A severe, relapsing case of myelin oligodendrocyte glycoprotein IgG-associated CNS inflammation

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A 55-year-old man presented in October 2004 with general unease, vomiting, and gait disturbance. Initially diagnosed with an inner ear infection, the patient's symptoms did not improve and he was evaluated further. MRI revealed a cerebellar lesion, which led to the suspicion of a posterior circulation stroke, and he was started on antiplatelet drugs. However, an angiogram suggested no vascular pathology. In March 2011, he had another episode of ataxia and MRI showed a right brainstem lesion. Cryptogenic stroke was reconsidered. In March 2013, the patient developed paraparesis with urinary and bowel symptoms. MRI revealed myelitis of the mid-thoracic spinal cord. Oligoclonal bands were present in both serum and CSF and steroids were begun. In February 2014, he was admitted with expressive aphasia and right hemiparesis. MRI (figure 1) confirmed a new T2-hyperintense lesion in the left frontal lobe and he was given IV methylprednisolone and subsequently underwent plasma exchange. Aquaporin 4 (AQP4) IgG was negative. The working diagnosis was tumefactive multiple sclerosis. He was started on glatiramer acetate in August 2014. A few months later, he developed right-sided weakness, left optic neuritis (ON), and confusion. MRI (figure 2) showed left occipital and left parietal cortical and subcortical white matter lesion spreading across the corpus callosum to the opposite side. There were changes bilaterally in the cerebellum, cerebral peduncles, and along the corticospinal tracts on the left side. Further scans showed swelling of the splenium of the corpus callosum. He was put back on prednisolone 60 mg. Markers for systemic inflammation (erythrocyte sedimentation rate, C-reactive protein) were normal and autoantibody testing (antinuclear antibodies, extractable nuclear antigen, paraneoplastic antineuronal antibodies) was negative. The diagnosis of fulminant seronegative NMO was re-entertained but AQP4 antibodies were negative. However, MOG antibodies returned positive (October 2014, live cell-based assay, John Radcliffe Hospital, Oxford, UK). Azathioprine 125 mg was begun in February 2015.

In March 2015, the patient had 8 generalized seizures and was started on phenytoin, which was then switched to levetiracetam. Blood cultures revealed coagulase-negative staphylococci and he was put on teicoplanin and tazocin. CSF virology was negative. A month later, he had another seizure. MRI showed new lesions in the left occipital cortex. Azathioprine was stopped and switched to mycophenolate. Six months later, he had further seizures, which was thought due to concurrent use of amitriptyline, which was stopped. At last review, the patient remains disabled, with dysphasia, poor vision in the left eye, a right homonymous hemianopia, and a right hemiparesis. Though ataxic, he is ambulant. His MOG antibodies have since been retested 4 times (March 2015, January 2016, January 2017, and February 2017) and have remained positive, including in periods of clinical quiescence (figure e-1, links.lww.com/CPJ/A1). AQP4 antibodies tested at these times were negative.

PRACTICAL IMPLICATIONS

Consider myelin oligodendrocyte glycoprotein (MOG) immunoglobulin G (IgG)-associated demyelinating disease in the differential diagnosis of neuromyelitis optica (NMO) spectrum disorder (NMOSD) and atypical relapsing white matter disease.

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Figure 1 MRI sequence illustrates inflammatory change after the patient presented with expressive aphasia and right hemiparesis

(A) Axial T2 fluid-attenuated inversion recovery shows a new T2 hyperintense lesion in the left frontal lobe extending to the cortex. (B) Coronal T2 image 2 months later shows T2 hyperintensity along the left corticospinal tract, which likely represents Wallerian degeneration and gliosis, in keeping with the severity of the lesion. (C) One year later, the affected area is atrophic with dilated lateral ventricle, and changes extend bilaterally posterior to the lateral ventricles. There is also a new cortical lesion in the left occipital pole.

Discussion

We describe a patient with a relapsing CNS inflammation of at least 12 years' duration, with considerable residual disability. He satisfies the 2015 criteria for NMOSD without AQP4 IgG.¹ He has ON as one obligatory core clinical criterion and further core criteria with supportive MRI findings: brainstem lesions with ependymal involvement and hemispheric lesions. He also had transverse myelitis with less than 3 vertebral segment lengths. The cortical involvement (uncommon in AQP4 IgG disease) is presumably responsible for the seizures and cognitive impairment.

MOG IgG demyelination was described initially as mostly monophasic and mild, often with good recovery compared to

AQP4 IgG NMO.² A multicenter study of patients with NMOSD with MOG IgG presenting mainly with ON and transverse myelitis $\pm$ brainstem supports our experience with this case. This study of 50 patients shows that it is disabling in more than a third of cases and relapses occurred in up to 80%.³ Clinical presentations of MOG disease can include ON (unilateral and bilateral), myelitis (both short and long length, including conus lesions), cortical damage (including cognitive dysfunction, seizures, hemianopia), and brainstem lesions.⁴ A recent study using full-length human MOG protein reports a sensitivity of 24% and specificity approaching 100% for a disease distinct from MS and AQP4 IgG NMO.⁵ MOG IgG assay is currently unavailable as a routine clinical orderable test in the United States, but should become available in the first quarter of 2018 through Mayo Medical Laboratories

Figure 2 MRI sequences during relapse with left optic neuritis, right-sided weakness, and confusion

(A) T2 axial image before relapse. (B) T2 axial image shows extensive white matter lesions in the left occipital and parietal cortical and subcortical regions spreading across through the corpus callosum to the opposite side. (C) Brain atrophy with ventricular dilation and thinning of corpus callosum at 3 months and (D) at 1 year.

(personal communication, Dr. Andrew McKeon, codirector, Neuroimmunology Laboratory, Mayo Clinic).

While limited studies indicate that MOG IgG is associated with a demyelinating illness and AQP4 IgG is an astrocytopathy with demyelination as secondary effect,⁶ many questions about MOG IgG disease remain unanswered or require further confirmation. First is whether all cases relapse, similar to most AQP4 IgG disease. Second, if effective treatments are begun early, are the lesions and signs reversible? This is often not the case in AQP4 IgG disease. If not, then the need to immunosuppress all MOG IgG disease after an index event (as we do for AQP4 IgG disease) and identification of patients with MOG IgG from among those with diagnoses of tumefactive demyelination or other hitherto unclassifiable demyelinating conditions pose challenges to neurologists.

Author contributions

M. Saviour: acquisition of information, manuscript editing and revision. S. Hamid: acquisition of information, critical review of manuscript. P. Moore: acquisition of information, neuropsychiatric and cognitive testing. K. Mutch: acquisition of information. M. Bhojak: acquisition and interpretation of imaging. M. Duddy: acquisition of information. A. Jacob: acquisition of information, critical review of manuscript.

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