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Abstract:	

ANDERSON-FABRY DISEASE: A RARE CAUSE OF LEVODOPA-RESPONSIVE EARLY ONSET PARKINSONISM

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Early onset parkinsonism is defined when onset of symptoms occurs before age 50. The differential diagnosis is broad, and it encompasses not only monogenic parkinsonism gene variants but also a few treatable causes[1].

Case Report

A 45-year-old woman came to our attention due to involuntary posturing of both her feet when walking. She had positive family history for ischemic heart disease (her father), chronic kidney disease leading twice to kidney transplant (one sister) and vascular dementia (one sister).

Examination in June 2011 showed steppage on the right lower limb when walking, “en griffe” posture of the toes of the right foot, mild slowness without decrement in the right hand (Video S1). On follow-up, one year later, she had clear right-side parkinsonism (Video S2). She reported constipation, pain localized distally to her hands and feet and worsening of pre-existing anxiety and depression. Early-onset parkinsonism was diagnosed, and she was started on pramipexole up to 1.5 mg/day.

Due to development of excessive sleepiness and minor visual hallucinations, pramipexole was discontinued after a few months and Levodopa (300 mg/daily) was initiated. Three years after onset, she started to complain of worsening of painful episodes in her feet which occurred at night. Over the disease course, she displayed good and sustained response to Levodopa, with development of non-motor fluctuations characterized by anxiety at 4-years follow-up. She did not develop significant dyskinesia. Neuropsychological testing administered at onset and last follow-up in 2019 did not disclose any cognitive abnormality.

Auditory, somatosensory and visual evoked potentials, nerve conduction studies and electromyography were normal. Urinalysis revealed microalbuminuria on repeated samples. All other laboratory investigations including copper and ceruloplasmin were

normal. An echocardiogram showed left ventricular hypertrophy. Single-photon emission computed tomography of the dopamine transporter (age 47) showed bilateral nigrostriatal degeneration (Figure, panel A). Brain magnetic resonance imaging (age 50) revealed a few inframillimetric white matter changes in the centrum semiovale. She tested negative for *parkin* and *glucocerebrosidase* gene variants.

Genetic analysis of the α-galactosidase A (*GLA*) gene detected a heterozygous likely pathogenic variant (c.337T>A) and confirmed the diagnosis of Anderson-Fabry disease (AFD). On family genetic screening, the same gene variant was found in five family members, two of whom were asymptomatic (Figure, panel B). The proband was started on enzyme replacement therapy with agalsidase alfa at age 51. At last videotaped follow-up, eighteen months later, she did not have significant progression or onset of additional neurological signs (Video S3).

Discussion

This is a case of levodopa responsive parkinsonism in a heterozygous female carrying a pathogenic AFD gene variant. AFD is a rare, X-linked lysosomal storage disease caused by absent or minimal enzymatic activity of α-galactosidase A. It classically affects males, in whom it has full penetrance[2]. The most frequent neurological features associated are small fibre neuropathy and early cerebrovascular events.

Parkinsonism is a very rare presentation of AFD, particularly in the absence of cerebral small vessel disease[3, 4]. Yet, slower gait and impaired fine manual dexterity as well as non-motor symptoms (pain, depression, excessive daytime sleepiness) have been reported in the absence of clear parkinsonism in heterozygous females and hemizygous males with pathogenic *GLA* variants[5]. This case of AFD expands the spectrum of lysosomal diseases associated with levodopa responsive parkinsonism[6]. It also highlights the need for careful assessment of family history and systemic

features in subjects with early onset parkinsonism and consideration of gene variants not classically associated with monogenic parkinsonism.

FIGURE.

Bilateral nigrostriatal degeneration on single-photon emission computed tomography of the dopamine transporter (panel A). Pedigree of the family (Panel B): Black symbols denote affected individuals carrying the c.337T>A GLA mutation; grey symbols denote asymptomatic carriers of c.337T>A *GLA* mutation. A thin horizontal line above symbols denotes clinically and genetically examined individuals. Dead members are marked with a diagonal bar. The arrow indicates the proband with levodopa-responsive parkinsonism (red symbol).

LEGEND TO VIDEOS

Video S1. June 2011 (age 45): the video shows steppage on the right foot when walking, reduced gait velocity with mildly reduced arm swing on the right side. Clear bradykinesia is absent.

Video S2. April 2012 (age 46): the video demonstrates gait impairment with dragging of the right lower limb, moderate bradykinesia in the right body side and rigidity.

Video S3. August 2019 (age 53): examination performed at 1 hour after 150 mg of levodopa shows sustained levodopa response on long term follow-up during treatment with agalsidase alfa.

ETHICAL COMPLIANCE STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. We also guarantee that patient have given her consent to anonymously report her clinical reports and videos in accordance with current ethical standards.

FUNDING SOURCES AND CONFLICTS OF INTEREST: This study did not receive any industry funding. The authors do not have any conflicts to report.

FULL FINANCIAL DISCLOSURE FOR THE PREVIOUS 12 MONTHS

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AUTHOR ROLES

1. Research project: A. Conception, B. Organization, C. Execution;
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript: A. Writing of the first draft, B. Review and Critique;

IC: 1C, 3A, 3B

CS: 1C, 3B

AT: 1C, 3B

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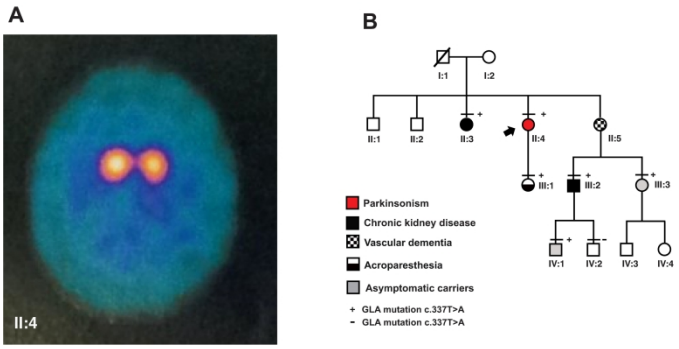

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387x198mm (300 x 300 DPI)

Video S1. June 2011 (age 45): the video shows steppage on the right foot when walking, reduced gait velocity with mildly reduced arm swing on the right side. Clear bradykinesia is absent.

227x180mm (144 x 144 DPI)

Video S2. April 2012 (age 46): the video demonstrates gait impairment with dragging of the right lower limb, moderate bradykinesia in the right body side and rigidity.

461x278mm (144 x 144 DPI)

Video S3. August 2019 (age 53): examination performed at 1 hour after 150 mg of levodopa shows sustained levodopa response on long term follow-up during treatment with agalsidase alfa.

501x276mm (144 x 144 DPI)