Shifting paradigms

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The classic paradigm of antibody-associated encephalitis is that the majority of these diseases evolve rapidly, with CSF or MRI abnormalities suggesting an inflammatory process and pathologic findings showing inflammatory infiltrates. Well, hold on to your hats because here comes anti-IgLON5 disease.[1] This remarkable disease develops with core symptoms that include abnormal behaviors and vocalizations during non-REM and REM sleep, preceded or accompanied by bulbar dysfunction, gait instability, cognitive deterioration, or chorea (see the editorial comment by Graus and Santamaria).[2] The clinical picture can evolve for several years and associates with features suggesting an autoimmune disorder (antibodies against a neuronal cell surface protein [IgLON5] and a strong association with the HLA-DRB1*10:01), but on the other hand, the pathologic studies show a novel neuronal tauopathy predominantly affecting the hypothalamus and brainstem.[3] Moreover, different from most encephalopathies associated with neuronal cell surface antibodies, the response to immunotherapy seems to be suboptimal. Although the disease is rare (the incidence and prevalence are still unknown), it has stirred up the interest from different specialties with an increasing number of single case reports and a few series. In this issue of *Neurology® Neuroimmunology & Neuroinflammation*, Honorat et al.[4] report their experience at Mayo Clinic, with 26 patients harboring these antibodies, 20 of them with clinical information. This report is important for 3 reasons: (1) it confirms the sleep disorder as the core manifestation of the disease, (2) it describes previously unreported symptoms of CNS or peripheral nervous system hyperexcitability (hyperekplexia, cramps, fasciculations, and stiffness) in 35% of the patients, and (3) it suggests that the disease may be more responsive to immunotherapy than previously thought. This is supported by the symptom improvement observed in the case report of Bonello et al.,[5] also included in this issue of *Neurology: Neuroimmunology & Neuroinflammation*, who used several immunotherapies (steroids, IV immunoglobulins, plasma exchange, and pulses of cyclophosphamide).

On a different topic, Solomon et al.[6] investigated whether MRI evaluation of thalamic volume differentiates MS from other disorders that cause white matter abnormalities. The question is important, considering the absence of highly specific biomarkers for MS and the considerable number of diseases that can mimic the clinical and radiographic findings of this disorder. The authors focused on thalamic atrophy, given that it is identified early in the course of MS, including pediatric MS, presymptomatic MS, "radiologically isolated syndrome," and "clinically isolated syndrome." The study included 40 participants, 10 for each of the following groups: MS without comorbidities for white matter abnormalities, MS with comorbidities for white matter abnormalities, migraine with MRI white matter abnormalities, and patients who had been incorrectly diagnosed with MS. The findings provide Class IV evidence that MRI volumetric evaluation of the thalamus, but not other deep gray matter structures, differentiates MS from the other disorders that cause white matter changes and that are often mistaken for MS. The authors indicate that future studies should include larger number of patients along with the development of automated and easily applied volumetric assessment applicable to clinical practice.

In another study, Radue et al.[7] applied structural image evaluation using normalization of atrophy to determine the effect of teriflunomide on brain volume loss (BVL) in patients with relapsing forms of MS enrolled in the phase 3 TEMSO study. Data from 969 MRIs were examined, including 808 patients with baseline and 1-year MRI and 709 patients with baseline and 2-year MRI treated either with placebo or teriflunomide. The findings show that BVL was significantly lower in patients treated with teriflunomide (14 mg) vs placebo at year 1 and year 2, respectively. Teriflunomide at 7-mg dosing was also associated with significant reduction in BVL vs placebo at year 2. The authors conclude that these

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findings, coupled with published work in animal models, suggest a potential neuroprotective activity for teriflunomide and support a link between BVL and disability worsening.

Derfuss et al.[8] determined the time course of α4-integrin receptor desaturation and disease activity in patients with relapsing-remitting MS who discontinued natalizumab in the course of the TOFINGO trial, a 32-week, patient and rater-masked multicenter, parallel-group study. The study included 142 patients who underwent measurement of α4-integrin receptor occupancy (RO) at baseline and regular time periods until 24 weeks. Patients were randomized (1:1:1) to 8-, 12-, and 16-week washout groups. The findings show that a faster decline in natalizumab RO, longer washout period, and higher T2 lesion volume at baseline defines a population with an increased risk of return of inflammatory disease activity. According to the authors, these findings, along with the main outcomes of the TOFINGO study, support initiation of fingolimod within 8 weeks of natalizumab discontinuation.

Varicella zoster virus (VZV) vasculopathy is caused by productive virus infection of intracerebral arteries leading to stroke or aneurysm. Recent studies have shown that VZV can also affect extracranial arteries, with VZV antigen detected in 70% of patients with giant-cell arteritis.[9] However, while the presence of VZV along with inflammation has been demonstrated in cerebral and temporal arteries in patients with these disorders, VZV as the direct cause of the arterial inflammation has not been shown. To address this question, Jones et al. investigated whether VZV infection induced proinflammatory cytokines that result in arterial inflammation using several human brain vascular cell lines. Compared with mock infection, VZV infection led to significantly increased levels of interleukin 8 (IL8), IL6, and other cytokines in all or several of the cell lines.[10] The authors indicate that the VZV-mediated increase in IL8 and IL6 is consistent with that seen in the CSF of patients with intracerebral VZV vasculopathy, and the arteries and blood of patients with giant-cell arteritis. Together with a previous study showing that VZV-infected arteries downregulate PD-L1 to promote persistent inflammation,[11] the findings demonstrate that VZV infection is sufficient to promote a proinflammatory environment that may potentially lead to a persistent vasculitis.

In addition to these studies, the September issue of *Neurology: Neuroimmunology & Neuroinflammation* contains other interesting articles that I hope will catch your attention.

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