Alzheimer's disease pathology concomitant with memory impairment in late-onset multiple system atrophy

Yasuo Miki[1,2], Conceição Bettencourt[2,3], Zane Jaunmuktane[2,4], Janice L. Holton[2], Thomas T. Warner[2,3,5] and Koichi Wakabayashi[1]

[1] Department of Neuropathology, Institute of Brain Science, Hirosaki University Graduate School of Medicine, Hirosaki 036-8562, Japan

[2] Queen Square Brain Bank for Neurological Disorders, UCL Queen Square Institute of Neurology, 1 Wakefield Street, London WC1N 1PJ, UK

[3] Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, University College London, London WC1N 3BG, UK

[4] Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, University College London WC1N 3BG, London, UK

[5] Reta Lila Weston Institute of Neurological Studies, UCL Queen Square Institute of Neurology, London WC1N 3BG, UK

Correspondence to Dr Yasuo Miki,

Department of Neuropathology, Institute of Brain Science, Hirosaki University Graduate School of Medicine, Hirosaki 036-8562, Japan

Email: yasuomiki@hotmail.com; y.miki@ucl.ac.uk

Keywords: late-onset multiple system atrophy; memory impairment; α-synuclein; hippocampus; concomitant Alzheimer's disease pathology

Number of words in the text: 788

Number of Tables: 1

Dear Sir,

Multiple system atrophy (MSA) is characterized pathologically by the accumulation of abnormal α-synuclein in oligodendrocytes (glial cytoplasmic inclusions) and neurons [neuronal cytoplasmic inclusions (NCIs)] in affected regions. Patients with MSA can develop a wider array of symptoms than thought previously – including cognitive impairment – in addition to parkinsonism, cerebellar ataxia and autonomic dysfunction. We investigated 148 patients with pathologically proven MSA, who were referred to Queen Square Brain Bank (QSBB) between 2002 and 2018. Thirty of these patients (20%) had manifested cognitive impairment (frontal subcortical dysfunction and/or memory impairment) during life [1]. Among those patients, the degree of memory impairment had been mild to moderate in 18. In addition, pathological examinations had revealed more NCIs in the hippocampus in MSA patients with memory impairment than in those without [1]. We further investigated the mechanism of memory impairment in MSA using a human α-synuclein-inducible MSA mouse model and human MSA cases with or without memory impairment [2]. We found that α-synuclein oligomers in the hippocampus caused synaptic dysfunction, leading to the development of memory impairment in MSA [1, 2].

Jellinger examined 50 patients with pathologically proven MSA, 11 (22%) of

whom had developed cognitive impairment during life [3]. The author then focused on two patients with late-onset MSA, defined as disease onset at 75 years of age or older, who had suffered from severe cognitive impairment. In addition to the accumulation of abnormal α-synuclein, both patients had considerable concomitant Alzheimer's disease (AD) pathology. Given the more severe cognitive impairment in these patients with late-onset MSA relative to those with typical-onset MSA (disease onset at 74 years of age or younger), the author speculated that overlapping AD-related co-pathology might exacerbate cognitive impairment in late-onset MSA [3].

In Parkinson's disease with dementia (PDD) and dementia with Lewy bodies (DLB), the cortical α-synuclein load is positively correlated with the neurofibrillary tangle (NFT) and senile plaque burden. These additive disease processes induce global cognitive impairment [4]. Jellinger's report raised two questions: 1) Are patients with late-onset MSA likely to develop severe concomitant AD pathology, and if so 2) is the concomitant AD pathology driven by the primary α-synuclein pathology, similar to PDD or DLB? In our previous study, no patients with late-onset MSA had developed cognitive impairment during life. In addition, there was no difference in the degree of concomitant AD pathology between MSA cases with memory impairment and those without [1]. In the present study, using the same cohort from the QSBB [1], we compared concomitant

AD pathologies between late- (N = 5) and typical-onset MSA (N = 143). Interestingly, the two groups had similar burdens of NFTs and senile plaques in the brain [late-onset MSA versus typical-onset MSA; Braak & Braak NFT stage 1.6 ± 1.5 versus 0.8 ± 0.7; Consortium to Establish a Registry for Alzheimer's Disease (CERAD) senile plaque score 1.0 ± 1.4 versus 0.3 ± 0.6] (Table 1). To better understand whether concomitant AD pathology can develop in patients with late-onset MSA, we identified 23 age-matched controls without neurodegenerative disease among a total of 363 cases referred to the Department of Neuropathology, Hirosaki University Graduate School of Medicine, between 2000 and 2022. We then compared demographic data and concomitant AD pathology between five cases of late-onset MSA from the QSBB and 23 controls from Hirosaki University. This revealed no differences in brain weight or the degree of concomitant AD pathology (late-onset MSA versus controls: brain weight 1301.2 ± 78.8 g versus 1221.2 ± 128.8 g; Braak & Braak NFT stage 1.6 ± 1.5 versus 2.2 ± 0.9; CERAD senile plaque score 1.0 ± 1.4 versus 0.7 ± 0.7) (Table 1).

In the present study, no evident difference was found in AD-related co-pathology between late-onset MSA cases and age-matched controls, suggesting that α-synuclein pathology in MSA may not exacerbate concomitant AD pathology. Sekiya *et al*. have reported the clinical and pathological features of typical- and late-onset MSA [5]. Unlike

the findings of the present study, they found that AD-related co-pathology increased in patients with late-onset MSA [5]. However, the Braak & Braak NFT stage (2.4 ± 1.6) in late-onset MSA they reported [5] seemed similar to that in the present age-matched controls. In the present study, we compared concomitant AD pathology of patients with MSA from the QSBB with that of age-matched Japanese controls. The profiles of concomitant AD pathology between these ethnic groups can be different. In fact, due to the higher frequency of the apolipoprotein E ε4 allele, a significant risk factor for AD, in Caucasians (13.7%) versus Japanese healthy individuals (8.8%) [6, 7], age-matched controls from the QSBB may have similar or more severe concomitant AD pathology compared with age-matched Japanese controls. Regardless of such potential differences between the different ethnic groups, concomitant AD pathology in late-onset MSA may still fall within that associated with normal ageing. Undoubtedly, when a patient with MSA develops severe concomitant AD pathology, severe cognitive impairment is highly likely to develop. However, this does not necessarily mean that cognitive impairment in late-onset MSA is always caused by pathogenic α-synuclein in the hippocampus as well as severe concomitant AD pathology. The two cases reported by Jellinger could be examples of late-onset MSA coincidentally overlapping with severe concomitant AD pathology. Given that no concomitant pathologies have been reported to co-exist in MSA

as MSA-related pathogenesis, memory impairment in MSA can be caused by hippocampal pathogenic α-synuclein per se.

Acknowledgements

The authors wish to thank the donors, their family members and carers, Mrs Nakata and all doctors. Without their understanding and help, this study would never have been done. This work was supported by JSPS KAKENHI Grant Numbers 21K07452 (Y.M.), 22H02948 (K.W.) and Hirosaki University Priority Research Grant for Future Innovation (Y.M.). Queen Square Brain Bank for Neurological Disorders receives support from the Reta Lila Weston Institute of Neurological Studies. C.B. is supported by the Multiple System Atrophy Trust and an Alzheimer's Research UK Research Fellowship. T.T.W. is supported by the Reta Lila Weston Trust and the MRC (N013255/1). J.L.H. is supported by the Multiple System Atrophy Trust; the Multiple System Atrophy Coalition; Fund Sophia, managed by the King Baudouin Foundation and Karin & Sten Morstedt CBD Solutions.

Author contributions

YM and KW designed the research project, performed the pathological analysis

and were responsible for writing the manuscript. CB, ZJ, JLH and TTW provided pathological data and revised the manuscript.

Conflicts of interest

Y.M. and T.T.W. are members of the Movement Disorder Society MSA criteria revision task force. All other authors have no competing interests to report.

Ethics

The brain donation programme and research protocols had received ethical approval from the NRES Committee London – Central and tissue for research had been stored under a license issued by the Human Tissue Authority (No. 12198). This study was also approved by the Institutional Ethics Committee of Hirosaki University Graduate School of Medicine (No. 2020-063-1).

References

1. Miki Y, Foti SC, Hansen D, Strand KM, Asi YT, Tsushima E, et al. Hippocampal α-synuclein pathology correlates with memory impairment in multiple system atrophy. Brain. 2020; 143: 1798-1810

2. Miki Y, Tanji K, Shinnai K, Tanaka MT, Altay F, et al. Pathological substrate of multiple system atrophy. Neuropathol Appl Neurobiol. 2022 in press.
3. Jellinger KA. Morphological substrate of memory impairment in multiple system atrophy. Neuropathol Appl Neurobiol. 2022 in press.
4. Lashley T, Holton JL, Gray E, Kirkham K, O'Sullivan SS, et al. Cortical α-synuclein load is associated with amyloid-β plaque burden in a subset of Parkinson's disease patients. Acta Neuropathol. 2008; 115: 417-25.
5. Sekiya H, Koga S, Otsuka Y, Chihara N, Ueda T, et al. Clinical and pathological characteristics of later onset multiple system atrophy. J Neurol. 2022; 269: 4310-21.
6. Takei N, Miyashita A, Tsukie T, Arai H, Asada T, et al. Genetic association study on in and around the APOE in late-onset Alzheimer disease in Japanese. Genomics. 2009; 93: 441-8.
7. Jarvik G, Larson EB, Goddard K, Schellenberg GD, Wijsman EM. Influence of Alzheimer's disease in a community-based sample. Am J Hum Genet. 1996; 58: 191-200.