INTERNAL MEDICINE

□ CASE REPORT □

Neuromyelitis Optica in Japanese Sisters

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Abstract

We report cases of Japanese sisters with neuromyelitis optica (NMO). The elder sister was 25, when she was diagnosed with right optic neuritis. After 3 months, she developed left optic neuritis and myelitis. At age 27, she had the second relapse, but she has been free from episodes thereafter. The younger sister was 26, when she was diagnosed with optic neuritis. Thus far, she has 9 relapses, comprising both myelitis and optic neuritis. Both sisters had normal brain MRI scans, longitudinally extensive transverse myelitis over 3 vertebral segments, and positive results for anti-aquaporin-4 antibody (AQAP4Ab). They fulfilled the Wingerchuk criteria for definite NMO. Both sisters shared some immunogenetic factors, but they were not exposed to the same environmental factors after their early twenties. The final disability status was almost the same in both cases, and both showed a very benign course. These data suggest that genetic factors affect the age at onset and environmental factors may affect the frequency of relapse.

Key words: neuromyelitis optica, familial, HLA, anti aquaporin-4 antibody, environmental factor

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Introduction

Neuromyelitis optica (NMO) is a demyelinating disorder of the central nervous system that generally affects the optic nerves and spinal cord but less often the brain (1, 2). Opticospinal multiple sclerosis (OSMS) in Asians has been suggested to be the same entity as NMO, because anti-aquaporin-4 antibody (AQP4Ab) has been reported to be present in 30% to 60% of OSMS patients (3). The incidence of human leukocyte antigen (HLA)-*DPB1*0501* was significantly increased in anti-AQP4Ab-positive Japanese patients as compared with healthy controls, but not in anti-AQP4Ab-negative OSMS patients (4). Furthermore, cases of familial NMO have been reported suggesting genetic influence (5-9). The mechanism of NMO is speculated to be associated with humoral immunity, but still remains to be fully elucidated (4, 10, 11). Here, we report cases of Japanese sisters with NMO, in which the onset age was similar, but the frequency of relapse was different.

Case Report

Patient 1: Elder sister

Patient 1 was a 54-year-old woman. She did not have any family history of immunological disorders. When she was 25, right-sided blindness developed and she was diagnosed as having optic neuritis. Steroid therapy completely improved her vision. After 3 months, she lost her left sight and had paraparesis and dysuria. The neurologic evaluation revealed blindness in the left eye, weakness of bilateral lower extremities, positive bilateral Babinski reflexes, and bilateral loss of sensation below the Th10 level. Steroid therapy improved her symptoms within several months. At age 27, she had paraparesis and dysuria. Steroid therapy improved her symptoms again. Thereafter, she has been free from episodes of neurological dysfunction. At age 50, a test for AQP4Ab was found to be positive (12, 13). Her HLA type was *A*31, B*61, *51, DRB1*0802*, and *DPB1*0501*. At age

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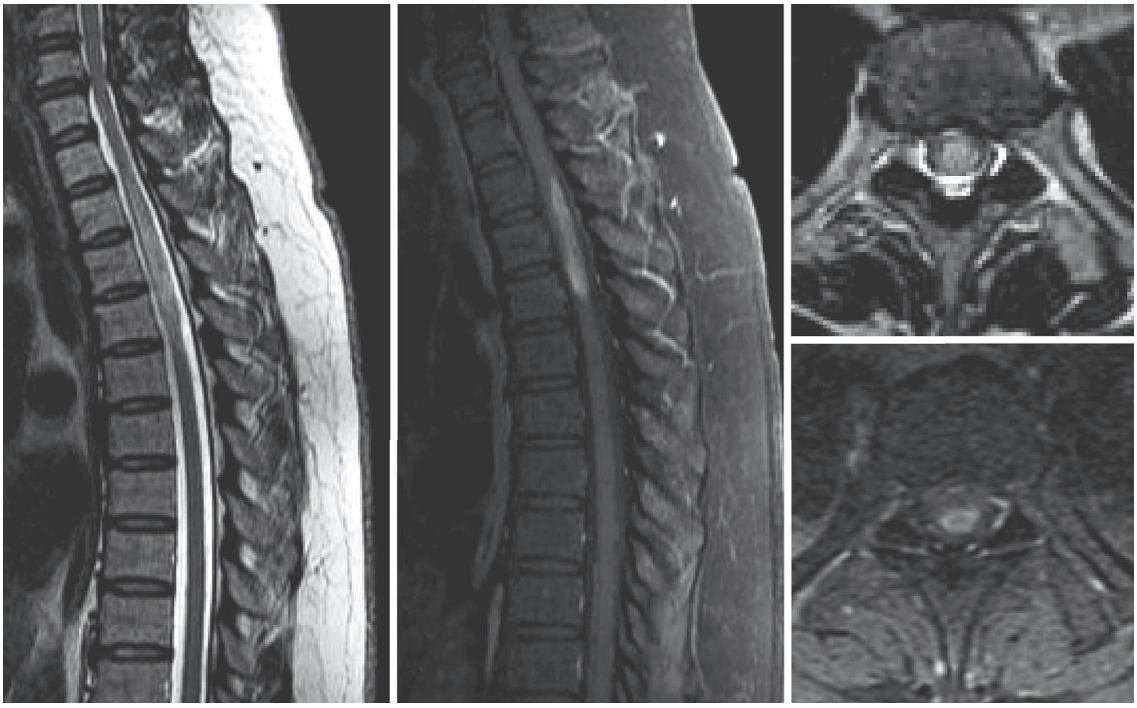

Figure 1. **Spinal magnetic resonance imaging (MRI) of patient 2: T2-weighted image (1.5 T, repetition time [TR] 3000 ms, echo time [TE] 90 ms) and T1-weighted image with gadolinium enhancement (1.5 T, TR 400 ms, TE 9 ms). When patient 2 had her last relapse at age 49, the spinal MRI scan showed high-intensity areas at Th2-4 on T2-weighted images with swelling and gadolinium enhancement.**

53, spinal magnetic resonance imaging (MRI) did not demonstrate apparent abnormality in parenchymal signal intensity, and her brain MRI was normal. There has been no medication for the prevention of relapse. The final Expanded Disability Status Scale of Kurtzke score was 1.0 (14) and the final visual function of both eyes was normal.

Patient 2: Younger sister

Patient 2 was a 53-year-old woman. When she was 26, right-sided blindness developed and she was diagnosed as having optic neuritis. Steroid therapy improved her vision completely. At age 27, she had paraparesis, loss of sensation below the L1 level and dysuria. The neurologic evaluation revealed weakness of bilateral lower extremities, positive bilateral Babinski reflexes, and bilateral loss of sensation below the L1 level. Steroid therapy improved her symptoms completely within several months. At age 29, she had loss of sensation below the Th5 level and steroid therapy improved her symptoms again. To date she has had 9 relapses, comprising of both myelitis and optic neuritis. At age 49, a test for AQP4Ab was found to be positive. Her HLA type was *A*31, B*61, *51, DRB1*0802*, and *DPB1*0501*, which is the same as that of her elder sister. At the last relapse, when she was 49, the MRI showed on T2-weighted images, and enlarged spinal cord lesions with gadolinium enhancement (Fig. 1). Her brain MRI was normal. Low-dose steroid treatment and immunosuppressant (azathioprine) treatment have been continued for the prevention of relapse. The final Expanded Disability Status Scale of Kurtzke score was 2.0 (14) and the final visual function of both eyes was normal.

Both patients fulfilled the criteria of NMO of Wingerchuk et al (15). The sisters had lived in the same area until the elder sister got married at age 23. The younger sister married at age 22 and moved to a northern rural area of Japan. Thus, they shared some immunogenetic factors but were not exposed to the same environmental factors after their early twenties.

Informed consents was obtained from both patients.

Discussion

These 2 cases of Japanese sisters met the criteria of NMO. Both sisters had positive results for AQP4Ab and shared some immunogenetic factors. Their onset ages of NMO were similar. The frequency of relapse was different. The final disability status was almost the same and both sisters showed a very benign course of the disease. These patients were the third cases of familial NMO in Japan (including that discussed in a Japanese language abstract) (7).

According to a literature search, several familial cases of NMO have been reported (5-9). Those cases included 7 cases of sisters, 2 mother-daughter pairs, 2 aunt-niece pairs, 2 brother-sister pairs, 1 father-daughter pair, 1 mother-son pair, and 1 family with 3 patients (mother-daughter-aunt). Ninety-three percent of these familial cases were fe-

male (11). The first report of familial NMO in 1938 described that identical twin women developed NMO at ages 24 and 26 years, respectively, but their HLA type was unknown (5). In the first report, 1 woman had 1 recurrence for 18 months; the other had 2 recurrences for 26 months (5). The second case of sisters in 1982 described 2 younger sisters who developed NMO at ages 3 years and 2 years 9 months. The HLA type of the elder sister was *A1, 2, BW35, W40*, and *BW622* and that of the younger sister was *A1, XBW35*, and *YBW622* (6). In another case of sisters, the women developed NMO at ages 62 and 59 years (7). The HLA type of the elder sister was *A2/33, B39/44, Cw7/-, DR 4/6*, and *DQ1/3* and that of the younger sister was *A26/33, B44/62, Cw3/-, DR6/12, DQ1/-*, and *DP1/-* (7). The onset ages in the forth case of sisters were 24 and 28 years (8). The HLA type of the elder sister was *A*24, B*07, *15, DRB1*01*, and **16 (DR2 positive)* and that of the younger sister was *A*02, 24, B*07, *40, DRB1*04*, and **08* (8). In the fifth report of 4 sibling cases, the onset ages were 29.2 and 28.1 years, 28.4 and 26.5 years, 33.9 and 32.1 years, and 40.7 and 25.1 years (9). There is little data regarding the long-term prognosis after onset. The fifth report described 4 sibling cases with recurrent episodes of optic neuritis and myelitis (1 and 6 times, 7 and 2 times, 5 and 13 times, and 3 and 7 times, respectively) (9). Interestingly, the initial episodes of NMO occurred at similar ages in these reports, except for the last pair of sisters. In the present cases, the onset ages of NMO were also similar (within 1 year). Such observation may suggest that there is a common trigger for the onset of NMO related to the immunogenetic background of NMO in sister cases.

In the present cases, although the frequency of relapse was different between the 2 sisters, the final disability status was almost the same and both sisters showed a very benign course of the disease. However, in previous reports on sisters with NMO, little data was provided on the final disability status. It would be interesting to study this aspect in the future. It is suggested that the clinical feature might be related to the immunogenetic background of NMO in sister cases.

The genetic contributions were supported by recent observations that have linked NMO to specific HLA loci, such as *DPB1*0501* in Japanese patients (10). The *HLA-DPB1*0501* allele was more frequent in 38 Japanese patients who were seropositive for NMO-IgG as compared to 52 patients with multiple sclerosis (MS) (4). Forty-five French Caucasian patients were compared to healthy controls and patients with MS for HLA class II A and B alleles; no association was found for *DRB1*1501* with NMO. *HLA-DRB1*03* was associated with NMO-IgG-seropositive NMO (16). The HLA type has been reported to be similar in sisters with NMO in 2 families (6-8). In the present cases, the sisters shared some immunogenetic factors because their HLA type was similar.

With regard to environmental factors, certain infections or cancers have been reported to complicate NMO (17, 18). However, there is no report on environmental or disease triggers that have a firm association with NMO (11). In the present cases, the sisters had lived in the same area just before the first episode of NMO, but 1 sister moved to a northern rural area and was then exposed to a different environment. The difference in environmental factors may have affected the frequency of relapse, although the precise factors are unknown.

These observations suggest that genetic factors affect the ages at onset and that environmental factors may affect the frequency of relapse in familial NMO.

The authors state that they have no Conflict of Interest (COI).

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