AQP4 in biopsied demyelinating lesions as a diagnostic clue to NMOSD and MS

Final answer?

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Tumefactive demyelinating lesions (TDL) manifesting as a solitary lesion larger than 2 cm may mimic a neoplasm on CT/MRI. TDL often present a diagnostic challenge, and surgical biopsy may be needed to confirm the diagnosis. Following the discovery of aquaporin-4 (AQP4) immunoglobulin G (IgG) specific to neuromyelitis optica (NMO), the unique clinical manifestations, MRI findings, laboratory data, and therapeutic response, especially in comparison with those in multiple sclerosis (MS), have been identified. An international panel is now proposing the new diagnostic criteria of NMO spectrum disorders (NMOSD), a unifying term to encompass the entire disease spectrum (optic neuritis, acute longitudinally extensive transverse myelitis [LETM], some brain syndromes, and the combinations including typical NMO).[1] Some brain lesions as well as LETM in NMOSD are tumefactive, and thus NMOSD has joined the list of clinical entities manifesting with TDL.

Classic pathologic findings of NMOSD include severe demyelination and cystic tissue necrosis with thickened vascular walls. Since 2006,[2] loss of AQP4 has been a neuropathologic hallmark of NMOSD, based on autopsy studies.[3,4] AQP4, a dominant water channel in the CNS, is abundant on astrocytic foot processes surrounding the vascular endothelial cells, and loss of AQP4 in NMOSD likely reflects dysfunction of or damage to astrocytes. In fact, AQP4 is accessible by AQP4-IgG that penetrates the blood–brain barrier by unknown mechanisms and AQP4-IgG may damage astrocytes through mechanisms of complement- and antibody-dependent cellular cytotoxicity in NMOSD, as suggested by experimental studies. In this situation, myelin in close contact with astrocytic processes may be affected secondarily. Although it is not difficult to imagine such pathologic processes and add NMOSD-specific pathologic examinations including AQP4 immunohistochemistry in autopsied cases with established clinical diagnosis of NMOSD, unless NMOSD is suspected in the initial diagnostic workup, reaching the correct diagnosis from biopsied TDL alone could be a challenge.[5]

In this issue of *Neurology*®, Popescu et al.[6] report how examining the AQP4 immunohistochemistry in such TDL can help differentiate NMOSD from MS. They retrospectively collected 19 cases with brain (n = 11) or spinal cord (n = 9) biopsies fulfilling at least 2 of 3 AQP4-unrelated neuropathologic findings relatively unique to NMOSD in the presence of active demyelinating lesions confirmed by an experienced neuropathologist. The AQP4-unrelated neuropathologic inclusion criteria were (1) tissue vacuolation, (2) granulocyte infiltration in the CNS parenchyma or perivascular region, and (3) astrocytic injury (small glial fibrillary acidic protein [GFAP]–positive dystrophic astrocytes or GFAP debris-containing macrophages). During a 4-year period, the biopsied samples were sent for neuropathologic examination before testing of AQP4-IgG. Five patients had been given alternative diagnoses (tumors or vascular malformation) or were undiagnosed. After detailed neuropathologic examination, including AQP4 immunohistochemistry, clinical and neuroimaging follow-up, and postbiopsy AQP4-IgG testing, was done in individual cases, the authors examined the association between the neuropathologic findings and final clinical diagnoses.

A main result was that perivascular and astrocytic cell surface AQP4 were absent in 18 cases, while the AQP4 immunoreactivity in the demyelinating lesions was increased in the remaining 2 cases. Importantly, all 14 patients who had loss of AQP4 and tested seropositive for AQP4-IgG eventually were diagnosed with NMOSD; in contrast, the 2 with increased AQP4 were seronegative and received the diagnosis of MS, strongly suggesting the usefulness of AQP4 immunoreactivity in biopsied TDL, without known AQP4-IgG serostatus, for diagnostic distinction between the 2 diseases. Meanwhile, none of the other neuropathologic features reported in NMOSD were 100% sensitive or specific. On the basis of these results, as a practical diagnostic approach, the authors suggested, in suspected NMOSD, examination of AQP4 immunoreactivity with subsequent AQP4-IgG testing when 1 or more of the 3 neuropathologic inclusion criteria, complement activation,

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vascular wall thickening, or absence of Creutzfeldt-Peters cells (reactive astrocytes with micronuclei), are detected in biopsied TDL.

Loss of AQP4 is an important diagnostic clue to NMOSD, but we cannot rely on this alone. False-positive or false-negative diagnoses could be made due to laboratory procedure, biopsy site, or condition of biopsied samples. In addition, in a subset of acute MS (pattern III pathology, distal oligodendrogliopathy), patchy loss of AQP4 is present in the initial phase of plaque formation,[7] possibly leading to a false diagnosis of NMOSD. Moreover, our recent study revealed 6 different lesion types in NMOSD.[8] Other than typical NMOSD lesions caused by complement-dependent cytotoxicity (lesion type 1), there are various active lesions without complement deposition, such as pure loss of AQP4 (type 4), pure astrocyte loss characterized by apoptotic astrocytes with beaded and disintegrated foot processes (type 5), and lesions with primary demyelination with patchy loss of AQP4 (type 6). Therefore, the pathologic diagnosis of NMOSD in biopsied samples needs a measured judgment, and early suspicion of NMOSD and AQP4-IgG testing may avert invasive surgical biopsy. Likewise, in the revised diagnostic criteria of NMOSD, the importance of comprehensive consideration of all available information including AQP4-IgG serostatus, clinical data, and neuropathologic findings, if any, was emphasized,[1] as was done in the study by Popescu et al. Early differentiation of NMOSD from MS is critically important because some disease-modifying drugs for MS (interferon-β, natalizumab, and fingolimod) can aggravate NMOSD.

Finally, no case with loss of AQP4 in the study by Popescu et al. was AQP4-IgG-seronegative, but some patients with NMOSD are consistently seronegative despite the use of highly sensitive AQP4-IgG assays.[9] A fraction of such patients are myelin oligodendrocyte glycoprotein–IgG-seropositive.[10] Though the neuropathologic finding in this form of NMOSD has not been clarified, those cases are likely to be different from AQP4-targeted autoimmune astrocytopathy in AQP4-IgG-positive NMOSD[3] or classical MS lesions. Therefore, we will need to evaluate the neuropathologic findings of NMOSD more carefully.

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