CASE REPORT

Autopsy-Proven “Pure” Parkinson’s Disease with Rapidly Progressive Dementia and Cognitive Fluctuations in a Patient with GBA Mutation

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ABSTRACT

BACKGROUND: Parkinson’s disease (PD) progresses at highly variable rates in different individuals but, in general, has a fairly stable rate of progression in each patient. In cases where the decline in cognition and behavior suddenly accelerates, we usually think of co-existent Alzheimer pathology, as most demented PD patients also have Alzheimer disease (AD) changes, although not necessarily meeting criteria for a distinct pathological diagnosis of AD.

METHODS: Clinico-pathological case

RESULTS: A 75-year-old woman presented with a typical PD course including a good response to L-Dopa. Four years after diagnosis she developed a rapid decline in motor symptoms, severe cognitive fluctuations, and rapidly progressive dementia, dying within one year of the onset of the rapid progression.

CONCLUSIONS: While most cases of Parkinson’s disease dementia (PDD) show concomitant Alzheimer’s pathology, the sudden acceleration of the disease does not necessarily indicate the presence of concomitant Alzheimer’s disease.

KEYWORDS: Parkinson’s Disease, Rapidly Progressive Dementia, GBA Mutation, Cognitive Fluctuation

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A 75-year-old woman was first seen in our movement disorders clinic in April 2021, having been diagnosed with PD in 2018 with a positive response to L-Dopa. The patient first noticed resting tremors and a change in her walking in 2017. She denied hallucinations or symptoms of REM sleep-behavior disorder. Her past medical history was significant for type 2 diabetes, hypothyroidism, renal calculi, gout, left knee replacement, and insomnia. Her mother had been diagnosed with late onset PD. The patient’s fraternal twin brother had amyotrophic lateral sclerosis (ALS).

She was fully oriented, with normal speech and affect, but struggled with the Luria 3 step task and spelled “earth” backwards as “HRAE”. Cranial nerves and muscle strength were normal. Deep tendon reflexes were normal. She had a 1+ rest tremor in the right hand, and a 3+ rest tremor in the left but no action or postural tremor. Left-sided rigidity and bradykinesia were noted. The patient had a 2+ stooped posture, walked unassisted, with a normal base but was slow, with a reduced stride length and no arm-swing, requiring eight steps to turn.

The clinical diagnosis of PD was confirmed. Carbidopa/Levodopa was increased and pramipexole added. No improvement was observed. Within several months, she experienced a significant and relatively sudden decline in her mobility, a new problem of multiple falls, worsening bradykinesia, cognitive decline, and confusion. Her medications were increased to: Carbidopa/Levodopa 25/100 mg 2 tablets four times daily and Pramipexol 0.75 mg three times daily, but the increased dose was not helpful so that pramipexol was reduced to 0.25 mg TID.

Ten months later, she developed new episodes of behavioral change, lasting 30–60 minutes, which increased in frequency and duration over the next several months. During a typical behavioral alteration, she was confused, slow to respond, dysarthric, and unable to move as at her baseline. She made a full recovery after each episode. She also developed frequent episodes during which she adopted peculiar postures, like being slumped over, or jerking, [not witnessed by us]. She had been seen at night standing alone, with purposeless movements of her fingers or hands. As part of her work-up, she underwent electroencephalography (EEG) which showed rhythmic theta runs, evolving into 3–4 Hz sharp waves without any clinical change, concerning for electrographic seizures arising from the bilateral temporo-occipital regions. MRI showed scattered white matter T2 and FLAIR hyperintensities, and mild to moderate diffuse cerebral atrophy. Levetiracetam 250 mg bid was started. During the next month, anxiety and restlessness developed with a marked decline in language. A basic work-up including complete blood count and comprehensive metabolic panel for rapidly progressive dementia was unremarkable. Genetic studies revealed a single gene GBA pathogenic variant (c.1448T>C p.Leu483Pro). Her EEG was repeated, and the initial EEG was re-interpreted as muscle artefact rather than epileptiform activity so that her levetiracetam was discontinued.

Two months later, on her last visit, while receiving hospice care, the patient was taking Carbidopa/Levodopa 25/100 2 QID, lorazepam 0.5 mg q6h, and morphine 7.5 mg q6h. She was mute, unable to control her urine, severely akinetic and
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+ rigid in all joints. She never smiled. She turned to the sound of her name and followed the examiner’s moving face. Carbidopa/Levodopa was tapered, and an LP was declined. The patient passed away three months later.

**PATHOLOGICAL FINDING**

Microscopic examination of her brain (which weighed 1148 g) revealed findings consistent with Parkinson’s disease Braak stage 5/6. Lewy bodies were identified in the dorsal motor nucleus of the Vagus nerve, locus coeruleus, substantia nigra, and olfactory bulb [Figure 1]. Occasional Lewy bodies were also detected within the cingulate cortex [Figure 2], medial temporal cortex, and posterior frontal cortex. No diagnostic features of Alzheimer’s disease were present on light microscopy or following application of immunohistochemical stains. [Figure 3]. Diffuse mild to moderate arteriosclerosis was also noted.

**DISCUSSION**

In this report, the patient presented with typical signs and symptoms of PD, which progressed at a typical rate for four years, at which point there was a sudden acceleration of the disease punctuated by episodes of greater confusion, slowness, and non-purposeful behaviors. The patient’s condition rapidly deteriorated, with progressive dementia and death within 15 months of the onset of deterioration.

PD can lead to cognitive impairment, with up to 50% of individuals developing mild cognitive impairment within six years of PD onset and over 80% of patients developing dementia within 20 years.1 Risk factors for Parkinson’s disease dementia (PDD) include advanced age, older age of disease onset, limited cognitive reserve, hallucinations, and predominant gait dysfunction.2 In general, Rapidly progressive dementia (RPD) refers to conditions in which the interval from first symptom to dementia onset is measured in weeks or months, with the majority of patients with RPD progressing from independence to complete [or near-complete] dependence within one to two years.3 During the initial evaluation at our clinic, our patient exhibited minor difficulty in cognition which progressed in an average fashion. Then, her cognition rapidly declined.

PDD shares the same clinical profile as Dementia with Lewy Bodies (DLB), being distinguished from DLB if the motor symptoms precede the dementia by 12 months or

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**Figure 1.** Photomicrograph of substantia nigra at 40x magnification demonstrating intracytoplasmic inclusions (arrows) positive by alpha-synuclein immunostaining consistent with Lewy bodies.

**Figure 2.** Photomicrograph of right anterior cingulate cortex at 40x magnification demonstrating intracytoplasmic inclusions (arrows) positive by alpha-synuclein immunostaining consistent with Lewy bodies.

**Figure 3.** Photomicrograph of right hippocampus at 4x magnification demonstrating a lack of diagnostic features of Alzheimer’s disease by beta-amyloid immunostaining.
more.⁴ DLB is clinically defined by the presence of dementia together with its core clinical features: fluctuating cognition, well-formed recurrent visual hallucinations, rapid eye movement (REM) behavioral sleep disorders, and parkinsonism.⁵ Both PDD and DLB share the same pathology, characterized by the presence of neuronal inclusions of α-synuclein aggregates, often coupled with a varying degree of concomitant Alzheimer pathology.⁶ In both DLB and PDD, the coexistence of tau pathology with Aβ and α-synuclein contribute to the development of dementia. In general, tau aggregates in PD correlate with the severity of cognitive impairment. Autopsy studies have consistently revealed the presence of tau aggregates in the majority of both PDD and DBL, particularly in the later stages of the diseases. Notably, DBL has shown a higher burden of tau pathology compared to PDD tissue in general.⁷ This patient exhibited no concomitant Alzheimer pathology, so sudden acceleration of the disease does not reflect the effects of Alzheimer’s disease.

Fluctuating cognitive abilities with disturbances in cognition, attention, and arousal are frequently seen in dementia syndromes, including Alzheimer’s disease and vascular dementia, but are most characteristic of Lewy body dementias, including DBL and PDD. Studies have reported that approximately 29–90% of patients with Parkinson’s disease demonstrate cognitive fluctuations. These fluctuations can range from reduced responsiveness, disturbances in arousal such as drowsiness and hypersomnolence, to global and dramatic changes in function affecting speech, memory, or behavior. Some patients may experience episodes of staring spells that resemble absence seizures. Fluctuations may occur in short episodes lasting seconds, minutes, hours, or in longer periods over days or weeks.⁸ Our patient had fluctuating confusion, slowness, and speech disturbance.

Some genetic causes or risk factors for PD, such as α-synuclein duplication and triplications, GBA, and MAPT mutations have been linked to cognitive deficits and dementia. While only 5–15% of PD patients have GBA mutations, it is the most common genetic risk factor for the disease. Pathogenic GBA mutations lead to a decreased activity in the lysosomal enzyme glucocerebrosidase (GCase), which impairs alpha-synuclein metabolism and contributes to Lewy body formation. Individuals with GBA mutations may have a more diffuse pattern of Lewy body distribution throughout the brain compared to non-carriers.⁹

Clinically, GBA-associated PD is identical to sporadic PD, except for an earlier age of onset, an earlier and higher frequency of cognitive impairment, and a more rapid progression. The risk of dementia in PD patients with GBA mutations is increased sixfold in carriers compared to non-carriers.¹⁰ Furthermore, GBA-associated PD patients have been found to have reduced survival compared to those without the mutation.¹⁰

Our patient’s rapid cognitive decline and disease progression cannot with confidence be attributed to the GBA mutation. The onset of her PD was older than typical for GBA, and the GBA mutation is not known to cause a suddenly accelerated course. These observations suggest the likelihood that other genetic or environmental factors modified the expression of GBA-related neurodegeneration.

Two studies suggested a potential association between GBA mutations and Lewy body disorders characterized by a “purer” Lewy body pathology, with fewer concurrent Alzheimer’s pathological features. This finding corresponds to what we observed in our patient as well.¹¹,¹²

Given the family history of ALS in our patient’s twin brother, neurodegeneration in PD and ALS raises the question of shared mechanisms. A complex overlap between parkinsonian and motor neuron syndromes has long been recognized with parkinsonism and ALS co-occurring within families, as well as in individual patients, suggesting a possible genetic basis.¹³

References

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