Myasthenia Gravis–Associated Neuromyelitis Optica–Like Disease

An Immunological Link Between the Central Nervous System and Muscle?

Adi Vaknin-Dembinsky, MD, PhD; Oded Abramsky, MD; Panayiota Petrou, MD; Tamir Ben-Hur, MD, PhD; Marc Gotkine, MD; Livnat Brill; Talma Brenner, PhD; Zohar Argov, MD; Dimitrios Karussis, MD, PhD

Background: Although overt involvement of the central nervous system (CNS) in myasthenia gravis (MG) is considered rare, hyperreflexia is a common and yet unexplained finding. Aquaporin 4 (AQP4), the target autoantigen in neuromyelitis optica, is expressed both in the CNS and in the neuromuscular junction.

Objectives: To evaluate the prevalence of even mild CNS involvement in patients with MG and to identify features indicative of neuromyelitis optica–like disease.

Design: Cohort study.

Setting: Outpatient clinic.

Patients: A cohort of 164 patients with MG.

Methods: In 24 patients with MG, signs of CNS involvement were detected; 15 of these patients had at least 1 additional paraclinical indication of neuromyelitis optica–like disease (presence of antibodies against AQP4, pathological visual evoked potentials, or white matter lesions detected on brain and/or spinal magnetic resonance imaging scans) and fulfilled the inclusion and exclusion criteria for our study.

Results: Of the 15 patients who had at least 1 additional paraclinical indication of neuromyelitis optica–like disease, 14 had abnormal visual evoked potentials, and in 6 of 9 patients in whom magnetic resonance imaging was performed, there was evidence of lesions in the white matter of the brain and/or spinal cord. Anti-AQP4 antibodies were detected in 7 patients (out of the 14 tested). Thymic enlargement (hyperplasia or thymoma) was more frequent in patients with MG who had signs of CNS involvement than in patients with MG who did not.

Conclusions: The incidence of CNS involvement in MG is higher than previously reported and is expressed predominantly as a pyramidal syndrome accompanied by optical tract involvement (frequently subclinical). These features bear some resemblance to neuromyelitis optica spectrum disease, supported also by the presence of anti-AQP4 antibodies in 7 of the 14 patients tested. This association may represent a new nosological entity or may indicate that an autoimmune process targeting AQP4 is an integral part of the immunopathogenetic mechanisms in MG.


MYASTHENIA GRAVIS (MG) is the most common acquired disorder of the neuromuscular junction and is caused by autoantibodies targeting mainly the acetylcholine receptor (AChR) or other proteins (such as the muscle-specific kinase) of the postsynaptic membrane. It represents the best-characterized autoimmune disease. Other autoimmune diseases are frequently associated with MG, the most common being autoimmune thyroid disease.

One of the frequently described clinical findings in MG is hyperreflexia, which may be a sign of central nervous system (CNS) involvement. In general, CNS involvement is rare in patients with MG and includes mild cognitive disorder, epilepsy, and Parkinson disease. Lately, immune-mediated CNS involvement has been described in association with MG. In the patients with signs of CNS involvement, the most frequent presentation was that of myelitis or neuromyelitis, as reported by our group and other investigators.

Neuromyelitis optica (NMO), also known as Devic disease, is an idiopathic, severe demyelinating disease of the CNS that preferentially affects the optic nerves and spinal cord. It has a worldwide distribution and a poor prognosis. About 70% of patients with NMO have highly specific serum autoantibodies that target the water channel aquaporin 4 (AQP4).

Aquaporins are integral membrane-pore proteins that selectively conduct wa-
ter molecules in and out of the cell, while preventing the passage of ions and other solutes. There are several types of aquaporins, which are unequally distributed in the various body tissues. Aquaporin 4 is expressed in glial cells (especially within the spinal cord and brain stem) and is the target of autoimmunity in NMO. It is also expressed in neuronal cell bodies in the brain and spinal cord, representing a common target in autoimmune diseases.

In our study, we screened patients with MG for signs of CNS involvement and used paraclinical tests to identify features indicative of an NMO-like disease.

**METHODS**

**PATIENTS**

During the period from January to December 2009, a senior neurologist in our outpatient clinic evaluated 164 patients with MG for signs of CNS involvement. Signs of CNS involvement were evident in 24 patients on the basis of significant hyperreflexia and plantar extensor responses at the least (the Babinski or Chaddock reflex). Additional indications of CNS involvement included symptoms or signs of a reduction in neurological visual acuity or symptoms of myelopathy (including neurogenic sphincter disturbances). These 24 patients were further evaluated by use of brain or spinal magnetic resonance imaging (MRI) for detection of white matter lesions, visual evoked potentials (VEPs) for detection of conduction abnormalities in the optic nerves, and were also tested for the presence of anti-AQP4 antibodies (which are all indicative of an NMO spectrum disease). Of the 24 patients, 19 had pathological findings in at least 1 of the 3 tests (ie, MRI, VEP, or test for anti-AQP4 antibodies), and 15 were finally included in our series (4 were excluded owing to the presence of systemic autoimmunity or evidence of cerebrovascular disease). The presence of other etiologies for pyramidal syndrome, such as significant cervical degenerative disease, represented an additional exclusion criterion in our series of 15 patients.

**INCLUSION AND EXCLUSION CRITERIA**

Our inclusion criteria were (1) a definite diagnosis of MG; (2) the presence of significant hyperreflexia and plantar extensor responses at the least (ie, the Babinski or Chaddock reflex), as evidence of CNS involvement; and (3) additional indication of NMO spectrum disease, including at least 1 of the following 3 criteria: the presence of lesions in the white matter of the brain or spinal cord; a finding of pathologically increased conduction time of the optic nerves in the VEP; or the presence of serum anti-AQP4 antibodies. Our exclusion criteria were (1) the presence of other etiologies for signs of CNS involvement, such as cervical degenerative disease and significant cerebrovascular disease, and (2) the presence of systemic autoimmune diseases, excluding autoimmune thyroiditis.

**PARACLINICAL TESTS**

**Visual Evoked Potentials**

Visual evoked potentials were recorded monocularly to pattern reversal full-field checkerboards. The latency of the major positive component (P100) was measured. Responses were considered abnormal when the latency of the P100 was above 112 ms (which is 3 SDs above the mean in our laboratory).

**Magnetic Resonance Imaging**

Magnetic resonance imaging was performed for 9 of the 15 patients with MG who fulfilled the inclusion and exclusion criteria of our study. Brain MRI (at 1.5 T) was performed using standard T1-weighted, T2-weighted, diffusion-weighted imaging, and postgadolinium T1-weighted sequences. Cervical spine MRI was performed using standard T1-weighted, T2-weighted, and postgadolinium T1-weighted sequences.

**Antibodies Against Aquaporin Testing**

Blood samples were obtained from 14 of the 15 patients in our study, at the time of inclusion. Antibodies against AQP4 were tested in our Neuroimmunological Laboratory by a standard commercial enzyme-linked immunosorbent assay (RSR Limited, Cardiff, Wales), according to the manufacturer’s instructions, and 4 samples were also sent to the Mayo Clinic for additional confirmation. Similar results were obtained in the 2 laboratories.

**RESULTS**

**DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE MG COHORT**

The clinical and demographic characteristics of the 164 patients from our MG cohort, including the proportion of patients who underwent thymectomy and those with thymoma, are summarized in Table 1. Routine workup of all the patients with MG included a computed tomographic scan of the chest. In patients with indications of thymic enlargement per computed tomographic scan (ie, 9 patients with signs of CNS involvement and 34 patients without), a thymectomy was performed. The proportion of patients who underwent thymectomy (based on the computed tomographic findings) was higher in

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients Without Signs (n = 149)</th>
<th>Patients With Signs (NMO-like) (n = 15)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. of patients</td>
<td>96 (65%)</td>
<td>10 (67%)</td>
<td>.90</td>
</tr>
<tr>
<td>Female</td>
<td>53 (36%)</td>
<td>5 (33%)</td>
<td>.35</td>
</tr>
<tr>
<td>Anti-AChR antibodies</td>
<td>130/149 (87%)</td>
<td>11/15 (73%)</td>
<td>.69</td>
</tr>
<tr>
<td>Enlargement of the thymus</td>
<td>34/149 (23%)</td>
<td>9/15 (60%)</td>
<td>.901</td>
</tr>
<tr>
<td>Thymoma</td>
<td>18/34 (53%)</td>
<td>7/9 (78%)</td>
<td>.16</td>
</tr>
<tr>
<td>Thymic hyperplasia</td>
<td>16/34 (47%)</td>
<td>2/9 (22%)</td>
<td>.16</td>
</tr>
</tbody>
</table>

Abbreviations: AChR, acetylcholine receptor; NMO, neuromyelitis optica.

a Determined by use of the Fisher exact test.
b Detected on computed tomographic scan; all 9 patients with signs and all 34 patients without underwent a thymectomy.
the group with signs of CNS involvement than in the group without (9 of 15 patients vs 34 of 148 patients; \( P = .004 \), determined by use of the Fisher 2-tailed exact test). In all the thymectomized patients (\( n = 43 \)), a histopathological evaluation was performed. Among these patients, thymoma was diagnosed at higher percentages in the group of patients with signs of CNS involvement (7 of 9 patients) than in the group of patients without (18 of 34 patients). This difference did not reach statistical significance. However, the total number of patients with either thymoma or hyperplasia was significantly higher in the group with signs of CNS involvement than in the group without (47% vs 12%; \( P = .002 \)) (Table 1).

The clinical presentation of CNS involvement included systemic lupus erythematosus or antiphospholipid syndrome (6 patients), immune thrombocytopenic purpura (3 patients), polymyositis (1 patient), rheumatoid arthritis (1 patient), pemphigus (1 patient), chronic inflammatory demyelinating polyneuropathy (1 patient), psoriasis (1 patient), Crohn disease (1 patient), ulcerative colitis (1 patient), scleroderma (1 patient), insulin-dependent diabetes mellitus (1 patient), alopecia areata (1 patient), rheumatic fever (1 patient), and Sjögren syndrome (1 patient). We excluded all these patients who had other systemic autoimmune diseases because these diseases may also cause CNS syndromes; however, we did not exclude those patients who had thyroid autoimmunity (3 of 15 patients in our final group) or those who had serum antinuclear antibodies only because thyroid autoimmunity and antinuclear antibody seropositivity are very common in patients with MG and are not associated with signs of CNS involvement, similar to the patients described in our study. Among these patients with additional autoimmune diseases, only 2 had signs of CNS involvement.

In total, clinical indications of CNS involvement were found in 24 of the 164 patients. The patients were referred for further evaluation with brain and/or spinal MRI, VEP testing, and testing for anti-AQP4 antibodies. Of the 9 patients who were excluded from our study, 2 were excluded because they had a systemic autoimmune disease (both had systemic lupus erythematosus). In 1 of the 2 patients, the result of the brain MRI was abnormal, but the lesions were interpreted as vascular and were accompanied by antiphospholipid antibodies; in both patients, the VEP was pathologic and the anti-AQP4 antibodies were negative. In addition, 5 patients were excluded because they did not fulfill the criterion of having at least 1 paraclinical indication of NMO-like disease (they all had only minimal pyramidal signs), and 2 patients were excluded because of suspicion of significant cerebrovascular disease. A total of 15 patients constituted the final study group because they fulfilled all the inclusion and exclusion criteria.

The clinical presentation of CNS involvement included pyramidal signs in all 15 patients, pyramidal weakness in 5 patients, neurogenic sphincter disturbances in 4 patients (all accompanied by pyramidal weakness), and visual disturbance in 1 patient. The detailed clinical and paraclinical characteristics of these 15 patients are presented in Table 2. The VEP was pathologic in all the 14 patients tested; the results of the MRI scans of the brain or spinal cord were abnormal (showing white matter lesions or a long lesion in the cervical spine) in 6 of 9 patients in whom an MRI was performed. Fourteen patients were tested for the presence of anti-AQP4 antibodies, 7 of whom were found to be positive.

Of the 5 patients with MG who had a major neurological disability attributed to CNS pathology, 4 had a history of thymoma, and all 5 had an abnormal VEP, of whom 4 were positive for anti-AQP4 antibodies. Of the 7 patients with thymoma, 6 were tested and found to have pathologically increased conduction time of the optic nerves, in VEP; of these 6 patients, 4 were positive for anti-AQP4 antibodies.

<table>
<thead>
<tr>
<th>Patient No./Sex/ Age, y</th>
<th>Clinical Finding</th>
<th>MRI Result</th>
<th>Autoantibody Test Result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pyramidal Signs</td>
<td>Pyramidal</td>
<td>Visual</td>
</tr>
<tr>
<td>1/8/56</td>
<td>+</td>
<td>+</td>
<td>NP</td>
</tr>
<tr>
<td>2/8/40</td>
<td>+</td>
<td>+</td>
<td>NP</td>
</tr>
<tr>
<td>3/8/49</td>
<td>+</td>
<td>-</td>
<td>NP</td>
</tr>
<tr>
<td>4/8/60</td>
<td>+</td>
<td>-</td>
<td>NP</td>
</tr>
<tr>
<td>5/8/49</td>
<td>+</td>
<td>-</td>
<td>NP</td>
</tr>
<tr>
<td>6/8/59</td>
<td>+</td>
<td>-</td>
<td>NP</td>
</tr>
<tr>
<td>7/8/21</td>
<td>+</td>
<td>-</td>
<td>NP</td>
</tr>
<tr>
<td>8/8/50</td>
<td>+</td>
<td>-</td>
<td>NP</td>
</tr>
<tr>
<td>9/8/38</td>
<td>+</td>
<td>-</td>
<td>NP</td>
</tr>
<tr>
<td>10/8/39</td>
<td>+</td>
<td>-</td>
<td>NP</td>
</tr>
<tr>
<td>11/8/60</td>
<td>+</td>
<td>-</td>
<td>NP</td>
</tr>
<tr>
<td>12/8/49</td>
<td>+</td>
<td>-</td>
<td>NP</td>
</tr>
<tr>
<td>13/8/50</td>
<td>+</td>
<td>-</td>
<td>NP</td>
</tr>
<tr>
<td>14/8/48</td>
<td>+</td>
<td>-</td>
<td>NP</td>
</tr>
<tr>
<td>15/8/48</td>
<td>+</td>
<td>-</td>
<td>NP</td>
</tr>
</tbody>
</table>

Abbreviations: AChR, acetylcholine receptor; ANA, antinuclear antibodies; AQP4, aquaporin 4; MRI, magnetic resonance imaging; NP, not performed; VEP, visual evoked potential; +, positive; -, negative.
In our study, we found that CNS involvement in MG is more frequent than previously reported (with an incidence of 10%-15%, depending on the criteria used) and expressed predominantly as a pyramidal syndrome accompanied by optical tract involvement (both frequently subclinical) and evidence of white matter CNS lesions. These features resemble an NMO-like disease, which was also accompanied by the presence of anti-AQP4 antibodies in half of the patients.

Hyperreflexia, which is frequently observed in MG, is not readily explained solely on the basis of neuromuscular involvement. Our findings suggest that significant hyperreflexia and pyramidal signs in patients with MG may represent a manifestation of mild, often subclinical, CNS involvement with features of NMO-like disease. The high percentage of subclinical abnormalities in the VEP tests also supports this possibility.

In our series, significantly more patients with signs of CNS involvement had indications of thymic enlargement and underwent thymectomy. Patients with thymoma had more severe and disabling CNS findings. Thymomas are frequently associated with autoimmune syndromes other than MG. Epithelial cells in the thymus express several self-antigens, such as titin and the ryanodine receptor; the expression of AQP4 has recently been documented in the thymus. It is possible that the thymic abnormality associated with MG predisposes to the production of specific autoantibodies targeting CNS structures such as AQP4. Additionally, several groups, including our own, have reported the increased incidence of CNS demyelination in patients with MG, especially following thymectomy. The role of the thymus in the preservation of self-tolerance is well established. Although this process occurs during childhood, it is possible that residual thymic tissue is important in maintaining self-tolerance even during adult life. In patients with MG, the thymus is frequently hyperplastic, suggesting its more active immunological role in these patients. In support of this notion, various inflammatory molecules have been shown to be produced by the hyperplastic thymus in patients with MG.

There are also numerous case reports of autoimmunity developing following thymectomy. Production of autoreactive T cells and depletion of regulatory cells, following thymectomy, have been suggested as being responsible for this. Autoimmunity targeting the CNS in patients with MG and thymic tumors may also be part of a paraneoplastic syndrome.

In previous studies, it was shown that anti-AQP4 antibodies and clinical NMO spectrum disorders may represent CNS manifestations of paraneoplastic syndromes. Because thymoma was diagnosed in 7 of the patients in our series, it is logical to assume that, in some cases, this comorbidity (of MG and NMO-like disease) may be explained by paraneoplastic mechanisms.

The reverse association (namely, that of MG and anti-AChR positivity in anti-AQP4–seropositive patients with NMO) has also been described in a study by McKeon et al., who were the first to systematically evaluate the association of additional neurological autoimmunity in NMO. In their study, MG was diagnosed in 4 (2%) of the 177 patients with NMO, and muscle autoantibodies were detected in 11% of patients. McKeon et al concluded that “the coexistence of NMO and MG should be considered in atypical or refractory presentations of either disorder.” In contrast to this assumption, we believe that our study does not simply provide an additional indication of the coexistence of 2 distinct autoimmune conditions but may suggest a more substantial and integral correlation between MG and NMO-like disease, possibly reflecting common immunopathogenetic mechanisms that target antigens expressed both in the muscles (the neuromuscular junction) and in the CNS, such as aquaporin. Aquaporin 4 is expressed at the neuromuscular junction.

In conclusion, our study suggests that CNS involvement in MG is much more frequent than previously acknowledged; the expression and the clinical phenotype of this involvement are highly variable and may range from a very mild pyramidal syndrome (usually reflected only by hyperreflexia or soft pyramidal signs) or subclinical optic tract involvement to full-blown NMO.

In most of the cases, the CNS syndrome includes features of an NMO-like disease, which may frequently be detected only by paraclinical tests (such as VEP, which was pathologic in all the patients tested in our series, even in the absence of overt visual symptoms). This association may represent a new nosological entity rather than an overlapping autoimmune syndrome and could indicate that, in addition to the AChR, the immunogenetic mechanisms in MG may target AQP4, providing an immunological link between the CNS and the muscles. Thymoma and/or thymectomy may also play a role, either through immune dysregulation or via a paraneoplastic mechanism.

REFERENCES