Autoimmunity
The good, the bad, and the ugly

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Some readers may remember, as I do, that we were taught to consider autoimmunity as the result of an imbalance of the immune system, often with bad or ugly (translation: very bad) consequences, including refractoriness to treatment, irreversible deficits, or death. We now know that there is protective (good) autoimmunity that can prevent the development of disease, at least in animal models. Indeed, an article by Ortega et al. shows that, depending on the type of antigen and mouse strain, it is possible to generate CD8+ T cells that suppress the development of experimental autoimmune encephalitis (EAE). The authors had previously reported this protective effect in C57BL/6 mice showing that MOG35-55-specific CD8+ T cells suppressed EAE development. In the current article, they demonstrate that using other myelin peptides, such as PLP178-191 and other susceptible mouse strains (SJL), the generated myelin-specific CD8+ T cells were able to suppress disease. The disease-preventing function of these cells was dependent on the specific cognate myelin antigen. Moreover, the generation of the T cells depended on the presence of both CD4+ and CD8+ T-cell epitopes in the antigen used to immunize the mice, and did not appear to be affected by thymic selection. Findings from these models improve our understanding of autoregulatory CD8+ T cells, and have implications for the development of novel therapies for immune-mediated diseases. In contrast, most common treatment approaches to autoimmune disorders use drugs that rebalance the abnormal immune response toward suppressive mechanisms. Molnarfi et al. show in another article in this issue that glatiramer acetate inhibits the type I interferon (IFN) pathway in monocyte type II (M2) polarization.

The case report of Di Pauli et al. represents an example of the very bad: a fulminant autoimmune disorder in which the outcome and autopsy findings were surprising. The patient, a 71-year-old man, presented with acute bilateral vision and gait disturbance as initial symptoms of demyelinating encephalomyelitis associated with oligodendrocyte glycoprotein (MOG) antibodies. At disease onset, aquaporin 4 (AQP4) antibodies were negative, but became positive at week 9. Additionally, CSF glial fibrillary acid protein and myelin basic protein levels were elevated at onset, and decreased during the disease. The symptoms did not respond to immunomodulatory treatment, and the patient died 4 months after onset, with autopsy findings consistent with acute multiple sclerosis (MS). The authors classified the disease as MOG-antibody-associated encephalomyelitis, recognizing the existence of overlapping syndromes and immune mechanisms that appear relevant to this case. This clinical–pathologic report is an example of the complexity and variety of inflammatory demyelinating disorders (IDD) that occur in association with MOG antibodies.

With the goal of clarifying the clinical relevance of MOG antibodies, Kim et al. examined a cohort of 270 adult patients with IDD for MOG and AQP4 antibodies; 17 (6%) had MOG antibodies and 49 (18%) had AQP4 antibodies. The MOG-antibody-positive patients predominantly manifested with isolated symptoms of optic neuritis (83%); one third had relapses involving only the optic nerve and all relapses occurred within 1 year of disease onset. Patients with MOG antibodies did not meet the diagnostic criteria for definitive neuromyelitis optica (NMO) and had less spinal cord involvement, suggesting to the authors that MOG antibodies may be a disease-specific biomarker in adults with IDD, separating this entity from NMO or MS. Although the predominance of optic neuritis among adults with MOG antibodies has been reported previously and the underlying mechanisms (MOG, oligodendropathy; AQP4, astrocytopathy) are different, the specificity of MOG antibodies for a clinical syndrome is uncertain, with cases that clinically resemble NMO or can be categorized as NMO spectrum disorder, and others as acute demyelinating encephalomyelitis or other syndromes.
In another article, Flanagan et al. compared the clinical and MRI features of 26 patients with LGI1 antibodies and faciobrachial dystonic seizures (FBDS) with those of 22 patients with LGI1 antibodies without FBDS. Notably, 10 of the patients with FBDS had been diagnosed previously with a psychiatric disorder, and 20 of 23 cases had normal EEGs. While patients with FBDS were most likely to develop basal ganglia T1 and T2 MRI abnormalities (42% vs 0% of cases without FBDS), those without FBDS were more likely to develop medial temporal lobe abnormalities (91% vs 42% of cases with FBDS). The findings suggest a basal ganglia dysfunction underlying FBDS, with T1 hyperintensity (that persisted longer than T2 abnormalities) as a potential biomarker of this disorder.

The study of Maat et al. addresses the issue of misdiagnosing sporadic Creutzfeldt-Jakob disease (sCJD). These authors investigated the autopsy findings of 384 patients with suspected sCJD. Definite sCJD was diagnosed in 203 patients and 181 with other disorders, mainly neurodegenerative diseases. In 22 patients, the pathologist identified inflammatory infiltrates consistent with the diagnosis of autoimmune encephalitis. Focusing on 21 of these 22 cases (information was not available from 1 case), the authors found that 14 fulfilled the CDC’s 2010 diagnostic criteria for possible or probable sCJD and 7 did not. The CSF showed pleocytosis or increased proteins in 14/18 patients and 6/21 had neuronal antibodies. Interestingly, the type of symptoms, presence of 14-3-3 protein in CSF, and EEG were not substantially different between patients with sCJD and those with autoimmune encephalitis, but none of the latter had MRI abnormalities typical of sCJD (with the limitation of lacking DWI sequences in many). The study did not address whether patients with sCJD had neuronal CSF antibodies, but a previous report did not identify these antibodies. The findings of these and other studies emphasize the occasional similarity between autoimmune encephalitis and sCJD, and the utility of CSF neuronal antibody studies in some cases. The MRI features of a recently reported patient with AMPA receptor antibody-associated encephalitis suggest that even the MRI findings of sCJD can be mimicked by autoimmune encephalitis.

The investigation for ovarian teratomas in patients with anti-NMDA receptor (NMDAR) encephalitis is complicated by the fact that a substantial number of patients do not appear to have a tumor, and in some cases there is evidence that the tumor is microscopic or missed in the initial investigations. The article by Desestret et al. suggests that in women with anti-NMDAR encephalitis, the detection in CSF of immunoglobulin G (IgG) and immunoglobulin A (IgA) NMDAR antibodies should raise the suspicion for an underlying teratoma. Indeed, in a cohort of 94 patients with anti-NMDAR encephalitis, 41% also had CSF IgA NMDAR antibodies. While 49% of these patients had associated tumors, mainly ovarian teratomas, only 5% of those without IgA NMDAR antibodies had teratomas. The significance of this finding is unclear given that IgA NMDAR antibodies occurred more frequently in patients with high titer IgG NMDAR antibodies and it is known that high titer IgG antibodies associate more frequently with teratomas. The findings deserve further study to confirm this association.

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