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“Minimal change” multiple system atrophy with limbic-predominant α -synuclein pathology

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Keywords

minimal change MSA; hippocampus; glial cytoplasmic inclusion; neuronal cytoplasmic inclusion; tyrosine hydroxylase; neuronal loss; microgliosis

Multiple system atrophy (MSA) is a progressive neurodegenerative disease characterized by autonomic failure, parkinsonism, and cerebellar ataxia [3]. The striatonigral and olivopontocerebellar systems are most vulnerable regions in MSA. A variable degree of neuronal loss and astrogliosis are observed in addition to glial cytoplasmic inclusions (GCIs). “Minimal change” or “preclinical” MSA has been reported to as an early pathologic form of MSA [7,6,2,4,5]. These cases have minimal neuronal loss confined to the striatonigral and/or olivopontocerebellar systems [7,6,2,5]. Some have no neuronal loss [4], but GCIs are observed throughout the brain, even in regions without neuronal loss. This finding suggests that formation of GCI may precede neuronal loss, and both striatonigral and olivopontocerebellar systems are the brain regions affected in the earliest stage of the disease. We herein report a limbic counterpart of “minimal change” MSA with abundant α -synuclein pathology in the limbic system.

This patient was a 70-year-old Caucasian man who had a medical history of depression and anxiety for more than 20 years. He noticed bilateral arm stiffness and difficulty with swallowing at age 65. One year later, he was evaluated by a neurologist and found to have slow gait, with multi-step pivot, and rigidity in his arms. He also developed imbalance and leg stiffness, which caused multiple falls. He was on a feeding tube because he could not swallow. On neurological examination at age 69, moderate hypophonia, hypomimia, bradykinesia in his arms, moderate symmetric rigidity in the four extremities, shuffling gait with decreased arm swing, and mild retropulsion were observed. Because of the 1-year history of taking olanzapine, drug-induced parkinsonism was suspected; however, his symptoms did not improve after discontinuing olanzapine. He was diagnosed with Parkinson disease and started taking carbidopa-levodopa, but discontinued because of intolerance. He developed a head drop at age 70. A suprapubic catheter was inserted for bladder dysfunction. Based on symmetrical parkinsonism without tremor, dysphagia, head drop, constipation, bladder dysfunction, and the absence of cognitive decline, he was given a diagnosis of MSA.

At autopsy, the brain had no atrophy (fixed brain weight was 1140 grams). The substantia nigra and locus coeruleus had a normal degree of pigmentation. On hematoxylin and eosin-stained sections, no neuronal loss or gliosis were observed throughout the brain, except the substantia nigra where rare extraneuronal deposits of pigment indicated minimal neuronal loss. Microgliosis was not observed on IBA-1-immunostained sections in all brain regions. Immunohistochemistry for α -synuclein revealed that GCIs and neuronal cytoplasmic inclusions (NCIs) distributed throughout the brain (Table 1). The limbic structures, especially hippocampus, were most severely affected; by contrast, the striatonigral and olivopontocerebellar systems had only sparse inclusions. NCIs in the dentate gyrus were ring-shaped. Pick body-like NCIs, which are thought to correlate with neuronal loss, were not detected [1]. Neuronal intranuclear inclusions were rare in the hippocampal pyramidal layer, substantia nigra, pontine base, and inferior olivary nucleus. Representative images are given in Supplementary Figure 1. Although neurodegenerative changes in striatonigral or olivopontocerebellar systems were minimal, considering the specificity of GCIs to MSA, the neuropathologic diagnosis of “minimal change” MSA was made. On thioflavin S microscopy, Alzheimer’s-type pathology was minimal (Braak neurofibrillary tangle stage III; Thal amyloid phase III). No pathological TDP-43 aggregates were observed in the amygdala, hippocampus, striatum, and midbrain. Antibodies and staining conditions are summarized in Supplementary Table 1.

The present case showed an unusual distribution of α -synuclein pathology. Limbic structures, especially components of the Papez circuit (i.e. the hippocampus, fornix, mammillothalamic tract, and anterior thalamic nuclei), were predominantly affected while striatonigral and olivopontocerebellar systems were less affected. To characterize the distribution pattern of GCIs, we quantified the burden of GCIs in white matter regions of 184 MSA cases in the Mayo Clinic brain bank and compared to this patient (Supplementary Figure 2).

Some MSA patients have limbic-predominant α -synuclein pathology with neuronal loss and dementia, abnormal behavior, or corticobasal syndrome [1]; however, this patient did not have any of these symptoms possibly because of the absence of neuronal loss in the limbic system. On the other hand, the patient developed parkinsonism and autonomic dysfunction despite minimal neuronal loss in the substantia nigra. Moreover, immunohistochemistry for tyrosine hydroxylase did not detect dopaminergic degeneration in the substantia nigra or the dorsolateral putamen (Supplementary Figure 3). The neuropathological substrate of his symptoms remains unclear; α -synuclein aggregates may lead to neuronal dysfunction sufficient to cause these symptoms even without apparent neuronal loss [5]. The present case implies that not only the striatonigral or olivopontocerebellar systems, but also the limbic system can be affected predominantly by α -synuclein pathology in “minimal change” MSA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

GCI	Glial cytoplasmic inclusion
MSA	multiple system atrophy
NCI	neuronal cytoplasmic inclusion

References

1. Aoki N, Boyer PJ, Lund C et al. (2015) Atypical multiple system atrophy is a new subtype of frontotemporal lobar degeneration: frontotemporal lobar degeneration associated with alpha-synuclein. *Acta Neuropathol* 130:93–105. 10.1007/s00401-015-1442-z [PubMed: 25962793]
2. Fujishiro H, Ahn TB, Frigerio R et al. (2008) Glial cytoplasmic inclusions in neurologically normal elderly: prodromal multiple system atrophy? *Acta Neuropathol* 116:269–275. 10.1007/s00401-008-0398-7 [PubMed: 18553090]
3. Gilman S, Wenning GK, Low PA et al. (2008) Second consensus statement on the diagnosis of multiple system atrophy. *Neurology* 71:670–676. 10.1212/01.wnl.0000324625.00404.15 [PubMed: 18725592]
4. Kon T, Mori F, Tanji K et al. (2013) An autopsy case of preclinical multiple system atrophy (MSA-C). *Neuropathology* 33:667–672. 10.1111/neup.12037 [PubMed: 23581648]
5. Ling H, Asi YT, Petrovic IN et al. (2015) Minimal change multiple system atrophy: an aggressive variant? *Mov Disord* 30:960–967. 10.1002/mds.26220 [PubMed: 25854893]
6. Wakabayashi K, Mori F, Nishie M et al. (2005) An autopsy case of early (“minimal change”) olivopontocerebellar atrophy (multiple system atrophy-cerebellar). *Acta Neuropathol* 110:185–190. 10.1007/s00401-005-1029-1 [PubMed: 15971057]
7. Wenning GK, Quinn N, Magalhaes M et al. (1994) “Minimal change” multiple system atrophy. *Mov Disord* 9:161–166. 10.1002/mds.870090206 [PubMed: 8196676]

Table 1:The semiquantitative assessment of neuronal loss, microgliosis, and α -synuclein pathology

Region	Neuronal loss	Microgliosis	GCI	NCI	NII
Middle frontal gyrus	-	-	+	-	-
Superior frontal gyrus	-	-	+	-	-
Cingulate gyrus	-	-	+	-	-
Precentral gyrus	-	-	+	+	-
Superior temporal gyrus	-	-	+	-	-
Inferior parietal lobule	-	-	+	-	-
Occipital lobe	-	-	+	-	-
Caudate	-	-	+	-	-
Putamen	-	-	+	-	-
Globus pallidus	-	-	+	-	-
Internal capsule	-	-	+	-	-
Basal nucleus	-	-	++	+	-
Hypothalamus	-	-	++	+++	-
Amygdala	-	-	+	++	-
Parahippocampal gyrus	-	-	+	+	-
Dentate gyrus	-	-	-	+++	-
Subiculum	-	-	+	++	-
Hippocampus	-	-	+++	+++	+
Fimbria	-	-	+++	-	-
Mammillothalamic tract	-	-	+++	-	-
Anterior nucleus of thalamus	-	-	++	+	-
Ventral thalamus	-	-	+	+	-
Subthalamic nucleus	-	-	+	+	-
Substantia nigra	+	-	+	+	+
Locus coeruleus	-	-	+	+	-
Pontine tegmentum	-	-	+	+	-
Pontine base	-	-	+	+	+
Medullary tegmentum	-	-	++	+	-
Inferior olivary nucleus	-	-	+	+	+
Dentate nucleus	-	-	+	-	-
Cerebellar white matter	-	-	+	-	-
Purkinje cell layer	-	-	-	-	-

Abbreviation: GCI, glial cytoplasmic inclusion; NCI, neuronal cytoplasmic inclusion; NII, neuronal intranuclear inclusion.

- none

+ minimal/sparse

++ moderate

+++ frequent