

# Diagnostic challenges and pitfalls of myelin oligodendrocyte glycoprotein antibody–associated demyelination

## Lessons from neuropathology

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Antibodies against myelin oligodendrocyte glycoprotein (MOG) are associated with a wide spectrum of demyelinating CNS diseases such as clinically isolated syndrome (CIS), neuromyelitis optica spectrum disorder (NMOSD), optic neuritis (ON), myelitis, acute demyelinating encephalomyelitis (ADEM), or multiphasic demyelinating encephalomyelitis (MDEM).<sup>1</sup> Several brain biopsy–based cases of MOG antibody–associated demyelination have been described so far and have reported perivascular (ADEM) or confluent (CIS, MS, NMOSD) demyelination with relative preservation of axons, numerous macrophages, and well-preserved astrocytes. The inflammatory infiltrates have been mostly described as perivascular and parenchymal T cells along with some perivascular B cells. Moreover, actively demyelinating lesions may also show terminal complement complex (C9neo) deposition and can display relatively well-preserved, partly MOG-negative preoligodendrocytes.<sup>2–4</sup>

The article by Patterson et al. published in this issue of *Neurology*<sup>®</sup> *Neuroimmunology & Neuroinflammation* addresses the challenges and potential pitfalls in the differential diagnostic work-up of brain biopsies in patients with MOG-spectrum disorders. The authors described 2 patients, 1 child and 1 adult, who clinically presented with meningoencephalitis, and brain biopsy revealed predominantly perivascular lymphocytic infiltrates involving the vessel wall, which led to the (mis)diagnosis of small-vessel vasculitis. Both patients were retrospectively tested positive for MOG antibodies and the diagnosis was changed into anti-MOG encephalitis.<sup>5</sup> The treatment of the pediatric patient was subsequently changed into a B-cell depletion with good clinical and serologic response. In the second patient, the finding of MOG antibodies did not change the treatment strategy as she was already clinically stable; however, an earlier detection of MOG antibodies could have prevented the brain biopsy.<sup>5</sup>

The histopathologic diagnosis in small brain biopsies in the context of an inflammatory disease can be a major challenge, and an algorithmic approach for the neuropathologic work-up has been recommended to establish a correct diagnosis.<sup>6</sup> Lymphocytic infiltrates within the brain parenchyma involving gray and/or white matter and around vessels may raise several differential diagnoses, including different inflammatory demyelinating diseases (e.g., ADEM, acute hemorrhagic leukoencephalitis, and X-linked adrenoleukodystrophy), autoimmune or paraneoplastic disorders, other inflammatory or infectious diseases (e.g., vasculitis, viral infections, and sarcoidosis), sentinel lesions preceding lymphomas, tumors (e.g., lymphomas and astrocytomas), and infarcts, among other rare conditions. The neuropathologic hallmark of CNS vasculitis comprises inflammatory infiltration of the vessel wall, fibrinoid necrosis, and inflammatory destruction of the vessels resulting in luminal thrombosis, ultimately causing ischemic brain lesions or hemorrhages. The vasculitis may be accompanied by mild-to-severe

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inflammatory infiltrates of the CNS parenchyma, but in contrast to ADEM or MS, demyelination is typically absent.<sup>6</sup>

In the 2 brain biopsies presented by Patterson et al.,<sup>5</sup> the retrospective analysis of the histopathology could not confirm the initial diagnosis of small-vessel CNS vasculitis. In both patients, the inflammatory infiltrates did not affect the vessel walls, and fibrinoid necrosis, hemorrhage, or ischemia was absent. In the first (pediatric) case, the inflammation was accompanied by a small rim of perivascular demyelination, fulfilling the neuropathologic criteria of ADEM. At the time of biopsy, the brain MRI showed T2 abnormalities in the basal ganglia, cerebellar peduncles, and supratentorial white matter. Several months after disease onset, the child developed an episode of ON and 2 years later, another relapse with extensive white matter abnormalities. Children with ADEM and MOG antibodies are at risk of developing clinical relapses, often with ON, subsequently leading to a diagnosis of ADEM associated with recurrent ON (ADEM-ON), MDEM, or NMOSD.<sup>1</sup> The MRI of the second (adult) patient showed unilateral hyperintense gyriiform fluid-attenuated inversion recovery (FLAIR) signal abnormalities over the left temporal, parietal, and occipital lobes. The brain biopsy revealed perivascular inflammatory infiltrates, but no clear evidence of demyelination.<sup>5</sup> Unilateral cortical lesions depicted in FLAIR images were previously described in adult patients with steroid-responsive encephalitis associated with MOG antibodies.<sup>7</sup> Subsequently, this syndrome has been included in the spectrum of MOG antibody-associated diseases; however, neuropathologic descriptions were lacking so far. The current case may add this information to the existing literature. The absence of demyelination described by Patterson et al. may result from a sampling error of the small brain biopsy; alternatively, it may reflect the far end of a spectrum of MOG antibody-associated diseases with only minor or even absent demyelination. From experimental autoimmune encephalitis models, we learned that the extent of demyelination in MOG-induced autoimmunity seems to depend on the balance between the levels of encephalitogenic T cells and demyelinating MOG antibodies. Although an excess of T cells occurred with inflammatory infiltrates in meninges and perivascular spaces, an excess of MOG antibodies was found associated with confluent demyelinating lesions.<sup>8</sup> Accordingly, intensive perivascular inflammation but sparse or even absent demyelination in human MOG-spectrum diseases may, among other factors (e.g., genetic, infectious), reflect a scenario, where an encephalitogenic T-cell response dominates over a demyelinating antibody response (with variable antibody titer, affinity) against conformational MOG epitopes.

The 2 patients described by Patterson et al., and other reports of patients diagnosed with CNS small-vessel vasculitis by brain biopsy, who later developed ON or myelitis<sup>7</sup> raise the possibility that misdirecting diagnoses may not be unusual because biopsy

specimens are frequently small and often represent only part of the entire pathologic process. Small CNS biopsies with inflammation should be thoroughly analyzed for demyelination, extent, and localization of inflammation (perivascular vs parenchymal), and axonal damage. Additional immunohistochemical stainings for T and B cells, plasma cells, astrocytes, and macrophages may narrow the differential diagnosis. Neuropathology requires a multidisciplinary approach, and the findings should be assessed together with neurologic and neuroradiologic data. The current study emphasizes that in some cases, testing for autoantibodies in serum and CSF provides useful additional information for the proper clinicopathologic classification of a disease.

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