Neuromyelitis Optica in a Mother and Daughter

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Background: Neuromyelitis optica (NMO) is a rare demyelinating disease of the central nervous system that most often results in selective involvement of the optic nerves and spinal cord. Although most cases are sporadic, several familial cases have been reported. All of those patients have been siblings who experienced disease onset at similar ages. To our knowledge, there has not been a documented case between a mother-daughter pair, nor has there been a reported case in which family members developed the disease at different stages of life.

Objectives: To illustrate the clinical courses of NMO in a white mother-daughter pair, which supports a hereditary predisposition to this disorder, as well as to reinforce that onset of disease can occur at different ends of the age spectrum even within the same family.

Design, Setting, and Patients: Case report of a mother-daughter pair with NMO treated at the University of Michigan Medical Center.

Results: After multiple occurrences of optic neuritis and transverse myelitis as well as extensive workups, both mother and daughter were eventually diagnosed with NMO but with different ages at onset, at ages 62 and 29 years, respectively.

Conclusions: Development of NMO is in part genetically influenced. Our familial cases show that NMO may differ clinically within a family. While current diagnostic criteria include an extensive spinal cord lesion, the second case (mother) illustrates that milder cases of NMO might not fulfill that requirement, in which case NMO-IgG antibody seropositivity may confirm the diagnosis.

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posed a revision to the 1999 diagnostic criteria that incorportates NMO-IgG antibody seropositivity and acknowledges that cerebral involvement may occur. In the revised criteria, 2 of 3 supportive criteria must be met: (1) brain MRI must not be diagnostic of multiple sclerosis; (2) the spinal cord lesion must still be 3 or more segments in length; and (3) the patient must be NMO-IgG antibody seropositive.

Given the suspected genetic underpinnings, it is somewhat surprising that few familial cases of NMO have been described. Here we describe familial NMO in a mother and daughter.

REPORT OF CASES

CASE 1, DAUGHTER

A 29-year-old woman had a history of myasthenia gravis that had been inactive since childhood (she had a thymectomy in 1978). In 1992, she came to the University of Michigan with quadriparesis. Cerebrospinal fluid analysis revealed a white blood cell count of 70/mL, a protein level of 81 mg/dL, 2 oligoclonal bands not present in serum, and an increased IgG index (0.74). Rheumatology analysis results were normal. Brain MRI results were normal (Figure 1A). Cervical spine MRI showed a contrast-enhancing T2 signal abnormality from C2 through C6 (Figure 1B and C). She was diagnosed with transverse myelitis, and after a course of intravenous steroids, she recovered with the exception of persistently decreased vibration and proprioception at the toes. She then developed optic neuritis in the left eye at age 36 years, from which she recovered after receiving intravenous steroids.

At age 37 years, she had another episode of transverse myelitis unresponsive to intravenous steroids. She was left with left-sided weakness and sensory loss. Six weeks later, she developed optic neuritis in the left eye and then in the right eye, with only minimal light perception detected in each eye. At this point, NMO was considered. High-dose intravenous steroids were initiated, along with 6 plasma exchanges. On discharge, vision was improved in each eye, as were strength and sensation. After discharge, the patient developed a pulmonary embolism and required hospitalization. Subsequently, she became debilitated and quadriparaetic. Three weeks later, she developed acute respiratory distress requiring intubation. She remained quadriparaetic, eventually became ventilator dependent, and died 4 years later of pneumonia at age 42 years.

CASE 2, MOTHER

A 62-year-old woman, the mother of the first patient, was otherwise healthy until 2001, when she developed a lower thoracic sensory level. She came to the University of Michigan 1 month later, when she experienced painful loss of vision in the right eye. Examination showed visual acuity of 20/400 OD, a right afferent pupillary defect with superior altitudinal defect, and decreased perception of light touch and vibration in both lower extremities. Cerebrospinal fluid analysis revealed a white blood cell count of 5/mL, a protein level of 75 mg/dL, a normal IgG index (0.49), and no oligoclonal bands. Rheumatology analysis results were normal. Brain MRI revealed only a few small-vessel ischemic changes (Figure 2A). Magnetic resonance imaging of the cervical spine revealed a contrast-enhancing T2 signal abnormality at C4 through C5 (Figure 2B and C). Intravenous steroids led to some improvement in her sensory symptoms but not in her visual symptoms. Owing to the close temporal association between her visual loss and transverse myelitis and ancillary study results, NMO was suspected. However, as the altitudinal defect was felt to be somewhat atypical for optic neuritis (ischemic optic neuropathy was considered), NMO was not confirmed.

Visual acuity in the right eye showed minimal improvement on follow-up. She remained free of new symptoms until 2002, when she developed painful loss of vision in the left eye, intact only to finger counting.
Intravenous steroids were ineffective, and she presently has no light perception in the left eye. She was diagnosed with NMO, and mycophenolate mofetil was initiated in 2003. She has had no further episodes. In 2006, serum NMO-IgG antibody testing results were positive (titer, 1:240).

COMMENT

These 2 cases satisfy both the 1999 and 2006 revised NMO criteria. In case 1, NMO-IgG antibody testing was not performed. Applying the 1999 criteria to case 2, the patient did not have a spinal cord lesion extending 3 or more vertebral segments, nor did she have cerebrospinal fluid pleocytosis. It is conceivable that had a spinal cord MRI been obtained earlier than 5 weeks after symptom onset, the lesion length criteria might have been satisfied, as lesions may recede over time. Applying the revised criteria, case 2 is IgG seropositive. These results emphasize that in an individual without an extensive spinal cord lesion, NMO-IgG antibody testing results will influence diagnosis.

Several familial cases of NMO have been reported. In 1938, McAlpine described NMO in identical twin women who developed myelitis followed by bilateral optic neuritis at ages 24 and 26 years. Another familial case was described by Ch’ien et al in 1982, once again affecting 2 sisters, aged 10 and 6 years, who developed NMO at ages 3 years and 2 years 9 months, respectively. Finally, Yamakawa et al described a familial case of NMO between 2 elderly sisters aged 62 and 59 years.

Our cases are unique because, to our knowledge, they are the first in which NMO between a parent and child has been described, as all cases reported to date have been between siblings. Moreover, in previously reported cases, initial episodes of NMO occurred at similar ages, whereas our patients had different ages at onset. Despite this heterogeneity, however, genetic contributions to the disease cannot be ignored. The greatest implication that this finding may have is its contribution to earlier diagnosis and treatment. As there is often a significant delay in diagnosing NMO, either because other demyelinating diseases are suspected or because clinicians may not feel entirely justified in obtaining testing for NMO-IgG antibody, having a family member with documented NMO may justify additional testing rather than waiting for the next clinical episode.

Several recent case reports suggest that the prevalence of NMO in patients with myasthenia gravis (as in case 1) and other autoimmune diseases is substantially higher than in the general population. Kister et al illustrate this point in a recently published case series of 4 patients who developed NMO after thymectomy for myasthenia gravis. All of the 4 patients presented with optic neuritis and subsequent transverse myelitis after thymectomy, and they were eventually diagnosed with NMO. One possible explanation for the increased prevalence of NMO may be the removal of T-suppressor cells with thymectomy, which may disrupt the balance of B-cell immunity. As our patient demonstrated a similar outcome after thymectomy, we feel that this association again deserves mention.

CONCLUSIONS

Despite our growing understanding of NMO, there is still much to be learned about its etiologic contributions. We have reported these cases with the hope that they will emphasize a genetic contribution. We also wish to spotlight the observation that family members with NMO need not present at the same time. Instead, NMO presentations even within the same family may be quite heterogeneous. Finally, with recent literature demonstrating the necessity for revised NMO diagnostic criteria, including NMO-IgG antibody seropositivity, the second case highlights the diagnostic utility of the NMO-IgG antibody assay.

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REFERENCES


Announcement

Calendar of Events: A New Web Feature

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