Name a brain protein, and an autoantibody shall be found!

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Neurol Neuroimmunol Neuroinflamm
2015;2:e159; doi: 10.1212/NXI.0000000000000159

Exciting studies on autoimmune mechanisms of neurologic disorders are leading to the continuous discovery of novel syndromes and autoantibodies of potential clinical utility. Two studies in this issue highlight this discovery process and how findings may be translated into clinical decisions. The first study pertains to the recent discovery of antibodies to cell-adhesion proteins of the nodal and paranodal regions in some patients with chronic inflammatory demyelinating polyneuropathy (CIDP) or Guillain-Barré syndrome. The isotype of these antibodies is usually IgG4, and the target antigens include, among others, contactin-1, neurofascins (NF186 and NF155), and gliomedin, which are important for glial-axonal interactions. Because diseases mediated by antibodies of the IgG4 isotype (such as myasthenia gravis with muscle-specific tyrosine kinase antibodies) often respond to rituximab, Querol et al.[1] used a similar approach for 3 patients with severe CIDP and IgG4 antibodies to contactin-1 or NF-155 who were refractory to steroids and IV immunoglobulin (IVIg). Two of the patients had remarkable improvement, and the third showed mild improvement after 10 years of severe disease. As Lancaster and Scherer point out in their editorial, this preliminary observation should encourage determination of whether patients with CIDP who show a poor response to IVIg and steroids have associated IgG4 antibodies. In these cases, B cell–depleting drugs such as rituximab may be effective even after a prolonged course of severe disease.

The second study relates to the discovery of a novel autoantibody against a cell surface protein named "plasticity-related gene 5" (PRG5) in a patient with paraneoplastic cerebellar degeneration (PCD) and squamous cell lung carcinoma. PRG5 is a transmembrane protein expressed in the hippocampus and cerebellum that is involved in dendrite spine formation. As often occurs with other autoantibodies to neuronal cell surface proteins, the PRG5 antibodies of this patient internalized PRG5, which accumulated in early endosomes. Drs. van Coevorden-Hameete et al.[2] suggest that the antibodies may have a direct pathogenic role in the patient's neurologic symptoms. This study adds a new member to the extensive list of antibodies associated with PCD. Indeed, any classical paraneoplastic antibody against intracellular antigens can associate with PCD, and additionally there are now 4 cell surface autoantigens (DNER, VGCC, mGluR1, and PRG5) that also occur with PCD. The clinical significance of PRG5 antibodies remains to be determined. In the current study, 351 controls were negative for these antibodies. Time and future studies will define the antibody frequency and specificity.

Highlights from some of the other articles in this volume include a study by Absinta et al.[3] These authors investigated 308 high-resolution MRI scans at 3T and 7T from 29 patients with active multiple sclerosis (MS) to look for signal changes occurring prior to the parenchymal contrast enhancement that typically defines the radiologic onset of plaque formation. The study showed that in 16% of new active lesions, the parenchymal enhancement had directly visible antecedent MRI changes centered on the central vein. Supporting the "venulocentric model" of lesion development, there was linear enhancement along the central vein preceding the parenchymal enhancement on postcontrast T1 sequences by days to weeks. The authors suggest that slow flow along with leukocyte rolling and perivascular contrast entrapment without passage through the glia limitans may explain the findings. In other instances, small areas of T2 signal change around the vein were detected before parenchymal enhancement, suggesting hypercellularity due to reactive astrocytes, activated microglia, and lymphocytes. At times, the newly forming lesions arose from areas that were previously (months to years) abnormal, suggesting that previously affected perivenular regions may be prone to subsequent demyelination. Overall, the findings suggest that early perivenular changes, likely related to

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Funding information and disclosures are provided at the end of the editorial. Go to Neurology.org/nn for full disclosure forms.

cellular infiltration, occur frequently in MS, although these changes are not necessarily visible with gadolinium.

Using a model of experimental autoimmune encephalomyelitis (EAE), Dr. Ji et al.[4] explored the role of macrophage migration inhibitory factor (MIF) in the development of disease resistance to steroids. They induced EAE in wild-type (Wt) and knockout (MIF $^{-/-}$) mice followed by treatment with dexamethasone before or upon disease onset. The treatment was found to be more effective in MIF $^{-/-}$ than in Wt mice; dexamethasone decreased cytokine production by CD4 T cells in both groups of animals at the onset of EAE but inhibited upregulation of T-bet during acute and chronic phases of the disease mainly in MIF $^{-/-}$ mice. In addition, the expression of VLA-4 was decreased in the CD4 T cells of MIF $^{-/-}$ mice compared with Wt mice. These data suggest that in the EAE model, MIF is an important molecule in the resistance of pathogenic CD4 T cells to steroids and a potential target to enhance the efficacy of steroids in neuroinflammatory disorders.

The clinical case described by Dr. Ryerson et al.[5] illustrates the difficulty in diagnosing Susac syndrome in some patients. The authors report a 66-year-old man with episodes of encephalopathy and hearing loss and extensive leptomeningeal enhancement who had marked symptom exacerbation after natalizumab. Additional findings suggestive of Susac syndrome included the presence of myelin changes in the central portion of the corpus callosum ("snowball lesions") and anti-endothelial antibodies. Brain biopsy showed confirmatory findings such as focal microangiopathy, T cell perivascular inflammation, and complement deposition along with prominent myelin loss, which has not been previously reported in Susac syndrome. The exacerbation of the disease caused by natalizumab is intriguing; the authors suggest that natalizumab altered the balance of the immune system, decreasing circulating T regulatory cells and subsequently increasing proinflammatory cytokine-producing T cells.

Previous studies have pointed to the rare association of overlapping syndromes and immune mechanisms such as anti-NMDA receptor (NMDAR) encephalitis and demyelinating disorders with aquaporin-4 or myelin oligodendrocyte glycoprotein antibodies.[6] To address this issue, Ramberger et al.[7] investigated the frequency of IgG NMDAR antibodies in the serum of 215 patients with various well-defined inflammatory demyelinating disorders, such as acute disseminated encephalomyelitis, neuromyelitis optica spectrum disorder, clinically isolated syndrome, and MS. The authors found NMDAR antibodies in the 9 control cases with anti-NMDAR encephalitis and in only 1 of the 215 patients with demyelinating diseases. Interestingly, this patient had NMDAR antibodies at the onset of MS, with an increase of antibody titers linked to the onset of psychiatric symptoms and cognitive decline, likely representing a case of overlapping syndromes.

These are just a few examples of the interesting articles in the October issue of *Neurology® Neuroimmunology & Neuroinflammation*. After reading them, the following question comes to mind: How many unknown disease-related autoantibodies are yet to be identified?

We look forward to publishing those future studies!

DISCLOSURE

J. Dalmau is the editor of *Neurology: Neuroimmunology & Neuroinflammation*; is on the editorial board for Neurology UpToDate; holds patents for and receives royalties from Ma2 autoantibody test, NMDA receptor autoantibody test, GABA(B) receptor autoantibody test, GABA(A) receptor autoantibody test, DPPX autoantibody test, and IgLON5 autoantibody test; and received research support from Euroimmun, NIH, and Instituto Carlos III (FIS, Spanish Government). Go to Neurology.org/nn for full disclosure forms.

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Neurol Neuroimmunol Neuroinflamm 2015;2;
DOI 10.1212/NXI.0000000000000159