

Identifying targets for diagnosis, prognosis, and treatment

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This issue of *Neurology*[®] *Neuroimmunology & Neuroinflammation* (N2) incorporates exciting studies on the biology of immunologic and inflammatory biomarkers and the importance of knowing the benefits and complications of targeted therapies. In addition, the issue includes several clinically relevant reports on viral and autoimmune encephalitis. The concept of precision medicine, recently re-enhanced by public media, is not new in clinical and basic research. An interesting example is the case presented by Euskirchen et al.¹ of a patient with life-threatening brainstem neurohistiocytosis in the context of Erdheim-Chester disease and cutaneous Langerhans cell histiocytosis. Detection of a BRAF mutation in affected tissues led to the selection of a specific BRAF inhibitor (vemurafenib), resulting in a rapid clinical response. On the other hand, Kornberg et al.² suggest that the use of targeted therapies in an inappropriate context, such as fingolimod and natalizumab in neuromyelitis optica (NMO) instead of multiple sclerosis (MS), carries the risk of disease exacerbation. The authors postulate that a combination of drug effects, including an increase of blood-brain barrier permeability allowing CNS entry of Th17 lymphocytes, was responsible for the clinical worsening in the case they present. In another report, Hillen et al.³ postulate that natalizumab may have contributed to fulminant liver failure related to hepatitis B infection in a patient receiving the drug for relapsing-remitting MS (RRMS). Svenningsson et al.⁴ show that rituximab, a drug used for both MS and NMO, rapidly distributes to the peripheral compartment following intrathecal administration. Ultra-low doses of intrathecal rituximab were sufficient to cause complete and prolonged depletion of B lymphocytes in both the CNS and systemic compartments, an observation with potential implications for other disorders, such as autoimmune encephalitis.

Three additional studies use immunologic cells or autoantibodies as biomarkers of disease or treatment outcome. In a study of children with a first episode of acquired demyelinating syndrome, Hacoen et al.⁵ found that the presence of myelin

oligodendrocyte glycoprotein (MOG) antibodies at symptom onset predicted a non-MS disease course. These findings confirm previous studies indicating that patients with optic neuritis and MOG antibodies have a low probability of developing MS or NMO.⁶ De Raedt et al.⁷ describe that the detection of a high circulating natural killer (NK) cell count within the first hours after an acute ischemic stroke, followed by a drop in all lymphocyte subsets, identifies patients prone to develop infections, likely as a result of autonomic dysfunction with sympathetic overdrive. Elkins et al.⁸ investigated the relationship between CD56^{bright} NK cells and disease activity in patients with RRMS treated with daclizumab high-yield process (DAC HYP). In this preliminary study, the authors found a statistically significant inverse relationship between CD56^{bright} NK cell counts measured after DAC HYP and the number of new or enlarged T2-hyperintense lesions that developed between weeks 24 and 52 post-treatment. The findings, which need validation in prospective studies, suggest that CD56^{bright} NK cell counts should be considered as a potential surrogate to understanding individual variation in the treatment response to DAC HYP.

A study by Bar-Or et al.⁹ provides Class II evidence that in normal subjects treated with teriflunomide (a drug used in RRMS that blocks pyrimidine synthesis), antibody titer responses to rabies vaccination are lower than with placebo but sufficient for seroprotection. The findings support the view that teriflunomide decreases autoaggressive immune responses in MS but does not limit the ability to mount primary adaptive humoral immune responses or alter delayed T-cell hypersensitivity. The work of Guptill et al.¹⁰ shows that patients with muscle-specific tyrosine kinase myasthenia gravis have higher plasma B cell-activating factor levels and lower percentages of B10 cells than healthy controls. The authors suggest that the reduction of regulatory B10 cells, which produce the anti-inflammatory cytokine interleukin (IL)-10, likely explains a previously reported increase of proinflammatory Th1 and Th17

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responses, breaking down immune tolerance and resulting in the generation of autoreactive B cells.¹¹ In another study, Moore et al.¹² used human fetal and adult microglia to confirm that expression of the P2Y12 receptor (an ADP-responsive G protein-coupled receptor also expressed by platelets) is enhanced under alternatively activated (M2, IL-4, and IL-13) conditions, mediating cell migration and participating in acute proinflammatory responses toward danger-associated molecules that are released during CNS injury. The findings may provide a novel strategy for treating CNS inflammatory disorders.

In the fields of viral, paraneoplastic, or autoimmune encephalitis, 5 interesting articles are included in this issue. Marques et al.¹³ describe a challenging case of varicella-zoster encephalitis mimicking toxoplasmosis relapse; the clinical and MRI features suggesting hemorrhagic encephalitis with vasculopathy were important clues to the diagnosis, which was confirmed with CSF viral studies. Liba et al.¹⁴ describe a patient with Rasmussen encephalitis who dramatically responded to aggressive immunotherapy with steroids, cyclophosphamide, and mycophenolate mofetil; the short clinical follow-up suggests caution in the interpretation of this intriguing result. Probst et al.¹⁵ confirm that a novel cell-based assay expressing Delta/Notch-like epidermal growth factor-related receptor confers high sensitivity and specificity for determination of Tr antibodies, which usually occur in association with cerebellar degeneration and Hodgkin lymphoma. Körtvelyessy et al.¹⁶ provide the neuropathologic findings in the hippocampus and amygdala of a patient with autoimmune encephalitis and CASPR2 antibodies. Among moderate amounts of CD3⁺ and CD8⁺ T lymphocytes (without neuronophagic nodules) and small numbers of B cells and plasma cells, the authors found deposits of complement in a few neurons, suggesting a complement-mediated mechanism. The case is interesting because CASPR2 antibodies are usually IgG4, an isotype that does not fix complement. Finally, Simabukuro et al.¹⁷ report a case of recurrent thymoma and autoimmune encephalitis associated with cortical and subcortical fluid-attenuated inversion recovery MRI abnormalities and antibodies to both GABA_A receptor and LGI1. The tumor expressed both autoantigens, and the patient had a remarkable recovery after tumor removal and immunotherapy. This case highlights the complexity of autoimmune encephalitis associated with several concurrent autoantibodies.

I hope you enjoy reading these articles and encourage you to submit your work to N2.

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 and NMDA receptor autoantibody test; has patent applications for and receives royalties from 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 Fondo de Investigaciones Sanitarias de la Seguridad Social (Instituto Carlos III, Spanish Government). Go to Neurology.org/nn for full disclosure forms.

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