Movement Disorders
CLINICAL PRACTICE

CASE REPORT

Progressive Supranuclear Palsy–Like Phenotype in a *GBA* E326K Mutation Carrier

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Mutations in the beta-glucocerebrosidase gene (*GBA* OMIM *606463), encoding the lysosomal enzyme that is deficient in Gaucher's disease (GD), are important and common risk factors for Parkinson's disease (PD) and Lewy body dementia (LBD; i.e., α-synucleinopathies).[1] PD patients with GBA mutations have younger age at onset and are more likely to develop cognitive dysfunction.[2] There are approximately 300 known GBA mutations and determining accurate exact genotype-phenotype correlations is challenging. In general, GBA mutations were found to variably influence PD risk according to their impact on the protein function. For instance, the "severe" mutations L444P bears the highest risk of developing PD (OR:10–21), whereas the risk is much lower for the "mild" mutation N370S.[3] The GBA variant, E326K, has long been considered a polymorphism, given that homozygous individuals do not develop GD.[4] However, this variant was found to reduce GBA enzymatic activity *in vitro* and mildly increase the risk to develop PD (OR:1.7), with frequent development of associated dementia.[3,5]

The impact of GBA mutations on the risk to develop tauopathies is less defined, given that previous studies failed to report a significant association with PSP and corticobasal degeneration.[6] Yet, more recent data suggest that the clinical phenotype of GBA-associated neurodegeneration is more heterogeneous than previously assumed, including phenotypes distinct from α-synucleinopathies.[7]

Herein, we report on a patient with an unusual phenotype characterized by supranuclear vertical gaze palsy at onset with late emergence of postural instability carrier of the GBA E326K variant.

Case Report

A 51-year-old man was referred to our clinic for a subjective feeling of dizziness and depression for the past 3 years. He specifically complained of difficulties in driving and going down the stairs, but he denied any falls. Familial history was negative for neurological disorders. On examination, he presented with supranuclear vertical gaze palsy and staring gaze as well as slow and hypometric horizontal saccades with increased latency. Neither overt parkinsonism nor cerebellar signs nor postural instability were detected (see Video 1, Segment 1). When PD nonmotor symptoms were investigated, he reported depression and mild apathy, but denied any hallucinations. He did not report constipation nor hyposmia nor vivid dreams/acting out during sleeping (both suggestive of rapid eye movement sleep behavior disorder [RBD]). At that time, a descriptive clinical diagnosis of supranuclear vertical gaze palsy was made. A trial with rasagiline and levodopa (800 mg/day) was attempted with no response. Brain MRI was unremarkable (Fig. 1A). Neuropsychological examination showed a Mini–Mental State Examination (MMSE) score of 29/30 with mild impairment in immediate and delayed recall verbal memory, whereas frontal, visuospatial, and constructive functions were within the normal range, although in the lower side. Cognitive evaluation was repeated 1 year later, showing an MMSE score of 27/30 along with overt executive and visuospatial deficit and severe apathy.

Last assessment was performed at the age of 54 years, after 6 years from onset (see Video 1, Segment 2). He complained of dysphagia and frequent falls. At this stage, the patient presented a PSP-like phenotype. Brain MRI was repeated and showed mild frontal lobe and midbrain atrophy (Fig. 1B).

Because he reported a long-standing history of nonalcoholic, nonviral liver enlargement and steatosis, although without splenomegaly, adult forms of Niemann-Pick type C disease (NPC) or GD were suspected in the first place. Because Filipin staining of skin biopsy showed inconclusive results as regards the diagnosis of NPC, conventional sequencing of coding regions and

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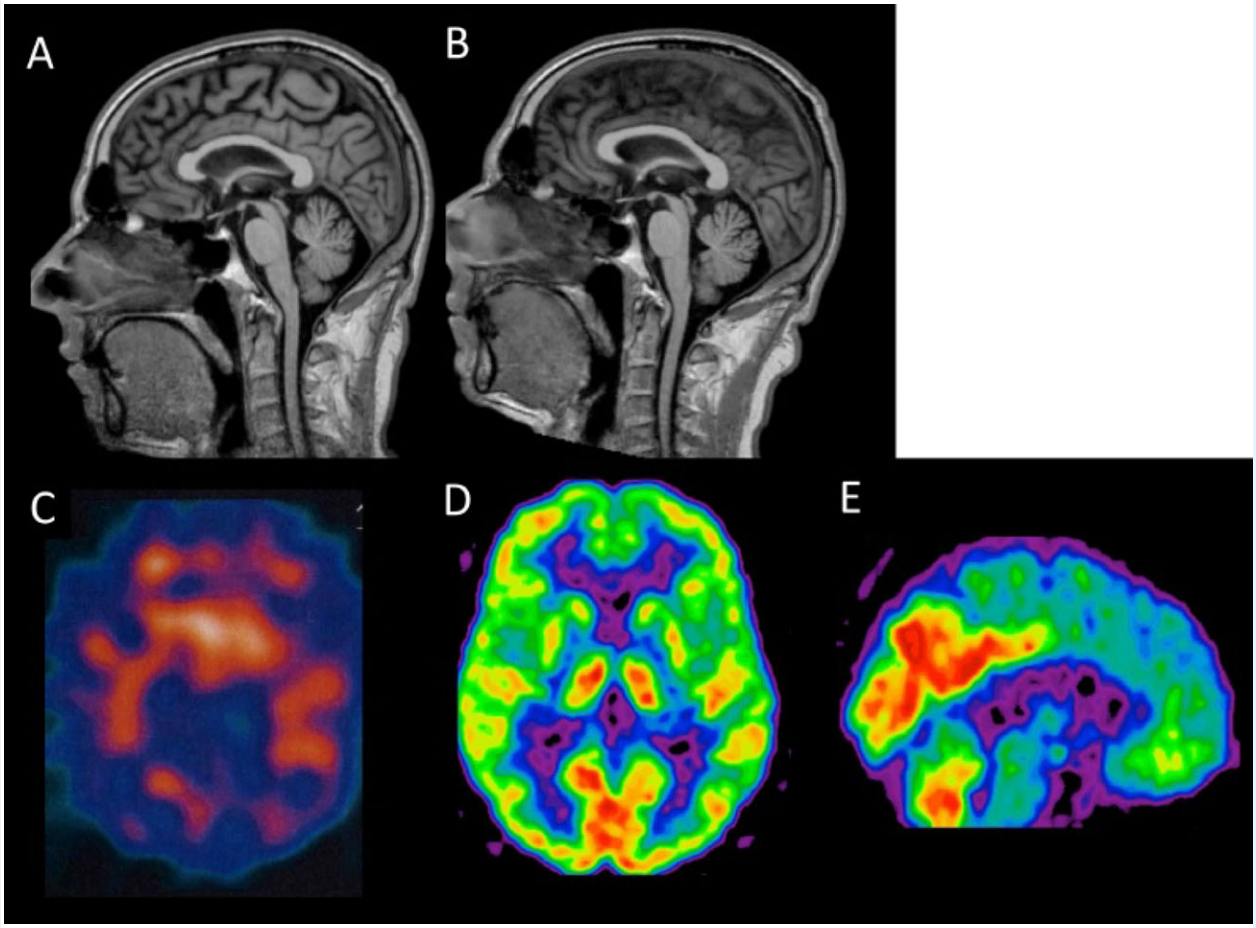

Figure 1 First brain MRI showing unremarkable findings (A) and second brain MRI after 2.5 years showing mild midbrain atrophy (B). I-123 FP-CIT SPECT DaTscan (C) showing severe nigrostriatal deficit. Axial (D) and sagittal (E) ^{18}FDG-PET images showing relative hypometabolism in the frontal cortex, anterior cingulate, and, to a lesser extent, in the striatum.

exon-intron boundaries of both *NPC1* and *NPC2* genes was performed, failing to identify pathogenic mutations. Subsequent sequencing of the whole coding sequence of the GBA gene disclosed only the E326K variant in a heterozygous state. A single-photon emission computed tomography (SPECT) DaTscan showed severe bilateral uptake reduction in both putamen and caudate (Fig. 1C), whereas 18F-fluorodeoxyglucose ([^{18}F]FDG)-PET (Fig. 1D,E) revealed a pattern of metabolic alterations similar to that reported in PSP patients.[8]

All known genes associated to PSP-like phenotypes or atypical parkinsonism with supranuclear gaze palsy were investigated. Pathogenic GGGGCC repeat expansions in the *C9orf72* gene (>60 repetitions) were excluded by fluorescent fragment-length polymerase chain reaction analysis. Haloplex-based targeted sequencing (on a MiSeq Illumina platform; Illumina, San Diego, CA) was adopted to simultaneously investigate mutations in the *LRRK2*, *ATP13A2*, *FBXO7*, *MAPT*, *POLG1*, and *C10orf2* genes, as well as in several other genes causative of other parkinsonian syndromes (*C19orf12*, *COASY*, *DJ-1*, *DNAJC6*, *EIF4G1FA2H*, *PANK2*, *PARK2*, *PINK1*, *PLA2G6*, *SNCA*, *SYNJ1*, *VPS35*, and *WDR45*). Moreover, quantitative copy number analysis by Multiplex Ligation–dependent Probe Amplification (SALSA MLPA Kit P051 Parkinson; MRC-Holland BV, Amsterdam, the Netherlands) was used to search for exon deletions or multiplications in PD-related genes. All these studies yielded negative results.

Besides its mild effect on the risk to develop PD, the E326K variant was also detected in patients with other α-synucleinopathies such as PD dementia, LBD, and MSA, and, more rarely, in patients with other movement disorders, such as essential tremor and Machado Joseph disease with parkinsonian phenotype and mutation in spinocerebellar ataxia type 3.[9,10] However, this variant was found with similar frequency in healthy control groups, questioning its effective contribution in determining these phenotypes.

To date, *GBA* mutations have been reported only in 3 of 257 PSP patients, but none of them carried the E326K variant. However, because GBA screening was limited to searching the

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two common mutations, N370S and L444P, in one study, and to sequencing exons 9 and 10 in the other one, the occurrence of other GBA mutations, including E326K, in PSP patients cannot be ruled out at present.[6,7] Although the clinical features, the lack of typical PD nonmotor symptoms (i.e., constipation, hyposmia, and RBD), and the absence of response to L-dopa, prompted us to speculate a tauopathy as the underlying pathology, we cannot exclude that our patient might have a synucleinopathy alone or in addition to tauopathy.[11]

The E326K has been reported as a polymorphic variant, with a global frequency in the European population of around 1% according to public databases (e.g., ExAC, EVS). In line with these figures, we detected 1 E326K carrier among a cohort of 103 Italian healthy controls. Because of these observations, along with the lack of data on the frequency of E326K in PSP patients, we cannot confidently exclude that our finding is an incidental discovery. On the other hand, the early impairment in horizontal eye movements might support the pathogenic role of the E326K variant, given that increased latency of horizontal saccades has been described in type 3 GD.[12]

Further comprehensive screenings of the GBA gene in larger cohorts of PSP-like patients are needed to better assess the potential impact of this gene in determining PSP-like phenotype.

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.

M.P.: 1A, 1B, 1C, 3 A
S.P.: 1C, 3 A, 3B
E.M.V.: 3B
S.B.: 1C, 3B
F.S.: 1C, 3B
M.G.: 1C, 2B
P.B.: 1A, 3B
M.T.P.: 1A, 3B

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Supporting Information

A video accompanying this article is available in the supporting information here.

Video 1. Segment 1: Gait characterized by hesitation during turning with normal tandem. Mild reduced arm swing. Pull test negative. Slight dysarthria. Staring gaze with frontalis muscle overactivity. Impaired finger tapping (left > right). Slowing of the saccades and limitation of the vertical gaze during both saccades and smooth pursuit of a target. The gaze limitation can be overcome by eliciting the vestibulo-ocular reflex. Extreme slowing of saccades resembling smooth pursuit may be observed on the horizontal plane as well. Segment 2: Severe gait impairment with need of assistance. Pull test positive. Severe dysarthria and marked staring gaze. Impaired finger tapping (left > right). Severe limitation of the eye movements with absence of saccades and extreme slowness of smooth pursuit, which are present only on the horizontal plane. Still, the gaze limitation can be overcome by the vestibulo-ocular reflex.

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