Editor's Corner

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"Time to recharge"

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This has been a challenging spring, and we all hope that the summer will bring the needed relief. To help you unwind, the July issue of *Neurology® Neuroimmunology & Neuroinflammation* contains excellent articles on a wide variety of topics that should hold your interest and help charge your brain batteries. Here I highlight 4 studies that I choose for the common theme of dealing with rare inflammatory disorders. I took the liberty of including a study of pregnant and lactating women with MS/NMOSD because investigations of this cohort are relatively rare.

Antimyelin-associated glycoprotein (MAG) antibody neuropathy is a slowly progressive, chronic polyneuropathy, associated with IgM monoclonal gammopathy. The current standard of care is rituximab, but approximately only 50% of patients benefit from it use. It was recently shown that the $MYD88^{L265P}$ mutation is the most common mutation in patients with Waldenström macroglobulinemia and IgM-monoclonal gammopathy of undetermined significance. This mutation results in constitutive activation of Bruton's tyrosine kinase (BTK) and NF-kB signaling. Ibrutinib is the first in-class inhibitor of BTK and has shown promising activity in a few patients with B-cell lymphomas especially those with $MYD88^{L265P}$. Further support for the efficacy of ibrutinib is now provided in the article by Castellani et al.[1] reporting the successful treatment of 3 patients with anti-MAG neuropathy associated with Waldenström macroglobulinemia with $MYD88^{L265P}$. All 3 patients had stable improvement of their neuropathy that in one patient it was described as a dramatic improvement in gait stability. Ibrutunib was well tolerated, and all patients remain on treatment. Although a larger number of patients are needed to confirm these results, it is exciting that we may have an efficacious option for this disabling neuropathy.

CTLA4 deficiency is a rare primary immune deficiency disorder with a wide range of systemic manifestations. Neurologic manifestations have been reported in approximately 30% of cases, including autoimmune encephalitis or encephalomyelitis with perivascular lymphocytic infiltration, inflammatory demyelinating processes, and optic neuritis, among others. Ayrignac et al.[2] add to this list in their case descriptions of 3 patients. Two of the patients were siblings who had symptom onset during childhood, including recurrent episodes of brain or spinal cord inflammatory processes, as has been described before. However, the third patient became symptomatic in her early 40s and developed progressive cerebellar ataxia and visual loss with bilaterally symmetric white matter changes similar to that seen in inherited leukodystrophies. Although the neurologic symptoms of these 3 patients occurred after the diagnosis of the CTLA4 deficiency, in 5% of patients, neurologic symptoms predate the diagnosis, supporting the importance of keeping in mind the broad neurologic phenotype.

Sarcoidosis is an enigmatic disorder that may present with a wide range of clinical manifestations. Neurologic involvement occurs in approximately 5% of cases and in approximately half of these patients is the initial manifestation of the disease. Sarcoidosis-associated myelopathy has features

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that may overlap with other inflammatory spinal cord disorders that can confound the diagnosis. To determine if there is a clinical and imaging phenotype of sarcoidosis-associated myelopathy, Murphy et al.[3] reviewed the characteristics of 62 patients with this complication. Most of the patients had a chronic course with predominant sensory symptoms. Four imaging patterns were identified on spine MRI with longitudinally extensive myelitis with predominantly dorsal subpial and/or meningeal enhancement being the most common. This has been previously reported, and the authors consider that this pattern should be considered the "classic" imaging phenotype of sarcoidosis-associated myelopathy. Enhancement was present in all but one case and across all lesion types; subpial enhancement frequently occurred at locations with coexisting structural changes such as disc herniations or cervical spondylosis. This novel observation lead the authors to hypothesize that increased permeability of the spinal cord barrier at the sites of mechanical stress may be a key step in the evolution of the inflammatory lesions in sarcoidosis-associated myelopathy.

Ciplea et al.[4] identified 23 patients with MS or NMOSD who received monoclonal antibodies during pregnancy and/or lactation to determine possible adverse effects on the infants. After a median follow-up of 1 year, they found no negative effects on overall health and development. Those infants who were exposed to natalizumab during the third trimester had lower birth weight and more hospitalizations in the first year of life but still had normal development. Several infants had transient hematologic abnormalities including mild or moderate anemia and/or thrombocytopenia. There was a slightly higher than expected rate of premature deliveries noted in the cohort without a clear attribution to the underlying demyelinating disease or exposure to monoclonal antibody. Based on this study and previous reports and with the caution that the overall sample size is limited, the authors conclude that there is a low probability of harmful effects for infants exposed to breastmilk after monoclonal antibody treatment of the mother.

In addition to these studies, the July issue of *Neurology: Neuroimmunology & Neuroinflammation* contains a review on the current knowledge of the transfer of monoclonal antibodies into breastmilk that complements nicely the study of Ciplea et al. and 2 clinical/scientific notes describing COVID-19 infection concurrent with Guillain-Barré syndrome and MS.[5–7] I hope that these and all the other interesting articles in this issue will catch your attention.

Study funding

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Disclosure

J. Dalmau holds the patents for the use of Ma2, NMDAR, GABABR, GABAAR, DPPX, and IgLON5 as autoantibody tests and receives royalties from the use of these tests. He is the editor of *Neurology: Neuroimmunology & Neuroinflammation*. Go to Neurology.org/NN for full disclosures.

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