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Early-onset pathologically-proven multiple system atrophy with *LRRK2* G2019S mutation

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CONFLICT OF INTERESTS

E.C. has no conflict of interest.

M.I. has no conflict of interest.

T.S. has no conflict of interest.

B.H. has no conflict of interest.

R.H.W. has no conflict of interest.

S.F.: has no conflict of interest.

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.

AUTHORS' ROLES

G.M.R.: data collection, analysis, conception, design, drafting the article and editing the manuscript for important intellectual content.

J.A.P.: data collection, analysis, conception, design, drafting the article and editing the manuscript for important intellectual content.

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Keywords

α -synuclein; Glial cytoplasmic inclusions; LRRK2; Multiple system atrophy; Synucleinopathies

Although considered a sporadic synucleinopathy, genetic variants associated with increased risk of multiple system atrophy (MSA) are being increasingly reported.^{1–3} Here we describe the first neuropathology-confirmed case of MSA with the G2019S-*LRRK2* mutation, thus expanding the phenotypic spectrum of *LRRK2*-associated synucleinopathies.

A Caucasian male with noncontributory family history was reported to act out and scream in his dreams at 31 years of age. At age 35, he noticed increased urinary frequency, with incontinence at age 37. At age 38 he developed left-sided resting tremor, rigidity, bradykinesia, mild dysphagia, constipation, and erectile dysfunction. He was diagnosed with probable MSA-P at age 40. He had a good levodopa response (600 mg/day), although he soon developed fluctuations and dyskinesia. Deficits progressed over the course of ~10 years during which he developed worsening dysarthria, hypophonia, and diplophonia. Autonomic testing at age 41 showed normal cardiovascular reflexes with no neurogenic orthostatic hypotension. Annual autonomic evaluations confirmed no cardiovascular involvement. Brain MRI at age 45 showed cerebellar and midbrain volume loss, as did subsequent MRIs performed at age 46 and 47. Eye movements showed rare square-wave and macro square-wave jerks. Cognitive function and olfaction remained normal. He required urinary intermittent catheterization and a walker at age 45. Levodopa response was still present with higher dosages (1,400 mg/day) with marked dyskinesia. Dysphagia worsened and he was hospitalized twice for aspiration pneumonia. A percutaneous gastrostomy was placed at age 47. He became wheelchair-bound at age 47 and died at age 49 during his sleep.

Brain macroscopic evaluation showed severe atrophy of putamen, medulla, and cerebellum, with white matter compartmentalization loss in pons, inferior olivary nucleus and cerebellum. Microscopic evaluation showed extensive α -synuclein-positive glial cytoplasmic inclusions (GCI) in multiple areas, diagnostic of MSA (Figure). A targeted genetic screen for common *GBA* and *LRRK2* pathogenic mutations associated with Parkinson disease (PD) performed on peripheral blood revealed a heterozygous *LRRK2* G2019S (p.Gly2019Ser) mutation, confirmed with Sanger sequencing using DNA extracted from the frontal cortex.

The G2019S-*LRRK2* mutation accounts for 1% of sporadic and 4% of familial PD, and, until now, an association with MSA had not been reported.⁴ Genetic screening of the *LRRK2*-G2019S mutation in ~700 cases failed to demonstrate an association with MSA^{5–8} (Supplementary Table) although *LRRK2* variants other than the G2019S have been reported in association with MSA.^{5–11} Compared to patients with non-*LRRK2* PD, patients with PD carrying the G2019S-*LRRK2* mutation have milder motor involvement, good response to levodopa, more preserved olfaction, normal cognition, and less prominent dysautonomia.¹² In this regard, our case had features that were unusual for MSA. He had asymmetric parkinsonism, sustained response to levodopa with levodopa-induced dyskinesia; and no neurogenic orthostatic hypotension. The onset was very early, with REM behavior disorder at age 31, genitourinary involvement at age 35, and parkinsonism at age 38, yet the duration of disease was relatively prolonged. We hypothesize that the G2019S variant contributed to

these unusual features. Conversely, because the G2019S variant has low penetrance,¹³ the mutation might be an incidental finding unrelated to the phenotype. Additional descriptions of this variant in other pathologically-proven MSA cases should clarify the impact of this mutation in the phenotype.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Microscopic examination showing cell loss and α -synuclein positive inclusions.

α -synuclein deposits in neuronal cytoplasm and nuclei (neuronal cytoplasmic inclusions (NCI) and neuronal nuclear inclusion (NNI), respectively) were widespread in the substantia nigra (SN), pons, and medulla, with uneven density. The distribution of GCI was frequently found in a gradient pattern. The brunt of the neuronal loss is in the SN pars compacta (SNpc) and reticular formation of the medulla oblongata (MO). There is severe demyelination of the middle cerebellar peduncle, hilus, olivocerebellar fibers, cerebellum, spinal cord, and dorsal root ganglia (DRG). **a-b.** Pre- and posterior frontal subcortical areas. **c.** Caudate nucleus, body. **d.** Putamen, dorsal third. **e.** Globus pallidus, external segment, dorsal third. More abundant GCI and NCI in the external than the internal segment. **f-g.** Rostral midbrain, SNpc. The GCI/NCI gradient in the SN is even with a few thick, sausage-like shaped α -synuclein-positive neurites in the rostral middle field of the SNpc. **h.** Caudal midbrain, superior cerebellar peduncle, decussation. **i.** Ventral pons, middle cerebral peduncle. The pons shows more GCI in the ponto-cerebellar fibers than the fronto-pontine

fibers, and some GCI in the cortico-spinal tract. **j.** MO, hilus of the ION showing pallor. **k-l.** MO, olivocerebellar fibers. The MO (j) shows more GCI in the reticular formation than the ION or pyramids (k-l). **m.** Cerebellum, dorsal folia. **n.** Spinal cord, sacral, Onuf nucleus. In the spinal cord, the extent of motor neuron loss is proportional to the density of GCI especially within the thoracic and sacral levels. **o-p.** Infrequent ganglion neurons in sacral DRG displaying α -synuclein-containing cytoplasmic inclusions. *Stains: α -synuclein (a-g, m and p); hematoxylin-eosin (i, k, and o); and luxol-hematoxylin-eosin (h, j, l, and n). Labeling with antibodies directed against phosphorylated tau (AT8) was negative. Magnification: x20 (n); x40 (o); x100 (h-k); x200 (e-f); x400 (a-d, g, l-m, and p).*