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Case Report
***Case report of an early-onset dystonia-parkinsonism associated with a
novel PLA2G6 gene variant***

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Short Title: PLA2G6-associated dystonia-parkinsonism

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Abstract

Introduction. Monogenic forms account for a minority of Parkinson's disease cases but offer valuable insights into disease mechanisms. PARK14 is an atypical autosomal recessive dystonia-parkinsonism caused by mutations in the *PLA2G6* gene. The disorder typically presents in early adulthood with a wide range of symptoms such as dystonia, initial responsiveness to levodopa, cognitive impairment and levodopa-induced dyskinesias. The phenotypic spectrum also includes signs like cerebral or cerebellar atrophy or iron accumulation in the brain. **Case Presentation.** We present a case of adult-onset dystonia-parkinsonism in a patient carrying a novel heterozygous *PLA2G6* (NM_003560.4) variant c.1805A>G (p.Tyr602Cys). The patient exhibited levodopa-responsive parkinsonism, severe dyskinesias, dystonia, cerebellar atrophy and underwent subthalamic nucleus deep brain stimulation surgery after 4 years of the initial symptoms. In contrast to typical PARK14 cases, cognitive function remained preserved after 5 years of disease duration (MoCA 29/30). **Conclusion.** Although the phenotype of the patient aligns with PARK14 diagnosis, a causal role for this heterozygous variant cannot be established from the present data. PARK14 is classically an autosomal recessive disorder and a single monoallelic variant is not sufficient to explain the phenotype – an undetected second variant, an alternative genetic cause or a coincidental finding cannot be excluded. Moreover, additional data is needed to understand whether monoallelic *PLA2G6* variants could be a causative factor for PARK14 and act dominantly, or if single gene variants only increase the risk of Parkinson's disease in combination with other genetic or environmental factors. This case is therefore presented as a detailed clinical observation in a patient with a novel *PLA2G6* variant rather than as confirmation that the variant is responsible for the patient's PARK14-like presentation.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative movement disorder that causes motor symptoms like tremor, rigidity and bradykinesia, and non-motor symptoms such as sleep disorders and autonomic dysfunction. Although, the majority of cases are multifactorial and idiopathic, about 10-15% of PD cases are caused by genetic mutations [1,2]. Most genetically determined forms of PD present as early-onset Parkinson's disease (EOPD), with symptoms typically beginning from age 21 to 50. These cases represent around 3-7% of all Parkinson's patients in Western populations. Several gene variants cause EOPD that differ in prevalence, inheritance patterns or penetrance, with the most common being *PRKN*, *LRRK2*, *PINK1* and *DJ-1* [3,4].

PARK14 is an autosomal recessive early-onset dystonia-parkinsonism caused by *PLA2G6* variants [3,4]. The *PLA2G6* gene, located on chromosome 22q13.1, encodes calcium-independent group 6 phospholipase A2 β (iPLA2 β), an enzyme expressed in the mitochondria that contributes to lipid metabolism by hydrolysing phospholipids at the sn-2 position and generates lysophospholipids and free fatty acids. It is responsible for homeostasis of cell membranes, cellular signalling and mitochondrial function. Variants of this gene result in mitochondrial dysfunction, oxidative stress and, in PARK14 cases, accumulation of α -synuclein, leading to neurotoxicity and apoptosis of neuronal cells [5]. PARK14 typically presents in adolescence or young adulthood, before age 30. These patients show good initial levodopa response but quickly develop levodopa induced dyskinesias, along with dystonia, marked cognitive decline and brain magnetic resonance imaging (MRI) findings such as cerebellar atrophy or iron accumulation [3,6,7]. Diagnosing PARK14 is difficult due to high genotypic and phenotypic variability of *PLA2G6* variants. These diagnostic challenges, combined with the lack of disease-modifying treatment, create a significant social and economic burden for patients, especially since many become disabled during their most productive years (ages 30-40) [8,9].

Considering the importance of PARK14 symptom awareness, the diagnostic challenges and the need for further research, especially in the genetic field, we present in this article a unique clinical case of a young patient with a novel heterozygous variant heterozygous variant *c.1805A>G* (*p.Tyr602Cys*) in the *PLA2G6* gene. Whether this monoallelic variant contributes to the patient's phenotype remains unclear. We therefore report the case as a detailed clinical observation, not as proof of causality. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material.

Case Report/Case Presentation

The patient is a 38-year-old Caucasian female born to non-consanguineous parents. From childhood she has iron deficiency anaemia, however no other chronic diseases were present until 34 years old.

In autumn 2021 at age 34, she developed leg weakness, foot numbness and pulling sensation which worsened after contracting COVID-19 in January 2022 – gait instability, left hand tremor, fatigue and difficulties with concentration appeared. Neurological evaluation in May 2022 revealed impaired feet sensation and cerebellar signs. After positive anti-SOX antibodies, Myasthenia syndrome was suspected, and treatment of plasmapheresis was implemented. However, there was no effect on a patient as her symptoms progressed furthermore – gait instability worsened, she experienced left side symptoms worsening: bradykinesia, rigidity, resting tremor in the left hand, pulling sensation and heaviness of the left leg.

One year after the onset of her symptoms, Single-Photon Emission Computed Tomography (SPECT) imaging revealed pronounced neuronal loss characteristic of Parkinson's syndrome (shown in Fig. 1 a). The treatment with ropinirole and rasagiline (levodopa equivalent daily dose (LEDD) – 260-340 mg) showed good initial effect for 4 months after which all previously noted symptoms reoccurred and worsened (Table 1. D. MDS-UPDRS part III score 18 p.; LEDD – 340 mg). Starting in spring 2023 at 36 years old, as an additional treatment levodopa/carbidopa 100/25 mg/day was introduced with good initial response – dystonia, leg numbness, hand tremor decreased and gait improved (Table 1. E. MDS-UPDRS part III score 8 p.; LEDD – 440 mg). However, within months, the patient's condition worsened and required levodopa dose adjustment (Table 1. F. MDS-UPDRS part III score 15 p.; LEDD – 620-720 mg). Slight and gradual increase of the dose led to ballistic dyskinesias in the legs at 300 mg/day and generalized dyskinesias at 600 mg/day. Notably, only 7 months passed before dose escalation from 300 mg/day to 600 mg/day became necessary (Table 2).

By 2024-2025 the patient reached disabling motor fluctuations – even 50 mg of levodopa triggered generalised dyskinesias lasting up to 2 hours, alternating with painful dystonia and rigidity during “OFF” states (Table 2). Increase of medication showed no relief in symptoms and resulted in additional side effects. Furthermore, anxiety and depression developed, which improved with duloxetine. During this same period, follow-up brain MRI revealed early cerebellar atrophy and susceptibility-weighted imaging (SWI) MRI showed absence of normal hyperintense substantia nigra signal (shown in Fig. 1 b). Next-generation sequencing (NGS) was performed using the Illumina Nextera Rapid Custom Capture Enrichment protocol and 150-bp paired-end sequencing on the NovaSeq platform (Illumina, San Diego, California, USA). Genetic analysis was performed using a custom-designed NGS panel for neurodegenerative disorders, including genes associated with

Parkinson's disease and other movement disorders. Sequencing reads were aligned to the human reference genome (hg38). The mean target coverage was 100×, with more than 90% of target regions adequately covered. Rare variants were filtered using a quality score threshold >20. Sequence variants were classified according to the guidelines of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) [10]. Population allele frequencies were obtained from the Genome Aggregation Database (gnomAD v4.1.1), and variants with a minor allele frequency (MAF) of less than 0.01% were considered sufficiently rare to support pathogenicity assessment under the PM2 criterion. An analysis of copy number variants (CNVs) was also performed, but it did not reveal any clinically significant findings. NGS analysis identified a heterozygous likely pathogenic *PLA2G6* variant NM_003560.4:c.1805A>G (p.Tyr602Cys). Segregation analysis of the identified variant was performed on both parents and revealed that the mutation was inherited from an asymptomatic father, while the mother tested negative.

Due to inadequate response to pharmacological treatment (LEDD – 1200 mg), deep brain stimulation (DBS) surgery was considered. An acute levodopa challenge demonstrated 76% improvement in motor signs (Table 1. L. MDS-UPDRS part III score: 37 points before and 9 points after levodopa administration), which confirmed DBS candidacy. As there were no contraindications, bilateral subthalamic nucleus (STN) DBS surgery was performed in August 2025. STN DBS was selected following interdepartmental discussion based on literature evidence of its superior reduction of dopaminergic medication, OFF time and main parkinsonian symptoms compared to GPi DBS [11,12]. Improvement of symptoms lasted one month – patient achieved reduction of dyskinesias, bradykinesia and rigidity, minimal “OFF” periods and levodopa reduction to 100-200 mg/day (Table 1. P. MDS-UPDRS part III score 8 p.; LEDD – 920-1020 mg). Over the following five months, peak-dose ballistic dyskinesias recurred and levodopa dosage increased. Several stimulation adjustments and medication corrections gave only short time of improvement (Table 2). At hospitalisation in February 2026, levodopa was discontinued, long-acting pramipexole was prescribed and STN-DBS amplitude was increased to 1.7 mA (right STN (C+, 9-), left STN (C+, 0-), 130 Hz, 60 µs, 1.7 mA bilaterally). Following treatment correction dyskinesias became minimal and disabling motor fluctuations with limb rigidity decreased (Table 1. S. MDS-UPDRS part III score 7 p; LEDD – 1028 mg).

Discussion

To date, PARK14 is classically described as an autosomal recessive disorder, where affected individuals carry homozygous or compound heterozygous variants in *PLA2G6* [5]. Interestingly, genetic test results of our patient showed only variant of *PLA2G6* (c.1805A>G) that has not been

reported in the literature or ClinVar database. This variant is classified as likely pathogenic (ACMG criteria: PM1, PM2, PP3). Although many computational prediction tools indicate that this variant has a deleterious effect on protein function, no functional studies have been conducted to confirm its biological impact. Biallelic *PLA2G6* variants are known to cause PARK14, however, the role of monoallelic variants is still unclear. Several publications on case reports of heterozygous *PLA2G6* mutations suggest a possibility of autosomal dominant inheritance [13,14], although the presence of the same variant in the patient's asymptomatic father makes this less likely. Age of onset in PARK14 varies widely and subclinical dopaminergic changes have been reported in asymptomatic carriers [15]. Therefore, the father's asymptomatic status does not exclude the possibility of age-dependent onset or variable penetrance, which could only be assessed with neurological evaluation and neuroimaging, which were not performed in this case. Another possibility is that the standard short-read NGS could have missed a second pathogenic variant as this approach targets coding regions of the genome and cannot identify noncoding variants or large structural rearrangements [16]. There are reported cases of deep intronic *PLA2G6* variants associated with PARK14 that were detected only with genome or transcriptome sequencing – methods that analyse non-coding regions [17,18]. In addition, in recent years it has been found that EOPD can be caused by large inversions in genes such as *PRKN*. These variants were missed by short-read sequencing but were detected through long-read sequencing approaches [16]. Large deletions in *PLA2G6* have also been reported – one published case described a PARK14 patient carrying a large exon deletion. The variant was detected by Multiplex Ligation-dependent Probe Amplification (MLPA) rather than NGS, which is better suited for detecting small mutations such as missense or nonsense variants [19]. An alternative interpretation is that this heterozygous variant may act as a risk factor and increases susceptibility to Parkinson disease in combination with other genetic or environmental factors [20]. A limitation of this case is that, in our clinical setting, we were unable to perform additional genomic and transcriptomic analyses, such as whole-genome sequencing (WGS) and RNA sequencing. Therefore, based on currently available data, the identified heterozygous *PLA2G6* variant c.1805A>G (p.Tyr602Cys) should be considered a plausible but not proven causal variant of PARK14 in this patient.

This case is unique both genetically and clinically (Table 3). Generally, EOPD is associated with slower disease progression, including cognitive decline [8]. However, in PARK14, cognitive dysfunction and psychiatric manifestations are among the main features of the disease. Psychiatric symptoms may include depression, aggressive behaviour, psychosis, paranoid thoughts and hallucinations, while cognitive dysfunction may manifest as word retrieval difficulties, frontal executive dysfunction or impairment of verbal and visual memory [7,21]. Magrinelli *et al.* reported that these symptoms appear early in the disease course (in 76.1-87.1% of patients) and are among the most common

initial symptoms of PARK14 (31.6% of patients) [21]. However, our patient scored 29/30 (not adjusted for education) on the Montreal Cognitive Assessment (MoCA) test, conducted in January 2026 – 5 years of disease duration and after STN DBS surgery. This remained well above the standard cutoff of 26, indicating preserved cognitive function (Table 3). Additionally, she has experienced only mild anxiety and depression, which quickly improved with low-dose medication. Interestingly, published case of monoallelic *PLA2G6* variant showed cognitive decline only after 13 years of disease onset, suggesting that cognitive impairment may manifest late in disease course [13]. However, it remains debatable whether symptoms such as mild anxiety and depression are components of PARK14 or rather non-specific features of EOPD related to the psychosocial burden of developing the disease at a young age [8].

This dystonia-parkinsonism belongs to the *PLA2G6*-associated neurodegeneration (PLAN) spectrum of disorders, which have characteristic brain MRI findings [3]. However, these signs are not pathognomonic or mandatory for diagnosing PARK14. PLAN cases often show iron accumulation, particularly in the globus pallidus, though it occurs in only around 25% of PARK14 cases. In contrast, cerebral or cerebellar atrophy is more common, occurring in almost half of PARK14 patients (33.33%-54.12%). Notably, brain atrophy may develop several years after disease onset, requiring follow-up neuroimaging [6,7,19,21,22]. In our patient, cerebellar atrophy was detected on a follow-up brain MRI 3 years after symptom onset, which was absent on the previous scan. However, no iron accumulation was observed on either scan (Table 3). While these imaging signs are not specific to PARK14, when present, PLAN disorders should be considered, especially PARK14 if the disease begins in adulthood. Importantly, the absence of these findings does not exclude PARK14.

The patient's quality of life is mostly affected by motor symptoms and medication-induced complications. While PARK14 patients typically respond well to levodopa (97.3% of cases), levodopa-induced dyskinesias and wearing-off develop notably quickly [3,7,21]. Typically, in sporadic PD, wearing-off occurs 5-10 years after starting levodopa therapy, in contrast, PARK14 patients develop this phenomenon much faster, usually after 1-2 years of initiating dopaminergic treatment [8,21–23]. In our patient levodopa-induced dyskinesias appeared within one year and wearing-off developed after approximately 1.5 years. Interestingly, early levodopa-induced dyskinesias occur in 80.7% of PARK14 patients and are considered a hallmark of the disease [21]. When optimized pharmacotherapy is of limited effect, DBS is an alternative treatment option. Published reviews show that PARK14 patients typically receive DBS within 5 years of symptom onset due to early and refractory motor complications. DBS highly improves motor symptoms by reducing OFF time, dystonia and levodopa-induced dyskinesias, as well as the amount of dopaminergic medication

[21,24,25]. Our patient received STN-DBS after just 4 years of disease onset and showed notable benefit after 6 months, however longer follow-up period is required to determine the impact of the surgery.

In this case report we describe a patient with adult-onset dystonia-parkinsonism in whom a novel heterozygous PLA2G6 variant was identified. The patient's phenotype is characterised by a good initial levodopa response and early motor complications requiring DBS. Should this variant ultimately prove to contribute to the phenotype, the absence of psychiatric symptoms, cognitive decline and iron accumulation on brain MRI would support a broader phenotypic spectrum of PLA2G6-associated dystonia-parkinsonism. It is worth stressing that with the data currently available this association remains unproven and should be interpreted with caution. Biallelic *PLA2G6* variants are known to cause PARK14, however, the role of monoallelic variants – whether causative, risk increasing or sporadic – remains unclear and requires further studies of PARK14 genetics. In future patients with a similar presentation or monoallelic PLA2G6 variants, extended genetic investigations such as WGS, MLPA, long-read sequencing or functional studies may be beneficial in establishing a definitive molecular diagnosis.

Limitations. This case has several limitations. First, in our clinical setting, we were unable to perform additional genomic, transcriptomic analyses or functional testing of the patient, such as whole-genome sequencing and RNA sequencing. Second, familial segregation analysis was restricted to parental testing. Further clinical evaluation of the father and genetic testing of additional family members were not feasible, which limits the interpretation of the variant's pathogenicity and penetrance in this family. Third, dyskinesias were assessed clinically but not quantified using a standardized instrument such as the Unified Dyskinesia Rating Scale (UdysRS) and retrospective application of this scale was not feasible. Fourth, the post-DBS follow-up period remains relatively short and longer follow-up is required to fully evaluate the long-term efficacy of STN DBS in this patient.

Statements

Statement of Ethics

This study was approved by the Institutional Review Board of Vilnius University Hospital Santaros Clinics - approval: No. SR-816. The adult patient provided written informed consent to participate in this study. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

Conceptualization: G.B., N.T., visualization: G.G., G.B., data curation and writing – original draft: G.G., investigation, validation and writing – review and editing: G.B., B.B., R.K.L., N.T., supervision: G.B., R.K.L., N.T.

Data Availability Statement

All data generated or analysed in the preparation of this case report are included within this article. For additional information, contact the corresponding author.

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Figure Legends

Fig. 1. **a** – Axial projection of Single-Photon Emission Computed Tomography (SPECT) DaT-scan shows reduced striatal dopamine transporter uptake bilaterally, with more severe involvement of the left putamen (Z-score: right putamen -5.03, left putamen -5.24, right nucleus caudatus -4.31, left nucleus caudatus -3.5). Performed on 26th of October 2022 (1 year after disease onset). **b** - Susceptibility-weighted imaging (SWI) MRI shows absence of normal hyperintense signal in substantia nigra, known as “swallow tail sign”. Follow-up MRI performed on 12th of February 2024 (3 years after symptom onset and 2 years after initial MRI).

Table 1: Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III scores and levodopa equivalent daily dose (LEDD) during disease progression and treatment.

MDS-UPDRS part III scores		LEDD scores
A	October 2022	260 mg: Ropinirole 8 mg and rasagiline 1 mg.
B	November 2022	300 mg: Ropinirole 10 mg and rasagiline 1 mg
C	December 2022	340 mg: Ropinirole 12 mg and rasagiline 1 mg
D	March 2023	340 mg: Ropinirole 12 mg and rasagiline 1 mg
	18 points: Rigidity in the left hand – 1 p., right hand – 2 p.; finger tapping of the left hand – 2 p., right hand – 1 p.; hand movements of both hands – 1 p.; pronation-supination movements of both hands – 1 p.; gait – 1 p.; body bradykinesia – 1 p.; postural tremor of both hands – 1 p.; rest tremor in the left hand – 1 p.; constancy of rest tremor – 1 p.; Hoehn and Yahr stage – 2	
E	April 2023	440 mg: Ropinirole 12 mg, rasagiline 1 mg, levodopa/carbidopa 100/25 mg
	8 points: Rigidity in both hands – 1 p.; finger tapping of both hands – 1 p., pronation-supination movements of the left hand – 1 p.; body bradykinesia – 1 p.; Hoehn and Yahr stage – 2	
F	May 2023	620-720 mg: Ropinirole 16 mg, rasagiline 1 mg, levodopa/carbidopa 100/25 mg x 2-3
	15 points: Rigidity in the left hand – 1 p., right hand – 2 p.; finger tapping of both hands – 1 p., hand movements of both hands – 1 p., pronation-supination movements of both hands – 1 p.; gait – 1 p., body bradykinesia – 1 p.; rest tremor in the left hand – 1 p., constancy of rest tremor – 1 p., Hoehn and Yahr stage – 2	
G	November 2023	960 mg: Ropinirole 18 mg, rasagiline 1 mg, levodopa/carbidopa 100/25 mg x 4, amantadine 100 mg
H	December 2023	1360 mg: Ropinirole 18 mg, rasagiline 1 mg, levodopa/carbidopa 100/25 mg x 6, amantadine 300 mg
I	January 2024	1160 mg: Ropinirole 18 mg, rasagiline 1 mg,

MDS-UPDRS part III scores		LEDD scores
J	February 2024	levodopa/benserazide 200/50 mg x 2, amantadine 300 mg 1260 mg: Ropinirole 18 mg, rasagiline 1 mg, levodopa/benserazide 200/50 mg x 2, amantadine 400 mg
K	March 2024	1000 mg: Ropinirole 20 mg, rasagiline 1 mg, levodopa/benserazide 200/50 mg, amantadine 300 mg
L	December 2024	1200 mg: Ropinirole 20 mg, rasagiline 1 mg, levodopa/benserazide 200/50 mg x 1.5, amantadine 400 mg
M	December 2024	Levodopa challenge – 76% improvement in motor signs MDS-UPDRS part III score: 37 points before (speech – 1 p., facial expression – 1 p., rigidity in the: neck – 2 p., left hand – 1 p., right hand – 2 p.; left leg – 1 p., right leg – 2 p., finger tapping of both hands – 2 p., hand movements of the left hand – 1 p., right hand – 2 p., pronation-supination movements of both hands – 2 p.; toe tapping of the left leg – 1 p., right leg – 2 p., leg agility of the left leg – 1 p., right leg – 2 p., arising from chair – 1 p., gait – 2 p., body bradykinesia – 2 p.; rest tremor in both hands – 1 p., constancy of rest tremor – 2 p., Hoehn and Yahr stage – 2) and 9 points after levodopa administration
N	March 2025	1300-1400 mg: Ropinirole 20 mg, rasagiline 1 mg, levodopa/benserazide 200/50 mg x 2-2.5, amantadine 400 mg
O	June 2025	1220-1320 mg: Ropinirole 16 mg, rasagiline 1 mg, levodopa/benserazide 200/50 mg x 2-2.5, amantadine 400 mg
P	September 2025	MDS-UPDRS part III score 8 p.: speech – 1 p., facial expression – 1 p., finger tapping of both hands – 1 p., pronation-supination movements of both hands – 1 p.; Hoehn and Yahr stage – 2 920 mg: Ropinirole 16 mg, rasagiline 1 mg, levodopa/benserazide 200/50 mg x 0.5, amantadine 400 mg
Q	October 2025	1100 mg: Ropinirole 20mg, rasagiline 1 mg, levodopa/benserazide 200/50 mg x 1, amantadine 400 mg
R	November	1140 mg: Ropinirole 12 mg, rasagiline 1 mg,

MDS-UPDRS part III scores		LEDD scores
2025		levodopa/benserazide 200/50 mg x2, amantadine 400 mg
S February 2026	MDS-UPDRS part III score 7 p.: speech – 1 p., finger tapping of both hands – 1 p., pronation-supination movements of both hands – 1 p.; Hoehn and Yahr stage – 2	1028 mg: Ropinirole 12 mg, rasagiline 1 mg, amantadine 400 mg, pramipexole 2.88 mg

MDS-UPDRS: Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale; LEDD: levodopa equivalent daily dose; p.: points; mg: milligrams.

Table 2: Chronological timeline of clinical and therapeutic events.

Date	Clinical/therapeutic event	Notes
Autumn 2021	First symptoms	Leg weakness, foot numbness and pulling sensation gait instability, left hand tremor, fatigue and difficulties with concentration
May 2022	Positive anti-SOX antibodies	Myasthenia syndrome suspected Treatment of plasmapheresis
May-October 2022	Progression of neurological symptoms	Gait instability, left side symptoms: bradykinesia, rigidity, resting tremor in the left hand, pulling sensation and heaviness of the left leg
October 2022	SPECT DaT-scan	Pronounced neuronal loss characteristic of Parkinson's syndrome
October 2022	Treatment with ropinirole and rasagiline initiated	LEDD – 260 mg
October-December 2022	Ropinirole and rasagiline doses increased	LEDD – 340 mg
March 2023	Progression of neurological symptoms	MDS-UPDRS part III score – 18 points
April 2023	Treatment with levodopa/carbidopa initiated Neurological condition improved	LEDD – 440 mg MDS-UPDRS part III score – 8 points
May 2023	Progression of neurological symptoms Ropinirole and levodopa doses increased	MDS-UPDRS part III score – 15 points LEDD – 620-720 mg
May 2023	Onset of dyskinesias	Ballistic dyskinesias in the legs at 300 mg/day of levodopa
November 2023	Additional treatment with amantadine	LEDD – 960 mg
November-December 2023	Increase of ropinirole, levodopa and amantadine dosages	LEDD – 1360 mg
December 2023	Onset of generalized dyskinesias	Levodopa dose – 600 mg/day
January 2024	Levodopa/carbidopa changed to levodopa/benserazide Reduced levodopa dose	LEDD – 1160 mg
February 2024	Increased amantadine dose	LEDD – 1260 mg
February 2024	Follow-up brain MRI and SWI MRI	Early cerebellar atrophy and absence of normal hyperintense substantia nigra signal
February 2024	Genetic testing (NGS)	Novel heterozygous likely pathogenic <i>PLA2G6</i> variant

Date	Clinical/therapeutic event	Notes
		NM_003560.4:c.1805A>G (p.Tyr602Cys)
March 2024	Increased ropinirole dose Reduced levodopa (due to severe dyskinesias) and amantadine doses	LEDD – 1000 mg
March 2024	Anxiety and depression	Additional treatment with duloxetine 30 mg/day
April 2024	Onset of severe motor fluctuations	
September 2024	Generalised dyskinesias induced by levodopa 50 mg	
December 2024	Increased levodopa and ropinirole doses	LEDD – 1200 mg
December 2024	Evaluation for DBS surgery candidacy	Levodopa challenge – 76% improvement in motor signs
March 2025	Increased levodopa dose	LEDD – 1300-1400 mg
June 2025	Reduced ropinirole dose	LEDD – 1220-1320 mg
August 2025	STN DBS surgery	Right STN (C+, 9-), left STN (C+, 0-), 130 Hz, 60 μ s, 1.0 mA bilaterally
September 2025	Improvement of neurological symptoms Reduced levodopa dose	MDS-UPDRS part III score – 8 points LEDD – 920 mg
October 2025	Increased ropinirole and levodopa doses STN DBS stimulation adjustment – amplitude increased to 1.1 mA	LEDD – 1100 mg Right STN (C+, 9-), left STN (C+, 0-), 130 Hz, 60 μ s, 1.1 mA bilaterally
November 2025	Reduced ropinirole dose Increased levodopa dose STN DBS stimulation adjustment – amplitude increased to 1.3 mA	LEDD – 1140 mg Right STN (C+, 9-), left STN (C+, 0-), 130 Hz, 60 μ s, 1.3 mA bilaterally
October 2025- february 2026	Peak-dose ballistic dyskinesias recurred	
February 2026	Levodopa discontinued Treatment with long-acting pramipexole initiated STN DBS stimulation adjustment – amplitude increased to 1.7 mA	LEDD – 1028 mg Right STN (C+, 9-), left STN (C+, 0-), 130 Hz, 60 μ s, 1.7 mA bilaterally
February 2026	Improved neurological symptoms – reduction of dyskinesias, motor fluctuations and limb rigidity	MDS-UPDRS part III score – 7 points

LEDD: levodopa equivalent daily dose; MDS-UPDRS: Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale; SPECT: single-photon emission computed tomography; DaT: dopamine transporter; MRI: magnetic resonance imaging; SWI: susceptibility-weighted imaging; NGS: next-generation sequencing; DBS: deep brain stimulation; STN: subthalamic nucleus; Hz: hertz; μ s: microseconds; mA: milliamperes; mg: milligrams.

Table 3: Main clinical, neuroimaging and treatment-response features of the present case compared with published PLA2G6-related parkinsonism series.

Feature	Present case	Magrinelli et al., 2022 (n = 86) ²¹	Cheng et al., 2025 (n = 118) ²²
Age of onset	34	Median age – 23	Mean age – 24.53 ± 8.84
Levodopa responsiveness	Good initial	97.3%	91.59%
Early levodopa-induced dyskinesias	Yes (< 1 year of levodopa treatment onset)	80.7% (most cases – < 1 year of levodopa treatment onset)	81.71%
Cerebral atrophy	Absent	47.9%	33.33%
Cerebellar atrophy	Yes (follow-up brain MRI 3 years after symptom onset)	39.5%	54.12%
Iron accumulation	Absent	25.6%	26.61%
Cognitive impairment	Absent (MoCA 29/30 at 5 years of disease duration)	76.1%	70.65%

MRI: magnetic resonance imaging; MoCA: Montreal Cognitive Assessment; n: number of patients.

