Neuromyelitis Optica in Patients With Myasthenia Gravis Who Underwent Thymectomy

Ilya Kister, MD; Sandeep Gulati, MD; Cavit Boz, MD; Roberto Bergamaschi, MD; Giuseppe Piccolo, MD; Joel Oger, MD; Michael L. Swerdlow, MD

Background: Myasthenia gravis (MG) and neuromyelitis optica (NMO, also known as Devic disease) are rare autoimmune disorders, with upper-limit prevalence estimates in the general population of 15 per 100,000 and 5 per 100,000, respectively. To our knowledge, an association between these diseases has not been previously reported.

Objectives: To describe 4 patients with MG who developed NMO after thymectomy and to analyze possible causes of apparent increased prevalence of NMO among patients with MG.

Design: Case series.

Patients: Four patients with MG who underwent thymectomy.

Interventions: None.

Results: The prevalence of MG within the published cohort of patients with NMO is more than 150 times higher than that in the general population.

Conclusion: Dysregulation of B-cell autoimmunity in myasthenia, possibly exacerbated by loss of control over autoreactive cells as a result of thymectomy, may predispose patients to the development of NMO.

Arch Neurol. 2006;63:851-856

EUROMYELITIS OPTICA (NMO) is characterized by 1 or more attacks of optic neuritis (ON) and myelitis. It can be differentiated from multiple sclerosis (MS) with the aid of magnetic resonance imaging (MRI),1-3 cerebrospinal fluid analysis4-8 and NMO-IgG antibody.9 The lesions in NMO differ from those of MS with respect to patterns of immunoglobulin and complement deposition and populations of inflammatory cells.10,11 Patients with NMO often have coexisting autoimmune disorders, such as systemic lupus erythematosus, Sjogren syndrome, and pernicious anemia.12,13 Ours is the first case series, to our knowledge, of coexisting MG and NMO. All 4 of our patients were diagnosed as having MG, underwent thymectomy, and subsequently developed NMO. We discuss the evidence for B-cell dysregulation in NMO and for the possible role of thymectomy in potentiating the emergence of autoimmune disease.

REPORT OF CASES

CASE 1

An African American woman with mild asthma, distant history of smoking and cocaine snorting, and family history of MS in her mother developed symptoms of ocular myasthenia at age 38 years. The diagnosis was confirmed by neostigmine test and an elevated anti–acetylcholine receptor (anti-AChR) antibodies titer. That same year, her thymus was excised, and histologic examination revealed hyperplasia. The symptoms resolved and pyridostigmine bromide therapy was tapered.

A year after the surgery, she experienced acute-onset visual loss in her right eye, followed by visual loss in the left eye 10 days later. Her clinical picture and visual evoked potentials were typical of ON. Magnetic resonance imaging of the brain disclosed a questionable increased T2 signal in the right optic nerve and a few non-enhancing scattered subcortical foci of in-
increased T2 signal (Figure 1). These were unchanged after several years of follow-up.

During the next 5 years the patient experienced 7 relapses of ON. Four years after the initial attack, she was given a brief trial of interferon beta-1a (Avonex) but soon developed progressive left-sided weakness. She was admitted to the hospital with a partial Brown-Sequard syndrome and T7 sensory level. An eccentric lesion extending from C2 to T1 was seen on MRI. She was diagnosed as having NMO and began azathioprine therapy. During the next 2 years she experienced 2 relapses of ON and 2 relapses of myelitis. At last follow-up, she had only shade perception and ambulated with assistance. Results of an extensive rheumatologic and infectious workup were unremarkable. Table 1 and Table 2 summarize the essential clinical, radiological, and laboratory data, including NMO-IgG antibody status and cerebrospinal fluid analysis for all of our patients. Figures 2, 3, 4, and 5 show representative MRI views of spinal cord during myelitis attack for each of our 4 patients.

CASE 2

A healthy 36-year-old African American woman presented with ocular symptoms of MG and was found to have an elevated anti-AChR antibodies titer, decrementing responses on repetitive stimulation, and positive response to neostigmine. She was treated with pyridostigmine therapy and thymectomy, with excellent response. Thymus hyperplasia was seen on histologic examination.

At age 41 years, she acutely lost vision in the right eye. The examination results were consistent with bulbary ON. Brain MRI was normal, and increased T2 signal was seen in the left optic nerve. Visual acuity did not improve with time.

At age 42 years, she was admitted to the hospital with swelling and pain in the forearms precipitated by vigorous clapping. Her urine was dark red, and her creatine kinase level was 25,000 U/L. Rhabdomyolysis resolved with aggressive hydration.

At age 43 years, she developed leg paresthesias and midthoracic back pain. She had profound sensory dysfunction in all modalities below T8 level, symmetric hyperreflexia of the legs, and bilateral extensor plantar responses. Magnetic resonance imaging demonstrated abnormal cord signal from the lower cervical spine to T9 and enhancement in T2 through T4. An MRI of the brain was normal, as were rheumatologic and infectious serologic test results, except for a mildly elevated antinuclear antibody titer (1:80). She was started on azathioprine therapy.

Later that year, she was readmitted for progressive stiffness and spasms of all extremities. The clinical picture suggested stiff-person syndrome. Her serum anti–glutamic acid decarboxylase antibody titer was 2 U/mL (reference threshold, <1.0 U/mL). A course of intravenous immunoglobulin and methylprednisolone acetate yielded a substantial improvement of her spasticity.

At age 44 years, she had a milder relapse of myelitis. An MRI showed cord edema and enhancement from T3 through T5 and abnormal T2 signal at C5-C6. She again responded well to a short course of intravenous immunoglobulin and methylprednisolone.

CASE 3

A 17-year-old white girl complained of fluctuating difficulties with speech and chewing. She exhibited nasal voice and facial, tongue, and neck weakness that worsened with exercise. Decrementing response on repetitive stimulation test, elevated anti-AChR antibodies, and positive response to neostigmine confirmed the diagnosis of MG. Good control of symptoms was achieved with pyrostigmine. Her thymus was resected and revealed hyperplasia.

At age 19 years, she sustained acute severe loss of vision in both eyes. Visual evoked response was absent on the right and of low amplitude and delayed P100 latency on the left. She was diagnosed as having bilateral ON. During the subsequent 5 months, she had 3 relapses of ON leading to blindness in the right eye and severely impaired vision in the left.

At age 33 years, she developed leg weakness and sensory loss below the thorax. A large swollen lesion extending from C8 to T3 was seen on MRI. During 10 years of follow-up, she experienced 9 relapses of myelitis and 1 of ON. At last follow-up, she had a sensory T2 level and required a cane for walking because of moderate paraparesis. During the relapses, a cervical-dorsal lesion was always detected on MRI, variable in size from 3 to 5 spinal segments. On 2 occasions the lesion was enhanced with gadolinium. Brain MRI continued to show normal findings.
CASE 4

A 27-year-old Chinese woman presented with ptosis and diplopia. She was diagnosed as having MG in her native Hong Kong and underwent thymectomy the same year. There was no evidence of thymoma on pathologic examination. Her symptoms were initially controlled with pyridostigmine and prednisone, but at age 31 years she was admitted to a Canadian hospital with worsening diplopia and limb weakness. Her anti-AChR antibody titer was elevated. Azathioprine was added to her treatment regimen. Repeat exploration of her anterior chest was performed in view of a suggestion of residual thymic tissue on chest computed tomography.

At age 37 years, her vision acutely declined in both eyes and she complained of weakness and abnormal sensation in the arms and urinary retention. Visual evoked potentials were consistent with ON. Spinal MRI showed loci of high signal within the cervical cord, most prominently alongside C4 and C5 but extending to the C2 level.

A year later, her vision deteriorated acutely in both eyes. She also complained of paroxysmal tonic spasms, which later resolved. Magnetic resonance imaging showed T2 signal alongside C4 through C6 and a lesion at the level of C2. Brain MRI was unremarkable.

Our case series of coexisting MG and relapsing-remitting NMO is in line with the well-documented observation that autoimmune disorders are vastly overrepresented within this subset of patients with NMO. In the largest published NMO cohort,1 as many as a third of patients with relapsing disease, but none in the monophasic group, had a concomitant autoimmune disorder.

Within the published cohort of approximately 200 cases of NMO,1-3,5,6,8,14-20 there are now 5 patients with a dual diagnosis of NMO and MG—4 of them are described here and 1 by Antoine et al.21 The association between the 2 diseases is unlikely to be due to chance because NMO and MG are both rare, with prevalence estimates from 0.4 per 100 000 to 5.4 per 100 000 for NMO,22,23 and 15 per 100 000 for MG.18 Although a rigorous demonstration of an association between the 2 diseases would require a population-based analysis, the wide discrepancy between the prevalence of MG in the published NMO cohort (2%-3%) compared with its prevalence in the general population (<0.02%) is quite remarkable. Three of our 4 patients in our series are of African or Asian descent—consistent with previous reports of higher prevalence and greater severity of NMO among nonwhite individuals.19,22,23

The number of patients with both MG and NMO may be even higher, if one were to include patients with a suggestive clinical picture but without radiographic confirmation, such as a patient with MG and recurrent bilateral ON who developed myelitis after thymectomy,24 or the patient with a presumed dual diagnosis who was described by Martikainen et al.25 There are also reports of individuals with MG who underwent thymectomy and then developed relapsing-recurrent myelitis26 or bilateral ON,27,28 possibly formes frustes of NMO.

Table 1. Clinical and Radiological Findings in 4 Patients With MG and NMO

<table>
<thead>
<tr>
<th>Patient No./Sex/Race</th>
<th>Age at Event, y</th>
<th>Onset of MG</th>
<th>Onset of NMO</th>
<th>First Attack of NMO</th>
<th>No. of ON Relapses</th>
<th>No. of Myelitis Relapses</th>
<th>MRI Lesion at First Myelitis Attack</th>
<th>Other Medical Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/AA</td>
<td>38</td>
<td></td>
<td>38</td>
<td>39</td>
<td>ON</td>
<td>7</td>
<td>C6-T1</td>
<td>HTN, asthma</td>
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<tr>
<td>2/F/AA</td>
<td>36</td>
<td></td>
<td>37</td>
<td>42</td>
<td>ON</td>
<td>1</td>
<td>C7-T9</td>
<td>Asthma, SPS</td>
</tr>
<tr>
<td>3/F/white</td>
<td>17</td>
<td></td>
<td>17</td>
<td>19</td>
<td>ON</td>
<td>6</td>
<td>C8-T3</td>
<td>None</td>
</tr>
<tr>
<td>4/F/Asian</td>
<td>27</td>
<td></td>
<td>28</td>
<td>36</td>
<td>ON/M</td>
<td>2</td>
<td>C2, C4-6</td>
<td>None</td>
</tr>
</tbody>
</table>

Table 2. Laboratory Findings in 4 Patients With MG and NMO

<table>
<thead>
<tr>
<th>Patient No./Sex/Race</th>
<th>CSF Analysis</th>
<th>Antibodies</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WBC Count, Cells/µL</td>
<td>Oligoclonal Bands</td>
<td>NMO-IgG</td>
</tr>
<tr>
<td>1/F/AA</td>
<td>10</td>
<td>None</td>
<td>+</td>
</tr>
<tr>
<td>2/F/AA</td>
<td>2</td>
<td>None</td>
<td>+</td>
</tr>
<tr>
<td>3/F/white</td>
<td>55</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>4/F/Asian</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: AA, African American; HTN, hypertension; M, myelitis; MRI, magnetic resonance imaging; NMO, neuromyelitis optica; ON, optic neuritis; SPS, stiff-person syndrome.

Abbreviations: AA, African American; anti-AChR, anti–acetocholine receptor; ANA, antinuclear antibodies; anti-GAD, anti–glutamic acid decarboxylase antibody; CSF, cerebrospinal fluid; NA, not available; NMO-IgG, neuromyelitis optica–IgG; WBC, white blood cell; +, present; −, absent.
A possible association between MG, an antibody-mediated autoimmune disease, and NMO is intriguing in view of the considerable body of evidence implicating dysfunction of humoral immunity in the pathogenesis of NMO. Especially noteworthy is a recent finding9 of NMO autoantibody marker, which reacts against a self-antigen localized at the blood-brain barrier and has a reported sensitivity and specificity of 73% and 91%, respectively, for this disease. Others29 showed that serum of patients with NMO reacts with myelin oligodendrocyte glycoprotein antigen. This is in agreement with an experimental model of myelin oligodendrocyte glycoprotein–induced allergic encephalomyelitis in rats in which 39% of the rats exhibited “NMO-type illness” with an appearance of major lesions in optic nerve and spinal cord.30 The index of IgG1 in the cerebrospinal fluid of patients with NMO was not significantly elevated, in contrast to the index in patients with MS,7 suggesting that IgG1-associated, cell-mediated response is relatively unimportant in NMO and possibly explaining the absence of oligoclonal bands, mostly composed of IgG1 subclass, in most patients with NMO.

The case report21 of NMO in an individual with MG and a thymoma provides the most direct evidence for a temporal, if not necessarily causal, relationship between production of aberrant autoantibodies and emergence of NMO: In that case, only antibodies from the patient’s serum taken early in the course of NMO stained rat’s central nervous system tissues, whereas serum taken either before or 10 days after onset did not.

The role of humoral immunity in NMO is highlighted by immunohistopathological studies11 suggesting that activation of the classical complement pathway and recruitment of macrophages in NMO lesions may be triggered by a specific antibody found in the blood-brain barrier. This idea has been corroborated by the recent discovery of an NMO-IgG autoantibody against aquaporin 4.9

It is of considerable interest that, in all 5 patients with MG and NMO, thymectomy preceded development of NMO by months to years. By contrast, in the MS/MG cohort, MG anticipated MS in only half of the cases.18 The fact that NMO followed thymectomy may not be a mere coincidence. A long-term study31 of thymectomized patients showed that 12.5% of them developed autoimmune diseases and more than 60% had at least 1 expansion within the CD8 and CD4 T-cell reper-
toire, compared with less than 15% of control subjects. Patients who underwent thymectomy also had significant increase in total IgM, anti-cardiolipin, and anti-double-stranded DNA and high-titer antinuclear antibodies compared with patients with MG who had not undergone operation and healthy controls. These data suggested that suppressor T cells in the adult thymus may be necessary to keep in check autoreactive cells and to prevent the emergence of autoimmune disease. Gerli et al also cited numerous extant reports of autoimmune disease after thymectomy (references 7-23 in that article). It is interesting to note that 2 of our 4 patients tested positive for non-MG autoantibodies and 1 patient developed stiff-person syndrome. A paradoxical role of thymus in protecting against some autoimmune conditions, while potentiating others, was demonstrated in animal models.

The present article describes 4 patients with MG and NMO, 2 rare and seemingly unrelated autoimmune disorders. The 150-fold increase in prevalence of MG within the published cohort of patients with NMO compared with the general population suggests that this association is not random. We speculate that dysregulation of B-cell autoimmunity seen in MG and possibly exacerbated by loss of control over autoreactive cells as a result of thymectomy predisposed our patients to development of NMO. Future research is required to establish whether there is indeed a small long-term excess risk of developing autoimmune disease in individuals with MG who undergo thymectomy.

Accepted for Publication: January 24, 2006.

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Author Contributions: Study concept and design: Kister and Swerdlow. Acquisition of data: Kister, Gulati, Boz, Bergamaschi, Piccolo, and Oger. Analysis and interpretation of data: Kister and Bergamaschi. Drafting of the manuscript: Kister, Gulati, Boz, and Bergamaschi. Critical revision of the manuscript for important intellectual content: Kister, Gulati, Bergamaschi, Piccolo, Oger, and Swerdlow. Administrative, technical, and material support: Kister and Gulati. Study supervision: Bergamaschi and Swerdlow.

Acknowledgment: We thank Richard Lipton, MD, for critical review of the manuscript and Todd Miller, MD, for technical assistance.
REFERENCES


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Correction

Error in Byline: In the Original Contribution by Kister et al titled “Neuromyelitis Optica in Patients With Myasthenia Gravis Who Underwent Thymectomy,” published in the June issue of the ARCHIVES (2006;63:851-836), an error occurred on page 851. In the byline, the full name of Dr Piccolo should have appeared as “Giovanni Piccolo, MD.”