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Ten Years of *Neurology® Neuroimmunology & Neuroinflammation*

Decade in Review

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It has been a decade since the first issue of *Neurology® Neuroimmunology & Neuroinflammation* (*N2*) launched in June 2014. In these 10 years, *N2* has evolved to become a leading journal in clinical and translational neuroimmunology. The parallel timings of the rising impact of the journal and the extraordinary advances in the field of neuroimmunology are not due to serendipity. Dr. Richard Ransohoff, the founding editor, together with Dr. Robert Gross, the editor of *Neurology* in 2014, shared the vision that the rapidly developing field of autoimmune neurology was going to have a home in *N2*. I became editor of *N2* a few months after the journal was introduced, and now, 10 years later, I am glad to transfer the baton to Dr. Scott Zamvil, professor of neurology at University of California, San Francisco. I have been fortunate to work with Dr. Zamvil in his role as deputy editor during the past 10 years; his enthusiasm, work ethic, and encyclopedic knowledge of neuroscience, particularly in regard to multiple sclerosis (MS), myelin oligodendrocyte glycoprotein (MOG) autoimmunity, neuromyelitis optica (NMO), and animal models make him the ideal person to lead the journal forward. This transition coincides with the first decade of *N2*, and I would like to express my gratitude to all associate editors, editorial board members, and editorial office staff for their dedication to the journal and readiness to help since day one. Importantly, *N2* would not be the journal it is without our authors and readers, and we are all grateful for their work and interest shown during these 10 years.

To celebrate this first decade, we have included in this issue of *N2* several invited reviews by experts on relevant topics (included as separate publications), as well as section editors' views and comments (included further) on a selection of articles published in *N2* and elsewhere during this decade.

Paraneoplastic and Autoimmune Encephalitis

In 2021, an international group of experts published in *N2* updated diagnostic criteria for paraneoplastic neurologic syndromes (PNSs).[1] Previous criteria were published 16 years earlier, and many developments had occurred that made the 2004 criteria outdated.[2] A goal of the new criteria was to redefine the terms "classical paraneoplastic syndromes" and "onconeuronal antibodies" that until then were considered almost synonymous with disorders associated with antibodies against intracellular antigens. This concept was inaccurate; for example, some disorders with antibodies against intracellular neuronal proteins are rarely paraneoplastic (e.g., anti-GAD65–associated syndromes or anti-AK5 encephalitis), whereas disorders associated with antibodies against neuronal cell surface proteins (e.g., anti-GABAb receptor or anti-AMPA receptor encephalitides) are frequently paraneoplastic. Therefore, the panel of investigators proposed to substitute "classical syndromes" with the term "high-risk phenotypes" for cancer and introduced the concept of "intermediate-risk phenotypes." The term "onconeural

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antibody" was replaced by "high-risk" (>70% associated with cancer) and "intermediate-risk" (30%–70% associated with cancer) antibodies. The panel classified 3 levels of evidence for PNS: definite, probable, and possible. Each level can be reached by using a PNS-Care score, which combines clinical phenotype, antibody type, the presence or absence of cancer, and time of follow-up.[1] These criteria have clear diagnostic, treatment, and prognostic implications regarding the need to search for an associated tumor, the likelihood of a disorder to respond to immunotherapy, and the long-term outcome.

The irruption of immune checkpoint inhibitors (ICIs) in the treatment of many types of cancers has modified (albeit less than expected) the frequency of paraneoplastic neurologic syndromes. One study performed in a center focused on PNS showed an increase in the frequency of anti-Ma2–associated encephalitis (6 [35%] of 17 patients had received ICI) during a 2-year study period.[3] The increase in frequency of this particular paraneoplastic encephalitis was found to be disproportionally high compared with that of other PNSs, and although the clinical manifestations of ICI-related anti-Ma2 encephalitis were similar to those of patients who did not receive ICI, the tumors were different. For example, none of the 6 patients (5 men) with ICI-related anti-Ma2 encephalitis had germ-cell tumors (4 lung cancer, 1 mesothelioma, 1 renal cancer). This could be explained by the age of the patients because it is known that the predominance of germ-cell tumors in anti-Ma2 encephalitis occurs in patients younger than 50 years, and for those older than 50, other tumors are usually associated (mainly lung cancer).[4]

A similar study by the same group comparing anti-Hu syndromes related and not related with ICI showed that both groups of patients developed similar anti-Hu–related symptoms, but those treated with ICI were more likely to have co-occurring involvement of central and peripheral nervous systems and limbic, brainstem, and dorsal root ganglia involvement, and poorer outcome and higher mortality.[5] The ICI-related mechanisms responsible for this poorer outcome were unclear but likely associated with an enhanced anti-CNS immune response, as suggested by an animal model of ICI-induced PNS.[6] Single case reports of ICI-induced brainstem encephalitis associated with antibodies against Kelch-like protein-11,[7] ICI-induced relapse of MOG antibody-associated disease (MOGAD),[8] and ICI-related opsoclonus-myoclonus-ataxia in a patient with metastatic small-cell lung cancer[9] were also described.

In 2020, *N2* published a clinical diagnostic algorithm for pediatric patients suspected to have autoimmune encephalitis.[10] Inspired by a previously reported general algorithm (focused on adults, but also applicable to children),[11] both algorithms show substantial similarities but also an important difference. The common goal is to facilitate the clinical recognition of the many forms of autoimmune encephalitides that can affect children and adults, without the dependency on upfront autoantibody testing. Although, for many disorders, autoantibodies are required to establish the category of "definite" autoimmune encephalitis (exceptions include acute disseminated encephalomyelitis [ADEM] and some presentations of limbic encephalitis),[11] both algorithms also offer guidance in the diagnosis of probable autoimmune encephalitis supporting the initiation of immunotherapy while antibody testing is ongoing.[12-17] The important difference between the algorithms is in the categorization of "antibody-negative but probable autoimmune encephalitis" (ANAE), for which the general algorithm requires the presence of brain inflammation confirmed by at least 2 tests (CSF pleocytosis or oligoclonal bands, brain MRI showing inflammatory changes, or neuropathologic alterations) while the pediatric algorithm only requires one of these tests. Although this difference may seem trivial, it is important: a recent study comparing both algorithms (pediatric[10] vs general[11]) in 729 children suspected to have autoimmune encephalitis showed that the pediatric algorithm included 4 times more patients in the category of ANAE (potentially leading to immunotherapy initiation or escalation in a higher number of patients who may benefit from it) but also included as ANAE 7.8 times more patients who did not turn out to have an inflammatory disorder and, therefore, did not need immunotherapy.[18] The authors concluded that both algorithms perform well in the diagnosis of definite antibody-associated encephalitis but show limitations in the diagnosis of pediatric ANAE.

Mimics of autoimmune encephalitis were investigated in a retrospective study of 239 patients of all ages with suspected autoimmune encephalitis. The study found that the most common mimics and cause of misdiagnosis were neuroinflammatory CNS disorders, psychiatric disorders, epilepsy of noninflammatory cause, CNS infections, neurodegenerative diseases, and CNS neoplasms. These findings resembled those of the above-noted prospective study of 729 children with suspected autoimmune encephalitis, in which the most frequent mimics were infectious, epileptic, and psychiatric disorders.[18]

During this decade, many studies on anti-NMDAR encephalitis (NMDARe) have been published in *N2* including, among others, 1 study showing the racial and ethnic disparities in the incidence of the disease (more frequent in Black, Hispanic, and Asian/Pacific Island persons compared with White persons) and the increased frequency of ovarian teratomas in Black female individuals compared with the other groups.[19] Another study emphasized the high frequency of hospitalization of patients with NMDARe in psychiatric institutions (45 [40%] of 111 patients), and that 21 (47%) of these patients developed symptoms suggesting intolerance to antipsychotic medication (hyperthermia, muscle rigidity, mutism, coma, or rhabdomyolysis),[20] although in our experience, similar symptoms can occur in neuroleptic-naïve patients. A study of 489 patients with NMDARe showed that 75 (15%) were seronegative (antibodies only detected in CSF), and that these patients, compared with those who had antibodies in both serum and CSF, had milder neurologic

symptoms with less frequency of tumors.[21] International consensus recommendations for the treatment of pediatric anti-NMDAR encephalitis were published in *N2* in 2021.[22]

Multiple studies on NMDARe published in *N2* and elsewhere demonstrated an overall good functional neurologic outcome (mostly assessed with the modified Rankin Scale [mRS]),[23] but many patients, in particular children, have long-term problems in adaptive behavior,[24] cognitive impairment and fatigue,[25] and academic difficulties in general.[26] The very long-term functional outcomes in children with NMDARe were determined in a study of 76 patients (median follow-up 7.1 years, range 5.0–10.1) assessed with the Liverpool Outcome Score (a 15-domain question format): 73% had full recovery; 18% had behavioral and school/working deficits; and 9% had multidomain deficits involving self-care ability, behavioral-cognitive impairment, and seizures.[27] This study also found that the younger the patient at disease onset, the more probable it was to remain with multidomain deficits and dependent on sociofamilial support. Findings from all these studies aligned with the concept derived from previous reports and reviews suggesting that earlier treatment of anti-NMDAR encephalitis in children results in better outcomes.[28,29]

The anti-NMDAR Encephalitis One-Year Functional Status (NEOS) score was introduced as a tool to predict disease progression in NMDARe.[30] It consists of 5 variables (intensive care unit admission, treatment delay >4 weeks, lack of clinical improvement within 4 weeks, abnormal MRI, and CSF white count >20 cells/μL), each of these assigned 1 point, which provides the NEOS score. Two studies in *N2*, one including children and adults (n = 111)[31] and the other only children (n = 59),[32] confirmed that the NEOS score reliably predicts clinical outcomes in the first year after diagnosis of NMDARe. One of the studies suggested that age at disease onset and history of herpes simplex encephalitis could potentially be useful to define risk groups, and that the NEOS score also predicted cognitive outcomes, with higher scores associated with persistent deficits of executive functions and memory.[32]

Two animal models of placental transfer of pathogenic antibodies (IgG from patients with NMDARe and from patients with AChR antibody–associated myasthenia gravis) showed that blockade of the neonatal Fc receptor (FcRn) with monoclonal antibodies prevented the placental transfer of the pathogenic antibodies and the development of symptoms and neurodevelopmental or systemic alterations in the offspring.[33,34] Two other studies using a mouse model of cerebroventricular transfer of patients' NMDAR antibodies showed that a positive allosteric modulator of the NMDAR (synthetic analogue of 24(S)-hydroxycholesterol [SGE-301]) reversed the antibody-mediated reduction of NMDARs and restored their function, as well as the antibody-mediated disruption of the receptor surface dynamics, overall resulting in faster recovery of memory.[35,36] Thus, although these animal models are imperfect reproductions of the human disease, they offer insights into pathogenic mechanisms and potential new treatments.

Regarding other types of autoimmune encephalitis, the novel observation that some patients with anti-CASPR2–associated encephalitis develop paroxysmal episodes of cerebellar ataxia was published in 2017.[37] All patients (index case and retrospective identification of 5 additional cases among 37 patients with anti-CASPR2 encephalitis) had limbic encephalitis (none with neuromyotonia or Morvan syndrome), and the episodes of ataxia (gait imbalance, dysarthria, and dysmetria) and the encephalitis resolved with immunotherapy. The triggers of the episodes of ataxia were orthostatism and emotional upset. A single case report without triggers of the episodes of ataxia (multiple per day) and also responsiveness to immunotherapy was subsequently published.[38]

Over the past 10 years, we have seen an important change of concepts regarding autoimmune epilepsy and acute symptomatic seizures in the context of autoimmune encephalitis. Different from many initial reports that considered any autoimmune encephalitis with seizures synonymous with autoimmune epilepsy, it has become clear that although many patients with autoimmune encephalitis develop seizures, they do not develop epilepsy.[39-41] This is important for 2 reasons: first, a premature diagnosis of epilepsy can lead to unnecessary and prolonged use of antiepileptic medication, and second, according to International League Against Epilepsy, epilepsy might resolve but not be cured; thus, it becomes a preexisting condition that has important socioeconomic implications.[42] Moreover, in an international study published in *N2* that included 981 patients with several types of autoimmune encephalitides, and considering a <20% recurrence risk within 12 months as sufficient, the authors concluded that patients with anti-NMDAR or anti-LGI1 encephalitis could be considered eligible for noncommercial driving after having been seizure-free for 3 months.[43]

Multiple novel or recently described neuronal autoantibodies were reported in studies published in *N2* during the past decade, including antibodies against septin-5,[44] synapsin,[45] plasticity-related gene 5,[46] glutamate receptor delta 2,[47] neurochondrin,[48] inositol 1,4,5-triphosphate receptor 1,[49] metabotropic glutamate receptor 2,[50] RGS8,[51] argonaute,[52] seizure-related 6 homolog like 2,[53] and ZSCAN.[54] Many of these antibodies are in the exploratory phase (small number of patients, pending of replication, or unclear syndrome specificity), but others such as ZSCAN seem to be associated with a distinctive syndrome (rapid-onset obesity, hypothalamic dysregulation, hypoventilation, and autonomic dysregulation, known as ROHHAD).[55] In addition, several studies have addressed the treatment of anti-IgLON5 disease, an intriguing disorder in which neuronal-specific autoimmunity seems to lead to deposits of phospho-tau and neurodegeneration (available in this issue of *N2* as a separate article that extensively reviews this disorder).

In the emerging era of chimeric antigen receptor (CAR) T-cell therapy for autoimmune neurologic diseases, an interesting case of a patient with MOGAD has been reported in *N2*.[56] The patient, who was 16 years old at the time of the first

episode of the disease (myelitis), developed multiple episodes (myelitis, optic neuritis) over 6 years and became refractory to treatments, in association with persistent MOG antibody detection in serum. After CAR T-cell therapy, he developed an episode of optic neuritis within the first month of treatment but, since then, has remained free of new symptoms for more than 1 year; serum levels of MOG antibodies have become negative for the first time since the disease was diagnosed. This patient and those with other disorders such as stiff person syndrome (SPS)[57] (further discussed in the section SPS, GAD, and GlyR Autoimmunity), myasthenia gravis,[58] and MS, who have shown clinical responses to CD19 CAR T-cell therapy, forecast a new decade for *N2* in which we will likely see remarkable new treatment approaches for autoimmune encephalitis and neurologic disorders in general.

Infectious Diseases and Neuroimmunologic Complications

Numerous developments in the field of neuroinfectious diseases have been brought to the attention of neurologists and neuroimmunologists in articles presented in *N2* during the past decade. In this issue, an accompanying review (to which the reader is referred) entitled "Re-emerging infectious diseases and neuroimmunologic complications" discusses features of CNS virus infections believed to be of particular interest and importance, with the understanding that all pathogenic neurotropic agents cannot be covered under 1 review. The following section complements, highlight, and broadens those areas while providing additional information and perspective.

The global infectious pandemics that have drawn the greatest attention, HIV and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), represent established and newly emerging infections with profound impact on the neurologic functioning of tens of millions of people worldwide. The development of effective antiviral agents against HIV and SARS-CoV-2 has greatly reduced their direct mortality rates, but a significant burden of neurologic disease remains in surviving populations. Additional emerging neuroinfectious diseases involving the spread of mosquito transmission vectors are the arbovirus (arthropod-borne virus) diseases, which will increase their global neurologic impact as climate conditions promote vector spreading. Effective antiviral agents have not yet been developed for these arbovirus infections, and this is a major gap in prevention and cure of these diseases. Nonetheless, within the neuroinfectious disease field, basic research and clinical investigations for therapeutics for viral and nonviral diseases (classic bacterial, fungal, protozoan, rickettsial, amoebic, parasitic, and prion) continue.[59] Although most attention in *N2* has been given to SARS-CoV-2 and the more familiar viruses (herpesviruses, John Cunningham [JC] virus) that neurologists deal with, some investigations of the rarer infectious diseases have also received attention.

Highlighting the range of disorders caused by the family of herpesviruses are studies of varicella zoster virus (VZV), herpes simplex virus (HSV)-1 and HSV-2, human herpesvirus (HHV)-6, and Epstein-Barr virus (EBV).[60-69] Management of herpesvirus infections is a common part of neurologic practice. Neurologists are aware of the propensity for VZV reactivation with associated aggressive lytic injury in the CNS in immunocompromised individuals, and the development of new immunomodulating therapies for the treatment of MS has raised this risk, however, modestly for those patients. Acute VZV retinal necrosis was reported in a natalizumab-treated patient after 12 years of treatment, which is consistent with the known vasculopathic effects of VZV in intracranial and extracranial vessels.[63,65] Other complications of VZV infection occur in patients receiving immunomodulating therapies. Cutaneous VZV (shingles) infection associated with extremely low $CD8^+$ T-lymphocyte counts has been reported in 2 patients with MS treated with dimethyl fumarate (DMF), but VZV reactivation is a rare occurrence with DMF treatment.[67] Herpesvirus complications often occur with other neuroimmune disorders. We are reminded that HSV-1–associated encephalitis (HSE) brings a risk of autoimmune encephalitis associated with antibodies against NMDAR and other neuronal antigens (including LG-1 and GABAA receptors) in approximately 25% of patients with HSE.[69,70] We should also be aware that VZV encephalitis can also associate with NMDAR encephalitis, albeit rarely.[62] Neurologic complications of HSV-2 are also relatively rare. The association of HSV-2 with acute lumbosacral radiculitis and myelitis (Elsberg syndrome [ES]) was viewed in a retrospective Mayo Clinic study of 30 patients with suspected ES, which also proposed diagnostic criteria for this rare syndrome.[61] The association of EBV with MS, which is well-recognized, was further emphasized by the demonstration of higher prevalence of EBV-encoded RNA-1 (an EBV RNA transcript) in brain tissue of patients with MS (85%) compared with rare detection in control patient brain tissue.[64] Finally, a retrospective review of patients with HHV-6 infection (n = 43 patients with CSF HHV-6 detection), including children and adults, confirmed that HHV-6 CNS manifestations are rare and, when present, associate with febrile seizures or encephalitis in children and limbic encephalitis in adults, more typically after hematopoietic stem cell transplantation.[71] Thus, the family of herpesviruses continues to drive serious neurologic complications throughout the age spectrum, and the development of newer immunomodulating therapies for neurologic disorders is likely to increase the prevalence of these complications.

Progressive multifocal leukoencephalopathy (PML), which results from reactivation of the JC virus within the CNS, continues to be investigated as a complication of immunomodulating therapies. To this point, among 91 patients diagnosed with PML over a 25-year period at 2 US academic centers, HIV was the most prevalent risk factor (49%), followed by leukemia, lymphoma, or myelodysplasia (31%); chemotherapy exposure (30%); and monoclonal antibody

exposure (17%).[72] The risk of PML in patients with MS treated with natalizumab is well known, and dozens of natalizumab-treated patients with PML have survived.[73] Treatment of patients with MS with fingolimod also carries a PML risk (<0.1/1,000 worldwide).[74,75] Treatment of PML has thus far been relatively ineffective. Treatment with the ICI pembrolizumab (targets PD-1) has shown disappointing results.[76,77] Treatment of patients suffering from various immunologic disorders with newer and perhaps more aggressive immunomodulating therapies is likely to result in virus (herpes, JC virus) reactivation in the CNS and neurologic disease in increasing numbers of patients with iatrogenic immune deficiencies.

Although the risk of severe immune deficiency associated with HIV-1 infection is now dramatically reduced by suppression of viral replication through combination antiretroviral therapy (cART), a significant burden of neurologic dysfunction (mild-moderate neurocognitive impairment) persists in persons living with HIV (PWH).[78,79] Remarkably, those rare individuals with HIV-1 infection who naturally suppress the virus replication without receiving cART treatment ("elite controllers") show no evidence for CNS inflammation.[80] Suppression of HIV replication with cART does not eliminate the risk of chronic inflammation, including the CNS, in some PWH despite the lack of CNS virus replication in those receiving cART.[81,82] Nonetheless, some evidence suggests a profound reduction of CNS inflammation in PWH through viral suppression. A retrospective study of archived blood and CSF samples from 121 PWH showed that CSF levels of the microglia activation marker, TREM2, were normalized to control levels in patients receiving cART.[82] Because CSF TREM2 levels were found to correlate strongly with CSF NFL levels, this suggests a potential neuroprotective effect through suppression of microglial activation. The challenge of treating and/or preventing neurocognitive impairment in PWH who have achieved effective virus control is daunting nonetheless. Some investigators have proposed the use of CNS-penetrating drugs used to treat MS as candidate neuroprotectants (dimethyl fumarate, fingolimod) against HIV.[83-85] The testing of a variety of candidate adjunctive neuroprotectant drugs in PWH receiving cART has received much attention.[86] Lessons learned from application of therapeutic agents that target microglial activation and other drivers of neuroinflammation in disease states such as HIV and MS are likely to inform management strategies of other infectious, postinfectious, inflammatory, and neurodegenerative diseases.

The coronavirus disease 2019 (COVID-19) pandemic, like the HIV pandemic, rapidly evolved to dramatically increase awareness of acute and chronic neurologic complications of emerging infectious diseases. Investigative studies of the neurologic and neuroimmunologic aspects of acute SARS-CoV-2 infection and the postinfectious condition known as long COVID are discussed in detail in the review "Re-emerging infectious diseases and neuroimmunologic complications" in this issue. Acute SARS-CoV-2 infection is associated with neuroinvasion, disruption of the blood-brain barrier, neuroinflammation, and relatively rapid clearance of the virus from the CNS. Severe and mild acute neurologic symptoms (headaches, meningismus) and complications (encephalopathy, seizures, stroke) are parainfectious responses to virus replication, and acute interventions targeting the virus (antiviral drugs, antibodies) are effective at reducing the viral load and aiding recovery. However, neurologic recovery from SARS-CoV-2 infection may be difficult to determine because persistent symptoms (sometimes poorly defined) linger in approximately 10% of patients as long COVID.[87,88] A major focus of research is the possibility of SARS-CoV-2–induced autoimmunity, including CNS and PNS autoimmunity in triggering neurologic symptoms.[89-93]

Among the neurologic disorders, the current evidence seems to be strongest for linking SARS-CoV-2–induced autoimmunity to GBS.[93] Immune responses, both innate and adaptive immune responses to SARS-CoV-2 infection, are likely to remain a major focus of investigation and therapeutic targeting of COVID-19 neurologic complications.

SPS, GAD, and GlyR Autoimmunity

During the past 10 years, significant progress has been made in defining the clinical spectrum, pathophysiology, autoimmunity, and immunotherapies in patients with SPS and GAD-antibody (GAD-ab) spectrum disorders as recently detailed.[94,95] This section discusses the progress made, highlighting the impact of more than 15 key articles published in *N2* during the past decade, which advanced the field on diagnostic and pathomechanism of GAD and GlyRa1-antibodies (GlyR-abs), immunogenetics, and therapeutic approaches, outlined as follows.

GlyR-Abs and the Expansion to GlyR-Ab Spectrum Disorders

GlyR-abs, initially associated with progressive encephalomyelitis with rigidity and myoclonus (PERM), were reported in 2013 by 2 independent groups to be also associated with SPS; McKeon et al.[96] detected GlyR-abs in 13% of patients with SPS using a fixed cell-based assay and Alexopoulos et al.[97] in 15% among patients with GAD-positive SPS using a live cell-based assay. A year later, Zulinai et al.[98] using live cell-based assay found GlyR-abs in 2 patients with refractory epilepsy and limbic encephalitis responding to immunotherapies, collectively expanding the role of these antibodies in CNS hyperexcitability disorders because glycine is a key neurotransmitter in spinal inhibitory interneurons. The importance of GlyRα1-IgG modulating antibody was subsequently explored by Hinson et al.[99] using a cell-binding assay on fixed cells. They found that among 247 patients with suspected SPS, 21 (8.5%) were positive and all, except one, had SPS spectrum disorders (SPS-SDs); 4% of the controls, however, with coexisting systemic autoimmune diseases were also positive. After modifying the methodological assay, they demonstrated that only the antibodies that exert modulating

effects causing antigenic endocytosis resulting in GlyRα1 loss from the plasma membrane had specificity for SPS-SDs, highlighting early on that methodology does matter in confirming GlyRα1-abs diagnostic specificity for SPS-SDs. A novel clinical phenotypic spectrum of GlyR-abs was subsequently identified by Piquet et al.[100] In a series of 17 patients with the SPS phenotype, 13 had SPS similar to GAD-SPS but several had parkinsonism (even with positive dopamine transporter scan) or cerebellar signs and 1 had rapidly progressive multiple system atrophy with dysautonomia; 10 of 17 had various visual symptoms including visual snow, spider web–like with 3-dimensional images, photophobia, visual hallucinations, and intermittent diplopia while 3 of 17 had autoimmune epilepsy with psychiatric symptoms.

Such a wide clinical spectrum indicates that GlyR-abs are now not only associated with SPS or PERM but also with temporal lobe epilepsy with or without encephalitis, overlapping with visual disturbances, parkinsonism, or dysautonomia collectively suggesting the need to recognize the concept of *GlyRa1-SD*. This is clearly justified because GlyRa1 is highly expressed in the motor, auditory, vestibular, and sensory nuclei of the brainstem, basal ganglia, striatum, globus pallidus, substantia nigra, hippocampus, ventral and dorsal horns of the spinal cord, retina, and olfactory bulb. Our proposal of GlyRa1-SD is exemplified by the case described by Soleimani et al.[101] of a GlyRa1-positive patient who presented with severe neuropathic pain and allodynia as part of autoimmune brainstem and spinal syndrome, who, 8 months later, developed tetraparesis, central hypoventilation, muscle spasms, and worsening neuropathic pain like that due to electric barbed wire that improved fast with immunotherapy. Impaired glycinergic neurotransmission was suggested as a factor contributing to modulation of neuropathic pain and allodynia.[101]

In contrast to GAD-abs, GlyRα1-abs recognize extracellular epitopes and are considered pathogenic because they rapidly abolish glycinergic synaptic currents through direct antagonism of the receptor, disrupting glycinergic neurotransmission and altering the potency of glycine.[102] Of interest, Wiessler et al.[103] recently reported that in some of the patients, the antibodies can also target the *glycine receptor β subunit*, which antagonizes inhibitory glycinergic neurotransmission by altering glycine receptor efficacy and function rather than the potency of glycine.[103]

GAD-Abs Titers in Diagnosis and Immunopathology of SPS-SDs

Although we know for years that only high serum GAD-abs titers relate to SPS-SD and high serum titers often reflect GAD-ab presence in the CSF,[104] there is liberal interpretation of GAD-ab titers, frequently complicated by different laboratory methodologies including ELISA, immunohistochemistry (IHC), cell-based assay (CBA), or radioimmunoassay. This clarification is important because low GAD-abs titers are also seen in type 1 diabetes mellitus (T1DM) or after IV immunoglobulin (IVIg) infusions because all IVIg preparations contain GAD-abs as part of the normal immune repertoire.[105] The diagnostic specificity of GAD-abs titers has been now excellently clarified by Muñoz-Lopetegi et al.[106] in a series of 56 patients with GAD-SDs, including SPS, cerebellar ataxia, epilepsy, encephalitis, or overlapping conditions, by testing the patients' serum and CSF with ELISA, IHC against rat hippocampal brain tissue, and CBA using human embryonic kidney cells expressing recombinant GAD65, in conjunction with clinical features and response to immunotherapy. Serum, with an ELISA cutoff value of 10,000 IU/mL, had highly concordant results with the other 2 methods with 97% being positive with IHC, 100% positive with CBA, and 100% with CSF concentration >100 IU/mL. Up to 94% of patients with titers >10,000 IU/mL had typical SPS-SD (SPS, encephalitis, cerebellar ataxia, epilepsy, or overlap) with some response to immunotherapies; by contrast, patients with lower concentrations had heterogeneous clinical phenotypes suggesting diagnostic alternatives. Accordingly, serum GAD-ab titers >10,000 IU/ml indicate SPS-SD, less than 10,000 but >2,000 need to search for another disease or check the CSF, and <2,000 a non-neurologic disease, such as T1DM or post-IVIg infusion.

GAD antibodies target an intracellular antigen, but without evidence for their internalization into neurons.[94,95] Although there is increased GAD65-specific IgG in the CSF with intrathecal antibody response in 85% of patients with SPS,[106] oligoclonal IgG bands in 67%,[107] and clonal GAD-specific B-cell activation with the CSF GAD-IgG exhibiting a tenfold higher binding avidity compared with serum IgG,[108] the role of intrathecal B-cell activation was unexplored. On this background, Biljecki et al.[109] generated a panel of monoclonal antibodies from B cells extracted from the CSF of 7 GAD-positive patients with limbic encephalitis or epilepsy and analyzed their sequence characteristics and somatic hypermutations. GAD65-specific B cells detected in 3 patients showed antigen-driven affinity maturation early in the disease, suggesting that B-cell–mediated or Ab-mediated mechanisms can be an important factor in early disease stages, a finding of potential importance in considering the timing for applying anti–B-cell therapies; their significance, however, in disease pathogenesis remains unclear because GAD-abs are not necessarily pathogenic and activated $CD8^+$ and $CD4^+$ T cells are also increased in the CSF.[110]

Potential Viral Triggers, Genetic Autoimmunity, and Prevalence

In SPS, the muscle spasms and stiffness are often triggered by various excitability factors, such as anxiety, external stimuli, or emotional upset, but what triggers the disease is unknown. Although viruses can trigger autoimmunities, their role in SPS as triggering immune dysregulation or episodic spasms is unexplored. The coxsackie B4 P2-C viral protein has sequence homology with GAD, and GAD-reactive T cells cross-react with the same coxsackie B4 P2-C viral protein, implicating possible molecular mimicry for T1DM (reviewed by Dalakas[94]). Similarly, partial amino acid sequence homology

between GAD and West Nile virus protein was identified when a patient developed SPS after West Nile virus infection.[111] Two well-documented instances provide compelling evidence that SARS-CoV-2 has the potential to trigger GAD-SD. Dalakas[112] reported a patient being followed for mild GAD-ab stiff limb syndrome who developed severe, video-documented, generalized SPS with high GAD-abs 1 week after mild COVID-19; the patient, from being able to run before COVID-19, needed a walker 3 weeks later requiring long-term treatments with IVIg. A 67-year-old healthy man developed typical PERM with ophthalmoparesis, spasms, hyperexcitability, and GlyR-abs in the CSF 1 week after COVID-19.[113] Although both associations do not necessarily prove causation, the strict temporal connection raises the question whether viruses need to be explored as possible triggering factors in some GAD or GlyR abs-mediated autoimmunities or have the potential to worsen disease status.

Patients with GAD abs-positive SPS have a genetic predisposition not only to T1DM but also to autoimmune diseases or GAD-SD in other family members, even in different generations, indicating a role of hereditary factors and unique human leukocyte antigen (HLA) haplotypes.[94] This was first highlighted by Belbezier et al.[114] who reported 1 family where the aunt had cerebellar ataxia and limbic encephalitis and her niece had SPS with high serum and CSF GAD-ab titers; of interest, both had the same rare recombinant DRB1*15:01:01–DQA1*01:02:01–DQB1*05:02:01 haplotypes while other unaffected family members had either the same HLA haplotype but negative GAD-abs or different HLA types but high serum GAD-abs suggesting cumulative effects. A similar complex genetic susceptibility is now reported by Tsiortou et al.[115] in a 3-generation family; the proband presented with GAD-abs–associated epilepsy but transitioned into severe SPS with very high GAD-ab titers while her father has T1DM and her grandmother has late-onset diabetes without neurologic disease but all with very high GAD-ab titers directed against linear GAD epitopes although only 1 has SPS. This family triggered a search with whole-exome sequencing, which identified sequence variants of *Kallikrein10* gene in 18 more patients with sporadic SPS.[115] Of interest, all 3 family members shared the same very rare haplotype (HLA-DRB1*15–DQB1*05), like the one family reported by Belbezier et al.,[114] collectively supporting a strong genetic predisposition to GAD autoimmunity even without developing a neurologic disease.

SPS-SD is arguably a rare disease with no nationwide information on incidence or prevalence. Toward this goal, Matsui et al.[116] performed an epidemiologic survey throughout Japan to identify the incidence of GAD or patients with GlyR-abs–positive SPS seen between 2015 and 2017 along with the key clinical phenotypes. The total estimated number of patients with GAD-abs–positive SPS was 140, with an estimated prevalence of 0.11 per 100,000 population; the median time from symptom onset to diagnosis was significantly longer in the high-titer GAD-abs group than in the low-titer group (13 months vs 2.5 months, $p = 0.01$) while the coexistence of T1DM and lack of long-term immunotherapy were independent risk factors of poor outcomes.

Treatment Strategies, Prognosis, and Future Prospects

As presented by Dalakas,[117] the rationale for applying specific therapies is based on SPS pathophysiology highlighted by (1) impaired reciprocal inhibitory GABAergic neurotransmission responsible for co-contraction of agonists and antagonist muscles resulting in prominent hyperlordosis, due to concurrent stiffness of thoracolumbar and abdominal muscles, stiff gait, uncontrolled falls, and episodic muscle spasms and (2) GAD autoimmunity. Because SPS is a progressive disease if not properly treated leading to disability, a combination of symptomatic therapy along with immunotherapy is needed from the outset.[117] The recommended therapeutic schemes are with (1) GABA-enhancing drugs, such as GABAA receptor-binding benzodiazepines (diazepam, clonazepam); GABAB receptor-binding antispasmodics such as baclofen; and GABA-enhancing antiepileptics that also improve pain such as gabapentin and (2) immunotherapies with IVIg, followed by rituximab based on data from 2 previous controlled studies.[117] Based on case series, plasmapheresis can also help as an adjunct short-term therapy for exacerbations of severe spasms. Autologous hematopoietic stem cell transplantation (aHSCT), although failed in a large prospective GAD-SPS study, may be of potential value for some refractory progressive GlyR-positive SPS cases as highlighted by Celli et al.[118] in a patient who achieved sustained clinical improvement after aHSCT, documented by various clinical scales.

The value of maintenance therapy with IVIg, the most used immunomodulating drug based on a controlled study, was assessed by Yi and Dalakas[119] in 36 patients treated with monthly maintenance IVIg over a 40-month median period. Twenty-four (67%) of 36 patients continued having clinically meaningful response with improved gait and balance and decreased stiffness spasms and startle responses with some patients becoming able to walk unassisted without devices. Although in 25% of responders, the benefit was sustained for a 40-month median period, in 29.1%, it declined over a 39-month period with diminishing benefit due to disease progression, highlighting that IVIg offers long-term benefits in most patients with SPS, but in 30%, the benefit declines necessitating the need for more effective long-term therapies.

An important factor of poor prognosis is the *late-onset SPS* (*LOPS*) defined when symptom onset is above the age of 60. In a series of 9 patients with median age at onset of 61 years (range 60–78) and median age at the time of analysis of 73 years, Dalakas and Yi[120] demonstrated that LOPS is almost always misdiagnosed, mostly treated for lumbosacral radiculopathies even with laminectomies in late 70s, Parkinson disease, MS, or cerebellar degeneration. Because LOPS declines quickly to clinically severe disease due to delayed treatment initiation, poor response or tolerance to therapies,

other comorbidities, and possibly immunosenescence, increased awareness that SPS can occur in the older population mimicking other disorders is needed.[120]

The effects of pregnancy in SPS were explored by Esch and Newsome[121] in 7 patients with SPS with 9 pregnancies. In 5 (56%) of 9 pregnancies, there was stabilization or improvement in symptoms throughout pregnancy with reduction of antispasmodic medications resulting in 9 healthy deliveries. All 7 women experienced, however, worsening of symptoms after birth requiring resumption or increase of antispasmodic medication indicating that immunomodulatory shifts during pregnancy may also influence SPS symptomatology.

Challenges in Future Trial Designs and Ongoing Therapies

Because of the highly subjective nature of SPS symptomatology and the emotional charge connected with painful spastic and unexpected attacks from sudden stimuli, Dalakas[117] stressed the need to document effectiveness of therapeutic interventions in future trials with objective means considering the placebo effect noted in the rituximab-controlled trial. Among the future trials, the author discussed various anti-CD19 or anti-CD20 B-cell agents, currently approved in other autoimmune neurologic diseases, including ocrelizumab, ofatumumab, ublituximab, or inebilizumab, that also target antibody-producing CD19-positive plasmablasts and plasma cells, but also others in ongoing trials such as obexelimab, obinutuzumab, bortezomib, daratumumab, and Bruton tyrosine kinase inhibitors. The FcRn inhibitors and anti–interleukin-6-receptor antagonist satralizumab were also stressed because of some indirect promising effects[117]; of interest, since this publication, efgartigimod is now funded for 2 planned studies and satralizumab for 1 small pilot study in GAD-abs–positive SPS.[94]

It is important to note that among the future trials relevant to refractory SPS is the CD19 CAR T-cell therapy that has revolutionized the treatment of hematologic malignancies and is now emerging as a promising therapy in neuro-autoimmune diseases. In a notable case, a patient with refractory SPS treated with anti-CD19 CAR T cells experienced remarkable clinical improvements.[57] About 2 months after CAR-T cell infusion, the patient experienced reduction in leg stiffness and improved gait with increased daily walking distance from less than 50 m before therapy to over 6 km within 3 months, with reduction of antispasmodics and excellent tolerance with only a mild cytokine release syndrome. This case has now led to an ongoing trial in 25 patients with refractory SPS. CD19 CAR T cells not only target B cells, plasma cells, and plasmablasts, the key drivers of B-cell autoimmunity, but also penetrate the CNS and potentially target the intrathecal expansions of GAD B-cell clones mentioned earlier.

MS, NMO, and MOGAD

In the first 10 years, *N2* published many key articles and reviews advancing our understanding of MOGAD, NMO spectrum disorder (NMOSD), and MS. During this time, MOGAD became widely recognized as a distinct CNS inflammatory demyelinating disorder and new medications were approved for treatment of NMOSDs. The field of MS saw the introduction of several biomarkers and advancements in understanding both the immune modulation and safety of established and new treatments, including B-cell–depleting therapies. In the following section, we highlight several of those advances, including ones described in publications in *N2*, recognizing that it is not possible to cover all of them.

MOG was initially described as a CNS autoantigen in experimental autoimmune encephalomyelitis (EAE) and considered a candidate target in MS.[122] Yet, it was the development of the CBA, an improvement over earlier immune assays for MOG antibodies, and the insight to evaluate CNS inflammatory demyelinating conditions other than MS that led to the discovery of MOG antibodies in up to one-half of the children with ADEM.[123,124] In 2014, several investigations also detected MOG antibodies in association with transverse myelitis and optic neuritis, suggesting that MOG antibodies might define a subtype of NMOSD.[125-127] It was a 2015 *N2 Views and Reviews* "Does MOG Ig-positive AQP4-seronegative opticospinal inflammatory disease justify a diagnosis of NMO spectrum disorder?" that initially highlighted the need to separate disease associated with MOG antibodies from NMOSD and MS,[128] preceding introduction of the term, MOGAD. Although the clinical phenotype of MOGAD frequently overlaps with NMOSD, the separation of these conditions seemed inevitable. MOG is a myelin protein, and MOGAD is a CNS inflammatory demyelinating disease associated with lymphocytic infiltration. By contrast, aquaporin-4 (AQP4), the primary target of antibodies in NMOSD, is expressed on astrocytes and NMOSD is an astrocytopathy characterized by infiltration of mostly neutrophils and eosinophils.

This past decade has seen progress in detection of MOG-specific antibodies, the clinical description of MOGAD, and the understanding of the role of MOG-specific antibodies in MOGAD. These advances are reflected in a large number of publications in *N2*. The spectrum of MOGAD phenotypes has expanded with identification of MOG-specific antibodies in cases of cortical encephalitis, hemorrhagic cerebral lesions, and brainstem and cerebellar syndromes.[122,129,130] While MOG-specific antibodies in MOGAD primarily target its extracellular domain, a 2015 *N2* article by Waters et al.[131] described the importance of selectively evaluating IgG1 MOG antibodies by expressing full-length human MOG, which includes extracellular and transmembrane domains and its cytoplasmic tail, in the serum CBA analysis, providing greater specificity distinguishing CNS inflammatory disease associated with MOG antibodies from MS and AQP4-seropositive NMO. The live CBA using full-length MOG has since become the gold standard for detection of MOG-specific antibodies[131,132] and is a center piece in the 2023 MOGAD diagnostic criteria.[133] MOG antibodies are sometimes detected in the CSF,

even in the absence of serum anti-MOG IgG.[134] Thus, testing CSF for MOG antibodies may be helpful for diagnosis in MOG IgG-seronegative individuals who have features of MOGAD. Recently, MOG IgA antibodies have been detected in a subset of MOG IgG-seronegative patients suggesting that MOG IgA may serve as an additional diagnostic biomarker of MOGAD.[135,136] Ongoing efforts in validating these findings in larger cohorts will shed light on the clinical spectrum and specificity of MOG IgA.

Studying the epidemiology of MOGAD has been challenging. MOG antibodies are sometimes detected in other CNS inflammatory conditions.[137,138] Yet, in 1 study, published in *N2*, MOG antibodies were exceptionally rare in MS, suggesting that routine testing is not indicated in typical MS.[139] A smaller proportion of patients with MOGAD relapse in comparison with NMO or early relapsing MS.[140] Recent studies, published in *N2*, have reported that those who do relapse may have a higher risk of cognitive impairment,[141] and seroreversion, from MOG-positive to MOG-negative, confers a significantly reduced risk of relapse.[142] Prevalence of MOGAD shows only a slight female predominance,[143] in contrast to MS and NMO. Susceptibility to NMO is associated with HLA-DRB1*03:01,[144] a linkage shared with complement component 4. A 2020 *N2* publication by Bruijstens et al.[145] first reported that in comparison with NMO, in individuals of European ancestry, there was no clear HLA association in MOGAD, a finding that was also found in a later study.[146] In China, however, an association with DQB1*05:02–DRB1*16:02 was described in pediatric-onset MOGAD.[147] All 3 studies[145-147] were relatively small and included <100 patients with MOGAD in each, highlighting the need for larger, more comprehensive epidemiologic investigations in this newly established CNS autoimmune inflammatory demyelinating disease.

CNS damage induced by AQP4-specific antibodies is highly dependent on activation of the classical complement pathway, which is underscored by the remarkable success of NMO treatment by the complement C5 convertase inhibitors eculizumab[148] and ravulizumab.[149] The role of complement in MOGAD is less clear. Unlike in NMO, complement deposition is not consistently identified in CNS MOGAD lesions,[150] and the binding of MOG-specific antibodies may not be optimal for complement activation.[151-153] Indeed, in a recent publication in *N2*, Kaneko et al.[154] evaluated CSF complement levels in patients with MOGAD or AQP4-seropositive NMOSD and observed that although complement proteins were detected in CSF of both MOGAD and NMOSD, formation of the terminal membrane attack complex was lower in MOGAD, especially in those with mild attacks. Thus, one may not necessarily anticipate that complement inhibitors will be beneficial in MOGAD.

Introduction of the complement inhibitor eculizumab in NMOSD in 2019 was followed shortly by the approval of 2 more treatments for AQP4-seropositive NMOSD, the anti-CD19 B-cell–depleting antibody inebilizumab[155] and the anti-IL-6 receptor satralizumab.[156] Currently, there is no convincing evidence that CD20-mediated B-cell depletion provides benefit in MOGAD.[140,157] However, a recent publication in *N2* reported benefit of anti-CD19 CAR T cells in a patient with relapsing MOGAD refractory to anti-CD20 antibody and oral immunosuppressant medication.[56] While there are no approved therapies for MOGAD, different interventions are being evaluated in clinical trials.[122] IL-6 has a critical role in pathogenesis of EAE, a model for MOGAD. As in exacerbations of NMO, reports indicate that CSF IL-6 levels are frequently elevated in acute MOGAD.[130,158] In *N2*, a retrospective analysis of patients with MOGAD who were refractory to treatment with rituximab or oral immunosuppressants[159] found that anti–IL-6 reduced the risk of relapse. Satralizumab is now being tested in MOGAD in a phase 3 placebo-controlled trial.[160]

N2 published seminal reports that have advanced our knowledge of immune modulation and safety of MS disease-modifying therapeutics. We highlight a few examples. The fumaric acid ester (FAE), DMF (Tecfidera), was approved for treatment of relapsing MS in 2013,[161] 1 year before the *N2* inaugural issue. DMF was advanced in MS for its capability of inducing expression of the antioxidative *Nrf2* pathway and to possibly promote neuroprotection.[161] However, previous use of FAEs in treatment of psoriasis revealed a risk of PML from an FAE treatment–associated lymphocytopenia,[162] which unfortunately also reared its nasty head in DMF MS treatment in 2015.[163] At this time, a study in *N2* reported for the first time that the lymphocytopenia from DMF treatment in MS reflected a more prominent reduction in $CD8^+$ T lymphocytes,[164] the T-cell subset primarily responsible for antiviral immunity. Based largely on this finding and subsequent studies reported in *N2* that identified increased susceptibility of depletion of memory T cells in DMF treatment[165-167] and observations that PML treatment can develop without severe lymphocytopenia,[168] many neurologists now monitor both total lymphocyte and lymphocyte subsets in their patients with MS treated with DMF or other FAEs.

The 2017 introduction of anti-CD20 B-cell–depleting treatment in relapsing[169] and primary progressive[170] MS altered the landscape in MS therapy. Anti-CD20 is highly efficacious in relapsing MS and beneficial in progressive MS. Development of B-cell depletion therapy was founded on presence of CSF oligoclonal IgG bands in most patients with MS and identification of myelin-specific antibodies that promoted demyelination in animal models.[169,171] It is now believed that principal beneficial effect of B-cell depletion is due to elimination of B-cell antigen presentation to T cells and reduction in proinflammatory T and B cell–derived cytokines, consistent with the role of B cells in the MS model, EAE,[172] and clinical observations that the benefit of B-cell depletion in MS does not associate with antibody reduction.[169,170] In a recent *N2* publication, Hauser et al.[173] reported in a post hoc analysis of the ocrelizumab pivotal trials that higher serum ocrelizumab levels correlated with reduced disability progression,

a finding that inspired development of the ongoing trials testing higher dose ocrelizumab. Many studies have addressed safety of anti-CD20 B-cell–depleting studies in MS, MOGAD, and NMOSD. Development of hypogammaglobulinemia is not uncommon with extended anti-CD20 treatment, although it is not entirely clear whether it associates with increased risk of severe infections.[174,175] Although some studies indicate that anti-CD20 therapy is not associated with adverse pregnancy outcomes,[176] there may be an elevated risk of preterm births.[177] One study reported in *N2* found only minimal transfer of anti-CD20 rituximab into breast milk, although more studies are needed to determine safety for lactation.

Publications in *N2* have contributed substantially to the advancement of biomarkers of tissue damage in MS, NMOSD, MOGAD, and other CNS neuroinflammatory disorders toward clinical application for monitoring disease activity and immunotherapy. In the first few years of *N2*, several articles highlighted the occurrence and relevance of tissue damage in radiologically isolated syndrome, for example, an article by Azevedo et al.[178] on early CNS neurodegeneration and the article by Alcaide-Leon et al.[179] on spinal cord microstructural changes. Both of those studies were in alignment with the concept of the "MS prodrome" evolving later on and provided scientific arguments for the early intensive immunotherapy approach as opposed to the escalation strategy, a concept now supported by large registry data, for example, from Denmark and Sweden.[180] A review by Stankiewicz and Weiner in *N2* in 2020,[181] coining the term "the perils of escalation," has taken an unambiguous stance in this regard that will hopefully arm neurologists to act against still widespread "therapeutic inertia," describing the hesitancy of physicians to prescribe highly efficacious immunotherapies in early disease stages despite knowing better. More arguments for the changing treatment paradigms in MS come from serum biomarker studies with NfL and glial fibrillary acidic protein (GFAP), which are now quantifiable with high precision in small amounts of serum—an indispensable prerequisite for clinical applicability. An article by Barro et al.[182] published in *N2* in 2022 reported serum GFAP to correlate with subsequent progression in patients with MS while NfL reflected acute disease activity. In line with other studies such as the one by Häring et al.[183] on the added value of longitudinal NfL measurements, such work may help establish 2 complementary serum biomarkers reflecting distinct aspects of immunopathobiology of MS for use in management of patients in the very near future. It is hoped that these biomarkers will prove value in adjacent diseases such as NMOSD, as suggested by a recent article in *N2* by Carta et al.[184] who reported that GFAP but not NfL may help discriminate between AQP4-IgG$^+$ NMOSD and double seronegative NMOSD.

Another biomarker domain that has seen major advancements is retinal imaging with optical coherence tomography (OCT). Beyond publications in *N2* on new OCT findings such as hyperreflective foci or foveal changes in MS and NMOSD,[185] the field has looked into how various biomarkers are intertwined and whether there is added value of combining various biomarker modalities. For example, combining measures of NfL and ganglion cell-inner plexiform layer may improve prognostication in MS as shown in *N2* publications by Tavazzi et al.[186] and Lin et al.[187] Moreover, recent developments in the OCT field such as OCT angiography are represented by publications in *N2*, for example, in a report by Aly et al.[188] associating retinal vascular changes with visual outcomes after optic neuritis. Because acute optic neuritis studies are inherently difficult to design regarding inclusion criteria and end points, enrollment is cumbersome. In this regard, a recent article by Küchlin et al.[189] in *N2* on the treatment of optic neuritis with erythropoietin (TONE study) failed to show an effect of the drug on visual outcomes but, nonetheless, may be valuable by informing future trial designs in acute optic neuritis.

With a goal of advancing education in MS and neuroimmunology research, since 2018, *N2* has collaborated with the National Multiple Sclerosis Society (NMSS) to publish selected clinical cases presented by NMSS clinical fellows forming the "National Multiple Sclerosis Society Case Conference Proceedings" within the *N2* "Diagnostic and Treatment Challenges." Reports within this section have broad interest to neurologists and neuroimmunologists. Currently, *N2* has published 19 reports by NMSS fellows, covering important clinical aspects in differential diagnosis and treatment of MS, NMO, MOGAD, NMDAR encephalitis, and other autoimmune conditions; mitochondrial disorders; metabolic conditions; PML; and other CNS infectious diseases. *N2* looks forward to continuing its collaboration with the NMSS and their fellows' program.

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References

1. Graus F, Vogrig A, Muniz-Castrillo S, et al. Updated diagnostic criteria for paraneoplastic neurologic syndromes. *Neurol Neuroimmunol Neuroinflamm*. 2021;8(4):e1014. doi:10.1212/NXI.0000000000001014
2. Graus F, Delattre JY, Antoine JC, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. *J Neurol Neurosurg Psychiatry*. 2004;75(8):1135-1140. doi:10.1136/jnnp.2003.034447
3. Vogrig A, Fouret M, Joubert B, et al. Increased frequency of anti-Ma2 encephalitis associated with immune checkpoint inhibitors. *Neurol Neuroimmunol Neuroinflamm*. 2019;6(6):e604. doi:10.1212/NXI.0000000000000604

4. Dalmau J, Graus F, Villarejo A, et al. Clinical analysis of anti-Ma2-associated encephalitis. *Brain*. 2004;127(pt 8):1831-1844. doi:10.1093/brain/awh203
5. Farina A, Villagran-Garcia M, Ciano-Petersen NL, et al. Anti-Hu antibodies in patients with neurologic side effects of immune checkpoint inhibitors. *Neurol Neuroimmunol Neuroinflamm*. 2023;10(1):e200058. doi:10.1212/NXI.0000000000200058
6. Yshii LM, Gebauer CM, Pignolet B, et al. CTLA4 blockade elicits paraneoplastic neurological disease in a mouse model. *Brain*. 2016;139(11):2923-2934. doi:10.1093/brain/aww225
7. Aboseif A, Vorasoot N, Pinto MV, et al. Immune checkpoint inhibitor-associated kelch-like protein-11 IgG brainstem encephalitis. *Neurol Neuroimmunol Neuroinflamm*. 2024;11(3):e200218. doi:10.1212/NXI.0000000000200218
8. Syc-Mazurek SB, Zhao-Fleming H, Guo Y, et al. MOG antibody-associated disease in the setting of metastatic melanoma complicated by immune checkpoint inhibitor use. *Neurol Neuroimmunol Neuroinflamm*. 2024;11(4):e200249. doi:10.1212/NXI.0000000000200249
9. Farina A, Villagran-Garcia M, Benaiteau M, et al. Opsoclonus-ataxia syndrome in a patient with small-cell lung cancer treated with immune checkpoint inhibitors. *Neurol Neuroimmunol Neuroinflamm*. 2024;11(5):e200287. doi:10.1212/NXI.0000000000200287
10. Cellucci T, Van Mater H, Graus F, et al. Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(2):e663. doi:10.1212/NXI.0000000000000663
11. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol*. 2016;15(4):391-404. doi:10.1016/S1474-4422(15)00401-9
12. Van Steenhoven RW, de Vries JM, Bruijstens AL, et al. Mimics of autoimmune encephalitis: validation of the 2016 clinical autoimmune encephalitis criteria. *Neurol Neuroimmunol Neuroinflamm*. 2023;10(6):e200148. doi:10.1212/NXI.0000000000200148
13. de Bruijn M, Bruijstens AL, Bastiaansen AEM, et al. Pediatric autoimmune encephalitis: recognition and diagnosis. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(3):e682. doi:10.1212/NXI.0000000000000682
14. Lee S, Kim HD, Lee JS, Kang HC, Kim SH. Clinical features and treatment outcomes of seronegative pediatric autoimmune encephalitis. *J Clin Neurol*. 2021;17(2):300-306. doi:10.3988/jcn.2021.17.2.300
15. Lee WJ, Lee HS, Kim DY, et al. Seronegative autoimmune encephalitis: clinical characteristics and factors associated with outcomes. *Brain*. 2022;145(10):3509-3521. doi:10.1093/brain/awac166
16. Giordano A, Fazio R, Gelibter S, et al. Diagnosing autoimmune encephalitis in a real-world single-centre setting. *J Neurol*. 2020;267(2):449-460. doi:10.1007/s00415-019-09607-3
17. Pointon T, Ward R, Yeshokumar A, Piquet A, Schreiner T, Kammeyer R. Evaluation of multiple consensus criteria for autoimmune encephalitis and temporal analysis of symptoms in a pediatric encephalitis cohort. *Front Neurol*. 2022;13:952317. doi:10.3389/fneur.2022.952317
18. Olive-Cirera G, Fonseca E, Chen L, et al. Differential diagnosis and comparison of diagnostic algorithms in children and adolescents with autoimmune encephalitis in Spain: a prospective cohort study and retrospective analysis. *Lancet Neurol*. 2025;24:54-64
19. Alsalek S, Schwarzmann KB, Budhathoki S, et al. Racial and ethnic disparities in the incidence of anti-NMDA receptor encephalitis. *Neurol Neuroimmunol Neuroinflamm*. 2024;11(4):e200255. doi:10.1212/NXI.0000000000200255
20. Lejuste F, Thomas L, Picard G, et al. Neuroleptic intolerance in patients with anti-NMDAR encephalitis. *Neurol Neuroimmunol Neuroinflamm*. 2016;3(5):e280. doi:10.1212/NXI.0000000000000280
21. Guasp M, Modena Y, Armangue T, Dalmau J, Graus F. Clinical features of seronegative, but CSF antibody-positive, anti-NMDA receptor encephalitis. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(2):e659. doi:10.1212/NXI.0000000000000659
22. Nosadini M, Thomas T, Eyre M, et al. International consensus recommendations for the treatment of pediatric NMDAR antibody encephalitis. *Neurol Neuroimmunol Neuroinflamm*. 2021;8(5):e1052. doi:10.1212/NXI.0000000000001052
23. Gong X, Chen C, Liu X, et al. Long-term functional outcomes and relapse of anti-NMDA receptor encephalitis: a cohort study in western China. *Neurol Neuroimmunol Neuroinflamm*. 2021;8(2):e958. doi:10.1212/NXI.0000000000000958
24. Yeshokumar A, Gordon-Lipkin E, Arenivas A, et al. Younger age at onset is associated with worse long-term behavioral outcomes in anti-NMDA receptor encephalitis. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(5):e200013. doi:10.1212/NXI.0000000000200013
25. de Bruijn M, Aarsen FK, van Oosterhout MP, et al. Long-term neuropsychological outcome following pediatric anti-NMDAR encephalitis. *Neurology*. 2018;90(22):e1997-e2005. doi:10.1212/WNL.0000000000005605
26. Flet-Berliac L, Tchitchek N, Lepine A, et al. Long-term outcome of paediatric anti-N-methyl-D-aspartate receptor encephalitis. *Dev Med Child Neurol*. 2023;65(5):691-700. doi:10.1111/dmcn.15429
27. Chen LW, Olive-Cirera G, Fonseca EG, et al. Very long-term functional outcomes and dependency in children with anti-NMDA receptor encephalitis. *Neurol Neuroimmunol Neuroinflamm*. 2024;11(3):e200235. doi:10.1212/NXI.0000000000200235
28. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol*. 2013;12(2):157-165. doi:10.1016/S1474-4422(12)70310-1
29. Byrne S, Walsh C, Hacohen Y, et al. Earlier treatment of NMDAR antibody encephalitis in children results in a better outcome. *Neurol Neuroimmunol Neuroinflamm*. 2015;2(4):e130. doi:10.1212/NXI.0000000000000130
30. Balu R, McCracken L, Lancaster E, Graus F, Dalmau J, Titulaer MJ. A score that predicts 1-year functional status in patients with anti-NMDA receptor encephalitis. *Neurology*. 2019;92(3):e244-e252. doi:10.1212/WNL.0000000000006783
31. Peng Y, Dai F, Liu L, et al. Validation of the NEOS score in Chinese patients with anti-NMDAR encephalitis. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(5):e860. doi:10.1212/NXI.0000000000000860
32. Nikolaus M, Rausch P, Rostasy K, et al. Retrospective pediatric cohort study validates NEOS score and demonstrates applicability in children with anti-NMDAR encephalitis. *Neurol Neuroimmunol Neuroinflamm*. 2023;10(3):e200102. doi:10.1212/NXI.0000000000200102
33. Garcia-Serra A, Radosevic M, Pupak A, et al. Placental transfer of NMDAR antibodies causes reversible alterations in mice. *Neurol Neuroimmunol Neuroinflamm*. 2021;8(1):e915. doi:10.1212/NXI.0000000000000915
34. Coutinho E, Jacobson L, Shock A, Smith B, Vernon A, Vincent A. Inhibition of maternal-to-fetal transfer of IgG antibodies by FcRn Blockade in a mouse model of arthrogryposis multiplex congenita. *Neurol Neuroimmunol Neuroinflamm*. 2021;8(4):e1011. doi:10.1212/NXI.0000000000001011
35. Radosevic M, Planaguma J, Mannara F, et al. Allosteric modulation of NMDARs reverses patients' autoantibody effects in mice. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(1):e1122. doi:10.1212/NXI.0000000000001122
36. Maudes E, Jamet Z, Marmolejo L, Dalmau JO, Groc L. Positive allosteric modulation of NMDARs prevents the altered surface dynamics caused by patients' antibodies. *Neurol Neuroimmunol Neuroinflamm*. 2024;11(4):e200261. doi:10.1212/NXI.0000000000200261
37. Joubert B, Gobert F, Thomas L, et al. Autoimmune episodic ataxia in patients with anti-CASPR2 antibody-associated encephalitis. *Neurol Neuroimmunol Neuroinflamm*. 2017;4(4):e371. doi:10.1212/NXI.0000000000000371
38. Lopez Chiriboga AS, Pittock S. Episodic ataxia in CASPR2 autoimmunity. *Neurol Neuroimmunol Neuroinflamm*. 2019;6(2):e536. doi:10.1212/NXI.0000000000000536
39. de Bruijn M, van Sonderen A, van Coevorden-Hameete MH, et al. Evaluation of seizure treatment in anti-LGI1, anti-NMDAR, and anti-GABABR encephalitis. *Neurology*. 2019;92(19):e2185-e2196. doi:10.1212/WNL.0000000000007475
40. Yeshokumar AK, Coughlin A, Fastman J, et al. Seizures in autoimmune encephalitis-A systematic review and quantitative synthesis. *Epilepsia*. 2021;62(2):397-407. doi:10.1111/epi.16807
41. Kaaden T, Madlener M, Angstwurm K, et al. Seizure semiology in antibody-associated autoimmune encephalitis. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(6):e200034. doi:10.1212/NXI.0000000000200034
42. Geis C, Planaguma J, Carreno M, Graus F, Dalmau J. Autoimmune seizures and epilepsy. *J Clin Invest*. 2019;129(3):926-940. doi:10.1172/JCI125178
43. Rada A, Hagemann A, Aaberg Poulsen C, et al. Risk of seizure recurrence due to autoimmune encephalitis with NMDAR, LGI1, CASPR2, and GABA(B)R antibodies: implications for return to driving. *Neurol Neuroimmunol Neuroinflamm*. 2024;11(4):e200225. doi:10.1212/NXI.0000000000200225
44. Honorat JA, Lopez-Chiriboga AS, Kryzer TJ, et al. Autoimmune septin-5 cerebellar ataxia. *Neurol Neuroimmunol Neuroinflamm*. 2018;5(5):e474. doi:10.1212/NXI.0000000000000474
45. Piepgras J, Holtje M, Otto C, et al. Intrathecal immunoglobulin A and G antibodies to synapsin in a patient with limbic encephalitis. *Neurol Neuroimmunol Neuroinflamm*. 2015;2(6):e169. doi:10.1212/NXI.0000000000000169
46. van Coevorden-Hameete MH, de Graaff E, Titulaer MJ, et al. Plasticity-related gene 5: a novel surface autoantigen in paraneoplastic cerebellar degeneration. *Neurol Neuroimmunol Neuroinflamm*. 2015;2(5):e156. doi:10.1212/NXI.0000000000000156
47. Miske R, Hahn S, Rosenkranz T, et al. Autoantibodies against glutamate receptor δ2 after allogenic stem cell transplantation. *Neurol Neuroimmunol Neuroinflamm*. 2016;3(4):e255. doi:10.1212/NXI.0000000000000255
48. Miske R, Gross CC, Scharf M, et al. Neurochondrin is a neuronal target antigen in autoimmune cerebellar degeneration. *Neurol Neuroimmunol Neuroinflamm*. 2017;4(1):e307. doi:10.1212/NXI.0000000000000307
49. Fouka P, Alexopoulos H, Chatzi I, et al. Antibodies to inositol 1,4,5-triphosphate receptor 1 in patients with cerebellar disease. *Neurol Neuroimmunol Neuroinflamm*. 2017;4(1):e306. doi:10.1212/NXI.0000000000000306
50. Ruiz-Garcia R, Martinez-Hernandez E, Joubert B, et al. Paraneoplastic cerebellar ataxia and antibodies to metabotropic glutamate receptor 2. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(2):e658. doi:10.1212/NXI.0000000000000658
51. Miske R, Scharf M, Stark P, et al. Autoantibodies against the purkinje cell protein RGS8 in paraneoplastic cerebellar syndrome. *Neurol Neuroimmunol Neuroinflamm*. 2021;8(3):e987. doi:10.1212/NXI.0000000000000987
52. Do LD, Moritz CP, Muniz-Castrillo S, et al. Argonaute autoantibodies as biomarkers in autoimmune neurologic diseases. *Neurol Neuroimmunol Neuroinflamm*. 2021;8(5):e1032. doi:10.1212/NXI.0000000000001032
53. Landa J, Guasp M, Petit-Pedrol M, et al. Seizure-related 6 homolog like 2 autoimmunity: neurologic syndrome and antibody effects. *Neurol Neuroimmunol Neuroinflamm*. 2021;8(1):e916. doi:10.1212/NXI.0000000000000916
54. Serafim AB, Olive-Cirera G, Ortega-Gonzalez A, et al. Antibodies against ZSCAN1 in pediatric and adult patients with non-paraneoplastic ROHHAD syndrome. *Neurol Neuroimmunol Neuroinflamm*. 2024;11(5):e200276. doi:10.1212/NXI.0000000000200276
55. Mandel-Brehm C, Benson LA, Tran B, et al. ZSCAN1 autoantibodies are associated with pediatric paraneoplastic ROHHAD. *Ann Neurol*. 2022;92(2):279-291. doi:10.1002/ana.26380
56. Cabrera-Maqueda JM, Sepulveda M, Garcia RR, et al. CD19-directed CAR T-cells in a patient with refractory MOGAD: clinical and immunologic follow-up for 1 year. *Neurol Neuroimmunol Neuroinflamm*. 2024;11(5):e200292. doi:10.1212/NXI.0000000000200292
57. Faissner S, Motte J, Sgodzai M, et al. Successful use of anti-CD19 CAR T-cells in severe treatment-refractory stiff-person-syndrome. *Proc Natl Acad Sci USA*. 2024;121(26):e2403227121. doi:10.1073/pnas.2403227121
58. Haghikia A, Schett G, Mougiakakos D. B cell-targeting chimeric antigen receptor T cells as an emerging therapy in neuroimmunological diseases. *Lancet Neurol*. 2024;23(6):615-624. doi:10.1016/S1474-4422(24)00140-6
59. Ardakani R, Jia L, Matthews E, Thakur KT. Therapeutic advances in neuroinfectious diseases. *Ther Adv Infect Dis*. 2024;11:20499361241274246. doi:10.1177/20499361241274246

60. Salovin A, Glanzman J, Roslin K, Armangue T, Lynch DR, Panzer JA. Anti-NMDA receptor encephalitis and nonencephalitic HSV-1 infection. *Neurol Neuroimmunol Neuroinflamm*. 2018;5(4):e458. doi:10.1212/NXI.0000000000000458
61. Savoldi F, Kaufmann TJ, Flanagan EP, Toledano M, Weinshenker BG. Elsberg syndrome: a rarely recognized cause of cauda equina syndrome and lower thoracic myelitis. *Neurol Neuroimmunol Neuroinflamm*. 2017;4(4):e355. doi:10.1212/NXI.0000000000000355
62. Prakash PA, Jin J, Matharu K, et al. Anti-NMDAR encephalitis with concomitant varicella zoster virus detection and nonteratomatous malignancy. *Neurol Neuroimmunol Neuroinflamm*. 2019;6(2):e537. doi:10.1212/NXI.0000000000000537
63. Pawlitzki M, Teuber J, Campe C, et al. VZV-associated acute retinal necrosis in a patient with MS treated with natalizumab. *Neurol Neuroimmunol Neuroinflamm*. 2018;5(5):e475. doi:10.1212/NXI.0000000000000475
64. Moreno MA, Or-Geva N, Aftab BT, et al. Molecular signature of Epstein-Barr virus infection in MS brain lesions. *Neurol Neuroimmunol Neuroinflamm*. 2018;5(4):e466. doi:10.1212/NXI.0000000000000466
65. Jones D, Neff CP, Palmer BE, Stenmark K, Nagel MA. Varicella zoster virus-infected cerebrovascular cells produce a proinflammatory environment. *Neurol Neuroimmunol Neuroinflamm*. 2017;4(5):e382. doi:10.1212/NXI.0000000000000382
66. Carter-Timofte ME, Hansen AF, Mardahl M, et al. Varicella-zoster virus CNS vasculitis and RNA polymerase III gene mutation in identical twins. *Neurol Neuroimmunol Neuroinflamm*. 2018;5(6):e500. doi:10.1212/NXI.0000000000000500
67. Anagnostouli MC, Velonakis G, Dalakas MC. Aggressive herpes zoster in young patients with multiple sclerosis under dimethyl fumarate: significance of CD8(+) and natural killer cells. *Neurol Neuroimmunol Neuroinflamm*. 2021;8(4):e1017. doi:10.1212/NXI.0000000000001017
68. Armangue T, Baucells BJ, Vlagea A, et al. Toll-like receptor 3 deficiency in autoimmune encephalitis post-herpes simplex encephalitis. *Neurol Neuroimmunol Neuroinflamm*. 2019;6(6):e611. doi:10.1212/NXI.0000000000000611
69. Armangue T, Olive-Cirera G, Martinez-Hernandez E, et al. Neurologic complications in herpes simplex encephalitis: clinical, immunological and genetic studies. *Brain*. 2023;146(10):4306-4319. doi:10.1093/brain/awad238
70. Schuster S, Abrante L, Matschke J, et al. Fatal PCR-negative herpes simplex virus-1 encephalitis with GABAA receptor antibodies. *Neurol Neuroimmunol Neuroinflamm*. 2019;6(6):e624. doi:10.1212/NXI.0000000000000624
71. Berzero G, Campanini G, Vegezzi E, et al. Human herpesvirus 6 encephalitis in immunocompetent and immunocompromised hosts. *Neurol Neuroimmunol Neuroinflamm*. 2021;8(2):e942. doi:10.1212/NXI.0000000000000942
72. Anand P, Hotan GC, Vogel A, Venna N, Mateen FJ. Progressive multifocal leukoencephalopathy: a 25-year retrospective cohort study. *Neurol Neuroimmunol Neuroinflamm*. 2019;6(6):e618. doi:10.1212/NXI.0000000000000618
73. Maillart E, Vidal JS, Brassat D, et al. Natalizumab-PML survivors with subsequent MS treatment: clinico-radiologic outcome. *Neurol Neuroimmunol Neuroinflamm*. 2017;4(3):e346. doi:10.1212/NXI.0000000000000346
74. Nishiyama S, Misu T, Shishido-Hara Y, et al. Fingolimod-associated PML with mild IRIS in MS: a clinicopathologic study. *Neurol Neuroimmunol Neuroinflamm*. 2018;5(1):e415. doi:10.1212/NXI.0000000000000415
75. Nakahara J, Tomaske L, Kume K, et al. Three cases of non-carryover fingolimod-PML: is the risk in Japan increased? *Neurol Neuroimmunol Neuroinflamm*. 2019;6(3):e559. doi:10.1212/NXI.0000000000000559
76. Rauer S, Marks R, Urbach H, et al. Treatment of progressive multifocal leukoencephalopathy with Pembrolizumab. *N Engl J Med*. 2019;380(17):1676-1677. doi:10.1056/NEJMc1817193
77. Pawlitzki M, Schneider-Hohendorf T, Rolfes L, et al. Ineffective treatment of PML with pembrolizumab: exhausted memory T-cell subsets as a clue? *Neurol Neuroimmunol Neuroinflamm*. 2019;6(6):e627. doi:10.1212/NXI.0000000000000627
78. Ellis RJ, Marquine MJ, Kaul M, Fields JA, Schlachetzki JCM. Mechanisms underlying HIV-associated cognitive impairment and emerging therapies for its management. *Nat Rev Neurol*. 2023;19(11):668-687. doi:10.1038/s41582-023-00879-y
79. Moschopoulos CD, Alford K, Antoniadou A, Vera JH. Cognitive impairment in people living with HIV: mechanisms, controversies, and future perspectives. *Trends Mol Med*. 2024;30(11):1076-1089. doi:10.1016/j.molmed.2024.06.005
80. Sari H, Galbusera R, Bonnier G, et al. Multimodal investigation of neuroinflammation in aviremic patients with HIV on antiretroviral therapy and HIV elite controllers. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(2):e1144. doi:10.1212/NXI.0000000000001144
81. Kamtchum-Tatuene J, Mwandumba H, Al-Bayati Z, et al. HIV is associated with endothelial activation despite ART, in a sub-Saharan African setting. *Neurol Neuroimmunol Neuroinflamm*. 2019;6(2):e531. doi:10.1212/NXI.0000000000000531
82. Gisslen M, Heslegrave A, Veleva E, et al. CSF concentrations of soluble TREM2 as a marker of microglial activation in HIV-1 infection. *Neurol Neuroimmunol Neuroinflamm*. 2019;6(1):e512. doi:10.1212/NXI.0000000000000512
83. Cross SA, Cook DR, Chi AW, et al. Dimethyl fumarate, an immune modulator and inducer of the antioxidant response, suppresses HIV replication and macrophage-mediated neurotoxicity: a novel candidate for HIV neuroprotection. *J Immunol*. 2011;187(10):5015-5025. doi:10.4049/jimmunol.1101868
84. Gill AJ, Kolson DL. Dimethyl fumarate modulation of immune and antioxidant responses: application to HIV therapy. *Crit Rev Immunol*. 2013;33(4):307-359. doi:10.1615/critrevimmunol.2013007247
85. Ambrosius B, Gold R, Chan A, Faissner S. Antineuroinflammatory drugs in HIV-associated neurocognitive disorders as potential therapy. *Neurol Neuroimmunol Neuroinflamm*. 2019;6(3):e551. doi:10.1212/NXI.0000000000000551
86. Kolson DL. Developments in neuroprotection for HIV-associated neurocognitive disorders (HAND). *Curr HIV/AIDS Rep*. 2022;19(5):344-357. doi:10.1007/s11904-022-00612-2
87. de Havenon A, Callaghan BC, Xu Y, et al. Burden of neurologic health care and incident neurologic diagnoses in the year after COVID-19 or influenza hospitalization. *Neurology*. 2024;102(8):e209248. doi:10.1212/WNL.0000000000209248
88. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol*. 2023;21(3):133-146. doi:10.1038/s41579-022-00846-2
89. Wang EY, Mao T, Klein J, et al. Diverse functional autoantibodies in patients with COVID-19. *Nature*. 2021;595(7866):283-288. doi:10.1038/s41586-021-03631-y
90. Klein J, Wood J, Jaycox JR, et al. Distinguishing features of long COVID identified through immune profiling. *Nature*. 2023;623(7985):139-148. doi:10.1038/s41586-023-06651-y
91. Costello F, Dalakas MC. Cranial neuropathies and COVID-19: neurotropism and autoimmunity. *Neurology*. 2020;95(5):195-196. doi:10.1212/WNL.0000000000009921
92. Alexopoulos H, Magira E, Bitzogli K, et al. Anti-SARS-CoV-2 antibodies in the CSF, blood-brain barrier dysfunction, and neurological outcome: studies in 8 stuporous and comatose patients. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(6):e893. doi:10.1212/NXI.0000000000000893
93. Dalakas MC. Guillain-Barre syndrome: the first documented COVID-19-triggered autoimmune neurologic disease: more to come with myositis in the offing. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(5):e781. doi:10.1212/NXI.0000000000000781
94. Dalakas MC. Stiff-person syndrome and related disorders: diagnosis, mechanisms and therapies. *Nat Rev Neurol*. 2024;20(10):587-601. doi:10.1038/s41582-024-01012-3
95. Graus F, Saiz A, Dalmau J. GAD antibodies in neurological disorders: insights and challenges. *Nat Rev Neurol*. 2020;16(7):353-365. doi:10.1038/s41582-020-0359-x
96. McKeon A, Martinez-Hernandez E, Lancaster E, et al. Glycine receptor autoimmune spectrum with stiff-man syndrome phenotype. *JAMA Neurol*. 2013;70(1):44-50. doi:10.1001/jamaneurol.2013.574
97. Alexopoulos H, Akrivou S, Dalakas MC. Glycine receptor antibodies in stiff-person syndrome and other GAD-positive CNS disorders. *Neurology*. 2013;81(22):1962-1964. doi:10.1212/01.wnl.0000436617.40779.65
98. Zuliani L, Ferlazzo E, Andrigo C, et al. Glycine receptor antibodies in 2 cases of new, adult-onset epilepsy. *Neurol Neuroimmunol Neuroinflamm*. 2014;1(2):e16. doi:10.1212/NXI.0000000000000016
99. Hinson SR, Lopez-Chiriboga AS, Bower JH, et al. Glycine receptor modulating antibody predicting treatable stiff-person spectrum disorders. *Neurol Neuroimmunol Neuroinflamm*. 2018;5(2):e438. doi:10.1212/NXI.0000000000000438
100. Piquet AL, Khan M, Warner JEA, et al. Novel clinical features of glycine receptor antibody syndrome: a series of 17 cases. *Neurol Neuroimmunol Neuroinflamm*. 2019;6(5):e592. doi:10.1212/NXI.0000000000000592
101. Soleimani B, Board C, Yu T, Tracey I, Irani SR, Foley P. Immunotherapy-responsive neuropathic pain and allodynia in a patient with glycine receptor autoantibodies: a case report. *Neurol Neuroimmunol Neuroinflamm*. 2023;10(6):e200160. doi:10.1212/NXI.0000000000200160
102. Crisp SJ, Dixon CL, Jacobson L, et al. Glycine receptor autoantibodies disrupt inhibitory neurotransmission. *Brain*. 2019;142(11):3398-3410. doi:10.1093/brain/awz297
103. Wiessler AL, Talucci I, Piro I, et al. Glycine receptor β-targeting autoantibodies contribute to the pathology of autoimmune diseases. *Neurol Neuroimmunol Neuroinflamm*. 2024;11(2):e200187. doi:10.1212/NXI.0000000000200187
104. Dalakas MC, Li M, Fujii M, Jacobowitz DM. Stiff person syndrome: quantification, specificity, and intrathecal synthesis of GAD65 antibodies. *Neurology*. 2001;57(5):780-784. doi:10.1212/wnl.57.5.780
105. Dimitriadou MM, Alexopoulos H, Akrivou S, Gola E, Dalakas MC. Anti-neuronal antibodies within the IVIg preparations: importance in clinical practice. *Neurotherapeutics*. 2020;17(1):235-242. doi:10.1007/s13311-019-00796-3
106. Muñoz-Lopetegi A, de Bruijn M, Boukhrissi S, et al. Neurologic syndromes related to anti-GAD65: clinical and serologic response to treatment. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(3):e696. doi:10.1212/NXI.0000000000000696
107. Rakocevic G, Raju R, Dalakas MC. Anti-glutamic acid decarboxylase antibodies in the serum and cerebrospinal fluid of patients with stiff-person syndrome: correlation with clinical severity. *Arch Neurol*. 2004;61(6):902-904. doi:10.1001/archneur.61.6.902
108. Skorstad G, Hestvik AL, Torjesen P, et al. GAD65 IgG autoantibodies in stiff person syndrome: clonality, avidity and persistence. *Eur J Neurol*. 2008;15(9):973-980. doi:10.1111/j.1468-1331.2008.02221.x
109. Biljecki M, Eisenhut K, Beltran E, et al. Antibodies against glutamic acid decarboxylase 65 are locally produced in the CSF and arise during affinity maturation. *Neurol Neuroimmunol Neuroinflamm*. 2023;10(3):e200090. doi:10.1212/NXI.0000000000200090
110. Dik A, Widman G, Schulte-Mecklenbeck A, et al. Impact of T cells on neurodegeneration in anti-GAD65 limbic encephalitis. *Ann Clin Transl Neurol*. 2021;8(12):2289-2301. doi:10.1002/acn3.51486
111. Hassin-Baer S, Kirson ED, Shulman L, et al. Stiff-person syndrome following West Nile fever. *Arch Neurol*. 2004;61(6):938-941. doi:10.1001/archneur.61.6.938
112. Dalakas MC. Severe stiff-person syndrome after COVID: the first video-documented COVID exacerbation and viral implications. *Neurol Neuroimmunol Neuroinflamm*. 2024;11(2):e200192. doi:10.1212/NXI.0000000000200192
113. Giacomozzi S, Barone V, Merli E, et al. Glycine receptor antibody-associated progressive encephalomyelitis with rigidity and myoclonus (PERM) during SARS-CoV-2 infection: a video-case report. *Mov Disord Clin Pract*. 2023;10(5):824-826. doi:10.1002/mdc3.13712
114. Belbezier A, Joubert B, Montero-Martin G, et al. Multiplex family with GAD65-abs neurologic syndromes. *Neurol Neuroimmunol Neuroinflamm*. 2018;5(1):e416. doi:10.1212/NXI.0000000000000416

115. Tsiortou P, Alexopoulos H, Kyriakidas K, et al. Immunogenetic studies in patients with GAD-positive Stiff-person syndrome reveal novel lymphocytic genes and KLK10-gene mutations. *Neurol Neuroimmunol Neuroinflamm*. In press.
116. Matsui N, Tanaka K, Ishida M, et al. Prevalence, clinical profiles, and prognosis of stiff-person syndrome in a Japanese nationwide survey. *Neurol Neuroimmunol Neuroinflamm*. 2023;10(6):e200165. doi:10.1212/NXI.0000000000200165
117. Dalakas MC. Therapies in stiff-person syndrome: advances and future prospects based on disease pathophysiology. *Neurol Neuroimmunol Neuroinflamm*. 2023;10(3):e200109. doi:10.1212/NXI.0000000000200109
118. Celli SI, Nash R, Money KM, et al. Successful autologous hematopoietic stem cell transplant in glycine receptor antibody-positive stiff person syndrome: a case report. *Neurol Neuroimmunol Neuroinflamm*. 2024;11(2):e200197. doi:10.1212/NXI.0000000000200197
119. Yi J, Dalakas MC. Long-term effectiveness of IVIg maintenance therapy in 36 patients with GAD antibody-positive Stiff-Person syndrome. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(5):e200011. doi:10.1212/NXI.0000000000200011
120. Dalakas MC, Yi J. Late-onset stiff-person syndrome: challenges in diagnosis and management. *Ther Adv Neurol Disord*. 2023;16:17562864231214315. doi:10.1177/17562864231214315
121. Esch ME, Newsome SD. Improvement of stiff-person syndrome symptoms in pregnancy: case series and literature review. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(3):e684. doi:10.1212/NXI.0000000000000684
122. Moseley CE, Virupakshaiah A, Forsthuber TG, Steinman L, Waubant E, Zamvil SS. MOG CNS autoimmunity and MOGAD. *Neurol Neuroimmunol Neuroinflamm*. 2024;11(5):e200275. doi:10.1212/NXI.0000000000200275
123. O'Connor KC, McLaughlin KA, De Jager PL, et al. Self-antigen tetramers discriminate between myelin autoantibodies to native or denatured protein. *Nat Med*. 2007;13(2):211-217. doi:10.1038/nm1488
124. Probstel AK, Dornmair K, Bittner R, et al. Antibodies to MOG are transient in childhood acute disseminated encephalomyelitis. *Neurology*. 2011;77(6):580-588. doi:10.1212/WNL.0b013e318228c0b1
125. Sato DK, Callegaro D, Lana-Peixoto MA, et al. Distinction between MOG antibody-positive and AQP4 antibody-positive NMO spectrum disorders. *Neurology*. 2014;82(6):474-481. doi:10.1212/WNL.0000000000000101
126. Kitley J, Waters P, Woodhall M, et al. Neuromyelitis optica spectrum disorders with aquaporin-4 and myelin-oligodendrocyte glycoprotein antibodies: a comparative study. *JAMA Neurol*. 2014;71(3):276-283. doi:10.1001/jamaneurol.2013.5857
127. Hoftberger R, Sepulveda M, Armangue T, et al. Antibodies to MOG and AQP4 in adults with neuromyelitis optica and suspected limited forms of the disease. *Mult Scler*. 2015;21(7):866-874. doi:10.1177/1352458514555785
128. Zamvil SS, Slavin AJ. Does MOG Ig-positive AQP4-seronegative opticospinal inflammatory disease justify a diagnosis of NMO spectrum disorder? *Neurol Neuroimmunol Neuroinflamm*. 2015;2(1):e62. doi:10.1212/NXI.0000000000000062
129. Oh K, Iimuro Y, Takeuchi M, et al. Ameliorating effect of hepatocyte growth factor on inflammatory bowel disease in a murine model. *Am J Physiol Gastrointest Liver Physiol*. 2005;288(4):G729-G735. doi:10.1152/ajpgi.00438.2004
130. Virupakshaiah A, Moseley CE, Elicegui S, et al. Life-threatening MOG antibody-associated hemorrhagic ADEM with elevated CSF IL-6. *Neurol Neuroimmunol Neuroinflamm*. 2024;11(4):e200243. doi:10.1212/NXI.0000000000200243
131. Waters P, Woodhall M, O'Connor KC, et al. MOG cell-based assay detects non-MS patients with inflammatory neurologic disease. *Neurol Neuroimmunol Neuroinflamm*. 2015;2(3):e89. doi:10.1212/NXI.0000000000000089
132. Schanda K, Peschl P, Lerch M, et al. Differential binding of autoantibodies to MOG isoforms in inflammatory demyelinating diseases. *Neurol Neuroimmunol Neuroinflamm*. 2021;8(5):e1027. doi:10.1212/NXI.0000000000001027
133. Banwell B, Bennett JL, Marignier R, et al. Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: international MOGAD Panel proposed criteria. *Lancet Neurol*. 2023;22(3):268-282. doi:10.1016/S1474-4422(22)00431-8
134. Kwon YN, Kim B, Kim JS, et al. Myelin oligodendrocyte glycoprotein-immunoglobulin G in the CSF: clinical implication of testing and association with disability. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(1):e1095. doi:10.1212/NXI.0000000000001095
135. Ayroza Galvao Ribeiro Gomes AB, Kulsvehagen L, Lipps P, et al. Immunoglobulin A antibodies against myelin oligodendrocyte glycoprotein in a subgroup of patients with central nervous system demyelination. *JAMA Neurol*. 2023;80(9):989-995. doi:10.1001/jamaneurol.2023.2523
136. Lipps P, Ayroza Galvao Ribeiro Gomes AB, Kulsvehagen L, et al. Ongoing challenges in the diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease. *JAMA Neurol*. 2023;80(12):1377-1379. doi:10.1001/jamaneurol.2023.3956
137. Titulaer MJ, Hoftberger R, Iizuka T, et al. Overlapping demyelinating syndromes and anti-N-methyl-D-aspartate receptor encephalitis. *Ann Neurol*. 2014;75(3):411-428. doi:10.1002/ana.24117
138. Probstel AK, Thanei M, Erni B, et al. Association of antibodies against myelin and neuronal antigens with neuroinflammation in systemic lupus erythematosus. *Rheumatology (Oxford)*. 2019;58(5):908-913. doi:10.1093/rheumatology/key282
139. Cobo-Calvo A, d'Indy H, Ruiz A, et al. Frequency of myelin oligodendrocyte glycoprotein antibody in multiple sclerosis: a multicenter cross-sectional study. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(2):e649. doi:10.1212/NXI.0000000000000649
140. Virupakshaiah A, Schoeps VA, Race J, et al. Predictors of a relapsing course in myelin oligodendrocyte glycoprotein antibody-associated disease. *J Neurol Neurosurg Psychiatry*. 2024;96(1):68-75. doi:10.1136/jnnp-2024-333464
141. Kogel AK, Ladopoulos T, Schwake C, et al. Cognitive impairment, associated clinical factors, and MR volumetric measures in myelin oligodendrocyte glycoprotein-IgG-associated disease. *Neurol Neuroimmunol Neuroinflamm*. 2024;11(6):e200325. doi:10.1212/NXI.0000000000200325
142. Wendel EM, Thonke HS, Bertolini A, et al. Temporal dynamics of MOG antibodies in children with acquired demyelinating syndrome. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(6):e200035. doi:10.1212/NXI.0000000000200035
143. Jarius S, Ruprecht K, Kleiter I, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 1: frequency, syndrome specificity, influence of disease activity, long-term course, association with AQP4-IgG, and origin. *J Neuroinflammation*. 2016;13(1):279. doi:10.1186/s12974-016-0717-1
144. Estrada K, Whelan CW, Zhao F, et al. A whole-genome sequence study identifies genetic risk factors for neuromyelitis optica. *Nat Commun*. 2018;9(1):1929. doi:10.1038/s41467-018-04332-3
145. Bruijstens AL, Wong YYM, van Pelt DE, et al. HLA association in MOG-IgG- and AQP4-IgG-related disorders of the CNS in the Dutch population. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(3):e702. doi:10.1212/NXI.0000000000000702
146. Grant-Peters M, Passos GRD, Yeung HY, et al. No strong HLA association with MOG antibody disease in the UK population. *Ann Clin Transl Neurol*. 2021;8(7):1502-1507. doi:10.1002/acn3.51378
147. Sun X, Qiu W, Wang J, et al. Myelin oligodendrocyte glycoprotein-associated disorders are associated with HLA subtypes in a Chinese paediatric-onset cohort. *J Neurol Neurosurg Psychiatry*. 2020;91(7):733-739. doi:10.1136/jnnp-2019-322115
148. Pittock SJ, Berthele A, Fujihara K, et al. Eculizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. *N Engl J Med*. 2019;381(7):614-625. doi:10.1056/NEJMoa1900866
149. Pittock SJ, Barnett M, Bennett JL, et al. Ravulizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. *Ann Neurol*. 2023;93(6):1053-1068. doi:10.1002/ana.26626
150. Takai Y, Misu T, Kaneko K, et al. Myelin oligodendrocyte glycoprotein antibody-associated disease: an immunopathological study. *Brain*. 2020;143(5):1431-1446. doi:10.1093/brain/awaa102
151. Macrini C, Gerhards R, Winklmeier S, et al. Features of MOG required for recognition by patients with MOG antibody-associated disorders. *Brain*. 2021;144(8):2375-2389. doi:10.1093/brain/awab105
152. Lerch M, Schanda K, Lafon E, et al. More efficient complement activation by anti-aquaporin-4 compared with anti-myelin oligodendrocyte glycoprotein antibodies. *Neurol Neuroimmunol Neuroinflamm*. 2023;10(1):e200059. doi:10.1212/NXI.0000000000200059
153. Lerch M, Bauer A, Reindl M. The potential pathogenicity of myelin oligodendrocyte glycoprotein antibodies in the optic pathway. *J Neuroophthalmol*. 2023;43(1):5-16. doi:10.1097/WNO.0000000000001772
154. Kaneko K, Kuroda H, Matsumoto Y, et al. Different complement activation patterns following C5 cleavage in MOGAD and AQP4-IgG+NMOSD. *Neurol Neuroimmunol Neuroinflamm*. 2024;11(5):e200293. doi:10.1212/NXI.0000000000200293
155. Cree BAC, Bennett JL, Kim HJ, et al. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial. *Lancet*. 2019;394(10206):1352-1363. doi:10.1016/S0140-6736(19)31817-3
156. Yamamura T, Kleiter I, Fujihara K, et al. Trial of Satralizumab in neuromyelitis optica spectrum disorder. *N Engl J Med*. 2019;381(22):2114-2124. doi:10.1056/NEJMoa1901747
157. Durozard P, Rico A, Boutiere C, et al. Comparison of the response to rituximab between myelin oligodendrocyte glycoprotein and aquaporin-4 antibody diseases. *Ann Neurol*. 2020;87(2):256-266. doi:10.1002/ana.25648
158. Kaneko K, Sato DK, Nakashima I, et al. CSF cytokine profile in MOG-IgG+ neurological disease is similar to AQP4-IgG+ NMOSD but distinct from MS: a cross-sectional study and potential therapeutic implications. *J Neurol Neurosurg Psychiatry*. 2018;89(9):927-936. doi:10.1136/jnnp-2018-317969
159. Ringelstein M, Ayzenberg I, Lindenblatt G, et al. Interleukin-6 receptor blockade in treatment-refractory MOG-IgG-associated disease and neuromyelitis optica spectrum disorders. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(1):e1100. doi:10.1212/NXI.0000000000001100
160. ClinicalTrials.gov. Accessed April 9, 2024. clinicaltrials.gov/study/NCT05271409.
161. Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med*. 2012;367(12):1098-1107. doi:10.1056/NEJMoa1114287
162. Ermis U, Weis J, Schulz JB. PML in a patient treated with fumaric acid. *N Engl J Med*. 2013;368(17):1657-1658. doi:10.1056/NEJMc1211805
163. Rosenkranz T, Novas M, Terborg C. PML in a patient with lymphocytopenia treated with dimethyl fumarate. *N Engl J Med*. 2015;372(15):1476-1478. doi:10.1056/NEJMc1415408
164. Spencer CM, Crabtree-Hartman EC, Lehmann-Horn K, Cree BA, Zamvil SS. Reduction of CD8(+) T lymphocytes in multiple sclerosis patients treated with dimethyl fumarate. *Neurol Neuroimmunol Neuroinflamm*. 2015;2(3):e76. doi:10.1212/NXI.0000000000000076
165. Lundy SK, Wu Q, Wang Q, et al. Dimethyl fumarate treatment of relapsing-remitting multiple sclerosis influences B-cell subsets. *Neurol Neuroimmunol Neuroinflamm*. 2016;3(2):e211. doi:10.1212/NXI.0000000000000211
166. Gross CC, Schulte-Mecklenbeck A, Klinsing S, Posevitz-Fejfar A, Wiendl H, Klotz L. Dimethyl fumarate treatment alters circulating T helper cell subsets in multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm*. 2016;3(1):e183. doi:10.1212/NXI.0000000000000183
167. Ghadiri M, Rezk A, Li R, et al. Dimethyl fumarate-induced lymphopenia in MS due to differential T-cell subset apoptosis. *Neurol Neuroimmunol Neuroinflamm*. 2017;4(3):e340. doi:10.1212/NXI.0000000000000340
168. Nieuwkamp DJ, Murk JL, van Oosten BW, et al. PML in a patient without severe lymphocytopenia receiving dimethyl fumarate. *N Engl J Med*. 2015;372(15):1474-1476. doi:10.1056/NEJMc1413724

169. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus Interferon Beta-1a in relapsing multiple sclerosis. *N Engl J Med*. 2017;376(3):221-234. doi:10.1056/NEJMoa1601277
170. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med*. 2017;376(3):209-220. doi:10.1056/NEJMoa1606468
171. Genain CP, Cannella B, Hauser SL, Raine CS. Identification of autoantibodies associated with myelin damage in multiple sclerosis. *Nat Med*. 1999;5(2):170-175. doi:10.1038/5532
172. Molnarfi N, Schulze-Topphoff U, Weber MS, et al. MHC class II-dependent B cell APC function is required for induction of CNS autoimmunity independent of myelin-specific antibodies. *J Exp Med*. 2013;210(13):2921-2937. doi:10.1084/jem.20130699
173. Hauser SL, Bar-Or A, Weber MS, et al. Association of higher Ocrelizumab exposure with reduced disability progression in multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm*. 2023;10(2):e200094. doi:10.1212/NXI.0000000000200094
174. Kim SH, Park NY, Kim KH, Hyun JW, Kim HJ. Rituximab-induced hypogammaglobulinemia and risk of infection in neuromyelitis optica spectrum disorders: a 14-year real-life experience. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(5):e1179. doi:10.1212/NXI.0000000000001179
175. Langer-Gould A, Li BH, Smith JB, Xu S. Multiple sclerosis, rituximab, hypogammaglobulinemia, and risk of infections. *Neurol Neuroimmunol Neuroinflamm*. 2024;11(3):e200211. doi:10.1212/NXI.0000000000200211
176. Smith JB, Hellwig K, Fink K, et al, Rituximab, MS, and pregnancy. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(4):e734. doi:10.1212/NXI.0000000000000734
177. Kumpfel T, Thiel S, Meinl I, et al. Anti-CD20 therapies and pregnancy in neuroimmunologic disorders: a cohort study from Germany. *Neurol Neuroimmunol Neuroinflamm*. 2021;8(1):e913. doi:10.1212/NXI.0000000000000913
178. Azevedo CJ, Overton E, Khadka S, et al. Early CNS neurodegeneration in radiologically isolated syndrome. *Neurol Neuroimmunol Neuroinflamm*. 2015;2(3):e102. doi:10.1212/NXI.0000000000000102
179. Alcaide-Leon P, Cybulsky K, Sankar S, et al. Quantitative spinal cord MRI in radiologically isolated syndrome. *Neurol Neuroimmunol Neuroinflamm*. 2018;5(2):e436. doi:10.1212/NXI.0000000000000436
180. Spelman T, Magyari M, Piehl F, et al. Treatment escalation vs immediate initiation of highly effective treatment for patients with relapsing-remitting multiple sclerosis: data from 2 different national strategies. *JAMA Neurol*. 2021;78(10):1197-1204. doi:10.1001/jamaneurol.2021.2738
181. Stankiewicz JM, Weiner HL. An argument for broad use of high efficacy treatments in early multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(1):e636. doi:10.1212/NXI.0000000000000636
182. Barro C, Healy BC, Liu Y, et al. Serum GFAP and NfL levels differentiate subsequent progression and disease activity in patients with progressive multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm*. 2023;10(1):e200052. doi:10.1212/NXI.0000000000200052
183. Häring DA, Kropshofer H, Kappos L, et al. Long-term prognostic value of longitudinal measurements of blood neurofilament levels. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(5):e856. doi:10.1212/NXI.0000000000000856
184. Carta S, Dinoto A, Capobianco M, et al. Serum biomarker profiles discriminate AQP4 seropositive and double seronegative neuromyelitis optica spectrum disorder. *Neurol Neuroimmunol Neuroinflamm*. 2024;11(1):e200188. doi:10.1212/NXI.0000000000200188
185. Pengo M, Miante S, Franciotta S, et al. Retinal hyperreflecting foci associate with cortical pathology in multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(4):e1180. doi:10.1212/NXI.0000000000001180
186. Tavazzi E, Jakimovski D, Kuhle J, et al. Serum neurofilament light chain and optical coherence tomography measures in MS: a longitudinal study. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(4):e737. doi:10.1212/NXI.0000000000000737
187. Lin TY, Vitkova V, Asseyer S, et al. Increased serum neurofilament light and thin ganglion cell-inner plexiform layer are additive risk factors for disease activity in early multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm*. 2021;8(5):e1051. doi:10.1212/NXI.0000000000001051
188. Aly L, Noll C, Wicklein R, et al. Dynamics of retinal vessel loss after acute optic neuritis in patients with relapsing multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(3):e1159. doi:10.1212/NXI.0000000000001159
189. Kuchlin S, Ihorst G, Heinrich SP, et al. Disease course of clinically isolated optic neuritis. *Neurol Neuroimmunol Neuroinflamm*. 2024;11(3):e200223. doi:10.1212/NXI.0000000000200223