Parkinsonism and Related Disorders 69 (2019) 68–70

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Correspondence

# Conjugal cerebellar type of multiple system atrophy: Person-to-person transmission?

ARTICLE INFO

*Keywords:*
MSA-C
α-synucleinopathy
Genetics
Environment
Transmission

Multiple system atrophy (MSA) is a sporadic neurodegenerative disease involving autonomic dysfunction with parkinsonism (MSA-P) or cerebellar ataxia (MSA-C) [1]. Both subtypes share the neuropathologic hallmark of α-synuclein glial cytoplasmic inclusions [2]. MSA-C is more common than MSA-P in the Japanese population (relative frequencies, 67.4%–83.8%) [3]. Herein, we first report conjugal MSA-C in a Japanese couple.

The 57-year-old wife initially presented with difficulty performing fine finger movements three years ago. Then she developed gait disturbance, postural instability, slurred speech, severe constipation, and episodes of agitation during sleep. The neurological examination revealed slightly clumsy speech patterns, adiadochokinesia, dysmetria on finger-to-nose and heel-to-shin testing, positive Babinski signs with hyperreflexia in the limbs, and a wide-based gait. She exhibited orthostatic hypotension (a reduction in systolic blood pressure from 118 mmHg to 78 mm Hg) in the head-up tilt test. Since she underwent pacemaker implantation, magnetic resonance imaging (MRI) cannot be performed. Brain CT scanning revealed cerebellar and pontine atrophy. Brain SPECT scans showed perfusion decreases in the left frontal lobe, cerebellum and brain stem (Fig. 1 A and B). We clinically diagnosed her as having probable MSA-C.

Two years after the onset in the wife, the 58-year-old husband presented with mild gait disturbance and postural instability. The neurological examination revealed adiadochokinesia, dysmetria on finger-to-nose and heel-to-shin testing, poor one-foot standing on the left side and an impaired tandem gait. He also exhibited orthostatic hypotension (a reduction in systolic blood pressure from 148 mmHg to 103 mmHg) in the head-up tilt test. Brain MRI showed cerebellar and brainstem atrophy and a typical hot cross bun sign in the pons, as well as T2 hyperintensity in the middle cerebellar peduncles. Brain SPECT scans showed hypoperfusion of the brainstem and cerebellum (Fig. 1C and D). The diagnosis of probable MSA-C was made.

The wife worked as a mathematics teacher until 56 years of age. The husband worked as a physical education teacher, with no history of traumatic brain injuries. They reported no residential or occupational exposure to any known or possible environmental risk factors for developing Parkinson's disease (PD) and MSA (Supplementary Table 1) [4,5]. Although an influence from other environmental, not yet recognized factors cannot be excluded, all 25 items mentioned above could be excluded with certainty by our investigation. No nearby resident or same school colleague was reported to have been diagnosed with α-synucleinopathies, comprising PD, dementia with Lewy bodies (DLB) and MSA. Therefore, we may exclude exposure to renowned environmental factors as the cause of the MSA in this couple.

This couple denied having consanguineous parents or a family history of any neurodegenerative diseases. We carried out whole-exome sequencing of genomic DNAs from both the husband and wife. We examined variants of a total of 356 genes known to be responsible for or associated with MSA, PD, DLB, progressive supranuclear palsy (PSP), frontotemporal lobar degeneration (FTLD), and hereditary ataxias (Supplementary Table 2). We ruled out the possibility of any mutations in these genes as the genetic cause of the disease. Through Sanger sequencing, we excluded the possibility of mutations in the common Spinocerebellar ataxia (SCAs) caused by polyglutamine-coding CAG repeats in the couple, including SCA1, SCA2, MJD/SCA3, SCA6, SCA7, SCA8, SCA12, SCA17, DRPLA, and SCA31. We ruled out the possibility of *SNCA* multiplications using semiquantitative PCR. We further performed pairwise kinship analysis and ruled out a blood relationship between the couple (Supplementary Table 3), indicating no shared genetics in this couple. Finally, we evaluated the genetic risk of MSA in the couple by genotyping the variants suggested to be associated with the risk of MSA. We realized the couple were both genetically susceptible to MSA, especially the wife, with risk alleles in all the seven SNPs examined (Supplementary Table 4). However, all genetic association studies in MSA carried out to date had their own inherent limitations, so they need to be seen as hypothesis-generating rather than definitive.

The prevalence rate of MSA-C in the Japanese population is estimated to be 8/100,000, both sexes being affected equally [3]. Therefore, the probability of occurrence in two spouses in the Japanese population, by chance, is approximately $6.4 \times 10^{-9}$, making this unlikely (although not impossible) to occur by chance.

The last possibility is transmission, i.e., sexual or close personal contact. This couple has been married and lived together for 32 years. They kept an active sexual life until one year before the disease onset of the wife. Apart from that, they report no experience of other particular events or comorbidities. They have a daughter aged 30 and a son aged 27, who are both healthy at the moment. This couple shared the same clinical phenotype of MSA-C. Recent studies with MSA-derived α-

https://doi.org/10.1016/j.parkreldis.2019.10.026
Received 8 October 2019; Received in revised form 23 October 2019; Accepted 26 October 2019

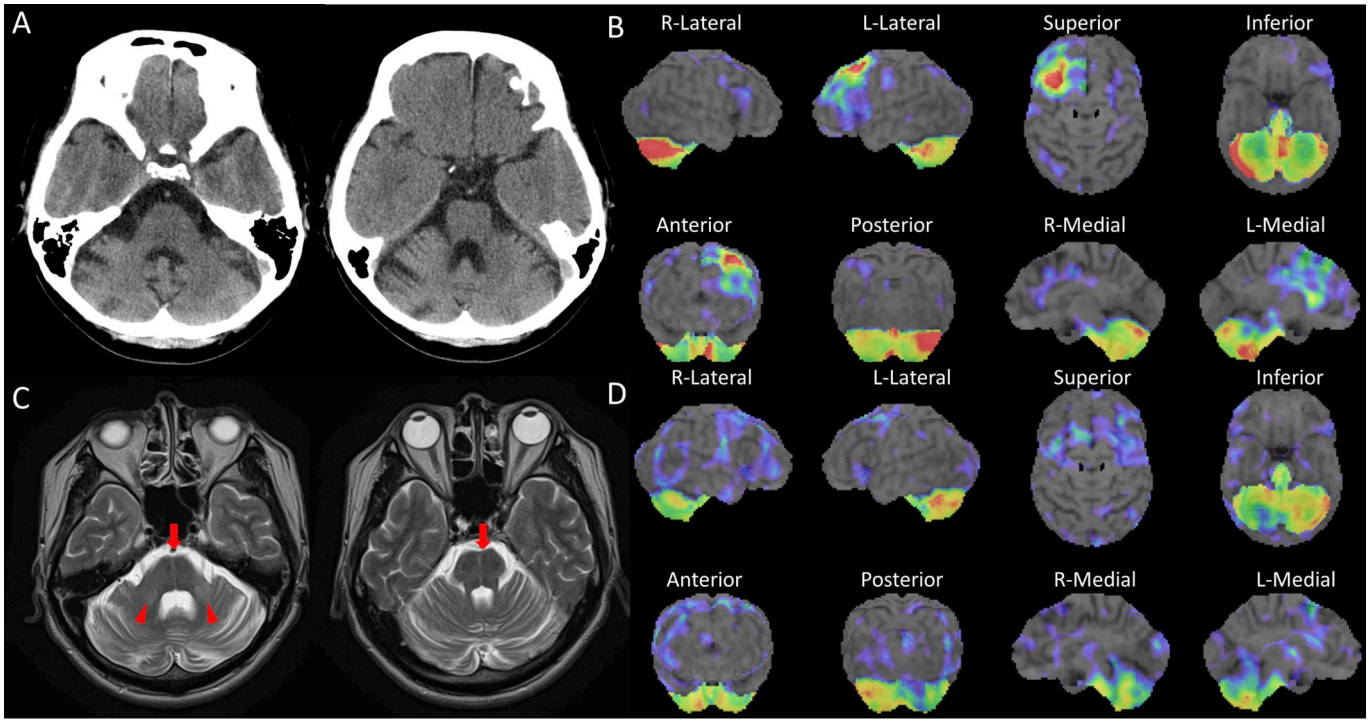


**Fig. 1.** Brain imaging of the MSA-C couple. We utilized $^{123}$I-IMP single photon emission computed tomography (SPECT) to compare regional cerebral blood flow. A. Brain CT images of the wife. B. Brain SPECT images of the wife. C. Brain MRI images of the husband. The red arrow indicates the hot cross bun sign in the pons, and the red arrowheads show T2 hyperintensity in the middle cerebellar peduncles. D. Brain SPECT images of the husband.

synuclein aggregates have shown that they have a similar ability to undergo template-directed propagation, like prions. α-synuclein is present in the saliva and plasma of MSA patients, and has been shown to infect cultured mammalian cells and also to transmit neurological diseases to transgenic mice [6]. As a result, if it is not merely a chance finding, we cannot exclude the possibility of person-to-person transmission. This study may have important implications for conjugal parkinsonism and provide an opportunity to further understand the pathogeneses of α-synucleinopathies.

## Authors' contributions

H. Nan, T. Natori, and Y. Takiyama conceived, designed and organized the study. Y. Ichinose, K. Koh, F. Kobayashi, K. Shindo, M. Hashiyada, N. Adachi, and Z. Yamagata performed the experiments and the data analysis. H. Nan wrote the manuscript. Y. Takiyama reviewed and critiqued the manuscript. All authors reviewed and approved the final draft of the manuscript.

## Ethical approval

The present study was approved by the institutional review board of Yamanashi University. Written informed consent was taken from all participants of the study.

## Declaration of competing interest

The authors have no conflicts of interest or other competing interests to declare.

## Acknowledgements

We thank the patients for participating in the present study.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.10.026.

## Funding

This work was supported by Grants-in-Aid from the Research Committee for Ataxic Disease (Y.T.), the Ministry of Health, Labor and Welfare, Japan, and JSPS KAKENHI Grant Number JP18K07495 (Y.T.) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

## References

[1] S. Gilman, G.K. Wenning, P.A. Low, D.J. Brooks, C.J. Mathias, J.Q. Trojanowski, N.W. Wood, C. Colosimo, A. Durr, C.J. Fowler, H. Kaufmann, T. Klockgether, A. Lees, W. Poewe, N. Quinn, T. Revesz, D. Robertson, P. Sandroni, K. Seppi, M. Vidailhet, Second consensus statement on the diagnosis of multiple system atrophy, Neurology 71 (9) (2008) 670–676.

[2] M.G. Spillantini, R.A. Crowther, R. Jakes, N.J. Cairns, P.L. Lantos, M. Goedert, Filamentous alpha-synuclein inclusions link multiple system atrophy with Parkinson's disease and dementia with Lewy bodies, Neurosci. Lett. 251 (3) (1998) 205–208.

[3] S. Tsuji, O. Onodera, J. Goto, M. Nishizawa, D. Study, Group on Ataxic, Sporadic ataxias in Japan–a population-based epidemiological study, Cerebellum 7 (2) (2008) 189–197.

[4] J.S. Vidal, M. Vidailhet, A. Elbaz, P. Derkinderen, C. Tzourio, A. Alperovitch, Risk factors of multiple system atrophy: a case-control study in French patients, Mov. Disord. 23 (6) (2008) 797–803.

[5] N. Vanacore, V. Bonifati, G. Fabbrini, C. Colosimo, G. De Michele, R. Marconi, D. Nicholl, N. Locuratolo, G. Talarico, S. Romano, F. Stocchi, U. Bonuccelli, M. De Mari, P. Vieregge, G. Meco, P. European Study Group on Atypical, Epidemiology of multiple system atrophy. ESGAP consortium. European study group on atypical parkinsonisms, Neurol. Sci. 22 (1) (2001) 97–99.

[6] A.L. Woerman, J.C. Watts, A. Aoyagi, K. Giles, L.T. Middleton, S.B. Prusiner, Alpha-synuclein: multiple system Atrophy prions, Cold Spring Harb. Perspect Med. 8 (7) (2018).

Haitian Nan
*Department of Neurology, Graduate School of Medical Sciences, University of Yamanashi, Yamanashi, 409-3898, Japan*
*E-mail address:* poseidon_1987427@sina.com.

Takahiro Natori
*Department of Neurology, Graduate School of Medical Sciences, University of Yamanashi, Yamanashi, 409-3898, Japan*
*E-mail address:* natorit@yamanashi.ac.jp.

Yuta Ichinose
*Department of Neurology, Graduate School of Medical Sciences, University of Yamanashi, Yamanashi, 409-3898, Japan*
*E-mail address:* yichinose@yamanashi.ac.jp.

Kishin Koh
*Department of Neurology, Graduate School of Medical Sciences, University of Yamanashi, Yamanashi, 409-3898, Japan*
*E-mail address:* jixin@yamanashi.ac.jp.

Fumikazu Kobayashi
*Department of Neurology, Koshu Rehabilitation Hospital, Yamanashi, 406-0032, Japan*
*E-mail address:* fumikazu@yamanashi.ac.jp.

Kazumasa Shindo
*Department of Neurology, Graduate School of Medical Sciences, University of Yamanashi, Yamanashi, 409-3898, Japan*
*E-mail address:* kshindo@yamanashi.ac.jp.

Masaki Hashiyada
*Department of Legal Medicine, Kansai Medical University, Hirakata, 573-1010, Japan*
*E-mail address:* hashiyam@hirakata.kmu.ac.jp.

Noboru Adachi
*Department of Legal Medicine, Graduate School of Medical Sciences, University of Yamanashi, Yamanashi, 409-3898, Japan*
*E-mail address:* nadachi@yamanashi.ac.jp.

Zentaro Yamagata
*Department of Health Sciences, Basic Science for Clinical Medicine, Graduate School of Medical Sciences, University of Yamanashi, Yamanashi, 409-3898, Japan*
*E-mail address:* zenymgt@yamanashi.ac.jp.

Yoshihisa Takiyama*
*Department of Neurology, Graduate School of Medical Sciences, University of Yamanashi, Yamanashi, 409-3898, Japan*
*E-mail address:* ytakiyama@yamanashi.ac.jp.

* Corresponding author.