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LETTER TO THE EDITOR

Dancing Feet Dyskinesia in a Patient with *GBA*-PD

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Dear Editor,

Dancing-like dyskinesia has been reported as part of a phenotype associated with pathogenic variants in the *parkin* gene responsible for autosomal-recessive Parkinson's disease (PD).[1] *Parkin* variants cause early-onset PD (EOPD, < age 50), with slow disease progression, sensitivity to levodopa, and frequent dystonia.[1,2]

A higher prevalence of motor complications, including dyskinesia (especially peak-dose dyskinesia), and motor fluctuations was also reported in patients harboring variants in the glucocerebrosidase (*GBA*) gene, recently described as the largest genetic PD risk factor (however, caution is needed, as dyskinesia is not genotype specific, and reports regarding the prevalence in *GBA* variant carriers are conflicting).[3] While homozygous (with the exception of E326K/E326K)[3] and compound heterozygous variants in the *GBA* gene lead to a lysosomal storage disorder termed Gaucher's disease, recent studies implicate both homozygous and heterozygous variants in PD pathogenesis (20-30-fold increased PD risk compared to noncarriers).[3]

The phenotype of *GBA*-PD overlaps with that of *parkin*-PD (dyskinesia, dystonia); however, in contrast to *parkin*-PD, the disease is more severe, with frequent occurrence of dementia, hallucinations, autonomic symptoms, and postural instability.[3]

We report for the first time a case of "Irish" dancing-like, symmetrical lower limb dyskinesia in a patient with *GBA*-PD.

CASE

A 70-year-old Irish woman was diagnosed with EOPD at age 49 shortly after developing right-hand bradykinesia and rigidity. There was no family history of note. She commenced levodopa/carbidopa/entacapone 100/25/200 mg four times/day (QID) [levodopa equivalent daily dose (LEDD) 532]. At age 51 years, she developed symmetrical dancing-like lower limb dyskinesia. Dyskinesia was reported to occur within 30 minutes of levodopa administration, last for 30 minutes, and recur 30 minutes before the next dose, suggesting a diphasic nature; therefore, the therapy was changed to levodopa/carbidopa 100/25 mg, and the dose was increased to two tablets three times/day (TID) (LEDD 600), which resulted in a worsening of the dyskinesia. Over the years, different strategies were tried, including the addition of amantadine 100 mg TID without benefit (LEDD 832) (discontinued). At age 67, while on levodopa/carbidopa two tablets TID, she had to sit down during the episodes of dyskinesia, resulting in a tendency to fall off the sofa (Supplementary Video 1 in the online-only Data Supplement). She used a walker, as her balance was severely affected by dyskinesia. A benefit was seen after the individual doses were decreased and the frequency was increased, from 2 tablets TID to 1.5 tablets QID (LEDD 600). At age 68, to improve the continuity of the dopaminergic delivery, a rotigotine patch was tried; however, it was discontinued (nausea, con-

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fusion). Dyskinesia, right-foot dystonia, and severe freezing of gait contributed to balance and gait difficulties, resulting in falls/fractures. Subsequently, levodopa/carbidopa was decreased to 100/25 mg 1 tablet QID and 1.5 tablets once/day (LEDD 550 mg), with further improvement (able to use a cane, no falls, did not have to sit down during dyskinesia). She developed hallucinations at age 63 years (transiently resolved with quetiapine 25 mg) and dementia at age 69 years (Montreal Cognitive Assessment test score 14/30). Currently (age 72), she is a nursing-home resident on levodopa/carbidopa 100/25 mg 5 times/day and a slow-release formulation at bedtime (LEDD 575). On 500 mg during the day, the daytime dyskinesia resolved and occurred solely as an end-of-dose evening phenomenon.

On examination (age 70, LEDD 550 mg, 1-hour post levodopa), there was slight neck rigidity, bradykinesia in both the upper (mild) and lower limbs (slight), severe retropulsion and dystonic posturing of both feet. There was no tremor or upper limb dyskinesia; however, dancing-like lower limb dyskinesia was present bilaterally (Supplementary Video 2 in the online-only Data Supplement). The MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS)-I score was 9, II:31, III:24, and IV:3. The Hoehn and Yahr (H&Y) scale score was 3.

Genetic testing for *parkin*, *PINK1*, and *DJ1* variants (full Sanger sequencing, multiplex ligation-dependent probe amplification analysis) was negative. Further testing revealed a missense homozygous *GBA* exon 8 variant p.Glu365Lys (c.1093 G>A, E326K/E326K) (Figure 1).

DISCUSSION

While *parkin* gene pathogenic variants are associated with symmetrical dopaminergic neuronal loss (pigmented neuronal loss, bilateral gliosis in the ventrolateral substantia nigra and more symmetric dopaminergic striatal innervation loss with a slower progression rate on dopamine transporter single-photon emission computerized tomography scan),[1,4] the deficit in *GBA*-PD is more asymmetrical, similar to that seen in IPD/*LRRK2*-PD.[4] The dancing feet phenomenon in *parkin*-PD was described in 2012 by Chang et al., who hypothesized that the symmetrical loss of neurons in *parkin*-PD could be responsible for the symmetrical pattern of lower limb dyskinesia.[1] The presence of this phenomenon in a *GBA* carrier may indicate a different yet unknown mechanism. Interestingly, E326K/E326K variants do not cause Gaucher's disease and are rarely reported in a homozygote state.[2]

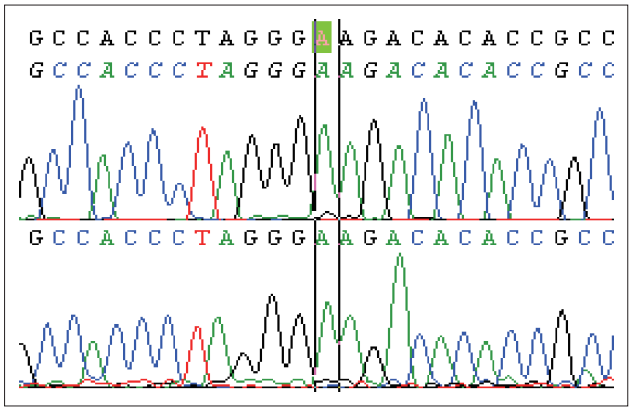

Figure 1. Sequencing chromatogram: a missense homozygous variant p.Glu365Lys (c.1093 G>A, E326K/E326K) in exon 8 of the glucocerebrosidase (*GBA*) gene (in between the black lines).

While lower limb dyskinesia is not specific to any particular type of dyskinesia, it occurs more frequently in diphasic dyskinesia. Diphasic dyskinesia usually appears within 30 minutes of levodopa administration and then subsides and recurs within an hour of the next dose (in keeping with the early description in our patient).[5,6] Different strategies were attempted to address dyskinesia in our patient, including a levodopa dose increase (reported to improve diphasic dyskinesia), which failed to benefit.[5,6] The initial change from levodopa/carbidopa/COMTI to levodopa/carbidopa alone resulted in a slight improvement. The greatest benefit occurred with a decrease in the individual dose and an increase in the frequency (more in keeping with a peak dose dyskinesia).[5,6] Based on the patient's observation (age 70), we concluded that there was peak dose dyskinesia at that point; however, diphasic dyskinesia may be mistaken for peak dose dyskinesia, especially at the lowest dose, when diphasic dyskinesia becomes dominant between levodopa doses.[6] This conundrum could be solved by apomorphine use or deep brain stimulation surgery; however, our patient was not suitable for these treatments at the later stage of her disease (dementia, hallucinations, dopamine agonist intolerance).[6,7]

With phenotypic overlap, reliable clinical genotype-phenotype correlations in PD are currently not possible. Dyskinesia occurs more frequently in EOPD, regardless of the genotype; however, the combination of an early age-at-onset, excellent response to low levodopa doses and early motor fluctuation development may aid the decision to proceed with genetic testing.

Our new observation emphasizes that the dancing feet phenomenon early in the course of EOPD may indicate the diagnosis of not only *parkin*-PD but also *GBA*-PD when the progression is faster and cognitive symptoms are present. Such patients should be considered for *GBA* testing, which is not included in the EOPD panel. The inclusion of *GBA* testing in the EOPD genetic test panel should be considered.

Ethics Statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Research Committee (Mater Misericordiae University Hospital, Dublin, Ireland, ethical ap-

proval number 1/378/1300) and with the 1975 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from the patient included in the study.

Supplementary Video Legends

Video 1. Patient's own video, demonstrating mask facies violent dancing-like lower limb dyskinesia (at age 67).

Video 2. Video of the patient at age 70, demonstrating mask facies dancing-like lower limb dyskinesia (interrupting the assessment of the lower limbs), bilateral foot dystonia, mild bilateral bradykinesia in the upper limbs and slight bradykinesia in the lower limbs.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.20169.

Conflicts of Interest

The authors have no financial conflicts of interest.

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Author Contributions

Conceptualization: Diana A. Olszewska, Owen A. Ross, Tim Lynch. Data curation: all authors. Formal analysis: all authors. Investigation: all authors. Methodology: all authors. Project administration: all authors. Resources: all authors. Software: Diana A. Olszewska, Alexandra I. Soto-Beasley, Ronald L. Walton Supervision: Owen A. Ross, Tim Lynch. Validation: Diana A. Olszewska, Alexandra I. Soto-Beasley, Ronald L. Walton. Visualization: Diana A. Olszewska. Writing—original draft: Diana A. Olszewska. Writing—review & editing: all authors.

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