fluorescein angiograms available to review. Although aquaporin-4-IgG may coexist with GFAP-IgG, we focused on isolated GFAP-IgG cases in this study, as overlapping clinical features would have been difficult to separate. The 3 patients with serum GFAP-IgG seropositivity alone did not have CSF available for testing, but all had the classic clinical phenotype of meningoencephalomyelitis. This is an important finding, as CSF testing of GFAP-IgG has been preferred, given its higher specificity for autoimmune central nervous system disease (1). Not all patients with GFAP autoantibody–positive meningoencephalitis underwent ophthalmic evaluation, and therefore, it is likely that optic disc edema in this condition is more common than reported here.

In summary, the clinical characteristics of GFAP autoantibody–positive meningoencephalitis are still being elucidated. We recommend testing CSF GFAP autoantibodies in patients with unexplained meningoencephalitis, particularly if they have bilateral optic disc edema, accompanying myelitis or radial perivascular enhancement on MRI. The optic disc edema may be due to an inflammatory papillitis affecting the venules as opposed to elevated intracranial pressure. Prospective and pathologic studies will be required to better determine the pathophysiology and frequency of optic disc edema in GFAP autoantibody–positive meningoencephalitis.

STATEMENT OF AUTHORSHIP

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Glial Fibrillary Acidic Protein Antibody: Another Antibody in the Multiple Sclerosis Diagnostic Mix

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Clinical practice and research of inflammatory demyelinating diseases is a dynamic and evolving field, particularly since the start of the 21st century. Our understanding the disease course of multiple sclerosis (MS) and the impact of disease modifying treatments, along with the discovery of novel antibody biomarkers, have greatly transformed the practice of neuroimmunology.

In 2017, updated criteria for the diagnosis of MS were released (1). One significant change was the inclusion of symptoms of supratentorial, infratentorial, or spinal cord lesions in satisfying criteria for dissemination in time or space. Two of 4 locations need to be involved to qualify
for dissemination in space, and previously, only the asymptomatic lesions were eligible. In addition, dissemination in time can now be achieved by detecting both enhancing and nonenhancing lesions on a single brain magnetic resonance imaging (MRI) or by detecting cerebrospinal fluid (CSF) oligoclonal bands in a patient with a characteristic clinically isolated syndrome. Although much has been learned about the clinical course of MS, the etiology remains elusive. However, the detection of new antibodies in cases previously thought to be MS makes for a “splitter’s delight.”

The discovery of disease-causing antibodies in other inflammatory demyelinating diseases has transformed clinical practice. In the early 2000s, antibodies targeting aquaporin-4 (AQP4-IgG) on astrocytic foot processes of the blood–brain barrier were discovered and were determined to be pathogenic in neuromyelitis optica (NMO) (2,3). As a result, revisions of the diagnostic criteria for NMO and the eventual change in terminology to NMO spectrum disorders (NMOSDs) occurred (4,5). The most recent diagnostic criteria for NMOSD, published in 2015, identified 6 core criteria: optic neuritis, transverse myelitis, acute encephalopathy, acute postrema syndrome, symptomatic narcolepsy associated with acute diencephalic syndrome with typical MRI lesions, acute brainstem syndrome, and symptomatic cerebral syndrome with typical MRI lesions (4). AQP4-IgG is positive in 73%–90% of patients with NMOSD, leaving many patients labeled as seronegative NMOSD (6,7).

Myelin oligodendrocyte glycoprotein (MOG-IgG) antibodies have been identified in a subgroup of NMOSD patients who are AQP4-IgG–negative (8–10). These antibodies bind an extracellular glycoprotein on the myelin sheath and oligodendrocytes (11). Patients with MOG-IgG positivity often present with bilateral simultaneous or sequential optic neuritis and transverse myelitis or as an ADEM-like disorder in children. Hamid et al (6) identified MOG-IgG to be present in 42% of patients with NMOSD who were AQP4-IgG–seronegative and 38% of AQP4-IgG–seronegative patients with NMO satisfying the Wingerchuk 2006 criteria (12). In addition, MOG-IgG was positive in 20% of patients with an atypical demyelinating presentation who met neither NMOSD nor MS criteria. MOG-IgG patients tend to have severe attacks but show better recovery with a lesser tendency for relapses compared with AQP4-IgG patients (13). Some studies have reported contradictory findings showing a higher risk of recurrence in MOG-IgG–associated disease. Optic neuritis is often bilateral and may present with optic nerve head swelling (14). MRI may show long segments of optic nerve enhancement along with enhancement of the optic nerve sheath (15). Seronegative NMOSD is often a prognostic and therapeutic dilemma for physicians. The addition of MOG-IgG to the spectrum of NMOSD has allowed guidance in the care of initially seronegative patients.

A newly characterized autoimmune meningoencephalomyelitis that is responsive to corticosteroids has been

**TABLE 1.** Comparison of inflammatory demyelinating disease antibody biomarkers

<table>
<thead>
<tr>
<th></th>
<th>AQP4-IgG</th>
<th>MOG-IgG</th>
<th>GFAP-IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical age at onset</td>
<td>30s–40s</td>
<td>20s–30s</td>
<td>40s (wide range)</td>
</tr>
<tr>
<td>Sex</td>
<td>Strong female predominance</td>
<td>More equal distribution</td>
<td>More equal distribution</td>
</tr>
<tr>
<td>Antibody target</td>
<td>Extracellular astrocytic foot processes at the blood–brain barrier</td>
<td>Extracellular protein on myelin sheath and oligodendrocytes</td>
<td>Intracellular intermediate filament in cytoplasm of astrocytes</td>
</tr>
<tr>
<td>Acute clinical optic nerve appearance</td>
<td>Usually normal</td>
<td>May have optic nerve head edema</td>
<td>May have optic nerve head edema</td>
</tr>
<tr>
<td>Typical MRI optic nerve findings</td>
<td>Often bilateral; more likely to involve optic chiasm and optic tract; long segments involved; swelling of optic nerve; optic nerve sheath enhancement</td>
<td>Not well characterized</td>
<td></td>
</tr>
<tr>
<td>Typical MRI brain findings</td>
<td>May be normal; lesions of dorsal medulla/area postrema, diencephalon, cerebral hemispheres</td>
<td>Involvement of deep gray matter, ADEM-like white matter lesions</td>
<td>Linear periventricular radial enhancement; leptomeningeal enhancement</td>
</tr>
<tr>
<td>Spinal cord involvement</td>
<td>LETM; central gray matter; extension into brainstem</td>
<td>LETM; cauda equina</td>
<td>LETM; thin and linear enhancement along the central canal; short myelitic lesions</td>
</tr>
<tr>
<td>Visual acuity at nadir</td>
<td>Severely decreased</td>
<td>Severely decreased</td>
<td>Most commonly normal</td>
</tr>
<tr>
<td>Visual recovery</td>
<td>Typically significant disability</td>
<td>More likely to have good recovery; potential for significant disability</td>
<td>Normal</td>
</tr>
<tr>
<td>Typical course</td>
<td>Most often recurrent</td>
<td>Tendency for recurrence; many cases are monophasic</td>
<td>Steroid responsive; may relapse with steroid taper</td>
</tr>
</tbody>
</table>

AQP4-IgG, aquaporin-4 immunoglobulin; GFAP-IgG, glial fibrillary acidic protein immunoglobulin; LETM, longitudinally extensive transverse myelitis; MOG-IgG, myelin oligodendrocyte immunoglobulin.
identified; this is associated with the glial fibrillary acidic protein (GFAP) autoantibody. In contrast to AQP4-IgG and MOG-IgG, which bind extracellular plasma membrane antigens (astrocytic and oligodendrocytic, respectively), GFAP-IgG binds an intracellular intermediate filament in the cytoplasm of astrocytes (16). The most common presentation is subacute cognitive deficits with variable meningeal involvement and myelopathy (17). Patients may have bilateral optic disc edema, although commonly remain visually asymptomatic. Distinguishing MRI findings include a characteristic radial perivascular pattern of enhancement extending from the ventricles or rarely in the cerebellum. CSF pleocytosis and elevated protein may be seen. These radiographical and CSF findings may mimic central nervous system vasculitis or even sarcoidosis, although cerebral angiography is typically normal (17).

In this issue of the Journal of Neuro-Ophthalmology, Chen et al (18) describe the ophthalmic findings in 10 patients with GFAP-IgG–positive meningoencephalitis and optic disc edema. In this study, 2 of 10 patients had mildly elevated intracranial pressure (ICP) (265 and 298 mm H2O), which possibly was secondary to elevated CSF protein. However, the median opening pressure among all patients was 144 mm H2O, indicating an alternative etiology to papilledema (optic disc edema secondary to elevated ICP). The etiology of the disc edema remains unclear, although Chen et al postulate that the pathophysiology of the optic disc edema may be venulitis and resulting in papillitis. The presence of venular leakage on fluorescein angiography in one patient along with the characteristic radial perivascular enhancement on brain MRI suggests a venular process. The performance of fluorescein angiography or perhaps optical coherence tomography angiography in patients with positive GFAP-IgG will be informative regarding this concept. An alternative etiology for the optic disc edema may be an optic perineuritis, as is seen in patients with anti-MOG antibodies. Optic perineuritis may cause optic disc swelling with normal visual acuity and a normal CSF opening pressure. Anti-GFAP antibodies are known to cause inflammation of the meninges, making involvement of the optic nerve sheath plausible. MRI of the orbs to assess for enhancement of the optic nerve sheath also may provide further insight to the pathogenesis of the disc swelling.

The discovery of antibody biomarkers in inflammatory demyelinating disease has opened the door to improving diagnostic clarity and for development of new treatment guidelines. There is still much to learn regarding the natural history and pathogenicity of these disorders. Knowing the distinguishing and overlapping features among the disease entities associated with these antibodies will allow for more precise and timely diagnosis (Table 1). Many more antibodies are likely to be discovered over the coming years, thus greatly expanding the ever-growing field of neuroimmunology and further refining the diagnostic algorithm for MS.

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