipexole hydrochloride (0.25 mg, QID) as the PD progressed, but the duration of their effects shortened. Eventually, the drugs caused many side effects (such as dyskinesia, marked ON-OFF time, severe constipation, and insomnia) and severe motor fluctuations. Moreover, the body posture of the patient was abnormally accompanied by severe anxiety during the OFF-med, making walking extremely unstable and prone to falls. In order to resolve the above problem, the patient sought a surgical alternative. Therefore, preoperatively, the Unified Parkinson's Disease Rating Scale (UPDRS), Hamilton Anxiety Scale (HAMA), and Hamilton Depression Scale (HAMD) were performed by a neurologist with expertise in movement disorders to evaluate the patient depicting 60% improvement on part III (OFF-med:65 ON-med:26). The UPDRS score of the patient, combined with her neuropsychological evaluation (HAMA:3 HAMD:4) and routine preoperative biochemical examination, revealed no contraindications to DBS.

The patient underwent bilateral placement of DBS leads (L301, PINS, Beijing, China) targeting the subthalamic nucleus. The DBS operation was performed under the guidance of a surgical plan (pre-operative MRI fused with framed CT) and the monitoring of intraoperative electrophysiology. The electrodes were implanted into the predetermined targets on both sides in a single pass. After the operation, the vital signs of the patient were stable without intracranial hematoma or edema based on the immediate postoperative CT imaging. The leads were optimal, as confirmed by fusing the postoperative image with the preoperative surgical plan. The amount of medicine taken within 1 week after the operation was significantly reduced to only 1/4 tablet of Medopa (TID) compared with the previous one. Turning the stimulator on for initial programming 3 weeks after surgery resulted in tremor relief on the right upper limb and a steady walk even in OFF-med (UPDRS-III:41 improvement:36.9%) through routine programming settings (voltage: 1.5 V, pulse width: 60 μs, frequency: 130 Hz). However, during follow-up, the patient presented a continuous leftward tilt of the body with a static tremor of the right upper extremity without significant cognitive decline. The physical examination suggested: a general increase in muscle tone, especially on the right side. There was a right limb static tremor, and bilateral rotation movement was not coordinated. At the 2-month postoperative follow-up, an axial CT and 1.5 T magnetic resonance imaging (MRI) were performed. The images revealed hypodensities or high signals surrounding the right lead, extending from the subcortical region to the deep

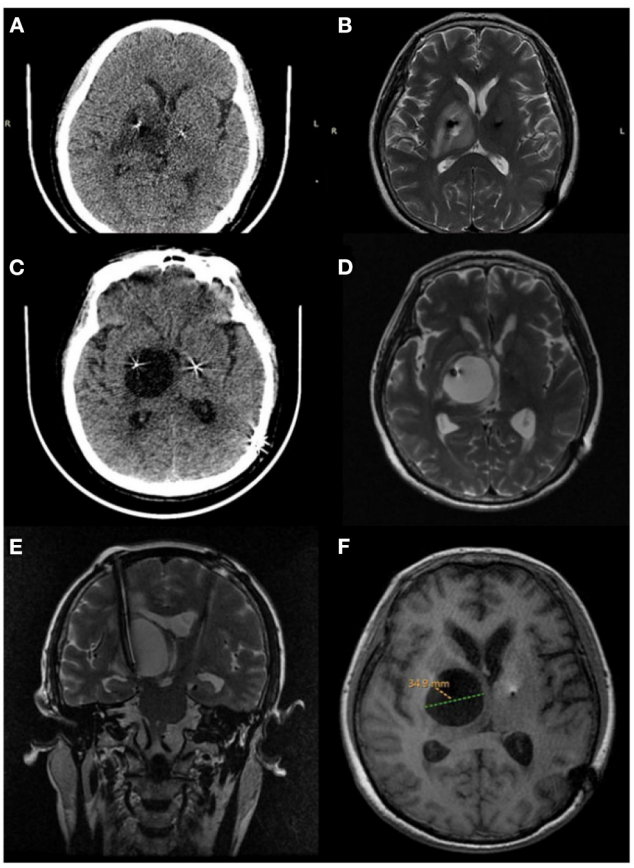

FIGURE 1 | Peri-lead edema 2 months after deep brain stimulation surgery. **(A)** Axial CT, **(B)** axial MRI T2. Cystic cavitation around the lead 4 months after deep brain stimulation surgery. **(C)** Axial CT, **(D)** axial MRI T2. Five months after deep brain stimulation surgery. **(E)** Coronal T2 (MRI) showing a large cyst, **(F)** axial T1 (MRI) the cystic cavitation with a maximum diameter of 34.9 mm.

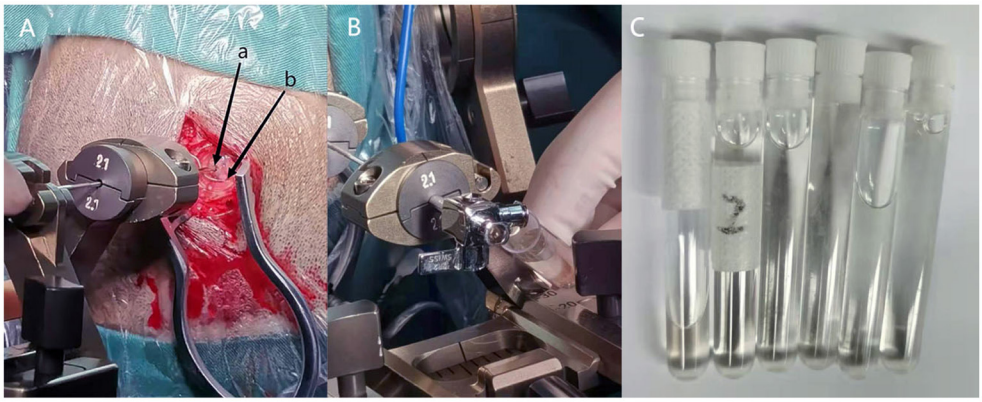

FIGURE 2 | (A) Stereotactic cyst puncture is performed (a: Brain puncture needle hole, b: previous electrode hole). **(B)** The clear cyst fluid will flow out automatically after the brain puncture needle into the cyst. **(C)** About 25 ml clear cyst fluid drained through stereotactic cyst aspiration.

white matter near the lateral ventricles (**Figures 1A,B**). In the fourth and fifth months after DBS, CT and 1.5T MRI of the brain revealed a right cystic cavity with a maximum diameter of 34.9 mm compatible with CSF in all sequences surrounding both leads and their contacts (**Figures 1C–F**). In addition, MRI with gadolinium revealed significant right peri-lead edema with large non-enhancing cystic cavities along the leads extending from the subcortical region to the deep white matter near the lateral ventricles. At the same time, CT imaging revealed no evidence to support intracranial hemorrhage. The electrode tip was close to the cyst wall, located on the ventrolateral side. Notably, the patient did not demonstrate infection-related symptoms, including fever or leukocytosis, negative blood cultures, and healed surgical incisions. Furthermore, her erythrocyte sedimentation rate and C-reactive protein were within the normal range. However, the mood of the patient was more anxious than before the operation (HAMA:14 HAMD:15). Even when the stimulation was turned on, the patient exhibited a significant decline in her motor function. Moreover, turning off the device did not yield any improvement.

Treatment

After obtaining the CT and MRI imaging features of this patient, the primary diagnosis we considered was a brain abscess. However, peri-lead edema and cavitation caused by infectious factors were ruled out based on the blood and the imaging results. Initially, this patient was given conservative treatment, such as steroid and antibiotic therapy and follow-up observation. However, the peri-lead edema did not abate and gradually developed into a large cyst over time (12).

After discussing the risks, benefits, and alternatives with the family of the patient and obtaining consent, stereotactic aspiration of the cyst was implemented through a puncture needle without removing the affected DBS lead. Ultimately, about 25 mL of clear cyst fluid was drained (6) (**Figure 2**). In order to prevent the recurrence of the intracranial cyst, bioprotein glue was injected into the puncture hole to block the electrode path, as the cyst fluid no longer flowed out. Then, the cyst fluid was sent for biochemical examination, which indicated that the sac fluid was pale yellow, clear, positive for Pan's test, with a red cell count of 5 × 10∧6/L, a nucleated cell count of 36 × 10∧6/L, a glucose content of 2.59 mmol/L, the protein content of 3.70 g/L, and chlorine content of 116.6 mmol/L. Furthermore, the results of the culture depicted no colony growth. The patient was discharged with significant improvement in her symptoms and continued tremor resolution, with ON-stimulation following surgery (**Figure 3**).

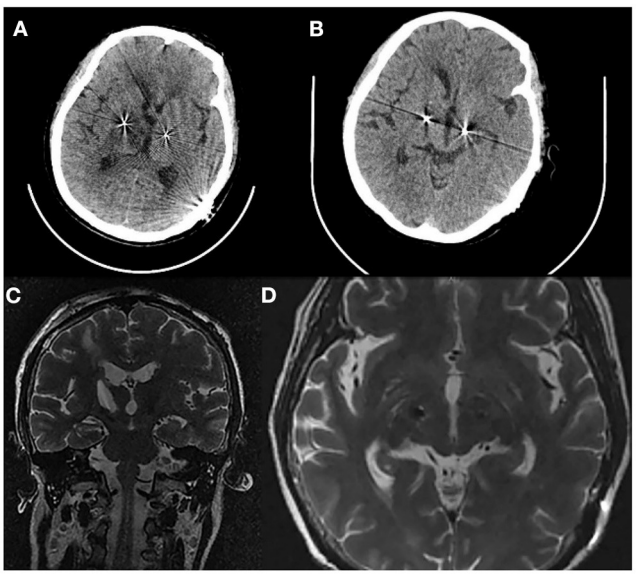

FIGURE 3 | (A) Axial CT 1 day after cyst aspiration demonstrates the cyst that have almost disappeared. **(B)** Axial CT 6 days after cyst aspiration. **(C)** Coronal T2 (MRI) 6 days after cyst aspiration. **(D)** Axial T2 (MRI) 6 days after cyst aspiration without displacement of the right lead.

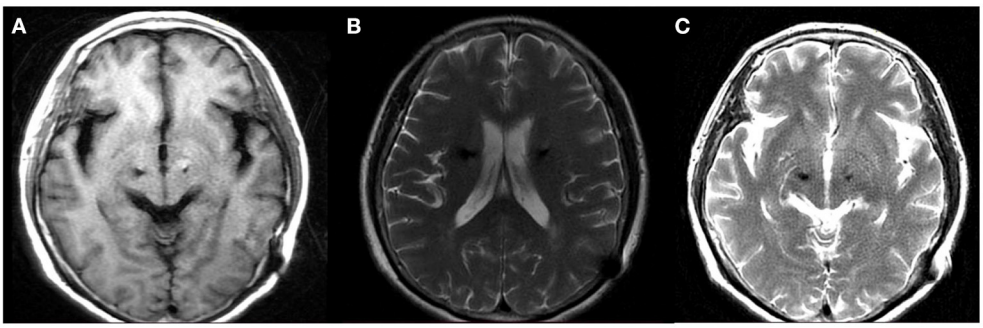

FIGURE 4 | MRI following 5 month stereotactic aspiration demonstrated significant regression of the peri-lead edema and cystic cavitation. **(A)** Axial T1 **(B)** axial T2 **(C)** axial T2.

Outcome and Follow-Up

During the follow-up period after treatment, the patient was generally in good condition accompanied with 3/8 tablet of Medopa (TID). After a 5-month stereotactic aspiration, the patient was admitted for a 1.5T MRI in the OFF-stimulation state, demonstrating that peri-lead edema and cystic cavitation had significantly regressed without recurring (**Figure 4**). Furthermore, the patient underwent stimulation ON/OFF Unified Parkinson's Disease Rating Scale part III (UPDRS-III) testing in ON-med, and the result indicated an 18.6% improvement rate (OFF-stimulation:43 ON-stimulation:35) (13). Therefore, stereotactic cyst aspiration was the first measure that could be considered when conservative treatment methods were ineffective, and it ultimately ensured that the electrodes continued to deliver effective stimulation to improve motor symptoms. Under the combined treatment of the above medication protocol and programming (left:voltage: 2.0 V, pulse width: 60 μs, frequency: 130 Hz; right:voltage: 1.5 V, pulse width: 60 μs, frequency: 130 Hz), the patient's right upper limb tremor and muscle tension can be significantly reduced, and the patient can keep upright and walk independently.

DISCUSSION

This case reported a rare—but potentially catastrophic—adverse event associated with the DBS surgery: the development of peri-lead edema to a large cyst. It also demonstrated that, in the case of ineffective conservative treatment measures, stereotactic cyst aspiration without removing the affected electrode is effective and safe (14). Furthermore, after the cyst was stereotactically aspirated, the patient returned to upright posture without left-leaning within days. Our center has placed more than 700 leads since beginning the DBS surgery in 2010, and the core surgeon, equipment used, and target nucleus remain unchanged. However, this was the first time we had encountered an unexplained complication. Initially, we suspected it to be an intracranial abscess caused by an intracranial infection based on the imaging results. However, intracranial infections usually appear within the first few weeks following the DBS surgery and are accompanied by systemic symptoms, which are inconsistent with the state of the patient (15, 16). Furthermore, the negative results of the blood of the patient and post-operative cystic fluid culture proved that it was a cyst and not an abscess. Therefore, we hypothesized that the immune response of the patient to the implanted lead resulted in the cystic cavity depicted on imaging and explored the cause (17). If the above hypothesis were true, bilateral intracranial cysts would occur. However, the patient had only a single intracranial cyst on the right side and self-reported no underlying autoimmune disorder or history of severe allergies, overturning our previous assumption (18). Another possibility was that CSF from the subarachnoid space in the punctured area migrated down the affected lead and accumulated as a large cyst at the tip of the lead due to a backflow prevention mechanism, as previously described in another study (18). Importantly, the cyst gradually grew, causing a mass effect associated with neurological symptoms (19). In addition, the motor symptoms of the patient returned to the pre-operative baseline. They were not significantly alleviated whether stimulation was on or off, and some new problematic symptoms were even demonstrated.

We reviewed the relevant literature, and specific risk factors and potential pathological mechanisms of this complication remained unclear. Some centers reported that edema around the electrodes subsided using conservative treatment or removing the electrodes. However, in this case, we found that stereotactic cyst aspiration without removing the affected electrode should be given priority when conservative treatment measures were ineffective. We hope that this unique treatment experience provides valuable reference for other neuromodulation centers.

CONCLUSION

As a rare but life-threatening complication, an intraparenchymal cyst after DBS lead placement would gradually disappear if the appropriate measures were taken. Therefore, steroid therapy and follow-up observation should be considered the first treatment choice. However, if these conservative treatment strategies do not work, stereotactic aspiration of the cyst without removing the affected DBS lead could be the best measure since it avoids the risk of secondary implantation of the electrode while ensuring that the electrode is within the optimal position of the target nucleus.

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

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

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Case report: A novel loss-of-function pathogenic variant in the KCNA1 cytoplasmic N-terminus causing carbamazepine-responsive type 1 episodic ataxia

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Episodic ataxia is an umbrella term for a group of nervous system disorders that adversely and episodically affect movement. Episodes are recurrent, characterized by loss of balance and coordination and can be accompanied by other symptoms ranging from nausea to hemiplegia. Episodic Ataxia Type 1 (EA1) is an inherited, autosomal dominant disease caused by sequence variants in *KCNA1*, which encodes the voltage-gated potassium channel, KCNA1 (Kv1.1). Here we report a novel loss-of-function *KCNA1* pathogenic variant [c.464T>C/p.Leu155Phe] causing frequent, sudden onset of clumsiness or staggering gait in the young female proband. The gene variant was maternally inherited and the mother, whose symptoms also began in childhood, has a normal MRI and EEG, slurred speech and dystonic movements involving upper extremities and mouth. Both mother and daughter are responsive to carbamazepine. Cellular electrophysiology studies of KCNA1-L155P potassium channels revealed complete but non-dominant loss of function, with reduced current and altered gating in heterozygous channels. To our knowledge this is the first EA1-associated pathogenic variant located in the KCNA1 cytoplasmic N-terminus, expanding the reported clinically sensitive domains of the channel.

KEYWORDS

Ataxia, carbamazepine, EA1, *KCNA1*, Kv1.1

Introduction

Ataxias are a group of movement disorders in which affected individuals exhibit loss of balance, loss of coordination, irregular gait and slurred speech. Episodic Ataxia 1 (EA1) is an autosomal dominant inherited form of ataxia caused by genetic variation in the human *KCNA1* gene, which encodes the KCNA1 (Kv1.1) voltage-gated potassium (Kv) channel (1). EA1 patients typically bear one wild-type and one pathogenic variant *KCNA1* allele. EA1 involves altered central and peripheral nerve function, as KCNA1 performs important functions in both the central nervous system and in peripheral

nerves (2–4). Centrally, KCNA1 is especially important in the hippocampus, cerebellum, and neocortex; peripherally, KCNA1 is especially critical at synaptic terminal sites and juxtaparanodal segments of the nodes of Ranvier of myelinated axons (5). EA1-associated *KCNA1* mutations generally cause loss of function in KCNA1, most commonly by altering channel functional properties and less commonly by impairing KCNA1 biosynthesis or anterograde trafficking (6, 7).

Episodic ataxia is relatively rare, affecting <1/100,000 people, and is subdivided into at least 7 forms, the most common being EA1 and EA2. EA2 is caused by pathogenic variants in *CACNA1A*, which encodes the α1A pore-forming subunit of the Cav1.2 neuronal voltage-gated P/Q-type calcium channel (8). Episodic ataxia symptoms include recurring episodes of poor coordination and balance, and in addition can comprise blurred vision, slurred speech, vertigo, nausea and emesis, migraines, tinnitus, muscle weakness, hemiplegia, seizures, and myokymia (predominantly in the interictal interval in EA1) (9, 10). EA1 and EA2 are typically treated with anticonvulsant/antiseizure medications such as carbamazepine, valproic acid and acetazolamide, although the latter is generally more effective at treating EA2 (11, 12).

Case presentation

A 13-year-old female (the proband) was first seen by a geneticist in 2019 for the chief complaint of a personal and family history of episodic abnormal movements involving sudden onset of clumsiness or staggering gait without any alteration in sensorium, lasting 30 s-2 min. Her neurological symptoms began at age two and she was first seen by a Valley Children's Hospital neurologist at age four, but was not genetically evaluated at that time. The longer the episode, the greater the likelihood that slurring of speech will occur in the proband. Her episodes can be triggered by heightened activity or by fatigue, but neither is necessary for an episode to occur, and the proband averages 1–2 episodes per week, responsive to carbamazepine. The proband's gestation, birth and developmental history are normal and there is no other medical or surgical history other than familial short stature. The short stature arises from a familial delayed growth pattern of unknown mechanism although it is possible there is transient growth hormone resistance.

The proband's physical exam and neurological exam were normal. No MRI was performed on the proband since the clinical impression was episodic ataxia - and she was responsive to the medication prescribed for this (carbamazepine) - based on family history. Specifically, the proband's mother began presenting with neurological symptoms at age 8, which included slurring of speech, ataxia, and dystonic movements involving her upper extremities and mouth. MRI and EEG were performed on the proband's mother when she was 8 years old and were reported as negative, yet her episodes were initially diagnosed as epilepsy. Later, upon presentation of the proband, a diagnosis of ataxia was proposed for mother and daughter, and genetic analyses conducted based on this.

The proband's EEG was read as negative by the same neurologist that has been following the proband for 11 years. Specifically, at 3 years of age, the proband underwent measurements with a 21-channel digital EEG machine with ECG, respiration and eye movement monitors using the International 10–20-electrode placement system. The EEG was collected using 28 leads including ECG, EOG and respiration artifact leads. During the record the patient was at various times awake, drowsy and asleep. At the onset of the record, the patient was awake and displayed a normal anterior-posterior gradient with faster rhythms anteriorly. Maximum posterior dominant rhythm was up to 9 Hz and was symmetric. Movement artifact was very prominent as well as muscle artifact during the awake portion of the record. Photic stimulation and hyperventilation were not performed during the study. As the patient fell into drowsiness and sleep, symmetric sleep spindles and vertex sharp waves were observed. At times the vertex sharp waves occurred in runs, but there were no focal asymmetries or epileptiform features seen during the awake portion or during sleep. Upon arousal, a normal awake background returned. Thus, the neurologist reported a normal awake and sleep EEG.

The initial karyotype and limited channelopathy/hereditary ataxia panels (*PRRT2*, *SLC2A1*, *ATP1A2*, and *ATP1A3*) of the proband were negative. More recently, an expanded ataxia panel (GeneDx.com) was conducted using next-generation sequencing with copy number variant (CNV) detection (Supplementary Data 1). The sequencing revealed a gene variant in the coding region of *KCNA1*: c.464 T>C, encoding KCNA1: p.(Leu155Phe). The proband was heterozygous for p.(Leu155Phe); 100% of the *KCNA1* coding region was covered at a minimum of 10x and there was no indication of a multi-exon deletion or duplication. The proband's mother was also found by next generation sequencing to be heterozygous for the p.(Leu155Phe) variant in *KCNA1*, while the proband's father does not harbor the variant. The mutation is apparently *de novo* in the proband's mother, as the maternal grandmother and grandfather of the proband were tested and were negative (Figure 1A). KCNA1-L155 lies in the S1-proximal portion of the cytoplasmic N-terminus, is highly conserved (Figure 1B), and is close to other EA1-linked sequence variants (Figure 1C).

Functional characterization of KCNA1-L155P potassium channels

KCNA1-L55P is not observed at significant frequency in large population cohorts (The Genome Aggregation Database; gnomAD) and has not to our knowledge been previously reported as either benign or pathogenic (13). KCNA1-L155P

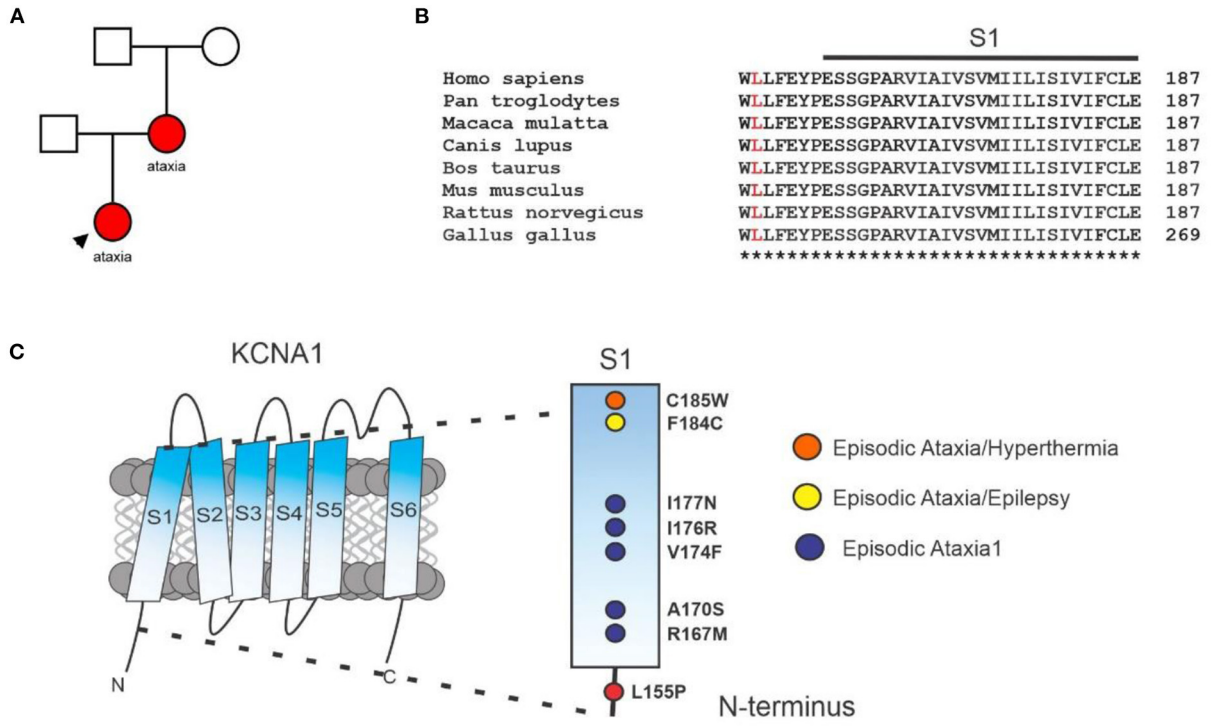

FIGURE 1
Clinical genetics. **(A)** Pedigree diagram for KCNA1-L155P (red) in the family under study. **(B)** Sequence alignment for S1 and S1-proximal N-terminal segment of KCNA1 with L155 highlighted (red). **(C)** Location of L155P and some previously reported EA1 sequence variants in KCNA1 (see Discussion).

cDNA was generated (Genscript, Piscataway, NJ) in the pTLNx expression vector, and then from this we generated cRNA by *in vitro* transcription with the mMessage mMachine SP6 kit (ThermoFisher, Waltham, MA). We injected wild-type KCNA1 (2 ng), KCNA1-L155P cRNA (2 ng) or wild-type KCNA1 + KCNA1-L155P (A1/A1-L155P) cRNA (2 ng each) into stage V and VI defolliculated *Xenopus laevis* oocytes. Oocytes were incubated at 16 °C for 2 days and then currents recorded using two-electrode voltage-clamp. Voltage protocols are shown in the figures.

As expected, wild-type KCNA1 channels generated robust, voltage-dependent outward currents in response to depolarizing voltage pulses. In contrast, homomeric KCNA1-L155P channels were nonfunctional. Currents generated by equal co-injection of wild-type and L155P KCNA1 (A1/A1-L155P) generated currents with 39% of the peak current magnitude of wild-type KCNA1 (Figures 2A,B, Table 1). Reflecting their inability to generate outward K^+ current at resting membrane potential in oocytes, the mean resting membrane potential (E_M) of unclamped oocytes expressing homomeric KCNA1-L155P was 34 mV more positive than oocytes expressing homomeric wild-type KCNA1, while the mean resting membrane potential of oocytes expressing A1/A1-L155P channels was 8 mV more positive than oocytes expressing homomeric wild-type KCNA1 (Figure 2C, Table 1). The shift in membrane potential for oocytes expressing A1/A1-L155P channels was attributable to voltage-independent reduction in current magnitude; there was no quantifiable difference in the voltage dependence of A1/A1-L155P compared to wild-type KCNA1 (Figures 2D,E).

Compared to wild-type KCNA1 channels, A1/A1-L155P channels exhibited twofold faster activation (Figures 3A,B) and several-fold faster deactivation (depending on voltage) (Figures 3C,D). KCNA1 channels also exhibit voltage-dependent inactivation following activation; compared to wild-type, A1/A1-L155P exhibited negative-shifted voltage dependence of inactivation such that there was, e.g., a threefold greater proportion of A1/A1-L155P channels inactivated at −40 mV compared to wild-type KCNA1, and a −8.4 mV shift in the voltage dependence of inactivation (Figures 3E,F, Table 1).

Discussion

KCNA1 channel activity generally dampens neuronal excitability; therefore, *KCNA1* loss-of-function mutations such as those in EA1 increase neuronal excitability, lowering the threshold for action potential generation. This in turn can result in increased firing frequency, broadening of individual

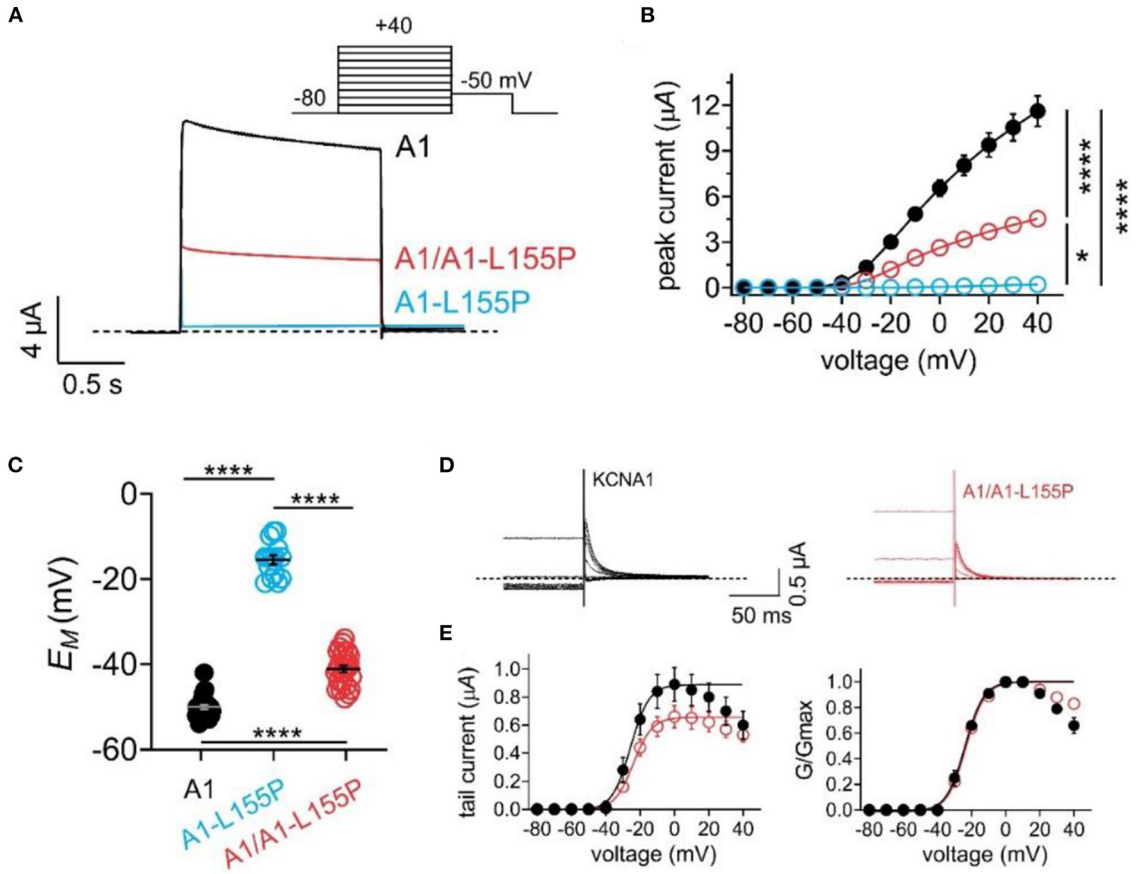

FIGURE 2
Effects of L155P on KCNA1 activity. Error bars indicate SEM. *n* indicates number of oocytes. Statistical comparisons by one-way ANOVA; $*P < 0.05$; $****P < 0.0001$. Dashed line indicates zero current level. **(A)** Mean traces for wild-type (A1), homozygous mutant (A1-L155P) and heterozygous mutant (A1/A1-L155P) channels expressed in oocytes. Scale bars lower left inset; voltage protocol upper inset; $n = 15–29$ per group (see Table 1 for values). **(B)** Mean peak current for traces as in **(A)**; $n = 15–29$ per group (see Table 1). **(C)** Mean unclamped oocyte membrane potential for oocytes as in **(A)**; $n = 15–29$ per group (see Table 1 for values). **(D)** Inset showing tail currents at −50 mV after prepulses similar to those shown in **(A)**. **(E)** Mean peak tail current (left) and normalized tail current (right) for currents as in **(D)** ($n = 26–29$) (see Table 1 for values).

TABLE 1 Cellular electrophysiological characteristics of wild-type (WT) KCNA1, and homozygous and heterozygous KCNA1-L155P potassium channels.

	Peak current density +40 mV (µA)	Non-normalized $V_{0.5}$ (mV)	*EM* (mV)	Inactivation $V_{0.5}$ (mV)
KCNA1	11.61 ± 0.9 ($n = 29$)	−25.41 ± 1.9 ($n = 29$)	−49.5 ± 0.5 ($n = 26$)	−37.9 ± 0.8 ($n = 16$)
KCNA1-L155P	0.21 ± 0.02 ($n = 15$)	*n.a*	−15.6 ± 1.1 ($n = 15$)	*n.a*
KCNA1/KCNA1-L155P	4.53 ± 0.5 ($n = 26$)	−23.73 ± 1.4 ($n = 26$)	−41.2 ± 0.7 ($n = 26$)	−46.3 ± 0.7 ($n = 12$)

n.a., not applicable.

action potentials, and an increase in neurotransmitter release (14). As KCNA1 channels form homomeric and heteromeric Kv channel complexes (e.g., with KCNA2) at juxtaparanodal regions and branch points of myelinated axons, their normal function is needed for healthy neuromuscular transmission and to limit aberrant axonal firing. These processes are disrupted when KCNA1 current is pharmacologically blocked or impaired by loss-of-function mutations (5, 15, 16), such as the newly discovered L155P variant.

KCNA1 channels generated from 50/50 wild-type and L155P cRNA to mimic the heterozygous proband and her mother described here, show 61% reduced peak current and oocytes expressing them exhibit +8 mV-depolarized resting membrane potential, i.e., increased excitability, compared to

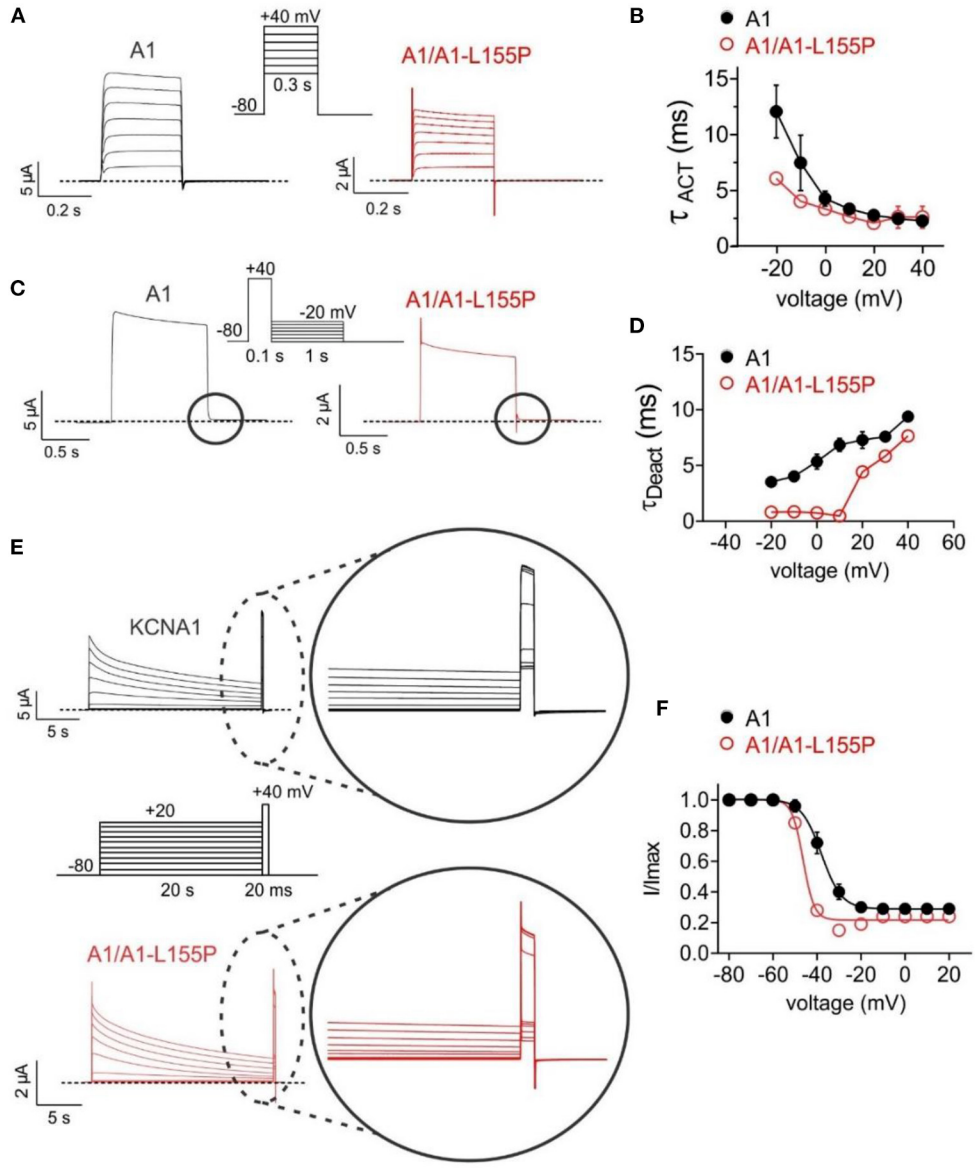

FIGURE 3
Effects of L155P on KCNA1 gating. Error bars indicate SEM. *n* indicates number of oocytes. Dashed line indicates zero current level. **(A)** Mean traces for wild-type (A1) and heterozygous mutant (A1/A1-L155P) channels expressed in oocytes using the voltage protocol shown (upper inset). Scale bars lower left inset; $n = 12–16$ per group. **(B)** Mean activation rate (T_{ACT}) calculated using a single exponential function from traces as in **(A)**; $n = 12–16$ per group. **(C)** Mean traces for wild-type (A1) and heterozygous mutant (A1/A1-L155P) channels expressed in oocytes using the voltage protocol shown (upper inset). Scale bars lower left inset; $n = 12–16$ per group. **(D)** Mean deactivation rate (T_{Deact}) calculated using a single exponential function from the circled portion of traces as in **(C)**; $n = 12–16$ per group. **(E)** Mean traces for wild-type (A1) and heterozygous mutant (A1/A1-L155P) channels expressed in oocytes using the voltage protocol shown (center inset). Scale bars lower left inset; $n = 12–16$ per group. **(F)** Mean proportion of remaining non-inactivated current calculated from the circled portion of traces as in **(E)**; $n = 12–16$ per group (see Table 1 for values).

oocytes expressing wild-type KCNA1 alone. Moreover, A1/A1-L155P channel deactivated several-fold faster at suprathreshold potentials (Figure 3D), which could prolong action potentials or decrease the time between action potentials. In addition, A1/A1-L155P currents inactivated more completely than those of wild-type KCNA1, especially around −20 to −40 mV, where the consequently reduced current could impair neuronal repolarization (Figure 3F).

The altered functional properties of homomeric L155P and heteromeric A1/A1-L155P channels suggest that L155P subunits are able to co-assemble with wild-type KCNA1 and alter its properties. L155P effects are not dominant negative

as otherwise, using a binomial distribution and tetrameric stoichiometry of KCNA1 channels, L155P would reduce peak current to 1/16 that of wild-type KCNA1. To our knowledge, L155P is the first reported EA1-associated mutation to be located in the cytoplasmic N-terminus of KCNA1. The EA1 pathogenic variants previously found that locate closest to L155P lie in KCNA1 S1, i.e., the first transmembrane segment (Figure 1C). Of these, R167M, A170S, V174F, I176R, I177N cause "pure" EA1; further up S1 and closer to its extracellular end lie F184C, linked to both EA1 and epilepsy, and C185W, linked to EA1 and hyperthermia. The other tight clustering of "pure" EA1 variants lies in the intracellular end of S4 (F303V, L305F, R307C) and intracellular S4-5 linker (G311D/S, I314T); throughout the remainder of the channel, pure EA1 and mixed-phenotype KCNA1-associated disorders are mingled (Supplementary Table 1) (13).

Future studies on L155P outside the scope of this case study will include an examination of its behavior in heteromeric complexes with KCNA2 and KCNA4, with which KCNA1 is thought to co-assemble *in vivo* in addition to forming homomeric KCNA1 channels as it is possible this may give some clues to why some KCNA1 mutants cause expanded phenotypes in addition to episodic ataxia (17–19). However, EA1 is notoriously variable in its phenotypes (20), with even identical twins exhibiting different degrees of ataxia severity (21). Some EA1 symptoms also overlap with those of epilepsy, which can lead to misdiagnosis. In the current case, the proband's mother was initially misdiagnosed with epilepsy based on overt neurological symptoms (but no seizures), despite her EEG and MRI being normal. The case emphasizes the importance of considering episodic ataxia as an alternate diagnosis to epilepsy under these circumstances. This first report of a KCNA1 variant in the N-terminus being associated with EA1, and in the absence of other EA1-linked disorders, expands the cluster of "pure" EA1 sequence variants near the intracellular end of S1 (Figure 1C, Supplementary Table 1).

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

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

RS contributed clinical and human gene sequencing data and analysis. RM conducted cellular electrophysiology studies and analysis. GA prepared the original manuscript draft. All authors contributed to the intellectual content, edited the manuscript, 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/fneur.2022.975849/full#supplementary-material

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Hashimoto's encephalopathy with cerebellar ataxia as the main symptom: A case report and literature review

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Hashimoto's encephalopathy (HE), also known as steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT), has a variety of clinical manifestations, with various neuropsychiatric characteristics, including tremors, transient aphasia, seizures, altered consciousness, myoclonus, cognitive impairment, and psychiatric manifestations. The hallmark presenting feature is a non-specific encephalopathy characterized by alteration of mental status and consciousness ranging from confusion to coma and impaired cognitive function, while those with cerebellar ataxia as the main manifestation is rare. We reported a case of Hashimoto's encephalopathy with cerebellar ataxia as the main manifestation, elevated anti-thyroid antibodies (anti-TPO/TG), and normal thyroid function. The symptoms of cerebellar ataxia improved after steroid treatment. Meanwhile, we reviewed the clinical features of 20 representative cases of HE with cerebellar ataxia as the core symptoms. In conclusion, based on our case findings and literature review, the diagnosis of HE should be suspected in cases of encephalopathy without an obvious cause, to quickly start an effective treatment.

KEYWORDS

Hashimoto's encephalopathy, Hashimoto's autoimmune thyroiditis, ataxia, antithyroid antibodies, autoimmune thyroiditis

Introduction

Hashimoto's encephalopathy (HE) is an autoimmune encephalopathy related to thyroid antibodies, which was first reported by Brain et al. in 1966 (1). It is believed that HE is related to the autoimmune reaction secondary to Hashimoto's thyroiditis, and the immune inflammatory reaction during the pathogenic process may lead to focal or diffuse brain damage in the brain, leading to clinical symptoms such as unconsciousness or focal neurological loss including cognitive impairment, tremor, altered consciousness, transient aphasia, seizures, myoclonus, gait disorder/ataxia (2). To date, clinical reports of cerebellar ataxia as the main symptom of HE are rare. Meanwhile, there are no clear diagnostic criteria for HE, so it is easy to be ignored or misdiagnosed in clinical practice.

Here we report a rare case of HE with acute cerebellar ataxia as the main manifestation, elevated anti-thyroid antibodies (anti-TPO/TG), and normal thyroid function. In addition, we summarized its clinical features, diagnosis, and treatment in conjunction with the literature to enhance the understanding of HE in clinical practice, expecting to reduce the missed diagnosis rate of the disease. Furthermore, we retrieved 20 representative patients diagnosed as HE with cerebellar ataxia as the main symptom from PubMed and reviewed their etiology, clinical manifestations, auxiliary examination, diagnosis, prognosis, and treatment.

Case presentation

A 64-year-old female with a complaint of dizziness and gait instability for 1 month was admitted to our hospital. The patient had a history of upper respiratory tract infection 2 days before the onset of these symptoms, which was characterized by nasal congestion and throat dryness, with no significant fever, cough, or expectoration. 2 days later, dizziness and gait instability with visual rotation, nausea, and intermittent vomiting occurred and progressively aggravated within 1 month. There was no headache, limb numbness, unconsciousness, or convulsive episodes during the course of the disease. No previous specific disease history, no drug exposure or alcohol consumption history, and no vaccination history in the last 1 year. On admission, physical examination revealed normal blood pressure of 132/83 mmHg, ataxic dysarthria, gross rotational nystagmus during horizontal and vertical eye movements, normal muscle strength of limbs, no eyelid ptosis, eye movement disorders or pupillary changes, no diminished or absent tendon reflexes, unstable bilateral finger-nose test and heel-knee-shin test, and truncal ataxia. We performed the first assessment of the severity of the patient's cerebellar ataxia using the Scale for the Assessment and Rating of Ataxia (SARA), with a score of 37. Serological examinations including blood routine, C-reactive protein, serum vitamin B1, vitamin B12, folic acid, human immunodeficiency virus (HIV) antibody, as well as other autoimmunity markers including antinuclear antibody (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), and rheumatoid factors were all unremarkable. Imaging examination including cranial magnetic resonance imaging (MRI) (Figure 1) and lung computed tomography (CT) was normal. Transcranial doppler (TCD) revealed there were no cerebrovascular stenosis, atherosclerosis, or other abnormalities. Breast and abdominal ultrasounds were normal. Lumbar puncture revealed clear cerebrospinal fluid (CSF) with an opening pressure of 100 mmH_2O. CSF biochemical tests showed slightly increased protein levels (0.47 g/L, reference range (RR): 0.15–0.45 g/L), positive Pan's reaction, while glucose and chlorine levels were normal. CSF cytology showed normal white blood cells (4.00×10^6/L, reference range (RR): 0.00–8.00×10^6 g/L) and visible lymphocytes, no cancer cells were seen. CSF results for infections (rubella virus, cytomegalovirus, and herpes simplex virus antibodies, general bacteria, fungi, and tuberculosis smears) were negative. Antibody analysis of autoimmune encephalitis and paraneoplastic syndrome including anti-NMDAR, anti-AMPA1, anti-AMPA2, anti-LGI1, anti-CASPR2, anti-GABA, anti-Hu, anti-Yo, anti-Ri, anti-MA2, anti-CV2, anti-Amphiphysin, anti-Tr (DNER), anti-Zic4, anti-SOX1, and anti-GAD65, were all negative in both serum and CSF.

Based on the above clinical data, the patient was first considered to have acute cerebellitis that might have been caused by a certain virus infection. The clinical conditions usually improved after 3–5 days of antiviral therapy in acute cerebellitis caused by viruses (3, 4). Another patient with acute cerebellitis caused by the virus received antiviral and low-dose dexamethasone (10 mg four times daily) treatment for a total of 4 days, with significant improvement of symptoms within 7 days (5). We referred to previous experience and gave antiviral and medium-dose steroid treatment (methylprednisolone 80 mg/day) for 7 days while cerebellar symptoms did not improve. Considering that the patient's symptoms lasted for more than 1 month with poor antiviral and medium-dose steroid treatment effects, whether there were other factors causing cerebellar ataxia, thyroid color ultrasound, and serum thyroid function were examined. Thyroid color ultrasound (Figure 2) showed that the internal echogenicity was diffuse, rough, and heterogeneous, and lamellar hypoechogenicity was seen, supporting the diagnosis of Hashimoto's thyroiditis. Serum thyroid function showed slightly decreased thyroid stimulating hormone (TSH, 0.3006 uIU/ml, RR: 0.35–4.94 uIU/ml), normal free triiodothyronine (FT3, 4.21 pmol/L, RR: 4.11–6.47 pmol/L), normal free thyroxine (FT4, 13.54 pmol/L, RR: 9.01–19.05 pmol/L), while significantly elevated anti-thyroglobulin autoantibodies (Tg-Ab, 87.72 IU/ml, RR: 0–4.11 IU/ml) and anti-thyroperoxidase autoantibodies (TPO-Ab, 13.18 IU/ml, RR: 0–5.61 IU/ml).

According to the main symptoms of cerebral ataxia, almost normal neuroimaging and CSF tests, by excluding other toxic, metabolic, and infectious causes of encephalopathy, the patient was diagnosed with HE. The patient was given the steroid methylprednisolone (1 g/d) for 3 days and reduced to oral prednisolone 60 mg/d, and then gradually reduced within 2 months to a maintenance dosage of 20 mg/day for 1 month. The patient's symptoms began to show improvement on day 3 of high-dose steroid therapy. 1 month later, her RASA score was 3 and she was discharged from the hospital with a marked improvement in ataxia, showing only slight dysarthria, and less obvious limb ataxia. After follow-up, the patient's symptoms were completely relieved within 3 months. In addition, after being discharged from our hospital, the patient completed a whole-body imaging Positron Emission Tomography Computed Tomography (PET-CT) examination

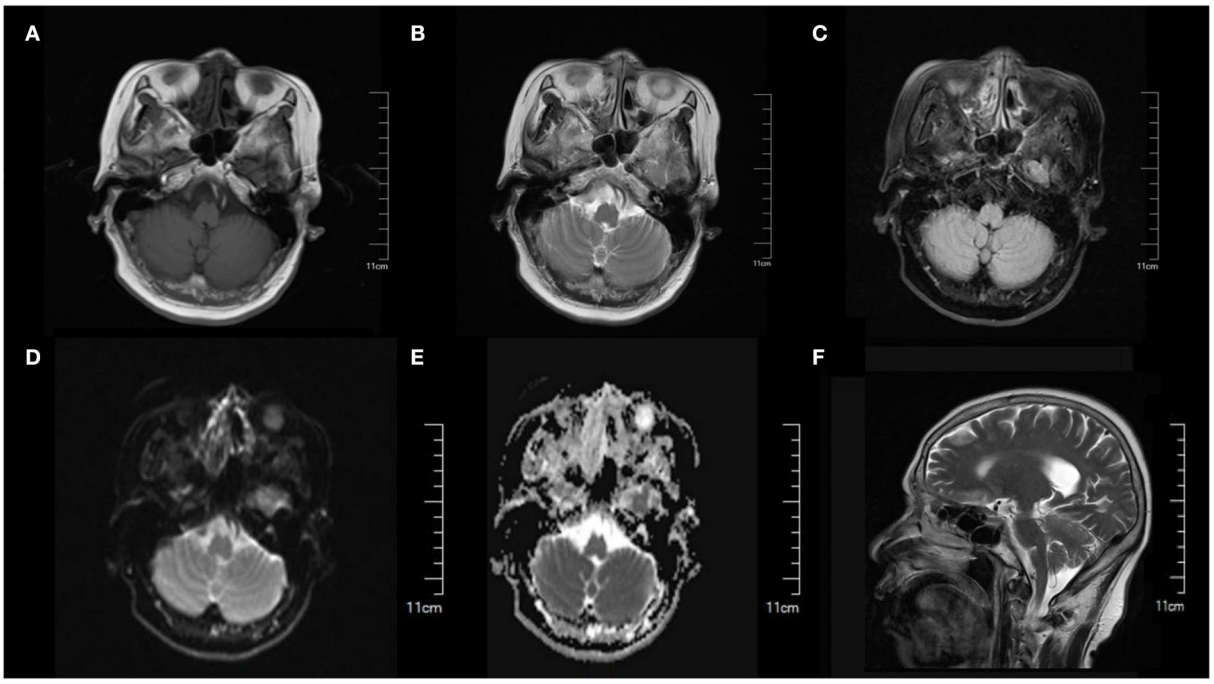

FIGURE 1
Cranial MRI showed normal brain structure and no obvious abnormal signal was found. **(A)** T1-weighted image. **(B)** T2-weighted image. **(C)** FLAIR image. **(D)** DWI image. **(E)** ADC image. **(F)** Sagittal section image.

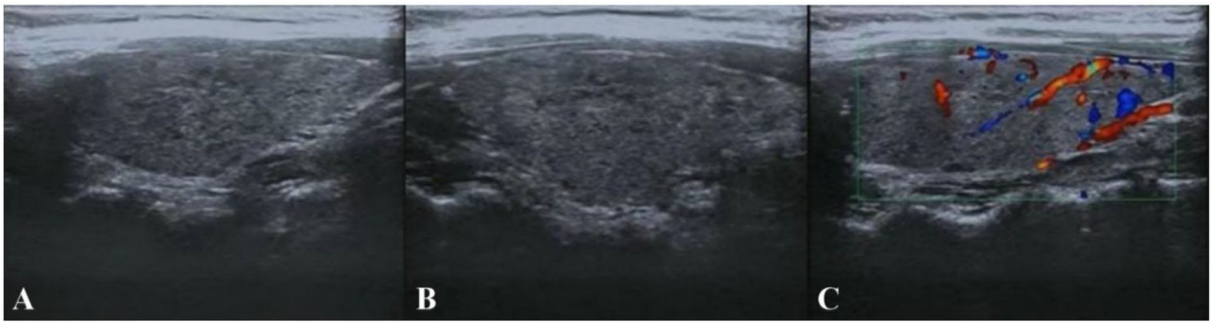

FIGURE 2
Thyroid color ultrasound. **(A,B)** The size and morphology of the left and right lobes of the thyroid gland were normal, the thickness of the isthmus was normal, the border was clear, the envelope was intact, the internal echogenicity was diffuse rough and heterogeneous, lamellar hypoechogenicity was seen. **(C)** No abnormal flow signals were seen.

at another hospital with no suspicious positive findings within 1 month.

Discussion

Common etiologies of acute cerebellar ataxia include stroke, vitamin deficiency, infectious, toxic, immune-mediated, paraneoplastic, structural, and metabolic diseases (6, 7). In the present case we reported, diseases such as alcoholic cerebellar degeneration, intoxication (drugs and metals), vitamin deficiency (vitamin B1 and B12), cerebellar stroke, tumors, benign paroxysmal torticollis, and migraine with brainstem aura and other vestibular disorders were excluded. Finally, acute cerebellitis due to viral infection was first considered. Then, the patient was given antiviral and medium-dose steroid treatment for 7 days with poor results. Subsequent abnormity of anti-thyroid antibodies and thyroid color ultrasound and together with significant effects of high-dose steroid therapy led to the final diagnosis of HE.

HE is also known as steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) (8) is a rare disease and it is difficult to estimate its incidence and prevalence. One prospective study summarized 26 cases of unexplained encephalopathy with detectable antithyroid antibodies and estimated a prevalence of 2.1/100,000 subjects (9). Patients are predominantly female and the proportion of males and females is 1:4.1 (10, 11). Usually, disease occurs in their 5–6th decades of life (12, 13). The prevalence in pediatric populations is relatively lower than that in adults (14).

Pathogenesis

It is commonly believed that the clinical manifestations of HE are associated with high levels of thyroid peroxidase (TPO) and thyroglobulin (TG) antibodies, but the exact underlying pathogenesis of HE is still unknown. Primarily, pathogenesis based on the presence of cerebral vasculitis was supported by the presence of perivascular lymphocytic inflammation in the brain tissue samples of some HE patients (15, 16). However, more scholars considered HE as an autoimmune disease because it is closely associated with autoantibodies that interact with shared thyroid antigens and respond well to steroid therapy (12, 17). In addition, serum anti-TPO antibodies in the CSF have also been measured in patients diagnosed with HE along with autoimmune reactions of these antibodies with the cerebral vascular and brain astrocytes that result in either vasculitis or damage to the brain cells (18, 19). Furthermore, it does not appear to be directly related to hypothyroidism or hyperthyroidism, and plasma antithyroid antibody titers do not correlate notably with the severity of HE (19–21). In addition, antithyroid antibody titers remain discoverable after treatment.

A range of autoimmune diseases has been associated with Hashimoto's thyroiditis, including rheumatoid arthritis, systemic lupus erythrematosus, ulcerative colitis, pernicious anemia, myasthenia gravis, multiple sclerosis, and thyroid ophthalmopathy (22). Simultaneously, in the cases we summarized, one patient (23) had ulcerative colitis before the onset of the disease, and five patients (5/20, 25%) had a previous history of Hashimoto's thyroiditis, which seems to prove that autoimmunity plays an irreplaceable role in the pathogenesis of HE.

Clinical presentations

The clinical manifestations of HE are diverse and the course is generally recurrent and remitting. The most common features of HE are subacute episodes of altered level of consciousness, stroke-like episodes, and myoclonus. Kothbauer-Magreiter et al. (17) have described two distinct presentations of HE, where the clinical overlap is common. The first is a vasculitic type with repetitive stroke-like episodes, such as hemiparesis, aphasia, and ataxia with only mild cognitive impairment. The second is an inert progressive type with an insidious onset of dementia, seizures, hallucinations, psychotic episodes, or altered consciousness. Seizures, comas, tremors, and myoclonus can occur in both types (17, 24). The hallmark presenting feature is a non-specific encephalopathy characterized by altered mental status and consciousness, ranging from confusion to coma and impaired cognitive function (25). Seizures, including both partial and generalized seizures (11, 26), and myoclonus have been reported to be the most common presentations (60–66% of patients) in adults (27). HE with cerebellar ataxia as the main clinical symptom is quite rare.

Diagnostic criteria

HE has no definitive diagnostic criteria and depends on the diagnosis of exclusion, due to its low incidence, diverse clinical presentation, and unknown specific pathogenesis (28). Abnormally elevated thyroid antibodies, including anti-TPO or anti-TG, are present in most cases and are necessary for the diagnosis of HE (28, 29). The most common detected antithyroid antibody is anti-TPO. Elevated protein in CSF occurs in most patients and decreases with disease treatment (30). In our case, the SCF protein level was increased, but regretfully, we did not perform detection for CSF antithyroid antibodies. Moreover, the amino (NH2) terminal region of alpha-enolase (NAE) was an antigen identified in HE patients' brain tissue, and NAE antibodies were elevated in the majority of diagnosed HE patients (31). Some scholars have suggested that NAE antibodies appear to be a useful diagnostic marker of HE (31–33). Anti-NAE antibodies together with antithyroid antibodies will improve the sensitivity of HE in the clinical setting. The majority of patients with HE have normal brain MRI findings (34) although abnormal MRI findings may include ischemic lesions, demyelination, edema, and atrophy (35). The most common EEG feature is diffuse slow wave activity, which reflects CNS involvement and also enables monitoring of the effectiveness of drug therapy.

A number of experts proposed a relatively authoritative diagnostic criterion for HE using a clinical approach in Lancet Neurology in 2016. HE can be diagnosed if a patient meets all of the following criteria: (1) encephalopathy with seizures, myoclonus, hallucinations, or stroke-like episodes; (2) subclinical or mild overt thyroid disease (usually hypothyroidism); (3) brain MRI normal or with non-specific abnormalities; (4) presence of thyroid antibodies in the serum (thyroid peroxidase, thyroglobulin); (5) absence of well-characterized neuronal antibodies in the serum and CSF; and (6) reasonable exclusion of alternative causes (36).

Encephalitis patients presenting with behavioral disturbances, delirium, psychosis, hallucinations, and mood

alterations, particularly females with a familial history of auto-immune disease, should be strongly suspected to have HE (9, 29, 37). The diagnostic tests for HE include EEG and serum anti-TPO antibody levels. MRI and lumbar puncture are suggested to rule out infection, stoke, and tumor.

Treatment

Corticosteroids are the first choice for the treatment of HE and have provided complete remission of symptoms in about 50% of patients after post-hormonal therapy (38). Approximately 40% of patients do not recur after the first course of corticosteroid pulse therapy (39, 40). The doses commonly used in clinical practice are oral prednisone (50–150 mg/d or 1–2 mg/kg/d) for patients with mild symptoms and high-dose methylprednisolone (500–1,000 mg/d) intravenous injection (IV) for those in severe condition (17, 41). In patients resistant to corticosteroids, combination therapy with immunosuppressive medications, such as azathioprine, cyclophosphamide, and methotrexate, is suggested (42–44). Relapse of HE even with high-dose methylprednisolone IV in some patients should prompt early intervention with these immunosuppressive drugs (37). In HE patients who present with paraneoplastic opsoclonus syndrome, while primary tumor treatment, adjunct therapy with immunosuppressive medications, such as rituximab and an anti-CD20 monoclonal antibody, has also been proven to be effective (45). Patients who are unable to tolerate taking corticosteroids or immunosuppressants may be treated with plasma exchange and intravenous immunoglobulin (IVIG). Plasma exchange has been shown to remove anti-TPO. However, no clinical or neurophysiologic improvement was observed despite the documented reduction of the anti-TPO antibody to levels below the limits of laboratory detection in HE patients (21). Steroid therapy is a specific treatment, and improvement with corticosteroids may confirm the diagnosis of HE (10). Although the majority of HE patients respond to steroid treatment, it has been suggested that the lack of response to steroid treatment should not exclude the diagnosis of HE (38). If HE is clinically diagnosed, early intervention with steroids should be initiated (46), and treatment does not differ according to the presence or absence of cerebellar ataxia.

HE with cerebellar ataxia

Cases with cerebellar involvement or ataxia as the main HE symptom are reported relatively rarely and are easily overlooked in clinical practice. Herein we report an unusual case of HE with cerebellar ataxia (henceforth referred to as HECA) as the main clinical manifestation. The patient presented with dizziness, cerebellar dysarthria, and trunk and limb ataxia and met all the above criteria (36) including mildly elevated CSF protein, elevated serum thyroid antibody titers, normal thyroid function, normal cranial MRI, abnormal thyroid color ultrasound indicating Hashimoto's thyroiditis, absence of well-characterized neuronal antibodies in the serum and CSF, and marked improvement of ataxia symptoms after corticosteroid treatment. For a more comprehensive understanding, we searched PubMed by entering the keyword "Hashimoto encephalitis, cerebellar syndrome, ataxia and cerebellar ataxia" and then identified 20 representative cases (not including the present case) for further analysis in this review. Table 1 summarized the epidemiological and clinical characteristics, laboratory features, brain MRI, treatment, and outcomes of all the 20 cases.

Epidemiology of HECA

According to our statistical analysis, there are ethnic differences in the prevalent population, with 18 patients (90%) of Asian origin and two patients (10%) of Europe origin. The patients consisted of 8 men (40%) and 12 women (60%), and the average patient age was 50 years (range: 17–84). This is consistent with the previous overall data of HE that patients are predominantly female and disease usually occurs in their 5–6th decades of life (12, 13). The different incidence rates in men and women from previous literature (10, 11) may be related to our small sample size.

Additional symptoms of HECA

All patients presented symptoms of ataxia, 13 patients (65%) also had dysarthria and 14 patients (70%) had other symptoms (covering hypotonia, nystagmus, diplopia, psychiatric symptoms, lightheadedness, and cognitive/hearing impairment or tremor). Only one female patient (23) claimed that she had ulcerative colitis 3 months before, which is a collection of chronic and recurrent inflammatory illnesses of the gut produced by aberrant immune-mediated diseases of various etiologies. Other cases did not mention the presence of other autoimmune diseases.

Laboratory examination of HECA

A total of 13 patients (65%) were positive for both serum anti-TPO and anti-TG antibodies, six patients (30%) showed positive anti-TPO antibodies alone, and one patient (47) was negative for serum anti-TPO antibodies and positive for anti-TG antibodies. In terms of thyroid function, most cases (12 patients, 60%) had normal thyroid function, two patients (10%) showed hyperthyroidism, two patients (10%) showed hypothyroidism, and four patients showed indeterminate thyroid function. The data showed no specific changes in CSF, with most patients (13 patients, 65%) having normal CSF proteins and six patients (30%) having mildly elevated CSF proteins, with a mean value of 0.84 g/L (range: 0.52–1.26 g/L). Intracranial pressure, white blood cell count, and glucose concentration were all in the normal range (except for 15 patients not mentioned in the

TABLE 1 The clinical characteristics of cases of HE with cerebellar ataxia as the main symptom.

Year/ Country	Sex/ Age	Clinical characteristics			Anti-TPO/TG	CSF			Cranial MRI	EEG		Time from onset to treatment (months)	Steroids therapy		Outcome	REFS
		Dysar-thria	Ataxia	Others		WBC	Protein (g/L)	Glucose		Wave-activity	Location		Initial dose (g/day) ×day	Maintenance treatment		
2017/Spain	F/47	+	+	Nystagmus hypotonia	+/-	NORM	0.678	NORM	MCA	slow wave	diffuse background	6.5	1.0 × 5	tapering prednisone until maintaining 10 mg/day×6 months	IMP	(50)
2015/Korea	M/30	-	+	Nystagmus	-/+	NORM	NORM	NORM	NORM	NORM	-	9	1.0 × 5	prednisolone 60 mg/day initially and gradually reduced to 20 mg/day within 20 days and maintained for 1 month, then 10 mg/day × 9 months	IMP	(47)
2014/China	F/56	+	+	somniloquy, delirim	+/+	NORM	1.056	UNSP	NORM	fast wave; slow wave	a fast θ wave: the central region of the frontal region; slow wave: diffuse background	3	0.5×3	Prednisolone: 30 mg/day×10 days, 25 mg/day×10 days, 20 mg/day×10 days, 15 mg/day×10 days, 10 mg/day×10 days, 5 mg/day×30 days	IMP	(23)
2013/Japan	M/52	-	+	Cognitive impairment/psychiatric symptoms	+/+	UNSP	NORM	UNSP	NORM	slow wave	diffuse background	120	UNSP	UNSP	IMP	(49)
2013/Japan	F/46	+	+	Cognitive impairment/psychiatric symptoms	+/+	UNSP	NORM	UNSP	NORM	NORM	-	12	UNSP	UNSP	IMP	(49)
2013/Japan	F/63	-	+	tremor	+/+	UNSP	NORM	UNSP	NORM	UNSP	UNSP	1	UNSP	UNSP	IMP	(49)
2013/Japan	F/66	+	+	tremor	+/+	UNSP	NORM	UNSP	NORM	NORM	-	2	UNSP	UNSP	IMP	(49)
2013/Japan	F/46	-	+	cognitive impairment/psychiatric symptoms, unconsciousness, myoclonus	+/+	UNSP	NORM	UNSP	NORM	slow wave	UNSP	12	-	IVIG and immunosuppressant (dose UNSP)	DTR	(49)
2013/Japan	F/84	+	+	NORM	+/+	UNSP	NORM	UNSP	MCA	NORM	-	72	UNSP	UNSP	DTR	(49)
2013/Japan	M/55	+	+	NORM	+/-	UNSP	NORM	UNSP	MCA	NORM	-	4	UNSP	UNSP	DTR	(49)

(Continued)

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TABLE 1 Continued

Year/ Country	Sex/ Age	Clinical characteristics			Anti-TPO/TG	CSF			Cranial MRI	EEG		Time from onset to treatment (months)	Steroids therapy		Outcome	REFS
		Dysar-thria	Ataxia	Others		WBC	Protein (g/L)	Glucose		Wave-activity	Location		Initial dose (g/day) × day	Maintenance treatment		
2013/Japan	M/55	+	+	cognitive impairment/psychiatric symptoms	+/-	UNSP	↑	UNSP	NORM	slow wave	UNSP	3	UNSP	UNSP	IMP	(49)
2013/Japan	M/54	+	+	NORM	+/+	UNSP	UNSP	UNSP	MCA	UNSP	UNSP	120	UNSP	UNSP	IMP	(49)
2013/Japan	M/61	+	+	nystagmus	+/+	UNSP	NORM	UNSP	NORM	NORM	-	12	UNSP	UNSP	IMP	(49)
2013/Japan	F/57	-	+	NORM	+/+	UNSP	NORM	UNSP	MCA	NORM	-	12	UNSP	UNSP	DTR	(49)
2013/Japan	F/46	-	+	nystagmus, tremor	+/-	UNSP	NORM	UNSP	MCA	NORM	-	6	UNSP	UNSP	DTR	(49)
2011/China	M/39	+	+	right central facial weakness, lingual fasciculations, briskjawjerk, hyperactivegag reflex	+/+	NORM	1.26	NORM	MCA	NORM	-	UNSP	1.0×5	tapering prednisone (dose UNSP)	IMP	(51)
2011/India	F/17	-	+	diplopia	+/UNSP	UNSP	0.52	UNSP	NORM	NORM	-	6.5	1.0×5	six pulses of steroids (once a month) and oral thyroxine 100 ug/day	IMP	(52)
2011/India	M/47	+	+	NORM	+/UNSP	UNSP	NORM	NORM	NORM	NORM	-	6	1.0×5	four pulses of steroids	IMP	(52)
2007/Japan	F/41	+	+	NORM	+/+	UNSP	NORM	UNSP	NORM	slow wave	diffuse background	9	1.0×3	oral administration of prednisolone 30 mg/day	IMP	(33)
2002/Athens	F/47	+	+	nystagmus	+/+	UNSP	0.70	UNSP	NORM	slow wave	diffuse background	UNSP	16 mg of prednisolone three times daily followed by a tapering dose	IVIG	IMP	(48)

MCA, mild cerebellar atrophy; NORM, normal; UNSP, unspecified; DTR, deteriorated; IMP, improved; REFS, references.

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references). No significant abnormalities were seen on MRI except for mild cerebellar atrophy (seven patients, 35%). A total of 11 patients (55%) had no significant EEG abnormalities, six patients (30%) showed diffuse background slow waves, and 1 case specifically showed a high-power θ wave in the central region of the frontal region and diffuse background slow waves.

Treatment and prognosis of HECA

The intervals between symptom onset and treatment start ranged from 1 month to 10 years (mean duration: 2.5 years), indicating the difficulty of disease recognition. Corticosteroid therapy was given to almost all of the patients (19 patients, 95%), and 15 patients experienced gradual relief of symptoms, including ataxia, dysarthria, and tremor, after receiving corticosteroid therapy. The first dose of corticosteroids varied from 0.5 to 1.0 g/day, applied continuously for 3–5 days in the seven patients who received corticosteroid therapy, and in 5 patients of them, it was gradually reduced to oral low-dose prednisone maintenance therapy for a maximum of 9 months. Anti-TPO or anti-TG antibody titers decreased or even returned to normal levels in 4 patients, and EEG improved in 1 patient (1/7,14%) (33). One patient (48) received IVIG of 6 g four times daily for 6 days and levothyroxine sodium (75 ug/day) with a slight improvement in dysarthria and ataxia symptoms. After 3 months, this patient was given IVIG along with methylprednisolone 16 mg three times daily while continuing sodium thyroxine treatment, followed by a tapering dose. This patient's symptoms further improved. One patient (49) was not treated with corticosteroid therapy for severe diabetes mellitus and was given IVIG and immunosuppressive therapy, but only limited recovery was achieved and severe sequelae remained. A total of 4 patients (20%) did not achieve significant effects after steroid therapy, probably due to their initial severe disease or other reasons. In summary, it can be seen that HE is not a self-limited disease, the vast majority of it is effective against steroids or immunoglobulin therapy. Consequently, if HE is definitely diagnosed, steroids or immunoglobulins should be used as soon as possible. There is no uniform dosage and duration of steroid therapy, which can be given as methylprednisolone (500–1,000) mg/d intravenously for 5 days and prednisone (1–2) mg/kg·d orally, and gradually reduced. Most patients improve within 10 days of steroid therapy (25), and the medication can be repeated for those with recurrent symptoms. The prognosis of HE is optimistic if the treatment is reasonable and timely. Only one patient (23) was followed up for more than 1 year and the patient recovered well-with no recurrence.

In total, we summarized the clinical characteristics of 20 cases of HE with cerebellar symptoms as the main manifestation. These patients were predominantly female (60%) with a mean age of 50 years and presented mainly with ataxia of the limbs or trunk and dysarthria. All patients showed elevated anti-TPO and/or anti-TG antibodies, and no specific abnormalities on brain MRI. 30% (six patients) had mildly elevated CSF proteins. Despite the effectiveness of corticosteroids or IVIG treatment, the time from the symptom onset to the initiation of steroid therapy was 23.1 ± 38.5 months in these 20 cases. It is easy to delay treatment due to the long diagnosis period. In conclusion, HE with cerebellar ataxia as the main symptom is not easy to recognize and often misses the best opportunity for treatment. Therefore, it is necessary to pay attention to this rare manifestation of HE in clinical practice and to diagnose and treat it as early as possible.

Conclusions

Based on our observations, the importance of recognizing HE is that it is treatable, and most patients have an obvious therapeutic response to corticosteroids or other immunosuppressive agents. We reported an uncommon case of HE with cerebellar ataxia as the main manifestation and reviewed the clinical features of 20 cases of HE with cerebellar ataxia as the core symptoms to highlight the rare clinical manifestation of HE in this clinical setting. Our case and most of the HE cases summarized showed elevated serum anti-TPO/TG, normal or reduced thyroid function, abnormal thyroid color ultrasound indicating Hashimoto's thyroiditis, cranial MRI showing only mild cerebellar atrophy or approximately normal, CSF showing mildly elevated protein, normal cell count and sugar and chloride, no well-characterized neuronal antibodies in serum and CSF, good response to steroids, etc., all of which greatly suggested the diagnosis of HE. Hence, HE should be considered in all patients presenting with encephalopathies, particularly especially in females with histories of auto-immune disease, followed by an early examination of serum thyroid antibodies, thyroid ultrasound, CSF, cranial MRI, and EEG to avoid misdiagnosis and omission, and timely treatment with corticosteroids or further immunoglobulins or immunosuppressive agents once the diagnosis is clear. In addition, patients with HE should be followed up for a long time to monitor disease recurrence or progression, so as to provide more adequate evidence for future disease diagnosis and treatment.

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/s.

Ethics statement

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

CW performed case information collection, literature review, literature information statistics, and drafted the manuscript. YS, WZ, and TS contributed to case information collection and literature information statistics. ZW, YW, and ML contributed to the literature review and manuscript preparation. YZ and LS performed a manuscript review and final version approval. 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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Case report: Blepharospasm in peak-dose dyskinesia may benefit from amantadine in Parkinson's disease

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Introduction: Blepharospasm is uncommon in Parkinson's disease, especially in the peak-dose dyskinesia period.

Case presentation: We herein present the case of a patient with PD who developed blepharospasm in the peak-dose dyskinesia period. The symptom was improved by taking amantadine.

Conclusion: The current report expands the phenomenology of peak-dose dykinesia in PD to include dystonic blepharospasm. This complication of levodopa therapy may respond to amantadine despite the dystonic appearance of movements.

KEYWORDS

blepharospasm, Parkinson's disease, peak-dose dyskinesia, amantadine, dyskinesia

Introduction

Parkinson's disease (PD) is a common age-related neurodegenerative disorder, with bradykinesia, rest tremor, and rigidity as its core features (1). In a more advanced stage, management of motor fluctuations, drug-resistant symptoms, and non-motor features become challenges and can reduce the quality of life (2, 3).

Peak-dose dyskinesia is the most common type of levodopa-induced dyskinesia, and it occurs during the plateau of levodopa plasma levels. Peak-dose dyskinesia usually consists of chorea, dystonia, and, less commonly, myoclonus in the head, trunk, and limbs (4–6). Sometimes, eye-related involuntary movements may be present in peak-dose dyskinesia and are usually accompanied by dyskinesia in other parts of the body. Conjugate involuntary upward or lateral eye deviation is uncommon but has been described (7–10).

Apraxia of eyelid opening (AEO) and blepharospasm in patients with PD are often of concern because they obstruct the patients' visual field. AEO is characterized by non-paralytic inability to reopen the eyes without a spasm of the orbicularis oculi

muscle, while blepharospasm is an involuntary spasm of the orbicularis oculi muscle and is considered focal dystonia (11). It is more prevalent in atypical parkinsonism, especially progressive supranuclear palsy (PSP) (12, 13). However, in patients with idiopathic PD, blepharospasm is more likely to occur during "off" periods and is usually accompanied by dystonia in other parts of the body (4).

Herein, we report a female patient with PD who developed blepharospasm as the main manifestation of peak-dose dyskinesia. The symptom was relieved by taking amantadine.

Case presentation

The patient is a 71-year-old Chinese woman who has been displaying bradykinesia, resting tremor in her left limbs, and hyposmia since she was 66 years old. Her medical history was unremarkable. The patient visited the First People's Hospital of Jiande at the age of 68 when she was diagnosed with PD. She was then treated with benserazide/levodopa 12.5/50 mg three times daily, and her symptoms were almost completely relieved. Two years later, the drug was adjusted to benserazide/levodopa 25/100 mg three times daily and pramipexole 0.25mg three times daily as her symptoms had worsened. Her symptoms were still well controlled, and she did not suffer any motor fluctuation. However, the patient developed recurrent blepharospasm within the past 6 months. Her blepharospasm lasted approximately 30 min and was not complicated by worsened parkinsonism at the same time. To further investigate the relationship between blepharospasm and parkinsonism, a levodopa challenge test was performed. The patient took 50/200 mg of benserazide/levodopa, and we evaluated her at baseline, 15, 30, 45, and 60 min, and every 30 min thereafter up to 4 h. As shown in Figure 1, her parkinsonism was relieved within 30 min, and the improvement persisted until the end of the evaluation. Interestingly, she displayed blepharospasm for around 1 h, and it lasted for 30 min (Figures 2A,B; Supplementary Videos 1, 2). During this period, she developed mild dyskinesia in her left upper extremity, which was quickly relieved (within 10 min). Therefore, we diagnosed the blepharospasm as a manifestation of peak-dose dyskinesia. Because the patient refused a botulinum toxin A injection, we prescribed amantadine 100 mg two times daily. The drug worked within 2 days, with the best improvement within 2 weeks. The blepharospasm continued to improve over a follow-up period of 6 months. At present, the patient only has increased blinking after taking benserazide/levodopa, which does not obstruct the field of vision, and she is satisfied with the treatment.

Discussion

Blepharospasm is a type of focal dystonia that may be idiopathic or secondary to a neurological condition such as PSP, tardive dyskinesia, and PD (11). It is of great concern to patients and physicians as it obstructs the field of vision and reduces the quality of life. In this report, we present the case of a patient with PD who developed blepharospasm as a manifestation of peak-dose dyskinesia, and it was relieved by taking amantadine.

Blepharospasm is uncommon in PD. Two independent studies reported its incidence as 0.9% (eight out of 913) (13) and 3.26% (nine out of 276) (12), respectively. However, it was more prevalent in PSP (6/57 and 7/10, respectively). Therefore, it is sometimes labeled as a clue to differentiate PD from atypical PD.

In idiopathic PD, blepharospasm is more recognized as a rare presentation of off-period dystonia (4, 14). Studies have also suggested that idiopathic blepharospasm is a risk factor for developing PD (15, 16). However, this conclusion is still controversial (17). In our report, we described a rare phenomenon in which blepharospasm appears as the main

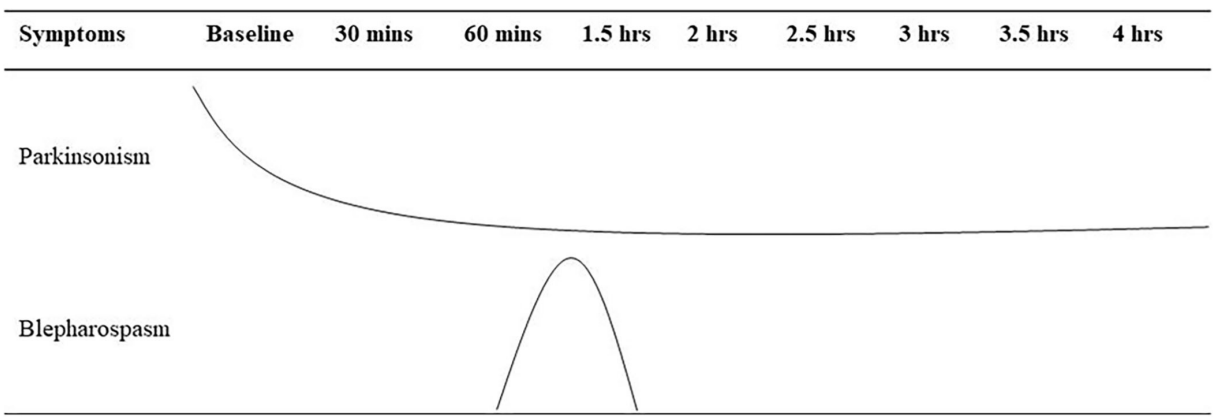

FIGURE 1
Summary of the levodopa challenge test for the case. Mins, minutes; hrs, hours.

FIGURE 2
(A) Patient took madopar for 1 h. **(B)** Patient took madopar for 1.5 h.

symptom of peak-dose dyskinesia in a patient with PD. Although the phenomenon is rare, it has been noticed and reported by other researchers (18).

The mechanisms underlying blepharospasm are, as yet, unknown. Multiple regions including the thalamus, lower brainstem, basal ganglia, cerebellum, midbrain, and cortex may participate in its pathophysiology (19). A functional magnetic resonance imaging-based study showed that basal ganglia circuits and cerebello-cortical circuits are involved in the triggering and development of blepharospasm (20). Interestingly, the two circuits also play an important role in PD (21). In addition, some pathological changes in advanced PD, such as hypersensitivity of the striatal dopaminergic receptors and abnormal striato-cortical connectivity, may add to the complexity of the mechanisms (4, 22). We suggest that "on" period and "off" period blepharospasm may be due to different pathological mechanisms.

Botulinum toxin A is the first choice in treatment of blepharospasm (23). Most patients benefit from it, and the improvement persists for several months (24). Trihexyphenidyl and clonazepam have been proven effective in improving blepharospasm (25, 26), but their application is limited due to the possibility of cognitive decline and sedative side effects. In our case, the patient refused the injection of botulinum toxin A. Given that blepharospasm is a manifestation of peak-dose dyskinesia, we tried amantadine, which is recommended by The International Parkinson and Movement Disorder Society (MDS) for treatment of dyskinesia (27), and it turned out effective in our patient.

To the best of our knowledge, it is rare that blepharospasm appears as the main manifestation of peak-dose dyskinesia in patients with PD, and its benefit from amantadine has not been reported before. Our report adds to the understanding and treatment of blepharospasm in PD.

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/s.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the First People's Hospital of Jiande. The patients/participants 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.

Author contributions

J-YW, Q-YF, and XZ examined the patient and carried out the treatment strategy. Q-YF, X-DZ, Z-DH, C-PC, S-SH, and S-GZ acquired and analyzed all the clinical data. Z-DH and J-YW reviewed the literature and drafted the manuscript. XZ and J-YW supervised the study. 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

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Case report: Electroacupuncture for acute pain flare-up of knee osteoarthritis

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Acute pain flare-up of knee osteoarthritis (KOA) is a common disease in orthopedics and is mainly treated with analgesic drugs. Patients usually refuse to take western medicines orally owing to gastrointestinal side effects or unsatisfactory treatment results. We report the case of a 69-year-old woman who had an acute pain flare-up of right KOA induced by long-distance walking. As the patient refused medication, we used electroacupuncture (EA) to relieve her symptoms. EA with a 2-Hz frequency and a 1–2-mA intensity had an analgesic effect on the acute pain flare-up of KOA. After 12 weeks of EA intervention, the bone marrow edema-like lesions (BMLs) improved significantly, as depicted on magnetic resonance imaging of the knee joint. However, more powerful evidence is needed to understand the mechanism of the EA technique that alleviates BMLs of KOA.

KEYWORDS

electroacupuncture, acute pain flare-up, knee, osteoarthritis, case report

Introduction

With the aging global population, the prevalence of knee osteoarthritis (KOA) is increasing (1). The primary complaints of patients with KOA are pain and poor joint mobility, which seriously affect their daily life and are the most common reasons for doctor visits. Pathological changes in patients with KOA mainly include cartilage damage and hyperosteogeny around the joints, which then irritates the surrounding soft tissues, resulting in soft tissue hypertrophy, inflammatory edema, and blood stasis.

An X-ray image of the knee joint is the most commonly used and popular method to diagnose KOA at a clinic. This facilitates the grading of KOA using the Kellgren–Lawrence (K–L) grading scale, which was made possible by improvements in X-ray imaging. Previous magnetic resonance imaging (MRI)-based studies have shown that the pain is related to many factors, including joint effusion, bone marrow edema, and osteoarthritis (2–4). Bone marrow lesions of knee joints in patients with osteoarthritis (OA-BML) are important clinical entities, which can explain progressive pain (5), decreased quality of life, and impaired function. MRIs of bone marrow edema-like lesions (BMLs) showed subchondral bone areas with hyperintense marrow signals on T2-weighted imaging and are closely related to the pain, subchondral bone cyst formation, and the progression of KOA (6, 7).

Multiple activity-related, psychosocial, and environmental factors easily trigger acute KOA flare-ups (8). Acupuncture is an effective non-drug strategy for treating acute and chronic pain (9, 10). Pain, stiffness, or swelling are common symptoms of acute flare-ups in patients with KOA (11). Bartholdy et al. (12) showed that a predefined and standardized "rescue" exercise may be beneficial in patients with exacerbated KOA symptoms. However, few clinical guidelines cover evidence-based management strategies of non-drug therapy for reducing the impact of KOA flare-ups. Acupuncture has been widely used as a non-drug therapy for neurological pain and arthropathy (13). Here, we report the case of a patient with an acute KOA flare-up, which was treated successfully using electroacupuncture (EA).

Case description

A 69-year-old woman presented at the acupuncture clinic on 30 June 2018. The patient was pushed in a wheelchair. Her primary complaints were knee pain and inability to walk. Just 1 month previously, the patient had completed a long-distance walk of approximately 445 km. This had induced an acute flare-up of knee pain. For almost 1 month, she anticipated that she could recover unaided and, hence, did not seek treatment, or self-administer Chinese or western medication; however, she was still experiencing pain.

The patient laid flat on the treatment bed and the doctor observed redness and swelling, without obvious deformation of the right knee joint during the examination; however, joint tenderness and a pronounced medial side were apparent. The range of motion of her knee joint was 40°, and her Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score was 92 points, including 25, 11, and 56 points for pain, joint stiffness, and physical function, respectively. Her Lequesne index and visual analogue scale (VAS) scores were 11 and 9 points, respectively. Immediately prior to treatment, X-ray (Figure 1) and MRI examination (Figure 2) of the right knee joint were performed.

According to the symptoms, physical examination, and radiograph, we diagnosed the patient with KOA (14), with an acute pain flare-up in the right knee joint. However, X-ray showed that KOA was more serious in the left knee. As she continued to refuse medication, we used EA to relieve her symptoms.

According to the principles of nearby acupoint selection and the synergistic effect of *yin* and *yang* relative acupoints of the knee joint, we selected *Liangqiu* (ST34), *Xuehai* (SP10), *Neidubi* (Ex-LE4), *Dubi* (ST35), *Yanglingquan* (GB34), *Yinlingquan* (SP9), and *Zusanli* (ST36) (Figure 3).

The operating procedure was as follows: The patient laid flat on the treatment bed, and the acupuncturist stood on the right side of the patient to locate the acupoints. After skin disinfection, the acupuncturist inserted the acupuncture needle (0.30 * 40 mm, Suzhou Medical Appliance Factory, Suzhou, China) to a 30-mm depth under the skin. After the patient experienced a sense of *deqi*, the acupuncturist connected two pairs of EA connectors to the needle handles of ST34–ST36 and SP10–SP9. The waveform of the electrical stimulation (SDZ-V electroacupuncture apparatus, Suzhou Medical Appliance Factory) was set to continuous wave, with a 2-Hz frequency, 1–2-mA intensity, and 30-min duration. Treatment was repeated three times per week for 12 weeks (36 treatments in total). EA was performed by the same experienced acupuncturist who was registered in China. During the treatment, no medications were used, and no abnormal acupuncture conditions (such as pain, subcutaneous hemorrhage, needle bending, broken needle, or needle stagnation) were observed.

As shown in Table 1 and Figure 4, at 30 min after treatment, the pain in the right knee joint of the patient was relieved, and the VAS score was 5. Subsequently, the VAS score was 2 after 1 and 4 weeks of treatment and further decreased to 0 after 8 and 12 weeks of treatment. The patient was followed up at the clinic after treatment, and her VAS score was 1. Her total WOMAC score decreased as treatment progressed, and the pain score remained low after the treatment was completed. The Lequesne index indicates the severity and activity index of KOA, and the score gradually decreased as the acupuncture treatment progressed. The joint range of joint motion increased as the pain was relieved. After 12 weeks of EA treatment, MRI showed that the area of bone marrow edema-like lesions had decreased.

There was no obvious pain in the knee joint at follow-up, and its range of motion had reached 100–110°. Over the following 2 years, the knee pain score was maintained at 1–2 points, with no negative influence on daily life, as determined by telephonic follow-up.

Discussion

This case greatly impressed the authors. The patient was unable to walk at the first visit and was pushed in a wheelchair. She was able to walk with crutches after the second treatment and walked unaided after the third. Compared with other treatments (such as drug therapy, weight loss, and joint function exercises) (15), EA has fewer side effects and higher safety and is readily accepted by patients in China. After three treatments, the patient, who had not previously undergone acupuncture, was satisfied with the therapeutic effect and referred to it as "the gift of acupuncture."

Long-term use of non-steroidal anti-inflammatory drugs has adverse effects on renal function and may cause gastrointestinal

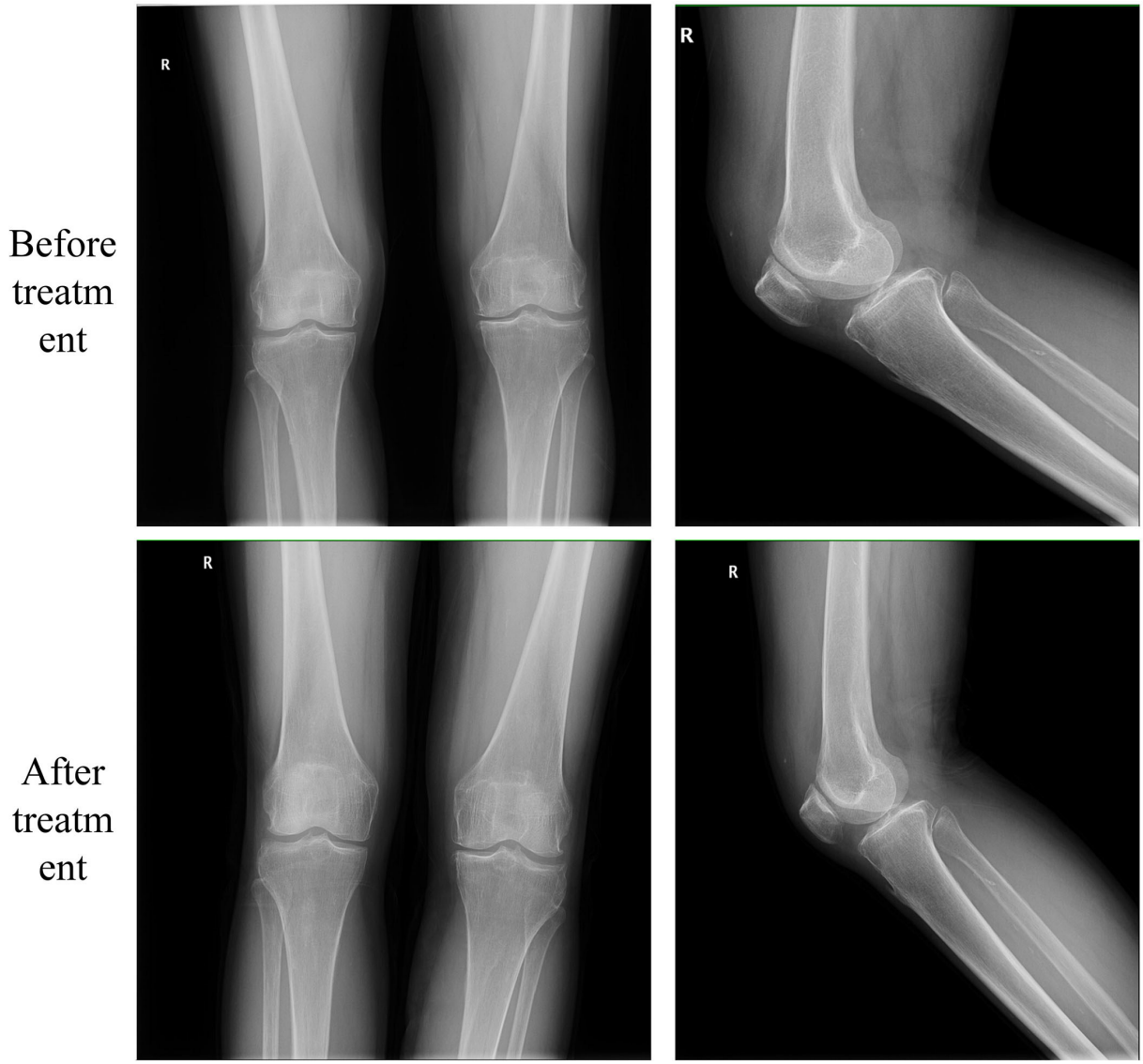

FIGURE 1
X-ray before and after treatment. X-rays of the knee before treatment were suggestive of knee osteoarthritis (Grade III on the K–L grading). K–L, Kellgren–Lawrence.

bleeding (16). Many recent studies havesuggested the use of non-drug therapy, and traditional Chinese medicine may be a viable alternative for patients with KOA. Acupuncture has a long history in osteoarthritis treatment (17). The American College of Rheumatology and the International Osteoarthritis Research Association also recommend acupuncture as a symptomatic relief treatment for patients with KOA who are unwilling to undergo total knee arthroplasty (18, 19). Commonly used acupoints for KOA are ST34, ST36, GB34, and SP9. These acupuncture points are very close to the knee joint, and most are located on the muscles attached to the tibia/fibula or patella (20). KOA is a complex chronic pain disease, partly due to its nociceptive and neurological mechanisms. It is usually accompanied by neuroplasticity and central nervous system pain sensitization (21–23). This case was of a patient with an acute pain flare-up of right KOA induced by long-distance walking. The patient showed obvious pain, and the symptoms had not disappeared after a month. Previous researches have shown that warming acupuncture and EA may be optimal acupuncture methods for treating KOA (24, 25). In this study, EA significantly reduced the VAS and WOMAC scores of our patient. Modern medical research shows that

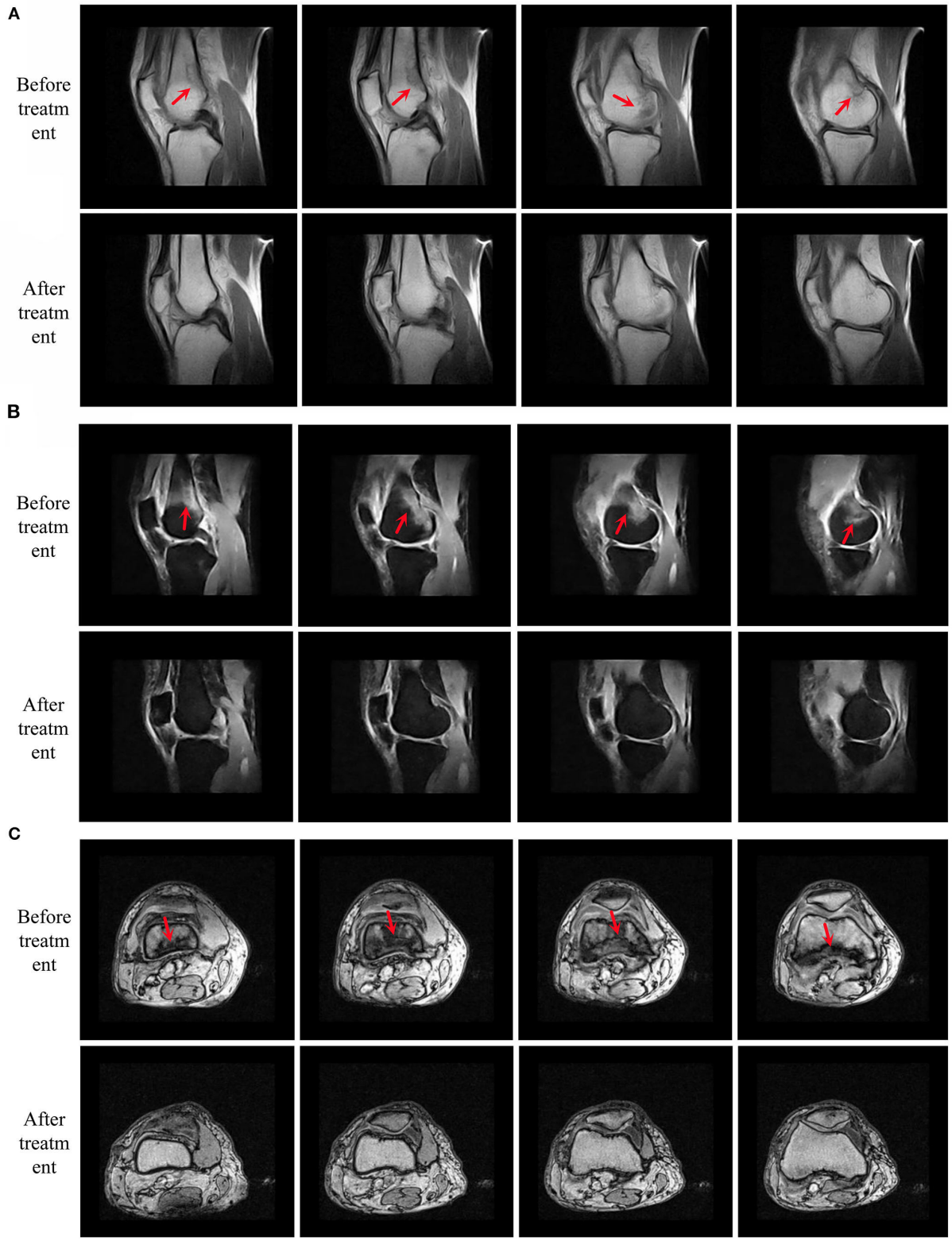

FIGURE 2
MRIs compared before and after treatment. Present four consecutive magnetic resonance images from left to right. **(A)** Sagittal conventional sequence. **(B)** Sagittal fat-suppressed sequence and **(C)** axial sequence. Serious bone marrow edema-like lesions (the red arrow). MRI, magnetic resonance imaging.

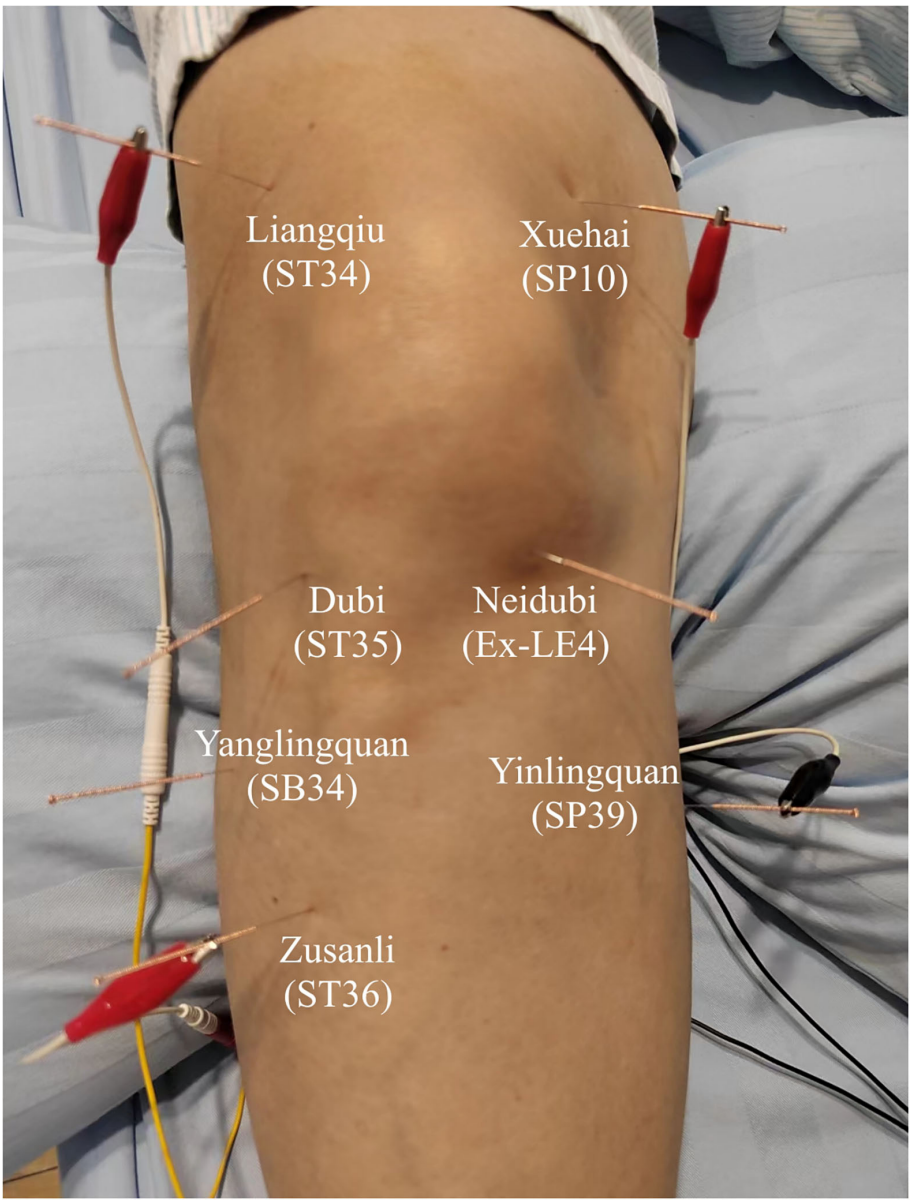

FIGURE 3
Locations of acupoints.

endogenous opioid peptides in the central nervous system play an essential role in mediating the analgesic effect of EA (26). Acupuncture encourages the release of endorphins or other monoamines through afferent nerve stimulation of the spinal cord, thus, blocking pain signals and producing analgesic effects (27).

The possible mechanism of acupuncture for improvement in KOA remains unclear. Ruan et al. (28) showed that EA alleviated the inflammation and histological changes in KOA rabbits by inhibiting the toll-like receptor-mediated innate synovial immune response. Li et al. (29) showed that acupuncture treatment may inhibit the MCP1/CCR2 axis and downregulate the inflaming factor and nerve growth factor in the cartilage and synovial tissue. However, only a few studies have examined acupuncture-associated improvement in local BMLs of the knee joint. Xu et al. (30) showed that MBLs were associated with the progression of articular cartilage loss and fluctuation of the pain in KOA. After EA intervention, the BMLs shown in the MRI of the knee joint of our patient were clearly improved. However, although our

TABLE 1 Clinical assessments for pain and knee joint function at each time points.

Clinical assessments		Before treatment	30 minutes after first treatment	1 week after treatment	4 weeks after treatment	8 weeks after treatment	12 weeks after treatment	4 weeks follow up	8 weeks follow up
VAS score		9	5	2	2	0	0	1	1
Lequesne index		11	–	8	5	1	0	0	0
ROM (°)		40	–	75	100	100	110	110	110
WOMAC Score	Pain	25	–	10	10	2	4	5	3
	Stiffness	11	–	10	9	0	0	0	0
	Physical function	56	–	31	39	16	14	17	10
	Aggregate score	92	–	51	58	18	18	22	13

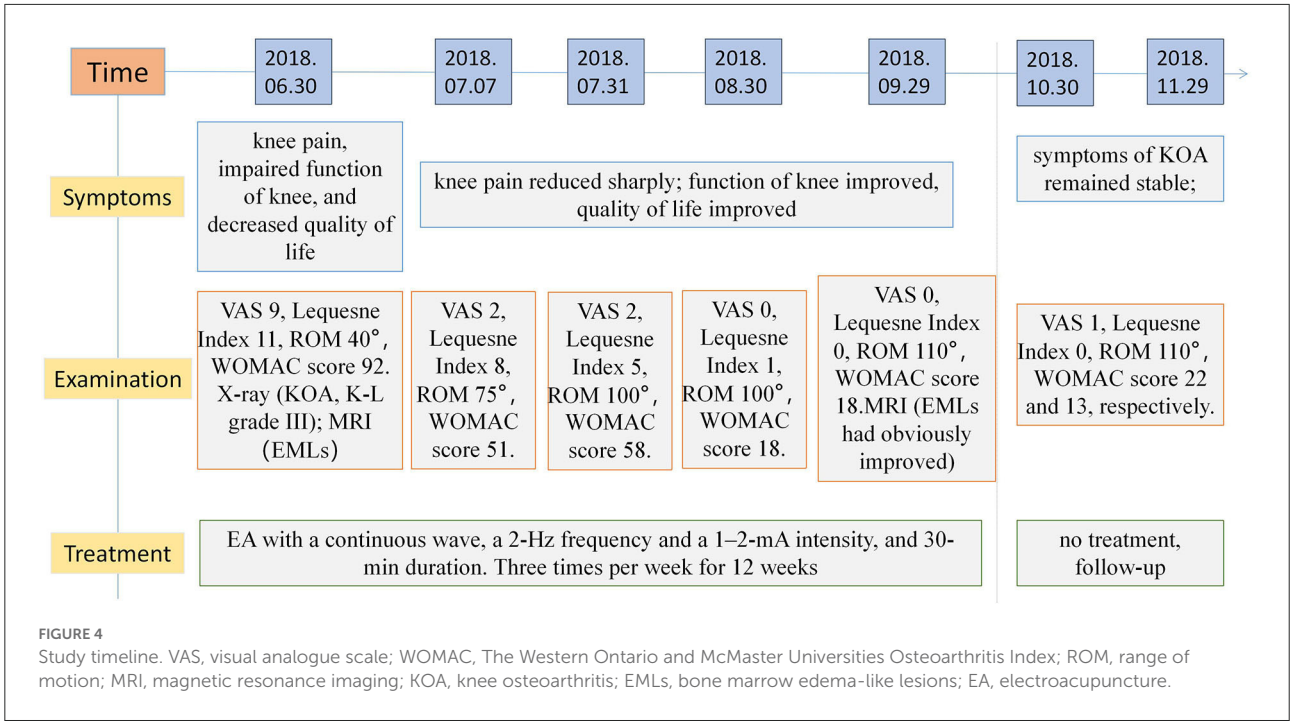

FIGURE 4
Study timeline. VAS, visual analogue scale; WOMAC, The Western Ontario and McMaster Universities Osteoarthritis Index; ROM, range of motion; MRI, magnetic resonance imaging; KOA, knee osteoarthritis; EMLs, bone marrow edema-like lesions; EA, electroacupuncture.

case report suggests that acupuncture could potentially alleviate BMLs of the knee joint to relieve symptoms, further placebo-controlled studies with larger sample sizes are required to verify this conjecture.

Conclusion

In this study, we present a case of acute pain flare-up of KOA that was successfully treated with EA. EA with a 2-Hz frequency and 1–2-mA intensity had an analgesic effect and was beneficial for the alleviation of symptoms. The potential mechanism of EA on acute pain flare-up associated with KOA is to reduce BMLs.

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 human participants were reviewed and approved by the Institutional Review Board of Guanghua Hospital, Shanghai University of Traditional Chinese Medicine.

The patients/participants 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.

Author contributions

LX and HW designed and drafted the manuscript. HH wrote the article and revised the manuscript. XC conducted the scale evaluation. YL and DH assisted in clinical treatment. All authors have read and agreed to the published version of the manuscript and contributed to the manuscript 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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Case report: Early-onset Parkinson's disease with initial spastic paraparesis and hyperreflexia caused by compound heterozygous *PRKN*-gene exon 2 and 4 deletions

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Pathogenic variants in the Parkin-gene (*PRKN*) are among the most common genetic causes of early onset Parkinson's disease (EOPD). Patients with EOPD can present with atypical clinical features and misdiagnosis is frequent. Here, we report a clinical phenotype with atypical signs and symptoms of a 35-year-old male patient with EOPD caused by a compound heterozygous *PRKN*-gene deletion of exons 2 and 4. After the initial diagnosis of stiff person syndrome, the patient was admitted to our department for a second opinion after 8 years of untreated disease progression. The patient presented with prominent spastic paraparesis pronounced on the right side and hyperreflexia as well as Parkinsonism with rigidity predominantly affecting the upper limbs, bradykinesia, and resting tremor. In the diagnostic assessment, magnetic evoked potentials to the anterior tibial muscles showed a low amplitude on the right side, compatible with pyramidal tract disturbance. However, an MRI of the head and the spine did not show any pathologies or atrophy. A [^{123}I] FP-CIT SPECT scan revealed profoundly and left-pronounced reduced striatal uptake suggesting a neurodegenerative Parkinson's syndrome. Even though an acute levodopa challenge did not show marked improvement of symptoms, the chronic levodopa challenge with up to 450 mg/day significantly reduced the rigidity and bradykinesia. Surprisingly, spastic paraparesis and hyperreflexia diminished under dopaminergic treatment. Finally, genetic analysis by next-generation sequencing *via* copy number variant analysis (CNV) and multiplex ligation-dependent probe amplification (MLPA) confirmed compound heterozygous deletions of exons 2 and 4 in the *PRKN*-gene. As presented in this case, the awareness of atypical clinical symptoms of EOPD is essential to prevent misdiagnosis in young patients.

KEYWORDS

***PRKN*-gene, Parkin, *PRKN2*, young onset parkinsonism, early onset Parkinson's disease (EOPD), exon 2, exon 4, case report**

Introduction

EOPD describes the early onset of parkinsonism under the age of 40 years (1). About 3–7% of all cases of Parkinson's disease (PD) in the Western world are classical EOPD (2–5). Homozygous or compound heterozygous pathogenic variants in the *PRKN*-gene, also known as Parkin or *PARK2*, are among the most common genetic causes of EOPD. They can be detected in 6–12% of PD cases with an onset before the age of 50 years and 30% of cases with an onset before the age of 30 years (6–8). The *PRKN* gene is ∼1.38 Mb long and one of the largest genes in the human genome. The protein product of the *PRKN*-gene is a 465-amino-acid E3 ubiquitin ligase that mediates mitochondrial intracellular Ca^{2+} homeostasis, adaptation to stress, and cell death (9–11). Pathogenic variants of the *PRKN*-gene have been described across all of its 12 exons (9). They are highly variable, including exonic rearrangement (deletion or duplication), small insertions, or point mutations (6, 12–15). They can be found in heterozygous (only one allele affected), compound heterozygous (both alleles affected by different mutations), or homozygous (both alleles affected by the same mutation) states (16–19). The average age of onset of patients with only one allele affected is about 40 years, while it is about 30 years in patients with mutations in both alleles (20). In general, patients with EOPD not only present with typical PD symptoms, such as bradykinesia, tremor, and rigor, but also with atypical symptoms such as dystonia and pyramidal signs (6). Some patients report an improvement in their symptoms after sleep (1). Concerning non-motor symptoms, depression and anxiety are frequent, while the incidence of cognitive impairment is low (14, 21–24). Patients usually show a slower disease progression than those with idiopathic PD and a remarkable improvement of symptoms in response to low-dose levodopa therapy. However, after long-term treatment, they also exhibit earlier motor complications such as dyskinesia or motor fluctuations (25). A specific genotype-phenotype correlation of *PRKN*-gene pathogenic variants has not been established yet as the symptoms vary substantially. Because of those clinical variations, delays in the EOPD diagnosis are commonly leading to significant deceleration in the treatment and genetic counseling of patients and their families.

Therefore, it is essential to expand the knowledge of different *PRKN* variants and their specific phenotypes. In the following case, we report atypical signs and symptoms as well as imaging features and treatment response of a 35-year-old male patient with EOPD caused by a compound heterozygous *PRKN*-gene deletion of exons 2 and 4. This case report aims to highlight the awareness of atypical symptoms in EOPD with particular pathogenic variants of the *PRKN*-gene which can prevent patients from misdiagnosis and lead to earlier sufficient treatment.

Case description

Medical history

The formerly healthy Caucasian patient reported an onset of symptoms at the age of 28 years. The patient recognized a progressing stiffness of the lower limbs, accompanied by muscle pain, especially in the lower back and lower limbs. He further recognized an increased tendency for muscle cramps and spasms after physical strain. Over the next 5 years, the stiffness of the lower limbs increased, leading to a broad-based gait. The patient felt exhausted by walking distances over 500 m and adapted his daily activities to avoid walking. He consulted a neurologist in 2018. However, no clear diagnosis explaining the symptoms was found and a stiff person syndrome was assumed.

In the following 3 years, a right-sided tremor, rigidity, and impairment of fine motor skills were added to the symptoms. The patient reported an improvement in motor symptoms through sleep. However, he generally recognized decreasing sleeping quality, increasing anxiety, and depressive symptoms.

Concerning the patient's family history, no neurological disorders were reported. Consanguinity did not occur in his family. At the age of 35 years, the patient visited our outpatient clinic with a progressing gait disturbance and muscular pain which led to admission (for the timeline of symptoms, see Figure 1).

Clinical findings

The physical examination revealed a prominent spastic paraparesis pronounced on the right side and hyperreflexia of the lower limbs. The patient presented a spastic broad-based gait pattern without signs of sensory ataxia, accompanied by muscle pain in the lower limbs and back. Furthermore, he showed Parkinsonism including arm-accentuated rigor with cogwheel rigidity and a right-pronounced resting-, action-, and postural tremor. A mild hypomimia was apparent but no speech problems occurred. Fine motor skills like finger-tapping or hand movements displayed an amplitude decrement and deceleration midway through the task.

Diagnostic assessment

Extensive diagnostic tests were performed to rule out several differential diagnoses that can present as Parkinson's disease look-alikes with early onset (26, 27). The serology of our patient only revealed a mild reduction of vitamin D and folate. A lumbar puncture showed an average leukocyte count (1.3 cells/µl) with normal protein (0.43 g/l) and lactate (1.40 mmol/l).

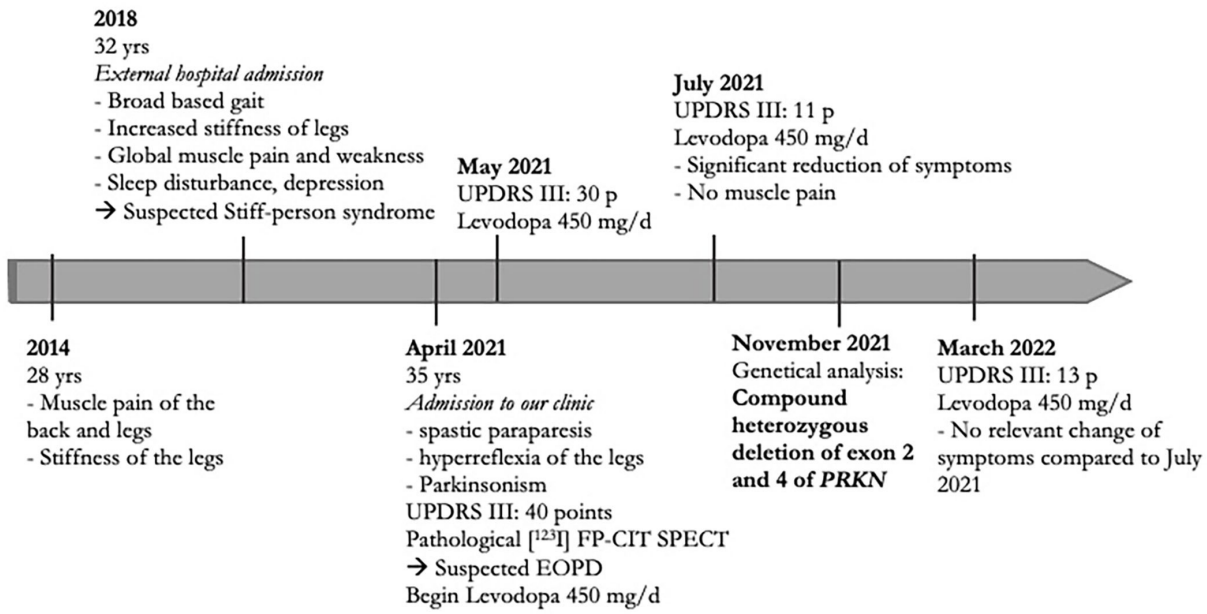

FIGURE 1
Timeline with relevant anamnestic data.

No specific intrathecal production of IgG was detected. The examination of autoimmune antibodies in serum and CSF remained negative, and diagnostics concerning M. Wilson remained negative. Nerve conduction and electromyography were unremarkable regarding a previously suspected stiff person syndrome. Interestingly, magnetic-evoked potentials to the anterior tibial muscles displayed a low amplitude on the right side, compatible with pyramidal tract disturbance. An MRI of the head and the spine did not detect any pathologies or pronounced atrophy.

The patient scored 40 points in the MDS-UPDRS III but did not show any immediate improvement of symptoms after an acute levodopa challenge, as he still scored 40 points in the "on"-state. Nevertheless, tremor analysis revealed a tremor frequency of 6.7 Hz, compatible with Parkinson's disease tremor. Montreal Cognitive Assessment (MoCA, German version) and extensive neuropsychiatric testing (Consortium to Establish a Registry for Alzheimer's Disease, CERAD) were normal (MoCA: 30/30 points; CERAD, $z = -1.0$). Concerning autonomic dysregulation, bladder sonography and a Schellong-test for circulatory function were unremarkable.

[^{123}I]*N*-ω-fluoropropyl-2β-carbomethoxy-3β-{4-iodophenyl}nortropane (FP-CIT) SPECT (Single-photon emission computed tomography) revealed profoundly and left-pronounced reduced striatal uptake at presynaptic dopamine transporters, suggesting a neurodegenerative Parkinson syndrome (Figure 2). [^{18}F]FDG-PET's search of the brain for signs of an atypical Parkinson's syndrome remained unremarkable. In particular, no significant reduction of glucose metabolism was detected in the striatum based on visual assessment and statistical parametric mapping.

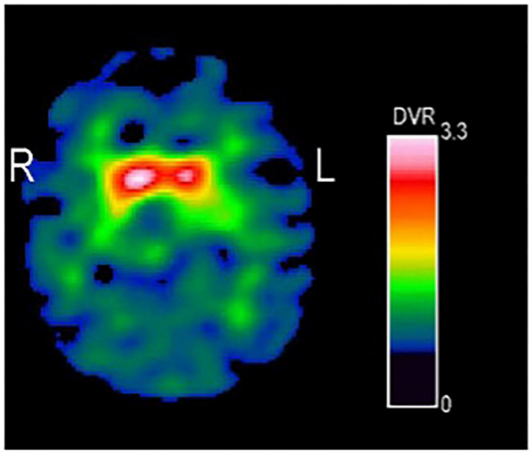

FIGURE 2
[^{123}I] FP-CIT-SPECT of our EOPD patient showed profoundly reduced binding at dopamine transporters on nigrostriatal neurons. Reductions were slightly more pronounced on the left side for the caudate nucleus (right: −41%; left: −48%) and the putamen (right: −67%; left: −71%) as compared to the age-related reference (DaTQUANT^{TM} software, GE Healthcare).

The young patient presenting with Parkinsonism and atypical symptoms (hyperreflexia and spastic paraparesis) and

the pathological [^{123}I] FP-CIT-SPECT led us to analyze EOPD-genes associated with spasms and hyperreflexia as atypical symptoms.

Genetic analysis

Genomic DNA was extracted from EDTA blood samples. DNA enrichment and library preparation were performed using the xGen Exome V02, IDT (Integrated DNA Technologies, Inc., Coralville, Iowa). Whole-exome sequencing (WES) was performed on an Illumina NextSeq 500 using the NextSeq 500/550 High Output v2 kit (Illumina, San Diego, California). Alignment to the reference genome build (GRCh37) was performed using megSAP, version 0.1-710-g52d2b0c (Institute of Medical Genetics and Applied Genomics, University of Tübingen, Germany). Variant prioritization and visualization were performed with GSvar, version 2018_04, and with Alamut visual, version 2.11 (Interactive Biosoftware, Rouen, France). Variants were classified according to the criteria proposed by the American College of Medical Genetics and Genomics (ACMG) and the genes *ATP13A2, DNAJC6, FBXO7, GBA, GCH1, LRRK2, PARK7, PINK1, SNCA, SPG11, VPS13C,* and *PRKN* including flanking intronic regions (at least-3 up to +8 bp) were analyzed. Additionally, *PRKN, PARK7, SNCA, PINK1,* and *GBA* were analyzed by multiplex ligation-dependent probe amplification (MRC-Holland) for deletions or duplications. The examination was performed according to the protocol (Kit P051, MRC-Holland, Amsterdam) with fragment analysis in a Beckman Coulter Sequencer GeXP. An evaluation was performed with the software Sequence pilot (JSI medical systems).

Genetic analysis by next-generation sequencing including copy number variant analysis (CNV) by using ClinCNV, Version 1.16.6, showed compound heterozygous deletions of exon 2 (NM_004562.3: c.(7+1_8–1)_(171+1_172–1)del p.? and exon 4 (NM_004562.3: c.(412+1_413–1)_(534+1_535–1)del.p? in the *PRKN*-gene indicating genetic Parkinson's disease. Both deletions were confirmed by MLPA. Subsequently, a complementary MLPA of the patient's parents was conducted. Both did not show any symptoms of a movement disorder at the age of 62 years. The MLPA revealed the heterozygous deletion of *PRKN* exon 2 of the patient's mother and the heterozygous deletion of *PRKN* exon 4 of his father. As both parents carried one variant of the deletions, compound heterozygosity in the patient could be confirmed.

According to the actual ACMG Standards and Guidelines, deletions of exons 2 and 4 were rated as "pathogenic" (class 5) (28). The gene-specific MDSGene database lists deletions of exon 2 as pathogenic. Deletions of exon 4 are listed as probably pathogenic and documented in combination with EOPD in several patients (25, 29–32).

Therapeutic intervention

After the [^{123}I] FP-CIT-SPECT had revealed nigrostriatal degeneration, we prescribed low-dose levodopa/carbidopa (125 mg three times a day) and recommended increasing the treatment up to 450 mg/day. Other treatment options such as dopamine receptor agonists were previously discussed but rejected by the patient. Additionally, amitriptyline (75 mg/day) was added to reduce depressive symptoms and anxiety. We also recommended a comprehensive rehabilitation program and Parkinson's syndrome training.

Follow-up and outcome

A follow-up in May 2021 at age 35 showed a significant improvement in all symptoms under treatment with 450 mg/day levodopa. He had recognized a further decrease in rigidity, stiffness, and muscle pain. His tremor was almost gone. The patient was able to walk long distances of about 3,000 m.

Furthermore, his sleep quality subjectively improved. Clinically, the patient scored 11 points in the MDS-UPDRS III in the "on"-state, a significant decrease of 72.5% compared to the beginning of treatment. Surprisingly, the spastic paraparesis and hyperreflexia also diminished under dopaminergic treatment. The tendon reflexes of the lower limbs were weak and no spasm in the lower limbs could be detected anymore. Concerning complications, the patient presented with mild dyskinesia of the trunk as a side effect of levodopa treatment. His gait was fluent and less broad-based with a residual spastic component. He stated that he had already tried a higher dosage of levodopa (600 mg/day) but had to stop because dyskinesia got worse and disrupted his daily activities.

The patient presented himself again at the age of 36 years, in the middle of March 2022. He reported that his symptoms and improvement under treatment with 450 mg/day levodopa remained stable. He scored 13 points in the MDS-UPDRS III. No cognitive decline or new symptoms were reported.

Discussion

We present a case of a 35-year-old patient with compound heterozygous exons 2 and 4 deletions in *PRKN* and uncommon clinical manifestation.

Unfortunately, many patients with EOPD remain undiagnosed for a long time due to atypical clinical features. This patient was initially diagnosed with stiff person syndrome due to spastic paraparesis and brisk reflexes. Over disease progression, the patient developed classical parkinsonian features which gave a clue for an EOPD and led to the diagnostic pathway.

A specific genotype-phenotype correlation of patients with pathogenic variants in the *PRKN* gene has not been established

yet. The correlations between phenotype and genotype are uncertain, as reported by Kasten et al., who investigated 958 Parkin mutation carriers of 663 families. Additionally, the authors described a huge proportion of non-reported phenotypic features, which complicates further definitions (25). Lücking et al. examined 73 families with EOPD. Among those, 36 families (49%) presented with *PRKN*-gene variants. Especially structural variants such as deletions and duplications, and also single nucleotide variants, were described (6). Those patients were more likely to have dystonia, symmetric involvement, and hyperreflexia. However, those symptoms tended to vary (6). Atypical symptoms, as seen in our patient, were described in other case reports of patients with *PRKN*-variants, especially Asian patients (30–32). However, our patient did not mention any Asian relatives. In other publications, clinical characteristics of North African and European patients with pathogenic *PRKN*-gene variants were indistinguishable from those of patients with idiopathic Parkinson's disease (33, 34).

The patient mentioned an improvement in his symptoms after sleep which was reported in association with pathogenic *PRKN*-gene variants before (6). Concerning non-motor symptoms, the patient suffered from depression that was described concerning EOPD (6). No cognitive decline or dementia was discovered which is in line with previously published cases (6). The substantia nigra and, to a lesser extent, the locus coeruleus seem to be more selectively affected in patients with *PRKN* mutations compared to patients with idiopathic Parkinson's disease (6).

The yet unclear genotype-phenotype correlation highlights the diagnostic value of genetic testing for correct diagnosis and prediction of patients' prognosis. Both CNV analysis and MLPA used in our genetic analysis revealed compound heterozygous deletions of exons 2 and 4 in *PRKN*. Those deletions lead to a frameshift and consequently to a premature stop codon. However, even though few case reports with similar pathogenic variants were described, the clinical phenotype of those cases remained largely uninformative which hinders a direct comparison.

The parkinsonian symptoms of our patient improved significantly after constant levodopa treatment which is frequent in EOPD (25). Surprisingly, the paraparesis and hyperreflexia were also not recognizable anymore after 5 weeks of treatment and the positive effect remained constant over 1 year. To our knowledge, this has not been described in a case before.

The patient reported that he could not further increase treatment over the dose of 450 mg levodopa/day due to dyskinesia. Early levodopa-associated dyskinesias in EOPD are well-known and can complicate treatment, even in minimal doses of levodopa (6, 9, 35). However, the patient was relieved because of the successful levodopa treatment and felt nearly as good as 8 years ago before his symptoms began.

In conclusion, we identified pathogenic compound heterozygous deletions of exons 2 and 4 in the *PRKN* gene in a 35-year-old patient with EOPD. The patient presented with an atypical phenotype and Parkinsonism. As presented in this case, the awareness of atypical clinical symptoms of EOPD, such as spastic paresis, is essential to prevent misdiagnosis in young patients. All of the patient's symptoms improved under oral levodopa therapy, highlighting the importance of deep phenotyping and early diagnosis for adequate treatment.

Data availability statement

The datasets presented in this article are not readily available because of ethical and privacy restrictions. Requests to access the datasets should 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. The patient provided his written informed consent to participate in the study. 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

IJ, MK, and FW contributed to clinical assessment. CH contributed to genetical analysis. GB contributed to imaging concerning the patient. IJ wrote the first draft of the manuscript. CH, GB, MK, and FW wrote sections of the manuscript. All authors contributed to manuscript revision, read, 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.

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Case Report: Deep brain stimulation improves tremor in *FGF-14* associated spinocerebellar ataxia

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Objectives: Spinocerebellar ataxia 27 (SCA 27) is a rare heredodegenerative disorder caused by mutations in the *fibroblast growth factor 14* (*FGF14*) and characterized by early-onset tremor and progressive ataxia later during the disease course. We investigated the effect of deep brain stimulation (DBS) of the ventralis intermedius nucleus of the thalamus (VIM) and subthalamic projections on tremor and ataxia.

Methods: At baseline, we studied the effects of high-frequency VIM stimulation and low-frequency stimulation of subthalamic projections on tremor and ataxia. The patient then adopted the best individual high-frequency stimulation programme at daytime and either 30 Hz-stimulation of the subthalamic contacts or StimOFF at night during two separate 5-weeks follow-up intervals. Both patient and rater were blinded to the stimulation settings.

Results: High-frequency stimulation of the VIM effectively attenuated tremor. At follow-up, intermittent 30 Hz-stimulation at night resulted in a superior tremor response compared to StimOFF at night. Ataxia was not affected.

Discussion: Stimulation of the VIM and adjacent subthalamic projections effectively attenuated tremor in a patient with confirmed SCA 27. Cycling between daytime high-frequency and night-time low-frequency stimulation led to a more sustained tremor response. This suggests to study in future if low-frequency stimulation of the subthalamic projection fibers may help overcome tolerance of tremor that is observed as a long-term limitation of VIM-DBS.

KEYWORDS

DBS, *FGF14*, spinocerebellar ataxia, case report, SCA 27, frequency

Introduction

Spinocerebellar ataxia 27 (SCA 27) is a rare cerebellar ataxia caused by mutations in the *fibroblast growth factor 14* (*FGF14)* gene characterized by postural tremor manifesting in early adulthood and slowly progressive ataxia in later decades (1).

Deep brain stimulation (DBS) of the ventralis intermedius nucleus (VIM) and subthalamic projections harboring the dentatothalamic tract (DTT) is highly effective in essential tremor (ET) (2). However, its effect in heredodegenerative ataxias associated with tremor such as spinocerebellar ataxias (SCA) or fragile X ataxia (FXTAS) remains poorly explored (Table 1). Stimulation of subthalamic projections can induce ataxia in ET (3) as a side effect caused by antidromic activation and maladaptive plasticity of the deep cerebellar nuclei (4). Experimental data from the shaker rat, a common ataxia model characterized by neurodegeneration of cerebellar Purkinje cells, suggested that high-frequency stimulation of the dentate nucleus (DN) induced ataxia, whereas low-frequency stimulation improved ataxia and even led to a superior tremor response (5). In this context, low-frequency stimulation was hypothesized to beneficially enhance cerebello-thalamo-cortical network activity involved in the manifestation of tremor and ataxia. Recent studies in ET patients suggested that effective attenuation of tremor is facilitated by stimulation along the DTT and not just in a specific anatomical region, highlighting the essential role of the DTT in tremor-associated network disorders (2, 6, 7). On this basis, we aimed to study in a patient with confirmed SCA 27, (i) if DBS of the VIM and subthalamic projections harboring the DTT is effective in treating tremor, and (ii) if a frequency modulation approach of high (180 Hz) vs. low (30 Hz) frequencies would benefit the tremor and ataxia outcomes.

Case description

The male patient developed a bilateral postural arm tremor at the age of 7 years and was initially diagnosed with ET. Medication regimens including levodopa, primidone (up to 250 mg/day) and propranolol (up to 240 mg/day) did not result in relevant symptom improvement. Due to slowly progressive symptom aggravation, the patient was referred to our center for DBS implantation at the age of 47 years. He clinically presented with postural and action tremor with an amplitude of 3–5 cm including a mild intention component of the upper extremities as well as a "no-no" head tremor. No signs of gait ataxia were evident in the initial examination. Moreover, the cognitive status was assessed by a Mini-Mental State Examination (MMSE) scoring 30/30 points. Brain imaging revealed no significant supra- and infratentorial atrophy patterns. The cerebellum was developed according to the patient's age including the middle cerebellar peduncles (MCP) thereby not revealing any evidence for FXTAS (Figure 1). The family history was positive, as the patient's mother had also been diagnosed with essential tremor, having developed the same symptomatology since early childhood. In addition, she became wheelchair-bound at the age of 72 and developed dementia starting in her mid-70s, which was attributed to age-related impairments and never associated with the tremor symptomatology. The patient was implanted with quadripolar electrodes (model 3389 Medtronic). In postoperative regular reprogramming, we detected the 2nd-lowermost contact placed in the VIM to achieve best tremor control. The patient developed signs of gait and limb ataxia 2 years from surgery. Ataxia persisted after StimOFF for 96 h ruling out stimulation-induced side effects. Given this emerging persistent ataxia further diagnostic work-up was initiated with advanced copy number variant analysis of exome sequencing. A heterozygous macro-deletion of the four last exons of *FGF14* was revealed leading to the diagnosis of SCA 27.

Timeline of the diagnostic assessment and programming

Figure 2 and the according figure legend 2.

Clinical assessment and DBS programming

As experimental models suggested benefits of low-frequency DN stimulation on ataxia and tremor (5), we performed differentiated assessments of subthalamic stimulation aiming for antidromic cerebellar neuromodulation. Before each programming session, DBS was turned off for 1 h in order to exclude a confounding rebound of tremor severity due to cessation of stimulation (3). In the immediate assessment, we reconfirmed that best tremor control was achieved by stimulation of the 2nd-lowermost contacts and stepwise ramping of the frequency up to 180 Hz increased this effect. Symmetrical stimulation settings were programmed in both hemispheres. Reconstruction of electrode placement indicated spatial vicinity between the DTT and the lowermost contacts (Figure 3). Therefore, the lowermost contacts were chosen for investigating the clinical effects of 30 Hz-stimulation with amplitudes ranging from 1 to 7 mA in a randomized order (Figure 4A). The highest amplitude tolerable for the patient (4 mA) was chosen for the follow-up. Simulation of the volume of tissue activated (VTA) by the 30 Hz-stimulation programme revealed a partial overlap of the VTA and the DTT (Figure 3B). In two follow-up intervals of 5 weeks, we used 180 Hz-stimulation of the 2nd-lowermost contacts for best tremor control at daytime. At night, 180 Hz-stimulation was turned off and the patient was instructed to use either StimOFF or 30 Hz-stimulation of the lowermost contacts. Investigator

TABLE 1 DBS for the treatment of tremor in heredodegenerative ataxias.

Genetic ataxia	DBS target	Outcome	References
SCA 2	VIM/ZI	Attenuation of postural tremor in 3 patients with the TRS improving from 33–26 (Oyama et al.) to 99–26 (Isobe et al.)	(11–13)
SCA 3	DN	Significant attenuation of cerebellar tremor after active stimulation vs. sham (18.0 ± 17.2 vs. 22.2 ± 19.5; $p = 0.039$) in 2 patients with SCA3 and 3 patients showing cerebellar lesions	(14, 15)
SCA 3, type IV	STN	Alleviation of parkinsonism including resting tremor in 1 patient	(16)
SCA 6	VIM	Attenuation of action tremor in 2 patients	(17)
SCA 31	VIM	Attenuation of action tremor in 1 patient	(17)
SCA unspecified	VIM/ZI	Favorable attenuation of intention tremor by stimulation of the ZI compared to the VIM in 1 patient	(18)
FXTAS	VIM/ZI	Long-term improvement of axial and intention tremor in 10 FXTAS patients reported with variable outcome concerning the tremor scores	(12, 19–25)

DBS, deep brain stimulation; SCA, spinocerebellar ataxia; FXTAS, fragile X ataxia syndrome; VIM, ventralis intermedius nucleus; ZI, zona incerta; DN, dentate nucleus; TRS, fahn-tolosa-marin-tremor-rating-scale.

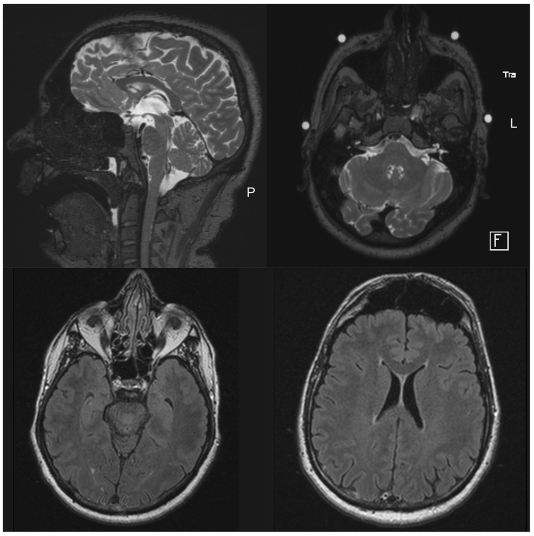

FIGURE 1
MRI scan before DBS implantation. At age 47 years, MRI showed no signs of cerebellar or supratentorial atrophy. The middle cerebellar peduncles (MCP) were normally developed according to the patient's age. The images presented in the sagittal and axial plane were acquired as T2-weighted sequences.

and patient were blinded to the night setting of the previous interval. Electrode placement and reconstruction of the VTA was conducted using the Lead-DBS toolbox (8) for Matlab (The MathWorks Inc., Natick, MA, USA) and anatomic atlases (9, 10). The Fahn-Tolosa-Marin-Tremor-Rating-Scale (TRS) items 1–9 and the Scale for the Assessment and Rating of Ataxia (SARA) were performed. Data analyses were conducted using GraphPad Prism 6.0 (GraphPad Software Inc, San Diego, CA, USA).

Outcome

In the immediate assessment, tremor severity was attenuated by 180 Hz-VIM-stimulation compared to StimOFF (TRS 13 vs. 21). Tremor was also attenuated by 30 Hz-stimulation of the lowermost contact at 1 mA (TRS: 14), but gradually aggravated with stimulation amplitudes >4 mA (TRS up to 27). Changes of the SARA where mainly driven by the tremor response (Figure 4A).

During the first follow-up interval, the patient adopted intermittent 30 Hz-stimulation at night. Tremor in the StimOFF condition (TRS: 12) improved to a TRS of 7 by activating the 180 Hz-programme (Figure 4B). After the second interval during which the patient adopted StimOFF at night, the baseline TRS was higher in the StimOFF condition (TRS: 23) and slightly improved (TRS: 17) when using 180 Hz-stimulation (Figure 4C).

Thus, 180 Hz-stimulation at daytime and 30 Hz-stimulation at night led to a superior tremor response without occurrence of stimulation-induced aggravation of ataxia. In contrast, 180 Hz stimulation at daytime and StimOFF at night showed a decrease in tremor response.

Discussion

Here we report the first case of a SCA 27 patient with favorable tremor response to DBS of the VIM and the subthalamic fiber tracts harboring the DTT. To date, a tremor-suppressing effect of high-frequency VIM-DBS was described in SCA 2, 3, 6, 31, and FXTAS (11–25) (Table 1). Stimulation of subthalamic projections provides the possibility of cerebellar neuromodulation by antidromic stimulation of the DTT (4, 26). We hypothesized that low-frequency stimulation of subthalamic projections may improve tremor and ataxia by entraining the cerebello-thalamo-cortical network as suggested

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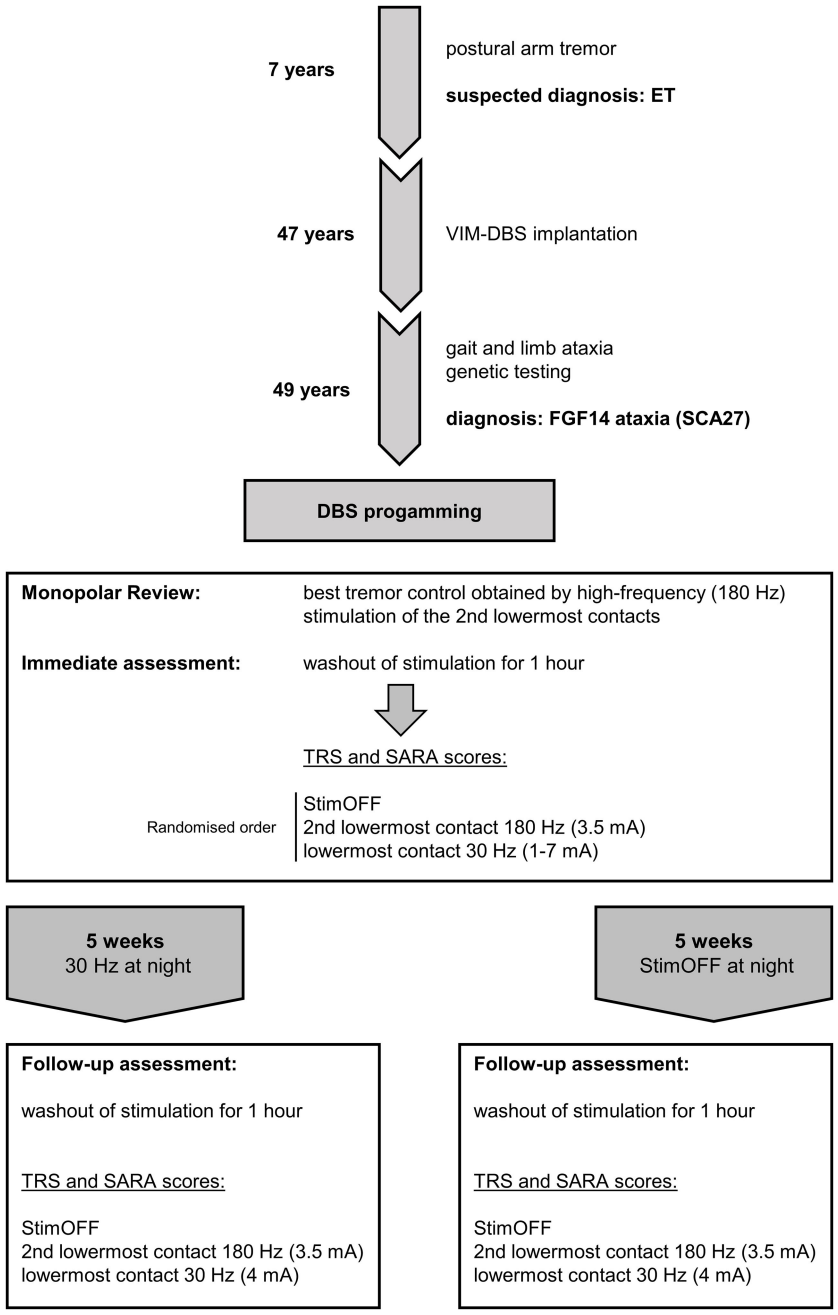
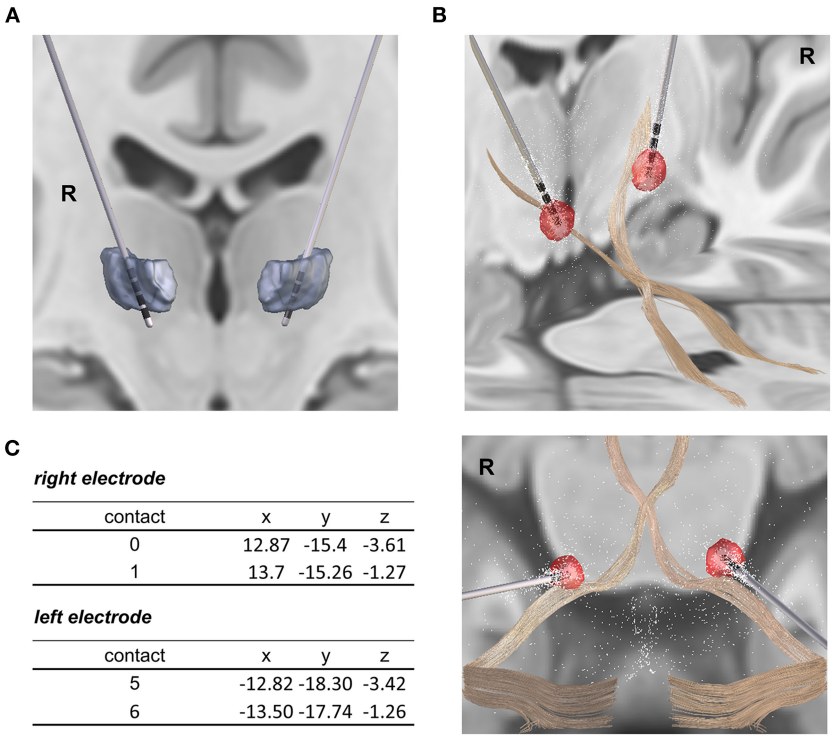


FIGURE 2
Timeline of the patient's history, diagnostic and therapeutic work-up. The patient was initially diagnosed with essential tremor (ET) due to early-onset postural arm tremor at the age of 7 years and implanted with VIM-DBS at the age of 47 years. Slowly emerging ataxia led to the diagnosis of spinocerebellar ataxia 27 (SCA 27) at the age of 49 years. Programming of deep brain stimulation (DBS) following a monopolar review showed relevant tremor attenuation by high-frequency stimulation of the 2nd lowermost contacts. The patient was randomized to follow-up stimulation settings meaning high-frequency stimulation at daytime and either StimOFF or 30 Hz stimulation of subthalamic fiber tracts (lowermost contacts) at night. Both stimulation paradigms were activated for 5 weeks in a randomized order followed by clinical examinations blinded to the settings of the previous interval.

by experimental models in direct DN stimulation (5). Whilst night-time low-frequency stimulation of the lowermost contact, placed in the subthalamic area with close vicinity to the subthalamic fiber tracts including the DTT did not affect the ataxia outcome, a superior tremor response was observed. Therefore, treatment of tremor at daytime with high-frequency



C

right electrode

contact	x	y	z
0	12.87	-15.4	-3.61
1	13.7	-15.26	-1.27

left electrode

contact	x	y	z
5	-12.82	-18.30	-3.42
6	-13.50	-17.74	-1.26

FIGURE 3
Reconstruction of DBS electrode placement. **(A)** Electrode placement in the VIM with the lowest contacts (0, 5) reaching beyond the thalamus border. **(B)** Topographic vicinity of the dentato-thalamic tract (DTT) and the volume of tissue activated (VTA) during low-frequency stimulation of the lowest contacts (30 Hz, 4 mA). The electrode position in relation to the DTT is shown from both a lateral and a superior perspective. The right side of the patient is marked with "R". **(C)** Electrode placement and MNI coordinates of the active contacts for the high-frequency stimulation programme (contacts 1, 6: 3.5 mA, 30 Hz, 60 μs) and the low-frequency stimulation programme (contacts 0, 5: 4 mA, 30 Hz, 60 μs) are displayed. Electrode placement was reconstructed by co-registration of preoperative MRI and postoperative CT images and normalization into the MNI_ICBM_2009b_NLIN_ASYM space and anatomic atlases using the Lead-DBS toolbox.

stimulation and prevention of habituation (3) and stimulation-induced ataxia (4) by intermittent low-frequency DBS may represent a novel approach.

However, this conclusion must take into account some limitations and pending issues, mainly based on the observation of a single patient in this case report. TRS scores in the StimOFF and StimON conditions after adopting intermittent low-frequency stimulation were considerably lower than after adopting StimOFF at night. Whether this difference may be attributed to a prolonged effect of the low-frequency stimulation cannot be conclusively determined on the basis of the observation of a single patient. Both conditions were tested at the same time of the day and in the same setting after a washout of stimulation for 1 h in order to minimize tolerance and rebound phenomena. Nevertheless, it is established that tremor severity is a fluctuating symptom affected by various confounders like anxiety and the overall noradrenergic tone which were not controlled in this case study. Moreover, entrainment of cerebello-thalamo-cortical networks by neuromodulation of the DTT was only assumed by a normative connectomic approach as recently adopted in other studies (7). Simulation of the VTA of the 30 Hz low frequency programme partially covered fibers of the DTT, but it should be considered that the stimulation programme tested may not have affected the entire DTT. The cerebello-thalamo-cortical networks involved are located within the "anatomical bottle-neck" (6) of the subthalamic area and the adjacent thalamus. Both lower electrode contacts tested here potentially interfere with these networks. Eventually, further electrophysiological or functional imaging data are required to assess the neurophysiological mechanisms behind the effects reported in this case report.

Here we report the first case of a SCA 27 patient experiencing relevant symptom relieve by DBS of the VIM and subthalamic fiber tracts including the DTT. Moreover, as before only described in experimental models the approach of low-frequency stimulation of the cerebello-thalamo-cortical network resulted in a superior tremor response. On this basis, stringent clinical studies may tie in and provide a new therapeutic perspective for patients with tremor and ataxia in SCA 27 and beyond.

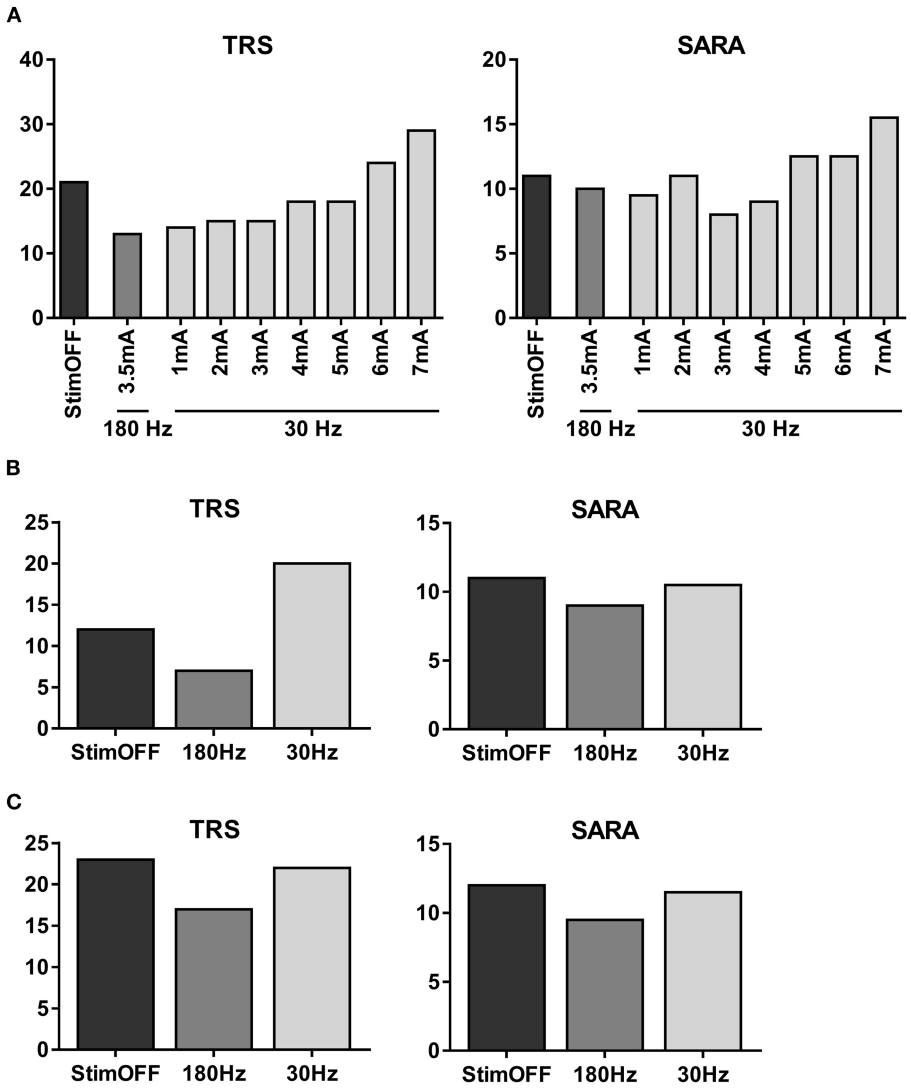


FIGURE 4
Clinical tremor and ataxia scores assessed with different stimulation paradigms. **(A)** In the immediate assessment, TRS and SARA were scored with StimOFF, 180 Hz-stimulation of the 2nd-lowermost (VIM) contacts and 30 Hz stimulation of the lowermost (subthalamic) contacts with increasing amplitudes from 1 to 7 mA in a randomized order. **(B)** The first follow-up examination was scheduled 5 weeks from baseline with preceding 180 Hz-stimulation (3.5 mA) at daytime and 30 Hz stimulation (4 mA) at night. **(C)** The second follow-up was scheduled 10 weeks from baseline with preceding 180 Hz-stimulation (3.5 mA) at daytime and StimOFF at night. For all assessments, the rater and patient were blinded to the respective previous stimulation settings.

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. The patients/participants 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.

Author contributions

ML: research project: conception, organization, execution, and manuscript preparation: writing of the first draft. MS: research project: conception, and manuscript preparation: review and critique. IC, PK, MH, TG, and AG: research project: organization, and manuscript preparation: review and critique.

DW: research project: conception, organization, execution, and manuscript preparation: review and critique. All authors contributed to the article and approved the submitted version.

Conflict of interest

Unrelated to this study, AG and DW received research support and speaker's honoraria from Medtronic, Boston Scientific, and Abbott, all three manufacturers of DBS equipment.

The remaining 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/fneur.2022.1048530/full#supplementary-material

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Unilateral upper limb chorea associated with hyperthyroidism: A case report and literature review

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Chorea, a hyperkinetic syndrome, is generally reported in patients with Huntington's disease (HD), hyperglycemia, and other diseases but occasionally occurs in patients with Grave's disease. Here, we report a 44-year-old woman presenting with a 1-year history of involuntary movements with a known history of primary hyperthyroidism. Physical examination revealed the continuous, rapid, irregular, and spontaneous choreic movement of her right arm. Laboratory investigations demonstrated increased triiodothyronine (T3) and free thyroxine (FT4) and suppressed thyroid-stimulating hormone (TSH) levels. An electroencephalogram and brain magnetic resonance imaging were normal. After antithyroid treatment, the patient achieved complete remission. Our case indicated that hemichorea might initially manifest hyperthyroidism. Therefore, thyroid function tests should be routinely performed in patients with chorea.

KEYWORDS

chorea, involuntary movement, hyperthyroidism, Graves' disease, initial presentation

Introduction

Chorea is a hyperkinetic syndrome characterized by irregular, brief and non-stereotyped movements resulting from abrupt twitching of the muscles, which flit from one body region to another (1). Chorea is commonly described in patients with Huntington's disease (HD) (2), hyperglycemia (3), autoimmune thyroid disease, drug toxication (4), etc. (5). However, chorea is a rare complication of hyperthyroidism, with <2% of chorea cases occurring in patients with Grave's disease (6). In this report, we present a case of hemichorea as the first manifestation of hyperthyroidism which was resolved with antithyroid therapy.

The study was performed according to the principles of the Helsinki declaration and the local ethical standards. Written informed consent was obtained from the patient.

Case report

A 44-year-old female patient was admitted to our neurology department in October 2021 due to a one-year history of involuntary movements of her right arm. She had

been diagnosed with uncontrolled hyperthyroidism due to Grave's disease in April 2021 and treated with methimazole (10 mg daily). There was an obvious improvement in her involuntary movements 1 month later, but she had to stop taking methimazole due to the development of urticarial and liver dysfunction. She has not received other antithyroid drugs or radioiodine treatment for hyperthyroidism.

After the discontinuation of methimazole, her involuntary movements gradually deteriorated, with symptoms occurring at any time, even during sleep. In addition, she complained of mild palpitations, irritability, and anxiety. By the time of admission, the choreiform movements were continuous, rapid, irregular, and spontaneous (Supplementary Video S1), and her right arm was totally out of control. She had lost weight and had a rapid heart rate of 126 beats per minute. Neurological examination was otherwise normal except for choreic movements predominating in the right upper limb.

Laboratory results revealed increased triiodothyronine (T3) level (8.26 nmol/L, normal range: 0.92–2.79 nmol/L) and free thyroxine (FT4) level (58.13 pmol/L, normal range: 11.50–22.70 pmol/L), suppressed thyroid-stimulating hormone (TSH) level (<0.01 mIU/L, normal range: 0.55–4.78 mIU/L), and a positive anti-thyroglobulin antibody titer (105.20 KIU/L, normal range: 0–60.00 KIU/L). Hematologic investigations, including a complete blood cell count, liver and kidney functions, glucose level, autoantibody titers, serum tumor markers, ceruloplasmin, and creatine kinase activity, were normal. Thyroid ultrasonography showed diffuse heterogeneity, focal hypoechogenicity of the thyroid gland, and a diffusely enhanced thyroid blood flow. The electroencephalogram was within normal limits. Brain magnetic resonance imaging (MRI) showed normal axial T1, T2, and DWI. Lumbar puncture confirmed normal opening pressure, and no abnormality was observed in the cerebrospinal fluid analysis.

Considering her methimazole intolerance, she was treated with radiation (^{131}I) therapy. Her symptoms gradually resolved (Supplementary Video S2), along with slightly decreased T3 and T4 and elevated TSH levels. The chorea movement almost disappeared 3 months later, and there was no recurrence after 6 months of follow-up.

Literature review and discussion

This unusual case of hemichorea secondary to hyperthyroidism was resolved with a (^{131}I) regimen. Chorea is an abnormal movement disorder typically manifesting as continual involuntary, abrupt, rapid, brief, and irregular movements that randomly flow from one body part to another in a non-stereotyped mode. In rare instances, chorea is related to poorly controlled hyperthyroidism, which was first reported by Gowers in 1983 (7).

We reviewed case reports of hyperthyroid-related chorea published between January 1990 and August 2022, identifying 27 cases of chorea due to hyperthyroidism. The clinical characteristics of all 28 cases, including our case, are presented in Table 1. The median age of patients with hyperthyroid chorea was 23 years old (range, 8–78 years) and was reported in 22 females (77.8%) and six males, five from China, four from the United States, three from Japan, and three from South Korea. Hyperthyroid-related chorea is typically manifested by acute or subacute and progressive choreiform movements with predominant distal involvement. The involuntary movements symmetrically (17 cases) or asymmetrically involve arms and legs, predominating on the left side (11 cases), and are more pronounced in the leg while walking, causing infrequent falls. The trunk, face, and bucco-oral-lingual region can also be affected, resulting in speech disturbance and dysphagia. Thyrotoxic symptoms, including weight loss, palpitations, sweating, and anxiety, usually appear weeks to years before involuntary movements. Neurological examinations are commonly normal, but some cases reported brisk deep tendon reflexes. The characteristics of hyperthyroid chorea on neuroimaging, including CT, MRI, and MRA of the brain, were normal, and the brain MRI and MRA of the current case also revealed no structural changes. In our case, the patient presented with acute onset of worsening involuntary movements of her right arm.

To date, the physiopathologic mechanisms of hyperthyroid-related chorea remain elusive. It has been suggested that chorea may result from a direct effect of thyrotoxicosis on the central nervous system in Graves' disease. Structural changes in the basal ganglia have not been demonstrated postmortem (33), which is consistent with the normal neuroimaging of the previously reported cases. Hypersensitivity of the dopaminergic system in the nigrostriatal pathway of basal ganglia has been suggested to be one of the underlying mechanisms. Homo-vanillic acid, a dopamine metabolite, was significantly decreased in the cerebrospinal fluid of hyperthyroid patients (34). Moreover, treatment with dopamine antagonists can alleviate the symptoms of hyperthyroidism-related chorea (35). Functional modification of adrenergic receptors may also be involved in hyperthyroid-related chorea (14, 28), which is also supported by the partially relieved chorea with propranolol (a non-selective β1 and β2 adrenergic receptor blocker) treatment. ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) showed elevated metabolism in the bilateral basal ganglia in a patient whose choreic movements predominately involved her right side (18), suggesting that hyperthyroidism may have a direct thyrotoxicosis effect resulting in excessive dopaminergic activity in the basal ganglia.

Treating hyperthyroidism-associated chorea consists of correcting thyroid function with antithyroid drugs and adding symptomatic agents, if necessary. In most patients, the choreic movements gradually improved over weeks or months with

TABLE 1 Clinical characteristics of 28 patients with hyperthyroidism-associated chorea.

Age/sex (ref)	Publication year/country	Clinical presentation	Medical history	Neurological syndromes	Disease duration	Treatment	Prognosis
44/F (PR)	2022/China	Involuntary movements of her right arm	Grave's disease	Normal	1 year	Radiation (^{131}I) therapy	Improvement within 3 months
67/M (8)	2022/Canada	Ongoing, non-distractible choreiform movements of the left upper extremity	Right frontoparietal stroke, thyroidectomy with ablation, thyroid hormone replacement	Spasticity, mildly reduced strength, and 3+ hyperreflexia/left	NR	L-thyroxine (dosage was decreased to 20 mg twice a day), beta blocker	Improvement within 2 months
14/M (9)	2021/Kenya	Chorea, tremors, a low BMI of 17	Unremarkable	Tremor/bilateral limbs	A few months	Gabapentin, carbimazole, and radioactive iodine therapy	Improvement
13/F (10)	2020/USA	Worsening left-sided upper extremity weakness and gait unsteadiness for 1 month	Unremarkable	Tremors, gait alterations with left foot drop, slurred speech/left	1 month	Methimazole and propranolol	Improvement within 12 months
8/F (10)	2020/Argentina	Subacute onset lost weight, gained height, involuntary movements	Asthma	Lingual fasciculations, dysarthria/bilateral limbs	1 month	Methimazole, atenolol and carbamazepine	Improvement within 1 month
62/M (11)	2019/China	Asymmetric involuntary movement, muscle weakness, inaccurate coordinate movement, and hypomyotonia of right limbs	Diabetes, atrial fibrillation	Normal	2 weeks	Methimazole, haloperidol, and bisoprolol	Improvement within 2 weeks
60/F (12)	2019/Switzerland	Erratic, intricate movement disorders in her left upper and lower extremities	Hypertension	Tremor/left	5 years	Carbimazole and propylthiouracil (switched to radioiodine therapy due to severe adverse effects)	Improvement within 2 months
32/F (13)	2016/India	Jerky, non-repetitive involuntary movements of the left upper and lower limbs	Unremarkable	Normal	NR	Carbimazole	Improvement within 6 weeks
25/F (14)	2016/USA	Muscle spasms of the left shoulder and arm	Hyperthyroidism, anxiety, bipolar disorder, depression, substance abuse	Normal	NR	Metoprolol and methimazole	Improvement within 1 week
60/F (15)	2015/Switzerland	Imbalance associated with falls evolving for 5 years	Unremarkable	Normal	5 years	Carbimazole, ^{131}I radiotherapy	Improvement within a few weeks

(Continued)

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TABLE 1 (Continued)

Age/sex (ref)	Publication year/country	Clinical presentation	Medical history	Neurological syndromes	Disease duration	Treatment	Prognosis
15/F (16)	2013/Canada	A series of falls over the month, choreiform episodes, insomnia, fatigue, and loss of appetite	Sickle cell disease	Normal	2 weeks	Methimazole first, then methimazole plus levothyroxine	Improvement
23/F (17)	2013/Poland	Palpitations, weight loss, and exercise intolerance	Unremarkable	Normal	NP	Thiamazole, Haloperidol, Prednisone	Improvement within 6 weeks
22/F (18)	2013/South Korea	Involuntary movement of her four extremities	Hyperthyroidism	Dysarthria	2 months	Propylthiouracil	Improvement within 1 month
16/M (19)	2012/South Korea	Choreic movement dominant in the right limb	Unremarkable	Brisk deep tendon reflex/bilateral limbs	9 days	Propylthiouracil, propranolol	Improvement within 8 months
14/M (20)	2012/China	Acute onset, generalized proximal muscle weakness, and hyporeflexia	Unremarkable	Normal	5 hours	Methimazole	Improvement within 4 weeks
23/F (21)	2011/USA	Involuntary, writhing, symmetrical movements involving arms, legs, neck, tongue, and face starting 10 days following delivery of her second child. weight loss	Toxic nodular goiter	Normal	NR	Propylthiouracil, atenolol, quetiapine, and a short prednisone taper	Improvement within 6 months
38/F (22)	2010/China	Ilateral blepharospasm with visual difficulty, and facial grimacing. involuntary choreic movements in her left side	Unremarkable	Bilateral blepharospasm, oromandibular dystonia; Irregular speech in volume and tempo, irregular and unsteady gait	3 months	Methimazole	Improvement within 4 months
17/F (23)	2009/China	Acute onset, involuntary movement of hands, forearms, feet, and face for 2 weeks	Graves' disease	Irregular and unsteady gait, irregular speech in volume and tempo	2 weeks	Propylthiouracil, propranolol, and haloperidol	Improvement within 6 weeks
42/F (24)	2008/South Korea	Continuous, involuntary movement in her left upper extremity and face for 1 month	Graves' disease	Normal	1 month	Methylprednisolone sodium succinate and oral antithyroid medication	Improvement
19/F (25)	2008/France	About 2 weeks before admission, she had progressively developed movement disorder, balance impairment, and dysarthria	Graves' disease	Mild dysarthria and impaired tandem walk	2 weeks	Carbimazole and levothyroxine	Improvement within 3 months

(Continued)

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TABLE 1 (Continued)

Age/sex (ref)	Publication year/country	Clinical presentation	Medical history	Neurological syndromes	Disease duration	Treatment	Prognosis
9/F (26)	2007/USA	A 2 month-history of weight loss, hyperactivity, tremulousness, and palpitations	Unremarkable	Ataxic gait, dysmetria, and dysdiadochokinesia	2 months	Propylthiouracil and propranolol	Improvement within 4 days
78/F (27)	2005/UK	A 1-week history of increasing agitation and worsening generalized involuntary movements	IHD, AF, AS, hypercholesterolemia, and total thyroidectomy	Impaired speech and dysphagia	1 week	Propranolol; discontinuation of thyroxine	Improvement within 3 months
50/M (6)	2004/Yugoslavia	Sudden development of vigorous bilateral, ballistic, and severe choreic movements of all limbs, more prominent on the left side	Hyperthyroidism	Normal	NR	Haloperidol, propranolol and thiamazole	Improvement within 10 days
23/F (28)	2003/Japan	Marked sweating, irritability, poor concentration, and tremors in both hands	Parkinson's disease	Right-hand tremor	15 months	Methimazole and β-adrenoceptor blocker	Improvement within 2 weeks
24/F (29)	1998/Japan	Acute left-sided chorea and dysarthria	Graves' disease	Normal	NR	Methimazole, propranolol, and diazepam	Improvement within 4 weeks
Elderly female (30)	1994/Italy	Chorea	Hyperthyroidism	Normal	NR	-	Improvement
16/F (31)	1992/Italy	Depression of the mood, tremors, motor incoordination, and chorea more evident in the right side	Operated on for closure of a ventricular septal defect, Graves' disease	Muscular hypotonia, decreased tendon reflexes, facial grimacing, and dysarthria/right	8 months	Methimazole	Improvement within 2 months
23/F (32)	1992/Japan	Severe involuntary movements in the left extremities	Unremarkable	Normal	2 years	Thiamazole and propranolol	Improvement within 2 months

F, female; M, male; PR, present case; NR, not reported; IHD, ischemic heart disease; AF, atrial fibrillation; AS, aortic stenosis.

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the normalization of their thyroid function. Although some patients must stop the antithyroid drug because of adverse effects such as severe muscle pain and myalgia, significant clinical alleviation was noticed in parallel with their improved thyroid function. These patients also benefited from radioiodine or thyroidectomy. Hence, it is indicated that hyperthyroidism-associated chorea is reversible after treatment with beta-adrenergic blockers, dopamine antagonists, and especially antithyroid drugs.

Conclusion

In summary, hemichorea is rare in hyperthyroidism patients and may be the initial manifestation of hyperthyroidism. Therefore, it is recommended that thyroid function tests should be routinely performed in patients with chorea. The rapid resolution of the chorea after controlling the hyperthyroidism in the absence of any structural lesion suggests that the movement disorder was likely a result of thyrotoxicosis-induced biochemical changes rather than the coexistence of a structural lesion. Further studies are needed to explore the etiology and pathogenesis of hyperthyroidism-induced chorea.

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 human participants were reviewed and approved by the Ethical Committee of the Second People's Hospital of Quzhou. The patients/participants 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.

Author contributions

WC designed the work and wrote the original draft. WC, BW, HA, KZ, DZ, JZ, and XW initiated the project, collected, and analyzed the data. XW wrote the review, edited, supervised, and validated the manuscript. All authors read and approved the final 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/fneur.2022.1074156/full#supplementary-material

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Case report: Pallidal deep brain stimulation for treatment of tardive dystonia/dyskinesia secondary to chronic metoclopramide medication

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Objectives: Tardive dystonia/dyskinesia (TDD) occurs as a side effect of anti-dopaminergic drugs, including metoclopramide, and is often refractory to medication. While pallidal deep brain stimulation (DBS) has become an accepted treatment for TDD secondary to neuroleptic medication, there is much less knowledge about its effects on metoclopramide-induced TDD.

Methods: We present the case of a woman with metoclopramide-induced TDD, whose symptoms were initially misjudged as "functional." After 8 years of ineffective medical treatments, she received bilateral implantation of quadripolar electrodes into the posteroventral lateral globus pallidus internus (GPi).

Results: GPi DBS led to significant symptom reduction [Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) motor score 24/44 at admission and 7/44 at discharge]. Chronic stimulation led to full recovery from TDD symptoms 9 years after surgery. The BFMDRS motor score decreased to 0.5 (98% improvement).

Discussion: Pallidal DBS may result in sustained improvement of TDD secondary to chronic metoclopramide intake in the long term.

KEYWORDS

pallidal DBS, metoclopramide, tardive dystonia, tardive dyskinesia, GPi DBS, case report

1. Introduction

Deep brain stimulation (DBS) of the globus pallidus internus (GPi) has become the standard treatment for dystonia (1, 2). Several studies have shown that DBS is similarly effective in patients with tardive dystonia/dyskinesia (TDD) as compared to inherited or idiopathic dystonia (3–7). While TDD has been a common adverse effect of neuroleptic treatment, it may rarely be secondary to chronic medication with metoclopramide (8, 9).

Thus far, no detailed information has become available on the effect of GPi DBS for the treatment of metoclopramide-induced TDD. Only data from three patients have been reported so far, but individual outcomes were not mentioned in the case series. We therefore, would like to present a case of metoclopramide-induced TDD with dystonia and dyskinesia after metoclopramide administration.

2. Case report

A 40-year-old woman presented with a 7-year history of TDD after chronic medication with metoclopramide. She had a history of migraine, gluten intolerance, and Crohn's disease. At 32 years of age, she was treated with metoclopramide for nausea and gastroparesis. About a year on metoclopramide medication, she developed oculogyric crises, and dystonic/dyskinetic involuntary movements of orofacial muscles, tongue, trunk, and scalp. Several months later, retrocollis and dystonic movements of the right leg appeared. She had never received metoclopramide or any other dopamine-blocking medication before. The hyperkinetic movements had started after months of chronic metoclopramide intake and before intake of any neuroleptics. The patient had no family history of dystonia and/or dyskinesias and moreover, no family history of any movement disorder, including Parkinson's disease or tremor. The diagnosis of metoclopramide-induced TDD was made after a neurological workup, including MRI, lumbar puncture, blood tests, and jejunal biopsy, all of which showed negative results. After receiving the diagnosis of metoclopramide-induced TDD, metoclopramide was withdrawn. Then, she received multiple medications for the treatment of TDD, including neuroleptics (dipiperon, risperidone, clozapine, and olanzapine), for several months without a clear effect on the movement disorder. Although the dyskinesias worsened over time, the patient did not feel a worsening or improving effect linked to the neuroleptic medication. After a trial with tetrabenazine, dyskinesias were slightly worse transiently. Benzodiazepines (oxazepam, clonazepam, and clobazam), antidepressants (mirtazapine, fluoxetine, and trimipramine), and other medications (tizanidine, baclofen, dantrolene, and buspirone) were administered without any improvement. The patient had botulinum toxin injections to the facial muscles and scalp several times along the course of the disease. She reported no improvement thereafter. At some point, the symptoms were classified as "functional" and she was treated in different psychiatric hospitals for depression and fatigue without any improvement.

At 40 years of age, she presented at the author's institution for the first time. At that time, she was unable to work or do housework, lived with her mother, and had suffered from insomnia and depression. The neurological examination revealed marked phasic dystonic/dyskinetic movements of facial muscles including blepharospasm, orofacial dyskinesias with tongue movements, involvement of occipital and cervical muscles with prominent rippling scalp movements, retroflexion and turn of the head, dystonic movements of her upper trunk, and posturing of the right foot resulting in abnormal gait. No deficits of the cranial nerves or sensorimotor dysfunction were detected. The motor score on the Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) was 24. The patient was psychiatrically stable, especially without suicidal thought. The Hamilton Depression Score (HAMD) did not indicate subclinical or overt depression.

She underwent the implantation of quadripolar DBS electrodes (Medtronic 3387, four contacts with a length of 1.5 mm per contact and spacing of 1.5 mm between contacts) bilaterally in the posteroventral lateral GPi guided by CT-stereotactic surgery and microelectrode recording under local anesthesia with techniques, as described in detail elsewhere (4, 10). After postoperative stereotactic CT-imaging confirmed the appropriate placement of the DBS electrodes (Figure 1), she received a non-rechargeable implantable pulse generator (IPG) (Medtronic, Activa PC). Automatic lead detection in postoperative CT scans showed the following coordinates for the lowest contact: Right GPi: $x = 20.4$, $y = 4.1$, $z = -4.8$; Left GPi: $x = 19.6$, $y = 2.5$, $z = -3.9$. During early programming, dystonia of the leg disappeared completely and the other involuntary movements were markedly improved, but the patient still felt considerable tension in the neck and scalp area. The stimulation settings upon discharge are shown in Table 1. The motor BFMDRS was reduced to seven (71% improvement).

Within the next few months, several stimulation settings were tested and the dystonic/dyskinetic movements slowly improved further. The motor BFMDRS at the 1-year follow-up was 1 (96% improvement). Two years postoperatively, the IPG was replaced by a rechargeable device. With continued adjustment of stimulation settings (refer to Table 1) and chronic stimulation, the involuntary movements almost completely subsided. At 9-year follow-up, at 49 years of age, the patient was living with a partner, worked full time, and took care of her family. She continued with chronic DBS with relatively high energy delivery without side effects (refer to Table 1). The motor BFMDRS was 0.5 (98% improvement).

3. Discussion

While the frequency of TDD, in general, has declined over the years with the use of second-generation neuroleptics, they still may present a debilitating side effect (3). If symptoms are recognized early and treated appropriately, improvement ranging between 62 and 76% can be achieved (7). Although metoclopramide was found to be the second most common drug after haloperidol to cause TDD (8), according to newer data, the risk for the occurrence of TDD after metoclopramide

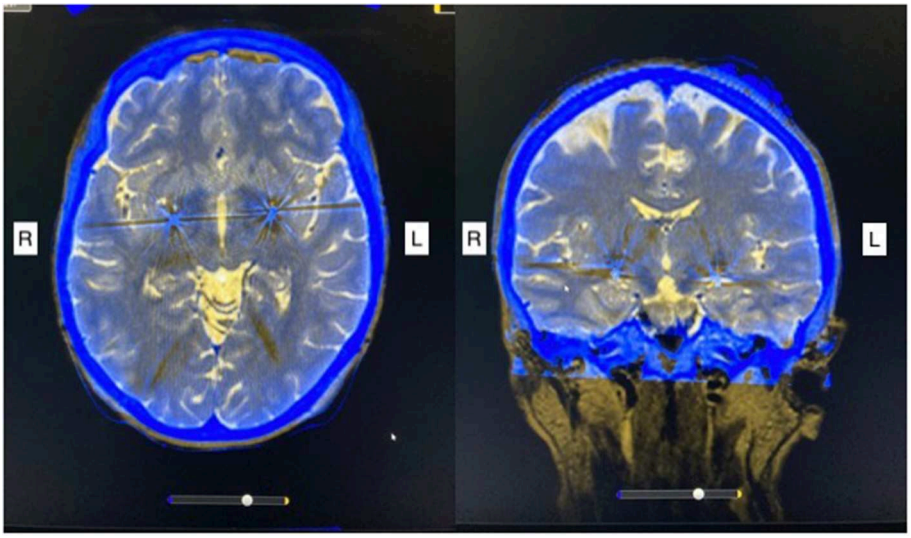

FIGURE 1
Post-operative stereotactic CT imaging fused with preoperative MRI scan shows bilateral electrode placement in the posteroventral lateral globus pallidus internus. R, right; L, left.

TABLE 1 Stimulation settings at discharge, 20 months post-surgery, and 9 years post-surgery.

Time point	Stimulation site	Active contacts	Amplitude	Pulse width	Frequency
At discharge	R GPi	1 (–), 2 (+)	4.8 V	210 μs	130 Hz
	L GPi	10 (+)	2.5 V	240 μs	130 Hz
20 months post-surgery	R GPi	0 (–), 1 (–), 2 (–)	1.1 V	450 μs	125 Hz
	Interleaving	3 (–)	2.3 V	450 μs	125 Hz
	L GPi	10 (–), 11 (–)	1.8 V	450 μs	125 Hz
	Interleaving	8 (–), 9 (–)	1.7 V	450 μs	125 Hz
9 years post-surgery	R GPi	0 (–), 1 (–), 2 (–)	1.2 V	450 μs	125 Hz
	Interleaving	3 (–)	4.3 V	450 μs	125 Hz
	L GPi	10 (–), 11 (–)	3.3 V	450 μs	125 Hz
	Interleaving	8 (–), 9 (–)	1.8 V	450 μs	125 Hz

At 20 months post-surgery, the stimulation was switched to an interleaving program. Contacts were named 0–3 on the right hemisphere and 8–11 on the left hemisphere with contacts 0 and 8 as the most ventral contacts.
GPi, globus pallidus internus.

intake might have been overrated. A recent review found the risk of TDD under metoclopramide medication to be around 0.1% per 1,000 patient-years (9). Nevertheless, the FDA recommends that the chronic use of metoclopramide medication should be avoided.

Tardive dystonia/dyskinesia has been reported to respond well to pallidal DBS yielding a 76% improvement of the BFM at a mean follow-up of 25.6 months according to a recent meta-analysis (7). In a multicenter randomized controlled trial, dystonia severity had improved significantly by 23% at 3 months of chronic stimulation and by 42% at 6 months with infrequent and transient side effects (6). However, it has been problematic that the degree of response to pallidal DBS varies widely in patients with TDD (11), possibly due to causative drug. Those studies including patients with metoclopramide-induced TDD showed better results on short-term (56% improvement in BFMDRS at 3 months and 40% on the ESRS) and long-term follow-up, ranging between 60 and 83% (5, 6). However, our patient improved even better in short term (71% improvement in BFMDRS at discharge and 96% improvement at 1-year follow-up as compared to baseline).

Our case also demonstrates that the beneficial effects of pallidal DBS in metoclopramide-induced TDD can be sustained

in the long term. Thus far, only summarized data of a total of three patients with metoclopramide-induced TDD have been reported in two previous series on pallidal DBS for TDD. The mean improvement of TDD in a series of 19 patients including two patients with metoclopramide-induced TDD reported by Pouclet-Courtemanche et al. (5) at 12 months of chronic DBS was 58% on the Extrapyramidal Symptoms Rating Scale (ESRS). The third patient, reported in the series of Gruber et al. (3), also benefitted from stimulation and experienced a rapid worsening of symptoms by 80% when stimulation was turned off. Again, no detailed information is available on the clinical improvement in this patient, but the overall improvement in this series was 59% on the BFMDRS at the last follow-up (3). Notably, all patients who underwent pallidal DBS for metoclopramide-induced TDD were female. They had received metoclopramide for the duration of several months up to 4 years before the development of TDD (5, 6).

It is noteworthy that the patient presented with right foot involvement, as tardive dyskinesias usually manifest in the face, head, and upper extremities (12, 13). Lower extremity involvement is more typical in genetic dystonias (14). Since the patient did not undergo genetic testing and also Levodopa was not tried to exclude L-Dopa-responsive dystonia, an additional underlying genetic cause, even if rare, cannot be completely excluded. However, the clinical presentation of the patient does not coincide with the phenotypes of the more common genotypes of dystonia. A limitation of this and also of the previous case reports that underwent DBS is the lack of information on the exact dosages and duration of medications, including the dose of metoclopramide. Other authors, however, had communicated that the risk for the development of tardive dystonia/dyskinesia is given, when the oral dose exceeds 10 mg 3–4 times daily (9, 15, 16).

Another remarkable finding in our patient, besides the peculiar dyskinesias of the scalp muscles, was the early response to pallidal DBS concerning mainly the phasic elements of dystonia. We demonstrated a major short- and long-term improvement of metoclopramide-induced TDD under pallidal DBS. However, experience with the effects of pallidal DBS in metoclopramide-induced TDD is needed. The limited data which are available, however, may suggest that these patients respond particularly well to chronic stimulation.

Data availability statement

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

Ethics statement

Ethical review and approval was not required for this case report in accordance with the local legislation and institution requirements. The patient provided written informed consent for the use of anonymized data for research purposes and for publication of any potentially identifiable images or data included in this article.

Author contributions

JN: data and material collection in research project and writing, review, and editing of the manuscript. JG: concept and data and material collection in research project and writing, review, and editing of the manuscript. JR and MW: data and material collection in research project and review and editing of the manuscript. JK: concept, supervision, data and material collection in research project, and review and editing of the manuscript. 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.

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A homozygous *PRKN*-associated juvenile Parkinson's disease with pregnancy in China

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Background: Although Parkinson's disease (PD) is the second most common neurodegenerative disorder, pregnancy in patients with PD is a relatively rare occurrence because the most common age of onset of PD is beyond the childbearing age, except in patients with Young-Onset PD (YOPD) caused by parkin RBR E3 ubiquitin protein ligase (*PRKN*) mutations.

Case: In this study, we report the case of a 30-year-old Chinese woman who was affected by *PRKN*-associated YOPD and was treated with levodopa/benserazide during pregnancy. She gave birth to a healthy baby boy with an Apgar score of 9 through an uncomplicated vaginal delivery.

Conclusion: This case further suggests that levodopa/benserazide during pregnancy is safe in the treatment of *PRKN*-associated YOPD.

KEYWORDS

Parkinson's disease, young-onset PD, pregnancy, *PRKN* gene, levodopa/benserazide

Introduction

Parkinson's disease (PD), first described by James Parkinson in 1817, is the second most common neurodegenerative disease after Alzheimer's disease, caused by the degeneration of dopaminergic neurons in the substantia nigra pars compacta of the midbrain (1). The main motor symptoms of PD include resting tremors, bradykinesia, rigidity, and postural instability, as well as a wide range of non-motor symptoms such as autonomic, sensory, sleep, and neuropsychiatric dysfunctions (2). PD is a geriatric disease affecting more than 1% of individuals aged 55 years and more than 3% of individuals aged 75 years and over, with the average age of the onset of PD being 60 years (3, 4). Only ∼5% of patients diagnosed with PD are below 40 years of age (3–6).

The etiology of PD, which is heterogeneous, multifactorial, and often complex, is as elusive as it was first described in 1817. Recent epidemiologic studies from around the world indicated that genetic risk factors are involved in the pathogenesis of PD. Genetic studies reported that mutations in α-synuclein (SNCA; *PARK1*) and leucine-rich repeat kinase 2 (LRRK2; *PARK8*) result in autosomal dominant PD, and mutations in parkin RBR E3 ubiquitin protein ligase [*PRKN*; parkin (*PARK2*)], DJ-1 [Parkinson protein 7 (*PARK7*)], and PTEN-induced putative kinase 1 (PINK1; *PARK6*) result in autosomal recessive PD (4, 7–9). *PRKN* gene (*PARK2*) mutation was initially reported in a sample of Japanese families with juvenile parkinsonism and was the most common cause of autosomal recessive PD, which was located on Chromosome 6 and was particularly prevalent in women with Young-Onset PD (YOPD), with the onset of PD before the age of 30 years (7, 8, 10). Therefore, there is a possibility that after diagnosis with *PRKN*-associated YOPD, a woman could become pregnant (3–5). However, in all cases of PD, mutations in these genes may result in fewer than 5% of cases (7). Pregnancy in patients with PD may be an uncommon occurrence (6), and in patients with *PRKN*-associated YOPD, it is even more uncommon. The question of how to manage these two situations is critical to

the health of both mothers and children. However, information on the clinical experience of pregnancy management in patients with PD is limited to case reports only. To our knowledge, there has never been a report demonstrating the effect of autosomal recessive *PRKN* mutations on pregnancy in Chinese individuals with YOPD. In the present study, we describe the case of a Chinese woman with YOPD associated with a homozygous mutation of the *PRKN* gene treated with low-dose levodopa/benserazide during her pregnancy. Through this case, we hope to guide neurologists and movement disorder experts to understand pregnancies in patients with PD better to ensure the best treatment for both mothers and children.

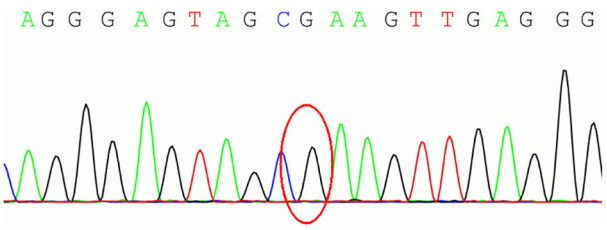

FIGURE 1
The homozygous mutation of p.G284R (chr6-162,206,825, c.850G > C) in exon 7 of parkin RBR E3 ubiquitin protein ligase (*PRKN*).

Case report

We report the case of a 36-year-old Chinese woman with an 18-year history of PD. The extrapyramidal diseases were negative in her family history, but her parents had a consanguineous marriage (Her mother's grandmother and her father's great-grandfather were shared parents). There was no history of drug, alcohol or tobacco consumption, poisoning, or head injury. Her symptoms started at the age of 18 years with a slow progression, and resting tremors, bradykinesia, and rigidity developed later. Her initial symptom was dystonia of the left lower limb, which was characterized by the toes being stiff and flexed during walking. She was diagnosed with dopamine-responsive dystonia at the age of 24 years and given levodopa/benserazide (50/12.5 mg/day) treatment, and consequently, she obtained considerable therapeutic benefit. Her symptoms improved significantly and progressed slowly, she did not return to the department for further consultation, and she self-adjusted her medications according to her symptoms.

At the age of 30 years, she was confirmed as being pregnant and referred to our department. Her motor symptoms were well-controlled by taking levodopa/benserazide 100/25 mg two times a day. The neurological examination revealed clear symptoms of PD ("off" periods), including mild hypomimia, mild rigidity of the bilateral limbs, bradykinesia, resting tremor (predominant on the left), and dystonic posture of her left leg. Other neurological examinations were normal. Her total score on the Unified Parkinson's Disease Rating Scale motor section (UPDRS III) was 16, and the Hoehn and Yahr (H-Y) staging was II. Her laboratory results (including routine blood examination, ceruloplasmin, and thyroid-related hormones) and the brain magnetic resonance imaging (MRI) findings were normal. According to the Movement Disorder Society's clinical diagnostic criteria for PD, the patient was diagnosed with PD.

During the first trimester of her pregnancy, her PD symptoms were similar to the preconception period. However, in gestation week 16, the patient refused to continue taking levodopa/benserazide because her PD symptoms improved for no apparent reason, with the UPDRS III being 6. At 32 gestational weeks, she gave birth to a healthy baby boy with an Apgar score of 9 through an uneventful vaginal delivery without complications. The infant was fed milk formula to avoid exposure to antiparkinsonian (anti-PD) drugs. Two weeks after her pregnancy, the PD symptoms of the patient became aggravated; therefore, she continued to take levodopa/benserazide (100/25 mg two times a day) and achieved a good curative effect. The child was followed up for 6 years, and his general neurological examination and the routine blood tests were normal.

To further define the diagnosis and identify the causative variant, at the age of 34 years, we recommended complete exome sequencing monitoring of the patient and her parents. Genomic DNA was extracted from the peripheral blood leukocytes using standard procedures. High-throughput sequencing and exon capture technology were performed. A homozygous mutation of p.G284R (chr6-162,206,825, c.850G > C) in exon 7 of *PRKN*, which was inherited from her unaffected father and mother, was detected. The sequencing results are shown in Figure 1. This mutation was demonstrated to be a pathogenic mutation for PD. All these results confirmed the diagnosis of autosomal recessive YOPD due to the *PRKN* homozygous mutation. At present (age 36 years), the patient is taking rasagiline 1 mg/day, in addition to levodopa/benserazide 100/25 mg two times a day, and her neurological status is currently stable. To show the patient's onset and treatment process more intuitively, an illustration of this patients clinical history has been drawn and is shown in Figure 2.

Discussion

The incidence of pregnancy during PD is unknown. PD is a disease that mostly affects older individuals. Thus, pregnancy in PD is uncommon, especially in patients with YOPD caused by *PRKN* mutations. In this study, we report for the first time a Chinese woman who was diagnosed with sporadic YOPD associated with a compound heterozygous mutation of the *PRKN* gene. She was treated with low-dose levodopa/benserazide during pregnancy and later gave birth vaginally to a healthy baby boy.

The etiology of PD is heterogeneous, multifactorial, and usually complex. For many years, PD has been considered to be caused by environmental factors. However, growing research shows that genetic factors seem to play a role in at least a subset of PD patients (7). *PRKN* gene (*PARK2*) mutations are the most common cause of autosomal recessive PD, especially prevalent in patients with PD, with onset before the age of 30 years. The gene located on Chromosome 6 was first identified in a sample of Japanese families with juvenile Parkinsonism (8, 10). To date, more and more allele variants of the gene, including point mutation and exon rearrangements (such as deletion or duplication), have been found, which complicate Parkinson genotyping (10–12). In 2000, Lucking et al. performed a study to analyze 73 families and found that mutations in the *parkin* gene were detected in 36 out of 73 families. This study also indicated that *parkin* gene mutation was the main cause of

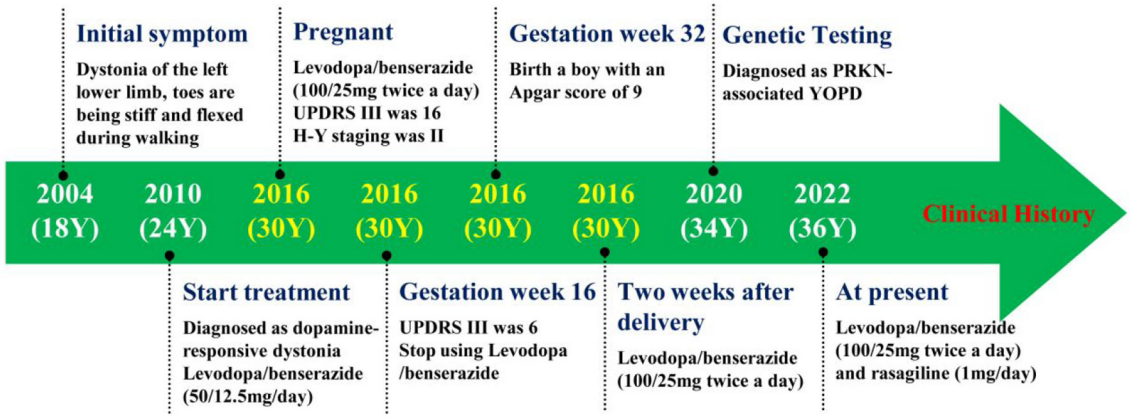

FIGURE 2
The figure showing the patient's clinical history. Y, years old; UPDRS III, Unified Parkinson's Disease Rating Scale motor section; H-Y, Hoehn and Yahr; YOPD, Young-Onset Parkinson's Disease.

early onset of autosomal recessive familial PD and isolated juvenile-onset PD (≤20 years old) (13). Since the first gene of PD was discovered 25 years ago (10, 14), more and more PD-related genes have been discovered. Therefore, in the clinical study, we recommend that genetic testing should be carried out for YOPD, hereditary or abnormal parkinsonian disorders, to perform a clear diagnosis.

At present, the pathogenesis of the *PRKN* gene lacks clarity. The *PRKN* gene could encode the Parkin protein. It is an E3 ubiquitin ligase protein that plays an important role in the normal functioning of the mitochondria and the ubiquitin–proteasome system. It can catalyze the transfer of ubiquitin to its specific target protein, guide protein degradation in the proteasome, and prevent cell apoptosis. The mutation of *PRKN* leads to a loss or decrease in the function of Parkin protein and destroys the activity of E3, thus increasing the risk of PD (7, 8).

The phenotypes of *PRKN* mutation are as follows: (1) The patient's age at the onset of the disease is early, mostly around 30 years. (2) It has typical PD features. (3) Dystonia is often symmetrical and more common. (4) Disease progression is slow. (5) An excellent response with levodopa was noted, but with frequent complications (levodopa-induced dyskinesia and fluctuation). (6) Cognitive impairment is rare (7, 8). In this case, the age of the onset of PD symptoms was 18 years, and the initial symptom was dystonia of the left lower limb. She responded excellently to levodopa and made slow progress. At present, although she has been suffering from this disease for the past 18 years, she only requires a low-dose of levodopa/benserazide to maintain a normal life without any cognitive impairment. It is consistent with the theory that the *PRKN* gene causes autosomal recessive juvenile PD.

The literature analyzing the effect of pregnancy on the motor symptoms of PD is controversial (6). Some studies indicated that pregnancy worsens the clinical symptoms of patients (15–17), but other reports showed that patients' symptoms remained stable (17, 18) or that the patients even displayed improvement in PD symptoms throughout (8, 19). The physiological mechanism of pregnancy leading to a change in symptoms is still complex. Several theories on worsening symptoms during pregnancy were proposed, including (1) the natural progression of PD; (2) the patient's plasma volume, the volume of distribution, diet, intestinal absorption, and metabolic state being altered during pregnancy (20); (3) the changes in physiological and psychological stress during pregnancy; and (4) changes in estrogen levels (6). The symptoms experienced by the patient improved during pregnancy, and she even stopped levodopa/benserazide. This improvement in the patient's symptoms may be related to an increase in the estrogen level in her body during pregnancy. Animal models suggest that estrogen has a neuroprotective effect on the dopaminergic neurons (21). Several epidemiologic studies suggest that estrogen has a protective effect on PD (6, 21–23). However, several population studies suggest that there is no link between estrogen exposure and the risk of PD (24, 25). Some studies even suggest that estrogen exposure increases the risk of PD (26). Therefore, the role of estrogen in the risk of PD is ambiguous.

Experience in the use and safety of anti-PD medication during pregnancy in patients with PD is minimal and limited to case reports and small case series. The main focus of the management of pregnancy in patients with PD is the safety of anti-PD medication on the fetus. Owing to the lack of human or animal evidence on their effects on fetal development, all anti-PD medications are contraindicated during pregnancy (27, 28). Undoubtedly, levodopa is the most effective drug for PD, and it also has the most widespread use and acceptance during pregnancy. Many studies used levodopa alone or in combination with dopa-decarboxylase inhibitors (carbidopa or benserazide) to treat PD during pregnancy. Studies showed that levodopa can cross the placenta and be metabolized by the fetus, but carbidopa and pheniramine do not cross the placenta or enter fetal circulation (29). Although some animal studies demonstrated that the levodopa treatment does not affect the pregnancy or the fetus, during levodopa monotherapy or dopamine decarboxylase therapy, however, two cases of early pregnancy miscarriage (30, 31) and one case of fetal osteomalacia (32) were reported. However, two reports published earlier indicated that no teratogenic effect was reported in seven cases of levodopa used as monotherapy (33, 34). In Mara Seier's review from 2017, who analyzed 114 pregnancies (47 women with PD and 67 other disorders) exposed to levodopa, the results showed that levodopa

did not increase the rate of miscarriage, birth complications, or teratogenicity during pregnancy (6). In our case, the patient continued to take levodopa/benserazide during pregnancy, and her symptoms remained stable or even improved. Although the baby was born through premature delivery, the reason for this premature delivery was considered to be due to cervical incompetence. Finally, the woman and the baby did not have any complications, which further proved that levodopa combined with dopamine carboxylase was relatively safe.

Although ergot-derived dopamine agonists (cabergoline, bromocriptine, and diuretic) have been used for the treatment of infertility in women with hyperprolactinemia for decades, there is little evidence to suggest that dopamine agonists are used in pregnancy to treat women with PD. Seier et al. (6) summarized 14 cases of pregnancy of individuals with PD who were exposed to dopamine agonists: three were exposed to pramipexole, three were exposed to ropinirole, five were exposed to bromocriptine, two were exposed to cabergoline, and one was exposed to pergolide. In these 14 cases, no teratogenicity was reported but one baby had a seizure shortly after birth but with subsequent normal development, and one placental abruption did occur (6). Based on these data, it is not enough to recommend the routine use of dopamine agonists during pregnancy. In animal and human studies, amantadine is associated with teratogenicity and increases the risk of pregnancy complications and malformations (35–37). Therefore, amantadine should be avoided during pregnancy. Other anti-PD medications, including anticholinergics, catechol-O-methyltransferase (COMT) inhibitors, and monoamine oxidase-B (MAO-B) inhibitors, are rarely used as monotherapy or alone with levodopa or combined with dopamine decarboxylase inhibitors during pregnancy, and adverse effects on fetal development have been reported.

Conclusions

We reported the case of a Chinese woman who was diagnosed with YOPD, with homozygous *PRKN* mutation, and who received levodopa/benserazide treatment during pregnancy. Although the patient stopped levodopa/benserazide due to an improvement in PD symptoms during pregnancy, we believe that levodopa/benserazide is safe for the treatment of patients with *PRKN*-related PD during pregnancy. More data on the safety of anti-PD drugs used in PD treatment and the impact of pregnancy on parkinsonian symptoms are needed. Obstetricians and neurologists need to learn how to manage pregnancy in patients with PD to ensure optimal maternal and infant outcomes.

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. The patients/participants 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.

Author contributions

H-xL was responsible for drafting and revision of the manuscript. MD and KZ were responsible for the revision of the manuscript. X-xP, Y-zL, HW, CL, and Y-yD were responsible for collecting the data. H-xL and QZ were responsible for the concept and revision of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

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Deep brain stimulation in posterior subthalamic area for Holmes tremor: Case reports with review of the literature

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Background: Holmes tremor (HT) is a refractory tremor associated with cortico-basal ganglia loops and cerebellothalamic tract abnormalities. Various drug treatments have been attempted; however, no treatment method has yet been established. Historically, thalamic deep brain stimulation (DBS) has been performed in medically refractory cases. Recently, the posterior subthalamic area (PSA) has been used for HT. Here, we report cases of HT and review the effectiveness and safety of PSA-DBS for HT.

Cases: We conducted a retrospective chart review of two patients with HT who underwent PSA-DBS. Improvement in tremors was observed 1 year after surgery without apparent complications.

Literature review: We identified 12 patients who underwent PSA-DBS for HT, including our cases. In six patients, PSA was targeted alone; for the rest, the ventralis intermediate nucleus (Vim) of the thalamus and PSA were simultaneously targeted. The Fahn–Tolosa–Marin Tremor Rating Scale improvement rates were 56.8% (range, 33.9–82.1%; $n = 6$) and 77.8% (range, 42.6–100%; $n = 5$) for the PSA-DBS and PSA+Vim-DBS, respectively.

Conclusion: Reasonable improvements in HT were observed after PSA-DBS. PSA might be an appropriate target for improving the symptoms of HT. Long-term observations, accumulation of cases, and randomized studies are required in future.

KEYWORDS

deep brain stimulation, posterior subthalamic area, cortico-basal ganglia loops, cerebellothalamic tract, Holmes tremor (HT)

Background

Holmes tremor (HT) is a slow below-4.5-Hz tremor observed during rest, action, and posture and was first reported by Holmes (1). HT is clinically defined in the recent consensus of the Movement Disorder Society as the presence of resting, postural, and intention tremors with tremor frequency below 4.5 Hz and onset with a variable delay between lesion occurrence and the first appearance of symptoms (2). The cortico-basal ganglia (BG) loop and the cerebellothalamic tract are suspected anatomical causative sites (3, 4). It has various causes, including cerebrovascular accidents, trauma, demyelinating diseases, and malignant tumors (5). Various medical and surgical treatments, including deep brain stimulation (DBS), have been attempted, but effective methods have not yet been established (6). We report two HT cases and compare them with previous cases to evaluate the efficacy and safety of DBS of the posterior subthalamic area (PSA) for HT.

Case reports

Case 1

An 18-year-old man with a Korean father and a Japanese mother visited our hospital due to a 3-year history of right-hand tremors owing to a brain hemorrhage. The initial symptom was right-sided ataxic hemiparesis at the age of 15 years. He had no previous medical history, and the workup identified any cause of the hemorrhage. A right-sided tremor developed 3 months after the onset of the hemorrhage. He presented with a 4–5 Hz tremor in his right hand and lip during rest, posture, and movement. Brain magnetic resonance imaging (MRI) revealed an old hemorrhage from the posterior limb of the left internal capsule to the midbrain and left cerebellar peduncle and pseudohypertrophy of the inferior olivary nucleus (Figure 1A). A dopamine transporter scan [iodine-123 fluoropropyl carbomethoxy-3 beta-4-iodophenyltropane (^{123}I-FP CIT)] revealed the absence of radiotracer activity in the left caudate and putamen. Clonazepam (0.5 mg/day), zonisamide (100 mg/day), and primidone (25 mg/day) were administered and showed a limited effect; however, these were discontinued owing to nausea. The levodopa challenge test (100 mg, intravenous) revealed no improvement in the Fahn–Tolosa–Marin Tremor Rating Scale (FTM-TRS) motor score, which was 62 (7). The patient decided to undergo DBS, and the left PSA was chosen as the target following an interdisciplinary team discussion. It was confirmed that the hemorrhage did not distort the anatomy of the target area (Figure 1A). Mapping and trajectory planning were performed with volumetric MRI using the Stealth Framelink^{TM} (Medtronic Japan) software. Permanent stimulating electrodes of the Vercise Cartesia^{TM} Directional Lead DBS system (Boston Scientific, USA) were implanted. The PSA target was identified using MRI as the white-matter region located outside the outermost edge of the red nucleus and posterior medial to the subthalamic nucleus (6 mm posterior, 5.5 mm inferior, and 8 mm lateral to the midcommissural (MC) point). Intraoperative macrostimulation showed that tremor was significantly improved by stimulus settings of (2–4)(–)Case(+), 2.0 mA, 60 μs, and 130 Hz. Subsequently, Vercise Genus R16 IPG^{TM} (Boston Scientific, USA) was implanted in the chest under general anesthesia. Brain CT revealed that the electrode was correctly placed in the target area, and analysis of the postoperative CT fused with preoperative MRI showed that the tip of the lead was at the coordinates of 6.8 mm posterior, 7.6 mm inferior, and 7.0 mm lateral to the MC point (Figure 1B). The patient presented with no postoperative side effects and showed improvement in his right arm tremors at rest, posture, and movement, even in the stimulation-off state. A monopolar review was performed when the stimulation was initiated 1 week after surgery, and it revealed that contacts 2–4 were the best contacts. Then, the horizontal directional steering found that the stimulation of contacts 4 and 7 worsened dysarthria, whereas stimulation of contacts 2 and 5 improved dysarthria. Then, stimulation was initiated with the following settings: (2–4)(–)Case(+), 0.5 mA, 60 μs, and 130 Hz. The tremor was further improved, and at 1-month evaluation post-surgery, the FTM-TRS motor score was 37 with increasing stimulation amplitude to 1.6 mA. Subsequently, the stimulation frequency was increased to 170 Hz, owing to insufficient efficacy, which was inferred to be caused by the decrease in the micro-lesioning effect over time. As the therapeutic effect was satisfactory, the stimulation intensity was reduced to 1.2 mA. At the 1-year evaluation after surgery, the motor score of FTM-TRS improved to 27 with stimulation settings of (2–4) (–) Case (+), 1.2 mA, 60 μs, and 170 Hz. After the 1-year evaluation, the horizontal directional steering was applied with stimulation settings of (2: 80%, 3:20%, 4:20%) (–) Case (+), 1.2 mA, 60 μs, and 170 Hz because the patient complained of dysarthria.

Case 2

A 52-year-old Japanese man was referred to our hospital because of action and resting tremor in his right hand, which developed 1 year after the onset of right-sided hemiparesis and dysarthria due to left hypertensive cerebral hemorrhage at the age of 49. The tremor gradually worsened, and palatal and pharyngeal tremors developed. Levodopa/benserazide (450 mg/75 mg/day) and clonazepam (1 mg/day) were previously tested but showed minimal improvement in symptoms. He presented with a slow 4–5 Hz tremor on his soft palate, pharynx, and left-dominant upper and lower limbs during rest, posture, and movement. Brain MRI revealed an old hemorrhage from the midbrain to the pons and pseudohypertrophy of the inferior olivary nucleus (Figure 1C). A dopamine transporter scan (^{123} I-FP-CIT) revealed the absence of radiotracer activity in the left caudate and putamen. Zonisamide (200 mg/day) and primidone (250 mg/day) were initiated and showed limited improvement and they were discontinued owing to somnolence. The patient decided to undergo DBS for bilateral PSA. At that time, the motor score of the FTM-TRS was 56. The Vercise Cartesia^{TM} Directional Lead DBS system was implanted into the target. The PSA target was defined using MRI similar to case 1, and the coordination of the target was 7.5 mm posterior, 5.5 mm inferior, and 10.75 mm lateral to the MC point on the left side and 7 mm posterior, 5.5 mm inferior, and 11 mm lateral to the MC point on the right side. Intraoperative macrostimulation revealed that tremor was improved by a stimulus of (5–7)(–)Case(+), 3.0 mA, 60 μs, and 130 Hz on both sides. After the implantation of the

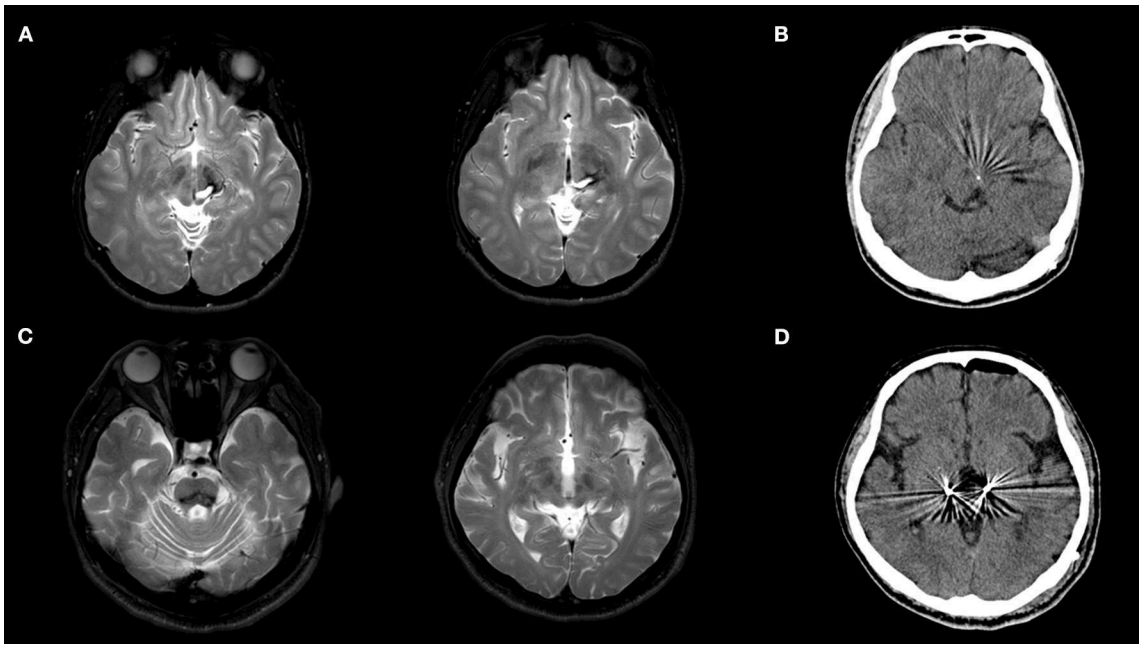

FIGURE 1
(A) Brain MRI showed an old hemorrhage in patient 1. **(B)** Postoperative CT showed the electrode was precisely implanted in the PSA in patient 1. **(C)** Brain MRI showed the old hemorrhage in the pons in patient 2. **(D)** Postoperative CT showed the electrodes were precisely implanted in the PSA in patient 2.

DBS lead, Vercise Genus R16 IPG^{TM} (Boston Scientific, USA) was implanted in the chest under general anesthesia. Brain CT revealed that the electrode was placed in the target area, and analysis of the postoperative CT fused with preoperative MRI showed that the tip of the lead was at the coordinates of 8.1 mm posterior, 7.2 mm inferior, and 10.0 mm lateral in right and 8.2 mm posterior, 7.3 mm inferior, and 10.0 mm lateral in left to the MC point (Figure 1D). Stimulation was started 1-week after surgery, and with increasing stimuli, the upturning of the eyeball was noted as a side effect. Therefore, directional stimulation was used to prevent oculomotor involvement. The stimulation settings were adjusted as follows: 1(−)8(+), 4.0 mA, 50 μs, and 185 Hz on the left side; and 1(−)8(+), 6.5 mA, 40 μs, and 185 Hz on the right side, and zonisamide was reduced to 100 mg/day. At 1-month postoperative evaluation, a motor score of FTM-TRS score was 44 and the pulse width was increased to 50 μs on the right side, owing to inadequate effectiveness. At the 1-year postoperative evaluation, the motor score of FTM-TRS remained at 37 without side effect.

Literature review

To investigate the relationship between HT and PSA-DBS, we reviewed published scientific reports using the PubMed database. The keywords used were "Holmes tremor," "Rubral tremor," or "midbrain tremor," "deep brain stimulation," and "posterior subthalamic area" or "caudal zona incerta." In addition, the references of the included articles were screened for eligible studies. Only studies published in English between 2006 and 2021 that examined the association between HT and PSA-DBS were reviewed. Of the four records identified, three were included in the review. Two additional articles were identified by screening their references. A total of five studies along with our study were included in the review (Table 1) (8–12). We identified 12 patients who underwent PSA-DBS, including our patients. In six patients, PSA was targeted alone, and in the rest, both ventralis intermediate nucleus (Vim) and PSA were targeted. The period from disease onset to surgery was 1–39 years old. The mean age at the time of surgery was 18–84 years. The average FTM-TRS improvement rates were 56.8% (range, 33.9–82.1%; $n = 6$) in the PSA group and 77.8% (range, 42.6–100%; $n = 5$) in the PSA+Vim group.

Discussion

Historically, Vim has been reported as a target for HT in stereotactic surgery (13–22). Subsequently, other targets, such as ventralis oralis posterior (14), ventralis oralis anterior (23), prelemniscal radiation (24), pallidotomy (25, 26), subthalamic nucleus (4), caudal zona incerta (Zi) (12), and globus pallidus internus (GPi) (27–29), have been reported. A previous systematic review compared GPi-DBS ($n = 21$) and Vim-DBS ($n = 37$) for HT and reported that GPi-DBS was more effective in suppressing tremors. Moreover, the study also compared the benefits among patients treated with multiple targets (two or three) vs. a single target; however, no significant difference was noted. It was speculated that GPi-DBS provides more robust tremor suppression because of stimulation involved in the BG-thalamocortical circuit (30). In this context, the stimulation of the ventralis oralis may be effective in suppressing the pallidal receiving area (15, 31).

TABLE 1 Clinical outcomes of PSA-DBS for HT.

References	Pt	Sex	Etiology of HT	Duration of HT, y	Age at DBS, y	DBS target	FTM-TRS motor score				SE
							Pre-DBS	1 m after DBS	12 m after DBS	Imp 12 m after DBS, %	
Our cases	1	M	CH	6	21	Lt PSA	62	37	27	56.4	Dysarthria
	2	M	CH	1	52	Bil PSA	56	44	37	33.9	Upturning of the eyeball
Dec-Cwiek et al. (8)	1	M	MS	10	38	Lt PSA + Bil Vim	54	-	31	42.6	Dysarthria
	2	F	CI	39	50	Lt PSA	39	-	7	82.1	None
	3	M	CI	1	48	Lt PSA	36	-	15	58.3	None
Yuk et al. (9)	1	M	CH	1	55	Rt PSA	47	39	30	36.1	None
Kobayashi et al. (10)	1	F	CH/tumor	6	19	Rt PSA + Vim	12	-	0	100	None
	2	M	CI	3	67	Lt PSA + Vim	17	-	3	82.4	None
	2	M	CH	1	44	Rt PSA + Vim	22	-	5	77.2	None
	3	M	Trauma	2	18	Rt PSA + Vim	15	-	2	86.7	None
O'Shea et al. (11)	1	F	CI	1	62	Rt PSA + Vim	-	-	-	-	None
Plaha et al. (12)	1	M	-	6	84	Bil PSA	50	-	13	74	Dysphasia

We have identified 12 patients with PSA-DBS, including our cases. Six cases targeted PSA alone, and five targeted both Vim and PSA. Pt, patient; HT, Holmes tremor; DBS, deep brain stimulation; y, year; m, month; imp, improvement; SE, side effect, CH, cerebral hemorrhage, CI, cerebral infarction; MS, multiple sclerosis; M, male; F, female; Lt, left; Rt, right; Bil, bilateral; PSA, posterior subthalamic area; Vim, thalamic ventral intermediate.

However, the best DBS target for HT has not been established due to the small number of cases. Table 2 shows the available literature on previous stereotactic targets for HT. The variability of the study period and the evaluation methods among studies made it difficult to directly compare the effect of each target. Recently, PSA has emerged as an alternative target for tremor treatment (32–34). The PSA is located anterior to the medial colliculus, lateral to the red nucleus, and posterior to the subthalamic nucleus and includes the Zi. PSA involves the pallidothalamic and cerebellar-thalamic tracts, descending fibers, and dentate-rubro-thalamic tract (DRTT) (35). PSA-DBS directly affects DRTT and pallidothalamic tract and has effects on tremors (36). A randomized, double-blind study confirmed that no differences between Vim and PSA related to the side effects of stimulation exist and that PSA-DBS can achieve the same level of efficacy with a lower stimulation amplitude in essential tremors (37). Several studies have reported PSA as a DBS target for HT (8–12). In some cases, PSA is chosen as an additional target, in addition to Vim. Dec-Cwiek et al. reported PSA-DBS performed in three patients with HT. The Vim+left PSA was selected as the target in one patient, and only the left PSA was selected in two patients. After 12 months of follow-up, the bilateral Vim+left PSA case showed a 42.6% improvement in motor score of FTM-TRS compared to the baseline, while left PSA cases showed an improvement of 82.1 and 58.3%. The left PSA+bilateral Vim cases developed dysarthria as a stimulus-induced side effect (8). Yuk et al. reported a case of right-sided PSA-DBS in a patient with HT with a 36.1% improvement in motor score of FTM-TRS (9). O'Shea et al. reported a case of right-sided PSA+Vim-DBS for HT; however, both the frequency and amplitude of tremor improved 2 weeks after surgery (11). Plaha et al. reported a case of bilateral PSA-DBS for HT with a 74.0% improvement in motor score of FTM-TRS at 1 year after surgery (12). Kobayashi et al. reported the efficacy of dual electrodes inserted into the Vim and PSA of four patients with HT. In one patient, the tremor disappeared after DBS surgery, and no symptoms were observed even when DBS was turned off; therefore, a comparison could not be made. The improvement rate of the motor score of FTM-TRS was 86.5% (range, 77–100%) 1 year after surgery. When Vim-DBS and PSA-DBS were compared, the improvement rate of the motor score of FTM-TRS was 62.3% (range, 50–77%) when only the Vim was stimulated and 63.3% (range, 40–100%) when only PSA was stimulated, with no significant difference between the two groups. However, when the Vim and PSA were stimulated simultaneously, the improvement rate was 93.3% (range, 77–100%), showing a predominant increase in the improvement rate. The authors concluded that the stimulation of both targets, instead of PSA or Vim alone, is important (10). Based on the cases from previous literature and our cases, the improvement rates in the motor score of FTM-TRS were 56.8% (range, 33.9–82.1%; $n = 6$) with the PSA and 77.8% (range, 42.6–100 %; $n = 5$) with the PSA+Vim.

TABLE 2 Clinical outcomes of other DBS targets for HT.

References	No. of pt	Scale	DBS target	Improvement	SE	FU period
Foote and Okun (14)	1	FTM-TRS and TDS	Uni Vim	TRS 37%, TDS 80%	None	1 y
Foote et al. (15)	3	FTM-TRS	Uni Vim	51.15% (38.46–66.67)	None	6–12 m
Diederich et al. (16)	2	CGI-global improvement	Uni Vim	Moderate improvement	None	5–7 y
Sanborn et al. (17)	1	CGI-global improvement	Uni Vim	Full tremor suppression	None	2 y
Acar et al. (18)	1	CGI-global improvement	Bil Vim	Moderate improvement	None	3 y
Follett et al. (19)	1	TETRAS	Bil Vim	Significant tremor reduction	None	1 y
Issar et al. (20)	5	FTM-TRS	3 Uni Vim, 1 bil Vim, 1 bil GPi	14–36% in 3 uni Vim	Dystonia in UE, ataxia	2–3 y in 3 uni Vim
Romanelli et al. (4)	1		Uni Vim + STN	Full tremor suppression	None	2 y
Nikkhah et al. (21)	1		Uni Vim	Full tremor suppression	Facial parethesia	6 m
Goto and Yamada (26)	1		Uni Vim DBS and Pallidotomy	Full tremor suppression	None	18 m
Peker et al. (23)	1		Uni Vim, Voa and GPi	Full tremor suppression	None	1.5 y
Martinez et al. (28)	10	FTM-TRS	2 uni Vim, 1 bil Vim, 6 uni GPi, 1 bil GPi	Rest 87.25% (80–100, $n = 9$), posture 100% ($n = 1$), intention 68.89% (55–80, $n = 9$)		2–12 y
Kilbane et al. (29)	4	FTM-TRS	Uni GPi	78.87% (59.9–94.4)	Dysarthria, ataxia	18–52 m
Franzini et al. (22)	9		6 uniVim, 3 bil Vim	>50% reduction in all cases	Dysarthria in 3 bil Vim	8 y
Martinez et al. (24)	1		Uni Raprl	Significant tremor reduction		2 y

No, number; Pt, patient; DBS, deep brain stimulation; FU, follow-up; SE, side effect; FTM-TRS, Fahn–Tolosa–Marin Tremor Rating Scale; Bil, bilateral; y, years; Uni, unilateral; Vim, ventral intermediate nucleus; TDS, tremor disability scores; m, month; CGI, Clinical Global Impression; TETRAS, Tremor Rating Assessment Performance Subscale; Voa, ventralis oralis anterior; Raprl, prelemniscal radiation.

Although the exact mechanism of HT is not known, both the cerebellothalamic pathway and the BG-thalamocortical circuit are thought to contribute to the pathophysiology of HT. PSA may be a relatively versatile target for stimulation that can further stimulate multiple circuits with fewer stimuli because PSA is the site where multiple pathways pass.

Regarding the side effect of PSA-DBS, Barbe et al. reported three events of ataxic gait and four events of dysarthria among 15 patients in a randomized, double-blind, crossover trial (37). The literature review shows similar results (Tables 1, 2). These are similar to Vim-DBS that is estimated to be induced by the stimulation of the same cerebellar connections (37). Owing to their anatomical location, dysarthria and ataxia have been reported as stimulus-induced side effects (37–39). Indeed, in our case, dysarthria was observed but these side effects were successfully managed using bipolar configuration or horizontal directional steering. Therefore, studies of the methods for detecting the more selective and precise target location for PSA-DBS, such as tractography, should be needed.

Our study revealed the efficacy and feasibility of PSA-DBS for HT. There is insufficient evidence to determine the best target among PSA, Vim, and GPi, and whether single or multiple targets should be stimulated for HT. Further prospective trials are required.

Data availability statement

The datasets presented in this article are not readily available because of ethical and privacy restrictions. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Juntendo University School of Medicine. The patients provided their written informed consent to participate in this study. Written informed consent was obtained from the individuals to publish any potentially identifiable images or data in this article.

Author contributions

HK: conception, organization, execution (research project), and writing of the first draft (manuscript preparation). GO, MI, HI, and AU: conception, organization, execution (research project), and review and critique (manuscript preparation). NH: conception, execution (research project), and review and critique (manuscript preparation). All authors contributed to the article and approved the submitted version.

Conflict of interest

GO has received speaker honoraria from Medtronic, Boston Scientific, Otsuka Pharmaceutical Co. Ltd., Sumitomo Dainippon Pharma Co. Ltd., Eisai Co., Ltd., Takeda Pharmaceutical Company Ltd., Kyowa Hakko Kirin Co. Ltd., and AbbVie GK. The Department of Research and Therapeutics for Movement Disorders, Juntendo University Graduate School of Medicine is an endowment department supported by an unrestricted grant from Medtronic and Boston Scientific.

The remaining 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/fneur.2023.1139477/full#supplementary-material

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GPi DBS treatment outcome in children with monogenic dystonia: a case series and review of the literature

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Introduction: Dystonia is the third most common pediatric movement disorder and is often difficult to treat. Deep brain stimulation (DBS) of the internal pallidum (GPi) has been demonstrated as a safe and effective treatment for genetic dystonia in adolescents and adults. The results of DBS in children are limited to individual cases or case series, although it has been proven to be an effective procedure in carefully selected pediatric cohorts. The aim of our study was to present the treatment outcome for 7- to 9-year-old pediatric patients with disabling monogenic isolated generalized DYT-*THAP1* and DYT-*KMT2B* dystonia after bilateral GPi-DBS.

Patients and results: We present three boys aged <10 years; two siblings with disabling generalized DYT-*THAP1* dystonia and a boy with monogenic-complex DYT-*KMT2B*. Dystonia onset occurred between the ages of 3 and 6. Significantly disabled children were mostly dependent on their parents. Pharmacotherapy was inefficient and patients underwent bilateral GPi-DBS. Clinical signs of dystonia improved significantly in the first month after the implantation and continued to maintain improved motor functions, which were found to have improved further at follow-up. These patients were ambulant without support and included in everyday activities. All patients had significantly lower Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) values, indicating >25% improvement over the first 15 months. However, there was a decline in speech and upper limb function, manifesting with bradylalia, bradykinesia, and dysphonia, which decreased after treatment with trihexyphenidyl.

Conclusion: Although reports of patients with monogenic dystonia, particularly DYT-*THAP1*, treated with DBS are still scarce, DBS should be considered as an efficient treatment approach in children with pharmacoresistent dystonia, especially with generalized monogenic dystonia and to prevent severe and disabling symptoms that reduce the quality of life, including emotional and social aspects. Patients require an individual approach and parents should be properly informed about expectations and possible outcomes, including relapses and impairments, in addition to DBS responsiveness and related improvements. Furthermore, early genetic diagnosis and the provision of appropriate treatments, including DBS, are mandatory for preventing severe neurologic impairments.

KEYWORDS

pediatric genetic dystonia, DYT6 gene, *KMT2B* dystonia, GPi-DBS, neurosurgery

Introduction

Dystonia (DYT) is *"a movement disorder characterized by sustained involuntary or intermittent muscle contractions causing abnormal, sustained, often repetitive movements, postures, or both"* (1). Dystonia may be focal, segmental, or generalized, resulting in twisting, sustained, and repetitive postures and movements, with the progressive development of severe motor disability and a negative impact on quality of life (1). The etiology, pathophysiology, and clinical presentation are heterogeneous, ranging from pediatric-onset to adult-onset generalized dystonia, with the possible development of life-threatening dystonic storm. In the last couple of decades, a great number of genes have been identified and linked to different types of dystonia, such as torsin family 1 member A (*TOR1A*) in 1997 [linked to dystonia type 1 [DYT-[*TOR1A*]] and thanatos-associated-domain containing apoptosis-associated protein 1 (*THAP1*) in 2009 [linked to dystonia type 6 with onset occurring usually during childhood or adolescence, including segmental or generalized dystonia with initial craniocervical or laryngeal and upper limb involvement (2–4)]. In addition, since 2016, several mutations in the lysine methyltransferase 2B (*KMT2B*) gene have been identified and linked to progressive childhood-onset dystonia, including development from focal toward generalized dystonia with pronounced craniofacial and laryngeal involvement (5).

Deep brain stimulation (DBS) of the internal globus pallidum (GPi) has been demonstrated as a safe and effective treatment for primary dystonia with a genetic cause, such as DYT-*TOR1A* and DYT-*THAP1* in adolescents and adults (6, 7). The number of adolescents and adults with DYT-*THAP1* dystonia who underwent GPi DBS to date is relatively small. The first published small case series, including several patients, reported only moderate responses to DBS (8, 9). However, medically refractory DYT-*THAP1* cases receiving GPi DBS showed favorable outcomes, more similar to those observed in other isolated dystonias (9–16).

Dystonia is the third most common pediatric movement disorder and is often difficult to treat (17). Coubes et al. were the first to report on the treatment of a child with dystonia using bilateral GPi-DBS (18). In the last decade, a number of reports of DBS in children have been published, showing excellent outcomes for monogenic isolated dystonia DYT-*TOR1A*, as well as the general consensus that DBS is safe and effective in the treatment of adults (7, 19–21). The results of DBS in children are limited to individual cases or case series, although DBS for childhood dystonia has been proven to be an effective procedure in carefully selected pediatric cohorts. Although it is suggested that DBS should be considered as a treatment approach in pharmacoresistent DYT-*THAP1* early in childhood to prevent more severe symptoms, such as disabling motor development and quality of life decline, including emotional and social aspects, the results are missing. Additionally, bilateral GPi-DBS has been reported as a valuable therapeutic option for DYT-*KMT2B*, especially for regaining motor function and mobility, but less so for speech if significant speech difficulties are developed (5, 22–37).

Thus, the aim of our study was to present efficient treatment outcomes of two siblings with DYT-*THAP1* and a boy with DYT-*KMT2B* with disabling monogenic generalized dystonia after bilateral GPi DBS in childhood.

Patients and results

We present three boys: two siblings at the of 9 (patient I) and 7 (patient II) years of age with DYT-*THAP1* and a boy of 7 years of age (patient III) with DYT-*KMT2B* who had DBS implanted.

Case 1

A boy was born after an uneventful pregnancy and birth; both the mother and father were non-consanguineous, with a negative family history for neurologic disorders. His development was normal until the age of three; he became clumsy, with coordination disturbances and lordotic posturing, with hypotonia, torticollis to the right side, and slurred speech. The initial extensive hospital diagnostic investigations excluded structural, infectious, autoimmune, metabolic, chromosomal, and paraneoplastic pathological conditions; however, the diagnosis and etiology remained unknown. No psychiatric or cognitive dysfunctions or disturbances were associated. Over 7 years, the progressive impairment of clinical signs occurred and he developed generalized torsion-type dystonia and became wheelchair-bound. His speech was severely affected as evidenced by slurring, and exhibited upper limb dysfunction with associated dyskinetic movements and tremor. On exam at admission, the boy was not ambulant and had generalized dystonia at rest and during activity, as well as dysphonic and dysarthric speech along with swallowing difficulties (Supplementary Video 1). A dystonia gene panel using PCR amplification and sequence analysis revealed a *THAP 1*, C270_273del (p.glu91ilefs*28) mutation. The patient was treated with clonazepam, trihexyphenidyl, and baclofen, but without meaningful improvement. The Burke–Fahn–Marsden Dystonia Rating Scale-movement scale (BFMDRS-M) was 116 and the BFMDRS-disability scale (BFMDRS-D) was 28 (Table 1).

Case 2

Patient 2, a male sibling of patient I, born after normal pregnancy and delivery. His motor, mental, speech, and cognitive development were normal. He started to walk unassisted at the age of 12 months. At the age of 4.5 years, he manifested with involuntary dystonic movements of the first upper limbs, and afterwards he became clumsy and could not run without frequent falls. On exam, bradylalia and dysarthria were present, with oromandibular dystonia, resulting in scarce verbal response. He could not maintain left side upper and lower extremities in antigravity positions nor walk downstairs without assistance. He also experienced gear phenomenon on lower limbs and waddling gait, absent tendon reflexes of the left side. He gradually developed generalized dystonia manifested at rest and provoked by activity (Supplementary Video 2). No psychiatric or cognitive dysfunction were registered other than slurred speech. A dystonia

TABLE 1 Preoperative characteristics of dystonia patients included in the study.

No.	Gender	Age at disease onset (years)	Initial anatomical distribution	Sequence variant	Preop BFMDRS-M	Preop BFMDRS-D	Preop medication
I	M	3	Upper limb dystonia and slurred speech	THAP 1, C270_273del (p.glu91ilefs∗28)	115	28	Clonazepam, tryhexyphenidyl, and baclofen
II	M	6	Upper limb dystonia and slurred speech	THAP 1, C270_273del (p.glu91ilefs∗28)	96	20	Clonazepam, tryhexyphenidyl, and baclofen
III	M	4.5	Speech developmental delay, anarthria, and lower limb dystonia	KMT2B c.5572dupC; pArg1858Profs ∗ 114	106	22	Valproat, clobazam, ethosuximide, levetiracetam, and petinimid

gene panel revealed a *THAP1*, C270_273del (p.glu91ilefs*28) mutation, the same as in his brother (patient 1). Treatment with trihexyphenidyl, clonazepam, and baclofen was introduced but without clinical significance. The preoperative BFMDRS-M was 96 and the BFMDRS-D was 20 (Table 1).

Case 3

Patient 3, a boy was born after an uneventful pregnancy, with the umbilical cord wrapped around his neck during childbirth. The Apgar score was 9/10 and he was discharged from hospital as a healthy newborn. He started to walk unassisted at the age of 12 months. Pronounced developmental speech delay was significant. At the age of 3, his speech was totally undeveloped and he manifested with anarthria. Motor development except speech was normal until the age of 3.5 years when tremor, chorea, and walking difficulties occurred; his gait became clumsy and ataxic, and he often fell. He could run only backwards with trunk rotation, and manifested occasional jerky arm tremor associated with attention deficit disorder. On exam, thoracic kyphosis, choreoathetoid movements, occasional jerky hand tremor, and coordination disturbances were observed. The patient could not hold extremities in antigravity positions due to muscle weakness. At the time he also manifested with significant speech developmental delay and anarthria. Owing to delayed speech development, EEG was recorded and revealed bilateral multifocal epileptiform discharges. Treatment with antiepileptics, including valproate, clobazam, ethosuximide, levetiracetam and petinimid, was introduced. A brain MRI showed small hypothalamic hamartoma and lipoma, and a conservative approach was suggested. The patient manifested further progressive speech regression, upper limb tremor, bizarre walking patterns, severe hand tremor, and anarthria (Supplementary Video 3). Diagnostic work up except brain MR and EEG was normal (EMNG, VEP and BAER, cerebrospinal fluid, and metabolic analysis), including spinal MRI and brain SPECT. A gene panel for dystonia revealed a pathogenic *de novo* variant in gene *KMT2B* c5572dupC;p.Arg1858Profs*114. The BFMDRS-M was in total 106 and the BFMDRS-D was 22 (Table 1).

All patients underwent bilateral GPi-DBS at the age 7 and 9. After surgical planning using anatomical targeting through preoperative frameless MRI and CT obtained with a mounted Leksell frame (Electa, Stockholm, Sweden) on patients head the electrodes have been implanted bilaterally in GPi (11). In patient I, Activa RC neurostimulator and model 3389 electrodes (Medtronic) were implanted, whereas in patients II and III, the Vercise rechargeable neurostimulator and directional electrodes (Boston Scientific) were implanted. The stimulation started with the following parameters: for patient I an amplitude of 1.9 V, a frequency of 125 Hz, and a pulse duration of 60 μs, and for patient II and III, an amplitude of 2 mA, a frequency of 130 Hz, and a pulse duration of 60 μs. The pulse amplitude was gradually increased over the 6 months following implantation.

On the first follow up, the first patient's signs improved significantly, enabling the patient to sit independently and to walk with the assistance of one person (Supplementary Video 1). In the weeks and months following the DBS procedure, he regained some manual abilities (he became able to write with moderate difficulty), discrete speech improvement was registered (dysarthria and dysphonia were still present and now bradylalia), mobility (he walked with minimal assistance), and could perform basic self-care tasks with some help (feeding, dressing, etc.). In general, his quality of life improved dramatically. The BFMDRS-M decreased to 64 after GPi DBS, and this persisted after more than 2 years of follow up, while the BFMDRS-D decreased to 8 and persisted (Table 2). However, dysphonia, bradykinesia, bradylalia, fatiguability, and dystonic posturing were still present and mildly increased 2 years after implantation.

Twelve months after DBS implantation, patient II had only mild and occasional upper limb dystonia, a stable gait, was able to run fast, had a stronger voice, and had more fluent and understandable speech (Supplementary Video 2). The BFMDRS-M decreased to 50 after GPi DBS, and this persisted after almost 1 year of follow up, while the BFMDRS-D decreased to 9 and persisted (Table 2).

After DBS implantation, only transitory but very discrete speech improvement occurred in patient III (although it was agrammatic and dysphonic), whose upper limb function and gait improved so he was able to walk unaided (Supplementary Video 3). His dystonia was worsened by specific activities (such as running, walking, chewing, swallowing, writing, and less targeting the objects) and he still had some cognitive and behavioral dysfunctions issues. His follow up EEG showed pronounced and intensive bilateral focal and multifocal discharges. His AEDs were tapered off prior to DBS implantation. He manifested freezing of the

TABLE 2 Outcome after GPi DBS of dystonia patients included in the study.

No.	Age at GPi DBS (years)	Disease duration prior to GPi DBS (years)	Follow up (years, months)	Change in BFMDRS-M, last follow-up compared to baseline	Change in BFMDRS-D, last follow-up compared to baseline	Responder (>25% improvement)	Effect on speech and/or swallowing	Long-term follow-up	DBS parameters at last follow up
I	9	6	2 years, 8 months	115 > 64	28 > 8	✓	✓	Bradykinesia and bradylalia (after 24 months)	GPi L (8+, 9–, 10+) 3.9 mA, 60 µs, 180 Hz GPi R (0+, 1–, 2+) 4.9 mA, 60 µs, 180 Hz
II	7	1	1 year	96 -> 50	20 > 9	✓	✓	No impairment	GPi L (C+, L3-10%, L4-11%, L5-18%, L6-53%, L7-8%) 2.8 mA, 90 µs, 113 Hz GPi R (C+, L1-1%, L4-22%, L5-62%, L6-6%, L7-9%) 3.6 mA, 90 µs, 113 Hz
III	7	2	1 year 11 months	106 -> 67	22 > 12	✓	+/-	Dysphonia (dys/anarthria), swallowing and chewing difficulties, and freezing of the gait impairment (after 15 months)	GPI L (C+, L1-20%, L2 2–22% 3–38%, L3 5–20%) 4.5 mA, 100 µs, 130 Hz GPI R (C+, L1-11%, L2 2–22% L3 5–13%, 6–28%) 4.0 mA, 90 µs, 130 Hz

gait 15 months after DBS and developed anarthria, and again manifested with upper limb dystonia during activity associated with swallowing and bolus clearance difficulties. The BFMDRS-M scale decreased to 58 after GPi DBS. After 6 months, as the progression of dystonia occurred, the BFMDRS-M score increased to 67 but still showed significant improvement, while the BFMDRS-D decreased to 12 (Table 2). During postoperative follow up no complications occurred in any of the presented patients.

Literature review

We did not follow the exact methodology of a systematic review, i.e., we performed a PubMed Search using the terms "*KMT2B*" or "*THAP1*" and "*dystonia*" and "*Deep Brain stimulation*".

In the period between 2010 and 2022, we identified 10 studies, including 38 patients with DYT-*THAP1* who underwent GPi DBS describing significant improvements in both BFMDRS-M and BFMDRS-D (Supplementary Table 1). Furthermore, in the period between 2017 and 2022, we identified 16 studies, including 64 patients with DYT-*KMT2B* who underwent DBS (Supplementary Table 2). In the vast majority of cases, the lead was implanted in the GPi bilaterally, and STN-DBS was only performed in one patient. Furthermore, during follow-up, significant changes were described in BFMDRS-M and BFMDRS-D, ranging from 20% to more than 95% improvement.

Discussion

We present two siblings with DYT-*THAP1* and a child with DYT-*KMT2B*, all pharmacoresistent with remarkable clinical improvement after GPi-DBS.

DYT-*THAP1* is an early-onset initially craniofacial and later typical generalized dystonia with autosomal-dominant inheritance, rostrocaudal progression, and a sex-independent penetrance of 60%, with causative mutations in the *THAP1* gene on chromosome 8 (38). The *THAP1* gene is part of a family of THAP proteins that bind specific DNA sequences and regulate cell proliferation through pRB/E2F cell cycle target genes, a pathway recently proposed to be involved in cell death in Parkinson's disease (21, 39). The phenotype of patients with DYT-*THAP1* is highly variable, with age of onset ranging from 8 to 69 years and the site of onset predominantly cervical, laryngeal, and in the upper limbs, and associated with tremor and signs of parkinsonism in some patients. The involvement of cranial muscles, leading to disabling dysarthria or dysphonia, as was also the case in our patients, is typical for DYT-*THAP1* (40).

DYT-*KMT2B* is a progressive childhood-onset disorder, evolving from a focal to a generalized pattern, either from lower-limb dystonia in the first decade of life, which accounts for up to 10% of cases, or first affecting the laryngopharyngeal region, speech development, and upper limb function, and developing into generalized dystonia in a craniocaudal manner (41). Gene mutations occur *de novo*, and are usually non-sense mutations,

rather than missense mutations. DYT-*KMT2B* is often associated with endocrinological symptoms, short stature, early onset with a median of 5 years of age, laryngeal dystonia, and onset on lower extremities. Developmental and pronounced delay in speech development, as in our patients, precede dystonia in 30% of patients (25). Further clinical characteristics, such as cognitive disability, psychiatric comorbidities, and dysmorphic features, have been reported in several patients (27–29). Bilateral GPi-DBS has been reported as an efficient therapeutic option, especially for improving movement disorder and regaining independent mobility (5, 22–37). GPi-DBS is sometimes associated with "dramatic" amelioration in gait but more commonly associated with truncal dystonia and scoliosis; it is rarely associated with speech dysfunction in severely affected patients with KMT2B gene mutations prior to DBS (23).

The first-line treatment for multifocal or generalized dystonia is trihexyphenidyl and baclofen, which provide limited and transient improvement in some patients. Intramuscular injections of botulinum toxin A are used mainly for the treatment of focal dystonia (42). L-dopa at low doses (50–200 mg) represents the first-line treatment for dopa-responsive dystonia. AnT empirical trial of L-dopa is usually offered to all patients with early-onset dystonia without evidence of neurodegeneration or brain structural lesions, partly due to a delay in treatment onset and a lack of feasibility of next-generation sequencing and the genetic screening of dystonia (42).

As already mentioned, the results of DBS in children are limited to individual cases or case series, although DBS for childhood dystonia has been proven to be an effective procedure in carefully selected pediatric cohorts. A positive response to treatment has been demonstrated in DYT-*TOR1A* patients after GPi-DBS (43, 44). Several adult and pediatric patients underwent GPi-DBS due to DYT-*THAP1* and DYT-*KMT2B.* Although the number of pediatric patients was lower, the results prove that bilateral GPi-DBS is a valuable therapeutic option for DYT-*THAP1* (8–16) and DYT-*KMT2B,* particularly for movement disorders and regaining mobility, but less so for speech issues (5, 22–37) (Supplementary Tables 1, 2). So far, the aforementioned patients presented with severe dystonic postures, majorly impacting their quality of life, as well as those of their families and caregivers. In the vast majority of patients who underwent bilateral GPi-DBS, a significant improvement was reported in both BFMDRS-M and BFMDRS-D, ranging from 20% to more than 95% during follow-up, from which the longest was 22 years (Supplementary Tables 1, 2). Systematic review and meta-analysis of GPi-DBS for DYT-*KMT2B* with a median follow-up of 12 months reported a 42% improvement in the BFMDRS scale, with better outcomes with more severe dystonia at baseline (24), which is compatible with our results.

Although highly effective in some patients, it is known that the stimulation response can be variable and difficult to predict, emphasizing the need for controlled studies in pediatric cohorts exclusively (7, 19, 20). As presented in the literature, stimulation parameters vary widely among patients; therefore, optimal programming is individual (Supplementary Tables 1, 2).

Furthermore, genetic or acquired causes of dystonia and other movement disorders lead to the development of basal ganglia, thalamus, cortex, dentate cerebellar nucleus, and brain stem lesions or dysfunction (45). GPi-DBS can affect neuronal activity in functional connections of the cortico-basal ganglia neural network and cause long-term plasticity changes at the cortical level, which can then reestablish normal movement (46, 47). Additionally, beside modulation in neuronal networks, DBS may play an important role in the neurochemical system, e.g., modulating neurotransmitter (dopamine, glutamate, and gamma-aminobutyric acid) release (46, 48). It is known that various genetic etiologies and dystonia pattern respond differently to DBS (49). The best results are achieved in DYT-*THOR1*. DBS efficiency in DYT-*THAP1* has been described as variable but improvement occurs in 50–70% of patients. Early identification of a genetic etiology for dystonia is critical because a correct diagnosis can ensure timely and appropriate treatment, such as DBS, before disability or deformity occurs (6). Impairments after initial improvement could be the result of either associated or induced parkinsonism related to specific gene mutation or induced after DBS implantation (50). Mild parkinsonian signs are an additional manifestation of dystonia arising from basal ganglia dysfunction. In DYT-*KMT2B* patients, decline is progressive after 7–22 years of post DBS implantation assessment (31).

Several studies have investigated the potential predictive factors (i.e., biomarkers) of DBS treatment outcome for early-onset dystonia in pediatric population. It was shown that the age at onset of dystonia, severity, and previous duration of disease and not age at surgery are associated with good treatment response and outcome, while a shorter time between diagnosis and DBS was significant. Although some studies did not show a correlation of preoperative dystonia severity and DBS efficacy, others indicated that a lower preoperative BFMDRS score is related to better treatment efficacy and outcome (20, 47). In addition, DBS treatment outcome is less efficient if speech has been severely affected prior to DBS implantation, if the disease duration is longer, and if disease onset is later; the outcome is also less efficient for complex or combined monogenic dystonia (20, 21). Factors such as age at onset, disease duration, specific gene mutation, dystonia pattern, and severity of preoperative dystonia will definitely be included and discussed in future studies. A better understanding of outcomes in pediatric dystonia is leading to the refinement of the indications for DBS, which continue to evolve (20, 21). Nevertheless, GPi-DBS should be considered in a timely manner once the symptoms cannot be controlled by medications.

Conclusions

Although the number of patients with dystonia, particularly DYT-*THAP1*, treated with GPi-DBS is still small, we believe that DBS should be considered in patients as an early treatment approach in pediatric pharmacoresistent dystonia to prevent more severe symptoms decreasing the quality of life, including emotional and social aspects. Parents should be properly informed about the expected and possibly variable improvement after DBS implantation. Using whole-exome sequencing, it is possible to establish the correct diagnosis early, which can be helpful in determining the appropriate treatment, such as DBS, before disability or deformity occur. Furthermore, we emphasize the

importance of genetic analysis in pediatric dystonia patients, particularly those with monogenic isolated generalized dystonia with normal brain MR, who are possible candidates for DBS treatment, especially because the identification of an underlying molecular defect could significantly help predict the efficacy and functional outcome of DBS. DBS treatment outcome is less efficient if speech has been severely affected prior to DBS implantation and in complex or combined monogenic dystonia.

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

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

Author contributions

DC, NB, and VV contributed equally to the conception and design of the study, investigation, and formal data analysis. NB, MR, VR, and EP organized the data and prepared Supplementary material. NB and DC wrote the first draft of the manuscript. VV, NN, NB, and MR wrote sections of the manuscript. All authors contributed to manuscript revision and read 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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1151900/full#supplementary-material

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Case report: Post-traumatic Tourette syndrome resolving with treatment of jugular venous narrowing; reconciling organic brain dysfunction following whiplash trauma with the absence of direct brain injury

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We describe a man aged 33years who developed multiple symptoms, personality change, and a severe tic disorder following a road traffic accident, which were undiminished for 3years until jugular venous narrowing between the styloid process of the skull and the transverse process of the C1 vertebra was treated by surgical decompression. Immediately following surgery, his abnormal movements almost completely resolved, with no regression in 5years of follow-up. Vigorously debated at the time was whether or not his condition represented a functional disorder. Unrecognized throughout his illness, however, was a complaint of intermittent, profuse discharge of clear fluid from his nose that began on the day of the accident and continued up to the time of surgery, after which it was substantially reduced. This outcome reinforces the idea that jugular venous narrowing can cause or perpetuate a cerebrospinal fluid leak. It suggests that the interaction between these two pathological defects may have a profound effect on brain function in the absence of any demonstrable brain lesion. It invites a reevaluation of normal head and neck venous anatomy. It should strike a cautionary note in the diagnosis of functional illness. It invites exploration of a remediable structural cause for Tourette syndrome.

KEYWORDS

Tourette syndrome, whiplash injury, cerebrospinal fluid leak, jugular vein stenosis, functional neurological disorder

Introduction

Tourette syndrome refers to a condition of involuntary motor and vocal tics of unknown cause, arising spontaneously in childhood and sometimes lasting a lifetime (1). Onset can be insidious or dramatic. Tics may be minor and easily disguised or severe and disabling (2). Not strictly Tourette's are cases, otherwise identical, in which there seems to have been a precipitating event even though the underlying pathophysiology is unknown, traumatic brain injury being one. Yet the relationship between traumatic brain injury and tics is unclear (3); cases

have been described following whiplash neck trauma or peripheral injury in which brain injury seems to have been minimal or absent (4, 5).

We describe a patient who developed a severe movement disorder, indistinguishable from Tourette syndrome, in the days after a road traffic accident in which he sustained a thoracic fracture but no evidence of brain injury. While he was under medical care, there was considerable debate as to whether his symptoms represented a functional disorder or were the result of an organic disturbance of intracranial pressure. However, 3 years after the onset of symptoms, partial relief of jugular venous narrowing brought an immediate and almost complete resolution of abnormal movements, with no regression in 5 years of follow-up.

Case report

History and initial investigations

A man aged 33 years was taken to the hospital after colliding with a car while riding his moped. There had been no loss of consciousness. There were no abnormal neurological findings. A CT brain scan was normal, and he was discharged after 6 h. The same night, he became confused, unable to see clearly, unsteady, and vomiting. He was brought back to the hospital but discharged again after a few hours. He was admitted 4 days later with increasingly aggressive behavior and numbness and weakness down his left side. A T9 compression fracture was treated with a brace. In the hospital, 7 days following the accident, he began to develop tics, first as minor oral movements, progressing over a matter of days to substantial vocal and motor spasms, the latter affecting his head, neck, trunk, and upper limbs. He also complained of headaches, visual disturbances, slurred speech, word-finding difficulties, and short-term memory impairment. Brain MRI was normal, and he was discharged.

When examined at our institution 2 months later, he was virtually housebound with a florid syndrome of tics and involuntary vocalizations. Abnormal movements included a stammer, humming, facial grimacing, and shoulder shrugging. Vocalizations involved clang associations "tick tock, rock rock" and repeated profanities. All were suppressible for short periods at the expense of extreme discomfort and emotional upset. All were exacerbated by anxiety and partially relieved by distraction. He was walking on crutches. MRIs of the brain and spine were unremarkable. There was no family history of Tourette syndrome.

Over the next 3 years, his tics were undiminished. There were no objective neurological findings, and there was broad agreement between neurology and psychiatry that his symptoms were largely functional. He was reviewed by the ophthalmology service, who recorded grossly disordered eye movements and grossly restricted visual fields but no papilledema. His premorbid personality had been boisterous and outgoing. After the accident, his mood varied between elation and depression, with outbursts of anger. With time, he became apathetic, fatigued, and withdrawn. His weight increased, and he noticed reduced facial hair and libido. Pituitary function tests were all normal except that gonadotrophin levels were not increased in the face of low testosterone levels. He was started on testosterone replacement therapy. He developed polydipsia, which was attributed after investigation to a constant sensation of dryness in his mouth.

Investigation of intracranial pressure and cranial venous outflow

With intractable symptoms and our group's interest in disordered cerebrospinal fluid (CSF) dynamics and cerebral venous outflow obstruction, he underwent CT venography. This showed normal intracranial venous sinuses but marked narrowing of both jugular veins between the styloid processes of the skull and the transverse processes of the C1 vertebra (Figure 1A). Lumbar puncture revealed an opening pressure of 20 cm H_2O, and his headache responded temporarily to cerebrospinal fluid (CSF) drainage, although tics were unchanged. Catheter venography confirmed the jugular narrowings, each associated with a 3 cm H_2O gradient (Figure 2A). He had bilateral jugular venoplasty (Figure 2B) with no immediate effect, but over the following week, his physical and vocal tics were greatly reduced. His headache had improved. His demeanor was calmer. His head felt

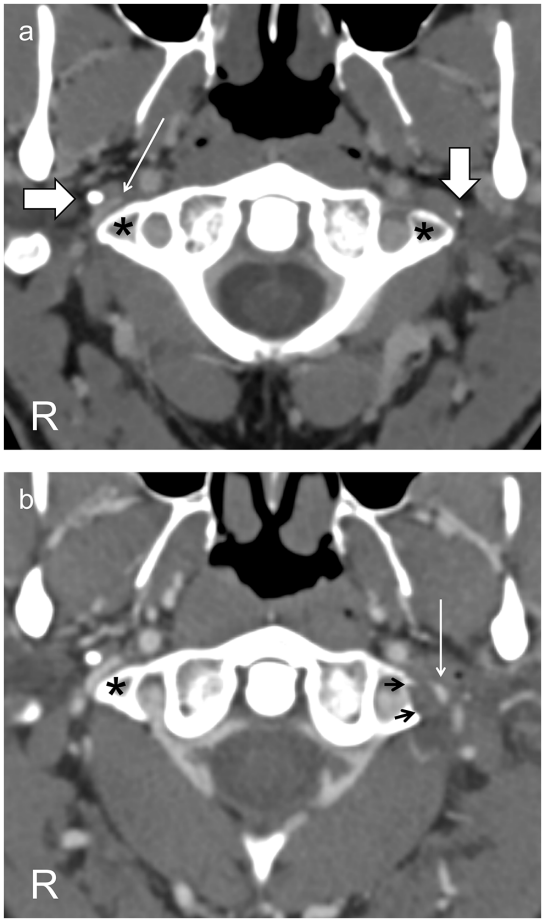

FIGURE 1
Axial CT scans through the C1 vertebra following intravenous contrast **(A)** before surgery show the jugular vein on the right side (thin arrow) markedly narrowed between the styloid process (horizontal thick arrow) and the C1 transverse process (asterisk) and on the left side compressed into invisibility between the styloid process (vertical thick arrow) and the C1 transverse process (asterisk). **(B)** After resection of the left styloid and C1 transverse process (resection margin, black arrows), the left jugular vein (thin arrow), though still narrowed, is now visible. The right jugular vein is unchanged, as expected.

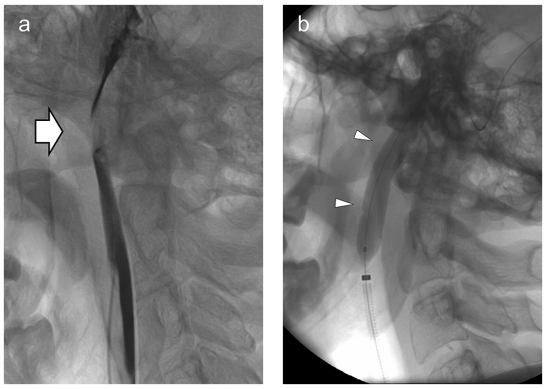

FIGURE 2
(A) Lateral view of the left jugular venogram showing marked narrowing of the jugular vein (arrow) between the (unseen) C1 transverse process and the (unseen) styloid. Intravascular contrast is dark, outlining the jugular vein above and below. **(B)** Same view with the angioplasty balloon (arrowheads) inflated across the site of narrowing.

clearer, and his memory was improved. Within 2 weeks, all symptoms had returned (see Supplementary Videos S1, S2).

Treatment of obstructed cranial venous outflow

He was diagnosed with cranial venous outflow insufficiency and, following appropriate counseling, had resections of the left styloid process and of the left C1 transverse process in a single procedure (Figure 1B) (6, 7).

The next day, barring the occasional facial tic, all his abnormal vocalizations and abnormal movements had resolved. His headaches, balance, and mood improved. At ophthalmology review 6 weeks later, his vision had returned to normal.

Progress

His headache reoccurred in the months following surgery, and there was residual mood and cognitive disturbance, as well as profound fatigue. He responded to repeat venoplasty, but further surgical and stenting procedures were not successful in effecting any further reduction in jugular narrowing or seemingly any lasting clinical benefit.

A review of his notes 2 years after his initial intervention revealed a brief mention of a fluid discharge from his nose around the time of the accident. This was not addressed by his treating physician at the time, but now, on direct questioning, his partner recalled copious volumes of clear fluid coming from his nose on the night of the accident, adding to the distress experienced by the family on his arrival home. Then, over the next 3 years, this nasal discharge was repeated frequently, with no obvious precipitating factor, sometimes, for example, when they were sitting together watching television. However, none of this was revealed in numerous follow-up medical consultations, and at no time prior to surgery was the possibility of a CSF leak considered.

Following surgery, these discharges were substantially reduced in frequency and volume, and late attempts to establish the presence or likely origin of a CSF leak were unsuccessful. Then, at around 3 years post-surgery, they ceased altogether, this coinciding with a pronounced improvement in his general health and restoration of his premorbid affect, although headache and fatigue have persisted, if less severe than previously (see Supplementary Video S3).

Discussion

There were two differing interpretations of this case while he was under medical care: the first was that a road traffic accident had precipitated a functional neurological disorder, and the second was that a road traffic accident had precipitated an organic disturbance of brain function from obstruction to cranial venous outflow caused by traumatic damage to the jugular veins. A third interpretation, possible only in retrospect, is that the accident caused a dural tear and CSF leak, which only healed after a procedure that improved cranial venous drainage, and that symptoms were largely a manifestation of CSF depletion syndrome (8–11), though unusual in the severity of the movement disorder and the absence of a postural component to headache (12).

The development of tics, or recrudescence of a tic disorder, after head injury is well recognized (3). Sometimes this can be attributed to damage to particular brain structures, but when there is no radiological evidence of injury, this attribution becomes more speculative (4, 5). Moreover, new-onset tics have been reported after whiplash trauma when there has been no loss of consciousness and no apparent brain injury (4, 5). In these circumstances, psychological mechanisms are likely to be invoked to explain the clinical picture, and when, as in the case we describe, there is such a multiplicity of symptoms and inconsistent neurological signs, it is inevitable that the differential diagnosis will include a primary psychiatric illness or functional neurological disorder.

What then prompted investigation of intracranial pressure and cranial venous outflow? CT venography showed narrowing of the jugular veins between the styloid processes of the skull and the transverse processes of C1. However, there were no signs of raised intracranial pressure. Moreover, there is no recorded association of venous obstruction or raised intracranial pressure with Tourette syndrome, and his other symptoms—headache, visual disturbance, nausea, vomiting, gait ataxia, fatigue, mood disturbance, cognitive disturbance, and memory disturbance—though frequent when intracranial pressure is chronically raised (as in idiopathic intracranial hypertension, IIH) would generally be regarded as being non-specific, not least because many of the same symptoms are also seen when intracranial pressure is chronically depressed (as in spontaneous intracranial hypotension) (8, 12–15).

Yet these two conditions can be connected. Thus, IIH is a disorder of raised intracranial pressure of unknown cause, arising spontaneously, mainly in obese young women (13). Spontaneous intracranial hypotension refers to a condition of low intracranial pressure caused by the spontaneous development of a CSF leak (8). Headache and visual disturbance are the signature complaints of the

first, and postural headache of the second. Increasingly, however, spontaneous intracranial hypotension is being seen as complication of IIH, developing when the dural lining of the subarachnoid space, attenuated by chronically elevated intracranial pressure, gives way at a weak point (16–18). Intracranial pressure may be in the normal range in these circumstances (8, 16), and the characteristic features of either condition may be absent, leaving the multiple other symptoms that are found in both (8, 14, 15). So, are these other symptoms simply the psychological accompaniments of chronic illness, or are they evidence of a disorder of intracranial pressure? (19).

A recent study suggests the latter. Two studies, one exploring chronic fatigue and the other fibromyalgia, have found mean intracranial pressures to be in the high normal range and that patients are symptomatically improved by CSF drainage. Both conditions are characterized by the multiple symptoms cited above, and the clinical improvement seen with lumbar puncture applied not just to headache (usually present) but to many of the other symptoms as well (20, 21). Various combinations of headache and these other complaints, therefore, rather than confounding the classical features of disordered intracranial pressure, may, in fact, be relatively strong indicators of a pressure disturbance (22).

In the case we describe, observing bilateral jugular venous narrowing and using these symptoms as a signal to investigate intracranial pressure further led to a diagnosis of cranial venous outflow obstruction, in retrospect accompanied by a CSF leak. This led, in turn, to a procedure designed to improve cranial venous outflow by creating space for the left jugular vein to expand, and the result was an immediate and almost complete cessation of abnormal movements along with (also in retrospect) a reduction in overt signs of CSF leakage. This lends support to the original diagnosis, and although a placebo effect cannot be excluded, his nuanced response to surgical intervention with respect to his CSF leak and other symptoms, in keeping with the gradual healing of a dural defect and reflecting the limited extent to which the intervention was successful in relieving venous obstruction (Figure 1B), suggests otherwise.

There are precedents for this approach in the literature. The development of pseudomeningoceles or CSF leaks following vestibular schwannoma resection, for example, has been linked to iatrogenic occlusion of the sigmoid sinus during surgery (23, 24). In these cases, a chronic mild elevation of intracranial pressure, caused by obstruction to cranial venous outflow, is hypothesized to maintain a pressure gradient across the surgical defect in the dura, preventing closure. Treatment by revascularization and stenting of the sinus removes the force driving the elevation of intracranial pressure and allows the dural defect to heal.

Similarly, addressing jugular venous narrowings in cases of spontaneous intracranial hypotension by removing the driving force tending to elevate intracranial pressure in the first place can allow a dural defect to heal on its own (25, 26). Thus, cranial venous outflow obstruction might cause a CSF leak or may perpetuate a leak if a leak has developed for another reason. Moreover, symptoms may be complex, reflecting the balance between the clinical effects of the primary pathology (venous obstruction), the mitigating influence of a CSF leak on intracranial pressure, and the compounding problem of CSF depletion on brain function (22).

In practice, attributing clinical significance to jugular venous narrowing is difficult. The styloid processes are often quite closely approximated to the transverse processes of C1, and jugular venous narrowing at this site is seen frequently enough in radiological practice that it does not usually invite comment (27). Moreover, the pressure gradients associated with skull base or extracranial venous obstruction are usually not impressive (24–26, 28–30). Yet, this anatomical configuration would seem likely to place the jugular veins at risk of damage in a whiplash injury (in fact, the small size of the jugular veins at this level in this case might reflect scarring from previous trauma), and the outcome here suggests that in the appropriate context, these radiological findings should be taken seriously.

Determining which symptoms are due to a CSF leak and which are due to cranial venous outflow compromise is also difficult. The explanation for movement disorders in spontaneous intracranial hypotension is speculated to be in the distortion of brain structures, and in the stretching of cranial nerves, which occurs when CSF is depleted (10, 19). No brain distortion was seen here. Thus, it is questionable whether a CSF leak would be necessary to cause the clinical syndrome we observed. Nevertheless, this case suggests a substrate for post-traumatic movement disorders that would link them with acquired CSF leaks, these leaks caused, exacerbated, or prolonged as a result of damage to the jugular veins from a whiplash neck injury. This etiopathological mechanism is easily reconciled not only with their association with traumatic brain injury but equally with its absence. Moreover, if this is the template for post-traumatic movement disorders, it will likely have relevance for other more subtle cognitive and psychological disturbances occurring in the same circumstances (31). It may also be relevant to non-traumatic Tourette syndrome.

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. The patients/participants 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.

Author contributions

JH advocated the management approach, directed the diagnostic procedures, and wrote the first draft of the manuscript. SK critically evaluated all aspects of the case and contributed to the final draft of the manuscript. 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

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1179596/full#supplementary-material

SUPPLEMENTARY VIDEO S1
Interview just prior to jugular venoplasty demonstrating severe tic disorder.

SUPPLEMENTARY VIDEO S2
Interview one week post jugular venoplasty catching short lived clinical improvement.

SUPPLEMENTARY VIDEO S3
Interview showing sustained benefit 4.5 years following surgery to decompress the left jugular vein.

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Case report: Atypical Parkinsonism following SARS-CoV-2 infection

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A wide range of neurological manifestations have been reported during the COVID-19 pandemic, including a variety of Parkinsonian cases. The association of numerous viruses with the development of persistent or transient Parkinsonism has been well-documented. We observed a patient who developed a levodopa non-responsive Parkinsonian syndrome with dysautonomia during a prolonged stay at home for COVID-19. Although the temporal proximity of the emerging Parkinsonian features with a COVID-19 diagnosis suggested a causal relationship, we considered the possibility of a coincidental occurrence of multiple system atrophy. We discuss the patient's clinical features in relation to the established clinical diagnostic criteria and review differential diagnoses as well as the role of SARS-CoV-2 infection.

KEYWORDS

COVID-19, multiple system atrophy, Parkinsonism, SARS-CoV-2, diagnosis

Introduction

Parkinsonian syndromes include idiopathic Parkinson's disease (PD), progressive supranuclear palsy, multiple system atrophy (MSA), corticobasal degeneration, and vascular Parkinsonism, among other rarer causes of Parkinsonism. Etiology is considered multifactorial, resulting from the contribution of environmental, genetic, and epigenetic factors. Viruses are recognized environmental causes of Parkinsonism, including influenza A, Epstein–Barr virus, hepatitis C virus, varicella zoster, West Nile virus, and Japanese encephalitis virus (1). The number of cases of COVID-19-related Parkinsonism have been described during the recent pandemic outbreak and linked to the premorbid infection (2). We observed a patient presenting with Parkinsonism and dysautonomia following a prolonged SARS-CoV-2 infection.

Setting and methods

Assessments were performed at the Department of Neurology, Humanitas Research Hospital (Rozzano, Milan, Italy). Patient clinical data were stored in the hospital's electronic medical records. Clinical and laboratory procedures were performed according to hospital protocols and good clinical practice guidelines. The case description conforms to CARE guidelines (3). Written informed consent was obtained from the participant for the publication of this case report, including clinical data and images.

Case presentation

A 62-year-old right-handed man, working as a swimming pool manager, received emergency admission in March 2020 because of fever and mild respiratory symptoms. Severe osteoporosis and bilateral glaucoma were reported in his medical records. He did not present hyposmia or sleep disorders. Family history was unremarkable for Parkinsonism or other neurological conditions. A nasopharyngeal swab tested positive for SARS-CoV-2, but chest CT did not show pneumonia. Having mild COVID-19 symptoms, he was treated at home with paracetamol and low-molecular-weight heparin. Respiratory symptoms recovered in approximately 20 days; in total, he remained isolated at home for approximately 3 months until a nasopharyngeal swab tested negative. During the last few weeks of isolation at home, his family members noticed abnormal cervical posturing associated with ideomotor slowing and progressive gait instability, causing a fall and rib fractures. Neck dystonia gradually progressed, and global bradykinesia became apparent. The patient received dopamine replacement therapy (up to 150 mg daily of levodopa with benserazide) that yielded no appreciable motor improvement.

In March 2021, a neurological examination showed bilateral rigid-akinetic Parkinsonism, with slight prevalence on the left-hand side. There was axial involvement with mild postural instability and neck dystonic posturing. The MDS-UPDRS motor score was 18/132, and the Hoehn and Yahr stage was 3. There were no cerebellar or pyramidal signs and no complaints of orthostatic hypotension. Dopamine replacement therapy was increased up to 450 mg daily (t.i.d.) of levodopa with benserazide, and a rotigotine patch was administered at a dose of 4 mg per day. These medications were well tolerated but provided no significant motor improvement. Brain MRI was unremarkable, and single-photon emission computed tomography (SPECT) with ^{123}I-Ioflupane showed a marked bilateral reduction in presynaptic dopaminergic binding. Brain ^{18}F-FDG-PET revealed right frontal and frontotemporal hypometabolism, especially in the medial regions (Figure 1). Neuropsychological assessment revealed mild long-term memory difficulties for visuospatial material, slight attentive and executive dysfunction, and apathy. Autonomic testing revealed mild sympathetic autonomic dysfunction. The SCOPA-AUT score was 11/69. An extensive whole-exome NGS test showed no variants in genes related to Parkinsonism or other movement disorders.

The patient's picture quickly worsened. In June 2021, gait became unsteady with frequent falls; there were initial dysphagia and inspiratory stridor. Urinary symptoms progressively worsened, with urge incontinence, increased urinary frequency, and incomplete bladder emptying (SCOPA-AUT score: 17/69). In July 2021, the patient was taking 450 mg of levodopa with benserazide and 4 mg rotigotine, still with no evidence of efficacy. The MDS-UPDRS motor score was 24/132. Rotigotine was withdrawn, and levodopa medication was maintained. In August 2021, intravenous immunoglobulins were administered (0.4 g/kg/daily, total dose 30 g) without appreciable benefit. The patient's motor condition continued to worsen: inspiratory stridor was reported, gait impairment and dysphagia became prominent, and urinary dysautonomia progressed. The Hoehn and Yahr stage was 4 (Figure 2).

In July 2022, the patient died suddenly at home while sleeping. He was found dead in the morning. Disease duration was reckoned to have lasted ~2 years from motor onset. The family did not agree on performing an autopsy.

Discussion

The patient in this vignette presented with a non-tremulous Parkinsonian syndrome characterized by rigidity, bradykinesia, dystonia, and gait impairment, associated with dysautonomia. Atypical Parkinsonian features included a lack of response to dopaminergic medication, early cervical dystonia, and early postural instability with falls. The differential diagnosis is reported in Box 1.

This patient met the diagnostic criteria for clinically probable MSA (4). The core diagnostic features were autonomic dysfunction, consisting of urinary urge incontinence, and Parkinsonism. The

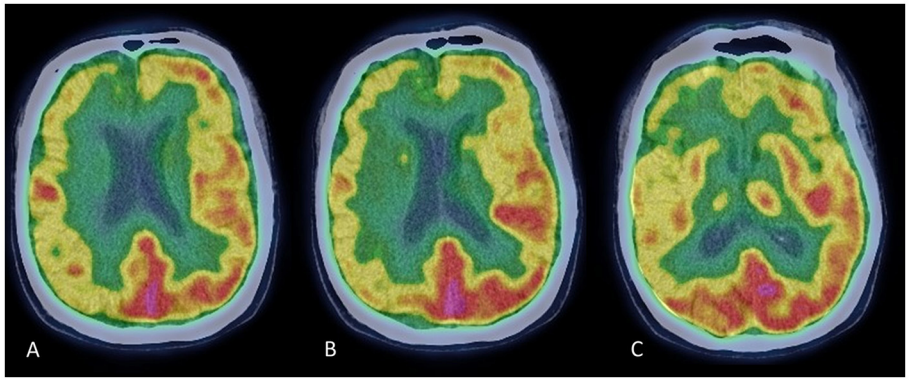

FIGURE 1
Brain FDG-PET scans at three rostrocaudal levels **(A–C)**. Images show a pattern of diffuse hypometabolism involving the right frontal and frontotemporal cortex, which is more evident in the medial regions.

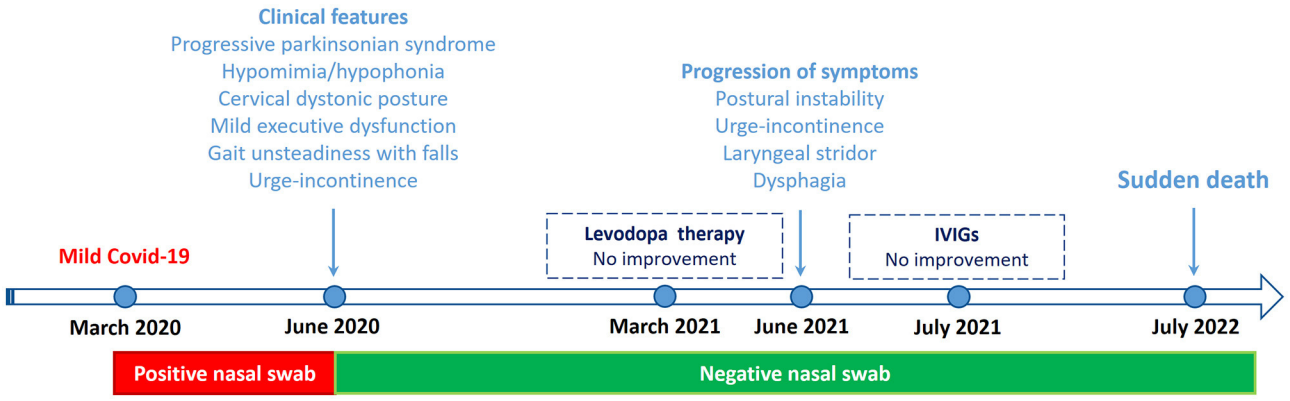

FIGURE 2
Clinical course and key events from March 2020 to July 2022. IVIGs, Intravenous immunoglobulins.

supportive diagnostic features were rapid progression and postural instability within 3 years of motor onset, craniocervical dystonia without limb dyskinesia, severe early dysphagia, and stridor. There were no exclusion criteria for MSA. Hyposmia, which is commonly associated with COVID-19 (5) and is an exclusion feature for MSA (4), was not present.

Sudden death, reported in this patient, is a relatively specific occurrence in MSA, uncommonly observed in other Parkinsonian syndromes (6). Age at onset was typical for MSA-P, but survival was shorter than average (slightly longer than 2 years). This short duration is however not outside the reported range of MSA progression trajectories. Parkinsonian presentation with predominant urinary dysautonomia, as observed in this patient, is associated with shorter survival (7).

Dopamine transporter (DAT) imaging with TRODAT-1 SPECT cannot distinguish between different Parkinsonian syndromes, including MSA, and cannot differentiate MSA-P from PD and MSA-C (8). However, MSA subtypes have been reported to have characteristic patterns of FDG uptake on PET scan. A typical pattern observed in MSA-P subjects shows diffuse hypometabolism in putamen–pallidum with relative sparing of the caudate nuclei (8); but hypometabolism in the frontal, temporal, parietal, and limbic areas has been observed in MSA patients, particularly among those with reduced MMSE scores (9, 10). In this patient, MMSE scored normal, but an extensive neuropsychological assessment revealed mild executive and visuospatial impairment.

The patient did not consent to perform both the MIBG scan and lumbar puncture. The first could have supported the differential diagnosis between PD and MSA (4, 11), while the search for onconeural and neural surface antibodies could have assessed the hypothesis of immune-mediated or paraneoplastic Parkinsonism.

Reported cases of Parkinsonism following COVID-19 encompass a variety of phenotypes and also include cases of encephalopathy (2). The heterogeneity of reported cases is remarkable and raises the question of whether other MSA cases may have been labeled generically as post-COVID Parkinsonism. Some reports of symmetric akinetic-rigid Parkinsonism without tremors suggest an atypical onset and disease course. Some of these cases may have had MSA or PSP, but their diagnosis may have been overshadowed by the COVID-19 emergency (2, 12). Different mechanisms have been postulated, by which COVID-19 may cause a neurodegenerative condition or accelerate a pre-existing one, but there is currently no robust experimental support. The hypothesized mechanisms include direct CNS invasion, hypoxia and vascular damage, virus-induced cytokine storm, post-infectious immune-mediated events, or the unmasking of prodromal Parkinsonism (13). A variety of movement disorders have been shown to occur or worsen following SARS-CoV-2 infections, including cases with a typical essential tremor phenotype (14).

As for other movement disorders, a chronological relationship between COVID-19 infection and the new onset of Parkinsonism may not necessarily indicate causality. Coincidental occurrence of common medical conditions has been described, for example, PD and multiple sclerosis have been reported to coexist (15). Until now, a few cases of COVID-19-related Parkinsonism have been reported. A causal relationship between SARS-CoV-2 infection and Parkinsonism was not found in any of them, raising the possibility that at least some were coincidental to COVID-19. Of note, this patient tested positive for COVID-19 for ∼3 months without respiratory symptoms, suggesting that a systemic inflammatory response to SARS-CoV-2 may have persisted. Hence, this observation raises the question of whether SARS-CoV-2 infection may have accelerated coincidental Parkinsonism. We report a chronological connection with COVID-19 without evidence of a deterministic causative link, notwithstanding the patient, and caregivers retained that Parkinsonism was consequent to COVID-19 infection.

We consider this a case of MSA-P coincidental with COVID-19. Arguably, SARS-CoV-2 infection could have provided an environmental trigger to aggravate the clinical course of the naturally occurring Parkinsonism. Parkinsonian syndromes usually have long prodromal phases when the cardinal features may escape the attention of patients or caregivers (16). In this patient, early motor features, prevalent to the non-dominant side, may have been unnoticed until a virulent SARS-CoV-2 infection raised attention to details of the patient's status. The implementation of the current diagnostic criteria for

BOX 1 Differential diagnosis of the reported patient.

1. COVID-19-related Parkinsonism. The main cue to this diagnosis is the close chronological relation between SARS-CoV-2 infection and the onset of motor Parkinsonian features. However, no additional evidence for a causal relationship was collected. The patient lacked clinical, laboratory, or neuroimaging findings of encephalopathy. Reduced presynaptic dopamine transporter uptake suggested a pre-existing neurodegenerative process involving the basal ganglia.
2. Other coincidental neurodegenerative Parkinsonism. The clinical presentation did not match the current clinical diagnostic criteria for PD (11). Rapid progression of gate impairment and recurrent falls within 3 years of onset were red flags, while the absence of observable improvement with dopamine replacing therapy was an absolute exclusion criterion. The criteria for diagnosis of corticobasal degeneration were also not fulfilled (17). The diagnosis of progressive supranuclear palsy (PSP) was consistent with a history of frequent falls but unsupported by other core clinical features and excluded by the occurrence of autonomic dysfunction (18).
3. Immune-mediated atypical Parkinsonism associated with dysautonomia has been reported. In these cases, however, Parkinsonian features are outweighed by cerebellar and hyperkinetic features; seizures and other neurological manifestations are also found (19). The patient had only Parkinsonism with dysautonomia; treatment with immunoglobulins was empirically tested without efficacy. High-dose steroids were not administered because of severe osteoporosis. A second cycle of immunoglobulins or plasmapheresis was not justified in this case.
4. Coincidental paraneoplastic syndrome. Isolated cases of paraneoplastic Parkinsonism with atypical presentation have been reported. One patient with anti-CV2 antibody manifested Parkinsonism and autonomic dysfunction with normal neuroimaging, suggesting a diagnosis of multiple system atrophy (20). This rather unique presentation benefitted from immunotherapy. Other Parkinsonian cases associated with anti-CRMP5 antibodies had no dysautonomia and additionally displayed bilateral signal hyperintensities in the basal ganglia. Rare presentations of anti-Ri and anti-Ma2 antibodies include Parkinsonism with supranuclear gaze palsy, usually associated with brainstem or cerebellar dysfunction, and oculomotor abnormalities (21): these features were not observed in this case. In these cases, MRI abnormalities are typically observed (12). Although this does not exclude with certainty a paraneoplastic cause, the patient had no evidence of malignancies, imaging was unremarkable, and no appreciable benefit from immunoglobulin treatment was assessed.

Parkinsonian syndromes is also supportive to discriminate against coincidental occurrences.

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. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the participant for the publication of any potentially identifiable images or data included in this article.

Author contributions

PP collected data and prepared the first draft. AA, AC, EP, and TD collected data and reviewed the manuscript. 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.

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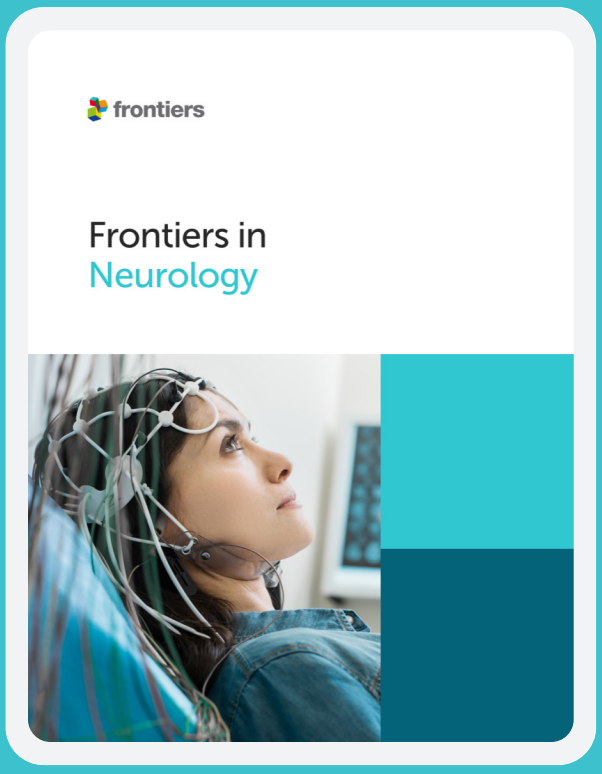

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