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Editorial

Multiple System Atrophy: What is the Factor Underlying Phenotypic Variation?

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EDITORIAL

Multiple system atrophy (MSA) is a rare neurodegenerative disorder with both clinical and pathological variants. Clinical examples include MSA with predominant parkinsonism (MSA-P) and MSA with predominant cerebellar ataxia (MSA-C) [1], whereas striatonigral degeneration and olivopontocerebellar atrophy are pathological variants [2]. Making a definitive diagnosis of MSA requires the neuropathologic findings of widespread and abundant CNS alpha-synuclein-positive glial cytoplasmic inclusions in association with neurodegenerative changes in striatonigral or olivopontocerebellar structures [3]. The reasons underlying predominant involvement of striatonigral versus olivopontocerebellar areas in MSA remain to be determined. The variation in the phenotypic spectrum in different ethnic groups has recently attracted considerable attention.

In the past few years, semi-quantitative pathological analyses of MSA have been carried out in the United Kingdom [2] and Japan [4] using autopsied brain material from 100 caucasian British cases referred to the Queen Square Brain Bank, United Kingdom, and 50 ethnic Japanese cases referred to the Brain Research Institute, Niigata University, Japan. The findings, reported separately in two papers [2,4] have recently been summarized in a review article [5], which provided useful information regarding the phenotypic spectrum of MSA in different ethnic groups. There was a trend for the British cases to feature greater involvement of the basal ganglia, while in the Japanese cases the olivopontocerebellar region tended to be more severely affected than striatonigral structures [5]. Interestingly, the occurrence of olivopontocerebellar-predominant pathology in the Japanese series (40%) was significantly higher than that in the British series (17%) [5]. These observations provide evidence for an actual difference in phenotype distribution between British and Japanese patients with definite MSA.

The accumulating evidence suggests that the relative clinical prevalences of MSA-P and MSA-C in Europe may differ from those in Asia. Studies of the natural history and epidemiology of more than 90 MSA patients, in which the relative frequencies of MSA-P and MSA-C were analyzed, have been reviewed. In the study of 100 British patients with clinical MSA, 82% were MSA-P and 18% were MSA-C [6]. A report from the European MSA study group involving 437 MSA patients demonstrated that the majority of patients exhibited MSA-P (68%) [7]. Recently, the European MSA study group has carried out a prospective cohort study with 141 patients with MSA, and they reported that 85 (61.7%) had MSA-P and 54 (38.3%) had MSA-C [8]. In the United States, it was reported that 62 of 99 (63%) MSA patients had MSA-P [9]. In the northern island of Japan, Yabe and colleagues studied 142 Japanese patients with MSA, and reported that the cohort included 119 (83.8%) cases of MSA-C and 23 (16.2%) of MSA-P [10]. From the main island of Japan, Watanabe and colleagues enrolled 230 Japanese patients with MSA, 155 (67.4%) of whom had MSA-C and 75 (32.6%) had MSA-P [11]. In Korea, a study of 100 Korean patients with MSA found that MSA-C patients accounted for 73% of the cohort [12]. In summary, the majority of patients exhibited features of MSA-C in studies from Asia, whereas in studies from Europe and North America MSA-P patients predominated. Although the potential drawback of selection bias should be taken into account when considering the published frequencies of clinical subtypes and pathological subtypes, the demonstrated difference between Europe and Asia in pathological subtypes is consistent with the demonstrated difference in clinical subtypes seen in those regions. This points to the need for further investigation to elucidate biological factors determining this regional difference in distribution of clinicopathological phenotypes of MSA.

For more than a dozen years, the relationship between the alpha-synuclein gene and a risk of MSA has been investigated. Previous studies, including sequencing of the *SNCA* coding sequence, gene dosage measurements, and microsatellite testing, have failed to identify significant associations of *SNCA* variants with MSA [13-15]. *SNCA* expression studies did not detect altered gene expression levels in MSA brains [16-18]. Furthermore, a haplotype study by Ozawa and colleagues using single nucleotide polymorphism (SNP) failed to demonstrate any association with MSA [19]. After all of these negative results, positive associations of variations of the *SNCA* gene in Caucasian patients with MSA have been reported [20]; however, this finding was not replicated in Korean patients with MSA [21]. Recently, Mitsui, Tsuji, and a large worldwide collaborative team (the Multiple-System Atrophy Research Collaboration) identified homozygous or compound heterozygous mutations in the COQ2 gene (*COQ2*) ,

which is involved in the biosynthetic pathway for coenzyme Q_{10}, in two of six multiplex families with MSA [22]. Interestingly, a common variant (V343A) of *COQ2* was found exclusively in the Japanese participants, including patients with sporadic MSA, with a high odds ratio, suggesting that V343A in *COQ2* is associated with an increased risk of MSA-C in the Japanese population [22]. Based on the concept of a disease susceptibility spectrum for MSA, it is hypothesized that different subsets of genetic factors are responsible for different ends of the spectrum, such as MSA-P and MSA-C [23]. In this regard, the discovery of *COQ2* mutations in Japanese MSA patients may potentially help to elucidate the mechanisms underlying demonstrated differences in the phenotypic spectrum present in different ethnic groups.

For environmental factors, the relationship between exposure to pesticides and an increased risk for MSA has been controversial, and whether exposure to pesticides modifies the MSA phenotype remains unclear. However, it is tempting to speculate that the synergistic interaction between genetic risk variants and exposure to some environmental toxins could play a role in the pathogenesis and phenotypic variation of MSA. Further investigation is needed to determine the precise environmental, genetic and epigenetic factors that account for the phenotypic variation of MSA.

REFERENCES

1. Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, et al. Second consensus statement on the diagnosis of multiple system atrophy. Neurology. 2008; 71: 670-676.
2. Ozawa T, Paviour D, Quinn NP, Josephs KA, Sangha H, Kilford L, et al. The spectrum of pathological involvement of the striatonigral and olivopontocerebellar systems in multiple system atrophy: clinicopathological correlations. Brain. 2004; 127: 2657-2671.
3. Trojanowski JQ, Revesz T; Neuropathology Working Group on MSA. Proposed neuropathological criteria for the post mortem diagnosis of multiple system atrophy. Neuropathol Appl Neurobiol. 2007; 33: 615-620.
4. Ozawa T, Tada M, Kakita A, Onodera O, Tada M, Ishihara T, et al. The phenotype spectrum of Japanese multiple system atrophy. J Neurol Neurosurg Psychiatry. 2010; 81: 1253-1255.
5. Ozawa T, Revesz T, Paviour D, Lees AJ, Quinn N, Tada M, et al. Difference in MSA Phenotype Distribution between Populations: Genetics or Environment? J Parkinsons Dis. 2012; 2: 7-18.
6. Wenning GK, Ben Shlomo Y, Magalhães M, Daniel SE, Quinn NP. Clinical features and natural history of multiple system atrophy. An analysis of 100 cases. Brain. 1994; 117 : 835-845.
7. Köllensperger M, Geser F, Ndayisaba JP, Boesch S, Seppi K, Ostergaard K, et al. Presentation, diagnosis, and management of multiple system atrophy in Europe: final analysis of the European multiple system atrophy registry. Mov Disord. 2010; 25: 2604-2612.
8. Wenning GK, Geser F, Krismer F, Seppi K, Duerr S, Boesch S, et al. The natural history of multiple system atrophy: a prospective European cohort study. Lancet Neurol. 2013; 12: 264-274.
9. Benrud-Larson LM, Sandroni P, Schrag A, Low PA. Depressive symptoms and life satisfaction in patients with multiple system atrophy. Mov Disord. 2005; 20: 951-957.
10. Yabe I, Soma H, Takei A, Fujiki N, Yanagihara T, Sasaki H. MSA-C is the predominant clinical phenotype of MSA in Japan: analysis of 142 patients with probable MSA. J Neurol Sci. 2006; 249: 115-121.
11. Watanabe H, Saito Y, Terao S, Ando T, Kachi T, Mukai E, et al. Progression and prognosis in multiple system atrophy: an analysis of 230 Japanese patients. Brain. 2002; 125: 1070-1083.
12. Seo JH, Yong SW, Song SK, Lee JE, Sohn YH, Lee PH. A case-control study of multiple system atrophy in Korean patients. Mov Disord. 2010; 25: 1953-1959.
13. Ozawa T, Takano H, Onodera O, Kobayashi H, Ikeuchi T, Koide R, et al. No mutation in the entire coding region of the alpha-synuclein gene in pathologically confirmed cases of multiple system atrophy. Neurosci Lett. 1999; 270: 110-112.
14. Morris HR, Vaughan JR, Datta SR, Bandopadhyay R, Rohan De Silva HA, Schrag A, et al. Multiple system atrophy/progressive supranuclear palsy: alpha-Synuclein, synphilin, tau, and APOE. Neurology. 2000; 55: 1918-1920.
15. Lincoln SJ, Ross OA, Milkovic NM, Dickson DW, Rajput A, Robinson CA, et al. Quantitative PCR-based screening of alpha-synuclein multiplication in multiple system atrophy. Parkinsonism Relat Disord. 2007; 13: 340-342.
16. Langerveld AJ, Mihalko D, DeLong C, Walburn J, Ide CF. Gene expression changes in postmortem tissue from the rostral pons of multiple system atrophy patients. Mov Disord. 2007; 22: 766-777.
17. Ozawa T, Okuizumi K, Ikeuchi T, Wakabayashi K, Takahashi H, Tsuji S. Analysis of the expression level of alpha-synuclein mRNA using postmortem brain samples from pathologically confirmed cases of multiple system atrophy. Acta Neuropathol. 2001; 102: 188-190.
18. Vogt IR, Lees AJ, Evert BO, Klockgether T, Bonin M, Wüllner U. Transcriptional changes in multiple system atrophy and Parkinson's disease putamen. Exp Neurol. 2006; 199: 465-478.
19. Ozawa T, Healy DG, Abou-Sleiman PM, Ahmadi KR, Quinn N, Lees AJ, et al. The alpha-synuclein gene in multiple system atrophy. J Neurol Neurosurg Psychiatry. 2006; 77: 464-467.
20. Al-Chalabi A, Dürr A, Wood NW, Parkinson MH, Camuzat A, Hulot JS, et al. Genetic variants of the alpha-synuclein gene SNCA are associated with multiple system atrophy. PLoS One. 2009; 4: e7114.
21. Yun JY, Lee WW, Lee JY, Kim HJ, Park SS, Jeon BS. SNCA variants and multiple system atrophy. Ann Neurol. 2010; 67: 554-555.
22. Multiple-System Atrophy Research Collaboration. Mutations in COQ2 in familial and sporadic multiple-system atrophy. N Engl J Med. 2013; 369: 233-244.
23. Ozawa T. Pathology and genetics of multiple system atrophy: an approach to determining genetic susceptibility spectrum. Acta Neuropathol. 2006; 112: 531-538.

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