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Clinical Features, with Video Documentation, of the original Familial Lewy Body Parkinsonism caused by α -Synuclein Triplication (Iowa Kindred)

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We previously reported triplication of α -synuclein in a large kindred with autosomal dominant parkinsonism¹⁻⁵. Here we share videotapes of selected cases (see abbreviated pedigree, figure 1A).

Case 9-77 (Video Segment 1)

This woman noted insidious, progressive, right upper extremity (RUE) resting and activation tremor and stiffness at age 30. She noted parasomnias suggesting REM Behavior Disorder (RBD) and depression several years prior to motor symptoms. Handwriting became small and tremulous. She also experienced urinary urgency. Examination (age 32) revealed RUE

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Michael J. Devine: Reviewed and edited videos and drafted and submitted manuscript.

Lee-Way Jin: Carried out pathological diagnosis of case 9-70.

Janel Johnson: Helped in family collection and mutation analysis.

Thomas Bird: Carried out clinical investigations on case 9-70 and other family members.

Henry Houlden: Clinical evaluation and fibroblast sampling of case 9-60.

Manfred Muentert: Evaluated cases 9-58,9-60, 9-70, 9-77. Built pedigree. Clinical and video documentation.

Grisel Lopez: Clinical evaluation of case 9-60 and IRB documentation.

Cheryl Waters: Evaluated case 9-246. Clinical and video documentation.

Charles H. Adler: Evaluated cases 9-70, 9-77. Clinical and video documentation.

Richard Caselli: Evaluated cases 9-70, 9-77. Neuropsychometric testing interpretation.

Amanda Singleton: Research coordinator of clinical and video evaluation.

John Hardy: Obtained funding and drafted manuscript.

Andrew Singleton: Supervised mutation analysis.

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resting and activation tremor, and cogwheel rigidity. She was diagnosed with Parkinson's disease (PD) and treated with carbidopa/levodopa with good response, although dyskinesias occurred within three years. Subsequently, ropinirole gave some benefit (Video Segment 1). Neuropsychometry (age 32) found no abnormalities. However, by age 41, there was significant reduction in IQ, working memory, executive functioning, visuospatial processing, and psychomotor speed. Donepezil was prescribed with some cognitive improvement. She was bedridden in twelve years. She suffered auditory and visual hallucinations, parasomnias, restless legs symptoms, and, intermittent myoclonus. On her last examination (49 years), she exhibited severe bradykinesia and rigidity with contractures. Hypophonia limited mental status testing, however audible speech content was appropriate. Eye movements remained full but pursuits were severely saccadic. There was no tremor. Myoclonus was intermittent. She expired due to pneumonia at age 49; no post-mortem examination was done.

Case 9-60 (Video Segment 2)

This otherwise healthy woman with a history of methamphetamine abuse during her third and fourth decades was first aged 44 for physical and mental "slowness". She was treated for depression, with some benefit, but the motor problems persisted. Within 18 months, she noted activation tremor and symptoms of RBD. By age 46 her cognition and movement would fluctuate over hours/days. Her weight decreased from 130 to 100 pounds over the first two years of her illness. She had spontaneous visual and auditory hallucinations, and complained of orthostatic dizziness. Carbidopa/levodopa gave moderate benefit in bradykinesia; donepezil improved cognitive fluctuations; clonazepam helped the RBD; and midodrine ameliorated orthostatic hypotension. Nonetheless, confusion mandated 24-hour care. On examination, sitting blood pressure (BP) was 98/67, and pulse (P) 81; standing BP 86/60, P 90. Folstein Mini-mental status examination score was 13/30, with particular difficulty on recall and sequential tasks. She scored 14 on the controlled oral word association test and 16/63 on the Beck Depression inventory. She had marked constructional difficulties (Figure 1B). She could not count backwards from 100, 20, or 12. She had anosmia (14/40, University of Pennsylvania Smell Identification Test). There was marked hypophonia, saccadic pursuits, and moderately masked facies. She had difficulty with rapid alternating movements. Gait was shuffling. She needed several corrective steps on the pull test. In the decade following presentation, she has become bedridden and is severely rigid and is tube-fed. She has no spontaneous vocalizations. She is doubly incontinent and requires full-time care.

Case 9-70 (Video Segment 3)

This man noted the gradual onset of RUE resting and activation tremor at age 24. Tremor was worsened by anxiety, and by intravenous cocaine, which he used prior to and during the first year of illness. Within that year, he suffered depression and attempted suicide; by age 34 he was treated with fluoxetine, with good response. Parkinsonian symptoms progressed with worsening tremor, rigidity, gait difficulties, and postural instability. Carbidopa/levodopa gave dramatic benefit, but was discontinued several years later due to orthostatic hypotension and hallucinosis. At his last examination, aged 39, (Video Segment 3), he had severe bradykinesia and hypophonia; mental status testing was not possible. Eye movements were severely saccadic; there was severe rigidity throughout and no tremor. He could stand and walk with marked slowness and severe postural instability, with one-person assistance. The patient was bedridden within the year, requiring tube feeding. The subject succumbed to pneumonia at age 43. Pathological examination was previously described⁷.

Case 9-246 (Video Segment 4)

The subject was diagnosed with Parkinson's disease when 46 y.o. with complaints of slowed gait and right shoulder pain.³ She responded well to carbidopa/levodopa treatment initially. Subsequently motor fluctuations and postural instability developed. She developed "toe walking", cognitive impairment, and orthostatic hypotension, and thereafter became wheelchair and subsequently bed-bound. She succumbed after 6 years. Pathological examination has been previously described³.

Summary

This family has autosomal dominant parkinsonism due to α -synuclein triplication. Dopamine-responsive parkinsonism, cognitive difficulties, RBD, and dysautonomia are common. End-stage illness includes contractures, myoclonus, and severe motor and cognitive impairment. Of note, there was pre-symptomatic amphetamine/cocaine use in two of the cases described.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Consultancies	None	None	None	None	None	None	Teva Pharmaceuticals	Biogen Idec, Eli Lilly, Ipsen, Merz, MerckSerono	None	None	None	None	Eli Lilly and MerckSerono Pharmaceuticals	None
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Figure 1A.
Abridged pedigree. Affected individuals are shown in solid black.

Figure 1B.
Progressive worsening of case 9-60's constructional apraxia over a three year period.