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Of primary and secondary CNS autoimmunity

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Over the past 15 years, the field of neuroimmunology has been enriched by the discovery of a large number of new antibody-associated CNS diseases that are clinically meaningful because of their frequent response to immunotherapy, and biologically interesting because they provide models of how antibodies can directly affect the brain function. Recently, we are seeing that some of these disorders can result from secondary autoimmunity triggered by treatments aimed at modifying the immunologic system, such as immune checkpoint blockers or monoclonal antibodies against regulatory T cells. This issue of *Neurology® Neuroimmunology & Neuroinflammation* (N2) includes 2 new examples of primary and secondary CNS autoimmunity and studies addressing other interesting topics.

Dr. Honorat et al. report the identification of antibodies against septin-5 in 4 patients with rapidly progressive cerebellar ataxia. The study was designed to identify novel autoantigens among a pool of patients with antibodies seemingly reacting with neuronal cell surface or synaptic proteins. After identifying 6 patients whose serum or CSF samples produced similar patterns of brain immunostaining, the authors used well-established techniques to immunoprecipitate the antigen with the samples of 2 patients, and subsequently characterized it by mass spectrometry. Then, they confirmed that the serum or CSF of the other 4 patients, but not from a large group of control samples, also reacted with septin-5. Among 6 patients with septin-5 antibodies, clinical information was available from 4, and all 4 had rapidly progressive cerebellar symptoms. Three of the 4 patients had coexisting antibodies, including glutamic acid decarboxylase (GAD) antibodies (1), N-type calcium channel antibodies (1), or both (1). In one, a high titer of GAD antibodies suggested that this immune response could have played a role in patient's symptoms. Outcome was available only for 3 patients: 1 recovered spontaneously, 1 improved with immunotherapy, and the third remained bedbound and eventually died. Overall, this is an interesting study that may be revealing another antibody-associated syndrome. The future task is to determine how meaningful septin-5 antibodies are in clinical practice by examining their frequency, confirming the findings with a larger number of patients, clarifying the role of other coexisting antibodies, and investigating their potential pathogenicity.

In another study, Luessi et al. describe a patient with MS treated with daclizumab (a monoclonal antibody against CD25, the alpha subunit of interleukin-2 receptor) who developed a nonspecific syndrome including dysarthria, memory loss, fatigue, depression, confusion, delusions, ataxia, and nystagmus. The CSF showed antibodies against glial fibrillary acidic protein (GFAP), and the case was categorized as a GFAP astrocytopathy. The patient partially responded to immunotherapy. The experience with this case led the authors to review 6 additional patients who developed a variety of neurologic complications associated with daclizumab, including acute disseminated encephalomyelitis, Drug Rush with Eosinophilia and Systemic Symptoms, anti-NMDA receptor encephalitis, or CNS vasculitis. Based on these findings, the authors raise a note of caution regarding treatment approaches that interfere with natural killer cells and Tregs, such as anti-CD25 antibodies, which might lead to secondary CNS autoimmunity.

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Karimian-Jazi et al. investigated the diagnostic value of gadolinium administration in MRI follow-up examinations of patients with MS if the T2 lesion load was stable. The study includes 100 patients with MS who had at least 2 cranial MRI examinations with a mean follow-up period of 4.0 ± 2 years. In a total of 559 MRI follow-up studies, the authors identified 343 new T2 lesions and 152 contrast-enhancing lesions. One hundred and forty-five of 152 gadolinium-enhancing lesions (95.4%) showed a correlate with new T2/fluid-attenuated inversion recovery (FLAIR) lesions. Among the other 7 enhancing lesions, 3 did not correlate with T2/FLAIR lesions and 4 showed lesion reactivation or persistent enhancement over time. Overall, the likelihood of missing active lesions was small (1.7%) if T2 lesions were stable compared with previous examinations. The fact that the study was retrospective led to varying numbers and time intervals of the MRI scans and follow-up periods. However, the findings are interesting and need validation in a prospective study with predefined imaging intervals and a larger number of patients.

In another article, Dr. Pihan et al. investigate the sensitivity and specificity of serum vascular endothelial growth factor (sVEGF) for the diagnosis of polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome in patients with neuropathy and discuss the main confounding causes of elevated sVEGF levels. The study includes a cohort of 38 patients with POEMS syndrome, 168 patients with non-POEMS neuropathy (88 with hematologic disease and 80 without hematologic disease), and 68 consecutive patients without neuropathy who underwent sVEGF testing. The authors found a sensitivity of an elevated sVEGF levels for the diagnosis of POEMS of 100% and a specificity of 91% for patients with neuropathy and 92% for patients with neuropathy and paraproteinemia. Multiple logistic regression analysis showed that anemia with low iron was a significant

predictor for elevated sVEGF levels (≥ 771 pg/mL) and that chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea hypopnea syndrome (OSAHS) were significant predictors for very elevated sVEGF levels ($\geq 1,000$ pg/mL). The authors suggest that when the sVEGF level is elevated without a paraprotein or an appropriate neuropathy, sVEGF testing should be repeated, particularly after acute illnesses, anemias with low iron, cancers, hematologic malignancies, COPD, OSAHS, and vasculitic and chronic inflammatory diseases before using sVEGF levels for the diagnosis of POEMS. In addition to the high sensitivity and specificity of sVEGF for the diagnosis of POEMS in the clinical context of a neuropathy, I found this study useful in helping to navigate through the differential diagnosis of disorders in which sVEGF levels may be elevated.

In addition to these studies, the September issue of N2 contains other interesting articles that I hope will catch your attention.

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Disclosure

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