Title; Heredity in Multiple System Atrophy

(Short Communication)

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Abstract

We investigated the family histories of 157 Japanese patients with probable or possible multiple system atrophy (MSA). A family history of neurodegenerative disorders was only detected in three MSA patients (1.9%). We evaluated these patients by careful neurological examination, neuroimaging studies, and genetic studies to exclude hereditary spinocerebellar ataxia with a similar clinical phenotype to MSA. The results indicated that one of them had a family history of MSA. Although the familial presence of neurodegenerative disorders is rare in MSA patients, the existence of such cases suggests that MSA may have a genetic background.

1. Introduction

Multiple system atrophy (MSA) is an adult-onset sporadic neurodegenerative disease that is clinically characterized by various combinations of poorly levodopa-responsive parkinsonism, cerebellar dysfunction, autonomic failure, and pyramidal tract involvement [1]. Neuropathologically, MSA is characterized by variable neuronal loss and gliosis in the putamen, substantia nigra, pontine nuclei, cereballar

cortex, inferior olive, and intermediolateral column of the spinal cord. Particularly, characteristic neuropathology of MSA is the presence of glial cytoplasmic inclusions (GCIs) containing alpha-synuclein in the oligodendrocytes [2, 3]. Therefore MSA is classified as a member of "alpha-synucleinopathy" together with Lewy body disease and Parkinson's disease [3]. At present, the clinical diagnosis of MSA is based on the Consensus Criteria (Gilman et al, 1999) [1]. The aetiology of MSA is unknown and it is considered to be a sporadic disorder with onset in adulthood. However, a familial case of MSA was recently reported [4] and such familial occurrence has potential implications for the aetiology of this disorder. Therefore, we investigated the family histories of patients with MSA to detect any familial cases.

2. Patients and Methods

We retrospectively reviewed the medical records of 157 Japanese patients with probable or possible MSA who were referred to Hokkaido University Hospital, Hokuyukai Neurology Hospital, Sapporo Minami National Hospital, and Ebetsu City Hospital between 1982 and 2004. The diagnosis of MSA was based on the Consensus

Criteria except for the item of family history [1]. There were 78 men and 79 women. One hundred and eighteen patients (75%) were classified as MSA-C (87 had probable MSA and 31 had possible MSA) and 39 patients were classified as MSA-P (13 had probable MSA and 26 had possible MSA). The mean age of onset was 57.7 ± 7.1 years (range: 38 – 78 years).

3. Results and Case Reports

A family history of neurodegenerative disorders was only detected in 3 of the 157 MSA patients (1.9%). Patient 1 (“probable MSA-P”) had a father who was diagnosed as having cortical cerebellar atrophy (CCA). Patient 2 (“probable MSA-C”) had a mother who was diagnosed as having Parkinson’s disease and Patient 3 (“probable MSA-P”) had an uncle who was also diagnosed as having Parkinson’s disease.

3.1. Patient 1

Patient 1 first noticed progressive slowing of her gait at the age of 57 years. She was admitted to our hospital at the age of 58 years. Neurological examination revealed

orthostatic hypotension, bradykinesia, rigidity of all four extremities, mild truncal and limb ataxia, and extensor plantar responses with symmetrical brisk tendon reflexes. Brain magnetic resonance imaging (MRI) showed a hyperintense rim at the dorsolateral border of the left putamen as well as atrophy of the brain stem and the cerebellum with a “hot cross bun” sign (Fig.1-A, B). She was diagnosed as having “possible MSA-P”, and did not receive levodopa therapy. Over a four-year period from the onset, orthostatic hypotension gradually became worse and she was diagnosed as having “probable MSA-P” at the age of 61 years. Genetic testing excluded spinocerebellar ataxia (SCA) type1, 2, 3, 6, 8, 10, 12,14, and 17 as well as dentatorubral-pallidoluysian atrophy (DRPLA) and fragile X-associated tremor/ataxia syndrome (FXTAS).

Her father first noticed an unstable gait at the age of 65 years. He was referred to our hospital at the age of 70 years, by which time he showed ataxic dysarthria, ataxic gait, and ataxia of the trunk and limbs. No signs of parkinsonism or orthostatic hypotension were detected. Brain MRI showed mild cerebellar atrophy and a hyperintense rim at the dorsolateral border of the putamen without atrophy of the brain stem (Fig.1-C, D). At that time, he was tentatively diagnosed as having “CCA”.

However, he developed orthostatic hypotension after 6 months and showed extensor plantar responses 2 years later. At the age of 72 years, he was subsequently diagnosed as having “probable MSA-C”. By 76 years old, he was unable to walk without a cane. Because he switched to management by another hospital thereafter, we could no longer follow his clinical course in detail, but he died at the age of 83 years (18 years after the onset). Patient 1 had no first- or second-degree relatives with neurodegenerative disorders except for her father.

3.2. Patient 2

Patient 2 first noticed a clumsiness of his hands at the age of 46 years, and his gait became unstable at 47 years. His symptoms gradually got worse and he was admitted to our hospital when he was 48 years old. Neurological examination revealed ataxic dysarthria, gaze-evoked nystagmus, limb ataxia, and gait ataxia. However, there was no evidence of orthostatic hypotension, parkinsonism, or corticospinal tract dysfunction. Brain MRI showed selective cerebellar atrophy and he was diagnosed as having “CCA” at that time. At the age of 50 years, he developed orthostatic hypotension, neurogenic

bladder, and extensor plantar responses with hyperreflexia. MRI showed severe atrophy of the brain stem and cerebellum with a “hot cross bun” sign (not shown). Over a period of seven years after the onset, his orthostatic hypotension gradually worsened. He was diagnosed as having “probable MSA-C” when he was aged 53 years. Although the patient was confined to a wheelchair, he had no signs of parkinsonism. Genetic testing excluded SCA 1, 2, 3, 6, 8, 10, 12,14, and 17 as well as DRPLA and FXTAS.

His mother was diagnosed as having Parkinson’s disease at the age of 74 years. Her response to levodopa therapy was good and brain MRI did not show any abnormal findings. She died of gastric cancer at the age of 89 years. No cerebellar ataxia was observed throughout her clinical course.

3.3. Patient 3

Patient 3 noticed an unstable gait at the age of 65 years, and she was admitted to our hospital. Neurological examination revealed bradykinesia, rigidity, and postural instability, as well as resting tremor and postural tremor of the left hand. Brain MRI did not show any abnormalities. She was suspected of having “Parkinson’s disease” and

received levodopa therapy, but her response to levodopa was poor. Six months later, she complained of obstruction in the throat and paralysis of the vocal cord muscles was observed by laryngoscopy. At the age of 67 years, she developed orthostatic hypotension and neurogenic bladder, and she was diagnosed as having “probable MSA-P”. Brain MRI revealed mild atrophy of the brain stem and the cerebellum (not shown).

Her uncle was diagnosed as having Parkinson’s disease at the age of 67 years and his response to levodopa therapy was consistent with Parkinson’s disease. Thereafter, symptoms progressed and he began to fall frequently. Brain MRI did not show any abnormalities. At the age of 75 years, he suddenly died in another hospital and the cause of his was unclear.

4. Discussion

Familial occurrence of MSA was only found in one of our subjects and the other MSA patients did not have any relatives who were diagnosed with MSA. In 1964, Lewis reported a family with orthostatic hypotension before Graham et al. first used the

term “MSA” in 1969 [5,6]. Because two members of this family had ataxia and parkinsonism in addition to orthostatic hypotension, they fulfilled the criteria for “probable-MSA”, but they also developed muscle atrophy and other family members presented with claw foot and diarrhea. These symptoms are not common in MSA, so the family might have had another neurological disease. Wüllner et al. reported a German family with MSA in 2004 [4]. Two members of the family fulfilled the criteria for “probable MSA”, and brain MRI showed changes that were typical of MSA. Furthermore, genetic studies excluded SCA 1, 2, 3, 6, 7, and 17. Although the members were not diagnosed as “definite MSA” (pathologically verified MSA), the clinical features were consistent with a diagnosis of “probable MSA”. In addition, Tsuji et al. recently reported 11 Japanese families with MSA through a nationwide survey [7]. Unfortunately, the detail of their clinical features is unpublished at present. We could not find any other reports of families with MSA during our search of the literature, so familial occurrence of MSA is very rare. In fact, a family history of a similar disorder is one of the exclusion criteria of the Consensus Criteria. The diagnosis of such cases needs to be based on careful neurological examination, neuroimaging studies, and

exclusion of hereditary SCA with a clinical phenotype resembling MSA.

Patients with MSA and a family history of other neurodegenerative disorders were also rare in our series. However, a higher frequency of neurological symptoms and neurological diseases was reported in the first-degree relatives of 60 European MSA patients than in controls [8]. In that study, three patients (5%) had a parent or brother with parkinsonism. In another report, five out of 38 MSA patients (13%) had at least one first-degree or second-degree relative with parkinsonism [9]. In our series, two out of 157 MSA patients had a family history of Parkinson's disease. Kusumi et al. reported that the age- and sex- adjusted prevalence of Parkinson's disease was 99.5 per 100,000 population in Japan in 1992 [10]. Schrag et al. reported that the age- adjusted prevalence of MSA was 4.4 per 100,000 population in England [11]. Since the prevalence of Parkinson's disease was very much higher than that of MSA, it is entirely possible that in our two families Parkinson's disease occurred as an incidental phenomenon. However MSA is neuropathologically classified as a form of "alpha-synucleinopathy" together with Parkinson's disease and dementia with Lewy bodies. Shimo et al. reported a Japanese patient with definite MSA-P whose mother was

pathologically diagnosed as having Parkinson's disease [12]. The existence of such families might indicate a common mechanism underlying "alpha-synucleinopathy" that can present as MSA or Parkinson's disease.

Although MSA is still considered to be a sporadic disorder, a few families with a history of MSA and other neurodegenerative disorders do exist. This may indicate that MSA has a multigenetic aetiology. In addition, MSA-C was the most common manifestation in our study. One hundred and eighteen patients (75%) were classified as MSA-C in our 157 MSA patients. In the other report, 155 patients (67%) were classified as MSA-C in 230 Japanese MSA patients [13]. On the contrary, MSA-P was the most common manifestation in Europe [14]. The cause of this difference is unknown, but it is likely that some genetic factors may modify the clinical phenotype of MSA. Recently, interleukin-1A, Interleukin-8, intercellular adhesion molecule-1 and tumor necrosis factor gene polymorphisms were reported to increase the risk of MSA [15-17], but no association was found between MSA and polymorphism of the alpha-synuclein, synphilin, tau, APOE, and Fragile X genes [18-20]. Genetic analysis of families with MSA might shed more light on its genetic background.

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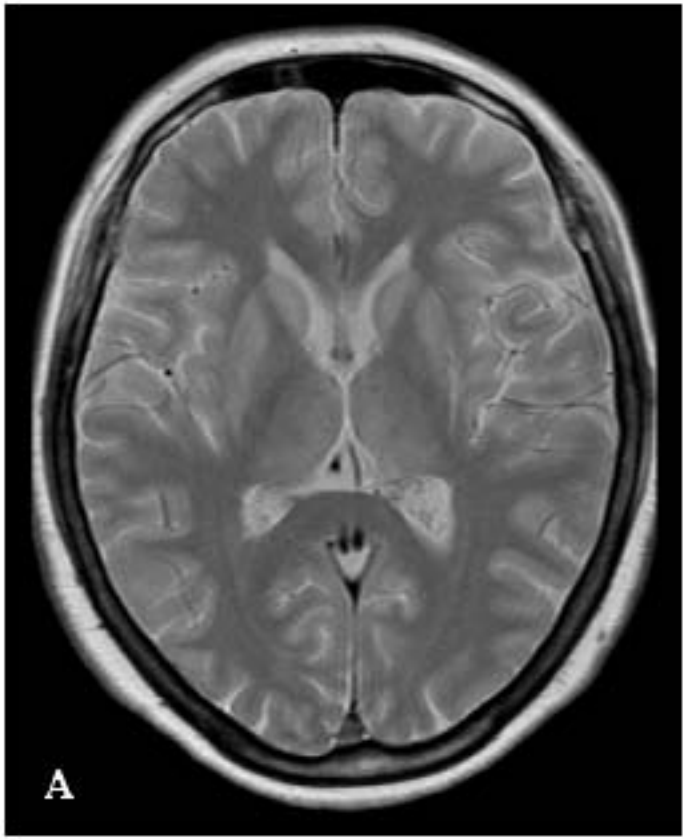
Figure Legend

Figure 1. Proton-density weighted axial magnetic resonance images at the level of the basal ganglia (A, C) and the brainstem (B), and T1 weighted sagittal magnetic resonance image (D). A and B; patient 1, C and D; the father of patient 1. A and C shows a hyperintense rim at the dorsolateral border of the left putamen. B shows a “hot cross bun” sign. D shows cerebellar atrophy, but no atrophy of the brain stem.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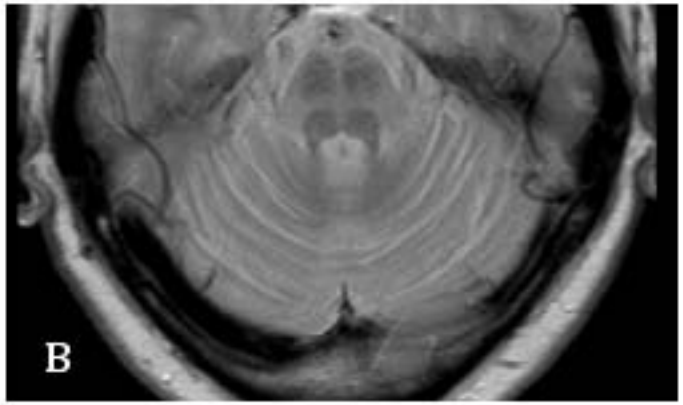
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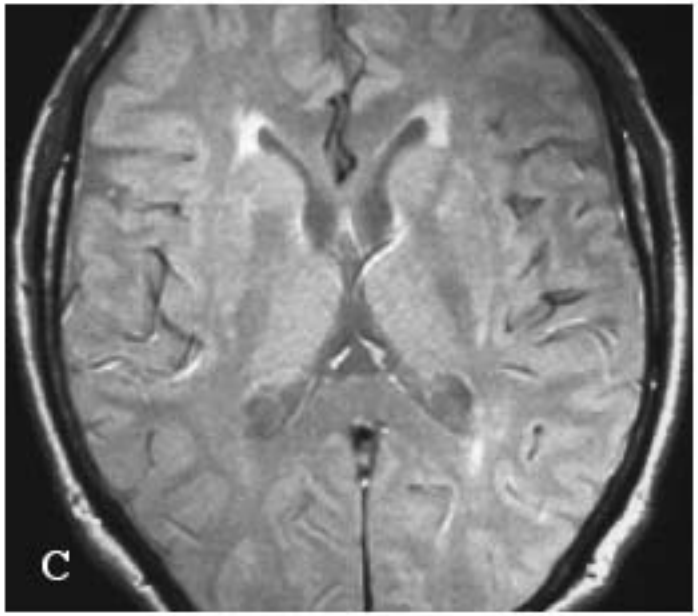
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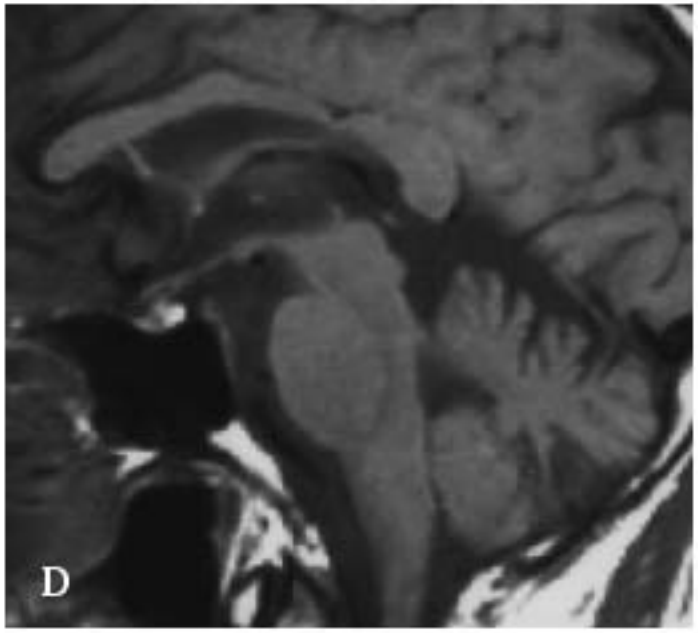
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