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Case reports in movement disorders, volume III - 2023

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Table of contents

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Case report: Early-onset parkinsonism among the neurological features in children with *PHACTR1* variants

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PACHTR1 is expressed in cardiovascular and neurological tissues. In the brain, it has a role in pre- and post-natal maturation. Previously reported *PHACTR1*-mutated patients showed early-onset epilepsy and intellectual disability. We describe two unreported cases with *de novo* pathogenic variants in *PHACTR1* and their clinical pictures, compared with those of cases already reported in the literature. In line with previous reports, the two patients presented early-onset developmental and epileptic encephalopathy. In addition, one patient developed a speech disorder and a progressive movement disorder characterized by hypertonus, hypo-bradykinesia, hypomimia, ataxic gait, and retropulsion. She was treated with levodopa without any clinical improvement. Pathogenic variants in *PHACTR1* may result in a cardiological or neurological phenotype. Severe developmental delay, intellectual disability, and early-onset developmental and epileptic encephalopathy are the main features of *PHACTR1*-mutated patients with neurological involvement. Movement and speech disorders have never previously been described and could be new features of the neurological phenotype.

KEYWORDS

***PHACTR1*, parkinsonism, movement disorder, epilepsy, developmental delay**

Introduction

Phosphatase and actin regulators (PHACTRs) are highly conserved proteins expressed in neuronal and non-neuronal cells (1). PHACTRs regulate cell morphology and motility during brain development (2) and modulate dendritic and axonal sprouting (1, 3).

PHACTR1 is a modulator of angiogenesis, and it is implicated in coronary artery diseases and early-onset myocardial infarction (2, 4–6). It is also expressed in the rat (1) and mouse (7) brains, especially in the cortex, hippocampus, and striatum (1) and in pre- and post-synaptic dendrites during cortical development (7). The expression of the mutations in mice,

through a dominant-negative manner, impairs developing brain neuronal migration, leading to mutant pyramidal cells that are misplaced and show abnormal morphology and polarity. These alterations were also seen in post-natal life, suggesting that PHACTR1 plays a role in post-natal brain maturation too (8).

PHACTR1 variants have been explored in cardiovascular disease, but little is known about their role in neurodevelopmental disorders. In the literature, *PHACTR1* pathogenic variants have been described in six patients with neurological features, including infantile epilepsy with severe psychomotor delay (9, 10), early-onset West syndrome (8), and (in one case also carrying a mutation in *CPT1B*) severe intellectual disability, attention deficit hyperactivity disorder, and inability to stand or walk (11). Cardiological problems were not reported in any of these patients.

We here describe two unrelated patients with *de novo* novel missense pathogenic variants in *PHACTR1*, focusing on their neurological features.

Cases

Patient 1 is a 17-year-old female, the second child of healthy non-consanguineous parents. She was born at term and the perinatal period was unremarkable. Psychomotor development was severely delayed with crawling reached at 2 years of age and walking starting at 3 years, with a rigid lower limb gait pattern. At 3 years, she was able to pronounce two words but subsequently lost this ability. Currently, she has a severe intellectual disability and communicates through guttural sounds, gaze, and a limited number of meaningful signs. She understands simple instructions.

Epilepsy appeared at the age of 2 months, with seizures characterized by fixation of gaze, perioral cyanosis, and hypotonia, followed by asymmetric spasms in clusters. EEG showed a poor organization of background activity with high-frequency multi-focal epileptic discharges. The patient was diagnosed with early-onset encephalopathy with spasms. Treatment with valproic acid, benzodiazepines, and ACTH was started, achieving a partial response. In the course of her childhood, she presented focal seizures, sometimes with focal to bilateral tonic-clonic evolution and spasms. Several antiseizure medications (vigabatrin, hydrocortisone, and benzodiazepines) were tried, without obtaining seizure control or clear EEG improvement, until the age of 10 years, when the patient started treatment with lamotrigine. Since then, she has been seizure-free. From the age of 5 years, the patient showed a rigid-bradykinetic movement disorder with a progressive course. She presented mixed hypertonus, hypo-bradykinesia, and hypomimia and became increasingly unstable, with ataxic gait and retropulsion. Over time, she also experienced freezing gait and festination, which could be broken only by tactile stimulation and oculomotor apraxia. L-dopa up to 10 mg/kg/day was not effective. At approximately 10 years of age, she lost the ability to walk independently. Brain MRI was normal at 3 months of age, but at 2 years, it showed corpus callosum and bihemispheric white matter thinning as well as midbrain hypoplasia. At 8 years of age, MRI findings were basically unchanged, and a diffuse subcortical T2w signal hyperintensity involving both temporal poles was still evident in the first examination, suggesting an incomplete myelination process/myelination defect. At the last evaluation at the age of 16 years, brain MRI showed moderate brain atrophy (Figure 1). The subcortical T2w signal hyperintensity involving both temporal poles was still evident.

Laboratory analysis and electrophysiological studies at the age of 16 years were normal. Chromosomal karyotype, array-CGH, and NGS panel for Rett and epileptic syndromes were normal. Trio (proband and parents) whole-exome sequencing (trio-WES) identified a *de novo* heterozygous variant (NM_030948.6:c.1529T>G, p.Val510Gly) in the *PHACTR1* gene.

Currently, her cardiological investigations remain normal.

Patient 2 is a 14-year-old male, the first child of healthy non-consanguineous parents, born at term. With the exception of the finding of oligohydramnios, the pregnancy and perinatal period were uneventful. Psychomotor development was severely delayed; the patient walked with help at the age of 2 years. Language has never been acquired, and he showed severe intellectual disability.

At 3 months of age, the patient displayed focal spasms, and multi-focal epileptic discharges were observed on EEG, mainly in the right central regions. A diagnosis of atypical West syndrome was made. He was treated with vigabatrin and ACTH without success. Over the years, he presented focal seizures characterized by oromandibular automatisms, stiffness of the upper limbs, and loss of head control. Multiple drugs have been tried, such as phenobarbital, valproic acid, topiramate, lamotrigine, nitrazepam, and fenfluramine, without ever achieving seizure freedom.

The patient currently presented acquired microcephaly and diffuse severe hypotonia with normal reflexes. He could only walk for short distances with support, and he presented a severe but stable clinical picture.

At the age of 4 months, the brain MRI was normal. At 12 years, it showed a diffuse reduction of the white matter, especially in the frontal and temporal-polar lobes, and thinning of the corpus callosum and brainstem. A slight but diffuse blurring of the T2w signal within the bihemispheric white matter was observed, indicating a widespread incomplete myelination process/myelination defect; in particular, the temporal poles continue to show subcortical T2w signal hyperintensity. The MR spectroscopy study documented a reduction of the NAA peak with the inversion of the NAA/Ch ratio. At 14 years, the brain MRI showed a slight expansion of the supratentorial cortical spaces, indicating brain atrophy progression (Figure 1). A diffuse myeline signal alteration on T2 weighted images was still present, especially at the temporal lobe.

Laboratory analysis, chromosomal karyotype, array-CGH, and NGS for epilepsy genes were normal. Trio-WES then identified a *de novo* heterozygous variant (NM_030948.6:c.1553T>C, p.Ile518Thr) in the *PHACTR1* gene.

Currently, his cardiological examinations remain normal.

Genetic analysis

The genome's exonic regions and flanking splice junctions were captured using the Clinical Research Exome v.2 kit (Agilent Technologies, Santa Clara, CA). Sequencing was done on a NextSeq500 Illumina system with 150 bp paired-end reads. The

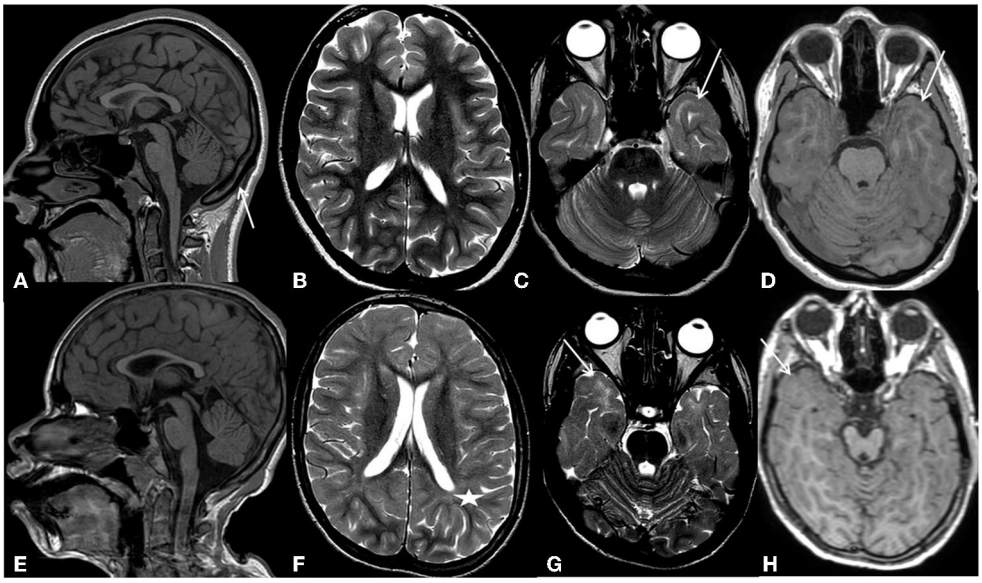

FIGURE 1
Patients' most recent MRI examinations. First row-Pt1: **(A)** (sagittal 3D T1-weighted image) shows thinning of the corpus callosum, reflecting brain volume reduction, and compensatory thickening of the skull (arrow). **(B)** (axial T2 weighted image) shows an overall slight reduction in white matter volume with moderately enlarged subarachnoid spaces. **(C)** (axial T2 weighted image), at the level of temporal poles, shows subcortical white matter signal hyperintensity (arrows). **(D)** (axial 3D-T1 weighted image), at the same level, shows a normal signal intensity of the subcortical white matter (arrow). Second row-Pt2: **(E)** (sagittal 3D T1-weighted image) shows microcephaly with thinning of the corpus callosum reflecting brain volume reduction. **(F)** (axial T2 weighted images) shows a diffuse reduction in white matter volume with moderate enlargement of the lateral ventricles and subarachnoid spaces. Diffuse blurring of the white matter signal is also evident in both hemispheres (asterisks). **(G)** (axial T2 weighted images), at the level of temporal poles, shows subcortical white matter signal hyperintensity (arrows). **(H)** (axial 3D-T1 weighted image), at the same level, shows a normal signal intensity of the subcortical white matter (arrow).

reads were aligned to human genome build GRCh37/UCSC hg19 and analyzed for sequence variants using a custom-developed analysis tool (12). Additional sequencing technology and a variant interpretation protocol have previously been described elsewhere (12).

Coverage on target for case 1 was ≥10x for 98.2% with a mean coverage of 210x, and for case 2, it was ≥10x for 87.4% with a mean coverage of 223x.

Both variants of the *PHACTR1* gene are in exon 13; in particular, the variant NM_030948.6: c.1553T> C, p.Ile518Thr affects the same base as the previously described mutation NM_030948.6: c.1553T> A, p.Ile518Asn (8). Variant p.Ile518Thr has been classified as probably pathogenetic (class 4 of the ACMG-American College of Medical Genetics); it is not described in the literature, and it is not present in gnomAD (MAF 0). Variant p.Val510Gly has never been described in the literature; it is disease-causative and is not present in gnomAD (MAF 0).

De-identified patient data are available upon request to the corresponding author.

Discussion

We here described two previously unreported patients with *de novo* missense pathogenic variants in *PHACTR1* and compared them with cases reported in the literature.

Severe developmental delay, intellectual disability, and early-onset epilepsy, observed in our cases, seem to be among the main features of *PHACTR1*-mutated patients with neurological involvement (Table 1). Instead, communication deficits and, in particular, the specific involvement of expressive language and speech observed in patient 1 have never been previously described. Similar to four of the six previously reported patients, our patients presented with spasms in the first months of life and received a diagnosis of West syndrome (8, 10). Despite the literature cases being diagnosed as West syndrome, we now refer to this condition as an early-onset developmental and epileptic encephalopathy, as stated in OMIM. Although the majority of reported cases have drug-resistant seizures, our patient 1 became seizure-free on lamotrigine.

The brain MRI findings in our patients support the idea that *PHACTR1* mutations can be associated with slightly progressive encephalopathy. Our long-term neuroimaging follow-up showed progressive brain atrophy and persisting diffuse subcortical T2w signal hyperintensity of the temporal poles, indicating an incomplete myelination maturation/myelin defect. Although temporal pole subcortical areas usually do myelinate in the later phases of the process, Parazzini et al. (13) demonstrated that the process of myelination is completed by 40 months of age. On the contrary, Maricich et al. (14), in their cohort, demonstrated that myelination of cortical areas was not complete at 46 months of age. However, in our cases, the T2w signal hyperintensity of the temporal poles persisted during the time, even at the teenage MRI control (Figure 2), confirming a myelination defect rather than delayed myelination. The myelination defect together with the brain atrophy represents unspecific MRI phenotypical features of the genetic defect. Similar findings have

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TABLE 1 Review of *PHACTR1*-mutated cases reported in the literature including the current cases.

Patient	Sex	*PHACTR1* variants - inheritance	Prediction software	Epilepsy	Drug resistance	Neuropsychiatric problems	Additional features	Brain MRI
De Ligt et al. (9)	F	c.1561C>T p.(Arg521Cys) - *de novo*	Predicted pathogenic	Yes – onset at 3 weeks	No	DD, psychomotor regression, severe ID, spastic tetraparesis	Scoliosis, microcephaly, difficulty thrivinging	Not reported
The Deciphering Developmental Disorders Study	F	c.1553T>A p.(Ile518Asn) - *de novo*	Predicted pathogenic	Not reported	NA	DD	Not reported	Not reported
Hamada et al. (8)	M	c.1499T>C p.(Leu500Pro) - *de novo*	Predicted pathogenic	Yes – WS at 3 months. Epileptic spasms and tonic seizures	Yes	DD, severe ID, hypotonia	Polyhydramnios, small for gestational age (SGA), cryptorchidism	Repeat brain MRIs at 3 months and 20 months of age revealed progressive atrophy and delayed myelination
	M	c.1436A>T p.(Asn479Ile) - *de novo*	Predicted pathogenic	Yes – WS at 3 months. Epileptic spasms and tonic seizures	No	DD, severe ID, autism, paroxysmal upward gazing	Facial dysmorphism: short eyebrows, fullness of upper eyelids, small mouth, widely spaced eyes, low-set ears	Normal
Riazudin et al. (11)	uk	c.1148C>T p.(Ser383Leu) - *de novo* Also, mutation c.2048G4A/ p.(Arg683His) in *CPT1B*	Predicted pathogenic	No	NA	Severe ID, ADHD, speech delay, severe hypotonia, inability to hold head, stand or walk	Not reported	Not reported
Marakhonov et al. (10)	M	c.1556T>G p.(Leu519Arg) - *de novo*	Predicted pathogenic	Yes – epileptic spasms and focal motor seizures evolving into bilateral tonic-clonic seizures from age 3 months	Yes	DD, generalized hypotonia	Not reported	At 4.5 m.o. hypoplasia of the corpus callosum, non-obstructive external hydrocephalus and delayed myelination. At 6 m.o. no changes
Patient 1	F	c.1529T>G p.(Val.510Gly)- *de novo*	Predicted pathogenic	Yes – epileptic spasms and focal seizures from age 2 months	Yes – now seizure-free	DD, psychomotor regression, severe ID, rigid-bradykinetic movement disorder	Mild facial dysmorphisms: deep-set eyes, long eyelashes	Moderate midbrain hypoplasia, diffuse thinning of the corpus callosum and mild delay in myelinization of the white matter of the cerebral hemispheres
Patient 2	M	c.1553T>C p.(Ile518Thr) - *de novo*	Predicted pathogenic	Yes – epileptic spasms and focal seizures from age 3 months	Yes	Severe ID, acquired microcephaly, not able to walk	Mild facial dysmorphisms: deep-set eyes, downslanting eyelids, flat nasal root, low-set ears, fullness of the upper lip, large mouth, hypothyroidism	Diffuse reduction of white matter, especially in frontal and temporo-polar lobes; thinning of the corpus callosum and brainstem.

F, female, M, male; WS, West syndrome; DD, developmental delay; ID, intellectual disability; ADHD, attention deficit hyperactivity disorder; m.o., months of age; uk, unknown; N.A, not applicable.

been described in early epileptic encephalopathies associated with *STXBP1* pathogenic variants (15). Anterior temporal lobe T2 white matter hyperintensity has also been described in other encephalopathies such as vascular diseases (cerebral autosomal dominant/recessive arteriopathy with subcortical infarcts and leucoencephalopathy-CADASIL/CARASIIL, respectively), infection diseases (congenital cytomegalovirus infection), dysmyelinating diseases (megalencephalic leukoencephalopathy with subcortical cysts-MLC), and neuro-degenerative diseases (Aicardi-Gutierres syndrome) (16). CADASIL/CARASIL is a progressive neurodegenerative condition with a rare but possible childhood onset. The subcortical anterior temporal involvement represents a specific neuroradiological characteristic, together with the involvement of the external capsule and the coexistence of lacunar infarcts and microbleeding; in this condition, the temporal findings represent areas of "leukoarariosis," indicating a degenerative leukopathy related to micro-vessels disease and consisting of white matter rarefaction/gliosis with numerous fluid-filled perivascular spaces (PVS) or increased number of PVS in the cortex (17). In the other conditions, the temporal lobe T2 hyperintensity is usually associated with temporal cysts, rather than indicating destroying parenchymal phenomena; in the MLC temporal lobe, swelling also coexisted due to intramyelin edema. Moreover, in all these conditions, the T2 signal was higher than in *PHACTR1* temporal lobe alteration, and in T1 weighted images, the signal results were low; on the contrary, in our patients' condition, T1-weighted images showed a normal signal at that level, as seen in hypomyelination disorders (Figures 1D, H).

Myelination is one of the most important factors influencing brain maturation and epileptogenesis (18). Our two cases confirm that *PHACTR1* plays a role in post-natal brain maturation (8). Until now, no other distinct MRI features can be ascribed to the syndrome even though non-specific alterations of the corpus callosum have been observed in one individual (11).

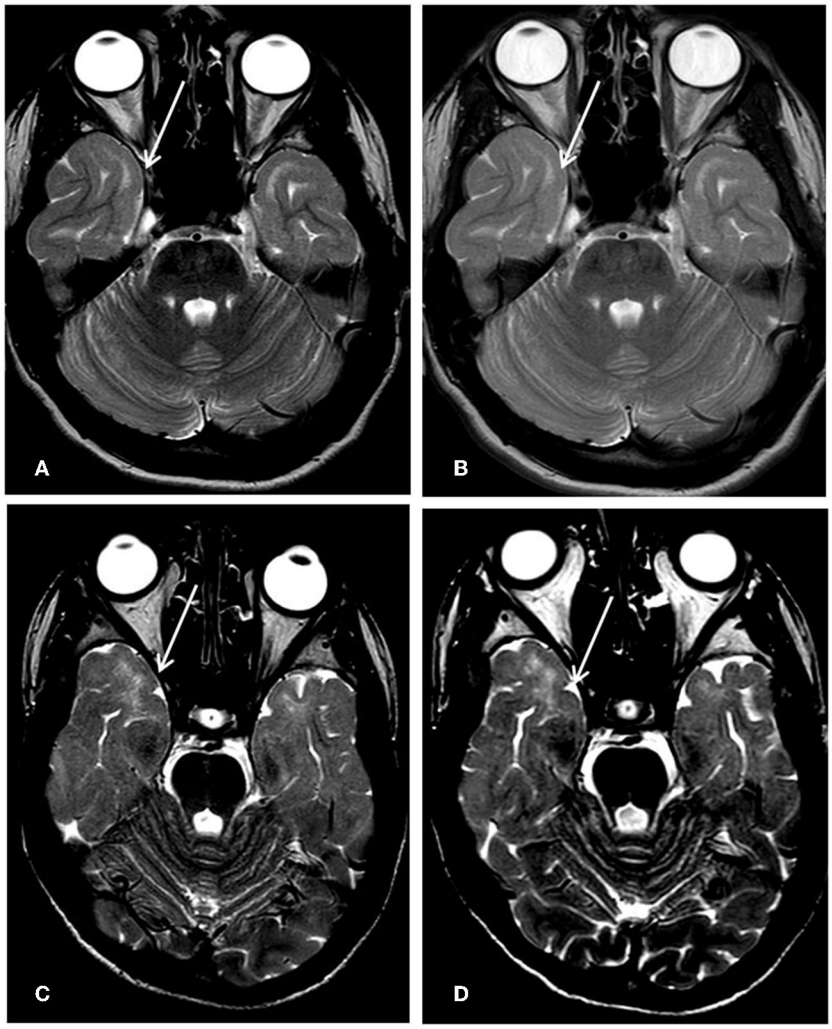

FIGURE 2
First row Pt1, 8-year-old's MRI **(A)** vs. 16-year-old's follow-up **(B)**; second row Pt2, 12-year-old's MRI; **(C)** and 14-year-old's follow-up **(D)**. The subcortical white matter signal hyperintensity on T2 weighted axial images at the level of temporal poles (arrows) resulted unchanged during the time.

The cardiological follow-up did not show any abnormalities in our patients; however, considering that in the described cases, cardiological involvement arises later in life, we cannot rule out that a long-term follow-up should be carried on.

As reported herein, our patient 1 developed a movement disorder consisting of mixed hypertonus, hypo-bradykinesia, hypomimia, ataxic gait with retropulsion, freezing of gait, festination, and oculomotor apraxia. Movement disorder has never previously been described in *PHACTR1*-mutated patients. Although the gene is known to be highly expressed in cortical neurons, some studies have also found *PHACTR1* expression in the basal ganglia, particularly the caudate putamen, in both the developing and the adult mouse brain (19). Notably, Wider et al. (20) found an association between a single nucleotide polymorphism in *PHACTR2* and Parkinson's disease; this association is yet to be fully investigated and clarified, but it could provide clues about the role of PHACTRs in movement disorders. These authors' findings highlight the need for a clearer and more specific understanding of the role of *PHACTR1* in the regulation of the extrapyramidal system.

Conclusion

PHACTR1 is reported as a genetic susceptibility locus as part of a complex genetic pattern of inheritance in cardiovascular diseases; moreover, in those patients, no neurological involvement is described. Conversely, the few cases with neurological problems showed no cardiac abnormalities. This suggests that different mutations in *PHACTR1* may result in two different phenotypes, one cardiological and the other neurological, which do not overlap in the same patient. So far, no direct genotype-phenotype correlations have been found in the described cases.

The core phenotype of *PHACTR1* mutation consists of severe developmental delay/intellectual disability and epilepsy. Our novel report of a *PHACTR1*-mutated patient presenting with a rigid-bradykinetic movement disorder, therefore, expands the phenotypic spectrum. Further studies are needed to assess whether this movement disorder should be classified as a different phenotype or an evolution of the disease. The different clinical presentations of the cases reported underline that gene mutations can show great phenotypic heterogeneity, making further clinical and biochemical studies necessary to identify the underlying pathophysiological mechanisms.

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. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

AL and RP wrote the first draft and performed data curation. GI performed the formal neuroradiological analysis. CS, AL, RP, and MB performed clinical data curation. MI performed genetic data curation. SB was responsible for the conceptualization and supervision of the study. AL, RP, MB, GI, CS, LS, MI, PV, and SB reviewed and approved the manuscript before submission. 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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Case report: Reversible encephalopathy caused by dyskinesia-hyperpyrexia syndrome

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Parkinson's disease (PD) is a common neurodegenerative disorder. Some patients with advanced-stage disease are accompanied by emergencies and critical issues such as dyskinesia-hyperpyrexia syndrome (DHS), parkinsonism-hyperpyrexia syndrome (PHS), and serotonin syndrome (SS). In this study, we report a patient with reversible encephalopathy caused by DHS who presented with an acute onset of fidgetiness, dyskinesia, and hyperpyrexia after antiparkinsonian drug abuse. In the present case, brain magnetic resonance imaging (MRI) showed multiple abnormal signals in the cortex and subcortex of the bilateral parietal and occipital lobes that resolved within weeks, which coincided with the characteristic MRI findings in posterior reversible encephalopathy (PRES). Our report expands on the neuroimaging features of DHS and highlights the importance of early identification, diagnosis, and treatment to improve patient prognosis.

KEYWORDS

reversible encephalopathy, Parkinson's disease, dyskinesia-hyperpyrexia syndrome, emergency, MRI findings

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease and is clinically characterized by static tremors, bradykinesia, myotonia, and postural balance disorders (1). Critical and severe complications of PD occur mainly in advanced-stage patients and require urgent medical intervention. They are most commonly associated with worsening motor symptoms but can also manifest as severe non-motor complications. PD emergencies include dyskinesia-hyperpyrexia syndrome (DHS), parkinsonism-hyperpyrexia syndrome (PHS), levodopa-related motor complications, serotonin syndrome (SS), acute psychosis, and autonomic nervous system complications (2).

DHS is a rare but severe complication of PD. It is characterized by the acute onset of persistent systemic dyskinesia associated with increased creatine kinase (CK) levels, hyperpyrexia, and an altered mental state, and affects patients with advanced PD (2, 3). It typically occurs in patients with long disease durations undergoing high daily dopaminergic doses and can be triggered by changes in dopaminergic therapy, infections, hot weather, dehydration, or trauma (2, 4, 5). Although this rare acute complication has been reported in recent years, neuroimaging of DHS has been underreported. Herein, we report a rare case of reversible encephalopathy caused by DHS, emphasizing the neuroimaging findings.

Case presentation

A 55-year-old man with a 10-year history of PD presented with an acute onset of consciousness disturbance and severe choreiform dyskinesia for 2 days. He had been diagnosed with PD 10 years earlier and showed a dramatic beneficial response to dopaminergic therapy. A pallidotomy had been performed 2 years earlier. No significant medical or family history was reported. The patient was treated for a long time with a combination of levodopa and benserazide (MADoPA), piribedil, selegiline, entacapone, and trihexyphenidyl. Only a few days prior, he increased the dosage of antiparkinsonian drugs on his own accord. The equivalent daily dose of levodopa was 1,750 mg per day. Two days earlier, he fell to the ground while going out on a hot afternoon. On admission, the patient exhibited confusion and continuous generalized involuntary movements without marked rigidity. Body temperature reached 40.6°C, and heart rate was 105 bpm. Systolic blood pressure was maintained at approximately 120–130 mmHg. The other neurological examination results were normal. Laboratory testing showed increased serum CK (1,468 U/L), CK-MB (38.8 U/L), and myoglobin (Mb) (374.2 μg/L). Other biochemical tests upon admission were negative, including alanine aminotransferase (130.1 U/L), aspartate aminotransferase (104.5 U/L), blood urea nitrogen (4.70 mmol/L), and creatinine (62.0 μmol/L).

Magnetic resonance imaging (MRI) performed 19 days after symptom onset revealed multiple abnormal signals of T1 and T2 hyperintensity in the cortex and subcortex of the bilateral parietal and occipital lobes, with hyperintensity on fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI), and apparent diffusion coefficient (ADC), suggestive of prompt vasogenic edema (Figures 1A–E).

Based on the patient's history and clinical presentation, a levodopa overdose was suspected. We immediately redistributed the total daily levodopa intake to 125 mg q. i.d., accompanied by amantadine hydrochloride 100 mg daily to control dyskinesia. Other general measures, such as rehydration and sedation, were used. After 5 days, dyskinesia improved dramatically, the CK level reduced to 529.6 U/L, and the CK-MB level reduced to 18.1 U/L as well. A further MRI performed at follow-up revealed that the lesions almost disappeared (Figures 1F–J). A time course of events can be found in Figure 2.

Discussion

DHS, a rare but severe complication of PD, was first reported and defined as an emergency condition by Gil-Navarro et al. (6). DHS typically occurs in patients with advanced PD. Almost all patients have fluctuating symptoms and take high-dose dopaminergic drugs (2). It is often caused by the abuse of antiparkinsonian drugs. Several other triggering factors for DHS include infection, hot weather, dehydration, and trauma (2, 4, 5). Only a few cases have been reported thus far (4, 6–12) and few have described the neuroimaging features of DHS (4, 9).

Posterior reversible encephalopathy (PRES) is an acute or subacute onset reversible neurological disorder accompanied by various neurological symptoms such as headache, impaired visual acuity or visual field deficits, consciousness disturbances, seizures, encephalopathy, and focal neurological deficits (13, 14). The symptoms and signs of PRES are not specific; therefore, brain imaging is usually helpful in confirming the diagnosis of PRES. Characteristic MRI findings include bilateral regions of subcortical vasogenic edema that resolve within days or weeks

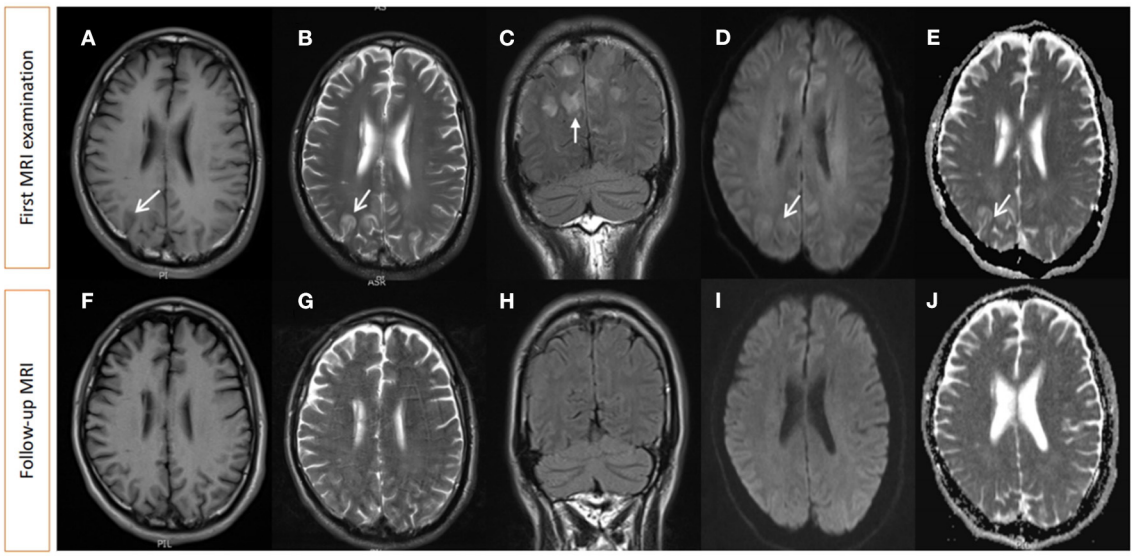

FIGURE 1
Brain MRI 19 days after symptom onset and at follow-up 3 months later. **(A)** T1 hypointensity and **(B)** T2 hyperintensity can be seen in the cortex and subcortex of the bilateral parietal lobe and the occipital lobe, with hyperintensity on T2 FLAIR **(C)**, DWI **(D)**, and ADC **(E)**. Follow-up MRI shows abnormalities have disappeared **(F–J)**. MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient.

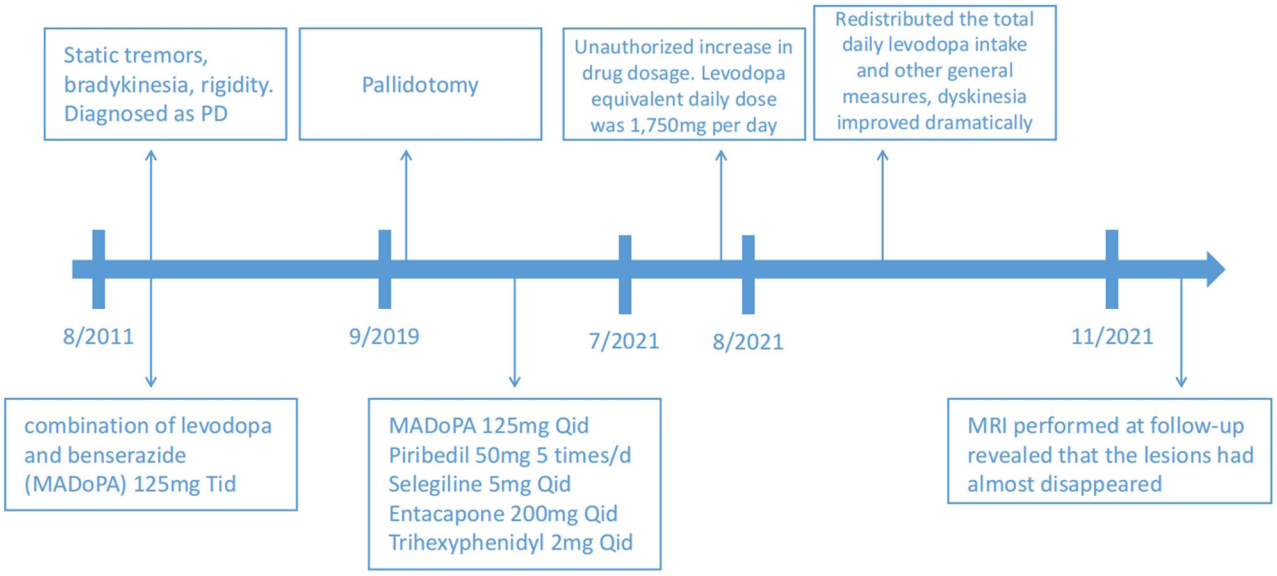

FIGURE 2
A timeline with relevant data from the episode of care.

(15). Our case coincided with MRI changes in PRES. This patient experienced consciousness disturbance, which can be classified as encephalopathy.

PRES often occurs due to abrupt blood pressure fluctuations, cytotoxic drugs, preeclampsia or eclampsia, sepsis, renal failure, or autoimmune diseases (13, 14). Cases of DHS leading to PRES have not been reported previously. We emphasize that DHS can cause reversible encephalopathy. However, the clinical manifestations of this patient did not conform to typical PRES. The patient did not have common clinical manifestations of PRES, such as elevated arterial pressure, seizures, and visual disturbances, and did not have the aforementioned causes; therefore, we speculate that the mechanism of DHS causing reversible encephalopathy in this patient may be related to direct endothelial injury reduced by hyperthermia, rhabdomyolysis, and high doses of antiparkinsonian drugs and not hypertension and cerebral hyperperfusion. Further studies are required to understand the underlying pathogenesis of this condition.

For the treatment of DHS, levodopa dosage should be gradually reduced. For patients with severe symptoms, appropriate sedation, fever reduction, hydration, and correction of electrolyte and acid-base imbalances can prevent renal failure, pneumonia, pulmonary embolism, and other complications. Most patients with DHS are relieved within a few days of active treatment and their prognosis is relatively good. PRES is generally benign. In many cases, PRES can be completely reversed within days to weeks of removing the triggering factors. After active treatment, the symptoms of DHS and PRES significantly improved. During follow-up, a head MRI showed that the original lesions had completely disappeared. Therefore, we believe that the prognosis of DHS-induced PRES caused by DHS is good.

Conclusion

DHS is a rare, acute, treatable syndrome. Early blood biochemical tests (CK, CK-MB, etc.) and brain imaging tests are crucial for the timely and differential diagnosis of DHS. Head MRI may reveal bilateral asymmetric cortical and subcortical vasogenic edema, particularly in the parietal and occipital regions. This case report provides new insights into DHS and expands on its neuroimaging features.

Patient perspective

"In 2011, I was diagnosed with PD and have been receiving oral anti-Parkinson's medication since then, with satisfactory symptom control. In July 2021, I felt that my symptoms were poorly controlled, so I increased my medication dosage on my own decision. A few days later, I suddenly experienced symptoms of severe involuntary movements and fell to the ground. My family sent me to the ICU for treatment. After the doctor helped me adjust my medication, my symptoms gradually recovered. After 2 weeks of treatment, I was discharged from the hospital and followed the doctor's instructions to take anti-Parkinson's drugs. No similar symptoms occurred again. Three months after discharge, I returned to the hospital for a re-examination of the head MRI, which showed that the lesion had almost disappeared."

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Second Xiangya Hospital. 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

HZ contributed to the conception of the case report. BL conducted data organization and wrote the manuscript. LQ reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Extensive spinal epidural abscess due to *Streptococcus intermedius*: a case report treated conservatively and literature review

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Purpose: To describe the clinical significance of prompt, adequate, and targeted intravenous antibiotic (IV antibiotic) therapy in the successful management of spinal epidural abscess (SEA) associated with *Streptococcus intermedius* (*S. intermedius*) infection.

Case description: SEA is a rare, but catastrophic infection that may result in a high risk of permanent neurological disability. A 52-year-old Chinese female patient was presented to the emergency department due to 2 years of low back pain and 3 days of decreased muscle strength in the extremities. The blood culture confirmed the presence of *S. intermedius* infection, and gadolinium-enhanced magnetic resonance imaging (MRI) demonstrated widespread epidural abscesses in the cervical, thoracic, and lumbar spine canal. Empirical IV antibiotic therapy with vancomycin was promptly initiated, with meropenem and moxifloxacin added subsequently based on blood culture results. After 5 days of IV antibiotic treatment, the patient's blood culture became negative. 6 weeks later, a follow-up MRI showed a decrease in the size of the abscess. The patient's muscle strength was mostly restored after 2 months of IV antibiotic treatment.

Conclusion: Repeat examinations or gadolinium-enhanced MRI should be considered when initial MRI findings are not diagnostic of SEA. For extensive SEA caused by *Streptococcus intermedius* infection, surgery may be non-essential, and the judicious antibiotic selection and adequate treatment duration are pivotal for successful conservative management. Furthermore, for patients who are not amenable to surgery, a comprehensive evaluation of their condition and meticulous implementation of a precise pharmacological regimen holds noteworthy clinical significance.

KEYWORDS

spinal epidural abscess, *Streptococcus intermedius*, antibiotic, decompression, magnetic resonance imaging

Introduction

Spinal epidural abscess (SEA) is a rare yet potentially devastating pyogenic injury that occurs between the spinal dura mater, posterior longitudinal ligament, and vertebral periosteum (1). Rapid abscess enlargement can lead to symptoms such as radicular pain, paralysis, and even death. Therefore, it is essential to diagnose infections early and treat them with a combination of intravenous antibiotic (IV antibiotic) and decompression surgery. Although life-threatening bacterial infections are uncommon, the clinical association of *Streptococcus intermedius* (*S. intermedius*) with abscess formation has long been recognized. *Streptococcus intermedius*, also referred to as *Streptococcus milleri* group (SMG) (2), is a member of the *Streptococcus anginosus* group (SAG). Within this group, *S. intermedius* has the capability to secrete a novel cytotoxin known as intermedilysin, which specifically targets human cells. Intermedilysin exhibits potent hemolytic activity exclusively toward human erythrocytes and no hemolysis on equine or goat blood agar, commonly employed in clinical microbiology. However, because this cytotoxin exhibits beta-hemolytic activity on human blood agar medium, *S. intermedius* is classified as a beta-hemolytic Gram-positive coccus. The first reported case of a brain abscess caused by *S. intermedius* dates back to 1975 (2). Subsequent cases have shed light on the pathogenesis of *S. intermedius*-associated abscesses in patients with congenital heart disease and sinusitis. Masalma et al. (3) conducted a study on 20 patients with brain abscesses associated with *S. intermedius* and found that this condition has several known risk factors for the development of invasive CNS disease, including endodontic infection, dental caries, and periodontitis, as confirmed by multiple 16S ribosomal DNA sequencing. To increase awareness of this rare condition, we present a case study of an extensive SEA patient with an *S. intermedius* infection, describing the clinical course, imaging characteristics, treatment, and patient prognosis.

Case presentation

A 52-year-old Chinese female patient was admitted to the emergency department due to 2 years of low back pain and 3 days of decreased muscle strength in the extremities. 2 years ago, she began experiencing lumbar back pain with mild lower limb radiating pain and numbness. After she underwent home physical therapy 1 week ago, the aforesaid symptoms intensified, and she went to the local hospital for an MRI of the lumbar spine, which revealed lumbar disc herniation. Three days ago, she started experiencing significant back pain and dysuria, followed by abnormal muscular strength and hypoesthesia in both lower limbs the next day. A day after that, the symptoms spread to both upper limbs. The patient had a history of Total Knee Arthroplasty (TKA) 6 years prior, which was performed under combined spinal-epidural anesthesia, with no reported history of diabetes or other diseases. Upon physical examination, the patient exhibited hypoesthesia below the inguinal plane, as well as biceps, triceps, finger flexors, and finger extensors muscle strength of grade 3 on both sides, muscle strength of grade 1 in both lower limbs, no fecal incontinence, and intact rectal tone. Upon admission, the patient presented with shortness of breath and confusion. A large amount of light red, thick sputum was aspirated by sputum suction. After face mask oxygenation, oxygen saturation was around 80%. Therefore, the patient was transferred to the intensive care unit (ICU) due to type II respiratory failure and a maximum temperature of 40.8°C. Blood tests showed elevated infection markers, including a total white blood cell (WBC) count of 26.6×10^9/L (normal range: 3.5–9.5×10^9/L), 85% neutrophils (normal range: 40–75%), increased C-reactive protein (CRP) levels of 25.03 mg/dL (normal range: <0.6 mg/d L), and increased procalcitonin (PCT) levels of 1.96 ng/mL (normal range: <0.05 ng/dL). Although a fluoroscopic-guided lumbar puncture was unsuccessful, an intravenous gadolinium-enhanced magnetic resonance imaging (MRI) revealed an abnormal signal shadow ventral to the spinal canal in the cervicothoracic segment and dorsal to T12-S1 level (Figure 1). Blood culture results confirmed the presence of *S. intermedius*, which was sensitive to vancomycin. Unfortunately, we did not rule out the possibility of false-positive blood cultures by means of genetic tests such as 16S rRNA or mNGS. Empirical IV antibiotic treatment with vancomycin (50u ivd q8h) was initiated, followed by the addition of meropenem (1 g ivd q8h) and moxifloxacin (0.4 g ivd qd) after receiving the blood culture results. Vancomycin dosing was adjusted dynamically based on blood concentration. The patient's clinical presentation of paraplegia and decreased muscle strength did not improve during the first 2 days of initial antibiotic treatment. The spine surgeons, in conjunction with the ICU physicians, discussed the following results: The patient's rapidly progressing and worsening neurologic symptoms within 72 h require urgent decompression surgery. However, the cervicothoracic segment abscess located ventrally may not drain adequately. Abscesses of the lumbar segment located dorsally have relatively poor outcomes after decompression surgery, and there is no additional benefit to early surgical treatment. Patients may not tolerate the shock of prolonged decompressive surgery of multiple spinal segments. Therefore, the patient was informed that progressive neurological deterioration may not be completely resolved even after delayed surgical treatment. After obtaining informed consent, we decided to continue treatment with antibiotics for at least 6 weeks. After 5 days of IV antibiotic treatment, blood culture results were negative. Following 1 month of antibiotic treatment, the patient's maximum temperature decreased to below 38.0°C, and her WBC count was 10×10^9/L with a CRP level of 6.19 mg/dL. After 43 days of IV antibiotic treatment, the patient exhibited grade 4 muscle strength bilaterally in the biceps, triceps, finger flexors, and finger extensors. At this time, a repeat MRI showed a significant reduction in the holospinal abscess, particularly in the upper lumbar segment (Figure 2). After 45 days of IV antibiotic treatment, the patient was transferred back to the general ward from the ICU. Laboratory examinations after 50 days of IV antibiotic treatment demonstrated normal findings in the patient's WBC count, neutrophil count, CRP level, and PCT level. However, despite 2 months of hospital treatment, there was no significant improvement in weakness observed in both lower extremities. At the 1.5-year follow-up, a repeat MRI revealed complete resolution of the epidural abscess (Figure 3), and the patient's muscle strength returned to grade 5 in the extremities. Nevertheless, numbness in both lower extremities persisted.

Discussion

Physiopathology

The anterior epidural space is mostly occupied by the dura, posterior longitudinal ligament, and periosteum of the vertebral

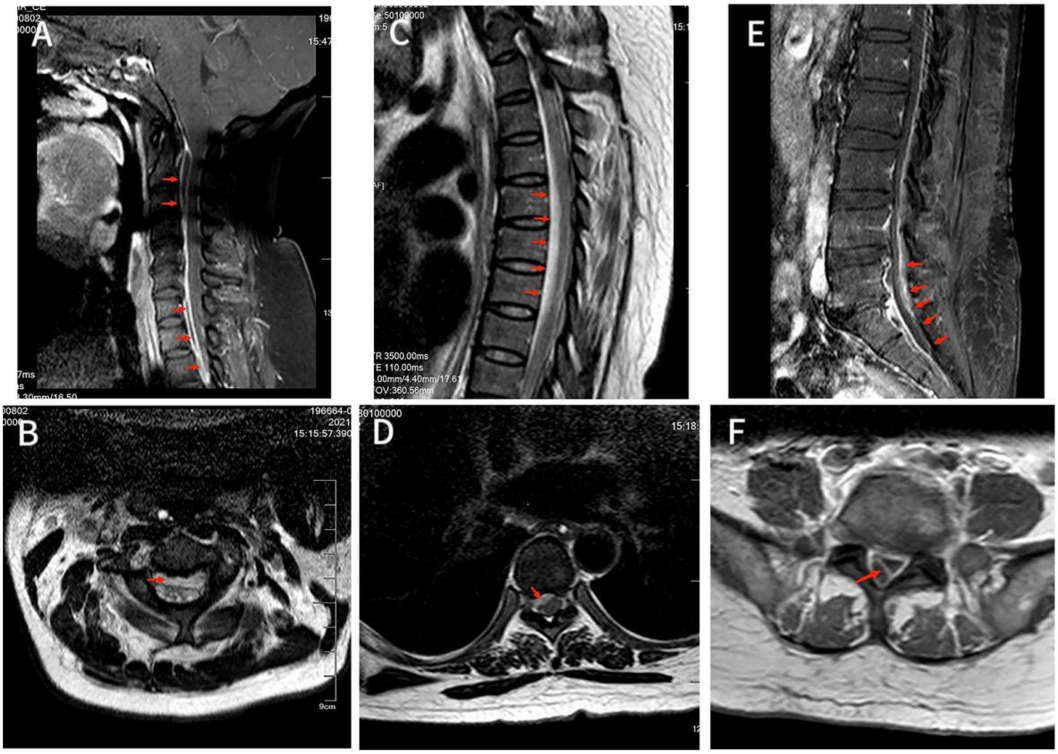

FIGURE 1
(A) MRI T2-weighted image showed hyperintensity of the lesion on the ventral side of the spinal cord in the C2-C6 spinal canal. Also saw C5/6 intervertebral disc herniation and the corresponding dura and spinal cord were compressed. **(B)** Axial T2-weighted image showed an annular high signal lesion in the anterior part of the spinal cord within the spinal canal of C2, and spinal cord compression at the C2. **(C)** T2-weighted image showed hyperintensity of lesions ventral to the spinal cord in the T2-T8 spinal canal, with corresponding levels of spinal cord compression degeneration. **(D)** Axial T2-weighted image showed annular high signal lesion in the right anterior part of the spinal cord within the spinal canal of T7 accompanied by nerve root and spinal cord compression. **(E)** T1-enhanced image showed disc bulging in L3/4, L4/5 and L5/S1 with annular enhancement of the lesion ventral to the spinal cord in the L4-S1 spinal canal with spinal cord compression at the corresponding level, but no significant internal enhancement. **(F)** Axial T1-enhanced image showed a large range of irregular non-enhanced areas in the soft tissue of the right posterior side of the at the L5 level, and a ring-enhancing lesion in the right posterior part of the intradural sac with no obvious internal enhancement.

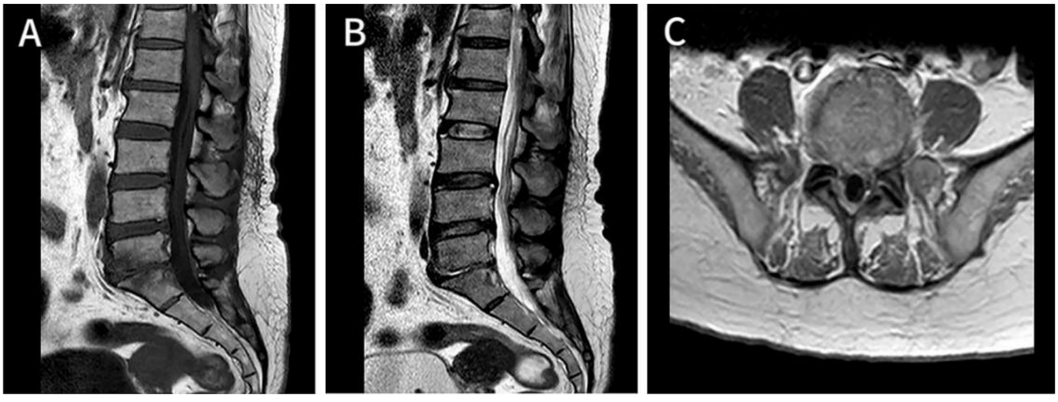

FIGURE 2
At 2-month follow-up, sagittal T1-weighted **(A)** and T2-weighted image **(B)** and showed the lumbar disc herniation was still present, and the epidural space in the posterior lumbar and anterior sacrococcygeal segments was wider than before, and the enhancement of the dural sac improved after enhancement compared with before. Axial T1-enhanced image **(C)** showed the previously large range of irregular non-enhanced areas has decreased compared to Figure 1F.

body, which are closely adherent. Hence, SEA occurs in the posterior epidural space (4). The etiopathogenic mechanism of spinal involvement in our patient remains to be determined. However, our case is unique as the cervicothoracic abscess occurred in the anterior epidural space, while the lumbosacral abscess occurred in the posterior epidural space, suggesting a

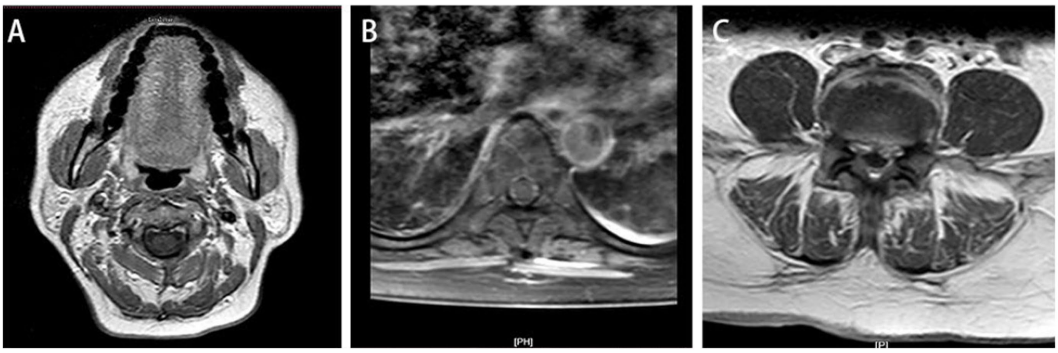

FIGURE 3
At 1.5-year follow-up, Axial T1-enhanced image of the cervical **(A)**, thoracic **(B)**, and lumbar **(C)** segments demonstrated that the epidural abscess was almost completely absorbed, and the epidural space now shows normal signal intensity, with a largely improved corresponding spinal cord compression.

possible route of infection. Tetsuka et al. (5) believed that SEAs secondary to septic spondylitis or intervertebral discitis tend to be located anterior to the dural tube, while those due to hematogenous infections tend to be located posterior to the dural tube. The vertical sheath of the epidural space enables the spread of abscesses from the level of origin to multiple levels longitudinally. Infections can enter the epidural space through various mechanisms, including hematogenous spread (50%), direct extension from adjacent infection (33%), inoculation from spinal procedures (15%), and unknown mechanisms (6, 7). The incidence of infection after combined spinal-epidural anesthesia is approximately 1/2000 (5, 6). Other potential risk factors include diabetes, human immunodeficiency virus (HIV) infection, trauma, tattooing, acupuncture, and infection of the adjacent bone or soft tissue (8, 9). Additionally, degenerative disk disease, large osteophytes, and chronically hypertrophied facet joints may be targets of hematogenous spread (10). Hematogenous spread is commonly caused by methicillin-resistant *Staphylococcus aureus* (MRSA), and the exotoxins, extracellular enzymes, and cell surface substances of MRSA can cause ischemic changes and tissue destruction in the spinal cord through various mechanisms, ultimately leading to spinal cord injury (11). Other bacteria causing hematogenous spread include negative cultures (13.9%), Gram-negative bacteria (8.1%), coagulase-negative *staphylococci* (7.5%), and *Streptococcus anginosus* group (SAG, 6.8%) (12).

Blood culture following an admission of our patient indicated *S. intermedius*. *S. intermedius* is one of the three species found in the SAG, also known as the *Streptococcus milleri* group (SMG) (2). SAG is a commensal in the oral and gastrointestinal tracts. But SAG is notorious for causing invasive infections, including head and neck abscesses, bacteremia with endocarditis, liver abscess, thoracic empyema, brain abscess, and spinal epidural abscess (13, 14). Although rare, patients with underlying diseases such as cirrhosis, diabetes, and malignancy are susceptible to SAG infection (15). We reported a case of an extensive SEA treated conservatively, along with a review of relevant literature and discussions on SEA caused by *S. intermedius*. We conducted a PubMed search using the keywords "*Streptococcus anginosus* group abscess" and "*Streptococcus intermedius* epidural abscess," to identify reports and studies on spinal abscess caused by *S. intermedius*. Only 6 cases were found, including the present case, with an average patient age of 61 (standard deviation: 18.01) years, and four of the seven patients were women. In contrast to the case report mentioned in Table 1 (14, 16–20), this patient had no known risk factors such as dental disease, surgery, or trauma. After 2 months of IV antibiotic treatment, the patient showed partial resolution of the epidural abscess on MRI. Gangone et al. (21) reported a case of an immunocompetent 72-year-old patient with a complaint of simple low back pain, who was found to have co-infection with *S. intermedius* and *Streptococcus griseus*. The patient was treated with IV antibiotics and recovered completely. Although Gangone et al. (21). found no such dental intervention in their patient's medical history, poor dental hygiene is a known predisposing factor for spinal abscesses and infective endocarditis. Similarly, our patient was immunocompetent, only had lumbar disc herniation and lumbar spondylolisthesis located at L5 level. Although we have not yet determined the exact cause of the patient's extensive SEA, the combination of imaging and medical history suggests that multiple confounding factors may have contributed to the condition. We believe this case highlights the importance of considering *S. intermedius* as a potential causative agent of SEA, particularly in patients with underlying diseases.

Clinical presentation

SEA is typically characterized by the triad of fever, back pain, and neurological dysfunction. However, only 0.8% of patients exhibit this classic presentation on admission, making the diagnosis of SEA challenging (22). The prevalence of back pain and the rarity of SEA create a diagnostic conundrum, resulting in delayed diagnosis in 75–89% of cases (23). In this case, the patient presented with typical symptoms, progressing through four stages of back pain, nerve root symptoms, muscle weakness, and paresthesia, ultimately leading to complete paralysis within 1 day of entering the third stage. This progression is consistent with Heusner's description of the four progressive stages of clinical presentation of SEA, which are variable in duration and may result in unpredictable neurological deterioration, underscoring the importance of prompt diagnosis and treatment (24). Although abnormal laboratory values such as leukocytosis or elevated

TABLE 1 Review of spinal epidural abscess (SEA) cases with pathogenic reports of *Streptococcus intermedius* (*S. intermedius*) infection.

Authors/year of study (reference)	Age	Sex	Predisposing factors	Symptoms	Affected levels	Surgery	Outcome	Following-up duration (months)
Lee et al., 2022 (16)	68	M	· Diabetes · Chronic periodontitis	· 5-day fever and back pain · urine retention · paraplegia	T2 to T4 L1 to S3	· Laminectomy · Discectomy	Return to daily activities	17
Ramhmdani and Bydon, 2017 (17)	74	M	· root canal procedures	· Urine retention · Paraplegia	L1 to L5 T10 to T11	· Laminectomy · Surgical drainage	Resolution of abscess on MRI	3
Heckmann and Pauli, 2015 (18)	77	F	· Single-tooth extraction	· 5-day neck stiffness	C1 to T7	· Neurosurgical therapy	Recovery	NR
Lampen and Bearman, 2005 (14)	25	F	· Pregnancy	· 2-week Shoulder pain · 3-day Urine retention · 3-h Paraplegia	T1 to T2	· Laminectomy	Return to daily activities	10
Yang et al., 2018 (19)	67	F	· percutaneous intradiscal injection	· 4-day Urine retention · 4-day lower limbs numbness	C2 to T1	· Surgical drainage	MRI abnormalities	12
Shiu et al., 2014 (20)	69	M	· Diabetes	· 1-week fever · Paraplegia	T4 to T8 L2 to L4	· laminectomy · vertebroplasty · surgical drainage	· Failed to recovery	2

M, male; F, female; NR, Not Referring.

inflammatory markers and isolation of pathogenic pathogens from blood cultures may be predictive of disease severity in established diseases, they are not specific for diagnosis (25). Furthermore, in this case, the patient's MRI performed before admission did not reveal SEA, further highlighting the diagnostic challenge associated with this condition.

Imaging diagnosis

In suspected cases of SEA, imaging should be promptly performed. While lumbar puncture results showing perimembranous inflammation can aid in the diagnosis, this method is invasive and carries the risk of spreading the infection to the subarachnoid space or causing meningitis, as is the case with CT myelography (26). Therefore, after two lumbar punctures were performed and failed, we did not attempt a third. Puncture failure may be caused by the patient's obesity (27, 28). MRI is the most accurate diagnostic tool for SEA, revealing not only the presence and extent of the abscess but also the degree of spinal cord compression. However, MRI findings in the early phase of the clinical course can be insignificant or subtle. Typical features of spinal infections include the contiguous involvement of two vertebrae and inflammatory changes within the intervertebral disc, but these are relatively chronic changes that may take weeks or months to manifest (29). A diagnostic delay of 4 months is not uncommon, given the time lag between initial symptoms and MRI (30). Intravenous gadolinium-enhanced MRI has high sensitivity and specificity, allowing for the diagnosis of SEA as epidural masses with surrounding septic or necrotic material exhibiting linear enhancement on T1-weighted contrast-enhanced MRI or hyperintensity on T2-weighted MRI (31). In cases where the diagnosis is still unclear after enhanced CT and plain MRI, a gadolinium-enhanced MRI should be performed, as recommended by Dunbar et al. (30) He reported a case of an immunocompetent patient who underwent two enhanced CT and one plain MRI with no results until undergoing enhanced MRI, which provided a clear diagnosis of SEA due to *Pasteurella multocida* (30). In our case, The patient presented with neurological root symptoms but no fever before admission. Initial MRI and plain radiography diagnosed the patient with simple lumbar disc herniation, which may have been either underdiagnosed or caused by a rapidly developing abscess in the week, leading to subsequent neurological impairment. Therefore, repeat examinations or gadolinium-enhanced MRI should be considered when initial MRI findings are not diagnostic of SEA.

Management

For SEA confirmed by imaging, the standard treatment has traditionally been urgent surgical decompression followed by 6 weeks

of IV antibiotic therapy. The literature suggests that surgical intervention is necessary in cases of acute or progressive neurological deficits, spinal instability, progressive deformities, or disease progression despite antibiotic therapy (7). Kim et al. (32) identified four independent predictors of nonoperative management failure in a cohort of 142 medically managed patients: age > 65 years, diabetes, neurologic impairment, and MRSA. If all four risk factors are present, they report a 99% failure rate. In a similar study, Patel et al. (33) reported three additional independent predictors of failure: leukocytosis >12.5, positive blood cultures, and CRP >115. If all three risk factors are present, they report a 77% failure rate (33). However, urgent surgical decompression is not always beneficial, as it may result in significant surgical trauma, impair spinal stability, and require spinal fusion surgery, which can reduce the patient's range of motion in the lower back (34). The timing of surgical intervention for SEA is also controversial (35). In this case, we considered the patient's poor condition and concluded that open surgery involving multiple segments may not be well-tolerated, despite the presence of independent predictors of non-surgical treatment failure and a high rate of non-surgical treatment failure as reported by Kim and Patel. The epidural compression was primarily caused by granulation tissue, and the size of the epidural abscess was relatively small. Therefore, we determined that excising only a small portion of the granulation tissue and performing decompression would not be particularly beneficial (36). Additionally, the origin of the abscess, whether it is ventral or dorsal, affects spinal stability after decompression surgery. Karikari et al.'s (37) regression model showed that ventral abscesses can be approached ventrally, preserving the posterior longitudinal ligament and reducing postoperative morbidity. We believed that this patient's lumbar abscess originated from the dorsal side and had a relatively poor prognosis compared to the ventral side.

MRI is a crucial diagnostic tool for SEA patients as it provides accurate and objective imaging, enabling conservative treatment options consisting of systemic antibiotics and CT-guided percutaneous needle aspiration. Adogwa et al. (38) examined 82 cases of SEA in patients over the age of 50 with multiple comorbid conditions and found that early surgical decompression combined with IV antibiotics was not superior to IV antibiotics alone in this small group of patients. Arko et al. (12) came to similar conclusions. He concluded that patients can usually be treated with intravenous antibiotics and do not always require surgery, even though the patient may deteriorate clinically at any time (12). Antimicrobial agents are best chosen for the causative organism identified in blood cultures. Without knowing the causative bacteria, treatment should be initiated empirically. However, it is likely that different diseases, such as spinal abscess, liver abscess, and cystic fibrosis, will display significant differences in antimicrobial susceptibilities relative to published reports, given the frequent exposure of patients with underlying diseases to chronic macrolide suppressive therapy, inhaled aminoglycosides, and frequent use of fluoroquinolones (39). The previous standard antibiotic regimen for the treatment of abscesses associated with *S. intermedius* was penicillin plus chloramphenicol, but increasing resistance of *S. intermedius* to some antibiotics and the possibility of antagonism between penicillin and chloramphenicol have been documented (2). The most potent empiric therapies for *S. intermedius* include vancomycin, teicoplanin, and imipenem (40, 41). The British Society of Antimicrobial Chemotherapy (BSAC) advises that abscesses may be treated with a combination of Cefotaxime (a beta-lactam antibiotic) and metronidazole parenterally for 3 to 4 weeks or between 4 and 6 weeks when they are aspirated (42). Our case involved a patient with extensive SEA caused by *S. intermedius* infection, who presented with type II respiratory failure upon admission and was immediately transferred to the ICU for tracheal intubation. She had no sinusitis, heart disease, dental procedures, or other known risk factors for abscesses caused by *S. intermedius*. Intravenous vancomycin was initiated before the results of the blood culture were available, and after the culture results became available, meropenem and moxifloxacin were added. Fortunately, the patient's drug sensitivity test results suggested sensitivity to these antibiotics. The duration of antibiotic administration is supported by the literature. After 5 days of antibiotic therapy, the blood culture became negative, and a repeat MRI performed 6 weeks later revealed a decrease in abscess size compared to the previous scan. After 2 months of antibiotic treatment, the patient's muscle strength was restored. These outcomes suggest that our conservative treatment approach was successful in managing the patient's condition.

Conclusion

SAG is a small contributor to spinal infections. However, neurological symptoms associated with SAG can deteriorate rapidly, with nerve root symptoms progressing to extremity paralysis in as little as 1 day. The classic triad of fever, back pain, and neurological dysfunction should prompt immediate suspicion of SEA, and a prompt repeat general MRI or intravenous gadolinium-enhanced MRI should be performed, even if the initial MRI was negative. Empirical therapies that have shown efficacy against *S. intermedius* include vancomycin, tacrolimus, and imipenem. Given our patient's circumstances involving multiple segmental spinal abscesses and respiratory failure, the timely and appropriate administration of sensitive IV antibiotic therapy may also be an effective approach in treating extensive SEA.

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

DL conducted the data analysis and wrote the first draft. WL critically revised the article. WH and WZ rearranged the figures and enriched the interpretation of the figures. QL was directly responsible

for the manuscript. All authors made significant contributions to the article's conception and design.

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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Cerebrotendinous xanthomatosis tremor successfully controlled post-ventral intermediate nucleus-deep brain stimulation: a case report

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Cerebrotendinous xanthomatosis (CTX) is a rare autosomal recessive disorder caused by a deficiency of the sterol 27-hydroxylase enzyme. This deficiency results in excess production and accumulation of cholestanol, which can lead to many clinical findings within the first three decades of life, including progressive neurological dysfunction. This is a treatable condition with improvements in neurological and non-neurological symptoms upon the early initiation of replacement therapy. This case report details a 42 years-old left-handed male in whom deep brain stimulation (DBS) intervention was pursued due to a limiting tremor related to delayed diagnosis and treatment of CTX at 22 years old. The application of DBS in treating tremors in a CTX patient has not previously been reported. For our patient, application of DBS led to meaningful and longstanding tremor control benefits that have required minimal changes to stimulation parameters post-DBS. These improvements to tremor were achieved without negative impact to his other CTX related comorbidities.

KEYWORDS

cerebrotendinous xanthomatosis (CTX), deep brain stimulation (DBS), tremor, hyperkinetic movement disorder, lipid storage disease

1. Introduction

Cerebrotendinous xanthomatosis (CTX) is a rare autosomal recessive disorder caused by a deficiency of the sterol 27-hydroxylase enzyme (1). This deficiency results in excess production and accumulation of cholestanol in multiple tissues, including the eyes, tendons, and brain (1). The excess accumulation can lead to early-onset cataracts, tendon xanthomas, and progressive neurological dysfunction. These clinical signs typically begin manifesting in early infancy and are more notably present within the first three decades of life (2, 3). Treatment of CTX with replacement chenodeoxycholic acid (CDCA) can prevent development of irreversible neurological and non-neurological symptoms and/or stabilize symptoms if initiated early (4). However, disease progression has been observed in patients initiated on CDCA replacement beyond the age of 24, making early diagnosis and replacement therapy critical (5–7). Neurologic symptoms that can develop—including epilepsy, spasticity, and a variety of hypokinetic and hyperkinetic movement disorders thought to be a late disease manifestation—are treated symptomatically (3). Deep brain stimulation (DBS) is an established therapy option for patients

with various movement disorders and has been applied to less common tremor disorders (8–12). However, the tolerability and response of DBS in treating tremor in a patient with underlying CTX has not previously been reported. This case report details a single case of CTX-tremor that was successfully treated with unilateral thalamic ventral intermediate nucleus (VIM) DBS.

2. Case description

The patient is a 42 years-old left-handed male with multiple CTX-related sequalae including developmental delay, cataracts, epilepsy, diabetes, chronic pancreatitis, anxiety, depression, parkinsonism, and postural/action tremor. CDCA replacement therapy, taken 250 mg orally three times a day, was delayed due to his CTX remaining undiagnosed until he was 22 years-old. His diagnosis and CTX management occurred at an outside institution based on elevated cholestanol levels, brain imaging findings as detailed below, and subsequent genetic testing that were not available to us upon his transfer of care at our institution. Onset of movement symptoms predominantly impacting his left hemibody have been present at least from the mid-2000s. He reported dramatic worsening of tremor in 2016 in the setting of long-standing use of aripiprazole since 2010 for mood stabilization without any recent adjustments. There was a transient initial improvement to tremor and parkinsonism with levodopa (carbidopa-levodopa IR 25 mg–100 mg 1 tablet with carbidopa 25 mg taken orally four times a day, ondansetron 8 mg taken orally 30 min prior to carbidopa-levodopa) and amantadine (100 mg 1 tablet three times a day); however, he subsequently developed gastrointestinal side effects with attempts at further titration. Trials with primidone and topiramate were unsuccessful and also led to intolerable side effects, and bradycardia limited the use of beta blockers.

On evaluation, his unified Parkinson's disease rating scale (UPDRS) part 3 OFF score was 37/108 and ON score was 31/108. Additionally, the tremor rating scale (Fahn–Tolosa–Marin) pre-DBS total score was 32/144 (moderate functional disability). On examination he exhibited left predominant rest tremor, rigidity, bradykinesia, gait changes without postural instability with additional findings of a primarily left upper extremity action/postural tremor. His main limitations subjectively reported were due to action/postural tremor impacting his dominant hand. Formal neuropsychological testing revealed baseline deficits in verbal memory (immediate recall 1st percentile) with delayed recall and recognition in the average range. Executive function was significantly impaired (Trails A 1st percentile, Trails B discontinued) with categorical fluency in the borderline range (5th percentile). Baseline physical therapy (PT) evaluations revealed a BERG balance scale 51/56 (range 0–56 with scores above 41 indicating independence with ambulation without assistance), timed-up-and-go 9.3 s (older adults who take longer than 14 s have an increased risk of fall), 5 times sit to stand 12.10 s (±15 s = risk of fall). A non-contrast MRI of the patient's brain at the age of 21, around the time of worsening of symptoms, demonstrated nonspecific findings of a diffuse increase in signal intensity of the white matter in the bilateral dentate on T2 and FLAIR weighted imaging persistent in his planning MRI obtained in 2018 (Figure 1).

The patient was counseled regarding the lack of evidence regarding the role of DBS to treat tremor in individuals with CTX. Given the extensive impact on his quality of life due to his left-sided tremor affecting his dominant side, the patient and his care team elected to proceed with surgery.

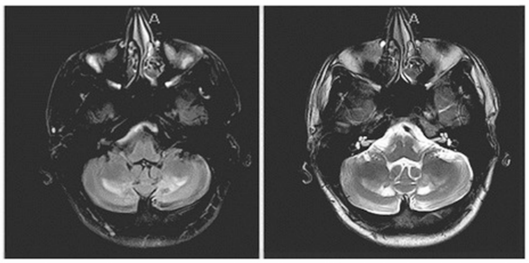

FIGURE 1
Sequela of known cerebrotendinous xanthomatosis on brain MRI: non-contrast MRI showing a nonspecific finding of diffuse increase in signal intensity of the white matter in the bilateral dentate on FLAIR weighted imaging (left image) and T2 (right image) sequences.

He underwent a unilateral right-sided Medtronic DBS lead placement to the VIM of the thalamus, followed by a right anterior chest wall placement of an Activa primary cell implantable pulse generator (IPG) 1 week later. He reported a "honeymoon" (lesion) effect of 75%–80% prior to turning on stimulation at initial programming session. Threshold evaluation was conducted at 90 pulse width (PW) and 130 Hz frequency, with noted improved tremor at lower voltages and more ventral contacts. Final initial settings 2-C+ 2.0v 90PW 130 Hz.

3. Results—follow up and outcomes

3.1. Initial and short-term effects

At the initial programming visit prior to turning on stimulation his tone was mildly increased bilaterally at baseline and there remained a subjective and objective reduction in tremor from suspected lesion effect (tremor remaining in left hemibody rest tremor 1/4, postural/action tremor 1/4, leg tremor 1/4, all other measures 0). Although patient had discontinued amantadine and carbidopa-levodopa on his own for concerns of GI side effects prior to initial programming session, he remained on propranolol 10 mg 1 tablet TID for concomitant diagnosis of portal hypertension. By 1 month visit post initial programming signaling short-term effects, he reported symptom improvement of his LUE tremor of 90% (tremor remaining in left hemibody rest postural/action tremor 1/4, all other measures 0) and reported no changes in mood, cognition, speaking, or swallowing. His 3 months post-operative neuropsychological performance was stable compared to his baseline performance. However, he did require seeing PT after the first month for concerns of imbalance with noted minimal changes to BERG balance scale 48/56, timed-up-and-go 11.5 s, 5 times sit to stand 12.28 s. He was optimized after the initial programming session and remained with settings unchanged over the first 6 months period. Post-DBS tremor rating scale improved to a total score of 15 with previous score of 32 and marked improvement (50%–100%) on subjective assessment by the patient compared with his last visit.

3.2. Complication

Unfortunately, the patient developed complications of right cranial and infra-auricular wound breakdown and presented to the OR for a wound revision 7.5 months after his DBS lead insertion surgery. He experienced another wound breakdown with serosanguineous drainage over the IPG incision site at the right anterior chest wall and underwent a second wound revision surgery 11 months after the initial IPG placement. Ultimately these wound revisions failed, and the patient underwent removal of the unilateral right DBS lead of the IPG 1 year after their original insertion. Following a 2 weeks course of postoperative intravenous ciprofloxacin 250 mg twice a day, he recovered well.

The patient's left-sided tremor re-emerged approximately two and a half weeks after DBS removal and he continued to experience issues, mainly with feeding himself and stuttering speech. According to the patient's mother, who is his primary caregiver, his tremors remained mildly improved from prior to DBS. These symptoms were significantly distressing to the patient, and he elected to proceed with DBS re-implantation.

3.3. DBS re-implantation

Three months after wound recovery, he underwent a fiducial screw implantation, a re-implant of his right unilateral DBS targeting the VIM, and an Activa SC IPG to the right anterior chest wall. His stimulation (2-C+ 2.0v 90PW 130 Hz) was initiated 1 day post-procedure, unchanged from his initial programming session. Three months post-implantation, the patient reported significant improvement of his tremor and being able to eat and write using his left hand, as well as improvement of his speech, memory, and balance with some unsteadiness while going down hills. Post-DBS tremor rating scale total score was not available.

3.4. Long-term effects

The patient has continued follow-ups with his interdisciplinary team, including his primary care provider, neurology, endocrinology, psychiatry, and ophthalmology. Two years after re-implantation of the right VIM lead, tremor symptom control remains very much improved (tremor remaining in left hemibody rest postural/action tremor 1/4, all other measures 0). He remains on propranolol 10 mg TID for his portal hypertension. While adjustments were made to the active electrode, overall settings have remained relatively stable (1-C+ 2.0v 90PW 135 Hz). He completed PT in April 2022, at which time he had a BERG balance scale 52–53/56, timed-up-and-go 9.70 s, 5 times sit to stand 14.67 s, which are all comparable to pre-DBS assessments except for increase in sit to stand time. Although he notes intermittent stuttering speech and gait changes, his most current neurology assessments as of October 2022 include a Fahn–Tolosa–Marin tremor rating of 6/80 on medication. His parkinsonian symptoms of bradykinesia and rigidity have remained largely unchanged in the setting of VIM stimulation. Due to worsening depression disorder and anger issues, patient's mood medications were adjusted, and he has remained well controlled. Overall, the patient's tremors remained stable with very good functional ability including eating, drinking, cutting food, using buttons and zippers. For his stutter, he completed speech therapy with good improvement of his speech, but he has recently had worsening of his stutter and is considering returning to speech therapy.

4. Discussion

Although the predictive value of the levodopa challenge score on parkinsonian symptoms control with DBS implantation is well documented (13) it was unclear whether the patient would benefit from the procedure given his mixed rest and action-postural tremor alongside a poor levodopa challenge score. Focusing on the limiting tremor symptoms impacting his dominant hand, meaningful improvements were achieved. Handwriting was found to improve in approximately 70% of patients following DBS implantation targeting the VIM (14). This patient's handwriting was found to improve significantly during DBS programming, exhibiting improved legibility and reduced tremor post stimulation (Figure 2). As medication regimen remained unchanged pre- and post-DBS programming, the observed effects on symptom control were attributed to VIM-targeted stimulation and less to pharmacologic control, although synergistic effect with ongoing beta blocker cannot be entirely ruled out.

Our patient had MRI changes involving the cerebellar dentate nucleus that may explain in part the movement disorder manifestations and in particular his mixed tremor symptoms. Although the precise mechanisms by which VIM-DBS influences tremor remain unknown, advances in technology and focus on neuronal synchrony as well as diffusion tractography have further emphasized the role of the cerebellothalamocortical pathway in tremor contribution (15–17). The association between cortical-subcortical pathways impacted by VIM-DBS stimulation in relation to CTX pathophysiology remains to be elucidated.

Possible side effects from DBS targeting the VIM include dysarthria, impaired gait and balance, and cognition difficulties, with more pronounced effects observed following bilateral lead placement (18). Although the patient did report stuttering and gait disturbances after DBS implantation, therapy significantly helped improve his speech and gait. Objectively, gait measures did exhibit some fluctuations but remained overall stable. Due to the patient's history of behavioral and cognitive issues prior to DBS therapy, there was hesitation on the part of the providers to proceed regarding tolerability of the DBS procedural process as well as stimulation. However, neuropsychological assessment offered insight into his baseline neurocognitive performance and helped provider confidence regarding his healthy social support system and his understanding of the risks and benefits of the DBS. Importantly, he did not exhibit a decline or worsening from a neuropsychological standpoint post-DBS. Continued monitoring by a multidisciplinary team has ensured patient safety.

While he did experience infectious complications requiring wound care, this is a risk in any surgery, including DBS implantation (19–21) and he opted for re-implantation given the benefits achieved from his initial procedure. While CTX is a rare and treatable disorder that should not be missed given promising improvements and stability of symptoms with early intervention, this report highlights the application of DBS in a case where a delay in treatment of CTX led to limiting tremors that were safely and effectively managed with DBS.

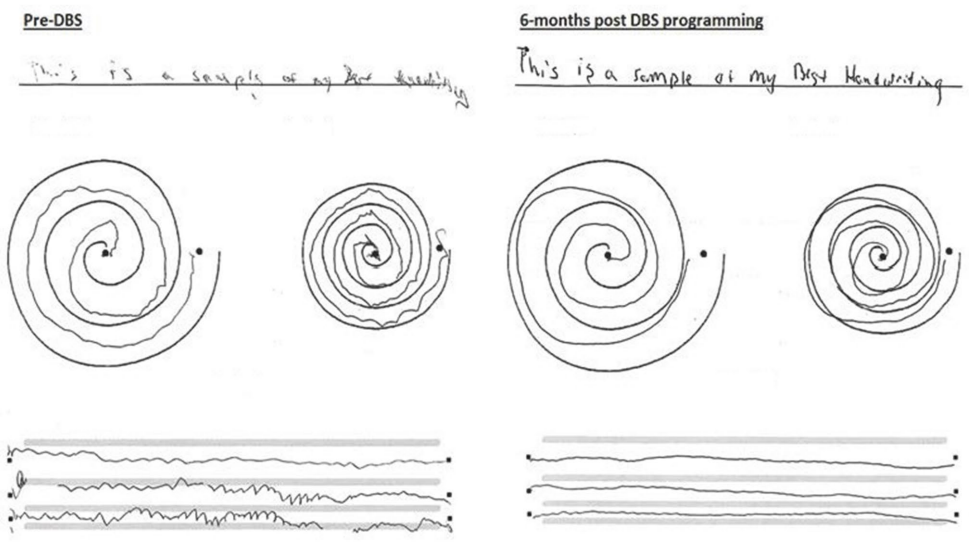

FIGURE 2
Handwriting and drawings of dominant left upper extremity: motor examination pre-DBS placement and 6 months post-DBS VIM placement.

5. Conclusion

This gentleman is the first case known to the authors demonstrating that DBS can be successfully used to treat tremors secondary to CTX. While in general, CTX patients stabilize in their course once on replacement therapy with CDCA, factors such as age of initiation, duration, and adherence to medication regimen can affect treatment efficacy and risks of developing complications (5). It is therefore imperative that a multidisciplinary team of neurologists, ophthalmologists, and metabolic specialists are available to monitor the comprehensive health of these patients, especially in cases of delayed onset of replacement therapy such as in this case.

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 approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

AR and SDJ contributed to the conception of the case report. EK organized patient data. EK and AR wrote the first draft of the manuscript. SDJ edited and wrote sections of the manuscript. JM and EF were directly involved with patient care and edited sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

SDJ has received support unrelated to this research for her role as an Educational Consultant for Medtronic Inc.

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.

Publisher's note

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Cervical dystonia and no oculomotor apraxia as new manifestation of ataxia-telangiectasia-like disorder 1 – case report and review of the literature

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Ataxia-telangiectasia-like disorder 1 (ATLD1) is a rare neurodegenerative disorder associated with early onset ataxia and oculomotor apraxia. The genetic determination of ATLD1 is a mutation in the *MRE11* gene (meiotic recombination 11 gene), which causes DNA-double strand break repair deficits. Clinical features of patients with ATLD1 resemble those of ataxia telangiectasia (AT), with slower progression and milder presentation. Main symptoms include progressive cerebellar ataxia, oculomotor apraxia, cellular hypersensitivity to ionizing radiations. Facial dyskinesia, dystonia, dysarthria have also been reported. Here we present a 45-year old woman with cervical and facial dystonia, dysarthria and ataxia, who turned out to be the first case of ATLD without oculomotor apraxia, and with dystonia as a main manifestation of the disease. She had presented those non-specific symptoms for years, before whole exome sequencing confirmed the diagnosis.

KEYWORDS

ataxia-telangiectasia-like disorder 1, cervical dystonia, MRE11 gene, ataxia, case report

Introduction

Ataxia-telangiectasia-like disorder 1 (ATLD1; OMIM#604391) is an extremely rare disease with only 25 confirmed cases worldwide (1), with the largest recognized cohort in Saudi Arabia (2, 3). It is associated with early onset ataxia with oculomotor apraxia. The genetic basis of ATLD lies in a mutation in the *MRE11* (meiotic recombination 11) gene, which causes an improper response to DNA damage (4, 5). The emergence of mutations during the cell cycle is not an unusual phenomenon in healthy organisms, but a proper response against them is essential for DNA-integrity maintenance and cell survival (6, 7).

Chromosomal instability (CIN) refers to the occurrence of an increased number of faults in genetic material, leading to chromosomal rearrangements such as translocations, inversions, duplications and/or deletions (8, 9). The basis of this phenomenon is an impaired mechanism

of repairing certain DNA damage. It is a characteristic feature of Chromosome Instability Syndromes (CIS) and is commonly seen in cancer cells (2, 10).

Some of the best known examples of CIS are ataxia-telangiectasia (AT) and Nijmegen breakage syndrome (NBS) (11). Although they are classified in the same group, considering their shared etiology, their clinical manifestations can be distinctly different. Recently conducted detailed genetic examination has allowed the isolation of diseases similar to them, called ataxia-telangiectasia-like disorders (ATLD) and NBS-like syndrome, which share some clinical features, but whose genetic origins turn out to be different (12).

AT syndrome (Louis-Bar syndrome) clinically presents with cerebellar ataxia (unsteadiness, lack of coordination) and cutaneous telangiectasia (numerous dilated small blood vessels) that is most apparent on the sclerae (13). Patients also suffer from immunodeficiency, radiosensitivity, cancer susceptibility, recurrent sinopulmonary infections and high levels of serum alfa-fetoprotein. AT phenotypes vary, from severe early-onset to milder adult-onset, depending on the type of mutation (14, 15).

The cause of clinical- AT symptoms is inactivation or deficiency of Ataxia-Telangiectasia-Mutated protein kinase (ATM) (16), which is one of the DNA damage response factors (DDR). ATM kinase activation is triggered by DNA double-strand breaks (DSBs) and results in phosphorylation of a variety of substrates, including p53, CHK2 and MDM2 (17), that cause DNA damage or eventually cellular apoptosis. Deficiency of ATM kinase leads to accumulation of abnormal DNA forms and disfunction of mitochondria which underlie development of AT syndrome with progressive cerebellar degeneration. This phenomenon is associated not only with pathologically increased risk of cancer development, but also prematurely aging of the body (18).

Another factor of general cellular response is MRN complex, that includes three genes (*Mre11*/*RAD50*/*NBS1*) (19) and is necessary for the process of effective DNA repair. It binds DNA ends in DSBs and activates kinase ATM monomerization (9, 17). By interaction with NBS1 protein, ATM is autophosphorilized, which is an indicator of its activation. MRN also possesses endo- and exo-nuclease activities that helps the cell to cut out and destroy defective DNA. Mutation-induced decreased levels of MRN complex components result in dysfunctions in kinase ATM actions and its accumulation at the site of DNA breakage. Moreover, deficiency of each element of MRN presents various range of symptoms.

Dysfunction of NBS1 (nibrin) protein determines the diagnosis of Nijmegen breakage syndrome (20). Neurodegeneration does not occur in NBS, but it is associated with microcephaly observed since birth, which influences craniofacial features. As in most of the CIS, the clinical picture of NBS includes immunodeficiency and an extremely high risk of developing cancer at a young age, especially of lymphoid origin (21). Other characteristic symptoms include growth inhibition, mild to moderate intellectual disability and hypogonadotropic hypogonadism in females. Prognosis is severe, due to early-onset cancers.

Nijmegen breakage syndrome-like disorder is caused by a mutation in the *RAD50* gene (22). Similarly to NBS, microcephaly, growth inhibition and intellectual disability are part of NBS-like syndrome's clinical picture. However, it does not present with cancer predisposition, immunodeficiency and severe infections.

Although MRE11 builds a complex with NBS1, mutations throughout the *MRE11* gene (located on chromosome 11q21) do not bear any resemblance to NBS. They result in syndromes with clinical presentation more similar to AT, therefore they are called ataxia-telangiectasia-like disorder 1 (ATLD1) (5, 23). The most specific symptom of ATLD1 is progressive cerebellar ataxia as a result of neurodegeneration. Brain magnetic resonance imaging may reveal cerebellar atrophy. Characteristic symptoms of ATLD1 include oculomotor apraxia (24), slow and dysmetric saccades, delayed convergence, gaze-evoked nystagmus, radiosensitivity. Telangiectasia and increased alfa-fetoprotein levels have not been reported. Researches into cancer susceptibility are inconclusive (4). Compared to ataxia-telangiectasia syndrome, ATLD1 has later onset, milder phenotype and progresses more slowly (25).

Interestingly, not only *MRE11* gene mutation is related to development of ataxia-telangiectasia-like symptoms. Recently published data suggest that a damaged form of another molecule, called PCNA (proliferating cell nuclear antigen), leads to a disease called ataxia-telangiectasia-like disorder 2 (ATLD2) (26). PCNA is a member of the DNA sliding clamp family (27). It protects the connection of DNA with its polymerase during replication, resulting in safe and effective DNA repair (28). The main clinical features of ATLD2 include ataxia, gait instability, dysarthria, dysphagia, prelingual sensorineural hearing loss, learning difficulties and cognitive decline with age, with no immunodeficiency reported (29).

In this article we report a 45-year-old-woman who presented non-specific symptoms for a few years, was hospitalized in various facilities and was diagnosed years after the first symptoms occurred. Whole exome sequencing enabled the discovery of a pathogenic variant in the *MRE11* gene that formed the basis of diagnosis of ATLD1. This is the first case of ATLD1 that presented without oculomotor apraxia and the only one whose most distinctive symptom was dystonia.

Case report

A 45-year-old woman was admitted to hospital for further diagnosis of speech and movement disorder, which was the reason for her repetitive hospitalization in the past. Unsettling symptoms first appeared approximately 7 years before, 2 years after the patient's second labor. Slurred speech occurred at first and was followed by tremor of the right upper limb and periodic tremor of the left upper limb. The symptoms gradually intensified. She reported stressful situations at work a few years before, that led to her first neurological referral.

Family history of neurological disorders was negative (both parents, sister and brother healthy, two healthy children age 13, 10). Perinatal and early childhood history was uncomplicated, however she always was clumsy. The first appearance of unspecified extrapyramidal symptoms was recorded at the age of 7. For that reason she was hospitalized, but no further diagnostic steps were taken. She also reported learning difficulties as a child, however, she received higher education. At the age of 31, she underwent a left ankle stabilization procedure due to generalized ligamentous laxity (diagnosed in early childhood). She did not report any other movement system-related disorders.

Neurological examination revealed slightly dysarthric speech, cervical dystonia, dystonia of the lower part of the face, positional and terminal tremor of the upper extremities (more intensified on the right), ataxia of both upper and lower extremities and dystonic-cerebellar gait disorder. Physical examination also showed proper muscle tone and strength in all extremities, with exaggeration of deep tendon reflexes.

Her pupils were properly reactive, slight exophthalmos was observed, no sign of Kayser–Fleischer rings. No oculomotor disturbances were noted, oculography showed no signs of latency extension, no signs of decrease in amplitude as well as normal velocity of saccadic movements in horizontal direction.

Consultation with a speech therapist showed a mild dysarthria with a predominance of the cerebellar component. According to the patient, speech disorders were persistent, but their intensity fluctuated, increasing in stressful situations. The patient also complained of excessive saliva and loud swallowing. Her handwriting presented a tendency to micrography.

Although patient did not notice any difficulties in cognitive functioning, neuropsychological consultation revealed a selectively diminished cognitive function. The process of verbal material learning was slowed down, susceptibility to interference and tendency to perserveration were noted. Short-time memory was decreased. The ability to retrive information from long term memory was preserved. Difficulty in planning complex actions was noted. The efficiency of working memory, attention switching and abstract verbal reasoning skills were also decreased. Praxis, visual–spatial and verbal functions were without relevant deficits. In comparison to the previous examination, a slight exacerbation of the deficits was noted during the second neuropsychological consultation. Patient no longer reported a depressed mood, but presented a trend toward an anxious response.

In spite of slightly diminished cognitive function, the patient is professionally active and raises two children by herself.

MRI showed no organic brain damage that could be the cause of these symptoms. Bilaterally widened cerebellar lobes, dilated cerebellar spinal tank and mega cistera magna were noted (Figure 1). Those findings can be classified as slight cerebellar atrophy, commonly seen in ATLD1 patients.

EEG was normal. Peripheral blood smear did not demonstrate features of acanthocytosis.

Differential diagnosis included genetic conditions, such as Huntington disease, Wilson disease, neuroacathocytosis – all were excluded. Functional disorders were considered and regarded as the most probable cause of disease for years.

In the course of the current diagnosis, due to an ambiguous clinical picture, Whole Exome Sequencing was performed. WES results detected the presence of two variants in the *MRE11* gene: c.77 T > C (p.Met26Thr) and c.1090C > T (p.Arg364Ter). Both gene variants are known and described in databases (HGMD, ClinVar) as pathogenic or potentially pathogenic.

Clinical manifestations and results of molecular studies were conclusive and indicated ataxia-telangiectasia-like disorder type 1, associated with *MRE11* gene mutation, inherited in an autosomal recessive manner.

Due to escalation of cervical dystonia, the patient had 100 units of botulin toxin injected in the cervical muscles. Dopaminergic agents were used in the past, but they did not help in the management of symptoms thus medications were discontinued. Genetic counseling was offered. Due to the autosomal trait of transmission, all patient's children are obligate heterozygotes asymptomatic carriers for MRE11 variants. Patient has got two children, who did not show any symptoms of ATLD1. In the event of reproductive planning, genetic consultation was advised. Prophylactic examinations were recommended, taking into account a lack of unequivocal data regarding cancer predominance (30). The patient was discharged in good general condition with a recommendation of further care in the outpatient clinic.

Discussion

Chromosome Instability Syndromes can present with a variety of clinical features, with different frequency and severity, so diagnosis is often challenging. Previously mentioned diseases are the result of inherited defects in the same pathway of response to DNA damage, so it is no surprise they share similarities. In some cases the only way to differentiate genetic conditions is to perform advanced genetic tests (5), which enable the detection of precise types of variants, responsible for certain phenotypes (31).

ATLD1 is an autosomal recessive disease, therefore the presence of two pathogenic alleles is necessary to develop symptoms. The occurrence of various pathogenic variants of the MRE11 gene results in different clinical manifestations of the disease in affected individuals. Missense mutation in the MRE11 gene was associated with higher levels of MRN proteins compared with truncating mutations (3, 5).

Previously reported cases of ATLD1 showed similar type, progression and intensity of symptoms. In contrast to our patient,

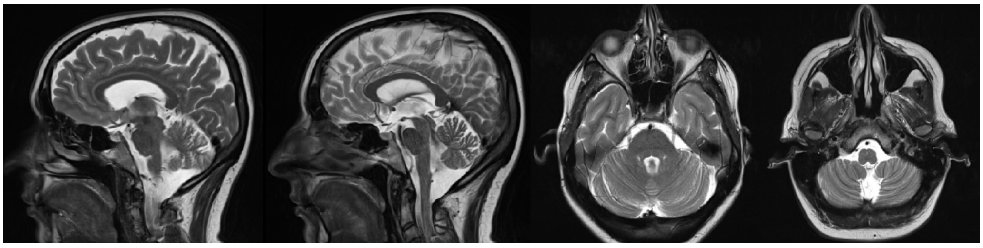

FIGURE 1
Brain magnetic resonance imaging (MRI).

most of the described cases showed their first symptoms in early childhood.

Although dystonia was present in some ATLD1 patients, it is not the main symptom of ATLD1. Dystonia is classically considered a basal ganglia disease, however now it is regarded as a network disorder with involvement of the cerebellum (32, 33). Le Bar et al. characterized familial phenotype associating dystonia and cerebellar atrophy (34). Miyamoto et al. reported a patient presenting a dystonia-ataxia phenotype with severe cerebellar atrophy visible in brain MRI (35). The findings from Batla et al.'s study suggest cerebellar involvement in some cases with cervical/segmental dystonia (36). Cases of ATLD1 patients may become next evidence of the potential connection between cerebellar atrophy and dystonia.

Stewart et al. (5) reported two families with three variants of the *MRE11* gene. In the first family two cousins were homozygous for nonsense variant (c.1897C > T, R633) and in the second family two brothers shared two variants: nonsense (c.1714C > T, R571X) and missense (c.350A > G, N117S). They all presented with early-onset (1-3yo) ataxia, with oculomotor apraxia, dysarthria and cerebellar atrophy (37, 38). Progressive, distal dystonia was observed in the second family.

Fernet et al. (3) reported 10 patients from three families in Saudi Arabia from ages 5 to 37, who presented early-onset (12 months-7 years old) ataxia and oculomotor apraxia without immunodeficiency and tumor development. Dystonia was not reported. All patients were homozygous for a novel missense variant (630G > C, W210C) of the *MRE11* gene. This variant results in dysfunctional MRN complex - mutated MRE11 protein is not able to interact with NBS1 protein.

Delia et al. (39) and Palmeri et al. (40) presented a case of a pair of siblings (37and 36yo), both of who were compound heterozygotes for *MRE11* gene variants: one missense (1422C > A, T481K) and one

TABLE 1 Clinical pictures and types of variants of some of the ATLD1 cases.

Study		MRE11 variants	Clinical picture						
			ataxia	deep tendon reflexes	facial dyskinesia	dystonia	dysarthria	ocular apraxia	cerebellar atrophy in MRI
Fernet et al. (Saudi Arabia) (3)	Family 1–4 cases	c.630G > C (p.Trp210Cys) (homozygous)	+	reduced	+	NM	NM	+	+/NA
	Family 2–3 cases		+	brisk	–	NM	NM	+	+
	Family 3–3 cases		+	reduced/ normal	–	NM	NM	+	+
Delia et al. (Italy) (39)	2 cases (siblings)	c.1442C>A (p.Thr481Lys); c.1714C>T (p.Arg572Ter)	+	reduced	+	slight dystonia of the hands/ face and hands	+	+	+
Mahale et al. (India) (41)	1 case	c.314 + 4_314 + 7 del (*as reported in the source*)	+	reduced	NM	mild finger dystonia	–	+	+
Raslan et al. (Brazil) (26)	2 cases (siblings)	c.1876_1895dup (p.Lys633fs) c.1516G > T (p.Glu506Ter)	+	absent	NM	mild dystonia in hands and feet	NM	+	–
Uchisaka et al. (Japan) (30)	2 cases (siblings)	c.727 T > C; g.24994 G > A (*as reported in the source*)	+	NM	–	–	+	+	+
Stewart et al. (United Kingdom) (5, 37, 38)	Family 1–2 cases (cousins)	c.1897C>T (p.Arg633Ter) (homozygous)	+	absent	NM	NM	+	+	+
	Family 2–2 cases (brothers)	c.350A>G (p.Asn117Ser); c.1714C>T (p.Arg572Ter)	+	normal	NM	present, distal	+	+	+
This report	1 case	c.77 T > C (p.Met26Thr); c.1090C > T (p.Arg364Ter)	+	brisk	+	severe dystonia of face and neck	+	–	+

NM, not mentioned; NA, not ascertained.

nonsense (1714C > T, R571X) – variant also reported by Stewart et al. (5). They showed similar progression of the disease (onset at 3 and 6 years of age), both suffered from early onset ataxia, ocular apraxia and cerebellar dysarthria. Furthermore, they presented with slight dystonic movements of the hands and (in one case) of the face.

A case of a 14-year-old boy, reported in India by Mahale et al. (41), presented early-onset, cerebellar ataxia with saccade and pursuit dysfunction, choreiform movements and mild finger dystonia of both outstretched hands. Exome sequencing showed compound heterozygous variants in the *MRE11* gene (c.314 + 4_314 + 7 del; the second variant was not reported).

Raslan et al.'s (26) study showed a pair of siblings (5 and 8 yo) with two heterozygous variants in the *MRE11* gene: c.1876_1895dup (p.Lys633fs) – frameshift variant, expected to disrupt the last 48 amino acid(s) of the MRE11 protein (42); and c.1516G > T (p.Glu506Ter) – nonsense mutation, known to be pathogenic (43). Both children presented with early onset (at 2 years of age), progressive gait ataxia. The elder also showed hypotonia, choreoathetosis, oculomotor apraxia and slow saccades, mild dystonia in hands and feet, absence of deep tendon reflexes and distal amyotrophy. The brain imagining was normal.

Uchisaka et al. (30) reported a case of a severe course of ATLD in two brothers, who had the same mutation in the *MRE11* gene (c.727 T > C and g.24994G > A). The ataxic gait first appeared when they were 2 years old, progression of cerebellar ataxia and cerebellar atrophy was observed. They also had developmental delay, slurred and explosive speech, and ocular apraxia, but no dystonia or dyskinesia. At the age of 15 and 9, they were both diagnosed with stage 4 non-small-cell lung cancer with multiple bone metastases.

We report a patient who is compound heterozygote in the *MRE11* gene. One of the variants - c.77 T > C (44) is a missense mutation that causes replacement of methionine at codon 26 by threonine, an amino acid with similar properties. This variant is rarely seen - it was previously reported in an individual with dystonia (45) and in an individual with abnormalities of the nervous system (46) and is associated with breast cancer susceptibility (47). Its clinical significance is described as likely pathogenic, due to insufficient data. A second variant of the *MRE11* gene – c.1090C > T – is more frequent and known to be pathogenic. It is a nonsense mutation, resulting in absent or disrupted protein product. The coexistence of these two variants has not previously been reported in ATLD1 patients, so it may be the reason for the unique clinical picture. In comparison to other reported ATLD cases, our patient was not only older, but also did not present with the full range of symptoms. At her age the clinical picture is usually more severe. Although unspecified extrapyramidal symptoms appeared in childhood, she was relatively symptom-free up until the age of about 37 (Table 1).

ATLD should be taken into consideration in cases of early onset ataxia with an absence of telangiectasia and a normal alfa-fetoprotein level. In the course of diagnostic procedures performed on our patient, a lot of neurological diseases were excluded. Due to the incomplete clinical picture and relatively late onset, ATLD was not considered separately for a long period of time, which may be the reason for the delayed diagnosis and the suspicion that functional disorder was the cause of symptoms.

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 were not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements. 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

AB and SS developed the presented idea. AB wrote the paper with support from DP. DK and MJ served as scientific advisors and approved the version to be published. DK and SS supervised the project. 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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Neuropsychiatric disturbance detecting polycythemia vera myelofibrosis: a case report and literature review

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Background: Neuropsychiatric disturbances and chorea are less recognized consequences of polycythemia vera (PV), and their role in post-PV myelofibrosis (MF) has not been reported. Clinical features that predict post-PV MF lack specificity.

Case presentation: We describe an elderly patient with PV who developed acute-onset reversible neuropsychiatric disturbances accompanied by generalized chorea and was finally diagnosed with post-PV MF after a bone marrow examination. We also reviewed four cases of late PV associated with neuropsychiatric symptoms since 1966 and analyzed their clinical characteristics and therapeutic effects.

Conclusion: Our case indicates that Janus kinase 2 (JAK2)-related PV is a treatable cause of late-onset chorea and that chorea may herald the deterioration of hematological parameters. Our case provides a clinically specific representation of post-PV MF. Patients with a long course of PV are recommended to undergo bone marrow re-examinations when they present with neuropsychiatric symptoms to achieve an early diagnosis of post-PV MF.

KEYWORDS

post-polycythemia vera myelofibrosis (post-PV MF), neuropsychiatric symptoms (NPS), chorea, microcirculation disorder, Janus kinase 2 (JAK2)

Background

Polycythemia vera (PV) is a characteristic Philadelphia chromosome-negative myeloproliferative neoplasm (MPN) (1). Neurological manifestations of PV, such as headache, vertigo, visual disturbance, paresthesia, tinnitus, and transient ischemic attack, are frequent (50%–78%) (2). However, chorea and neuropsychiatric disturbances are rarely reported.

Post-PV myelofibrosis (MF) is a unique advanced stage in the natural progression of PV (3). The reported 10-, 15-, and 20-year incidences of post-PV MF transformation among patients are 27.4%, 39.9%, and 61.1%, respectively (4). Once PV develops into post-PV MF, the incidence of acute myeloid leukemia transformation is 1.6/100 persons/year, and mortality significantly increases to 7.4/100 persons/year (5). The overall survival of patients with post-PV MF has been reported to be 5.7–8 years (4). Therefore, early diagnosis of post-PV MF is important. However, apart from the routine re-examination of blood, bone marrow, and gene monitoring, there is no specific clinical characterization of the transformation to fibrosis in PV patients with a long

disease course. The role of psychiatric disorders and chorea in post-PV MF has not yet been reported.

Here, we present the case of an elderly patient with $JAK2^{V617F}$-positive PV who developed acute-onset reversible psychiatric behavior accompanied by generalized chorea and was finally diagnosed with post-PV MF after a bone marrow examination. We also review the literature regarding this disorder and discuss the possible mechanisms for the central nervous system (CNS) symptom burden of post-PV MF.

Case presentation

A 68-year-old man was presented to the emergency department in November 2022 with an acute onset of psychotic derangement. He exhibited delirium, agitation, and slight involuntary movements involving the face, trunk, and left-sided limbs. These symptoms had suddenly developed a day earlier. The patient demonstrated, during admission, progressive behavioral changes characterized by sedentary inability, groping behavior, hallucinations, increased motor restlessness, night- and day-reversed sleep, and hypologia (Supplementary Video 1). The patient was diagnosed with $JAK2^{V617F}$-positive PV confirmed by bone marrow biopsy 10 years previously and had been successfully treated with hydroxyurea 500 mg once daily since then.

In the past 3 years, the patient had two episodes of choreiform movements after hydroxyurea withdrawal. The movements were quickly relieved after symptomatic treatment with tiapride hydrochloride tablets. His hematological test results deteriorated, accompanied by spontaneous hematoma of the hip and infarct of the spleen, thought to be complications of PV. However, his bone marrow aspirations showed no progress or change. The hematological indicators during the past two episodes of choreiform symptoms are shown in Table 1. However, the patient continued to take hydroxyurea.

The patient was not treated with chorea-inducing drugs such as antiparkinsonian drugs, tricyclic antidepressants, or anticonvulsants. There was no history of cognitive or behavioral issues. The patient's family history was unremarkable. There was no medical history of peripheral vascular disease, metabolic or endocrine disorders, or autoimmune diseases.

General examination revealed facial erythrosis but no splenomegaly or hepatomegaly. The patient's blood pressure was 130/80 mmHg, and his temperature was 36.6°C. Neurological examination revealed mild choreiform movements of the left limbs and orofaciolingual muscles with writhing tongue movements, pouting, and grimacing. Eye movements, muscle strength, and reflexes were normal. Neuropsychological testing was impossible to complete (secondary education). Other neurological tests showed no abnormalities or Parkinsonian, pyramidal, or cerebellar signs.

An extensive diagnostic laboratory workup for chorea and neuropsychiatric derangement was performed. The patient had a total white blood cell count of 36.5×10^9/L, erythrocyte width of 22.8%, total red blood cell count of 4.98×10^{12}/L, platelet count of 125×10^9/L, hemoglobin of 11.4 g/dL, and hematocrit of 41.9%. The peripheral blood smear revealed no abnormal cells or acanthocytes. Results of serum liver enzyme, TSH, antistreptolysin O titer, ceruloplasmin, vasculitis workup, human immunodeficiency virus, syphilis serology, and autoimmune encephalitis panel were negative. His initial creatinine was 275 μmol/L, but it recovered quickly after fluid rehydration, which rarely caused renal encephalopathy. Chest and abdomen CT showed no obvious signs of systemic inflammation, tumor, and splenomegaly. The cerebral magnetic resonance imaging showed encephalomalacia of the left frontal and right parietal lobes, gliosis, and signs of cerebral small-vessel disease (Fazekas 2) (Figure 1). There were no acute infarcts, bleeding, or space-occupying lesions in the brain parenchyma, including the striatum, basal ganglia, subthalamic region, and brain stem. Electroencephalography revealed a mild abnormality, characterized by a background of low-medium amplitude 8-10c/s alpha wave rhythm, with slightly more low-medium amplitude 5-7c/s theta wave rhythm, without epileptic waves. Bone marrow examination revealed global hyperplasia with fibrosis, consistent with post-PV MF. $JAK2^{V617F}$ mutation was detected in the peripheral blood, whereas the *BCR-ABL* gene was negative. All the above results demonstrated a diagnosis of chorea and neuropsychiatric derangement because of post-PV MF.

The dose of hydroxyurea was not increased, and it was not adjusted to a JAK2 inhibitor because of side effects and the limitation of thrombocytopenia. The severity of involuntary movement and mental and behavioral abnormalities gradually decreased, the involuntary facial and limb symptoms disappeared, and the patient could walk normally after 2 weeks of treatment with tiapride hydrochloride, clonazepam, and quetiapine tablets. A follow-up outpatient visit 6 weeks after his initial presentation showed a leukocyte count of 4.1×10^9 /L, a hemoglobin level of 12.5 g/dL, a platelet count of 115×10^9 /L, and an erythrocyte width of 11.9%. The chorea had completely subsided, and the tiapride hydrochloride tablet was slowly withdrawn. All sedating medications were discontinued, with no re-emergence of mental symptoms. The patient was referred to the hematology department for follow-up.

Discussion and conclusion

Chorea, a rare but acknowledged PV symptom (6), has been described as an exacerbation of myeloproliferative disease (7), as in our case. In the two initial chorea episodes, laboratory tests revealed increased hematocrit, hemoglobin, erythrocyte count, mild leukocytosis, and decreased platelet count. The patient also developed complications caused by abnormal coagulation, including hip hematoma and splenic infarction, but bone marrow examinations were negative. Improvement in the clinical picture occurred simultaneously with normalizing hemoglobin and hematocrit levels. Our case confirms JAK2-related PV as a treatable cause of late-onset chorea, reveals that chorea may herald the deterioration of hematological parameters (7, 8), and highlights the importance of the standardized use of hydroxyurea.

The exact pathophysiology of polycythemic chorea remains unclear, and corticobasal ganglia circuitry perturbation (9) may be its anatomic basis. It is hypothesized to be based on hyperviscosity because of the raised red cell mass in the neostriatal area, probably led to a sluggish cerebral blood flow, venous stasis, impaired oxygen, and glucose metabolism (10), causing movement disorder. However, this has not been uniformly confirmed with functional neuroimaging studies (9–11). In our patient, the indicators of hematologic deterioration at his third chorea episode were significantly different from those of the previous two, mainly represented by peripheral leukocytosis. However, hematocrit and red blood cell count were

TABLE 1 Laboratory findings in the patient.

Investigation	2020–8	2022–02	2022–11	Reference values
White cell count	11.3 ↑	13.3 ↑	36.5 ↑	3.0–10.0 × 10^9/L
Neutrophil ratio	0.670	0.731	0.700	0.40–0.75
Red cell count	6.82 ↑	6.91 ↑	4.98	4.3–5.8 × 10^{12}/L
Platelet count	97 ↓	77 ↓	125	150–400 × 10^9/L
Hematocrit	54.1 ↑	59.9 ↑	41.9	40–50%
Hemoglobin	166 ↑	181 ↑	114	115–155 g/L
Erythrocyte width	23.4 ↑	20.3 ↑	22.8 ↑	11–14.5%
Creatinine	103.3	121.4	275	49–92 μmol/L
C-reactive protein	63.43	5.32	41.52	≤6 mg/L
Presentation at onset	Involuntary movements involving four limbs, lips, and face	Involuntary movements involving the upper and right lower limbs, lips, and face	Involuntary movements involving the left-sided limbs and face; Neuropsychiatric disturbance	–
Concomitant symptoms/diseases	Spontaneous hematoma of the hip	Spleen infarction	renal insufficiency	–
Cerebral MRI	Multiple ischemic lesions in the right frontoparietal lobe and lateral ventricle; leukoaraiosis	Left frontal lobe and right parietal lobe softening foci; leukoaraiosis	Left frontal lobe and right parietal lobe softening foci with gliosis and signs of cerebral small vessel disease	–
Electroencephalogram	Negative	Negative	Mild abnormality	–
Use of hydroxyurea at the onset	Withdrawn for about four months	Withdrawn for about eight months	0.25 g once daily	–
Bone marrow examination	PV	PV	PV with fibrosis	–
JAK2 ^{V617F} mutation	+	+	+	–
Used therapies	Hydroxycarbamide 0.5 g qd; Tiapride hydrochloride 1#-1/2#-1#	Hydroxycarbamide 0.5 g bid; Tiapride hydrochloride	Clonazepam 1 mg qn; Hydroxycarbamide 0.25 g qd; Quetiapine 1/2 qn	–
Time to symptom relief	1 week	2 weeks	2 weeks	–

MRI magnetic resonance imaging; JAK Janus kinase; PV polycythemia vera.

normal, showing that the pathophysiological mechanism leading to this chorea symptom was not hyperviscosity alone.

Neuropsychiatric findings such as delirium, dementia, depression, mania, abulia, and frontal lobe syndrome in PV have been described in approximately 10 cases since 1960 (12–16). The currently reported numbers are probably underestimated because of the unfamiliarity of the link between specific neuropsychiatric symptoms and PV. The benefits of treatment appear ambiguous. In some cases, the mental disorder completely normalizes after phlebotomy and normalization of the hemoglobin levels, which supports the possible causal relationship between PV and the occurrence of these mental disorders (17–19). However, Mazzoli et al. (20) considered the possibility of a casual association between polycythemia and psychotic depression.

A literature search showed that most of the reported neuropsychiatric symptoms occurred in patients with PV who had been diagnosed many years ago, which is consistent with the natural course of PV. As a relatively indolent myeloid neoplasm, PV can progress to secondary MF, termed post-PV MF, and to the blast phase, worsening survival (21, 22). The median survival of patients with MF depends on the risk category and can range from 2 to 9 years, with hematopoietic stem cell transplantation being the only curative option (5, 23). The MYSEC (Myelofibrosis Secondary to PV and ET-Prognostic Secondary to PV and ET) database (5) showed that the longer the period between PV diagnosis and secondary myelofibrosis, the worse the survival. This finding indicates careful monitoring of patients with PV to identify the evolution of secondary MF earlier, especially if disease-modifying treatments are envisaged. The MYSEC Prognostic Model (5) considers constitutional symptoms, anemia, circulating blasts, thrombocytopenia, advanced age, and the absence of calreticulin mutations as risk variables. These variables may indicate the progression of a more indolent disease to an aggressive disease. Risk factors for overall survival include leukocytosis, venous thrombosis, and an abnormal karyotype. However, the clinical features that predict MF lack specificity; constitutional symptoms, including weight loss, night sweats, and fever, are easily overlooked. The neurological manifestations of post-PV MF mostly include thromboses (24), and some are intracranial extramedullary hematopoiesis (25). The role of psychiatric disorders and chorea in post-PV MF has not yet been reported. In this case, MF was detected by bone marrow puncture, we detected that the psychiatric symptoms may be a CNS manifestation of post-PV MF after excluding other common causes.

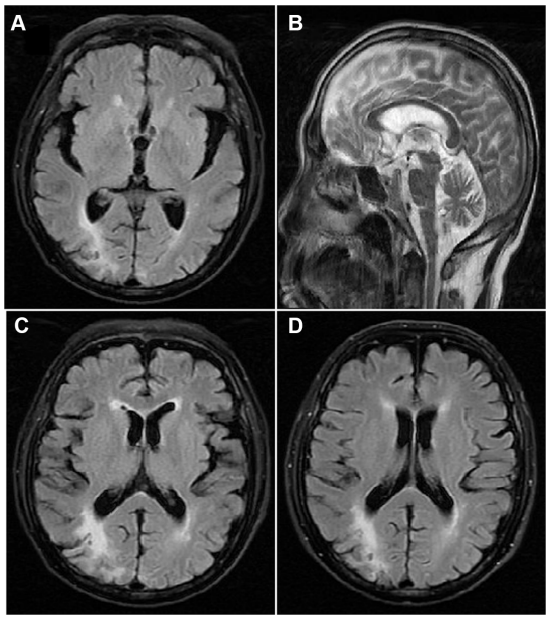

FIGURE 1
T2 weighted Axial view Magnetic resonance imaging showing **(A)** no infarct or space occupying lesion in the caudate nucleus, putamen or the globus pallidus, **(B)** and the third and fourth ventricle, and **(C)** encephalomalacia of the left frontal and right parietal lobes, gliosis, and signs of cerebral small-vessel disease; **(D)** encephalomalacia of the right parietal lobes at the second episode of chorea.

We reviewed four cases of late PV associated with neuropsychiatric symptoms since 1966, according to the clues above, and analyzed their clinical characteristics. The four reports (Table 2) describe four PV patients (two males and two females) with mental symptoms (13, 18–20). The mean age of the patients was 75.3 years (range 64–96), and the mean latency from PV to the development of mental symptoms was 10 years (range 9–11). Depressive symptoms were prominent, mental symptoms were severe, and treatments were difficult; one patient succumbed to absolute therapy-resistant depression (19). Chorea symptoms were present in two patients (13, 19). However, in one of them, the symptoms could not be distinguished from those related to the disease or psychotropic drug use (19). Three patients experienced various thrombotic events, including myocardial infarction, deep vein thrombosis of the lower extremities, TIA, and stroke. Laboratory examination indicated that the red blood cell count and hematocrit were nonspecific in patients at this stage, while two patients showed a leukoerythroblastic peripheral blood picture. According to the criteria (26) for post-PV MF, a diagnosis requires the presence of ≥grade 2 fibrosis accompanied by the development of progressive splenomegaly, anemia, leukoerythroblastosis, or constitutional symptoms. Splenomegaly and weight loss were present in three of the four patients, but no bone marrow examination or genetic testing was performed. In our case, bone marrow examination showed fibrosis (grade 2, on a 0–3 scale). Our patient also met another required criterion: medical history and two additional criteria: anemia and leukoerythroblastic peripheral blood image (26). He lacked splenomegaly and had none of the three constitutional symptoms. Neuropsychiatric symptoms and chorea were the most prominent clinical symptoms. Observing neuropsychiatric symptoms in PV should raise the suspicion of a fibrotic transformation.

None of these patients with PV-related neuropsychiatric disorders underwent bone marrow re-examination before treatment. Managements of their psychiatric symptoms, including antipsychotic symptomatology and cytoreductive therapy by hydroxyurea, were ineffective, which may signal disease progression and provide an opportunity for a shift in treatment decision-making. Hydroxyurea is the most used first-line cytoreductive agent for the treatment of PV, which is not as effective as ruxolitinib in relieving neurological symptoms in PV (27). A phase 3 open-label study to evaluate the efficacy and safety of ruxolitinib versus standard therapy included hydroxyurea in patients with PV (27) found that the rate of improvement in the ruxolitinib group (49%) with a reduction of at least 50% in the 14-item Myeloproliferative Neoplasm Symptom Assessment Form total symptom score was significantly higher than in the standard therapy group (4.9%) at week 32. Unexpectedly, ruxolitinib-treated patients had greater reductions in almost all individual symptoms. In contrast, patients receiving standard therapy had more neurological symptoms, including ear ringing, concentration problems, numbness or tingling in the hands or feet, headache, and dizziness. A dysfunctional microcirculation caused by chronic inflammation might account for neurological symptoms, and relief of symptoms depends on the anti-inflammatory effect of ruxolitinib.

Chronic inflammation is a highly important driving force of MPN development and progression (28), in which the JAK–STAT-signaling and the NF-kB pathways are activated because of driver mutations and play a major role (26). Mutated blood cells are involved in the occurrence of microcirculation disorders through various pathways (28). In the PV stage, the increased number of RBCs contributes significantly to high blood viscosity in the cerebral microcirculation with increased vascular resistance and slowing blood flow (29). Red blood cells from patients with PV also have been shown to adhere more strongly to endothelial cells. Elevated hematocrit is associated with decreased cerebral blood flow and cerebral hypoxemia (30) and gives rise to abnormally high shear stress on the vessel wall, which may facilitate endothelial dysfunction. In MF, leukocytosis and thrombocytosis occur in the early hyperproliferative phase, and pancytopenia often occurs in the advanced stages (31). Elevated cell counts, activated circulating myeloid cells, and micro-aggregates of leukocytes and platelets (31, 32) may intermittently plug the cerebral microcirculation. However, a decrease in cerebral blood induces hypoxemia and activation of several signaling pathways, ultimately eliciting a neuroinflammatory state with microglia activation and induction of inflammatory cytokines (28). In our case, the corticostriatal basal ganglia circuit was disturbed by microcirculation disturbance caused by long-term chronic inflammation. The first two chorea symptoms occurred in the PV stage because of the dysfunction caused by blood viscosity caused by the increase of red blood cells, and hydroxyurea was effective (33). When the patient developed into the early stage of MF, leukocytosis and cytokine storm led to mental symptoms and simultaneously caused motor dysfunction by affecting cerebral blood flow in the basal ganglia.

Psychiatric symptoms in patients with JAK2-related PV over a long course of disease should be alerted to a disease progression. Most patients have non-low risks currently, according to multiple prognostic models to predict survival in MF (26). However, hydroxyurea is usually suitable for low-risk or intermediate-risk patients with platelet count $<50\times10^9$/L (26). We need to adjust the treatment strategy. The COMFORT trials demonstrate that ruxolitinib can improve splenomegaly and symptom burden and reduce cytoses and proinflammatory cytokine levels (34).

TABLE 2 Summary of the findings in PV patients with mental symptoms after a long disease course.

Author, year	Sex, age	Latency from PV to mental symptoms (years)	Clinical features		Thrombosis	Routine blood tests		Bone marrow examination	Three constitutional symptoms: >10% weight loss in 6 months; night sweats; unexplained fever (>37.5°C)	Splenomegaly	Leukocytes	Anemia	Genetic testing	CT/MRI	Treatment	Prognosis
			Mental	Chorea		RBC (10^{12}/L)	Hematocrit (%)									
Murray et al. (18)	M, 72	11	Depression, Suicidal ideation, Auditory hallucinations, Paranoid delusions, Disorientation	–	Frequent TIA	*N*/A	Unknown	WNP	Weight loss (5 kg)	Yes	*N*/A	No	WNP	No focal lesion but generalized atrophy	Haloperidol and electroconvulsive therapy; lofepramine; fluoxetine	After 6 weeks, residual anxiety symptoms
Mazzoli et al. (20)	F, 69	9	Depression, Suicidal ideation Delusion	–	Two myocardial infarctions; frequent TIA; A stroke	9.9	Unknown	WNP	Weight loss	Yes	14	*N*/A	WNP	*N*/A	Busulfan and pentoxifylline	No effect on depression
Bauer (19)	F, 64	10	Severe depression; Temporary paranoid fears and delusions. Progressive cognitive impairment	Rhythmical trunk and pelvic movements; bucco-linguo-masticatory syndrome	Deep vein thrombosis of the leg	6.4	55	WNP	Considerable weight loss (20 kg)	Yes, Splenectomy	25.7	*N*/A	WNP	Normal	Busulfan; various antidepressant drugs; hydroxyurea; acetylsalicylic acid	Succumbed to absolute therapy-resistant depression
Garcia et al. (13)	M, 96	A long time	Progressive behavioral change, e.g., disinhibition, inappropriate verbal comments, unrestrained laughter	Sudden onset in left-sided chorea of the upper limb and face	None	*N*/A	46	WNP	*N*/A	No	*N*/A	No	WNP	Normal	Haloperidol and clonazepam Hydroxycarbamide	No effect; Subjective decrease in involuntary movements

CT, computed tomography; WNP, was not performed; MRI, magnetic resonance imaging; F, female; M, Male; N/A, unavailable data; RBC, red blood cell; TIA, ransient schemic ttack.

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In conclusion, this is the first reported case of post-PV MF with chorea and neuropsychiatric symptoms. The onset of chorea has been linked to worsening hematological values and PV progression, and the resolution of chorea has been related to PV treatment. Importantly, this case provides a possible clinical representation of post-PV MF. It is recommended that patients with a long course of PV receive prompt bone marrow re-examination when they have mental symptoms to achieve an early diagnosis of MF and avoid delays that may shorten their survival.

Data availability statement

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

Ethics statement

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

Author contributions

LL: Conceptualization, Data curation, Writing – original draft. MZ: Formal analysis, Investigation, Writing – original draft. Y-QW: Data curation, Visualization, Writing – original draft. W-NF: Supervision, Writing – review & editing. DL: Writing – review & editing.

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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.2023.1253468/full#supplementary-material

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Case report: Unilateral GPi DBS in secondary myoclonus-dystonia syndrome after acute disseminated encephalomyelitis

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Introduction: Deep brain stimulation (DBS) is an established and effective therapy for movement disorders. Here, we present a case of secondary myoclonus-dystonia syndrome following acute disseminated encephalomyelitis (ADEM) in childhood, which was alleviated by DBS. Using a patient-specific connectome analysis, we sought to characterise the fibres and circuits affected by stimulation.

Case report: We report a case of a 20-year-old man with progressive dystonia, myoclonic jerks, and impaired concentration following childhood ADEM. Motor assessments utilising the Unified Myoclonus Rating Scale (UMRS) and the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) revealed a greater improvement in dystonia compared to myoclonus following adjustments of DBS parameters. These adjustments were based on visualisation of electrode position and volume of tissue activated (VTA) 3 years after surgery. A patient-specific connectome analysis using the VTA as a region of interest revealed fibre tracts connecting to the cerebello-thalamo-cortical network and the superior frontal gyrus in addition to basal ganglia circuits as particularly effective.

Conclusion: Globus pallidus internus (GPi) DBS shows promise as a treatment for secondary myoclonus-dystonia syndromes. Personalised structural considerations, tailored to individual symptoms and clinical characteristics, can provide significant benefits. Patient-specific connectome analysis, specifically, offers insights into the structures involved and may enable a favourable treatment response.

KEYWORDS

myoclonus-dystonia, acute disseminated encephalomyelitis, deep brain stimulation, neuromodulation, connectome analysis

1. Introduction

Acute disseminated encephalomyelitis (ADEM) is a neuroinflammatory disorder characterised by central nervous system demyelination. Whereas the exact pathomechanisms remain elusive, the thalamus and the basal ganglia are commonly affected (1). Involvement of pathways within these motor circuits may result in complex secondary movement disorders (2), which necessitate tailored

treatments according to individual clinical characteristics. Meanwhile deep brain stimulation (DBS) targeting these pathological network dynamics may also provide valuable insights into symptom-specific structural correlates, given its efficacy to a plethora of movement disorders such as dystonia (3) and hereditary myoclonus-dystonia (4). However, due to clinical heterogeneity and limited systematic analyses, accurately predicting outcomes of DBS for secondary dystonia syndromes is challenging. This uncertainty in prediction may lead to the cautious application of DBS beyond routine clinical practise, potentially resulting in the withholding of this effective treatment from certain patients (5). This report presents a case of secondary myoclonus-dystonia syndrome following ADEM in childhood, alleviated by DBS surgery at the internal part of the globus pallidus (GPi). We used a patient-specific connectome analysis to investigate the fibres and circuits modulated by stimulation.

2. Case presentation

We evaluated a 20-year-old male patient with a history of progressive dystonia, myoclonic jerks, speech difficulties, and impaired concentration. He was diagnosed with ADEM at the age of 10 in November 2009 and underwent several weeks of intensive medical therapy followed by months of rehabilitation. While initial symptoms (meningismus, encephalopathy, and cranial neuropathy) resolved, dystonic symptoms first appeared in December 2009, manifesting as involuntary movements in his right index finger while writing. Over the course of 3 years, the patient's motor symptoms progressed beyond dystonia to myoclonic gestures.

On initial examination, the patient presented with involuntary movements of the right arm and face, which were characterised by focal dysrhythmic jerks that were exacerbated by certain postures, movements, and stimuli. He also presented with multifocal dystonia of the right arm and foot. Brain MRI revealed lesions in the pons, cerebellum, thalamus, and periventricular white matter around the lateral ventricles (Figure 1).

Despite the often self-limiting nature of ADEM, we hypothesised an association between focal demyelination in the thalamus (6–8) and brainstem (7, 8) and delayed onset of symptoms (Figures 1B,C). Especially in secondary dystonia, the time between structural lesions and the onset of symptoms can be several months or even years (7). In addition, there was no family history of neurological disorders in the entire family.

The patient was thus diagnosed with a secondary multifocal myoclonus-dystonia syndrome following ADEM. Dystonia and myoclonus had remained refractory to anticonvulsants (Piracetam, Levetiracetam) and anticholinergics (Trihexyphenidyl). Following thorough multidisciplinary evaluation, the patient decided to undergo unilateral lead placement in the left GPi using directional leads (Vercise Cartesia™ 2202-02 leads, Boston Scientific Neuromodulation Corporation, Valencia, United States). DBS programming according to monopolar review revealed the largest therapeutic window when the current was steered in the anterior direction of the distal three-segmented ring contact. Using a top-down approach, we gradually increased the stimulation amplitudes to the maximum tolerated voltage while maintaining a frequency of 130 Hz and a pulse width of 60 µs. The patient was allowed to adapt DBS settings according to his preferences and was informed about the known long-term effects in dystonia. He deliberately chose programme 2 [C+ 1−(30%), 2−(35%), 3−(35%), 4 mA, 60 µs, 130 Hz] because it provided the most significant relief of motor symptoms (Table 1).

During 3 years of follow-up, the patient reported worsening of dystonia and myoclonic jerks. To address these issues, we introduced four new stimulation programmes. In view of reports indicating efficacy of higher stimulation frequencies and pulse widths in the treatment of dystonia (9), increased pulse width (90 µs) was used in programme 6, higher frequency (185 Hz) in programme 7, and a combination of increased pulse width and frequency in programme 8, allowing the patient to adjust the settings prospectively. In addition, we used an imaging-guided optimisation of DBS parameters (programme 5) by directing the volume of tissue activated (VTA) towards proximal contacts moving from [C+, 1−(30%), 2−(35%), 3−(35%)] to [C+, 2−(10%), 4−(10%), 5−(40%), 7−(40%); avoiding contacts 3 and 6, respectively] in order to maximise the intersection between VTA and the ventral parts of the GPi, which are in close anatomical proximity to the pallidothalamic tract (PTT) (10). For dystonia, modulation of the PTT has been

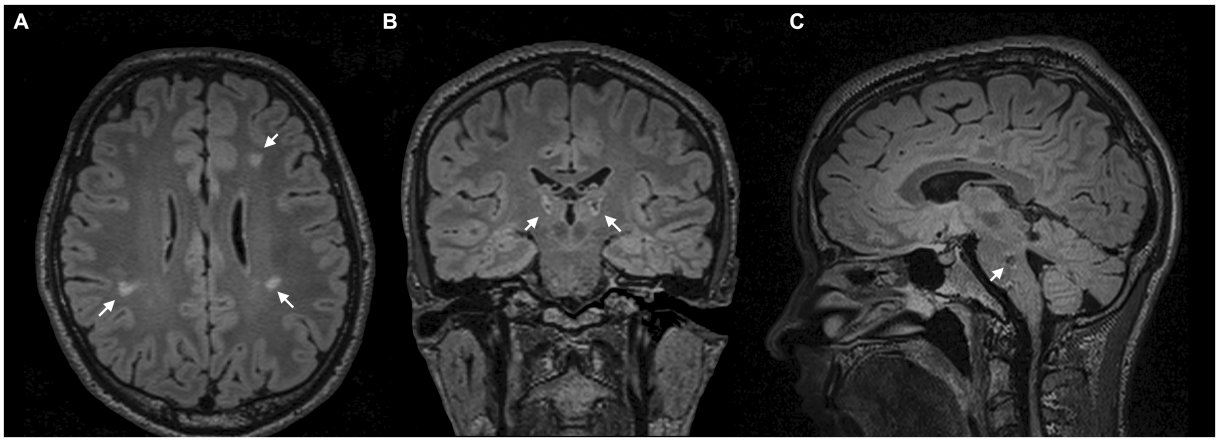

FIGURE 1
MRI scans. **(A)** Axial FLAIR-weighted MRI scans demonstrate periventricular white matter lesions around the lateral ventricles. **(B)** Coronal FLAIR-weighted MRI with bithalamic hyperintense lesions. **(C)** Sagittal FLAIR-weighted MRI reveals a hypointense lesion in the pons.

TABLE 1 DBS programming parameters.

	GPi DBS				
	Left				
Date	Programme	Active contacts	Amplitude (mA)	Pulse width (μs)	Frequency (Hz)
July 2019	1	C+ 1−(33%), 2−(33%), 3−(33%)	0.9	60	130
October 2019	2	C+ 1−(30%), 2−(35%), 3−(35%)	4	60	130
	3	C+ 2−(50%), 3−(50%)	1.8	90	130
	4	C+ 2−(50%), 3−(50%)	2	60	185
February 2023	5	C+ 2−(10%), 4−(10%), 5−(40%), 7−(40%)	2	90	185
	6	C+ 1−(30%), 2−(35%), 3−(35%)	3.5	90	130
	7	C+ 1−(30%), 2−(35%), 3−(35%)	5	60	185
	8	C+ 1−(30%), 2−(35%), 3−(35%)	3	90	185

demonstrated to improve symptoms after pallidal DBS (11), while relief of myoclonus has been reported after contralateral pallidothalamic tractotomy (12). For this programme, we set the pulse width to 90 μs and the frequency to 185 Hz. A figure illustrating the changes in active DBS contacts after imaging-guided programming is provided as Supplementary material.

We assessed motor symptoms employing the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) and the Unified Myoclonus Rating Scale (UMRS) with DBS turned off and on. This resulted in predominant improvement in dystonia (OFF: 26, ON: 4) relative to myoclonus (OFF: 85, ON: 60) after imaging-guided adjustments of DBS parameters. See Figure 2 for a timeline of the patient's medical history.

2.1. Patient-specific connectome analysis

Magnetic resonance imaging data were acquired 1 day before surgery on a 3 T scanner. The preoperative imaging protocol included b-values of 0 and 1,000 s/mm^2 and 30 independent diffusion gradient directions. The DBS lead and VTA visualisation was carried out using the LEAD-DBS software[1] (13, 14). Specifically, we co-registered preoperative diffusion tensor imaging (DTI) to T1 imaging with SPM12[2] and subsequently used Advanced Normalisation Tools (ANTs) to co-register the results with the postoperative CT scan (15). The Precise and Convenient Electrode Reconstruction for Deep Brain Stimulation (PaCER algorithm) (16) facilitated the electrode detection including its rotation. Structural connectivity was analysed using the Generalised Q-Sampling method implemented in DSI Studio[3] (17). The VTA served as a region of interest (ROI) for identifying connected fibre tracts, with an electric field threshold of 0.2 V/mm applied during estimation (18, 19). Using a finite element model, the stimulation volume was computed by estimating the gradient distribution of the electrical charge in space on a tetrahedral mesh that differentiated four compartments: grey and white matter, electrode contact, and insulation (20), as implemented in LEAD-DBS.

Utilising the DISTAL Minimal Atlas to define parcellation of grey matter structures (21), the VTA mostly overlapped with the prefrontal and sensorimotor subregions of the GPi (Supplementary Figure 2). As expected, our findings showed that the fibre tracts associated with the VTA of GPi DBS were connected to basal ganglia circuits and the superior frontal gyrus (SFG), which was characterised by the A6m region of the Brainnetome atlas (22). Furthermore, these fibre tracts were found to overlap with the dentato-rubro-thalamic tract (DRT), potentially indicating a modulation of the cerebello-thalamo-cortical network, as identified by the DBS tractography atlas (23) (Figure 3).

3. Discussion

To the best of our knowledge, this is the first published case of secondary myoclonus-dystonia syndrome after ADEM successfully treated with unilateral GPi DBS. Adjustments of DBS parameters according to connectomic data for a modulation of distributed brain networks (24) has been used to identify stimulation sweet spots in patients suffering from movement disorders such as Parkinson's disease (25, 26) and paediatric dystonia (27). In our patient, predominant improvement of dystonia relative to myoclonus was observed when the VTA was steered to overlap prefrontal and sensorimotor subregions of the GPi. This is consistent with recent findings suggesting that pallidal DBS effectively normalises dystonia-associated sensorimotor and prefrontal hyperactivity, which have been implicated in the pathophysiology of dystonia (28).

For secondary movement disorders, growing evidence highlights a key role of alterations in multiple anatomical pathways (29). For dystonia and myoclonus in particular, desynchronisation of the cortico-basal ganglia-cerebellar network has been put forward as an underlying mechanism (30). Our results indicate an alleviation of both symptoms upon modulation of basal ganglia circuits with fibre tracts intersecting the DRT and projecting to the SFG. The interpretation of a complex multinetwork model seems to be corroborated by findings indicating a synchronicity of pallidal oscillations and myoclonic jerks (31), whereas secondary myoclonus may also result from lesions in the cerebellum (32).

1 https://www.lead-dbs.org
2 http://www.fil.ion.ucl.ac.uk/spm/software/
3 https://dsi-studio.labsolver.org

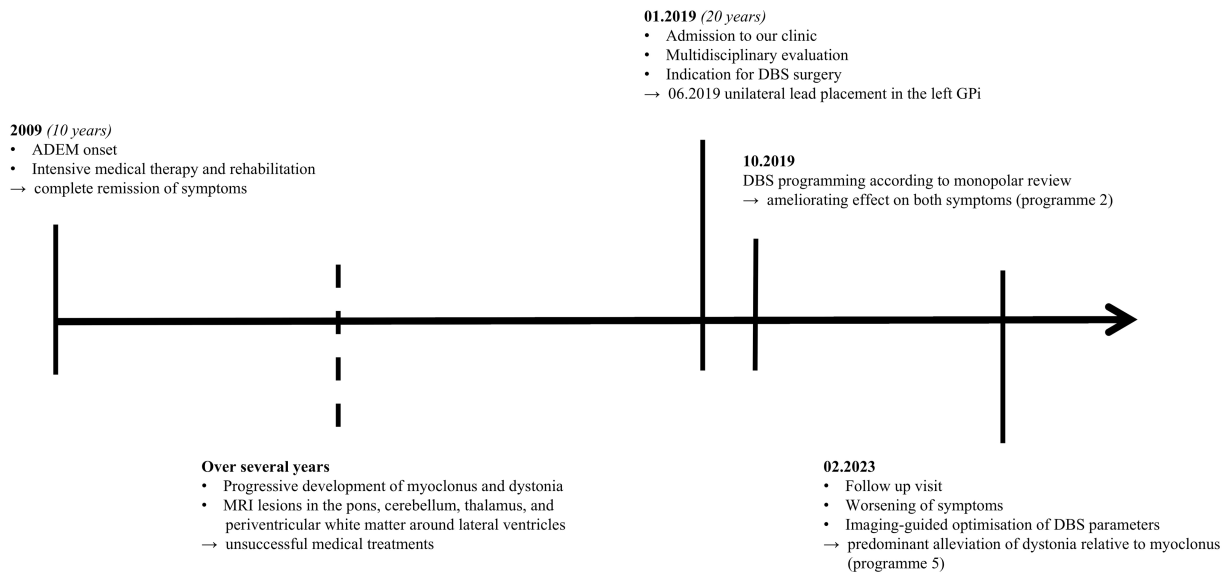

FIGURE 2
Timeline of medical history. ADEM, Acute disseminated encephalomyelitis; MRI, Magnetic resonance imaging; DBS, Deep brain stimulation; GPi, Globus pallidus internus.

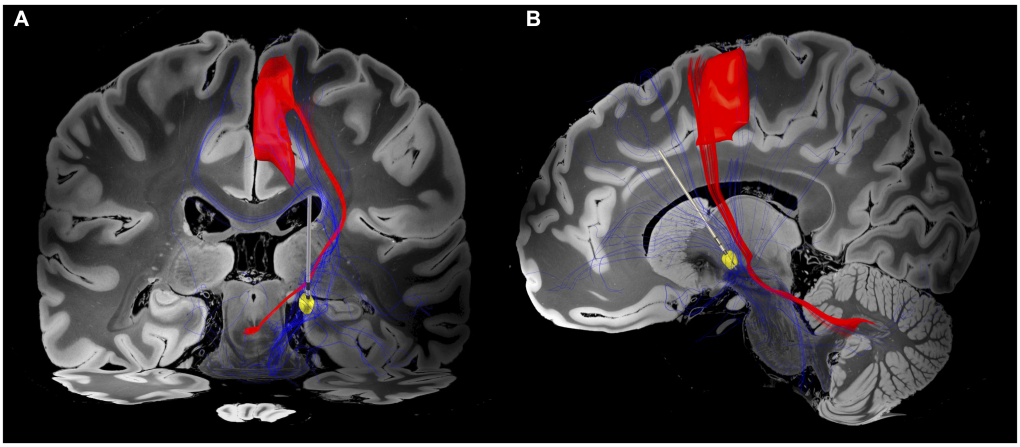

FIGURE 3
Electrode position and VTA associated fibre tracts. **(A)** Coronal view. Patient-specific connectome with VTA (yellow circle) associated fibre tracts (blue tractography) overlapping the dentato-rubro-thalamic tract (DRT; red tractography) and projecting to the superior frontal gyrus (SFG). **(B)** Sagittal view. Fibre tracts extend to prefrontal and sensorimotor regions. The closest spatial proximity to the DRT appears to be within cerebello-pallidal and pallido-thalamic connections. The VTA was generated based on the DBS parameters of programme 5 (Table 1). The DBS tractography atlas (23) and the Brainnetome atlas (22) were utilised to define DRT and SFG, respectively.

While DBS targeting the posterior part of the ventrolateral thalamic nucleus (VLp) can effectively address myoclonus (33, 34), in our patient, right-sided dystonic features were the predominant symptom, causing significant difficulties with activities of daily-living and severely affecting the patient's quality of life. This led us to choose the left GPi as the most appropriate target for DBS treatment, given its widely demonstrated efficacy for ameliorating dystonia (3). While this case highlights the importance of a thorough clinical assessment as the basis for selecting stimulation targets, future insights from patient-specific connectivity profiles could improve our understanding of the underlying neural dynamics and provide insights into the precise target for DBS leads in rare movement disorders.

3.1. Limitations

While this case report demonstrates the long-term effects of pallidal DBS in a secondary myoclonus-dystonia syndrome and thereby highlights the underlying networks, there are some limitations. Although imaging-guided optimisation of DBS parameters was carried out based on the VTA and its adjacent neuroanatomical structures, the stimulation parameters were not refined using the tractography results from the patient-specific connectome analysis. In addition, our preoperative imaging protocol prevented us from testing for abnormal kurtosis measures. Diffusion kurtosis imaging (DKI) has been shown to be more sensitive to microstructural changes in

demyelinating disorders (35) by quantifying the deviation of the water diffusion displacement profile from the Gaussian distribution (36). Another limitation is reflected in the absence of functional data, which may have provided supplementary insights into alterations in neural connectivity. Finally, this report describes a single case and therefore the findings may not be generalisable to a broader population. Despite these limitations, future studies could explore the potential of using patient-specific connectome analyses to fine-tune DBS parameters for movement disorders, tailoring the treatment based on individual symptoms and clinical characteristics.

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 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

AC and LB collected the clinical data and co-wrote the manuscript. AC performed the image analysis. MG, MB, and CN contributed to the data curation. LT and DP confirmed the diagnosis of the case and supervised the study. All authors contributed to the article and approved the submitted version.

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Conflict of interest

AC has participated in a training course which was industry funded by Stada Arzneimittel AG. LT reports grants, personal fees, and non-financial support from SAPIENS Steering Brain Stimulation, Medtronic, Boston Scientific, and St. Jude Medical, and has received payments from Bayer Healthcare, UCB Schwarz Pharma, and Archimedes Pharma and also honoraria as a speaker on symposia sponsored by Teva Pharma, Lundbeck Pharma, Bracco, Gianni PR, Medas Pharma, UCB Schwarz Pharma, Desitin Pharma, Boehringer Ingelheim, GSK, Eumecom, Orion Pharma, Medtronic, Boston Scientific, Cephalon, Abbott, GE Medical, Archimedes, and Bayer. DP received honoraria as a speaker at symposia sponsored by Boston Scientific Corp, Medtronic, AbbVie Inc., Zambon, and Esteve Pharmaceuticals GmbH. He received payments as a consultant for Boston Scientific Corp and Bayer, and he received a scientific grant from Boston Scientific Corp for a project entitled: 'Sensor-based optimisation of Deep Brain Stimulation settings in Parkinson's disease' (COMPARE-DBS). Finally, DP was reimbursed by Esteve Pharmaceuticals GmbH and Boston Scientific Corp for travel expenses to attend congresses.

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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1238743/full#supplementary-material

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Long-term, repeated doses of intravenous autologous mesenchymal stem cells for a patient with Parkinson's disease: a case report

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Parkinson's disease (PD) is a neurodegenerative disease that involves the loss of dopaminergic neurons in the substantia nigra pars compacta of the basal ganglia. Clinically, patient presentation involves a combination of motor and non-motor symptoms characterized by progressive worsening over time and significant decreases in overall quality-of-life. Despite there being no fully restorative cure for PD, Mesenchymal Stem Cell (MSC) therapy offers promising therapeutic potential. Here, we report a case of a 77-year-old female, living with idiopathic Parkinson's Disease for over 17 years. The patient received multiple infusions of autologous Hope Biosciences adipose-derived MSCs (HB-adMSCs). A total of 26 infusion treatments of HB-adMSCs were administered over the course of ~2 years that resulted in marked improvements in her typical Parkinsonian symptoms, as demonstrated by the decreases in her UPDRS (Unified Parkinson's Disease Rating Scale) scores. Changes in clinical scores mirrored concurrent changes in regional brain metabolism as quantified by FDG-PET (Fluorodeoxyglucose-Positron Emission Tomography), compared to baseline. Long-term, multiple infusions of HB-adMSCs were safely tolerated by the patient without any serious adverse events. Further research is needed to evaluate the safety and efficacy of HB-adMSC therapy for the treatment of PD patients.

KEYWORDS

mesenchymal stem cells, adipose derived, autologous, Parkinson's disease, case report

1. Introduction

Parkinson's Disease (PD) is a progressive neurological disorder characterized by the preferential loss of dopaminergic neurons in substantia nigra with involvement of multiple other cell types throughout the central and peripheral nervous system. PD is the second most common neurodegenerative disease after Alzheimer's disease that affects 2–3% of the population ≥65 years (1, 2). Pathogenesis of PD involves the progressive dopaminergic neuron degeneration, which leads to the loss of stimulation of the direct motor pathway and the loss of inhibition of the indirect motor pathway of the basal ganglia (3, 4).

Currently, there is no cure for PD, but patients are often candidates for medication-based treatment and, in some cases, neurosurgical intervention like deep brain stimulation (DBS) (5, 6). Among the numerous available medications non-ergot dopamine agonists as well as levodopa/carbidopa combination are usually first-line treatments. However, with levodopa-carbidopa therapy, there is an "on-off" phenomenon that occurs with progressive disease, which results in improved mobility during the "on" periods, but impaired motor function during the "off" periods (7).

Because of limited effectiveness, and the side effects associated with many of the available PD medications, alternative therapeutics are constantly under study. Owing to their anti-apoptotic, immunomodulatory, paracrine, and multidirectional differentiation abilities, mesenchymal stem cells (MSCs) are currently being evaluated in clinical trials to treat neurological disorders (8). Specifically, MSCs secrete neurotrophic factors, such as glial cell line-derived neurotrophic factor and nerve growth factor, which prevent the dopaminergic neurons from undergoing apoptosis and promote neurogenesis (9). Preclinical studies using bone marrow-derived MSC therapy have also demonstrated prevention of degeneration of dopamine-producing neurons (10). However, other studies have reported contradictory effects of MSC transplantation on PD treatment, demanding the need for further research (11, 12).

In this case report, we sought to demonstrate tolerability and efficacy of multiple infusions of HB-adMSCs in improving the signs, symptoms, and overall quality-of-life for a woman with Parkinson's Disease.

2. Case presentation

2.1. Case history

Herein, we present a case of a 77-year-old, white, non-Hispanic or Latino female diagnosed with PD in 2004, suffering from severe neurodegenerative deterioration for over 17 years. The patient's weight, height, and BMI at screening were 57.5 kg, 157.5 cm and 23.2 kg/m^2 respectively. What started out as a left-hand tremor progressed to cogwheel rigidity, bradykinesia, chorea, athetosis, dystonia, truncal swaying, head tremor and dyskinesia. Her past medical history displayed several other nervous system and musculoskeletal disorders that included: Kyphosis, Tendinitis de Quervain's, Distal Neuropathy, Restless Leg Syndrome, and insomnia, along with a history of fractures in her rib and LS spine. Her surgical history included total hip replacement, tonsillectomy, and cosmetic eye surgery. She experienced a combination of side effects and resistance to treatments, some of which included dyskinesia associated with Comtan, nausea and vomiting with Azilect, and the on-off phenomenon linked to Sinemet (which the patient started taking in 2013). The patient's complete medication regimen included: Sinemet (25/100 mg) 5x daily, Rytary (36.25/145 mg) 2 capsules 4x daily, Azilect (1 mg) daily, Comtan (200 mg) 5x daily, Neupro (4 mg) transdermal daily, Requip (8 mg) daily, Ambien (10 mg) nightly, Melatonin (15 mg) nightly, Gabapentin (300 mg) prn, and Tylenol (1,000 mg) prn. Despite being on all these medications, it was only enough to help her walk; she still experienced frequent falls, severe dyskinesias, and repetitive episodes of freezing. She would slide out of the chairs she sat in, was unable to turn around in bed, had very stooped posture, and required the assistance of an in-house caregiver. There were not many restorative treatment options available for this patient after she exhausted the extensive list of failed medications.

In August 2019, FDA authorized an expanded access protocol for intravenous administration of eight infusions of autologous HB-adMSC treatment for this PD patient. The patient responded quite well to the therapy with no safety concerns that led us to continue her treatment, and in December 2019, FDA approved another set of 12 monthly infusions. The infusion treatments resulted in positive findings associated with significant improvements in patient's parkinsonian symptoms. After completing 20 infusion treatments, FDA approved 6 more infusions to the patient's protocol in January 2021, which continued at the same dose, but the interval changed from every 4 weeks to every 8 weeks (Figure 1A). A total of 26 infusions were received by the patient over the course of ~2.5 years.

2.2. Isolation of patient's adipose derived MSCs

To isolate autologous adMSCs, 10 ccs of adipose tissue was extracted via liposuction, from the patient's abdomen. The extract was then tested by the quality control unit at Hope Biosciences LLC., for USP71 sterility and mycoplasma due to possible contamination from the fat extraction procedures, followed by centrifugation to phase-separate the adipose tissue. A total of 5 mL adipose tissue was then treated with collagenase to isolate stromal vascular fraction (SVF). Cells from the SVF were plated in Hope Biosciences' HB-103 medium to establish a P0 culture. The resulting adherent cells were further cultured with HB-101, Hope Biosciences' growth medium (with 5% FBS) and the MSCs were cryopreserved in Hope Biosciences' proprietary freezing medium (containing 10% DMSO) at passages #0, #1 and #2 to create a complete cell bank for the patient. An aliquot of #2 culture supernatant was cleared by the quality unit for USP71 sterility, mycoplasma, and endotoxin. For infusions, passage #2 cells were thawed, recovered in passage #3, and cultured to passage #4 (Figure 1B). Final release of the purified harvest of passage #4 cells was cleared by the quality unit for final release for USP71 sterility, mycoplasma, and endotoxin, gram stain and cell characterization via flow cytometry performed on a ThermoFisher AttuneNXT flow cytometer using labeled antibodies. Operation of the flow cytometer consists of using single color control samples to adjust the corresponding PMT voltage and gain. Then, an unstained cell sample is used to adjust the forward and side scatter gain, and to set the gate on the negative populations across all channels of interest. Single color controls are used to calculate the compensation matrix, which is then applied to the experiment and used to create an analysis template. This template is saved and used to analyze the final product cell samples using the Attune Software. Once completed, data analysis tables are created to summarize the results. The immunophenotype of all cultured HB-adMSCs are evaluated by QC to confirm the identity

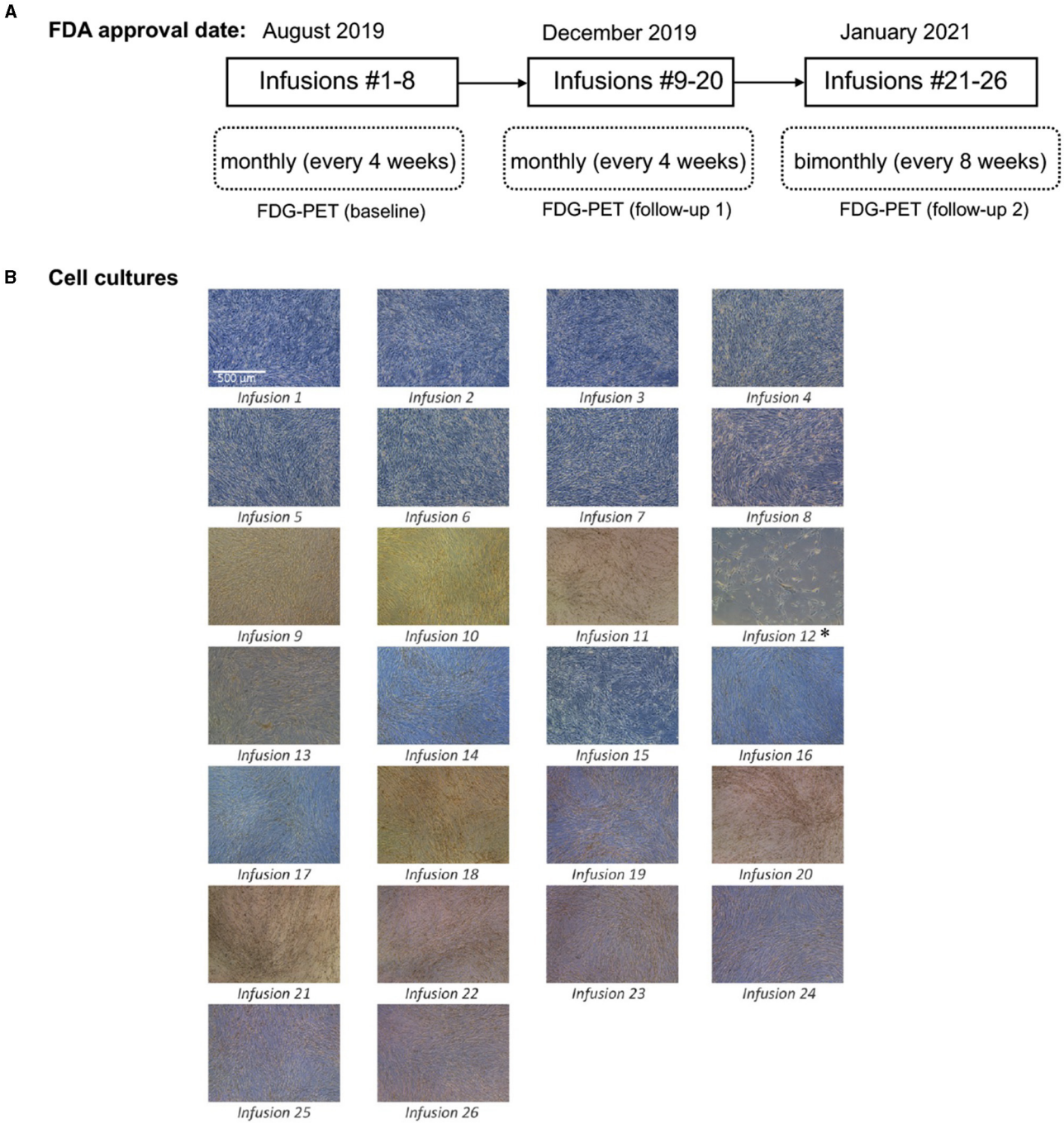

FIGURE 1
(A) Protocol approval timeline; **(B)** Cell culturing images for 26 infusions. Passage 4 culture images for all 26 infusions. Images were taken with a Leica inverted microscope at 50x magnification. Color variation is due to flask wall thickness, angle and light. *The product released for infusion #12 was lower than the minimum dose requirement of 200 (±20%) million live cells. Low cell count was because of compromised cell growth due to growth medium issue.

and purity as well as ensure that cells remain undifferentiated prior to release. A total of 26 infusions (manufactured from the cell bank created for the patient and freshly harvested from passage #4; Figure 1B), each with 200 million ±20% MSCs mixed in 20 mL of 0.9% sterile sodium chloride were administered intravenously over a period of ~2.5 year: 20 monthly infusions and remaining 6 infusions administered bimonthly. Each lot passed cGMP compliant quality control standard assessments to ensure a standardized product is delivered for each treatment and was administered within 48 h of packaging. Quality assessments included viability; appearance; sterility (USP71); gram staining; mycoplasma; endotoxin; and cell identity/purity as indicated by MSC defining surface markers (CD73+, CD29+, CD31- and CD45-) (Table 1).

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TABLE 1 Infusion details for all 26 infusions with MSC quality control metrics.

Infusion #	Date of administration (month/day/year)	Total cell count (million)	Cell viability (%)	CD73 (%)	CD29 (%)	CD31 (%)	CD45 (%)
1	08/22/2019	168	98.13	99.28	99.97	0.28	0.08
2	09/05/2019	232	97.32	95.66	99.95	0.18	0.09
3	10/17/2019	165	98.10	98.39	99.89	0.31	0.08
4	11/14/2019	238	97.39	98.92	99.93	0.40	0.18
5	12/12/2019	229	97.9	98.51	99.96	0.55	0.38
6	01/09/2020	226	98.60	96.19	99.89	0.59	0.19
7	02/06/2020	170	97.25	98.46	99.99	0.37	0.17
8	03/05/2020	192	97.56	99.17	99.82	0.31	0.07
9	04/02/2020	230	97.30	99.83	99.97	0.44	0.10
10	04/30/2020	192	93.02	99.10	99.90	2.88	0.60
11	05/28/2020	195	89.71	97.26	99.94	1.52	0.34
12	06/25/2020	27.2*	94.44	87.78	96.56	2.72	0.91
13	07/23/2020	234	98.65	95.58	99.54	0.15	0.31
14	08/20/2020	160	96.15	97.24	98.6	0.07	0.07
15	09/17/2020	239	93.00	87.71	98.49	0.06	0.13
16	10/15/2020	186	93.55	86.63	98.33	0.28	0.28
17	11/12/2020	176	92.44	97.58	98.33	0.00	0.00
18	12/10/2020	230	96.00	95.76	98.73	0.06	0.18
19	01/07/2021	168	94.59	94.81	99.37	0.19	0.00
20	02/04/2021	244	98.51	95.12	99.14	0.00	0.10
21	04/01/2021	218	94.44	86.76	96.29	2.59	0.40
22	05/26/2021	176	93.22	95.21	99.37	0.00	0.13
23	07/20/2021	208	97.01	99.24	99.83	0.00	0.17
24	09/16/2021	125**	100.0	96.52	99.54	0.00	0.23
25	11/10/2021	240	95.35	97.49	99.91	0.00	0.38
26	01/05/2022	202	96.92	98.77	98.77	0.00	0.29

The product released for infusion #12 and #24 was lower than the minimum dose requirement (200 million live cells ± 20%). *Low cell-count because of compromised cell growth due to growth medium issue. **Low cell-count due to low cell-yield from the patient. All HB-adMSCs were positive for CD73 and CD29 and negative for CD45 and CD31 cell surface markers, as expected.

2.3. Treatment and results

After receiving ∼ first 10 infusions, noticeable improvements were seen in her posture, accompanied by less frequent dyskinesias, or freezing, and no tremors. Additionally, she exhibited a normal gait and an overall improvement in her ability to carry out activities of daily living (ADLs) independently. These improvements were notable given the severity of her symptoms before receiving the intervention. Before MSC infusions, she was on very high doses of a variety of medications and required a 24-h live-in caregiver. However, following the HB-adMSC intervention, we observed notable improvements in her PD symptoms with greatly improved quality-of-life. Moreover, she discontinued her Ambien after experiencing significant improvements following 12 infusions and her neurologist also discontinued Sinemet, Azilect and Comtan along with 25% reduction in Rytary. She also started to prepare meals and perform other household chores and no longer required the help of a caregiver. To assess the effectiveness of HB-adMSC therapy, several evaluation methods including UPDRS scores, neuro-quality-of-life assessments, and neuroimmune imaging with FDG-PET, were employed.

2.3.1. Unified Parkinson's disease rating score

UPDRS assessment tool was used to evaluate motor functionality of the patient. Specifically, the parameters assessed under the UPDRS evaluations were (1) Activities of Daily Living (UPDRS part II), (2) Motor Examination (UPDRS part III), and (3) Complications of Therapy (UPDRS part IV). The patient showed significant improvements in each of these areas—post-therapy, the patient demonstrated remarkable improvements in UPDRS part II, for each of the activities of daily living, compared to baseline (Figure 2A, left). Also, the total score for UPDRS part II showed significant improvements (score improved from 18 to

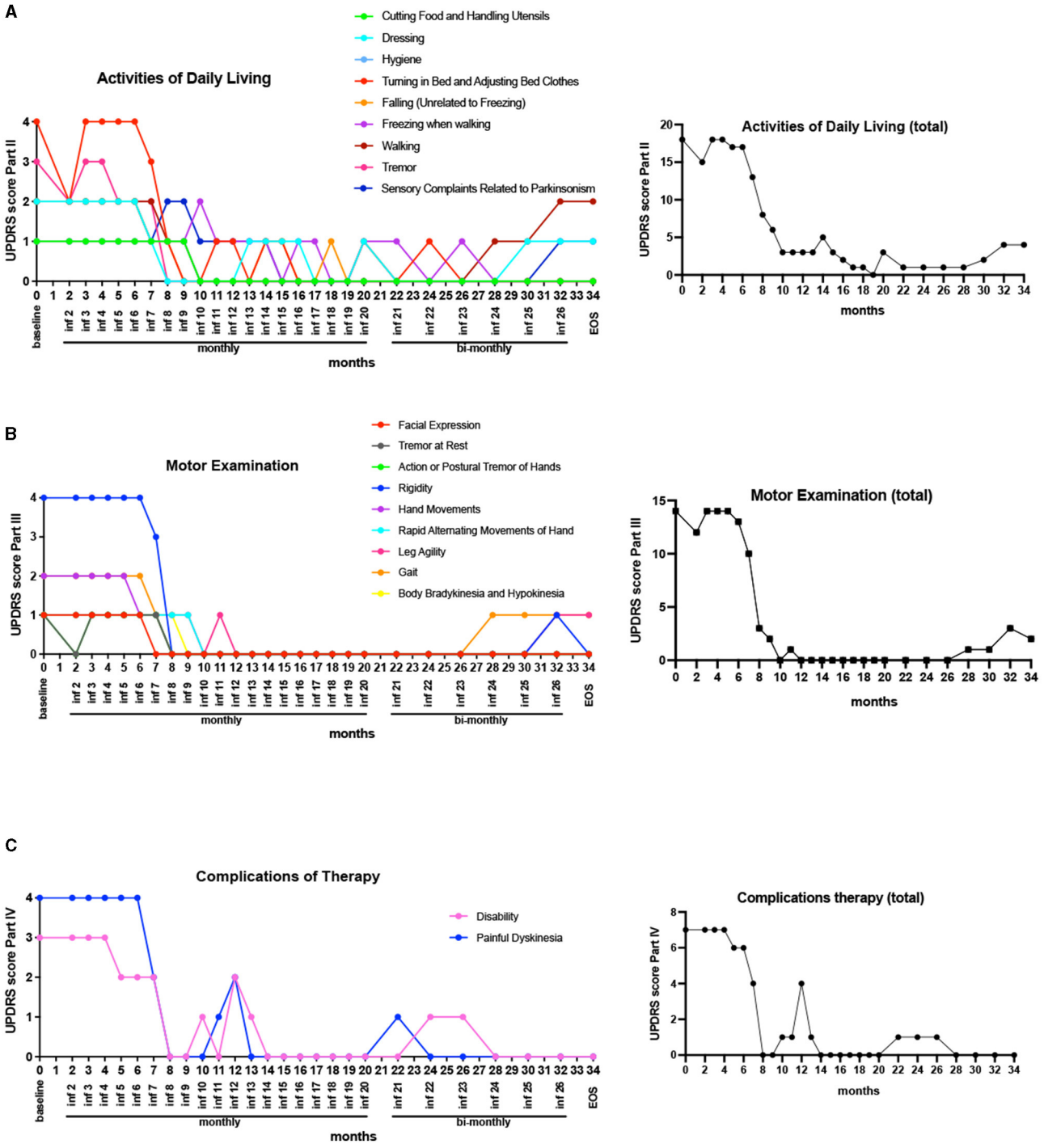

FIGURE 2
UPDRS scores **(A)** Activities of Daily Living (part II): Improvements were seen in all measured parameters with significant improvements observed in "turning in bed and adjusting bed clothes" as well as "tremor" (left), with overall improvement in the total score (right); **(B)** Motor Examination (part III): Major improvements were noted in "rigidity" after only eight infusions of HB-adMSC therapy. Other motor symptoms that showed improvements included "facial expression," "tremors at rest," "hand movements," "leg agility," "gait," and "body bradykinesia and hypokinesia" (left), with substantial improvements in the total score (right); **(C)** Complications of Therapy (part IV): Significant improvements were observed in patient's "painful dyskinesia" (left) with an overall improvement observed in the total score (right).

4) (Figure 2A, right). Similarly, several improvements were seen in the areas of motor examination UPDRS part III scores, with the most notable changes observed in patient's rigidity (Figure 2B, left). There was an overall improvement in her motor symptoms that included, tremors at rest, hand movements, leg agility, gait, as well as body Bradykinesia and Hypokinesia (the total UPDRS part III score improved from 14 to 2) (Figure 2B). Additionally, following HB-adMSC therapy, the patient's disabling dyskinesias

were no longer severe; the total UPDRS IV score improved from 7 to 0 (Figure 2C).

2.3.2. Imaging: fluorodeoxyglucose-positron emission tomography scan

A Parkinson's Disease Related Pattern (PDRP) has been known to be identified with FDG-PET, outlining brain regions of hypometabolism (parieto-occipital and pre-motor cortices) and other regions of normal or hyper-metabolism (cerebellum, pons, thalamus, and lentiform nucleus), associated with disease severity, progression, and treatment response (13–15). For this patient, three FDG-PET scans were completed to differentiate metabolically active brain regions from less metabolically active regions in a PDRP type pattern. A baseline FDG-PET scan was obtained on August 20th, 2019, a comparison FDG-PET scan (follow-up 1: FU1) obtained post-adMSC intervention, on August 11th, 2020, and a final FDG-PET scan (follow-up 2: FU2) was obtained on March 24, 2022. The first two scans were completed on a GE Discovery LS PET/CT scanner (GE Medical Systems) at the PET Imaging of Houston facility (Houston, TX) where CT attenuation correction was applied. The final scan was completed on a Siemens Biograph scanner (Siemens Healthcare GMBH) at the HMI-Richmond facility (Houston, TX) where CT attenuation was applied. Imaging analyses were completed in PMOD software wherein the individual SUV (standardized uptake value) images were calculated, smoothed (3 mm Gaussian kernel), co-registered, and normalized to the MNI template (Montreal Neurological Institute, Montreal, CA). Resulting SUV images were subsequently normalized to their respective whole brain average SUV by simple division to yield final SUVR images for comparison. In this case report, using the baseline image, we identified regions with relatively low metabolism within the parieto-occipital and those with relatively high metabolism within the cerebellum and thalamus, consistent with PDRP conceptualizations in PD. We then compared SUVR values in those regions, at the baseline to FU1 and FU2, to determine whether the pattern of changes in metabolism in these regions were consistent with patterns of clinical changes.

In the parieto-occipital cortex, relatively low metabolism was seen at the baseline (SUVR = 1.08), that was increased at FU1 (SUVR = 1.15) with a subsequent decline at FU2 (SUVR = 1.04) Figure 3A (left). The cross-hairs in Figure 3A (right), centered on a portion of the parieto-occipital cortex, showed relatively lower metabolism at baseline (SUVR = 1.18) that got increased at FU1 (SUVR = 1.26) with a subsequent decline at FU2 (SUVR = 1.15). As demonstrated in Figure 3B (left), SUVR values reduced from 1.33 at baseline to 1.29 at FU1 and subsequently increased to 1.41 at FU2. Similar findings were observed in the right thalamus. The cross-hairs in Figure 3B (middle), centered on the cerebellar vermis showed minimal change in SUVR values from baseline (SUVR = 1.27) to FU1 (SUVR = 1.29) with subsequent increase at FU2 (SUVR = 1.47). Similarly, cross-hairs (centered on an aspect of the left cerebellar hemispheres) in Figure 3B (right) where a reduction in SUVR values from baseline (SUVR = 1.24) to FU1 (SUVR = 1.13) and subsequent increase at FU2 (SUVR = 1.22) was noted. Similar changes were observed in various locations throughout the left cerebellar hemisphere and in the right cerebellar hemisphere.

2.3.3. Neurology Quality-of-Life assessments

Neuro-QoL survey was used to assess multidimensional aspects that include physical, mental, as well as social wellbeing. Improvements were noted in several areas of the assessment. For example, there were mild improvements in patient's cognitive function and her satisfaction with social roles and activities along with keeping up her social commitments. There were also improvements in her ability to keep up with work responsibilities, with improvements in her anxiety raw score (improved from 23 to 19, post-therapy), along with improvements in her feelings of exhaustion. Additionally, the assessment for upper and lower extremity function also demonstrated slight improvements in the score (correlated with UPDRS part II and III). However, several other parameters in the assessment remained stable with no signs of improvement or worsening.

2.3.4. Laboratory evaluations

Standard laboratory measures of complete blood count (CBC) and comprehensive metabolic panel (CMP) and coagulation panel (CP) were performed at various timepoints to evaluate the safety of the treatment. The laboratory values did not show any unusual changes when compared to baseline. Also, no treatment-related adverse or any serious adverse events were reported.

3. Discussion

Currently, there are no fully restorative treatments available for PD. The controversial long-term effects of the available therapeutics for PD paves way for MSC therapy. Mechanistically, MSCs secrete neurotrophic factors, thereby possess the potential to prevent apoptosis of dopaminergic neurons and stimulate neurogenesis through the release of fibroblast growth factor 2, vascular endothelial growth factor, endothelial growth factor, and more (16–18). There is also evidence to suggest that MSCs may play a role in limiting the degeneration of dopaminergic neurons (9).

Previous studies have demonstrated the efficacy of MSCs in PD patients. Boika et al. (19) used bone-marrow derived MSCs, to assess changes in motor and non-motor symptoms, using various scaled assessments and showed improvements in PD symptoms. Additionally, other studies employed stereotactic administration of bone-marrow derived MSCs into the sublateral ventricular zone in patients with PD (20, 21). Although improvements in PD symptoms were reported in these studies but only a fraction of patients demonstrated persistent improvements.

In this case report, administration of multiple infusions of HB-adMSCs resulted in substantial improvements in the patient's PD symptoms as demonstrated by the UPRDS scores that also corelated with the improvements seen on the FDG-PET scans. Consistent with the results of this report, another study by Shigematsu et al. also demonstrated improvements in the clinical scores (UPDRS) using multiple infusions of adipose-derived MSCs in three PD patients (22). However, the improvements in the clinical score results were not evaluated further with any imaging or any other clinical assessments. For this patient, in addition to numerous physical improvements, she also experienced several positive changes in measures related

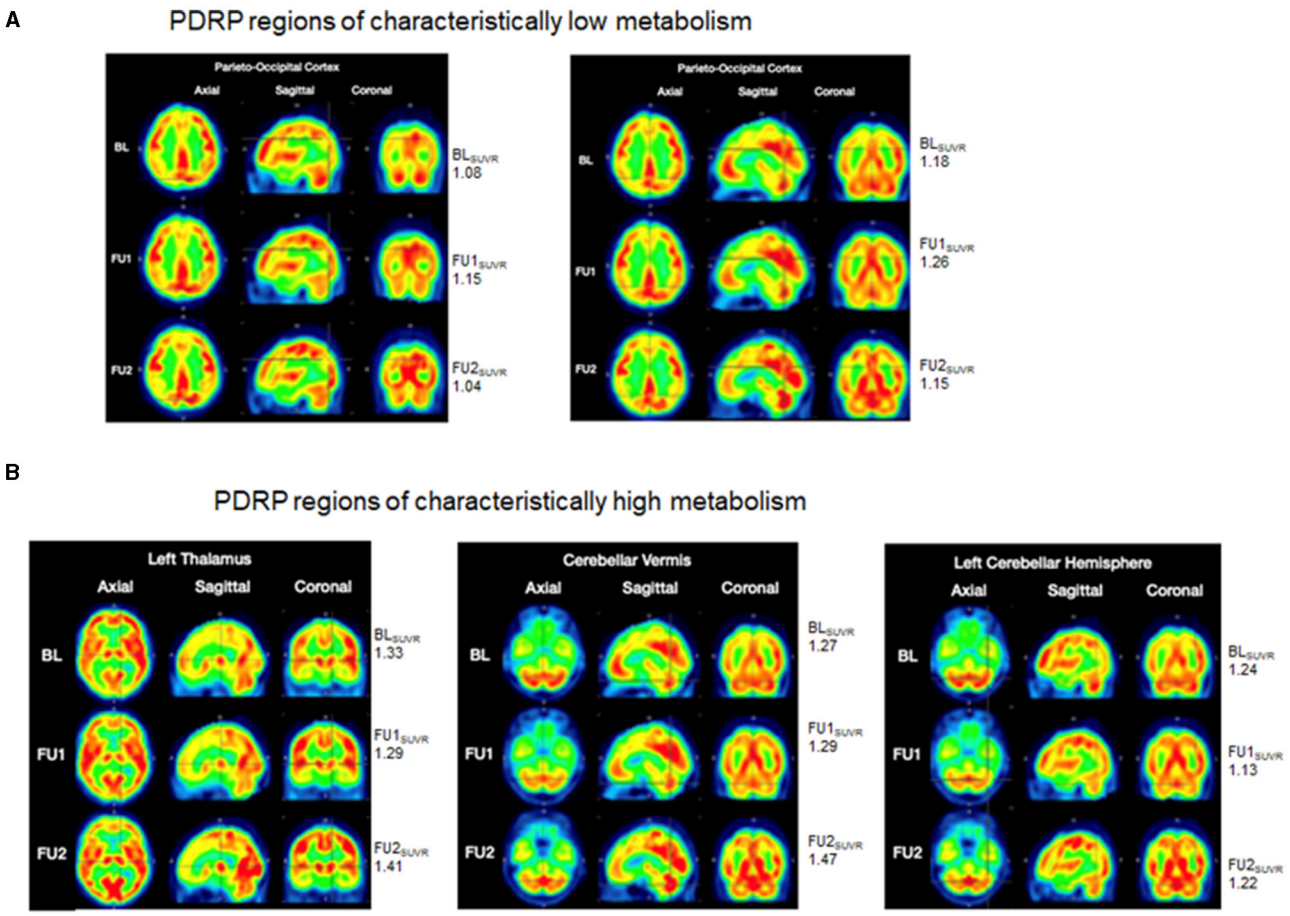

FIGURE 3
FDG-PET scans. Brain metabolism is represented via a color spectrum with SUVR values ranging from low to high, consistent with colors ranging from blue/green/yellow (low SUVR) to orange/red (moderate SUVR) and bright red (high SUVR). **(A)** PDRP regions of characteristically low metabolism (parieto-occipital cortices): (left) cross-hairs focus on a region with relatively low metabolism at BL (SUVR = 1.08) that is increased at FU1 (SUVR = 1.15) and exhibits a subsequent decline at FU2 (SUVR = 1.04); (right) cross-hairs focus on the another portion of the parieto-occipital cortex with relatively lower metabolism at BL (SUVR = 1.18) that is increased at FU1 (SUVR = 1.26) and subsequently declines at FU2 (SUVR = 1.15); **(B)** PDRP regions of characteristically high metabolism images (thalamus, cerebellar cortices): (left) cross-hairs are centered on the left thalamus wherein relatively higher metabolism at BL (SUVR = 1.33) was slightly reduced at FU1 (SUVR = 1.29) and subsequently increased at FU2 (SUVR = 1.41); (middle) cross-hairs center on the cerebellar vermis with minimal change in SUVR values from BL (SUVR = 1.27) to FU1 (SUVR = 1.29) and subsequent increase to FU2 (SUVR = 1.47); (right) left cerebellar hemispheres show a reduction in SUVR values from BL (SUVR = 1.24) to FU1 (SUVR = 1.13) and a subsequent increase to FU2 (SUVR = 1.22). BL, baseline; FU1, follow-up 1; FU2, follow-up 2.

to her quality-of-life. It should, however, be noted that the improvements were more pronounced and remained stable up to infusion #20, with a slight worsening in some of the UPDRS scores around infusion #21–26. These clinical findings also correlated with the final FDG-PET scan where reduction in regions of hypometabolism and enhancements in regions of hypermetabolism were noted, compared to scan at FU1. This phenomenon could be attributed to the change in the dosing interval from monthly to bimonthly (infusion #1–20 were administered every 4 weeks while infusions #21–26 were administered every 8 weeks). A similar trend was observed in one of our previous case report where the relapse of symptoms was observed in a patient with Systemic Lupus Erythematosus (SLE) when the dosing regimen was changed from every 4 weeks to every 8 weeks (23). Taken together, the results of this study demonstrate the need for optimal treatment frequency to overcome persistent degeneration associated with such diseases, however, further research with larger sample size is needed to confirm these findings.

The patient's neuro quality-of-life assessments did not correlate well with the improvements seen in the UPDRS scores and showed limited to no improvement at all when compared to the baseline. A possible explanation for these results may be attributable to the differences in the way these assessments are made—neuro-QoL are self-based assessments compared to the UPDRS scoring criteria that is purely based on the clinician's ratings—thus, better reflects the treatment outcome. Given the limited availability of data from a single patient with idiopathic PD, a larger sample population might be necessary to understand a correlation between neuro-QoL assessments with other PD evaluations.

Also, we would like to acknowledge potential limitations related to the FDG-PET imaging analyses. The values reported are in SUVR units, reflecting the ratio of regional SUV over the SUV averaged over the whole brain. While this method can be useful when

attempting to normalize data obtained across different scanners (e.g., FU2 scan was obtained from a different scanner than the baseline scan and FU2 scan), this scanner harmonization method is not perfect and can potentially lead to misleading results.

4. Conclusions

Overall, HB-adMSC therapy was efficacious in improving the patient's experience with a progressively degenerative neurological disease such as PD. Administration of monthly HB-adMSCs infusions had a promising therapeutic effect, specifically at the symptomatic levels of PD. Post-therapy, the patient experienced less dyskinesias, had pronounced improvements in her tremors, and had regained a significant level of independence. These results were in stark comparison to her experience while on the medications, during which she needed help with most ADLs. Also, HB-adMSCs therapy was well-tolerated by the patient. Given the progressive, chronic nature of Parkinson's disease, additional research using HB-adMSCs should be conducted to confirm the findings of this study.

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 Western Institutional Review Board, Inc. Washington, USA. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

Author contributions

RV: Formal analysis, Visualization, Writing—original draft, Writing—review and editing. AP: Formal analysis, Visualization, Writing—original draft, Writing—review and editing. MT: Writing—original draft. HK: Resources, Writing—original draft. HP: Resources, Methodology, Writing—review and editing. TC: Data curation, Investigation, Supervision, Writing—review and editing. DL: Data curation, Investigation, Supervision, Writing—review and editing. DC: Conceptualization, Funding acquisition, Project administration, Writing—review and editing.

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Conflict of interest

DC, HK, and HP are employees and shareholders of Hope Biosciences LLC.

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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Case report: Short-term efficacy and changes in ^{18}F-FDG-PET with acute multi-target stimulation in spinocerebellar ataxia type 3 (SCA3/MJD)

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Objective: Spinocerebellar ataxia type 3 (SCA3), also known as Machado-Joseph disease (MJD), is a rare neurodegenerative disease for which there is no specific treatment. Very few cases have been treated with single-target deep brain stimulation (DBS), and the results were not satisfactory. We applied multi-target DBS to an SCA3/MJD patient and performed positron emission computed tomography (PET) before and after DBS to explore the short-term clinical therapeutic effect.

Materials and methods: A 26-year-old right-hand-dominant female with a family history of SCA3/MJD suffered from cerebellar ataxia and dystonia. Genetic testing indicated an expanded CAG trinucleotide repeat in the *ATXN3* gene and a diagnosis of SCA3/MJD. Conservative treatment had no obvious effect; therefore, leads were implanted in the bilateral dentate nucleus (DN) and the globus pallidus internus (GPi) and connected to an external stimulation device. The treatment effect was evaluated in a double-blind, randomized protocol in five phases (over a total of 15 days): no stimulation, GPi, DN, or sham stimulation, and combined GPi and DN stimulation. ^{18}F-fluoro-2-deoxy-d-glucose and dopamine transporter PET, Scale for the Assessment and Rating of Ataxia, Fahn-Tolosa-Marin Clinical Rating Scale for Tremor (FTM), Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS), and SF-36 quality of life scores were compared before and after DBS.

Results: The Total Scale for the Assessment and Rating of Ataxia scores improved by ~42% (from 24 to 14). The BFMDRS movement scores improved by ~30% (from 40.5 to 28.5). The BFMDRS disability scores improved by ~12.5% (from 16 to 14). Daily living activities were not noticeably improved. Compared with the findings in pre-DBS imaging, ^{18}F-fluoro-2-deoxy-d-glucose uptake increased in the cerebellum, while according to dopamine transporter imaging, there were no significant differences in the bilateral caudate nucleus and putamen.

Conclusion: Multi-target acute stimulation (DN DBS and GPi DBS) in SCA3/MJD can mildly improve cerebellar ataxia and dystonia and increase cerebellar metabolism.

KEYWORDS

spinocerebellar ataxia type 3 (SCA3), Machado-Joseph disease (MJD), deep brain stimulation (DBS), dentate nucleus (DN), globus pallidus internus (GPi), ^{18}F-fluoro-2-deoxy-d-glucose positron emission computed tomography (^{18}F-FDG-PET), dopamine transporter (DAT) PET

1. Introduction

Spinocerebellar ataxia type 3 (SCA3), also known as Machado-Joseph disease (MJD), is a rare neurodegenerative disease characterized by progressive cerebellar ataxia and variable symptoms, including pyramidal signs, a dystonic-rigid extrapyramidal syndrome, significant peripheral amyotrophy and generalized areflexia, progressive external ophthalmoplegia, action-induced facial and lingual fasciculations, and bulging eyes (1). SCA3/MJD is caused by a CAG trinucleotide repeat expansion in exon 10 of the *ATXN3* gene on chromosome 14(p32). The core clinical feature of SCA3/MJD is progressive ataxia resulting from cerebellar and brainstem dysfunction. There is no specific treatment for SCA3/MJD, and treatment goals are to maximize function and reduce complications. It is important to remember, however, that numerous symptoms occurring in SCA3/MJD can respond to symptomatic therapy (2).

Deep brain stimulation (DBS) has been used to treat various symptoms in patients suffering from movement disorders, such as Parkinson's disease, dystonia, and essential tremor. Though ataxia syndromes have not been formally addressed with DBS, patients with ataxia, tremor, or dystonia have been administered DBS in different targets, resulting in partial relief of symptoms. Studies reporting treatment of SCA3/MJD with DBS have targeted the thalamus and cerebellum (3–8). These treatments were single-target stimulations, and the results were not very satisfactory. Although some results were statistically significant, no case showed an improvement of more than 50%. Some reports show no significant difference in Scale for the Assessment and Rating of Ataxia (SARA) scores before and after treatment. It is still unknown whether multi-target stimulation can have an improved therapeutic effect on SCA3/MJD.

Here, we tested whether bilateral dentate nucleus (DN) and globus pallidus internus (GPi) modulation can reduce SCA3/MJD symptoms of cerebellar ataxia and dystonia in a sham-controlled, double-blind study ($n = 1$).

2. Methods

2.1. Patient

The patient was a 26-year-old right-hand-dominant female with a history of a slight bilateral hand tremor, balance disorder, and gait abnormality since the age of 15 years. She had a family history of SCA3/MJD, with her mother and grandfather affected. Genetic testing revealed the CAG repeat numbers in the *ATXN3* gene to be 23 and 68, confirming a diagnosis of SCA3/MJD. She took oral medication and received rehabilitation training; however, her symptoms of tremor, balance disorder, and gait abnormality gradually worsened, and new symptoms, such as neck stiffness and facial dystonia, developed in recent years. Low-frequency transcranial magnetic stimulation on the DN has a certain effect, but the effect is short, and symptoms gradually became more aggravated. Therefore, patients and their families seek surgical treatment. After admission, we assessed the severity of the disease using the following scores (see Tables 1–3 for specific scores). The patient mildly reacts to levodopa; therefore, we also conducted a levodopa challenge test, which produced an improvement of 9%.

2.2. Magnetic resonance imaging

A 7T magnetic resonance imaging (MRI) scan (Siemens Healthcare, Erlangen, Germany) was first performed on the patient to examine the morphology and structure of the cerebellum and DN in greater detail. After processing, magnitude (Mag), phase (Pha), minimum-intensity projection (Mip), and susceptibility weighted images (SWI) were obtained (Figure 1).

2.3. The ^{18}F-fluoro-2-deoxy-d-glucose images and dopamine transporter imaging

Brain glucose metabolism was assessed by ^{18}F-FDG and DAT positron emission tomography/computed tomography (PET/CT) imaging using ^{11}C-labeled 2-beta-carbomethoxy-3beta-(4-fluorophenyl) tropane (^{11}C-β-CFT) and a Siemens Advance PET scanner (Biography Vision, Siemens Healthcare, Erlangen, Germany). A 5 mCi (185 MBq) of ^{11}C-β-CFT was injected intravenously, and images were acquired in the three-dimensional mode at 120 KVp and 380 mAs during a 10-min session. Patients fasted overnight for 6 h before FDG-PET. Patients were injected with 370 MBq of ^{18}F-FDG, in a dimly lit room with minimal background noise. Fifty minutes after ^{18}F-FDG injection, a scan lasting 10 min was acquired (Figures 2a–e).

2.4. The DN pathway and the design of its targeting

The DN is visible in T2WI-FLAIR MRI (Figure 1). It is situated adjacent to the fourth ventricle, buried in white matter, and measures ∼9–20 mm in width, 13–23 mm in length, and 7–20 mm in height. It has a unique shape and is oriented in a craniocaudal direction and from lateral to medial (8, 9, 11–13). With reference to previous studies (14, 15), we targeted the tip of each stimulation lead to the origin of the superior cerebellar peduncle such that the electrode contacted the anterior and upper third of the DN, a region related to motor function. In our patient, the anatomical target coordinates for DN stimulation were 15 mm lateral, 26 mm posterior, and 30 mm inferior to the midpoint of the anterior commissure-posterior commissure (ACPC) line on the left side, and 13 mm lateral, 28 mm posterior, and 31 mm inferior to the midpoint of the ACPC line on the right side. For the DN pathway, according to the DN position and the electrode covering the anterior and upper third of the DN, the entry point should be as close to the transverse sinus as possible (Figures 3a, b). For this patient, the trajectory of the "Ring" angle to the left and right DN was 4.6° and 8.8°, respectively. The "Arc" angle to the left and right DN was 82.2° and 92.4°, respectively. The posteroventral GPi is one of the most frequently used targets in Parkinson's disease DBS, and we did not target it here.

TABLE 1 SARA scores before and after stimulation.

SARA (9)			None	GPi	DN	"Sham"	GPi + DN
Day	Range	Baseline	0–3	4	7	10	13–15
Gait	0–8	7	6 (0.14)	6 (0.14)	4 (0.43)	6 (0.14)	4 (0.43)
Stance	0–6	4	4 (0)	4 (0)	2 (0.50)	4 (0)	2 (0.50)
Sitting	0–4	2	2 (0)	2 (0)	2 (0)	2 (0)	1 (0.50)
Speech disturbance	0–6	4	4 (0)	4 (0)	3 (0.25)	4 (0)	3 (0.25)
Finger chase	0–4	1	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)
Nose-finger test	0–4	2	2 (0)	2 (0)	1 (0.50)	2 (0)	1 (0.50)
Fast alternating hand movements	0–4	2	2 (0)	2 (0)	1 (0)	2 (0)	1 (0.50)
Heel-shin slide	0–4	3	2 (0.33)	2 (0.33)	1 (0.67)	3 (0)	1 (0.67)
Total score	0–40	24	23 (0.04)	23 (0.04)	15 (0.38)	23 (0.04)	14 (0.42)

SARA, Scale for the Assessment and Rating of Ataxia; GPi, globus pallidus internus; DN, dentate nucleus.

TABLE 2 BFMDRS movement scores before and after stimulation.

			None	GPi	DN	"Sham"	GPi + DN
BFMDRS movement (10)							
Day	Range	Baseline	0–3	4	7	10	13–15
Eye	0–8	6	4.5 (0.25)	3 (0.50)	6 (0)	6 (0)	3 (0.50)
Mouth	0–8	4.5	4.5 (0)	2 (0.56)	4.5 (0)	4.5 (0)	2 (0.56)
Speech and swallowing	0–16	8	8 (0)	8 (0)	8 (0)	8 (0)	8 (0)
Neck	0–8	1	1 (0)	0.5 (0.50)	1 (0)	1 (0)	0.5
R arm	0–16	1	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)
L arm	0–16	1	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)
Trunk	0–16	1	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)
R leg	0–16	9	9 (0)	6 (0.33)	9 (0)	9 (0)	6 (0.33)
L leg	0–16	9	9 (0)	6 (0.33)	9 (0)	9 (0)	6 (0.33)
Total score	0–120	40.5	39 (0.06)	28.5 (0.30)	40.5 (0)	40.5 (0)	28.5 (0.30)
BFMDRS disability (10)							
Speech	0–4	3	3 (0)	3 (0)	3 (0)	3 (0)	3 (0)
Writing	0–4	1	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)
Feeding	0–4	1	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)
Eating and swallowing	0–4	1	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)
Hygiene	0–4	2	2 (0)	2 (0)	2 (0)	2 (0)	2 (0)
Dressing	0–4	2	2 (0)	2 (0)	2 (0)	2 (0)	2 (0)
Walking	0–6	6	6 (0)	4 (0.33)	6 (0)	6 (0)	4 (0.33)
Total score	0–30	16	16 (0)	14 (0.125)	16 (0)	16 (0)	14 (0.125)

BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale; GPi, globus pallidus internus; DN, dentate nucleus.

2.5. The surgical procedure

Under local anesthesia, the patient was placed in a stereotactic head frame (Leksell model G head frame) before stereotactic CT was performed. CT data were combined with the preoperative plan that was developed using MRI performed with a 3.0-T scanner (Siemens Espree). We first performed GPi DBS and then DN DBS. The operation was performed under general anesthesia with Remifen and propofol. The PINSL301 electrodes for DBS were placed in GPi (PINS Medical Co., Beijing, China) and the PINSL303 electrodes (quadripolar leads with 3 mm active contacts and 4 spacing) in DN (PINS Medical Co., Beijing, China). The leads were temporarily stimulated, and the wound was sutured. Intraoperative MRI (Siemens Espree, 1.5T) was then performed.

TABLE 3 Other characteristics before and after stimulation.

Other scores	Range	Before surgery	GPI + DN stimulation
FTM (16)	0–144	29	25
SF-36 (17)	0–146	64	69
ADL (18)	0–56	36	36
MMSE (19)	0–30	28	28
MoCA (20)	0–30	28	28
HAMA (21)	0–56	9	11
HAMD (22)	0–76	8	8

FTM, the Fahn-Tolosa-Marin Clinical Rating Scale for Tremor; SF-36, SF-36 quality of life measurements; ADL, activities of daily living; MMSE, the Mini-Mental State Examination; MoCA, the Montreal Cognitive Assessment; HAMA, the Hamilton Anxiety Scale; HAMD, the Hamilton Depression Scale.

We reconstructed the dentatorubrothalamic tract by fiber tracking to observe its relationship with the lead (BrainLab, Feldkirchen, Germany) (Figure 3).

2.6. The programming design

The severity of cerebellar ataxia and dystonia was assessed 1 month before surgery and then after surgery with a double-blind, randomized protocol in five phases: no stimulation, GPi, DN, or sham stimulation, and combined GPi and DN stimulation. To reduce the chance of infection, we shortened the stimulation test time as much as possible to 3 days for each phase. The acute stimulation test was performed using an external stimulation device (T901 Temporary stimulator, PINS Medical Co., Beijing, China). The principle of selecting stimulation parameters and contacts is to achieve the best effect without side effects.

3. Results

3.1. Postoperative efficacy of DBS of two targets

3.1.1. Postoperative phase without stimulation

In most Parkinson's patients, after DBS surgery, especially for subthalamic nucleus DBS, there is a certain degree of "microlesioning". For this patient, to eliminate the interference of "microlesioning", no program control measures were taken 1–3 days after surgery. However, for this patient, we assessed various scores on the 3rd day. Most of the symptoms did not improve; only eye opening had a 25% improvement, and the heel-shin slide had a 33% improvement (Tables 1, 2).

3.1.2. Bilateral posteroventral GPi stimulation

On postoperative day 4, temporary external stimulation was commenced for the GPi. The stimulation parameters were programmed to maximally alleviate the dystonia but not to produce stimulation-related side effects. The final GPi stimulus parameters were: R: contacts 1–, 3+, 90 μs, 185 Hz, and 3 V; L: contacts 5–, 7+, 90 μs, 185 Hz, and 3 V. The BFMDRS movement scores were evaluated on the 3rd day of GPi stimulation. There was a slight improvement of ∼30% (from 40.5 to 28.5) in the eye, mouth, neck, and leg; however, there was no improvement in speech and swallowing, arm, or trunk. The BFMDRS disability and SARA scores improved by 12.5 and 4%, respectively (Table 2).

3.1.3. Bilateral DN stimulation

On postoperative day 7, temporary external stimulation was initiated for the DN. The stimulation parameters were programmed to maximally alleviate the balance disorder and gait abnormality but not to produce stimulation-related side effects. The final DN stimulus parameters were: R: contacts 2–, 3+, 200 μs, 60 Hz, and 2 V; L: contacts 6–, 7+, 200 μs, 60 Hz, and 2 V. The SARA scores were evaluated on the third day of DN stimulation. There was a slight improvement of ∼38% (from 24 to 15) in gait, stance, speech disturbance, nose-finger test, and heel-shin slide; however, there was no improvement in sitting, finger chase, or fast alternating hand movements. The BFMDRS disability and BFMDRS movement scores did not improve (Table 1).

3.1.4. "Sham" stimulation

On postoperative day 10, the stimulation was stopped. Improved symptoms and signs returned to preoperative scores (Tables 1, 2).

3.1.5. Bilateral posteroventral GPi + DN stimulation

On postoperative day 13, two targets were stimulated at the same time. The final evaluation showed that the total SARA scores improved by ∼42% (from 24 to 14), the total BFMDRS movement scores improved by ∼30% (from 40.5 to 28.5), and the total BFMDRS disability scores improved by ∼12.5% (from 16 to 14). Although SARA and BFMDRS movement scores were partially improved, the patient's BFMDRS disability and activities of daily living scores barely improved; therefore, the patient was slightly anxious about the efficacy of the treatment, with a HAMA score change from 9 to 11. The cognitive function of the patient did not change (Tables 1–3).

3.2. Differences in ^{18}F-FDG PET before and after stimulation

Preoperative ^{18}F-FDG images showed hypometabolism in the bilateral cerebellar hemisphere (Figures 2a–c) and normal metabolism in the bilateral cerebral cortex (Figure 2d). The patient had a slight reaction to levodopa before surgery; therefore, we performed DAT PET/CT. The patient had normal DAT density in the bilateral caudate nucleus and putamen (Figure 2e). After 2 weeks of stimulation, the patient underwent a multimodal imaging approach, including ^{18}F-FDG PET and 11C-β-CFT. Compared with the findings in preoperative images, ^{18}F-FDG uptake significantly increased in the cerebellum, especially in

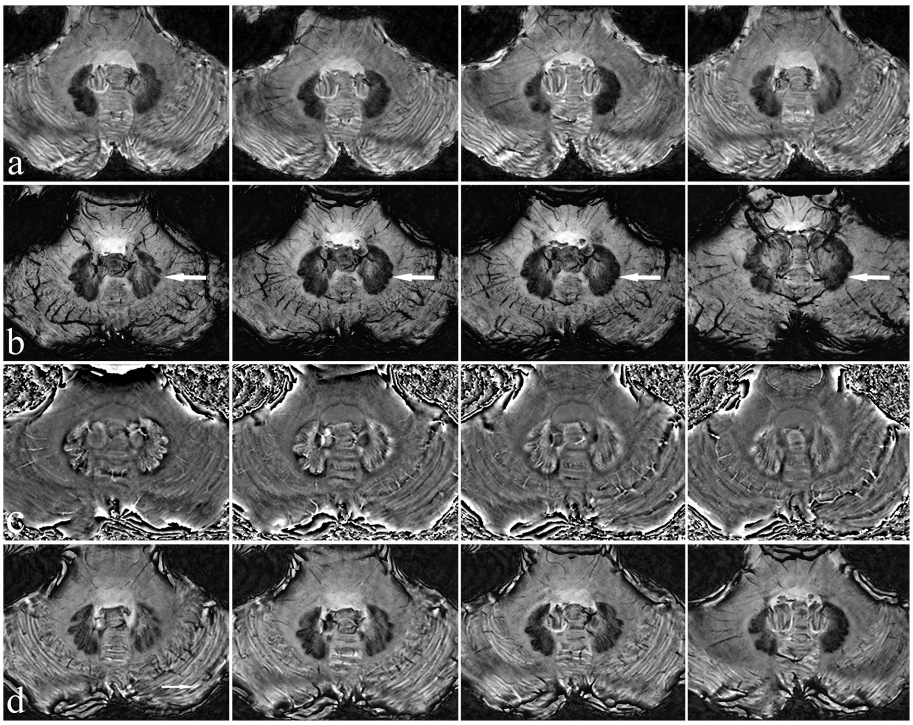

FIGURE 1
Characteristics of the patient's dentate nucleus on 7T MRI. There is a clear view of the dentate nucleus of the cerebellum. Mag **(a)**, Mip **(b)**, Pha **(c)**, and SWI images **(d)** have different characteristics, with Mip images being the clearest (see arrow).

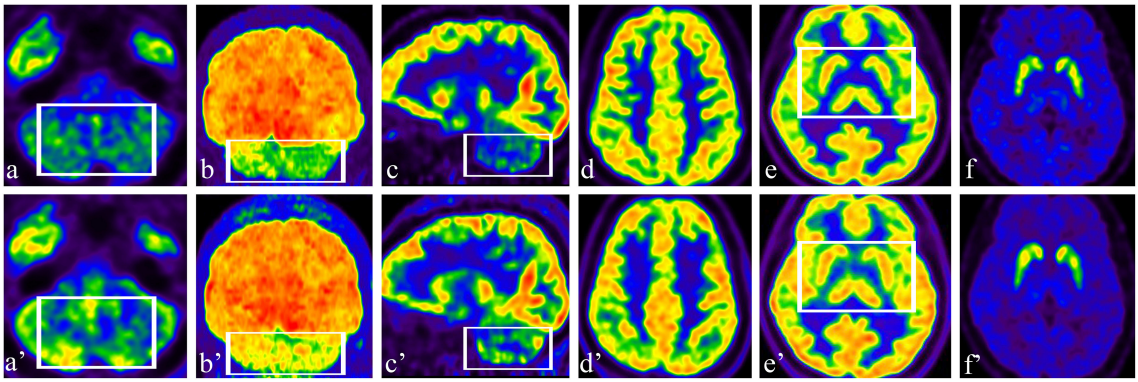

FIGURE 2
(a–c) Preoperative axial, coronal, and sagittal ^{18}F-FDG images showed hypometabolism in the bilateral cerebellar hemisphere; **(a'–c')** Postoperative axial, coronal, and sagittal ^{18}F-FDG images showed increased uptake in the cerebellum (see box). **(d, e)** Preoperative axial ^{18}F-FDG images showed normal metabolism in the bilateral cerebral cortex, GPi area, and basal ganglia; **(d', e')** There was no change in ^{18}F-FDG in the cerebral cortex, GPi area, or basal ganglia after stimulation (see box). **(f)** Preoperative axial DAT PET/CT showed normal DAT density in the bilateral caudate nucleus and putamen; **(f')** Compared with the findings in a pre-stimulation image, there were no significant differences in DAT binding in the bilateral caudate nucleus and putamen.

the right cerebellar hemisphere (Figures 2a'–c'). There was no difference in ^{18}F-FDG in the cerebral cortex (Figure 2d') or in DAT imaging (Figure 2e') before and after stimulation.

The brain MRI showed marked atrophy of the cerebellum and mild atrophy with enlargement of the fourth ventricle. The fused image of the intraoperative 3DT1-weighted sequence and the preoperative plan showed that the stimulation lead position and pathway were consistent with the preoperative plan and that the lead position was accurate (Figures 3a–c). We reconstructed the dentatorubrothalamic tract by fiber tracking. It can be seen that the lead is in close proximity to the fiber bundle passing through the DN (Figures 3d, e). The fiber bundle projects to the thalamus as the relay station and reaches the cerebral motor cortex (Figure 3f).

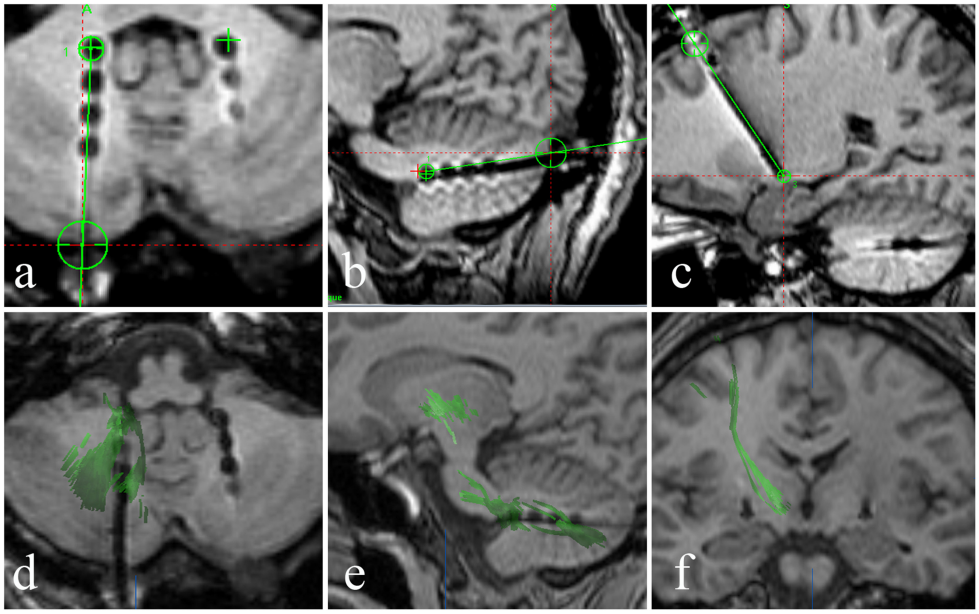

FIGURE 3
(a–c) A fused image of the intraoperative 3DT1-weighted sequence and the preoperative plan shows that the stimulation lead position and pathway (black dot and line) are consistent with the preoperative plan (green line), and the stimulation lead position is accurate. **(d, e)** Axial and sagittal diffusion tensor imaging shows the dentatorubrothalamic tract and the relationship between the dentatorubrothalamic tract and stimulation lead in the DN. **(f)** A coronal 3DT1 image showing the relationship between the pyramidal tract and the stimulation lead in the GPi.

4. Discussion

4.1. Postoperative efficacy

Although we used a short-term stimulation schedule, this is the first report of SCA3/MJD treatment using multi-target DBS (DN and GPi). For this patient, two targets were stimulated at the same time. The final improvement was 42% in SARA, 30% in BFMDRS movement, and 12.5% in BFMDRS disability scores. Daily living was barely improved; therefore, because the patient had high expectations for the procedure, she was slightly anxious about the efficacy of the treatment. Only a few SCA3/MJD cases with DBS treatment have been reported, and all of them were single-target DBS (3–8). In 2015, Teixeira et al. reported a 50-year-old right-handed woman who underwent resection of a right acoustic neuroma, which was complicated by an ischemic injury of the right cerebellar hemisphere. She developed severe ataxia, mostly right-sided, that significantly impaired her daily activities, and mild bilateral hand and cervical dystonia. The patient underwent DBS of her (healthy) left DN. After 1 year, there was an improvement in tremor (37% reduction) and cerebellar ataxia from 25.5/40 to 17/40 (SARA score) on stimulation; however, there were no changes in dystonia after treatment (3). In 2018, Aupy et al. reported a 19-year-old man with a positive family history of SCA3/MJD, generalized dystonia, cerebellar ataxia, recurrent falls, and swallowing difficulties who underwent bilateral GPi implantation. Twelve months after surgery, the patient was able to stand up without help, and his swallowing was dramatically improved. However, his cerebellar ataxia did not improve (4). In 2019, Cury et al. reported a 31-year-old female with SCA3/MJD and refractory ataxia who underwent bilateral DN DBS. She showed improvements in tremor of ∼30% and cerebellar ataxia of ∼22% (SARA score). This was the first time the DN was targeted in an SCA3/MJD patient (5). In 2021, Cury et al. also reported a group of five SCA3/MJD patients treated with DN DBS. The effects on ataxia were numerically better in four out of five patients after active vs. sham stimulation. The composite SARA score did not change after comparing active to sham stimulation ($p = 0.223$) (6). The FTMRS score showed significant improvement after active stimulation vs. sham ($p = 0.039$), as did the patients' global impression of change ($p = 0.038$). The quality of life was not modified by stimulation ($p = 0.337$) (6). Our patient has both dystonia and cerebellar ataxia. According to previous reports, it is very difficult to solve both dystonia and cerebellar ataxia in SCA3/MJD with single-target stimulation (such as DN or GPi). We, therefore, adopted double-target stimulation: the DN to relieve cerebellar ataxia and tremor and the GPi to relieve dystonia. Our results show that stimulation of the GPi can relieve some symptoms of dystonia, such as tension in the eye, mouth, neck, and leg; however, the effects were poor for speech and swallowing, and arm and trunk. DN stimulation can relieve some symptoms of cerebellar ataxia, such as impaired gait, stance, nose-finger test, heel-shin slide, and speech disturbance; however, the effect on sitting, finger chase, and fast alternating hand movements was poor. Although there was some improvement in dystonia and cerebellar ataxia, the patient was not satisfied with the improved symptoms or their quality of life. This eventually led to the patient's request to remove the leads and abandon the implantation of the pulse generator.

4.2. ^{18}F-FDG PET changes

The anatomical MR images of our patient revealed significant gray matter volume loss in the bilateral cerebellum and right cerebellar vermis, which is consistent with morphological imaging of SCA3/MJD (23–25).

Another finding was that, after DN stimulation, metabolism in the bilateral cerebellar hemispheres significantly changed, with metabolism significantly increasing compared with that before stimulation. This is the first demonstration of improvement of cerebellar hemisphere metabolism in an SCA3/MJD patient by stimulation of the DN and GPi. Local glucose metabolism and oxygen use are coupled with local brain activity, which indicates that *in vivo* measurement of regional glucose consumption by ^{18}F-FDG PET provides an index of regional neuronal activity (26). Under physiological steady-state conditions, cerebral blood flow is tightly coupled to the level of cerebral oxygen and glucose consumption (27). In our patient, metabolism increased after cerebellar hemisphere stimulation increased cerebral blood flow, which is conducive to the recovery of neuron function. Relative decreases in ^{18}F-FDG uptake in cerebellar hemispheres may reflect either impaired neuronal function caused by cellular pathology at that location or remote functional network changes caused by lesions elsewhere (28). It is uncertain whether the metabolic transition from low to high in our patient is stimulated by local neurons (DN DBS) or regulated by a remote functional network (GPi DBS). For our patient, we consider that cerebellar metabolism was promoted by DN DBS because DN DBS acts directly on the cerebellum; however, we cannot rule out an effect of GPi DBS.

Fukuda et al. (29) studied metabolic changes in the brain and cerebellum in Parkinson's disease patients treated with GPi DBS using ^{18}F-FDG PET. They found that GPi DBS improved Unified Parkinson's Disease Rating Scale motor scores by 36% and significantly increased regional glucose metabolism in the premotor cortex ipsilateral to stimulation and in the cerebellum bilaterally. In addition, subthalamic nucleus DBS can change cerebellar metabolism (30–32). In our patient, diffusion tensor imaging fiber bundle dentatorubrothalamic tract reconstruction showed the fiber connection between the thalamus, pyramidal tract, motor cortex, and DN. GPi DBS may indirectly stimulate the cerebellum through the pallidothalamic tract and the dentatorubrothalamic tract. If GPi DBS can change the metabolism of the cerebellum, DBS is more likely to function by regulating the entire neural network rather than merely exciting or inhibiting certain nuclei.

Altogether, acute DN and GPi DBS lead to increased cerebellar metabolism, which is an encouraging finding and supports DBS treatment of SCA3/MJD.

4.3. Limitations

The stimulation test used external stimulation, and the duration of each group of tests was short, only 3 days, especially for the GPi; however, prolonged stimulation can play a regulatory role. Although this was a prospective, double-blind study, it included only one case.

5. Conclusion

Multi-target acute stimulation (DN DBS and GPi DBS) in SCA3/MJD can mildly improve cerebellar ataxia and dystonia. Acute stimulation also increased cerebellar metabolism. Long-term efficacy and brain metabolic changes after SCA3/MJD DBS need further study.

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 Ethics Committee of the Chinese People's Liberation Army General Hospital. 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.

Institutional review board statement

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board (or Ethics Committee) of the Chinese People's Liberation Army General Hospital (S2019–268-02; October 1, 2019) (Chinese Clinical Trials: 2100045363).

Author contributions

Conceptualization and original draft preparation: ZC. Methodology and data curation: JW. Imaging materials: YL, XLi, and XLo. Nuclear medicine image data: YC and RW. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1246430/full#supplementary-material

SUPPLEMENTARY VIDEO S1
This patient has degenerative ataxia and walks with poor balance, no normal standing posture, and loss of independent walking ability, with a wide base, and irregular steps. There is also an occasional lurch.

SUPPLEMENTARY VIDEO S2
The patient's movement of straight walking and turn-back must be supported by someone, with the patient's center of gravity on her upper body, and relying on a forward leaning posture. The hands of the helper are used to maintain the balance of the patient's body.

SUPPLEMENTARY VIDEO S3
When the stimulator is turned on, the patient feels an increase in muscle strength in both lower limbs. Although there is still a significant balance disorder, she is able to stand and walk alone. But the turning motion is still slow and not yet fully completed.

SUPPLEMENTARY VIDEO S4
When the stimulator is turned on, there is also an occasional lurch. The patient is able to walk alone with their left hand supporting the wall.

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Cerebral infarction in centrum semiovale presenting with hemichorea: a case report and literature review

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Hemichorea caused by cerebral infarction in the centrum semiovale is a rare condition that can often be misdiagnosed. In this case report, we present a rare case of a 66-year-old man who experienced involuntary movement in his left limbs due to acute cerebral infarction in the centrum semiovale. The patient did not have any obvious inducements for the hemichorea. In this case, the treatment approach followed the guidelines for treating acute cerebral infarction, combined with the use of dopamine receptor blockers. The involuntary movements gradually improved and completely remitted after 5 days of treatment, with no relapse within the following 6 months. To summarize, this case report highlights the rare occurrence of hemichorea caused by cerebral infarction in the centrum semiovale. Prompt recognition and appropriate treatment are essential to prevent misdiagnosis and ensure optimal management of the condition.

KEYWORDS

hemichorea, centrum semiovale, stroke, movement disorder, chorea

Introduction

Hemichorea is a spectrum of involuntary movement involving one side of the body. It usually results from a lesion in the contralateral basal ganglia structure. Hemichorea can be caused by various factors, such as infections, autoimmune diseases, drug-induced disorders, metabolic diseases, neurodegenerative diseases (1), and cerebrovascular diseases like acute cerebral infarction (2, 3). However, the incidence of hemichorea caused by acute cerebral infarction is relatively low, around 1% (4, 5). It is important to identify this condition from other potential causes of hemichorea. We present a rare case of a 66-year-old man who experienced involuntary movement in his left limbs due to acute cerebral infarction in the centrum semiovale.

Case presentation

A 66 years old man with medical history of hypertension, type 2 diabetes and rectal cancer treatment was admitted to the hospital for experienced involuntary movement of the left side had started suddenly 10 h before. The principal manifestation of involuntary movement was

uncontrollable writhe, which is persistent and worsen during activity or negative emotion.

No abnormalities were noted on general physical examination. On neurological examination revealed involuntary，irregular movements of the left limbs without speech disturbances, loss of consciousness, hallucinations, or limb weakness. There were no abnormalities of tendon reflexes or the sensory system. The National Institutes of Health Stroke Scale (NIHSS) on examination was 0.

Blood cell counts, liver and kidney function, blood fat, electrolytes, thyroid function, tumor markers, antistreptolysin "O" test, rheumatoid factor, the three items of vasculitis, serology for human immunodeficiency virus and *Treponema pallidum* were all normal. Random blood glucose was 6.8 mmol/L on admission. Fasting serum glucose level (5.6–8.5 mmol/L) and postprandial blood glucose (10.0–14.9 mmol/L) were abnormal. Glycosylated hemoglobin was 9.20%.

The head diffusion weighted imaging (DWI, Figure 1) scan showed acute infarction in the right centrum semiovale. Head magnetic resonance imaging (MRI, Figure 2) results revealed multiple cerebral softening lesions with gliosis in the bilateral frontal, parietal, occipital, and temporal lobes.

Multiple cerebral arteriosclerosis and stenosis of the right middle cerebral artery were also observed from magnetic resonance angiography (MRA, Figure 1).

The acute infarction was corresponding to the timing of the hemichorea episode. The older infarct showed in the DWI, presented high signal intensity on ADC (pointed by red arrow in Figure 1), indicating that the lesion may be the lesion of subacute cerebral infarction and had nothing to do with the present attack. Therefore, the possibility of hemichorea caused by old cerebral infarction is unlikely.

Although our patient had elevated fasting and postprandial blood glucose levels upon admission, the presentation did not meet the diagnostic criteria for non-ketotic hyperglycinemia (NKH). Moreover, there were no characteristic imaging findings such as high T1W1 signal in the right striatum observed on the head MRI (Figure 3). Therefore, the possibility of hemichorea caused by NKH is ruled out.

Furthermore, we noted that the patient had a history of rectal cancer surgery and underwent relevant examinations after admission. Generally, lung cancer, breast cancer, and ovarian cancer are the main causes of paraneoplastic neurological syndromes, whereas rectal cancer is relatively rare in clinical practice. Considering that rectal cancer is associated with a high risk of brain metastasis, we still considered the impact of cancer. All results showed no tumor recurrence or metastasis.

In addition, the patient denied the history of taking special drugs (such as tricyclic antidepressants, central nervous system stimulants et al.) and poisons, so drug or poison-related hemichorea was not considered. The possibility related to thyroid abnormalities and central nervous system vasculitis were also not taken into consideration due to the normal items and lack of clinical manifestations.

Taking all factors into account, we diagnosed the patient with hemichorea caused by acute cerebral infarction in the centrum semiovale.

The patient was treated with aspirin, atorvastatin, troxerutin, and haloperidol. The regiment of treatment were 5 mg haloperidol administration through intramuscular injection on the day of admission, and then intramuscularly inject 5 mg once a day until discharge. Aspirin tablet 100 mg and atorvastatin 20 mg orally once a day, and troxerutin 300 mg intravenously once a day were also given while in hospital.

The involuntary movements gradually improved from the day after the admission and completely remitted after 5 days of treatment, with no relapse within the following 6 months.

Discussion

Cerebral infarction in the centrum semiovale typically leads to contralateral hemiparesis, sensory abnormalities, and aphasia, but rarely presents with hemichorea (6). The most common locations for hemichorea caused by stroke are the basal ganglia (caudate nucleus, putamen, globus pallidus) and subthalamic nucleus (4, 7, 8). Other reported sites of infarction include the frontal, parietal, occipital, midbrain, and pons (8–10). Hemichorea is associated with infarctions involving the territories of the middle cerebral artery and posterior cerebral artery, which supply the basal ganglia (8). Additionally, Pondal M et al. reported chorea of the lower limbs secondary to cavernoma (11).

Typically, when hemichorea accompanies small-sized cerebral infarctions, the pyramidal tracts are usually preserved. When the infarction area is large and involves the pyramidal tracts, paralysis of the contralateral limbs is usually severe, but hemichorea does not

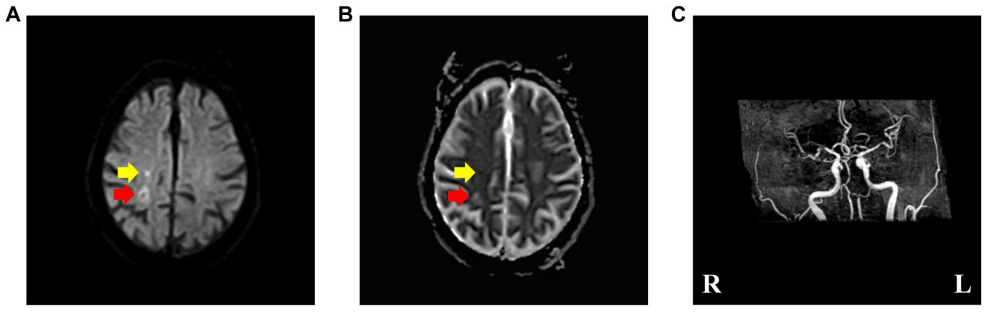

FIGURE 1
(A,B) Brain diffusion weighted imaging and apparent diffusion coefficient, revealing acute ischemic stroke (pointed by yellow arrow) and subacute ischemic stroke (pointed by red arrow) involving the right centrum semiovale. **(C)** Brain magnetic resonance angiography, suggesting multiple cerebral arteriosclerosis and stenosis of cerebral artery.

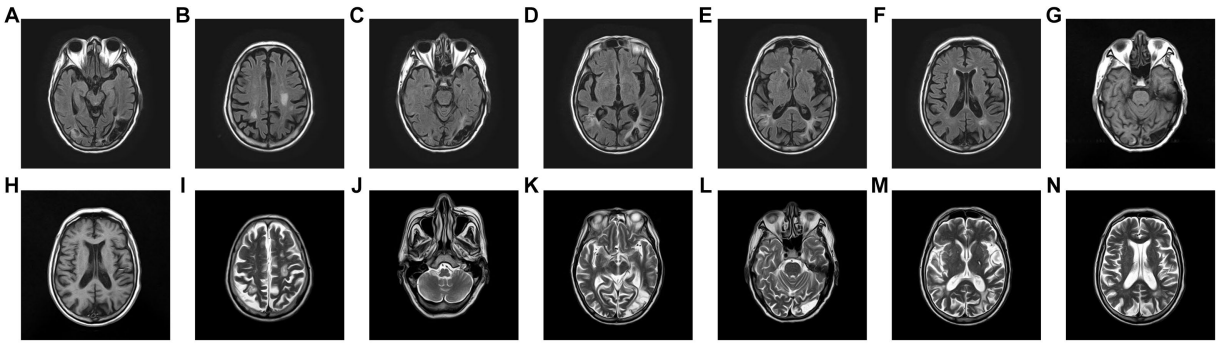

FIGURE 2
(A–F) Fluid-attenuated inversion recovery. **(G,H)** Brain T1-weighted image. **(H–N)** T2-weighted image, revealing multiple old infarction and encephalomalacia foci combined with gliosis of bilateral frontal, parietal, occipital and temporal lobe. Virchow-Robin Spaces and demyelination was observed in the basal ganglia of both sides, and no obvious abnormalities were observed in the brainstem.

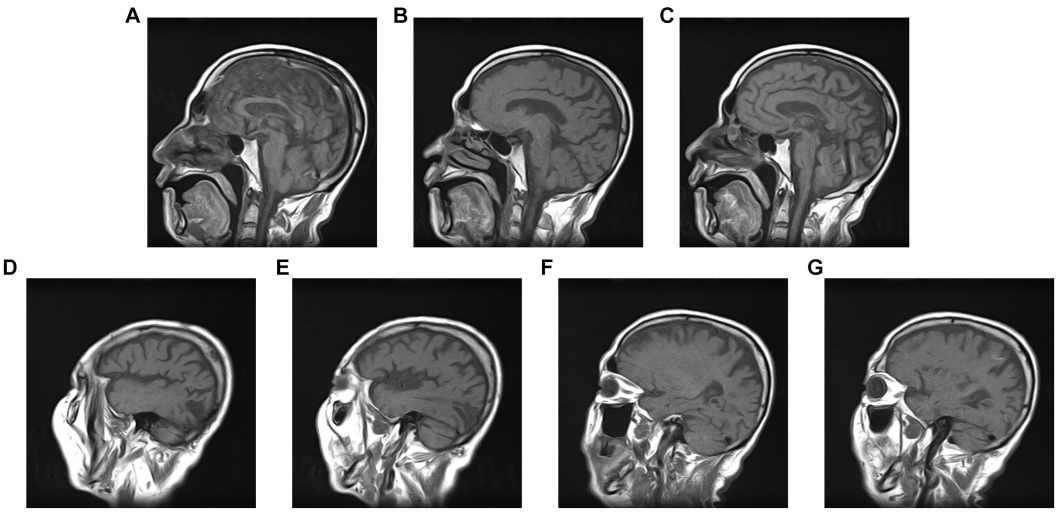

FIGURE 3
(A–G) No legions showed in striatum from Brain T1-weighted image sagittal images.

occur. However, ipsilateral chorea can occur due to compression of the contralateral brain. In our reported case, the patient only exhibited hemichorea and did not show signs of pyramidal tract involvement or limb weakness. The possible pathophysiology is as follows: (I) disruption of the neurotransmitter balance in the extrapyramidal system. Specifically, decreased activity of inhibitory neurotransmitters (gamma-aminobutyric acid) and enhanced activity of excitatory neurotransmitters (glutamate and dopamine) result in chorea and (II) Extrapyramidal circuits consist of the direct pathway (cerebral cortex – striatum – globus pallidus interna/ substantia nigra pars reticulata – ventral thalamus – cerebral cortex) and the indirect pathway (cerebral cortex – striatum – globus pallidus externa – subthalamic nucleus – globus pallidus interna – ventral thalamus – cerebral cortex) (1, 7, 9). Cerebral infarction in the centrum semiovale may damage the fibers in the cortical-basal ganglia-thalamocortical loop, leading to excessive inhibition of the indirect pathway or activation of the direct pathway, without damaging the pyramidal tracts, resulting in hemichorea as the sole clinical manifestation. Hemichorea caused by acute cerebrovascular disease typically occurs on the contralateral side while ipsilateral chorea usually occurs in patients with large cerebral infarction and intracerebral hemorrhage (7). It is worth noting that there have also been reports of generalized chorea caused by unilateral anterior cerebral artery infarction and hemichorea caused by ipsilateral subdural hematoma (12, 13).

Due to constraints, this study also has some other limitations. Although we considered the TOAST classification as being consistent with small artery occlusion, Holter monitoring and a bubble test were not performed to exclude the possibility of cardioembolic stroke due to patient preference. Additionally, the patient did not undergo a follow-up head MRI and DWI after symptom resolution, which would have been helpful in confirming our diagnosis. SPECT, electroencephalography, and cerebral perfusion imaging would have provided more persuasive evidence.

This rare case highlights the importance of considering acute cerebral infarction as a potential cause of hemichorea, even when the location is outside the basal ganglia, such as in the centrum semiovale. It's crucial for clinicians to be aware of this possibility to avoid misdiagnosis and ensure timely treatment.

The treatment principles for hemichorea caused by acute cerebral infarction are similar to those for acute cerebral infarction itself. Antiplatelet therapy to prevent further thrombus formation and improve cerebral circulation is important. Additionally, interventions aimed at improving cerebral arteriosclerosis and circulation, such as blood pressure control, lipid management, and lifestyle modifications, should be considered. In terms of symptomatic treatment for choreic movements, dopamine receptor blockers like haloperidol can be prescribed to alleviate symptoms (14). These medications help modulate the neurotransmitter imbalance in the extrapyramidal system and reduce excessive dopaminergic activity, thereby reducing chorea (15). This combination proved to be effective in relieving the patient's symptoms.

It's worth noting that patients with hemichorea caused by cerebral infarction often retain good reconstruction ability of the extrapyramidal system (16). This may contribute to the relatively favorable prognosis observed in these patients. Rehabilitation therapy, including physical and occupational therapy, could be beneficial in promoting functional recovery.

Overall, increasing awareness of the association between hemichorea and acute cerebral infarction, as well as implementing appropriate diagnostic and treatment strategies, can lead to better management and outcomes for patients with this condition.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Third Affiliated Hospital of Xi'an Medical University. 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

JY: collecting information and writing – original draft. LZ: diagnosing and treating. TZ: collecting information. JL and YZ: interpretation of imaging results. MZ: project administration. 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: Dopamine Dysregulation Syndrome, mania, and compulsive buying in a patient with Parkinson's disease

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Neuropsychiatric symptoms and syndromes are among the most common non-motor symptoms of Parkinson's Disease but they are frequently unrecognized and untreated. Dopamine Dysregulation Syndrome is an uncommon complication of the treatment of Parkinson's disease, characterized by an addictive use of dopamine far more than the dosage required for treatment of objective motor impairment, leading to severe dyskinesia, euphoria, aggressivity, or psychosis. We present a paradigmatic case of Dopamine Dysregulation Syndrome, Mania, and Compulsive Buying in a 55-year-old male with Parkinson's Disease. We also reviewed the risk factors and the therapeutic management of Dopamine Dysregulation Syndrome in Parkinson's Disease.

KEYWORDS

Parkinson's disease, dopaminergic Dysregulation Syndrome, mania, compulsive buying, impulsive-compulsive behaviors

Introduction

Dopamine Dysregulation Syndrome (DDS) is an addictive pattern of dopamine replacement therapy use, above the prescribed dosage and those required to control motor symptoms (1–3). This therapeutic abuse results in severe motor dyskinesias and psychosocial dysfunction (1–3). DDS occurs in Parkinson's Disease (PD) patients with a prevalence of about 8.8% (4). It is associated with younger age at onset of PD, male gender, impulsivity, and sensation-seeking personality traits, psychiatric history of depressive symptoms, and personal or family history of substance use (1–3). There are also reports of mania and hypomania associated with dopamine replacement therapy in PD with similar clinical factors associated with DDS and Impulsive Compulsive Behaviors (ICDs) (5).

We present a paradigmatic case of DDS, Mania, and Compulsive Buying in a 55-year-old male with PD.

Case report

A 55-year-old male with PD was referred to our institution for psychiatric evaluation to undergo Deep Brain Stimulation (DBS) surgery due to debilitating dyskinesias and unpredictable and large periods of "OFF" states. He was diagnosed with PD at 50 years although the first symptoms were reported at age 43. Motor fluctuations and debilitating dyskinesias were reported 2 years before. He also had a history of Depressive Disorder since

he was 41 years old. According to the information given by the patient and the family, there is no history in the family of knowing neurologic or psychiatric diseases. At admission, the patient presented dressed in colorful clothes and was wearing three gold necklaces. He presented an elated mood, disinhibition, logorrhea, an increase in speed of speech, increased self-esteem, diminished necessity to sleep, and paranoid delusions. He also displayed impulsive-compulsive behaviors namely compulsive buying and hoarding—he had bought over 5,000 pocket watches and 42 old and unusable cars, that he stored; he also stored old radio devices. He related these periods of excessive buying to periods of higher energy and higher doses of dopaminergic medication. At the time of this appointment, he was medicated with levodopa (total dose-−2,150 mg) and ropinirole 8 mg/daily corresponding to a levodopa equivalent daily dose (LEDD) of 2,310 mg. In a later appointment, he admitted to taking more levodopa pills than those prescribed by the doctor. He maintained the manic symptoms previously described. He also reported waking up in the middle of the night to take dopaminergic pills, associated with an increase in new activities and projects. The patient developed an interest in "old things" and new daily routines. He started leaving home early in the morning and buying old objects. Despite having no insight into these new behaviors, he was admitted voluntarily to the psychiatric ward. During the hospitalization, the dopaminergic medication was gradually reduced (LEDD-−2,030 mg), pill taking was controlled and he did not have access to extra pills. Valproic acid and quetiapine extended release were started and increased to 1,000 and 300 mg/daily, respectively and ropinirole was tapered off to 4 mg. The maniac symptoms gradually decreased and there was no worsening of Parkinson's motor symptoms or any change in dyskinesias. He was discharged 29 days after his admission to the psychiatry ward in clinical remission.

Discussion

We provide a clinical description of a paradigmatic case of DDS, Mania, and Compulsive Buying in a patient with Parkinson's Disease. Knowledge about the phenomenology of DDS in patients with PD is still limited and reports of DDS comorbid with other ICDs and Mania are still scarce.

DDS is an uncommon condition, described for the first time by Giovannoni et al. (1). The estimated prevalence of 3.4–4% (1, 6). It is associated with other compulsive impulsive behaviors like *punding* and impulse control disorders. The use of high doses of levodopa and dopaminergic agonists with short-acting profiles are known risk factors.

The pathophysiology is not clear (7) but it probably occurs due to the loss of dopaminergic neurons in the *substantia nigra pars compacta* (SNc) and in the ventral tegmental area (VTA) with depletion of dopamine in the nigrostriatal motor pathway (2, 8). The dopaminergic stimulation of the *nucleus accumbens* (NAc) is essential to the reward effect of medication. The over-stimulation of the mesolimbic system can impact the development of rewarding behaviors (2, 8). The addictive properties of dopaminergic medication can be explained by the dysregulation of dopamine in the ventral striatum. The compulsive use and chronic stimulation by dopaminergic medication can lead to the hypersensitivity of D3 receptors (2, 9).

Neuroplasticity induced by dopaminergic replacement therapy in ventral and dorsal striatal systems and subsequent long-term disruptions of signaling in the basal ganglia can be associated to behavioral and motor complications of compulsive medication use in PD. Dopamine in nucleus accumbens may be responsible for certain rewards in terms of seeking food or sex as well as financial and verbal rewards. Sensitization of ventral striatal networks to dopaminergic replacement therapy may be analogous to the neuroplastic changes in the dorsal striatum which can contribute to the motor complications such as dyskinesias and repetitive motor acts. Moreover, striatal dopamine denervation in Parkinson's disease and cortically-mediated impairments in goal directed function may enhance sensitization to dopaminergic replacement therapy which seem to contribute to DDS development (10).

The core symptoms of this syndrome are the early self-adjustment of dopaminergic medication with the use of total doses superior to the need to control motor symptoms (1). Patients report good response to levodopa in an early phase, describing elated mood after each dose taken (11). There are also descriptions of impulsivity, agitation, irritability, and low tolerance to frustration (1). Usually, patients develop incapacitating dyskinesias associated with peak dose (1). Despite dyskinesias, patients continue to try to anticipate taking levodopa and increase the daily dose ingested (1, 2). Patients try to buy dopaminergic medication without a medical prescription and try to hide it from family members (1).

PD patients treated with dopamine agonists have more ICD, in comparison with those not treated with dopamine agonists. The use of pramipexole and ropinirole showed more risk for ICD because of their selectivity for D2-like receptors (D3 and D4 receptors), which are localized in the mesocorticolimbic system, explaining the risk of developing ICD. Levodopa, especially at higher dosages, was also related with ICD but to a lesser level than DA treatment (12). However, besides the risk of dopamine agonists, levodopa was more related with DDS than dopamine agonists, in contrary to what was observed in ICDs (13). Parkinson's disease patients with DDS exhibited enhanced levodopa-induced ventral striatal dopamine release compared with levodopa-treated patients with Parkinson's disease without DDS (14). PD patients with DDS show higher levodopa-induced ventral striatal dopamine release as compared to levodopa-treated patients with PD but who do not compulsively ingest dopaminergic drugs (15). Levodopa is believed to be the most potent trigger for the development of DDS (14).

Therapeutic management of DDS is complex and involves gradual tapering or discontinuation of dopaminergic medication, although discontinuation may be associated with severe motor disorders, dysphoria, irritability, depression, and anxiety (1, 2).

Some of the features respond to the minimization of short duration response or reduction of the dosage, while behavioral disturbances often require antipsychotic treatment with clozapine or quetiapine. Other authors previously described the efficacy of valproate in PD patients presenting with DDS, without observing the valproic acid-associated worsening of parkinsonism (15, 16). Valproate may reduce the substantia nigra reticulata output once maybe the excess dopaminergic medication drives increased activity in the ventral striatal reward pathway (17). Can also

reduce the arachidonic acid cascade signaling pathway via D2-like receptors, modulating DDS behavior (15).

Mania and hypomania in PD are rarely reported besides the immediate post-DBS cases (5). Factors associated with the development of hypomania are similar to DDS and ICDs (higher LEDD, younger age of onset, and dyskinesias) (5). DDS is a significant clinical correlate of mania and hypomania, nevertheless, can exist independently (5). The pathophysiology is also identical to DDS, due to the sensitization of the ventral striatal dopaminergic receptors (5).

The effort in interrupting the processes of addiction may justify why limiting dopamine replacement therapy or changing to a non-pulsatile formulation can lead to these different symptoms. DBS, by acting in the subthalamic nucleus, can permit a reduction of dopamine replacement therapy and also attenuate the pulsatile nature. However, the use of DBS in resolving DDS has demonstrated ambiguous results, which may be related to the time taken from the start of PD to the use of DBS; less comorbidity, rapid withdrawal of levodopa post-DBS and use of dopamine agonists (13).

Increasing recognition of neuropsychiatric syndromes in PD patients is mandatory to improve treatment which frequently demands a specialized and multidisciplinary team.

Data availability statement

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

Ethics statement

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

Author contributions

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Dyskinesia-hyperpyrexia syndrome in Parkinson's disease triggered by overdose of levodopa — a case report and literature review

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Dyskinesia-hyperpyrexia syndrome, a rare medical emergency in Parkinson's disease, is first described in 2010. It is characterized by severe continuous dyskinesia associated with rhabdomyolysis, hyperthermia and subsequent alteration of the mental state. Gradual reduction of dopaminergic dose or DBS is recommended treatment. The prognosis is usually good, but sometimes fatal. But so far, this potentially fatal complication is not widely recognized by clinicians. In emergency, if clinicians fail to make prompt diagnosis and treatment, patients' conditions may get worse, and their lives may be threatened in serious cases.

KEYWORDS

Parkinson's disease, acute hyperpyrexia syndrome, dyskinesia, hyperpyrexia, treatment

Introduction

Acute hyperpyrexia syndrome related to Parkinson's disease usually occurs in advanced PD patients, especially in those who have received long-term treatment with levodopa. Acute hyperpyrexia syndrome includes Parkinson hyperpyrexia syndrome (PHS), dyskinesia-hyperpyrexia syndrome (DHS) and serotonin syndrome (SS) (1, 2). These acute hyperthermia syndromes are easily confused by clinicians. If emergency physicians cannot recognize these three hyperthermia syndromes timely and give treatment optimally, it may lead to poor prognosis, even threaten lives. Here, we reported a PD patient who presented with severe dyskinesia-hyperpyrexia syndrome, meanwhile performed a comprehensive literature.

Case description

Our patient was a 78-year-old female with a history of PD for 10 years. She had been taking levodopa/benserazide 600/150 mg/day, pramipexole 0.75 mg/day and selegiline 10 mg/day. She denied a history of current statins or serotoninergic drugs use. The season was summer during which she had a slight weight loss. A week before admission she had head trauma secondary to a fall, followed by appetite loss accompanied with a mild dyskinesia. The patient's family considered the symptoms to be tremors and added another compound tablet of levodopa/benserazide (200/50 mg), along with daily oral medication, including levodopa/benserazide 600/150 mg, pramipexole 0.75 mg and selegiline 10 mg, the LEDD was 975 mg. After that the abnormal movements worsened significantly.

On admission, she was in coma because of hypoglycemia, even though she had no history of diabetes and never received hypoglycemic treatment. In the emergency room, her body temperature was 39.6°C, and the heart rate was 118 beats/min. When hypoglycemia is rapidly corrected, the patient's consciousness recovered and severe generalized involuntary dyskinesia of limbs occurred, more intense in the upper limbs. Laboratory findings were mild leukocytosis (white blood cell count 10.07 × 10^9/L). Elevated BUN (13.6 mmol/L) with serum creatinine (87umol/L) indicated a mild decrease in renal function. Lac (8.4 mmol/L) and serum CK level (1579 U/L) were highly elevated. A chest CT scan showed ill-defined ground-glass opacity in right lower lobes. No space-occupying inflammatory lesion was observed. Head CT basically ruled out intracranial hemorrhage, head injury and strategic infarction (Figure 1). Unfortunately, No head MRI was performed due to the patient's involuntary movements. Since low PCT (0.1 ng/ml) and bacterial culture of sputum were negative, pneumonia was not considered as a fever source, and antibiotics were not prescribed.

Based on the clinical features and laboratory findings, a diagnosis of dyskinesia hyperpyrexia syndrome was made. We discontinued pramipexole and reduced the levodopa/benserazide dose to 300/75 mg/day. The dose of antiparkinsonian drugs was reduced progressively but the dyskinesia never disappeared. After the patient's drug was completely reduced on the 10th day of hospitalization, the abnormal movement completely disappeared but the patient developed fever again. So we added selegiline 5 mg/day, and after that the patient did not show any abnormal movement, with the temperature returned to normal.

Discussion

Acute hyperpyrexia syndrome related to Parkinson's disease is rare but life-threatening complication of PD. Approximately 30–40% of PD patients who have been treated with levodopa for more than 5 years may develop levodopa-induced dyskinesia (3, 4). When a PD patient experiences acute hyperpyrexia, the PHS, DHS and SS need to be considered. Wang's study elucidated the similarities and differences between PHS, DHS, and SS (5). The similarity of these three syndromes can exhibit hyperpyrexia, neuromuscular symptoms, autonomic symptoms and consciousness disturbance. Concerning potential triggers, it should be noted that high ambient temperature, dehydration, infection, and trauma can be common triggers for PHS and DHS, while excessive serotonin drugs are the only cause of SS. In terms of disease course, the course of PHS and DHS usually lasts for 1–2 weeks, while the course of SS usually lasts for <24 h. The neuromuscular symptoms of DHS are often manifested as dyskinesia, while PHS is often characterized by rigidity and oligokinesia. Compare to PHS, SS may have symptoms such as increased tendon reflexes and clonus in addition to rigidity. PHS and SS usually manifest as tachycardia, sweating, and unstable blood pressure as autonomic nervous symptoms, which are rare in DHS. The consciousness disorder of PHS usually manifests as a decrease in consciousness level from drowsiness to coma, while DHS typically manifests as blurred consciousness and hallucinations. SS usually exhibit anxiety and irritability, while severe patients may experience symptoms such as delirium and coma. The most effective treatment for the three syndromes is to remove potential triggers. PHS needs to gradually increase the dosage of dopaminergic drugs or restart DBS. Conversely, DHS needs to gradually reduce the dosage of dopaminergic drugs or reduce the stimulation of DBS. In addition, SS needs to discontinue the serotonergic drugs. Dyskinesia associated with hyperpyrexia was first described in a 68-year-old advanced PD patient by Gil-Navarro and Grandas (6). And DHS is even rarer compared with PHS or SS. To date, a total of 15 cases of DHS have been reported in 12 publications (Table 1). Sometimes, the dyskinesia may lead to

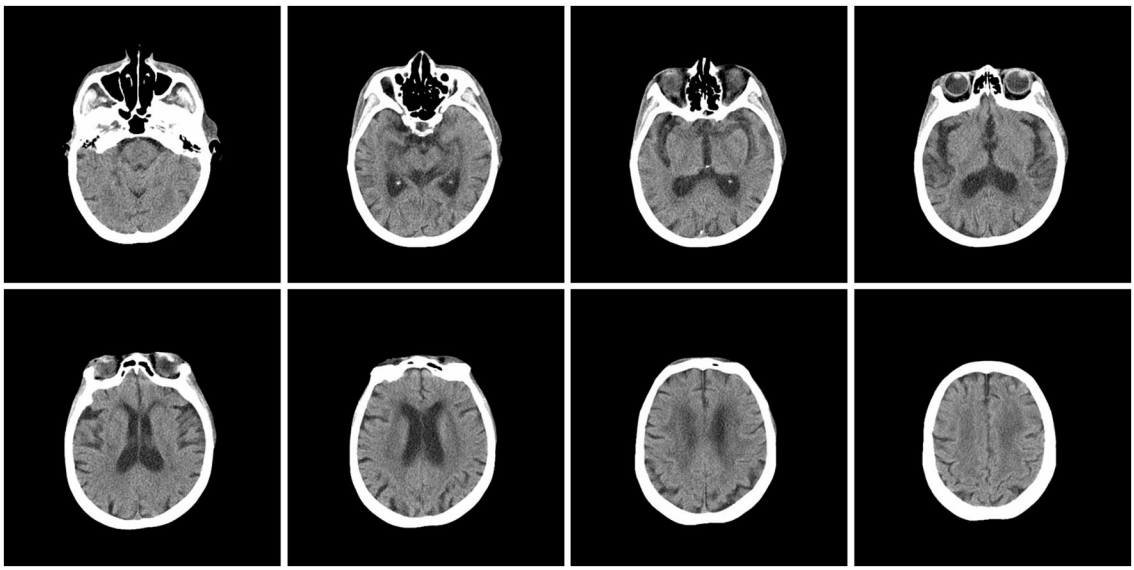

FIGURE 1
Head CT basically ruled out intracranial hemorrhage, head injury and strategic infarction.

TABLE 1 Overview of 14 affected patients with dyskinesia hyperpyrexia syndrome.

References	Age/gender	PD duration	Suspected provocation factor	Season	Peak body T (°C)	Symptoms	LEDD (mg)	Treatment	Outcome
Gil-Navarro and Grandas (6)	68/F	12	NA	NA	41.2	Generalized dyskinesias confusion and hallucination Tachycardia CK = 1455 IU/L	1680	Intravenous fluids antipyretic agents pramipexole tapered off Quetiapine 25mg	Recovered
Lyoo and Lee (7)	74/M	17	Dopaminergic drug dose increase (levodopa 1050 mg increased to 3400 mg)	NA	38.2	Generalized dyskinesias consciousness was normal acute renal injury (176.8 μmol/L) CK = 24651 IU/L	3400	Dopaminergic drug was stopped sedative	Recovered
Taguchi et al. (8)	70/F	13	Dopaminergic drug form change (pramipexole IR to ER)	Autumn	40.3	Generalized dyskinesias confusion and hallucination Tachycardia CK = 35000 IU/L	950	Intravenous fluids antipyretic agents reduced dopaminergic drugs	Recovered
Herreros-Rodriguez and Sanchez-Ferro (9)	74/F	16	High ambient temperature	Summer	40.2	Generalized dyskinesias Consciousness was normal CK = 178–2509 IU/L	1390	Receive an LCIG (1310 mg/d)	Died from an unrelated pulmonary embolism
Sánchez-Herrera et al. (10)	66/F	16	High ambient temperature, dopaminergic drug dose increase	Summer	40.2	Generalized dyskinesias confusion and hallucination CK = 7177 IU/L	1810	Intravenous fluids antipyretic agents sedative LCIG reduced amantadine, ropinirole and safinamide were stopped	Recovered
Baek et al. (11)	74/F	23	Trauma, infection	Spring	40.3	Generalized dyskinesias confusion and hallucination aspiration pneumonia acute renal injury (142μmol/L) CK = 10230 IU/L	675	LCIG reduced Amantadine and pramipexole were stopped Antibiotics Sedative	Recovered
Sarchioto et al. (12)	80/M	20	High ambient temperature, infection	Summer	42	Generalized dyskinesias confusion and lethargy Acute renal failure (186.5μmol/L) pneumonia CK = 16040 IU/L	1550	Pramipexole and AMA withdrawn LCIG dose reduced to 700mg antibiotics	Death
	76/F	18	High ambient temperature/infection	Summer	41	Generalized dyskinesias stupor pneumonia respiratory failure CK = 2967 IU/L	1060	Antibiotics	Death
	79/F	30	High ambient temperature/infection	Summer	39.5	Generalized dyskinesias consciousness was normal pneumonia acute renal injury (175μmol/L) CK = 1967 IU/L	1000	Intravenous fluids LCIG reduction (675 mg) antibiotics	Recovered
Novelli et al. (13)	62/M	34	High ambient temperature, infection	Summer	40.7	Generalized dyskinesias confusion tachycardia CK = 4891 IU/L	2528	Intravenous fluids antipyretic agents antibiotics DBS reduced to 1 V bilaterally Levodopa/carbidopa 125/12.5mg plus entacapone 200 mg for six daily doses	Recovered

(Continued)

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TABLE 1 (Continued)

References	Age/gender	PD duration	Suspected provocation factor	Season	Peak body T (°C)	Symptoms	LEDD (mg)	Treatment	Outcome
Zu et al. (14)	76/F	16	Dopaminergic drug dose increase	NA	40.2	Generalized dyskinesias unconsciousness tachycardia CK = 2489 IU/L	1150	Reduced dopaminergic drugs	Recovered
Pitakpatapee et al. (15)	64/M	10	Delayed gastric emptying time	NA	37.5	Generalized dyskinesia consciousness was normal sweating CK = 4246 IU/L	967	Intravenous fluids stopped all medications sedative	Recovered
	61/F	10	Infection, increasing dose of ropinirole	NA	37.8	Generalized dyskinesia consciousness was normal dehydration myalgia CK = 12094 IU/L	1222	Rehydration stopped all medications sedative	Recovered
Wang et al. (16)	74/F	4	Dopaminergic drug dose increase	Autumn	39.7	Generalized dyskinesias confusion and hallucination tachycardia CK = 821 IU/L	1500	Rehydration stopped all medications sedative	Recovered
Luo et al. (17)	55/M	10	Dopaminergic drug dose increase	Summer	40.6	Generalized dyskinesias confusion tachycardia CK = 1468 IU/L	1750	Rehydration reduced dopaminergic drugs sedative	Recovered

NA, not available.

rhabdomyolysis, acute renal failure and respiratory distress, which may become severe and life-threatening.

In our review, we found that DHS was more likely to appear in advanced PD patients accompanied with motor symptom fluctuation, particularly with high-dose dopaminergic therapy. The dyskinesia in DHS patients is usually systemic and persistent and may precede fever. Therefore, some patients may only present with dyskinesia without elevated body temperature in the early stages. The body temperature may fluctuate from 37.5°C to 42°C, and most of which is above 40°C. Elevations of CK are generally considered as secondary to severe dyskinesia, ranging from hundreds to 35000 IU/L, but not all DHS patients CK elevation. There were no characteristic changes through our patient's head CT scan. We speculate that other imaging examinations may have more implications. Previously study rarely described characteristic neuroimaging features of DHS. A recent research provides new insights into DHS and expands on its neuroimaging features. Luo's study showed that DHS can cause reversible encephalopathy, which was detected through head MRI (17). Thus, DHS still has many characteristics to be discovered. In previous study, there were 9 out of 14 patients manifested as confusion and hallucinations, which might be caused by dopaminergic hyperactivity in the mesocorticolimbic system. Three patients manifested with consciousness level reduction (stupor or lethargy). Furthermore, we observed that female patients are prone to develop this complication (ten female and four male). These gender differences might be induced by female hormonal patterns which could increase the individual dyskinetic sensitivity to levodopa (18). Besides, compared with male, female patients with lighter body weight are more likely to have higher plasma concentrations of levodopa with the same treatment protocol (19). Therefore, clinicians should pay more attention to individualized drug therapy.

The pathogenesis is still unclear. Previous literature review suggested a variety of suspected triggering factors, including adjustment in dopaminergic therapy, trauma, infection, hot weather, dehydration, gastrointestinal diseases and changes in deep brain stimulation (5). Dopamine dysregulation syndrome (DDS), an uncommon complication of medical treatment for PD, is characterized by addictive behavior and excessive use of dopaminergic medication. Levodopa is more likely to be associated with DDS compared to other drugs; in addition, there were higher rates of dyskinesias and motor fluctuations. Warren's study suggested that individuals at risk may have less efficient inhibitory dopaminergic systems. Thus, we speculate that DDS is also one of the reasons for DHS (20). The current hypothesis was considered as that DHS are prone to occur in high temperature environments. Dopamine is an important neurotransmitter in the hypothalamus, which can promote body heat dissipation and play an important role in regulating body temperature. In patients with advanced PD, degeneration of dopaminergic neurons in the substantia nigra leads to dopaminergic deficiency (10). Therefore, it is speculated that in summer, it is easier to trigger dyskinesia in advanced PD patients treated with high-dose dopaminergic drugs when under high ambient temperature and long daylight duration which may increase the dopaminergic activity (16). Furthermore, hyperpyrexia was also related to increased thermogenesis caused by excessive dyskinesia.

The combination of reduced dopaminergic medications with standard medical care is usually effective and the prognosis is generally favorable. Prompt identification and optimal treatment may improve patient outcomes. Reducing dopaminergic drug dosage as soon as possible is the most effective way to treat DHS. Sedation is effective for patients with refractory dyskinesia (15). Supportive treatments such as intravenous rehydration, cooling, anti-infection, and electrolyte balance are also critical for DHS. Among the 13 patients reported so far, only two patients died due to DHS (12). Complications including rhabdomyolysis, acute renal failure, and respiratory failure suggest a poor prognosis for DHS.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

Ethics statement

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

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Parkinson's disease and comorbid myasthenia gravis: a case report and literature review

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Background: Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease. Myasthenia gravis (MG) is a rare autoimmune disease caused by antibodies against the neuromuscular junction. PD and comorbid MG are rarely seen.

Case presentation: Here we report on a patient who was diagnosed with PD and MG. A 74-year-old man had a 4-year history of bradykinesia and was diagnosed with PD. He subsequently developed incomplete palpebral ptosis, apparent dropped head, and shuffling of gait. The results of neostigmine tests were positive. Repetitive nerve stimulation (RNS) showed significant decremental responses at 3 and 5 Hz in the orbicularis oculi. The patient's anti-acetylcholine receptor (anti-AchR) antibody serum level was also elevated. Meanwhile, 9-[^{18}F]fluoropropyl-(+)-dihydrotetrabenazine positron emission tomography–computed tomography (^{18}F-AV133 PET-CT) scan revealed a significant decrease in uptake in the bilateral putamen. After addition of cholinesterase inhibitors, his symptoms of palpebral ptosis and head drop improved greatly and he showed a good response to levodopa.

Conclusion: Although PD with MG is rare, we still need to notice the possibility that a PD patient may have comorbid MG. The underlying mechanism of PD and comorbid MG remains unknown, but an imbalance between the neurotransmitters dopamine and acetylcholine and the immune system are likely to play significant roles in the pathogenesis. In this article, we present our case and a literature review on the co-occurrence of PD and MG, reviewing their clinical features, and discuss the underlying pathogenic mechanism of this comorbidity.

KEYWORDS

parkinsonism, Parkinson's disease, myasthenia gravis, comorbidity, head drop

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease, with an incidence of 17 cases per 100,000 person-years (1). Myasthenia gravis (MG) has an incidence of 8 to 10 cases per million person-years, making it even rarer (2). Thus, PD and comorbid MG is a rarely seen combination, with its prevalence grossly estimated at 3 in 6 million (3), representing a cumulative incidence of roughly 0.5 to 40 per billion (4). PD patients may present with fatigue, gait disturbances,

dysphagia, dysarthria, and even limitations in eye movement, all of which can also be commonly seen in MG patients. The extremely low incidence and overlapping symptoms make it difficult for clinicians to diagnose this comorbidity. Since 1987, 57 cases of patients diagnosed with PD and comorbid MG have been reported. Coincidentally, we diagnosed a patient with PD and comorbid MG. We herein report our case of coexistence of PD and MG. We also summarize previously reported cases to enable further understanding of this comorbidity and discuss the underlying mechanism of pathogenesis.

Case presentation

A 74-year-old man with a 4-year history of bradykinesia was diagnosed with PD and reported a poor response to levodopa. His medication was increased from a levodopa equivalent dose of 300 mg to 948 mg per day, with little improvement. One year before his admission, he developed incomplete palpebral ptosis of both eyes and gradually deteriorated in terms of ambulation. Three months before his admission, he also developed dysphagia, dysphonia, and head drop.

On neurological examination, the patient had normal cognition (the Mini-Mental State Examination score was 27/30, with 16 years of education). He presented with slight facial masking, incomplete palpebral ptosis, slurring of speech, dropped head, and bradykinesia. Other cranial nerves were normal. His muscle strength and tone of limbs were almost normal, but the strength of his neck extensor muscles was 2/5 and there was slight rigidity in his neck. He presented with no apparent tremor but took very small steps, as in freezing of gait. He had normal cerebellar examination, sensory faculties and reflexes. The Hoffmann signs and Babinski signs were negative bilaterally.

As the patient had responded poorly to levodopa (with <30% improvement) and there was no prominent tremor or rigidity, we gradually adjusted his anti-parkinsonism medication from levodopa-benserazide 250 mg (200 mg levodopa plus 50 mg benserazide) t.i.d., entacapone 0.2 g t.i.d., piribedil 50 mg t.i.d. to levodopa-benserazide 125 mg t.i.d. within 10 days. There was no visible deterioration in any of his symptoms after this reduction in drug dosage.

To determine why the patient had palpebral ptosis, we carried out several tests to exclude MG. Interestingly, administration of neostigmine significantly improved his head drop and palpebral ptosis as well as his gait (Supplementary Video 1). Repetitive nerve stimulation (RNS) showed significant decremental responses at 3 and 5 Hz in the orbicularis oculi. His anti-acetylcholine receptor antibody (anti-AchR antibody) serum level was >20 nmol/L (normal value: <0.45 nmol/L) and he was negative for anti-muscle specific tyrosine kinase (anti-MuSK) antibody.

The patient was then treated with pyridostigmine 60 mg t.i.d. together with tacrolimus 3 mg q.d. One month later, his palpebral ptosis and head drop had improved greatly, but his parkinsonism symptoms had worsened and he experienced distinct "wearing off." He presented with prominent rigidity in the neck and limbs when in the off state. We gradually increased levodopa-benserazide to 250 mg t.i.d., but his parkinsonism symptoms were still worse than the first time he visited our hospital. To verify the diagnosis of parkinsonism, we performed a 9-[^{18}F]fluoropropyl-(+)-dihydrotetrabenazine positron emission tomography–computed tomography (^{18}F-AV133 PET-CT) scan. The mean standardized uptake value ratios (SUVRs) for the left posterior putamen, right posterior putamen, left anterior putamen, and right anterior putamen were 2.14, 2.18, 2.15, and 2.45, respectively [the mean SUVRs for a healthy person are 5.12, 6.05, 5.36, and 5.36, respectively, and the reference diagnostic value distinguishing PD patients from healthy controls in the posterior dorsal putamen is 3.43 (5)], revealing a significant decrease in uptake in the bilateral putamen (Figure 1).

One and a half years after discharge from our hospital, the patient's palpebral ptosis and head drop had completely resolved, but he was experiencing bradykinesia, rigidity, postural instability, and freezing of gait. He received a levodopa equivalent dose of 1,066 mg, and the effect of each levodopa dosage could be maintained for 3 h. His bradykinesia, rigidity, and freezing of gait were improved, with a 32.2% change in the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) III in a levodopa challenge test.

Discussion and conclusion

PD has an incidence of 17 cases per 100,000 person-years (1), and MG has a much lower incidence of 8 to 10 cases per million person-years (2). Thus, PD and comorbid MG are rarely seen in clinical practice. We have described herein a patient diagnosed with PD and MG. In our case, positive outcomes of neostigmine tests, anti-AchR antibody levels, and RNS proved the diagnosis of MG. Bradykinesia, limb rigidity, and shuffling of gait were symptoms of parkinsonism. Decreased uptake in the putamen on ^{18}F-AV133 PET-CT scan validated the impairment of the dopaminergic system. Motor fluctuation further confirmed the diagnosis of parkinsonism. As there were no absolute exclusion criteria or red flags, the patient was ultimately diagnosed with PD combined with MG.

In clinical practice, patients with PD may develop fatigue, gait disturbances, dysphagia, dysarthria, and even limitations of eye movement, which are also symptoms of MG; because of the rarity of PD comorbid with MG, it is difficult to consider a diagnosis of MG in PD patients with such symptoms. As fatigue is a frequent non-motor symptom of PD, the weakness presented by our patient initially did not remind us of the pathological fatigue occurring in MG.

We searched PubMed using "Parkinson's disease" and "myasthenia gravis" as key words and found 57 cases of this comorbidity from 1987 to Nov 20th, 2023. A retrospective observational study of 12 cases from a single center was also retrieved (6). Most of the cases were of male patients. Most patients were diagnosed with PD prior to the diagnosis of MG, and most had generalized MG. We summarize their demographic and clinical characteristics in detail in the Supplementary material.

To obtain more detailed information on PD and comorbid MG, we reviewed previous cases and identified a number of similarities and differences among the previously reported cases, presented in Table 1. Out of all these previous cases, nearly 80% (45/57) were of male patients. Their age at onset of their first

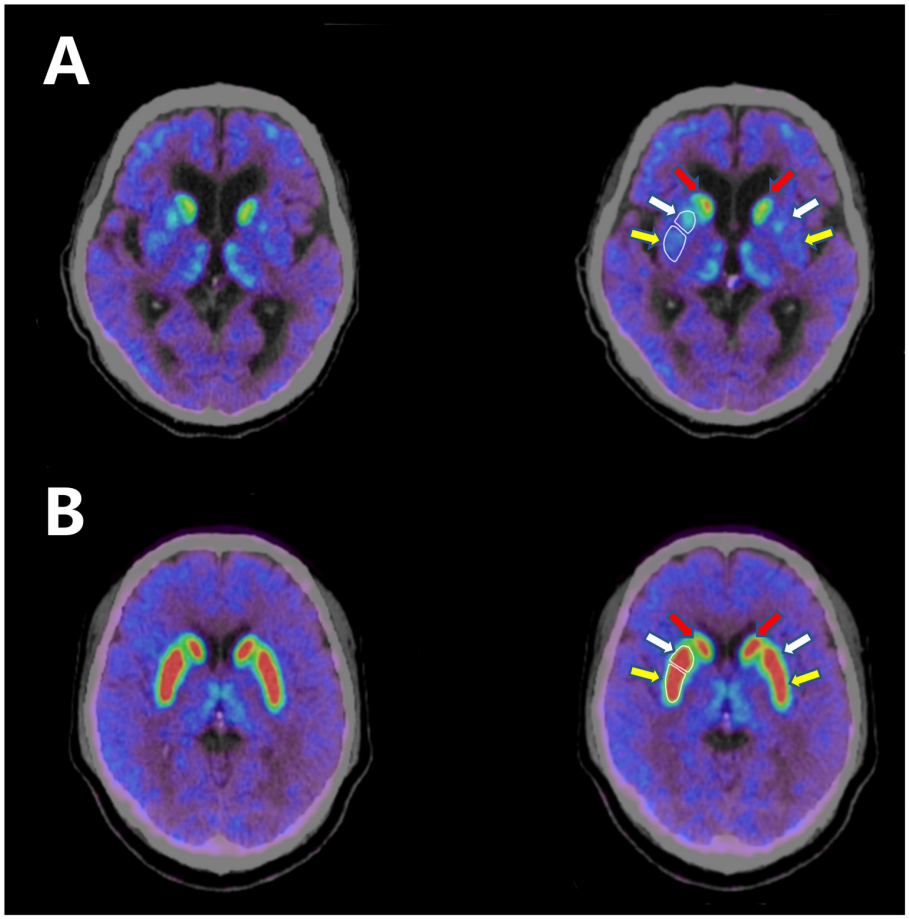

FIGURE 1
(A) ^{18}F-AV133 PET-CT scan of the patient shows significant decrease in uptake in the bilateral putamen. **(B)** ^{18}F-AV133 PET-CT scan of a healthy person shows symmetrical uptake in both the bilateral caudate nucleus and the putamen. White enclosed lines distinguish between the anterior putamen and the posterior putamen. Red arrow: caudate nucleus; white arrow: anterior putamen; yellow arrow: posterior putamen.

disease ranged from 49 to 90 years old. In more than 70% of the cases (41/57), PD preceded MG, and this was also the case in our patient. Our patient had generalized MG and exhibited dropped head. More than 75% of the cases (44/57) had generalized MG, and approximately 30% (17/57) exhibited dropped head. More specifically, seven patients presented with dropped head as their first symptom of MG and six presented with dropped head as their sole symptom. In former cases, the diagnosis of PD generally depended on the clinical manifestations, neurological examinations, and good responses to levodopa, while in our case, we performed an ^{18}F-AV133 PET-CT scan and confirmed impairment of the dopaminergic system. Regarding the diagnosis of MG, in addition to the typical clinical features of the patients, this was based on an increased anti-AchR antibody serum level in approximately 67.3% of the cases (35/52). The 19 patients who underwent an edrophonium test or neostigmine test all had positive outcomes. In 24 cases, RNS and/or single-fiber electromyography (SFEMG) were also performed, and the positive rate was 62.5% (15/24). Most patients responded well to cholinesterase inhibitors (pyridostigmine and/or neostigmine), or to immunosuppressive therapy such as steroids and azathioprine. In <20% of the cases, intravenous immunoglobulin or even plasma exchange was needed to control symptoms of MG.

Notably, the dropped head was a prominent sign in our patient, and dropped head in PD can be explained by either dystonia of the flexor neck muscles or weakness of the extensor neck muscles (7); however, the incidence of dropped head in PD appears to be <5 or 6% (7). Additionally, prominent or isolated neck extensor weakness is also distinctly less common in MG (8), with an estimated occurrence rate of only 10% (9). This occurrence rate rises to 23% for patients with an age of onset of MG of over 60 years (9). However, review of the previous cases of PD and comorbid MG showed that approximately one-third of the patients exhibited dropped head. Even so, we considered the differential diagnosis carefully. Disproportionate antecollis in parkinsonism, which presents as a form of head drop, is considered relatively rare in PD, while it is thought to occur more frequently in multiple system atrophy (MSA) (10). As a result, we had considered the diagnosis of our patient to be MSA at first, given his mild dysuria over the past 6 months, the relatively early presence of dysphagia, dysphonia, and head drop in his disease course (with a total duration of 4 years of parkinsonism), and his poor response to

TABLE 1 Similarities and differences among previously reported cases.

Total number of cases	57	**Ab of myasthenia gravis tested**	52
Average age at onset of PD (years old)	68.9	Anti-AchR Ab positive (%)	35 (67.3)
Average age at onset of MG (years old)	69.6	Anti-MuSK Ab positive (%)	1 (1.9)
PD preceding MG (%)	41 (71.9)	Seronegative MG (%)	16 (30.8)
Patients exhibiting dropped head (%)	17 (29.8)	**RNS/SFEMG conducted**	24
Dropped head as first symptom of MG (%)	7 (12.3)	RNS and/or SFEMG positive (%)	16 (66.7)
Dropped head as sole symptom of MG (%)	6 (10.5)	**Neostigmine/edrophonium test, Ab and EMG positive**	7[b]
Administration of L-dopa	28[a]	**Good response to MG treatment (%)**	39[c]
Good response to L-dopa (%)	28 (100)	Good response to single anticholinesterase drugs (%)	16 (41.0)
Neostigmine test/edrophonium test conducted	19	Good response to anticholinesterase drugs, glucocorticoids, and/or immunosuppressants (%)	17 (43.6)
Neostigmine test/edrophonium test positive (%)	19 (100)	Requiring other treatment[d] (%)	6 (15.4)

[a]Only 28 cases mentioned administration of L-dopa. [b]The number of cases with neostigmine/edrophonium test, Ab, and EMG positive. [c]Treatment of MG was mentioned in relation to only 41 cases, and 39 cases showed improvement or remained stable. [d]Other treatments included intravenous immunoglobulin and/or plasma exchange.

levodopa at the time of admission. Palpebral ptosis also looks similar to eyelid apraxia, which can also occur in MSA. Although the patient did not have prominent autonomic symptoms, he had no orthostatic hypotension, and the residual bladder volume was 15.6 mL. His finger-to-nose test and heel–knee–shin test were normal. All the evidence above made the diagnosis of MSA unlikely. Furthermore, head drop is common in amyotrophic lateral sclerosis (ALS), but the patient had no upper or lower motor neuron signs. Specifically, after his medication against MG was started, the patient exhibited significant improvement in his dropped head. Interestingly, in previous cases presenting with dropped head, we found that the symptom was almost always improved after treatment against MG, and cholinesterase inhibitors and/or immunosuppressive medications were used in most cases. In one case (11), the authors clearly pointed out that the patient's head drop responded weakly to levodopa, and in only one case (12), head drop was ameliorated by a custom head brace rather than pyridostigmine or intravenous immunoglobulin.

Although the comorbidity of PD and MG is unusual and seems like a coincidence, it is likely that there is an underlying mechanism. An imbalance between the neurotransmitters dopamine and acetylcholine (Ach) might be one of the reasons for the development of MG symptoms. In the second and the third case reported by Odajiu et al. (13), we noticed that both patients' anti-AchR antibody and RNS results were negative, with only the neostigmine tests positive. These patients' MG symptoms were improved by cholinesterase inhibitors. Therefore, we could hypothesize that the MG symptoms were induced by the relatively low level of Ach as treatment of PD raised the level of dopamine. In addition, it has been reported in previous cases that the anti-parkinsonism drug trihexyphenidyl (THP) induced or worsened the MG symptoms (3, 14). The first case reported by Ueno et al. (14) was that of a PD patient who developed MG 1 week after treatment with THP. Although the patient was positive for anti-AchR antibodies and thus it appeared to be unreasonable to suspect iatrogenic MG here, we could not ignore the fact that the severity of MG presented by the patient was closely related to the serum level of THP, which seemed to interfere with neuromuscular transmission through competition with acetylcholine receptor sites (14). In the case reported in 1993 (3), pyridostigmine worsened the patient's PD symptoms. However, after the MG symptoms of the patient were brought under control via steroids and pyridostigmine was withdrawn, the dosage of medications used to control PD symptoms was also decreased. In another case, pyridostigmine also appeared to cause an imbalance between dopamine and Ach by increasing Ach levels, thus inducing or worsening parkinsonism (15). Imbalanced interactions between the cholinergic and dopaminergic systems are observed in the pathological condition of PD (16). Thus, imbalanced interactions of the two systems may be one of the pathogenic mechanisms of PD with comorbid MG.

Another hypothesis with respect to the pathogenesis is autoimmunity. MG is an autoimmune disease and autoimmunity is also involved in the mechanism of PD. In six of the cases of PD and MG, the authors revealed that their patient had another autoimmune disease [Graves' disease (17), rheumatoid arthritis (18), psoriasis (6), polymyalgia rheumatica (6), or thyroiditis (6)]. It has been found that the risk of PD increases with some autoimmune disorders (19), and patients with an autoimmune disease generally have a 33% excess risk of PD (20). Accumulating evidence has suggested the significant role of the immune system in PD pathogenesis, either through inflammation or via an autoimmune response (21). α-synuclein (α-syn), the pathological hallmark of PD, is a potential target of autoimmune attack (22). Accumulation of misfolded α-syn is a trigger for PD and is involved in the pathology of neurodegeneration through innate and adaptive immunity (23, 24). Neuromelanin, another autoantigen released from dead dopaminergic neurons, is phagocytized by dendritic cells and subsequently induces the activation of microglia, leading to the autoimmune aggravation of PD (22). In addition to autoantibodies directed at α-syn and neuromelanin, antibodies directed at GM1 ganglioside have also been identified in PD patients. These antigens are associated with PD pathogenesis (25). Chen et al. (26) have reported that when rats receive plasma antibodies from PD patients, they undergo a marked loss of dopaminergic neurons. In contrast, rats that are injected with antibodies from healthy controls

undergo much less neuronal damage, suggesting that PD patients may generate autoantibodies that attack their own dopaminergic cells (26). Sulzer et al. have found that T cells from patients with PD recognize α-syn peptides, thus mistakenly attacking brain cells and leading to the progression of PD (27). They have also confirmed this result through analysis of blood from PD patients, which they found to contain large numbers of T cells able to respond to α-syn (28). In the 57 cases of PD and comorbid MG, 70% of the patients developed MG after the onset of PD. It is likely that MG is secondary to the autoimmune mechanism of PD in these cases. Of course, more evidence is needed to prove the relationship between autoimmunity and PD with MG.

In conclusion, although PD with MG is rare, we still need to keep in mind that it is possible for a PD patient to have comorbid MG. Most of the patients reported have developed MG after the onset of PD. Meanwhile, head drop and palpebral ptosis are not common phenomena in PD, and thus comorbid MG should be suspected in such situations. The imbalance between the neurotransmitters dopamine and Ach may be the reason underlying comorbidity of PD and MG, and autoimmune mechanisms may also be involved in the pathogenesis. As a curable disease, MG should not be neglected when it occurs against the backdrop of 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.

Ethics statement

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

Author contributions

QZ: Writing—original draft. EX: Conceptualization, Data curation, Writing—review & editing. H-FL: Conceptualization, Data curation, Writing—review & editing. PC: Conceptualization, Data curation, Writing—review & editing. ZZ: Conceptualization, Data curation, Writing—review & editing. JM: Writing—review & editing.

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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.2023.1303434/full#supplementary-material

SUPPLEMENTARY VIDEO 1
Two neostigmine tests. This video shows two neostigmine tests. In the first neostigmine test, the patient had apparent head drop and incomplete palpebral ptosis at baseline. Twenty min after administration of neostigmine, both the head drop and the ptosis improved. After starting treatment with pyridostigmine for 10 days, we performed another neostigmine test; the footage shows that the patient took very small steps, as in freezing of gait, at baseline. Twenty min after administration of neostigmine, his gait improved.

SUPPLEMENTARY TABLE 1
Demographics and clinical features of previously reported cases*. This table shows demographics and clinical features of previously reported cases of PD with MG in details, including their sex, age, age at onset of PD/MG, PD clinical features, MG clinical features, MG diagnosis, PD treatment and MG treatment.

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Acupuncture therapy for Parkinson's disease: a case report demonstrating symptomatic improvement without medication

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Background: Parkinson's disease (PD) often necessitates immediate medical intervention following diagnosis. In recent years, there has been a noticeable increase in clinical investigations assessing the efficacy of acupuncture in PD, with many studies reporting positive outcomes. Ethical guidelines commonly endorse pharmaceutical therapies for PD, leading ongoing research to combine acupuncture with standard drug-based treatments. At present, there is a conspicuous absence of dedicated clinical research exclusively examining the independent impact of acupuncture on PD treatment.

Case: In a clinical observation, we documented a case involving a 75-year-old male displaying progressive, characteristic PD symptoms, including evident limb tremors, rigidity, bradykinesia, fatigue, and additional non-motor symptoms. The patient received a confirmed diagnosis of PD. Due to the refusal of the patient to take medication, we exclusively administered acupuncture therapy. The outcomes indicated a noteworthy enhancement in the clinical symptoms of the patient solely through acupuncture intervention.

Conclusion: This case affirms that using acupuncture in isolation significantly improved both the motor and non-motor symptoms in the patient. Acupuncture could potentially serve as an alternative therapy for patients who decline or are intolerant to anti-Parkinson drugs. However, further studies are needed to assess its long-term efficacy. This case report obtained approval from the Ethics Committee of the First Affiliated Hospital of Guangzhou University of Chinese Medicine (Ethics number: K-2023-127).

KEYWORDS

acupuncture therapy, Parkinson's disease, alternative treatment, case report, symptomatic improvement

1 Introduction

Parkinson's disease (PD) stands as a prevalent neurodegenerative disorder (1) with treatment challenges that have yet to demonstrate the capability to halt long-term disease progression (2). Currently, pharmaceutical therapy remains the primary approach for managing PD (3, 4).

Traditional Chinese medicine (TCM) originally outlined symptoms akin to PD as shaking palsy in Huangdi Neijing around 100 A.D., maintaining a historical presence in the care of PD patients for thousands of years. Acupuncture, an ancient technique dating back 2000 years within TCM (5), has gained widespread utilization by physicians and patients globally in alleviating clinical symptoms in PD. Recent years have witnessed a discernible rise in clinical investigations exploring the use of acupuncture for PD, often reporting positive outcomes (6).

Furthermore, animal studies have provided a scientific basis, supporting the potential of acupuncture in improving the symptoms of PD patients. These studies have demonstrated the capacity of acupuncture to normalize brain functional connectivity, diminish neuronal apoptosis in the striatum, reduce lipid peroxide levels in dopaminergic neurons, and protect neurons from oxidative damage (7–9).

Nevertheless, the effectiveness of acupuncture as an independent treatment for individuals with PD remains uncertain. Given the ethical considerations favoring the use of drug therapies in PD, current clinical investigations have integrated acupuncture with medication-based treatments. At present, there is a lack of clinical observation reports specifically exploring the use of acupuncture in isolated treatment for PD. This case report presented a patient who declined anti-Parkinson drugs and opted solely for acupuncture treatment.

2 Case report

A 75-year-old male belonging to Huanggang, Hubei province, previously engaged in farming with a history of pesticide and herbicide exposure. He had no prior history of hypertension, diabetes, or cerebrovascular incidents, and there was no family history of PD. In March 2022, he developed unprovoked left-hand tremors, prompting his family to seek medical attention at Wuhan Union Hospital of China, where he received a diagnosis of PD. The patient declined anti-Parkinson drugs due to their lifelong requirement and common side effects, and the disease progressed, resulting in right-hand tremors as well.

On 12 June 2023, he visited the outpatient clinic of our hospital, seeking acupuncture therapy. At this time, he displayed characteristic PD symptoms, including limb tremors, rigidity, bradykinesia, and fatigue (Supplementary Video S1), which confirmed the PD diagnosis. Beyond motor issues, he experienced considerable stiffness from the neck to the back, difficulty in swallowing hard food, drooling on head lowering, occasional nocturnal foot cramps, dry mouth, and constipation. The patient had not started any medication, and no surgical treatment for deep brain stimulation had been performed prior to the acupuncture treatment.

This patient displayed evident motor and non-motor symptoms. We employed two distinct combinations of acupoints for alternating treatment positions. In the supine position, as shown in Figure 1, acupuncture therapy primarily targets specific acupoints within the Shen-regulation acupuncture point set, with the selection of other acupoints tailored in accordance with presenting symptoms. The Shen-regulation acupuncture point set predominantly encompasses several key acupoints, namely, Sishenzhen (comprising GV 21, GV 19, and bilateral points 1.5 cun next to GV 20), GV 24 (Shenting), EX-HN 3 (Yintang), SP 6 (Sanyinjiao), LI 4 (Hegu), and LR 3 (Taichong). This specific acupuncture point set has been employed in previous clinical studies, demonstrating its effectiveness in alleviating clinical symptoms among individuals diagnosed with PD (10, 11). Supplementary acupoints such as ST 25 (Tianshu), CV 4 (Guanyuan), and ST 37 (Shangjuxu) are included based on the presentation of constipation symptoms (10). For limb tremors, acupoints such as LI 11 (Quchi), LI 10 (Shousanli), GB 34 (Yanglingquan), SP 9 (Yinlingquan), and GB 39 (Xuanzhong) have been integrated.

Acupuncture administered in the prone position was primarily focused on regulating the balance function of the patient. The selection of acupuncture points (Figure 2) was primarily guided by previous clinical expertise and experience (12–14). These include the utilization of the brain three needles, comprising three acupoints: GV 17 (Naohu) and GB 19 (Naokong) on its side, as well as Du three needles [three acupoints, consisting of GV 14 (Dazhui), GV 8 (Jinsuo), and GV 4 (Mingmen)]. Additional acupoints integrated into the treatment protocol were BL40 (Weizhong) and BL57 (Chengshan).

Acupuncture was performed with disposable, sanitized stainless steel needles (Tianxie, Suzhou Medical Appliance Factory, Suzhou, China; 0.25 × 25 mm, 0.25 × 40 mm). After routine disinfection, the acupuncturist inserted the needles into the corresponding acupoints. Head acupoints were treated with transverse insertion, back acupoints were treated with oblique insertion, and other points were treated with perpendicular insertion. The needles were twisted to stimulate qi flow, and the patient obtained the de qi sensation (a combination of feelings, such as numbness, soreness, and heaviness). All needles were kept in place for 30 min post-qi arrival. The acupuncture treatment was administered three times a week for 1 month, totaling 12 sessions.

Before and after acupuncture treatment, we appraised the condition of the patient across the three dimensions. Initially, concerning PD severity and health-related quality of life, post-acupuncture treatment revealed a 17-point reduction in UPDRS score, including an 11-point decrease in Part II. The PDQ-39 score exhibited an 11-point reduction.

Subsequently, non-motor symptoms were evaluated using the Non-Motor Symptoms Scale (NMSS) and the Hamilton Anxiety Scale (HAMA). The patient predominantly exhibited evident fatigue, diminished mood, and gastrointestinal issues (swallowing difficulty, drooling, and constipation). Comparative assessment indicated a 4-point enhancement in fatigue, a 36-point improvement in mood, and the complete resolution of gastrointestinal complications. The HAMA scores decreased by 5 points.

Third, motor function, primarily focusing on balance, was assessed using the Berg Balance Scale, demonstrating a seven-point increase. Further measurements of static and dynamic balance were conducted using Footscan V9 and TUGT, respectively. The 30-m walking test revealed a 0.11 m/s increase in walking speed and a 6 cm increase in stride length. Detailed outcomes and their associated

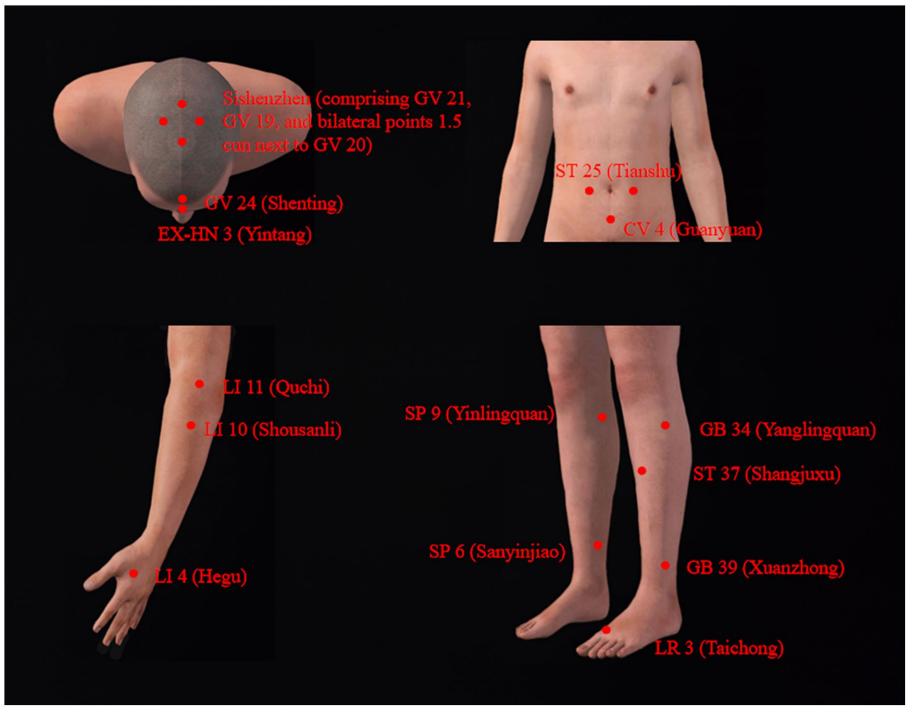

FIGURE 1
Acupuncture points selected in the supine position.

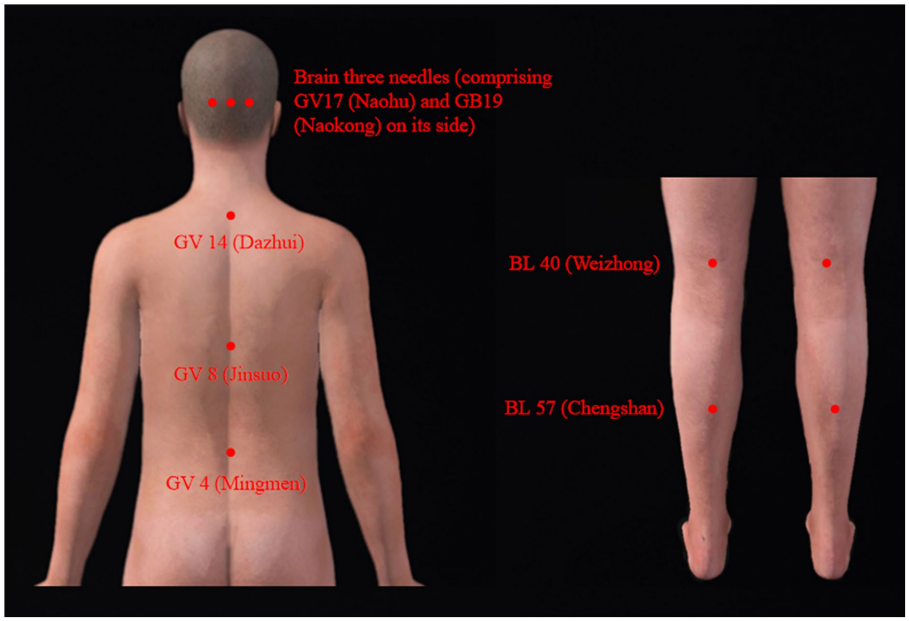

FIGURE 2
Acupuncture points selected in the prone position.

values for minimal clinically important differences (MCID) are presented in Table 1.

After 1 month of the treatment, the patient reported significant improvements in mood, reduced drooling, notably decreased stiffness in the neck and back, and overall alleviation of other symptoms. Additionally, he expressed enhanced confidence in managing PD. Subsequent telephone follow-up findings after the 1-month acupuncture treatment indicated an absence of recurring non-motor symptoms such as choking, drooling, and cramps.

TABLE 1 The parameter changes before and after acupuncture treatment.

Substance			Before treatment	After 1 month	D	MCID
NMSS		Cardiovascular	0	0	0	–
		Sleep/fatigue	8	4	−4	–
		Mood/cognition	37	1	−36	–
		Perceptual problems/hallucinations	0	0	0	–
		Attention/memory	0	0	0	–
		Gastrointestinal tract	20	0	−20	–
		Urinary	0	0	0	–
		sexual function	0	0	0	–
		miscellaneous	0	0	0	–
		Total	65	5	−60	–
HAMA			10	5	−5	−4 (11)
UPDRS		I	4	3	−1	–
		II	20	9	−11	–
		III	39	34	−5	−5 (15)
		Total	63	46	−17	−8 (15)
PDQ-39			19	8	−11	−4.72 (16)
Berg			42	49	7	6.5 (17)
Static balance	Eyes open	Enveloped area (mm)	7	2	−5	–
		Xd	7	5	−2	–
		Yd	12	6	−6	–
	Eyes closed	Enveloped area (mm)	7	5	−2	–
		Xd	5	5	0	–
		Yd	13	8	−5	–
TUGT			16.40	13.75	−2.65	–
The 30-m walk test		Speed (m/s)	0.70	0.81	0.11	–
		stride length (m)	0.42	0.48	0.06	–

MCID, minimal clinically important difference; D, the difference between 1 month after treatment and before treatment; UPDRS, Unified Parkinson's Disease Rating Scale; PDQ-39, 39-item Parkinson Disease Questionnaire; Berg, Berg Balance Scale; TUGT, the Timed Up and Go test; NMSS, the Non-Motor Symptoms Scale; HAMA, Hamilton Anxiety Scale.

3 Discussion

3.1 Non-pharmacological approaches in PD management

The management of PD predominantly revolves around pharmaceutical interventions (3, 4). However, the constraints associated with drug-based therapies (2) have prompted clinicians to explore the amalgamation of non-pharmacological modalities such as acupuncture (18, 19), cognitive behavioral therapy (20), physical exercise (21), and music therapy (22) alongside pharmacotherapy. This combined approach aims to attenuate adverse effects while enhancing therapeutic outcomes in the care of individuals afflicted by PD.

Exercises that incorporate goal-based training and aerobic activity hold promise for augmenting cognitive and automatic components of motor control in individuals with mild to moderate PD through experience-dependent neuroplasticity (21). Clinical studies have evidenced the capacity of physical exercise to modify brain function and structure among PD patients, leading to the stabilization of disease progression within the corticostriatal sensorimotor network and contributing significantly to bolstering cognitive abilities (23). Sleep dysfunction observed in PD can also show signs of improvement through the intervention of exercise (24).

Cognitive behavioral therapy (CBT), a comprehensive therapeutic approach employing diverse techniques and concepts (21), stands as a valuable intervention aiding individuals in navigating the multifaceted challenges linked to Parkinson's disease (PD), thereby fostering heightened well-being and an augmented overall quality of life. Evidence suggests its efficacy in ameliorating depressive and anxious symptoms, which are prevalent in individuals with PD (23, 24). A study integrating CBT among PD patients showed promise in alleviating neuropsychiatric disturbances and reducing symptom severity (25).

Acupuncture therapy, supported by a number of clinical studies, demonstrates efficacy in ameliorating motor symptoms such as myotonia in PD patients (12). Additionally, it addresses prevalent non-motor symptoms including anxiety (11), constipation (10), and insomnia (26). Notably, the therapeutic impact surpasses placebo acupuncture, highlighting its significant clinical efficacy (10, 11).

Several recently published meta-analyses also suggested that acupuncture-related therapies combined with conventional medication showed a moderate or large effect on movement function in patients with PD (6, 27). Animal studies have established a scientific foundation supporting the potential of acupuncture in ameliorating symptoms observed in Parkinson's disease (7–9).

In a comprehensive meta-analysis evaluating non-pharmacological interventions for adult depression, significant superiority over placebo was observed for physical exercise, CBT, and acupuncture. Additionally, the analysis indicated that acupuncture exhibits superior effectiveness in managing major depressive disorder when compared with exercise therapy and CBT (28).

3.2 Efficacy of acupuncture as a standalone therapy for PD improvement

Ethically, drug utilization is standard in PD care, and consequently, ongoing studies have integrated acupuncture as an adjunct to medication-based treatments. Given the substantial impact of anti-Parkinson drugs on PD patients, the efficacy of acupuncture as a standalone treatment for PD remains uncertain.

The therapeutic effects of acupuncture treatment solely on the PD symptoms of this patient encompass three key aspects. First, significant enhancements in UPDRS and PDQ-39 scores exceeded their respective minimal clinically important difference (MCID) values, demonstrating the clinical relevance of acupuncture as an independent approach for ameliorating PD symptoms. Second, the non-motor symptoms of the patient, predominantly involving fatigue, mood, and gastrointestinal challenges, notably improved. Fatigue decreased, mood enhanced significantly with greater initiative, and symptoms of drooling and choking on hard food disappeared. The reduction in the HAMA score surpassed the MCID, indicating the clinical importance of acupuncture in alleviating anxiety. This is consistent with previous findings (11, 29). Third, improvements in motor symptoms included enhanced static and dynamic balance, supported by the Berg scale, TUGT test, and Footscan V9 findings. The 30-m walking test showed improved stride length and step count. Visual enhancements in autonomous arm movement and left-hand vibration amplitude were observed in the video analysis. Subsequent follow-up demonstrated the safety and effectiveness of acupuncture treatment, with no post-improvement symptom relapse.

The particular case in this report highlights that acupuncture alone could effectively improve the motor and non-motor symptoms in this patient. This underscores the potential of acupuncture as an alternative or complementary therapy for individuals who refuse or are not suitable for conventional anti-Parkinson drugs, providing an additional option for symptom management. The absence of recurring non-motor symptoms post-acupuncture suggests potential long-term benefits. However, further studies are needed to assess its long-term efficacy.

3.3 Medication refusal in PD: factors and mitigation

In clinical settings, few patients decline treatments that could potentially enhance their wellbeing and quality of life (30). Instances of medication refusal among individuals with neurodegenerative conditions are infrequent but do occur (31).

The causes behind medication refusal in PD are varied. Treatment for PD often involves lifelong medication, commonly leading to side effects such as impulse control disorders (32) and Levodopa-induced dyskinesia (33). Patients frequently require adjustments in levodopa dosage as the disease advances (34), while healthcare expenses also negatively affect medication adherence (35). These challenges may directly lead to patient refusal and indirectly contribute to heightened anxiety and stress.

Enhancing physician–patient communication could reduce the incidence of treatment refusal (36). Psychological interventions also proved beneficial in enhancing the adherence of patients to medication regimens (37).

Animal experiments found that electroacupuncture could act on depression by modulating the HPA axis and enhancing hippocampal 5-HT/5-HT1AR in chronic unpredictable mild stress rats (29). An additional clinical randomized controlled trial of PD patients with anxiety yielded the same results (11).

In this case, acupuncture as a standalone therapy demonstrated significant mood enhancement in the individual with PD, indicating its potential efficacy for PD patients who decline medication due to emotional issues.

Regrettably, as the hometown of the patient was in Hubei Province, he faced various inconveniences during the treatment period while residing near the hospital, impacting his daily life and limiting the possibility of continued long-term treatment. With only 12 acupuncture sessions received, further studies are necessary to comprehensively evaluate the long-term effectiveness of acupuncture treatment for PD.

Data availability statement

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

Ethics statement

The study has been reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou University of Chinese Medicine (Ethics number: K-2023-127). Written informed consent from the patient was not required to participate in this study in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

Author contributions

SL: Methodology, Writing – original draft, Writing – review & editing. QL: Investigation, Writing – original draft. IL: Supervision, Writing – original draft. JF: Validation, Writing – review & editing. YT: Resources, Writing – original draft. XL: Data curation,

Writing – review & editing. XX: Investigation, Writing – original draft. LZ: Funding acquisition, Resources, Writing – review & editing.

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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.2023.1330054/full#supplementary-material

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MR-guided focused ultrasound thalamotomy for lithium-induced tremor: a case report and literature review

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Drug-induced tremor is a common side effect of lithium with an occurrence of approximately 25% of patients. Cessation of the offending drug can be difficult, and many medical treatments for drug-induced tremor are ineffective. Deep brain stimulation (DBS) has been shown in a limited number of case reports to effectively reduce drug-induced tremor, however, which remains an invasive therapeutic option. MR-guided focused ultrasound (MRgFUS) thalamotomy is an FDA-approved non-invasive treatment for essential tremor (ET). To the best of our knowledge, MRgFUS thalamotomy has never been reported to treat drug-induced tremor. Here, we present a case of a left-handed 55-year-old man with a progressive, medically refractory lithium-induced tremor of the bilateral upper extremities. The patient underwent MRgFUS thalamotomy targeting the right ventral intermediate nucleus (VIM) of the thalamus to treat the left hand. There was almost complete resolution of his left-hand tremor immediately following MRgFUS. There were no side effects. The patient continues to show excellent tremor control at 90-day follow-up and remains free from side effects. This case demonstrates MRgFUS thalamotomy as a possible novel treatment option to treat drug-induced tremor.

KEYWORDS

tremor, lithium, MR-guided focused ultrasound (MRgFUS), high-intensity focused ultrasound (HIFU), case report

1 Introduction

Tremor is a common side effect of many medications and can significantly impact quality of life (QoL). Psychotropic drugs, including neuroleptics and mood stabilizers, are the most common offenders owing to their long-term use and subsequent dependence (1). In 2018, the prevalence of antipsychotic use was 1.6% among adults in the US (2). Antipsychotic use is increasing, with the number of people prescribed at least one antipsychotic rising from 5.0 million in 2013 to 6.1 million in 2018 in the US (3). Tardive tremors seen with neuroleptics use have been reported in 2.4% of cases (4). Bipolar disorders affect more than 1% of people worldwide, and lithium continues to be the mainstay treatment. Tremor is seen in

approximately 25% to 27% of patients taking lithium (1, 4). Similar to most drug-induced tremors, lithium-induced tremor is generally symmetric and predominantly postural or intentional. It may emerge at any time during lithium treatment and can range in severity from a minor inconvenience to debilitating (5, 6). As the number of neuroleptics and mood stabilizer prescriptions increases, this potentially debilitating adverse effect will impact more people (7). More effective treatments for drug-induced tremor are much needed.

Drug-induced tremors are typically managed initially by reducing the dose or stopping the offending medication. In psychiatric conditions such as bipolar disorder, this is often not recommended given the disease severity and dearth of suitable alternatives. If the tremor persists or the offending drug cannot be altered, symptomatic treatment with tremor-reducing medications is initiated. Amerika et al. conducted a systematic review of the literature to identify and analyze treatments for drug-induced tremor (8). Their review found that β-blockers, most notably propranolol, have shown the most effectiveness. Unfortunately, there are several downsides to using drugs to control drug-induced tremor (8). In patients with neuropsychiatric conditions, certain tremor-reducing medications may be contraindicated. For example, tetrabenazine is contraindicated in patients with depressive symptoms (8). There is a need for alternative options for the treatment of drug-induced tremor.

Given the uncertainty of the diagnosis and poor understanding of the underlying pathology, surgical options for drug-induced tremor have been hesitantly tried. There are very few reports of deep brain stimulation (DBS) successfully attempted in these patients (Table 1) (8–11). However, DBS may be contraindicated in active or poorly controlled neuropsychiatric conditions, and certain DBS targets can aggravate mood and psychiatric symptoms when stimulated (12–14). Recently, MR-guided focused ultrasound (MRgFUS) thalamotomy emerged as a non-invasive effective treatment for ET and tremors of other etiologies (15, 16).

MRgFUS thalamotomy is commonly used to treat tremor via ablation of the ventral intermediate nucleus (VIM) of the thalamus (17). MRgFUS has been explored since the 1950s, but recent technological advances have allowed it to be used safely to target precise structures in the deep brain (18). In 2016, the FDA approved MRgFUS thalamotomy for essential tremor (ET) (15). It has been shown to reduce ET by 75%–89% (19, 20). MRgFUS thalamotomy has also been found to be effective for other non-ET tremors such as Parkinson's disease (PD) tremor (15, 16). However, a comprehensive literature search of procedural treatment for drug-induced tremor yielded no published report of MRgFUS thalamotomy for drug-induced tremor.

Here, we present a case of medically refractory lithium-induced tremor successfully treated with MRgFUS VIM thalamotomy. We also present a comprehensive literature review on surgical treatment of drug-induced tremor in PubMed, Embase, and Cochrane Libraries from January 1960 to 11 June 2023, following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (Figure 1) (21).

2 Case description

A 55-year-old left-handed man presented to the multidisciplinary movement disorder clinic for surgical evaluation of tremor. His past medical history was significant for bipolar 1 disorder. He had been treated with lithium for 20 years. He was also on bupropion, hydroxyzine, lamotrigine, metoprolol, omeprazole, primidone, propranolol, and ropinirole. Over the last 10 years, he developed a bilateral, progressive postural and action tremor of the upper extremities. He has no family history of ET or other movement disorders. No Parkinsonian symptoms were evident in him, such as bradykinesia, rigidity, shuffling in gait, or postural instability. The patient's tremor significantly impacted his QoL. As an administrative officer, tremors impeded his fine motor skills, making it difficult to type, organize documents, and perform other office tasks. Due to challenges using utensils, potential food spills, and self-consciousness, tremors affected his psychosocial functioning outside the workplace. As a result of these challenges, he experienced personal and professional difficulties. He was unable to effectively perform his job and had significantly affected psychosocial function. Based on the presence of the temporal relationship with lithium and the absence of a strong family history of tremor, a predominantly high frequency and low amplitude postural and action tremors accompanied by jerky episodes that cause poor dexterity (22–24), he was diagnosed with drug-induced tremor.

When he presented to the multidisciplinary movement disorder clinic, he was taking a total of 120 mg of propranolol and 750 mg of primidone. His blood pressure was 98/66 during the clinic visit, his heart rate was 70, and he complained of being sluggish, so the propranolol dose was not recommended to be increased. We briefly discussed botulinum toxin injections with him. However, since he lives a 4-h drive away from the clinic, returning to the clinic every 3 months was not an option for him. Because his bipolar disorder had been well-controlled with lithium for 20 years, the 600 mg BID lithium dose was not altered. In addition, he could not recall whether the amount had ever been lowered to treat tremor in the past.

Institutional multidisciplinary movement disorder conference review approved surgical treatment for the refractory and disabling tremor. Given prior positive case reports, bilateral VIM DBS therapy was offered. However, the patient was apprehensive about receiving DBS surgery due to the invasiveness of surgery, the idea of having an implant, and the many follow-up appointments required as he lived 4 h from the clinic. A detailed discussion was held with him regarding MRgFUS irreversibility due to its ablative nature, unilateral treatment option at that time, and no case reports of this therapy being effectively used to treat drug-induced tremors. Despite these limitations, he decided to undergo MRgFUS right VIM thalamotomy for his left-hand tremor (Figure 2) since it is a minimally invasive procedure and requires fewer follow-up clinic visits.

3 Diagnostic assessment

Blood work revealed normal TSH and lithium levels. His score on the Activities of Daily Living Subscale of the Tremor Research Group Essential Tremor Rating Assessment Scale (TETRAS) was 34 (Supplementary Table S2). Physical examination revealed severe action and postural tremor and mild-to-moderate rest tremor (Supplementary Table S3; Supplementary Video 1). Based on clinical presentation and by ruling out other possible causes of tremor, the patient was diagnosed with medically refractory drug-induced tremor. As a part

TABLE 1 Results from systematic review of the literature on surgical treatments for drug-induced tremor.

Study	Intervention and rationale	Drug	Tremor characteristics	Justification for drug-induced tremor diagnosis	Results
Rodrigues et al. (9) (United States)	DBS – VIM Left side As tremor predominantly affected QoL, DBS-VIM was chosen, as it is an established DBS target for treating Parkinsonian and ET	Haloperidol Aripiprazole	• Bilateral UE rest, postural, and action tremor; intermittent head tremor • Not responsive to propranolol, primidone, topiramate, clonazepam, gabapentin, or trihexyphenidyl • Mild improvement with alcohol • Mild Parkinsonism	Temporal relation between initiation of haloperidol and onset of hand tremor	Absence of R hand tremor at 12 months post-operatively
Milosevic et al. (10) (Canada)	DBS – Vop Right side Three trajectories were attempted intraoperatively (targeting the VIM, STN, and Vop). The trajectory targeting the Vop showed the most significant tremor suppression	Lithium	• Bilateral rest and action/ kinetic tremor • Not responsive to alcohol or Propranolol • No evidence of Parkinsonism	Temporal relation between starting Lithium and onset of tremor	Improvement of TETRAS score from 43 pre-operatively to 29 at 3 months post-operatively
Kashyap et al. (11) (United States)	DBS – STN Bilateral In addition to tremor, bradykinesia and rigidity also affected QoL, so the STN DBS target was chosen	Quetiapine Fluoxetine Trazodone	• Bilateral UE and LE postural and kinetic tremor • Not responsive to propranolol, amantadine, sinemet, pramipexole, or primidone • Drug-induced Parkinsonism also present	Temporal relation to switching medications	Near-complete resolution of lower and upper extremity tremors at 2 years post-operatively
Amerika et al. (8) (United States)	DBS – VIM Bilateral As tremor predominantly affected QoL, DBS-VIM was chosen	Lithium	• Progressive bilateral UE rest, postural, and kinetic tremor • Not responsive to levodopa/carbidopa • No evidence of Parkinsonism	Clinical presentation (progressive rest, postural, and kinetic tremor) and history of long-term use of lithium Temporary reduction of Lithium resulted in improvement of tremor	Improvement of TETRAS score from 28 pre-operatively to 4 at 3 years post-operatively

of the surgical evaluation, he underwent brain MRI and neuropsychological testing. Both were unremarkable.

4 Intervention

The patient underwent MRgFUS thalamotomy targeting right VIM to treat the dominant left-hand tremor (Figure 3). The ablative temperature was reached with high-intensity focused ultrasound (HIFU) sonication with real-time MR guidance and clinical assessment. Tremor response and adverse effects were assessed between sonication.

The patient tolerated the procedure well. Greater than 90% improvement of tremor was achieved during the procedure (Figure 4). There were no adverse effects including numbness, tingling, dysmetria, corticospinal tract abnormalities, dysarthria, gait abnormalities, or other neurological deficits. The patient was discharged on the same day after a few hours of observation.

4.1 Outcomes

The patient returned to his administrative office job and began normal socialization, including eating in restaurants, 2 weeks following the procedure, which was not possible prior to the procedure. At the 30-day and 90-day follow-up appointments, he showed no residual tremor or adverse effects (Figure 4). He reported "100% satisfaction." His score on the TETRAS Activities of Daily Living Subscale was 0 for the left hand (Supplementary Table S2). Physical examination revealed no noticeable rest tremor and trace postural tremor and action tremor (Supplementary Table S3; Supplementary Video 3).

The patient enjoys singing bass in his church choir. Prior to the procedure, his embarrassment had prevented him from singing in

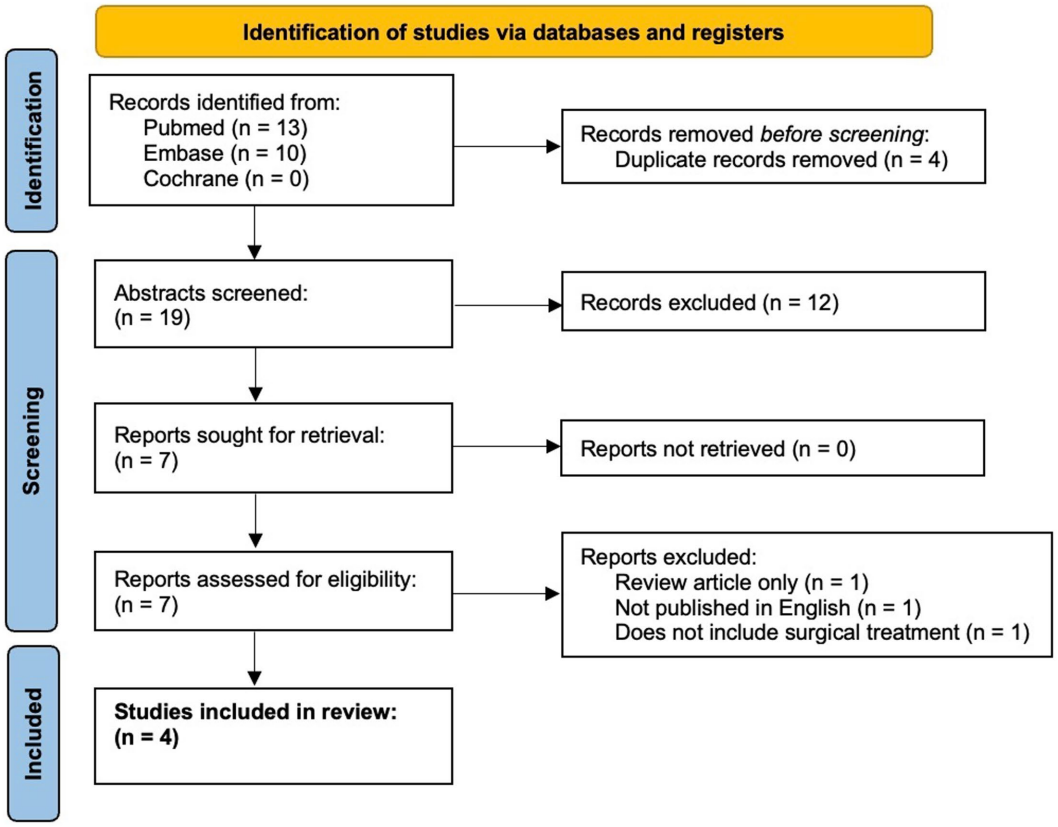

FIGURE 1
PRISMA flow diagram (21).

FIGURE 2
Timeline from initiation of lithium to the 90-day post-MRgFUS follow-up.

public. At 30 days after the procedure, he reported elation that he had returned to singing with renewed confidence.

5 Discussion

Drug-induced tremor continues to be a challenge to providers and patients. It can cause constant impairment of simple activities, leading to significant decrease in QoL and aggravation of anxiety and depression symptoms associated with psychiatric condition. Taper or withdrawal of the offending medication is often not an option in cases of well-managed psychiatric disorders, and drug-induced tremor may persist even when withdrawal is achieved. Medications used to combat drug-induced tremor have conflicting support. While some medications have been shown to provide some benefit, most studies lack the necessary quality and sample size to suggest strong evidence for their use (8). A systematic literature review aimed at identifying procedural treatment options for drug-induced tremor revealed only four case reports, all of which reported the use of DBS. To the best of our knowledge, this is the first reported use of MRgFUS thalamotomy to treat refractory drug-induced tremor. This provides insight into an alternative, highly effective treatment option for a debilitating condition.

We conducted a systematic literature search from January 1960 to 11 June 2023 of surgical treatment for drug-induced tremor. The search yielded only four studies meeting full-text review criteria. All four studies were case reports reporting the use of DBS to successfully treat drug-induced tremor of the hand (8–11). The results varied from modest improvement to complete resolution of tremor (Table 1). Lithium was the culprit for the tremor in two studies (8, 10), and the VIM nucleus was the target in two studies (8, 9). There was no reemergence of tremor or worsening of psychiatric disorder in any of the cases across the follow-up periods ranging from 3 months to 3 years. These four cases demonstrate the effectiveness of DBS in drug-induced tremor; however, limitations should be noted. The small number of studies, and reliance on case reports may suggest publication bias and hinder generalization. Additionally, the unknown pathophysiological process and lack of

definitive diagnostics or biomarkers in drug-induced tremor render uncertainty in diagnosis.

DBS for tremor has been widely used in PD and ET (15, 25). It is highly effective in reducing tremor in these disease states but carries risks and limitations across all applications (17). As an invasive procedure, it carries innate risks including infection (in approximately 4% of patients) and hemorrhage (in approximately 2.4% of patients) (26). In addition, several follow-ups are required for device programming. Additional surgeries may be needed to address hardware complications such as recurrent infections or malfunctions, and over time, there is a need for battery replacement if a non-rechargeable pulse generator is used (27). These factors could limit its acceptability by the patients already challenged with neuropsychiatric conditions. Moreover, poorly controlled psychiatric and mood symptoms are considered contraindications for DBS implantation (28). Excitingly, in 2016, unilateral MRgFUS thalamotomy was approved for the treatment of ET (15). MRgFUS is a non-invasive procedure that does not carry the risk of hardware-related complications seen with DBS, and it has been found to be as effective as DBS in the treatment of unilateral tremor (15). However, poor understanding of the pathophysiology of drug-induced tremor has prevented advances in its use as a surgical option for drug-induced tremor. Although there are recent reports of DBS for medically refractory drug-induced tremor, MRgFUS had never been tried. MRgFUS was preferred over DBS by our patient because it was surgically less invasive, involved fewer outpatient follow-up visits, and had no device complications despite irreversibility and experimentality of MRgFUS. The patient had immediate relief of tremor following MRgFUS thalamotomy, reducing his TETRAS score from 34 to 0 in his left upper extremity. At 30-day and 90-day follow-ups, TETRAS score was 0 for his left hand. To the best of our knowledge, this is the first case reporting successful MRgFUS VIM thalamotomy in drug-induced tremor, however, with only short-term follow-up.

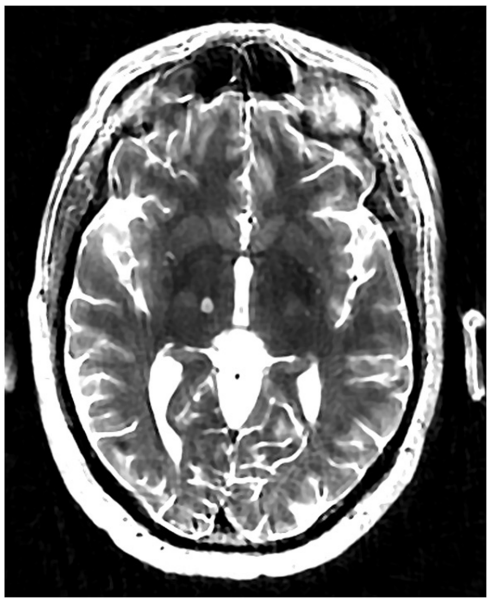

FIGURE 3
Volumetric T2-weighted image showing right VIM MRgFUS thalamotomy lesion.

MRgFUS could potentially be a more applicable tool in patients with psychiatric conditions where the use of DBS can be complicated. Recently, bilateral MRgFUS has been shown to be effective for ET if one side is done at a time and sufficient time elapses between procedures and was recently approved by the FDA (17, 29, 30).

Our study is not without limitations. This was an experimental treatment in a single case. The patient was diagnosed with drug-induced tremor based on the character of the tremor and the temporal relationship to lithium treatment. A diagnosis of drug-induced tremor is more reliable if the offending medication can be removed to expose a causal relationship. Unfortunately, this was not possible for our patient, whose psychiatric health is dependent on lithium. Furthermore, no neurophysiological studies were conducted, which would have enhanced diagnostic accuracy (24). Another limitation of the study is the possible presence of bradykinesia preoperatively. This raises the possibility of PD or drug-induced Parkinson's disease, even though lithium rarely causes it. We believe that the slowness of hand movements was caused by the presence of tremor as previous studies have shown that tremor leads to prolonged reaction times due to incomplete muscle contractions, leading to a perception of bradykinesia (31, 32). Additionally, tremors can cause pacing effects as a result of voluntary movements (33, 34). Furthermore, slowness in left-hand movement was resolved after right VIM MRgFUS, supporting this hypothesis since VIM is not a target for bradykinesia. As a result of these factors, we concluded that the patient did not have Parkinsonism and thus we did not order a DaT scan. Although the

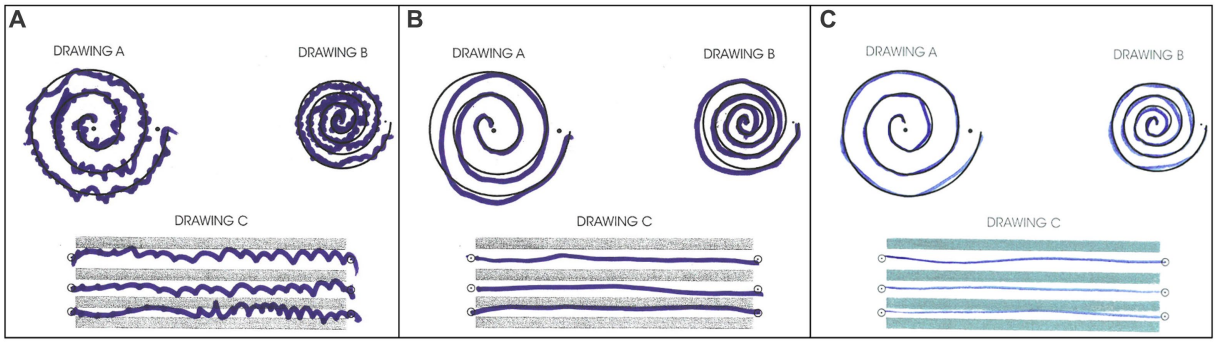

FIGURE 4
Archimedes spiral test during **(A)** pre-surgical evaluation, **(B)** immediate post-surgical examination, **(C)** 30-day follow-up post-surgical examination.

short-term outcome in our case is excellent, the long-term outcomes are unknown and should be observed for any delayed side effects or re-occurrence of tremor. More cases need to be explored and followed longitudinally.

MRgFUS VIM thalamotomy offers a non-invasive, safe, and effective treatment option for medication induced tremor; however, larger studies with a longer follow-up are needed to validate the result.

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 humans were approved by West Virginia University, School of Medicine, Department of Neurosurgery. The studies were conducted in accordance with the local legislation and institutional requirements. The 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

KG: Methodology, Writing – original draft, Writing – review & editing. JM: Methodology, Writing – review & editing, Writing – original draft. VT: Methodology, Writing – review & editing. AT: Visualization, Writing – review & editing. AB: Methodology, Writing – review & editing. PK: Methodology, Writing – review & editing. MR: Methodology, Writing – review & editing. AM: Conceptualization, Methodology, Supervision, Writing – review & editing.

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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.2023.1331241/full#supplementary-material

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Case report: Rapid-onset parkinsonism after a hornet sting

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Neurological manifestations with basal ganglia involvement following *Hymenoptera* stings are rare and clinically ill-defined conditions. We present a patient with acute parkinsonism non-responsive to levodopa, who developed striatal lesions after a hornet sting. We report his response to immunomodulatory treatment and subsequent clinical and brain magnetic resonance imaging (MRI) follow-up. We also searched the literature for patients with acute extrapyramidal syndromes following an insect sting. Fourteen cases have been published; 12 of them are reviewed here. The majority of cases presented with symmetric akinetic syndrome with axial rigidity and/or gait impairment. Six patients were treated with levodopa and only two of these had a modest response to therapy. Brain MRI/computed tomography scan revealed lesions of the basal ganglia, which resulted in fatal outcome in four patients, whereas only one achieved complete recovery. Clinicians should be aware of this rare but devastating cause of acute-onset parkinsonism and specific clinical presentation of this condition, and should consider prompt and prolonged immunomodulatory treatment to prevent irreversible basal ganglia damage.

KEYWORDS

rapid onset, parkinsonism, basal ganglia damage, sting, insect

Introduction

Neurological manifestations of *Hymenoptera* stings are rare and mostly present with central or peripheral demyelination syndrome, intracranial hemorrhage and stroke (1–4). In addition, involvement of basal ganglia including pallidostriatal necrosis, coupled with different types of acute-onset parkinsonism, has been previously reported (5–17). Clinical presentation, treatment reaction and disease outcome are still unknown in this rare condition. We present a patient with acute parkinsonism non-responsive to levodopa and striatal lesions after a hornet sting, and document his response to immunomodulatory treatment with clinical and brain MRI follow-up. We also reviewed the literature for similar cases and discuss clinical presentation and prognosis of this rare condition.

Case report

A 70-year-old, right-handed Caucasian male was referred to our department for a second opinion 2 months after he had developed acute neurological symptoms following a

hornet sting. On July 22, 2020, the patient had an anaphylactic reaction with hypotension and a brief loss of consciousness soon after a hornet had stung him in the nose. He was followed for the next 24 h in his local general hospital and discharged the next day after complete recovery following antihistamine therapy with desloratadine.

Over the next 3 days, he developed a feeling of malaise and noticed that his walk had become slower and with smaller steps. Desloratadine was discontinued after 8 days, but his gait became even worse with severe hesitation at gait initiation and sudden episodes during walking when he was unable to take a step. In addition, his family members noticed that he was more taciturn and slower to respond to questions. Up until the hornet incident, he had no major health problems except for well-controlled high blood pressure treated with lisinopril.

Diagnostic assessment

Non-contrast axial computed tomography (CT) scan of his brain performed 2 weeks after the hornet sting did not show any signs of acute stroke, tumor, or intracranial hemorrhage. Four days later, non-contrast head MRI showed a slight bilateral striatum hyperintensity signal (HIS) on T1-weighted images, mixed bilateral striatum signal intensity on T2-weighted images with HIS on fluid-attenuated inversion recovery (FLAIR) images, without restriction of diffusion, suggesting petechial blood products corresponding to a T2* susceptibility artifact on SWI sequence (Figure 1A). Levodopa/carbidopa was started and titrated slowly up to 1000 mg *per* day for the next 3 weeks, but no appreciable improvement was noted.

Two months after the hornet incident, he came to our hospital. On examination, the patient had an impassive face, speech was hypophonic and he manifested palilalia. He had symmetric rigidity of his neck and limbs, and mild symmetric bradykinesia was present in all extremities without tremor. Reflexes were brisk but his plantar responses were normal. On postural reflex testing, he recovered with 2–3 steps. The main problem was his gait with start hesitation and freezing, especially on turning or passing through the door (Supplementary Video 1_Segment 1).

His Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) III score was 35 and he was 2.5. on the Hoehn and Yahr scale. Levodopa/carbidopa treatment was slowly down-titrated and stopped. Lumbar puncture showed a small increase in protein content (0.548 g/L; reference interval 0.170–0.370 g/L) with normal cell numbers. There were no oligoclonal bands or signs of immunoglobulin intrathecal synthesis. Autoimmune antibodies (anti-NMDA-R, anti-AMPA-R1, anti-AMPA-R2, anti-GABAB-R, anti-LGI 1 and anti-CASP-R 2) from cerebrospinal fluid were normal. DaTSPECT showed normal findings. Non-contrast head MRI showed mixed striatum signal intensity on T1-weighted images with hyperintensity in ventral putamen, hyperintensity on T2-weighted and FLAIR images, predominantly in bilateral putamen and caudate nuclei with a patchy restricted diffusion-weighted image signal suggesting necrosis (Figure 1B).

Immunohistochemistry was performed using the patient's serum to evaluate antibodies in brain tissue (for procedure, see additional material). As shown in Figure 2, rat brains reacted with the patient's serum in several regions (nucleus arcuatus, cornu ammonis 1 region of the hippocampus, cerebellum, dentate gyrus of the hippocampus, putamen, reticular formation of the pons and substantia nigra).

With intravenous corticosteroid treatment (methylprednisolone 250 mg/day for 5 days slowly tapered down over the subsequent 2 weeks), marked improvement of gait was observed (Supplementary Video 1_Segment 2). At discharge, the patient still had hesitation while turning, but freezing of gait had ceased, his MDS-UPDRS III score was 18 and he was 2 on the Hoehn and Yahr scale.Continuation of oral pronisone therapy with gradual dose tapering was recommended. Over the next 6 weeks (during which the patient stopped corticosteroid therapy on his own), gradual deterioration of gait with reappearance of freezing occurred. On that time his MDS- UPDRS III score was 30. Five courses of plasma exchange followed by rituximab were administered but without any significant gait improvement.

At that time, head MRI scan (February 28, 2021) showed mixed striatum signal intensity and hyperintensity in the ventral putamen on T1-weighted, hyperintensity on T2-weighted and FLAIR MRI images, suggesting atrophy and gliosis of the striatum, without restriction of diffusion and without contrast enhancement on T1-weighted postcontrast images (Figure 1C). Symptoms remained unchanged and no new symptoms appeared over the next 6 months of follow-up.

Discussion

Basal ganglia necrosis associated with parkinsonism after an insect sting is a rare and ill-defined condition. In our case and the 12 previous cases from the literature (Table 1), presenting features consisted mainly of symmetric akinetic-rigid syndrome which developed within several days of the incident. Resting tremor was rare and mild, and in the majority of cases levodopa response was poor. Instead, the clinical picture consisted of gait impairment including freezing of gait, postural instabilities, and speech disturbances (including palilalia), all of which have been previously recognized as signs of pallidal damage (18). In addition, profound micrographia and akinetic mutism, which were presenting symptoms in one patient each, further support pallidal involvement (19). Interestingly, pyramidal signs including clonus and Babinski sign were noted in five out of eight patients (for the remaining cases, data are lacking). The combination of pyramidal signs coupled with specific, predominantly axial parkinsonism and gait disturbances after an insect sting more closely resemble distinctive, mainly genetically-determined pallido-pyramidal syndrome than Parkinson's disease (20).

MRI was performed in six out of 12 patients, and HIS on T2-weighted and FLAIR images in the region of basal ganglia (striatum, mainly pallidum), were noted in all of them. In three additional cases, CT scans also demonstrated mainly symmetric hypodensity in lenticular nuclei. In our patient, non-contrast brain CT scan and brain MRI performed 2–3 weeks after the hornet sting showed bilateral petechial blood products in the striatum. Non-contrast brain MRI performed 3 months after hornet sting showed signs of bilateral striatal necrosis, and follow-up brain MRI performed

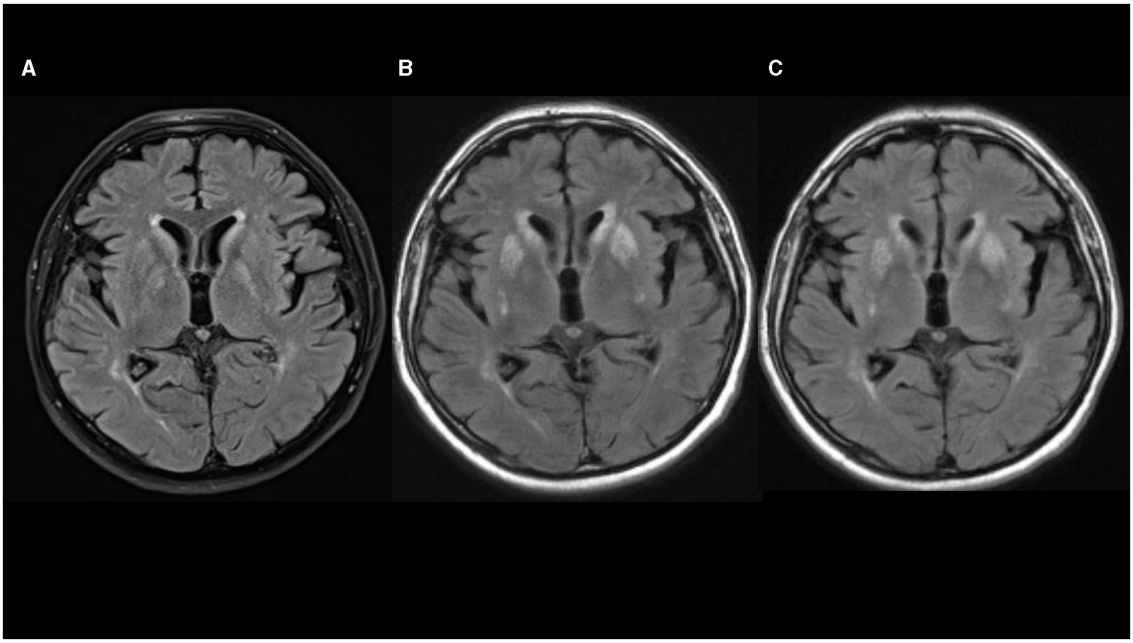

FIGURE 1
(A–C) Fluid-attenuated inversion recovery (FLAIR) sequences in axial plane show progression of hyperintensities in basal ganglia [**(A)** 08/2020; **(B)** 10/2020; **(C)** 02/2021].

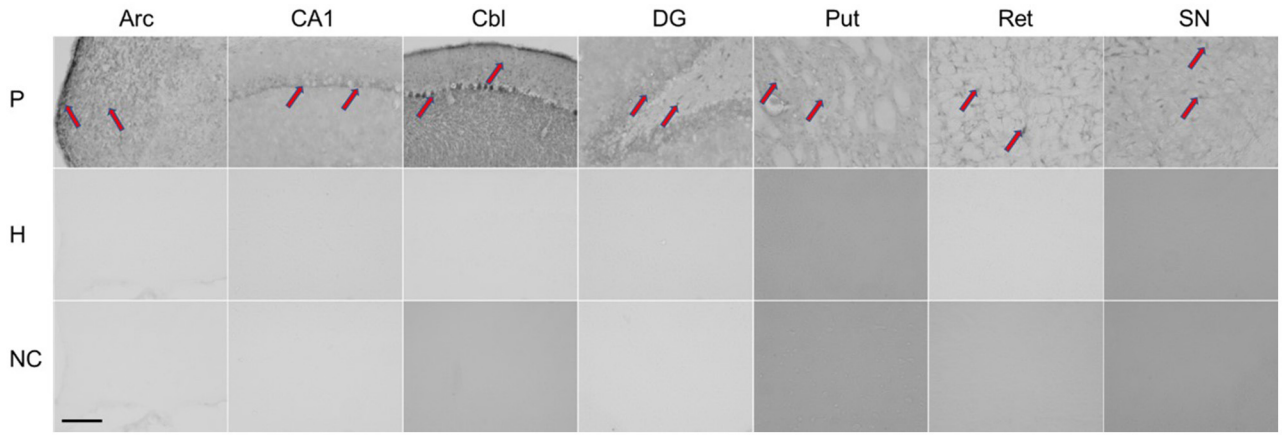

FIGURE 2
Immunohistochemical staining of rat brain slices using human serum as source of the primary antibodies. Red arrows indicate positive staining reaction in different regions of the rat brain. P, patient; H, healthy control; NC, negative controle; Arc, arcuatus; CA1, cornu ammonis 1 region of hippocampus; Cbl, cerebellum; DG, dentate gyrus of hippocampus; Put, putamen; Ret, reticular formation of pons; SN, substantia nigra. Total magnification of individual image 200x, scale 200 micrometers.

after 7 months showed atrophy and gliosis of the striatum. Combining those data with normal DaTSPECT in our case suggest a postsynaptic cause of parkinsonism predominantly due to striatal damage with sparing of the nigrostriatal dopamine bundle.

The etiology of basal ganglia damage in this rare condition is unknown. Hypoxic-ischaemic mechanism due to an exaggerated anaphylaxis, associated hypotension, and eventual prolonged cerebral hypoxia is one possible mechanism. This sequence of events might explain cases with severe hypotension, prolonged loss of consciousness and respiratory failure. Nevertheless, in case presented by Gallego et al. patient presented with stupor 1 h after incident, soon progressed to coma but without significant cardiovascular, electrolytic or respiratory failure (8). In addition, authors stated that histological pattern on necropsy did not suggest a hypoxic-ischaemic nature of basal ganglia damage. In case we presented, as well as in other cases collected here the anaphylactic reaction led to hypotension without or only with short-term loss of consciousness that did not require cardiopulmonary resuscitation, and there was no need for respiratory support suggesting the hypoxic-ischemic mechanism of brain damage unlikely (6, 17).

TABLE 1 Clinical characteristics, MRI findings, treatment response and outcomes of patients who developed parkinsonism following insect stings.

References	Species	Age (yr)	Anaphylaxis and latency to symptom onset	Extrapyramidal symptoms	Pyramidal symptoms	Brain MRI/CT scan	DaTSPECT	Pathology	L-dopa treatment	Immunoth response	Disease course and outcome
Tomic et al. (this case report)	Hornet	70	Anaphylaxis 3 days	Freezing of gait; bilateral symmetrical parkinsonism	No signs of lesions	MRI 1—slight bilateral striatum HIS on T1w images, mixed bilateral striatum signal intensity on T2w images with HIS on FLAIR images, without the restriction of diffusion. MRI 3—mixed striatum signal intensity and HIS in ventral putamen on T1w, HIS on T2w and FLAIR images	Normal	Not done	No response to 1,000 mg/day	corticosteroide; PE; rituximab	Partial improvement after the first 2 weeks of treatment with methylprednisolone; after discontinuation of corticosteroides returning of symptoms without further improvement
Leopold et al. (6)	Wasp	49	No anaphylaxis A few hours	Mild resting right hand tremor; bilateral symmetric parkinsonism; postural instability	Symmetrical exaggerated muscle stretch reflexes	MRI 1—bilateral HIS signal in the globus pallidum on T2w images MRI 2—marked destruction of the striatum and pallidum bilaterally	Marked decrease in metabolic activity of the basal ganglia with sparing of the thalamus	Not done	No response to 900 mg/day	PE; IvIg; azathioprine	Stable for 6 months; followed by rapid progression Partial but significant improvement after immunomodulatory therapy
Agarwal et al. (13)	Honeybee	No data	No data 3 days	Symmetric parkinsonism; short shuffling gait	No signs of lesions	MRI—diffuse HIS on T2w and FLAIR images in bilateral caudate and lentiform nuclei; diffuse effacement of the sulci on the right frontal lobe	No data	Not done	Levodopa/ carbidopa	Not given	Symptomatic improvement within 4 weeks; after 3 months parkinsonism had improved
Mittal et al. (5)	Honeybee	46	Anaphylaxis 2 days	Symmetric parkinsonism; hypokinetic dysarthria.	No signs of lesions	No data	No data	Not done	Levodopa/ carbidopa	Not given	Symptomatic improvement of speech over the next 2 months; no data for outcome

(Continued)

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TABLE 1 (Continued)

References	Species	Age (yr)	Anaphylaxis and latency to symptom onset	Extrapyramidal symptoms	Pyramidal symptoms	Brain MRI/CT scan	DaTSPECT	Pathology	L-dopa treatment	Immunoth response	Disease course and outcome
van Agt et al. (7)	Wasp	52	Anaphylaxis No data	Bradykinesia; rigidity	No signs of lesions	MRI—symmetrical bilateral caudate nuclei and putaminal HIS signal in T1w, T2w and FLAIR images. Iron deposition in the right external capsule in T2w images.	No data	Not done	Levodopa/carbidopa	Not given	Mild improvement with levodopa after 6 months
Gallego et al. (8)	Wasp	72	No anaphylaxis 1 h	Rigidity	Right hemiparesis bilateral Babinski sign; symmetrically brisk tendon jerks	MRI not done; CT scan—low density of both lenticular nuclei, most pronounced in the left globus pallidus	Not done	Bilateral cavitations of the globus pallidus and softening of the putamen and caudate nuclei in subcortical white matter pallor of the myelin	Not given	Not given	Death (72 h after the sting)
Castaigne et al. (10)	Wasp	No data	No data	No data	No data	Not done	Not done	Severe necrotic lesions in the putamen and less severe lesions in the caudate, thalamus, and red nucleus	Not given	Not given	Coma; death after 55 days
Bogolepov et al. (11)	Wasp	51	Anaphylaxis 1 h	Parkinsonism	No data	Not done	Not done	Bilateral pallidal necrosis with less profound lesions in the substantia nigra	Not given	Not given.	Death after 14 days
Laplane et al. (9)	Wasp	No data	No anaphylaxis No data	Chorea; buccofacial dyskinesias; compulsive movements	No data	MRI not done; CT scan –bilateral hypodense pallidostriatal lesions	Not done	Not done	Not given	Not given	Gait disorder and myoclonus lasted for several months with slow recovery; compulsive obsessive behavior developed several years later

(Continued)

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TABLE 1 (Continued)

References	Species	Age (yr)	Anaphylaxis and latency to symptom onset	Extrapyramidal symptoms	Pyramidal symptoms	Brain MRI/CT scan	DaTSPECT	Pathology	L-dopa treatment	Immunoth response	Disease course and outcome
Gale (12)	No data	36	Anaphylaxis 1 day	Dystonia; symmetric parkinsonism	Brisk tendon reflexes	MRI not done; CT scan—low attenuation in both posterior parietal regions	Not done	Not done	No response to levodopa	Not given	Partial improvement
Gale (12)	Wasp	38	Anaphylaxis A few hours	Akinetic mutism; plastic hypertonicity in the limbs; catatonic posturing	Tendon reflexes symmetrically brisk; Babinski sign bilaterally; clonus	Not done	Not done	Not done	Not given	Not given	Some improvement; regained speech; died 4 months later from pulmonary embolism
Sehgal et al. (16)	Wasp	No data	No data 2 days	Akinetic-rigid parkinsonism	No data	No data	No data	No data	No data	No data	No data
Kumawat et al. (17)	Honeybee	40	No anaphylaxis 3 days	Symmetric akinetic-rigid parkinsonism; extrapyramidal dysarthria; dystonic posture on all four limbs	No signs of lesions	MRI - in T2w and FLAIR images HIS signals in bilateral basal ganglia and left centrum semioval	Not done	Not done	Not given	Corticosteroide intravenously for 5 days	All symptoms and signs resolved promptly; no data on follow-up

*Minault et al., Nouv Presse Med 1981, article in French; Mavra et al., Srp Arh Celok Lek. 1983—not available.

CT, computed tomography; HIS, hyperintensive signal; IvIg, intravenous immunoglobulins; MRI, magnetic resonance imaging; PE, plasma exchange; T1w, T1-weighted; T2w, T2-weighted.

10.3389/fneur.2024.1365199

Given the acute onset of parkinsonism and neuroimaging findings, an immune-mediated early hypersensitivity reaction is most likely. In support of this are evidence for autoimmunity obtained from immunohistochemistry and the excellent treatment response observed in one patient who received corticosteroids in the acute phase, as well as the beneficial but limited clinical response to corticosteroid treatment observed in our case and those reported by Leopold et al. (6). In the latter two cases, immunomodulatory treatment was applied with significant delay. Although we found that antibody reacted with different brain regions (nucleus arcuatus, cornu ammonis 1 region of hippocampus, cerebellum, dentate gyrus of hippocampus, putamen, reticular formation of pons and substantia nigra), only the striatum was damaged by necrosis. Susceptibility of the basal ganglia to toxic and hypoxic lesions has already been described in human and animal studies, and mitochondrial failure with energy deprivation is considered as the main underlying mechanism (21).

Patient perspective

In conclusion, clinicians should be aware of this rare but devastating cause of acute-onset parkinsonism, it's specific clinical presentation and clinical course. Although limited, current knowledge suggest that prompt and prolonged immunomodulatory therapy could be a rational therapeutic choice in attempt to prevent irreversible basal ganglia damage.

Data availability statement

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

Ethics statement

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

ST: Conceptualization, Funding acquisition, Investigation, Writing—original draft, Writing—review & editing. MZ: Investigation, Writing—original draft, Writing—review & editing. ZP: Investigation, Writing—original draft, Writing—review & editing. ZK: Data curation, Investigation, Writing—original draft, Writing—review & editing. MH: Data curation, Writing—original draft, Writing—review & editing. DS: Data curation, Investigation, Writing—original draft, Writing—review & editing. DM: Data curation, Investigation, Writing—original draft, Writing—review & editing. SG: Data curation, Investigation, Writing—original draft, Writing—review & editing. IP: Conceptualization, Formal analysis, Methodology, Project administration, Resources, Validation, Writing—original draft, Writing—review & editing.

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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.2024.1365199/full#supplementary-material

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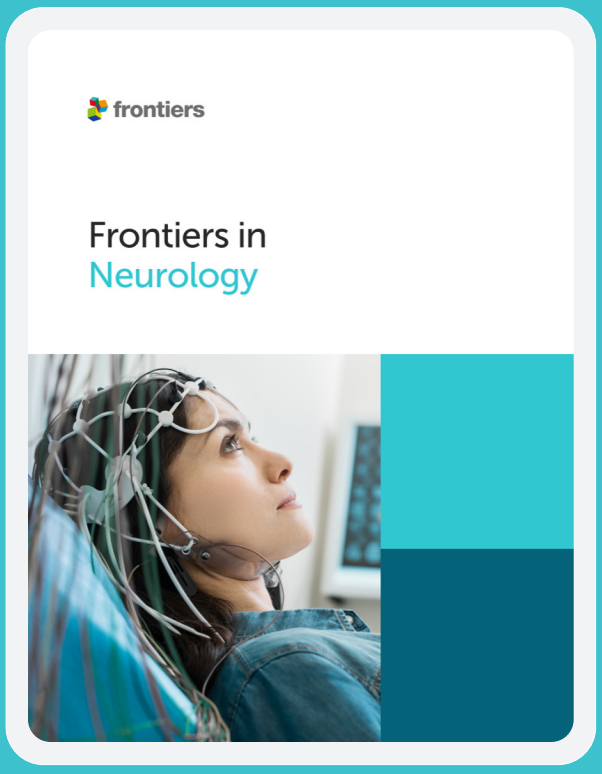

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