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Brain Pathology

COMMENTARY

Multiple system atrophy with hippocampal pathology

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Ando et al. [1], in a recent study of 146 autopsy-proven cases of multiple system atrophy (MSA) from various Japanese hospitals (82 males, 64 females, aged at disease onset 58.5 ± 9.3/33–83/years) identified 12 patients (8.2% - 7 MSA-P and 5 MSA-C) with severe hippocampal pathology due to prominent involvement by α-synuclein-immunoreactive neuronal cytoplasmic inclusions (NCIs) associated with severe neuronal loss and astrogliosis predominantly in the hippocampal granule cells, the CA1/subiculum, parahippocampal gyrus and amygdala. The NCIs showed ring-shaped or neurofibrillary tangle (NFT)-like configurations. In addition, 3 of the 12 patients showed atypical Pick body–like NCIs and severe atrophy of the medial temporal lobes with heavy NCI involvement. In addition, Lewy bodies in the brainstem were seen in one (8.3%) of the hippocampal MSA cases, which showed neuritic Braak NFT stages I-III (mean 1.6 ± 0.8), which was slightly higher than in the classical MSA cases. The patients with the hippocampal MSA variant were younger at disease onset than the classical MSA cases (mean 56.6 ± 9.3 vs. 60.4 ± 9.3 years), had a significantly longer disease duration (mean 13.2 ± 5.9 vs. 6.9 ± 3.6 years) and higher prevalence of cognitive impairment, associated with denser NCIs in the fronto-temporal cortex. This hippocampal subtype was considered a rare pathological variant of MSA and not a result of an advanced disease phase. Among 48 autopsy-confirmed cases of MSA from the files of the Institute of Clinical Neurobiology, Vienna, Austria (33 MSA-P and 15 MSA-C) with mean age at disease onset of 55.5 ± 6.5 years and a mean duration of 7.5 years, two females, both MSA-P with severe hippocampal pathology, showed disease onset at 61 and 73 years, respectively. They accounted for 4.3% of the total cohort. The time from diagnosis to death was 4 and 7 years, respectively. In both patients, the initial symptoms were rigidity, bradykinesia, and gait disorders, without tremor or essential autonomic symptoms (orthostatic hypotension, urinary difficulties, etc.), while the elder one developed mild cerebellar symptoms. The clinical diagnosis was Parkinson disease R-A type and MSA-P, respectively, with Hoehn & Yahr stage 4 to 5 at last visit. The elder patient developed psychotic symptoms, visual hallucinations, depression, and moderate cognitive impairment, later laryngeal stridor, and finally received a PEG probe. The younger one, in addition to parkinsonian symptoms, developed mild muscular atrophy and moderate cognitive impairment (MMSE 25/30). Neuropathology in both cases revealed frontal and hippocampal atrophy, striatonigral degeneration grade III [2], with OPCA grade I in the elder patient. In addition to multiple α-synuclein-positive glial cytoplasmic inclusions (GCIs) in the striatum, brainstem and less in cerebral cortices, there was severe involvement by NCIs with neuronal loss and astrogliosis predominantly in hippocampal subarea CA/1, granular cell layer, pre- and prosubiculum, and parahippococampal gyrus. In contrast to the cases reported by Ando et al. [1], no Pick body- or NFT-like NCIs and no Lewy bodies in the brainstem were observed, while Lewy pathology was seen in 23% of the total MSA cohort. Both cases showed moderate hippocampal tau pathology akin to Braak NFT stages III, with Thal amyloid phases 0–3 (mean 0.8 ± 0.1). No tau-positive astroglia, cerebral amyloid angiopathy (CAA), TDP-43 co-pathologies, and no limbic and FTLD-type α-synuclein pathology [3] were observed. The psychotic symptoms and cognitive impairment in both patients were suggested to be correlated to the severe hippocampal involvement by α-synuclein pathology, whereas mild to moderate cognitive impairment was reported in 35% of the total MSA cohort, these patients being significantly older than those without cognitive deficiencies. In two other MSA cases with disease onset at 75

and 80 years and duration of 2 and 4 years, respectively, cognitive impairment or dementia were associated with considerable Alzheimer-related co-pathologies including Thal amyloid phase 4–5, considerable CAA and tau pathology corresponding to Braak NFT stages IV and V [4]. These two phenotypes of MSA, the hippocampal variant and the late onset MSA, among other atypical MSA variants, highlight the clinical and pathological heterogeneity of this and other α-synucleinopathies [5].

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CONFLICT OF INTEREST

The author declares no competing interest.

ETHICS APPROVAL

All procedures involving human tissue have been approved by the Ethical Committee of the Medical University of Vienna following the tenants of the Declaration of Helsinki.

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REFERENCES

1. Ando T, Riku Y, Akagi A, Miyahara H, Hirano M, Ikeda T, et al. Multiple system atrophy variant with severe hippocampal pathology. Brain Pathol. 2022;32:e13002.
2. Jellinger KA, Seppi K, Wenning GK. Grading of neuropathology in multiple system atrophy: proposal for a novel scale. Mov Disord. 2005;20(Suppl 12):S29–36.
3. Coughlin DG, Dryden I, Goodwill VS, Pizzo DP, Wright B, Lessig S, et al. Long-standing multiple system atrophy-Parkinsonism with limbic and FTLD-type alpha-synuclein pathology. Neuropathol Appl Neurobiol. 2021 Nov 30. https://doi.org/10.1111/nan.12783
4. Jellinger KA. Neuropathological findings in multiple system atrophy with cognitive impairment. J Neural Transm (Vienna). 2020;127:1031–9.
5. Jellinger KA. Multiple system atrophy—a clinicopathological update. Free Neuropathol. 2020;1:17. https://doi.org/10.17879/freeneuropathology-12020-12813