Editor's Corner

Volume 6, Number 1, January 2019
Neurology.org/NN

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N2 year in review and message from the editor to our reviewers

Neurol Neuroimmunol Neuroinflamm January 2019 vol. 6 no. 1 e525. doi:10.1212/NXI.0000000000000525

For this January's issue of *Neurology: Neuroimmunology and Neuroinflammation* (N2), the editors have selected articles from this and other journals that they found interesting over the course of 2018. These articles are from different areas of the fields of neuroimmunology and neuroinflammation and are discussed in a brief commentary that we hope will inspire our readers to further explore these topics.

The use of immune checkpoint inhibitors (ICIs) has revolutionized the treatment of cancer, with an increasing number of histologic tumor types being considered for these treatments.[1] ICIs target molecules such as cytotoxic T lymphocyte–associated antigen 4, programmed cell death protein (PD1), and PD1 ligand that are expressed on activated immune cells (T cells, B cells, natural killer cells, and some myeloid cells) and regulate inflammatory and autoimmune responses through a negative feedback mechanism.[2] Boosting the immune system with monoclonal antibodies against these molecules can result in serious immune-related adverse effects (irAEs) that manifest with an extensive variety of symptoms affecting the peripheral or CNS. Several mechanisms have been proposed for irAEs, including, among others, (1) exacerbation of a preexisting immune disorder, such as multiple sclerosis (MS), during or after the initiation of ICIs and (2) exacerbation of subclinical immune responses against antigens expressed in the cancer and nervous system (onconeuronal antigens) resulting in paraneoplastic neurologic syndromes.[2] There are reports suggesting that these ICI-enhanced paraneoplastic immune responses can be mediated by autoantibodies (e.g., anti-N-methyl-D-aspartate receptor [NMDAR] encephalitis) or T cells causing some of the classic paraneoplastic syndromes (e.g., anti–Hu-associated encephalitis).[3] The study of these complications offers an opportunity to better understand the immune mechanisms involved in similar neurologic disorders when they occur without the use of ICIs. In the March 2018 issue of N2, Hottinger et al.[4] described a 71-year-old woman who developed anti–Hu-associated paraneoplastic encephalitis after the use of 2 ICIs (ipilimumab and nivolumab) to treat her metastatic small cell lung cancer (SCLC). Considering that this disorder is mediated by T cells against a family of onconeuronal antigens (Hu proteins), the authors reasoned that natalizumab would block the migration of these T cells into the brain mitigating the neuronal damage, while not affecting the T cell activity against the systemic cancer. Indeed, after treatment with natalizumab, the patient had substantial neurologic improvement and a durable oncologic response. This case suggests that with the increasing use of ICIs in patients with tumors prone to associate with paraneoplastic immune responses (e.g., SCLC), the number of irAE manifesting as paraneoplastic syndromes may increase. Moreover, the strategy of using natalizumab or similar drugs for T cell–mediated paraneoplastic disorders deserves further investigation with prospective clinical trials.

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Editor Summary
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Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/NN.

One of the initially recognized potential triggers of autoimmune encephalitis was the association with tumors, with histologic types varying according to the immune response (e.g., teratoma in anti-NMDAR encephalitis or SCLC in GABAb receptor encephalitis).[5] More recently, some of these disorders (anti-IgLON5, anti-LGI1, and anti-Caspr2) have been found to be associated with distinct human leukocyte antigen Class II haplotypes, suggesting an underlying genetic predisposition.[6–10] Despite these tumor associations or genetic susceptibility, the mechanisms that trigger the immune response in many patients remain unknown. The identification that autoimmune encephalitis, mainly associated with NMDAR antibodies, can occur a few weeks after herpes simplex encephalitis (HSE), suggested the possibility of viruses as triggers of brain autoimmunity.[11] One proposed mechanism is that the viral encephalitis causes a release of neuronal proteins (among them NMDAR or other cell surface proteins), which in the context of extensive inflammation leads to an autoimmune response against the neuronal antigens. This mechanism is supported by 2 findings: (1) the close time-relationship (less than 3 months) between HSE and the subsequent development of autoimmune encephalitis and (2) the variety of autoantibodies identified in these patients, including antibodies targeting the NMDAR, gamma-aminobutyric acid (GABA)a receptor, and unknown cell surface antigens.[11] Another proposed mechanism is that the immune response post-HSE is triggered by molecular mimicry. Although molecular homology between herpes simplex virus 1 (HSV-1) and NMDAR has not been identified, the study of Salovin et al.[12] in the July issue of N2 suggests this possibility. The authors used 2 cohorts of pediatric patients with anti-NMDAR encephalitis without a history of HSE and age-matched control groups. In each cohort, more participants with anti-NMDAR encephalitis than controls had anti-HSV-1 IgG antibodies. The findings were statistically significant for one of the cohorts and when the cohorts were combined. In addition to molecular mimicry, the authors raised several alternative hypotheses, such as virus-induced alteration of NMDAR outside the CNS, or HSV-1 modulation of the immune system in a manner that allows inappropriate recognition of native NMDARs.

The persistent risk of cognitive impairment syndromes in HIV-infected individuals despite complete suppression of virus replication with anti-retroviral therapy is a difficult diagnostic and therapeutic challenge. Cysique et al.[13] used 1H-MRS to assess neuronal and glia brain metabolic markers at baseline and ~23 months in a cohort of 73 HIV^+, virally suppressed patients in comparison with 35 HIV^- controls. The HIV^+ group had stably lower N-acetyl aspartate (NAA) levels in caudate and posterior cingulate cortex (PCC); however, a subgroup with progressive impairment had decreasing NAA levels in the PCC. Individuals with stable impairment also demonstrated decreasing frontal white matter (WM) creatinine, which suggests impaired cellular energetics. The message is clear: HIV suppression alone is insufficient to fully protect the brain from coactivated pathways associated with progressive injury. We need predictive risk markers for brain injury in virally suppressed HIV^+ individuals. The study by Fleischman et al.[14] of 66 HIV^+ virally suppressed patients showed that plasma neopterin levels were negatively correlated with hippocampal volumes (by 3T MRI) and episodic memory. Thus, this well-studied marker of monocyte/macrophage activation may, like neurofilaments (NFL), be useful for developing a plasma biomarker panel for not only assessing risk but also tracking the brain's response to persistent, suppressed HIV infection and response to adjunctive neuroprotective therapies.

Several articles in 2018 have touched on serious side effects of modern immunotherapies used in MS and neuromyelitis optica spectrum disorders (NMOSDs), 2 of which are highlighted here. Rituximab, a monoclonal antibody targeting the CD20 antigen on B lymphocytes, has been increasingly used over the past 15 years to treat patients with NMOSDs, a severe autoimmune condition of the CNS, in which the optic nerves, the spinal cord, and the brainstem are preferentially affected. Rituximab's clinical efficacy in reducing relapse frequency and severity is beyond doubt; however, safety issues also have to be taken into consideration because the number of patients with long treatment courses is growing. Marcinnò et al.[15] followed up 15 patients with NMOSDs (10 seropositive for the aquaporin-4 [AQP4] antibody) treated repeatedly with rituximab over a median of 70 months (range 17–124 months), 7 patients had a follow-up of at least 70 months. Median interval between rituximab infusions was 11 (3–36) months. Laboratory assessments comprised regular measurements of serum immunoglobulin A, G, and M levels (median sampling interval 4.9 months). In a subset of patients, serial AQP4 antibody measurements and anti-tetanus (TET), anti–varizella zoster virus (VZV), and Epstein-Barr virus nuclear antigen (EBNA) IgG were measured.

Treatment with rituximab caused a significant reduction of IgA, IgG, and IgM. Hypo-IgG (<7.0 g/L) was detectable in 11/15 patients (73%) at least once over the treatment course. Of interest, hypogammaglobulinemia for IgG (hypo-IgG) was present in 4 patients before initiation of rituximab. Similar observations were reported for hypo-IgA (<0.7 g/L) in 6/15 (40%), in 2 patients before rituximab, and hypo-IgM (<0.4 g/L) in 9/15 (60%), in 1 patient before rituximab. Three of 15 patients developed severe hypo-IgG (<4.0 g/L) in at least 1 measurement, whereas severe hypo-IgM (<0.2 g/L) was found in 2 of 15 patients at least once. The frequency of hypo-IgG, hypo-IgA, and hypo-IgM increased with longer rituximab treatment courses. Two patients with severe hypo-IgG had infectious complications after 8 and 9 years of rituximab treatment (pneumonia with hand, foot, and mouth disease and bilateral multifocal pyelonephritis). Anti-TET IgG levels were below the protection threshold (≤0.1 IU/mL) before rituximab commencement in 4/15 patients (27%). Anti-TET levels decreased in 10/15 patients during rituximab and fell below the protection threshold in 1. Moreover, anti-TET IgG levels during rituximab treatment were significantly lower compared with healthy controls. Anti-VZV and anti-EBNA IgG decreased over time in 8/15 patients and 0/6 controls and 12/15 patients and 1/16 controls, respectively.

This study is clinically very important despite the small sample size and the monocenter setting because it shows that severe hypogammaglobulinemia and reduction of anti-TET protection may develop under treatment with rituximab in a considerable number of patients with NMOSDs. The authors correctly recommend monitoring the total and class-specific IgG levels and the anti-TET IgG before and during rituximab treatment as a measure to mitigate risks of serious infectious complications of rituximab, in particular with prolonged treatment courses of 5 years or more.

Daclizumab, a monoclonal antibody inhibiting interleukin-2 signaling by blocking interleukin-2 receptor alpha (CD25) was approved for treatment of relapsing MS in 2016. However, the drug was withdrawn voluntarily from the market by the manufacturer in March 2018. The European Medicines Agency also recommended suspension and recall of the drug subsequent to 12 cases of severe inflammatory brain disorders including 3 deaths. Luessi et al.[16] performed a thorough and insightful workup of 6 cases of encephalitis following treatment with daclizumab in Germany and an additional vasculitis case from the United States. The index case in that report was a 32-year-old man with a typical clinical and radiographic disease course of relapsing-remitting MS who had been on disease-modifying treatment with daclizumab for 8 months when he developed aggressive behavior, incoherent thoughts, delusions, fluctuating dysarthria, and progressive memory loss, all of which are not regarded as classic symptoms of MS. MRI showed a new juxtacortical right frontal lobe lesion; EEG was suggestive of a moderately severe encephalopathy; CSF analysis revealed pleocytosis and elevated protein levels; and antibodies to glial fibrillary acidic protein were detected in CSF and serum. Treatment with high-dose steroids, plasma exchange, and rituximab lead to partial recovery, albeit with persistent neuropsychological deficits. The other 6 cases of serious inflammatory complications emerging on treatment with daclizumab comprise CNS vasculitis, inflammatory demyelinating CNS processes, anti-NMDAR-associated encephalitis, acute disseminated encephalomyelitis, and drug rash with eosinophilia and systemic symptoms syndrome. Outcome was partial recovery in some cases, whereas 1 patient had severe disability requiring foster care. The mechanisms underlying these and other cases remain speculative and presumably involve an impaired Treg/natural killer cell balance through inhibition of regulatory T cells without parallel expansion of immunoregulatory $CD56^{bright}$ natural killer cells. These cases are in line with previous reports of secondary autoimmunity under daclizumab treatment including 2 deaths in the pivotal clinical trials (autoimmune hepatitis and psoas abscess) and underscore the necessity for increased vigilance toward rare side effects of new immunomodulatory drugs both in clinical trials and after approval.

The recent successful introduction of the anti-CD20 antibody, ocrelizumab, in MS therapy has highlighted the role that B cells play in MS pathogenesis. Besides serving as a source of antibody-producing plasma cells, B cells can present antigens to T cells and secrete cytokines that promote differentiation of either proinflammatory or regulatory T cells. One important question is whether patterns of B cell cytokine production or B cell subsets associate with particular stages of MS. Guerrier et al.[17] evaluated proinflammatory IL-6 and anti-inflammatory IL-10 production in B cells from patients with radiologically isolated syndrome (RIS), clinically isolated syndrome (CIS), untreated patients with relapsing-remitting MS (RRMS), and healthy controls. They discovered that high baseline IL-6/IL-10 ratio in patients with RIS/CIS is associated with disease activity and that this cytokine imbalance reflected a decrease in $IL\text{-}10^{+}$ B cells, without a change in $IL\text{-}6^{+}$ B cells. "Double-negative" (IgD^{-}/$CD27^{-}$) memory B cells are a subset that are increased in systemic lupus erythematosus and Sjögren syndrome and are associated with increased activity of those autoimmune diseases. Of particular interest, this group observed an overrepresentation of double-negative memory B cells in CIS and RRMS, although there were no alterations in distribution of other B cell subsets examined in any disease phases. Overall, their data are exciting and support the concept that there may be skewing toward certain proinflammatory B cell phenotypes during the evolution of early MS, a possibility that deserves further investigation.

Although a majority of patients with MS present in the relapsing-remitting phase, at least one-half of those patients subsequently enter a progressive phase, which is characterized by a steady increase in disability. Unlike for RRMS, currently there is a lack of effective treatments for secondary progressive MS (SPMS). Whereas T cells and B cells, the lymphocyte subsets of the adaptive immune system, are thought to have a central role in directing inflammation associated with RRMS, the CNS inflammation in progressive MS is characterized by activation of resident CNS cells (e.g., microglia) that participate in innate immunity and promote demyelination and neurodegeneration. Unfortunately, it is not feasible to monitor the cellular changes associated with progressive MS by conventional MRI. Thus, Rissanen et al.[18] used PET with the radioligand [11C](R)-PK11195 that binds to a protein expressed on activated microglia and macrophages, and some astrocytes, to evaluate WM damage in SPMS. They observed that higher [11C](R)-PK11195 binding in normal-appearing WM (NAWM) was associated with higher clinical disability and reduced WM structural integrity and that increasing age contributed to greater microglial activation in the NAWM among patients with MS, but not in healthy controls. These exciting findings establish how PET can be used to quantitate microglial activation associated with MS progression and serve as complementary imaging modality in treatment studies of progressive MS.

Currently approved medications for treatment of RRMS reduce inflammation and promote immune modulation. In contrast, CNS repair, including remyelination and axonal regeneration, is a major goal for treatment of progressive MS.

Leucine-rich repeat and immunoglobulin-like domain-containing Nogo receptor-interacting protein 1 (LINGO-1) is an inhibitory transmembrane signaling protein expressed by neurons and oligodendrocytes, which prevents axonal outgrowth and oligodendrocyte differentiation, restraining myelination. Anti-LINGO antibody, opicinumab (BIIB033), is being advanced in clinical MS studies for its potential neuroprotection and capability to promote remyelination. In 2014, a phase I study demonstrated the safety of opicinumab in patients with MS and healthy controls,[19] and it is now in clinical trials evaluating its efficacy. Because the mechanism of action (MOA) of opicinumab is attributed to its action on neurons and oligodendrocytes, it is important to distinguish its MOA from approved MS therapies, which modulate activity of immune cells. In this regard, Ranger et al.[20] demonstrated that LINGO-1 is not expressed by immune cells from human peripheral blood or rat spleen, LINGO-1 blockade did not affect T cell proliferation or cytokine production, and opicinumab treatment of patients with MS did not cause significant changes in immune system gene expression in either blood or CSF. Together, their data provide further support that anti-LINGO-1 treatment exerts its novel activity via remyelination and/or neuroprotection, independent of immune modulation. If MS clinical trials demonstrate efficacy, opicinumab will be a welcome addition to the armamentarium of treatments.

Lastly, we want to thank our reviewers. We are able to accept only a minority of submitted manuscripts and must make difficult decisions regarding which articles will most benefit our readers and improve patient care. Your thoughtful comments regarding experimental research investigations, the uniqueness of study populations, novel methods and techniques, studies that are especially educational, or new strategies for diagnosing and treating neurologic disease are enormously helpful and highly appreciated. Our gratitude for your dedication to reviewing for *Neurology® Neuroimmunology & Neuroinflammation* cannot be adequately conveyed.

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Study funding

No targeted funding.

Disclosure

J. Dalmau is editor of *Neurology: Neuroimmunology & Neuroinflammation*; is on the editorial board of *Neurology UpToDate*; and holds patents for and receives royalties from Ma2 autoantibody test and from NMDAR, GABA-B receptor, GABA-A receptor, DPPX, and IgLON5 autoantibody tests. He received license fee payments from Euroimmun and has been funded by the NIH, Instituto Carlos III/FEDER (Madrid, Spain), CIBERER (Madrid, Spain), Agencia de Gestio d'Ajuts Universitaris i de Recerca (AGAUR), CERCA Programme Generalitat de Catalunya (Barcelona, Spain), and Fundació CELLEX. M. Heneka served on the editorial board of *Journal of Neurochemistry*, *Journal of Chemical Neuroanatomy*, and *Journal of Neurobiology*; serves as associate editor of *Neurology: Neuroimmunology & Neuroinflammation*; and received research support from DFG. D.L. Kolson serves as associate editor of *Neurology: Neuroimmunology & Neuroinflammation*; received research support from the NIH/NIMH and NIH/NINDS; and serves as consultant and scientific advisory for studies of HIV-associated neurocognitive disorders (HAND) and their relationship to psychiatric illnesses. F. Paul served on the steering committees of Novartis and MedImmune; received speaker honoraria and travel funding from Bayer, Novartis, Biogen, Teva, Sanofi-Aventis/Genzyme, Merck Serono, Alexion, Chugai, MedImmune, and Shire; is an academic editor of *PLoS ONE* and an associate editor of *Neurology: Neuroimmunology & Neuroinflammation*; consulted for Sanofi Genzyme, Biogen, MedImmune, Shire, and Alexion; and received research support from Bayer, Novartis, Biogen, Teva, Sanofi-Aventis/Genzyme, Alexion, Merck Serono, German Research Council, Werth Stiftung of the City of Cologne, German Ministry of Education and Research, Arthur Arnstein Stiftung Berlin, EU FP7 Framework Program, Arthur Arnstein Foundation Berlin, Guthy-Jackson Charitable Foundation, and NMSS. S.S. Zamvil served on data safety monitoring boards of Opexa, BioMS, Teva, and Eli Lilly; is a member of the clinical advisory board of the Myelin Repair Foundation; is deputy editor of *Neurology: Neuroimmunology & Neuroinflammation*; holds a patent for aquaporin-4 peptides; consulted for Biogen, Teva, EMD Serono, Genzyme, Novartis, and Roche; serves on the speakers' bureau of Advanced Health Media and Biogen; and received research support from Biogen, Teva, NIH, NMSS, and Alexander M. and June L. Maisin Foundation. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/NN.

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Neurol Neuroimmunol Neuroinflamm 2019;6;
DOI 10.1212/NXI.0000000000000525