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Editor's Corner

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N2 year in review

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2020 has been the year of coronavirus disease 2019 (COVID-19), and all of us have been affected. The impact on *Neurology® Neuroimmunology, Neuroinflammation* (*N2*) is reflected by the many articles on a variety of COVID-19–related topics such as whether patients with MS and other neuroimmunologic diseases are more vulnerable to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection[1–7]; how extending treatment dosing intervals (to reduce the risk of viral infections) affects the course of MS[8,9]; and the possible effects of the virus on the peripheral and CNS. An early review by Dr. Dalakas[10] covered many of the potential complications of COVID-19 on the peripheral nervous system. In addition, multiple clinical case reports described other infrequent COVID-19–related complications in the peripheral nervous system and CNS including Guillain-Barré syndrome (GBS),[11,12] acute encephalopathy attributed to cytokines,[13] acute necrotizing encephalitis and myelitis,[14,15] complications suspected to be CNS vasculitis (or vasculopathy),[16,17] ophthalmoparesis and hypothalamic deficits caused by unclear mechanisms,[18] and studies on SARS-CoV-2 antibodies in CSF and blood-brain-barrier (BBB) dysfunction potentially affecting neurologic outcome.[19] Despite the lockdowns and confinements (or perhaps because of them), the number of articles received in 2020 compared with the same period in 2019 has increased in 95.8%. In 2020, the impact factor of the journal increased to a competitive 7.724, which may have attracted some of these articles. Here, we review some studies published this year in *N2*.

In many patients, the clinical significance of glutamic acid decarboxylase 65 (GAD65) antibodies can be difficult to establish. These antibodies can be identified in many clinical scenarios including type I diabetes mellitus, several neurologic syndromes such as cerebellar degeneration, stiff-person syndrome, limbic encephalitis, seizures, and in up to 8% of healthy people.[20] The ability to detect the antibodies depends on the technique used, which from high to low sensitivity include ELISA, radioimmunoassay, brain tissue immunohistochemistry (IHC), and cell-based assays (CBAs), the latter 2 with a similar low sensitivity. However, for GAD65 antibody–associated neurologic syndromes, the lower sensitivity assays (IHC and CBA) are not necessarily the less useful, rather the opposite. The reason for this is that no cutoff values have been defined for the high sensitive assays (ELISA or radioimmunoassay) to establish that neurologic symptoms are in fact linked to GAD65 autoimmunity. In contrast, clinical experience and expert opinions have suggested that when antibodies are detected with low sensitive assays, particularly in CSF, the associated neurologic symptoms are most likely related to GAD65 autoimmunity. In line with this concept, some investigators indicate that a definite relationship can only be

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established if there is specific synthesis of intrathecal GAD65 antibodies.[20] To determine the cutoff values of the tests indicated above for the diagnosis of GAD65 antibody–associated neurologic syndromes, Muñoz-Lopetegi and colleagues[21] examined the serum and CSF (when available) of 56 patients with several types of neurologic symptoms using ELISA, IHC, and CBA. When the ELISA cutoff was ≥100 IU/mL, all tests in CSF showed 100% concordance. As far as serum was concerned, when the ELISA cutoff was 10,000 IU/mL, all samples with lower concentration of antibodies were negative by IHC, whereas 97% of those with higher (>10,000 IU/mL) antibody concentration were positive by IHC. Most IHC results corresponded well with CBA findings. Importantly, 34 (94%) of 36 patients with high-concentration (>10,000 IU/mL) antibodies had typical GAD65 antibody-associated neurologic syndromes (cerebellar ataxia, stiff-person syndrome, limbic encephalitis, epilepsy, or overlapping syndromes). In contrast, 12 (60%) of the 20 patients with low-concentration (<10,000 IU/mL) antibodies had alternative diagnoses, and the other 8 patients had chronic epilepsy, otherwise seronegative limbic encephalitis, or nonspecific ataxia and gait disorder. Immunotherapy was associated with a decrease in antibody concentration that frequently associated with partial clinical improvement. The study confirmed that in patients with low anti-GAD65 concentrations, particularly those without typical GAD65-associated phenotypes, alternative diagnostic etiologies should be considered.

In 2016, Graus and colleagues[22] reported an algorithmic diagnostic approach to autoimmune encephalitis including diagnostic criteria for some specific syndromes. The approach was mainly based on experience with adult patients, although data from children were also taken in consideration for some diseases (e.g., anti-NMDAR encephalitis). To validate these algorithmic diagnostic guidelines in children, de Bruijn and colleagues[23] investigated 113 children that were initially included in 3 categories: (1) children with antibody-mediated encephalitis (n = 21), (2) children with acute disseminated encephalomyelitis (ADEM, n = 34), and (3) children with neurologic symptoms suspected to be autoimmune (n = 60). Overall, 103 children fulfilled the criteria of possible autoimmune encephalitis. Among the 21 cases with antibody-mediated encephalitis, 19 had anti-NMDAR, 1 anti-AMPAR, and 1 anti-LGI1 encephalitis. Among the rest of the patients, 34 eventually had ADEM, 2 Hashimoto encephalopathy, and 46 other diagnoses that included possible autoimmune/inflammatory encephalitis (21), no evidence of autoimmune encephalitis and other etiology identified (10), and no evidence of autoimmune encephalitis and etiology unknown (15). The mean incidence rates were 1.54 children/million for antibody-mediated encephalitis and 2.49 children/million for ADEM. Thus, except for anti-NMDAR encephalitis and ADEM, other autoimmune encephalitis were uncommon in children. The authors concluded that current diagnostic guidelines for autoimmune encephalitis are also useful in children. Yet, in children with nonspecific symptoms (n = 46, 45%), it was important to review the data critically, perform comprehensive workup for alternative diseases, and consult specialized neuroinflammatory centers. Almost in parallel with this study, Celluci and colleagues[24] as part of a subcommittee of the Autoimmune Encephalitis International Working Group specifically adapted the guidelines to children. The subcommittee highlighted the main clinical features distinguishing adults and children with autoimmune encephalitis and provided 3 diagnostic categories (possible, probable, and definite) and a diagnostic algorithm. The task for the future is to validate this pediatric algorithm with a large cohort of children suspected to have autoimmune encephalitis.

One important challenge in the field of autoimmune and paraneoplastic encephalitis is the sensitivity and specificity of the clinical assays. To determine the accuracy of commercial tests for antibodies against onconeuronal (intracellular) paraneoplastic antigens, Déchelotte and colleagues[25] examined sera of 5,300 patients with suspected paraneoplastic neurologic syndromes (PNSs) with 2 different commercial immunoblot tests. The samples that were found positive were additionally examined with confirmatory tests that included rat brain IHC and a recombinant protein-based assay, either CBA or in-house immunoblot. Using one of the commercial tests, 128 (8%) of 1,658 sera were found positive, and of these, only 47 (37%) were established as truly positive for paraneoplastic antibodies. Using the other commercial test, 186 (5%) of 3,626 sera were positive, and of these, only 56 (30%) were identified as positive. The degree of correspondence between the commercial assays and the confirmatory tests varied broadly according to the antigens; for anti-Yo (PCA1), only 7% and 6% of the samples found positive by the commercial assays were eventually established as positive. In contrast, for anti-Hu (ANNA1), 88% and 65% of samples positive by commercial tests were confirmed with validation assays. Most of the false-positive cases by commercial tests were eventually diagnosed with nonparaneoplastic or autoimmune diseases, and most did not even have cancer. Therefore, although immunoblots may be useful for general screening of paraneoplastic antibodies, a threshold should be established for each antibody, and clinical information and confirmation of results with other techniques are essential.

Another study from Xu and colleagues[26] described 220 patients with anti-NMDAR encephalitis. Overall, the clinical findings and frequent improvement were similar to those reported in other series from Europe or the United States. However, 17% of the patients had relapses during the first 12 months, which is higher than previous studies (e.g., 12% over the first 2 years), and the frequency of tumors was lower (19.5%) than that previously reported (38%). In a separate study from China, Dr. Peng and colleagues[27] studied 111 patients with anti-NMDAR encephalitis and validated the anti-NMDAR encephalitis 1-year functional status (NEOS) score as a reliable predictor of poor functional status at 1-year follow-up.

Another study by Ruiz-García and colleagues[28] described a novel neuronal cell surface antibody against the metabotropic

glutamate receptor 2 (mGluR2) in 2 patients with paraneoplastic cerebellar ataxia. One of the patients was a 78-year-old woman with progressive cerebellar ataxia with an initial relapsing and remitting course who developed a small-cell cancer of unknown origin. The other patient was a 3-year-old girl who presented with steroid-responsive acute cerebellitis preceding the diagnosis of an alveolar rhabdomyosarcoma. In both cases, the serum and CSF antibodies immunolabeled the cell surface of cultured live neurons and produced a neuropil-like immunostaining, particularly involving the hippocampus and cerebellum. The antibodies did not cross-react with other previously characterized mGluR antigens (mGluR1 or mGluR5) and did not internalize the receptors. The study suggests that mGluR2 antibodies are novel biomarkers of paraneoplastic cerebellar ataxia and that the antibodies are potentially pathogenic, although the mechanisms involved are different from downregulation or receptor internalization. Although only 2 patients were included in the study, the partial improvement of one of the patients and full recovery of the other are noteworthy because paraneoplastic cerebellar ataxia rarely improves with treatment.

For the medical sleuths and those interested in the history of neurology, Tényi and colleagues[29] provided a likely resolution of a 190-year-old unresolved medical case. These authors while reviewing the historical medical literature found reference of a patient reported in medical journals from Hungary, Italy, and Germany. The patient was initially studied in 1830 and was presented in 1841 at the third meeting of the Italian Scientists held in Florence. Before symptom onset, she was a healthy 18-year-old woman who developed seizures followed by a 6-day-long clinical state characterized by unresponsiveness, catalepsy, and shallow breathing. These symptoms apparently resolved but returned over the following 18 months during which a progressively growing abdominal tumor was identified. One day she suddenly developed emesis that included pus and blood mixed with more than 100 bone fragments. In addition, she had evacuation from the anus and vagina of a membranous substance mixed with blood and pus. After this event, the seizures and catalepsy-like episodes resolved. Over the following years, she gave birth to 3 healthy children and was still well 11 years later. Tényi and colleagues[29] postulate that the shallow breathing was likely due to hypoventilation, and the catalepsy-like state was catatonia, which was not identified as an entity until more than 40 years later. They also suggest that the mass was likely an ovarian teratoma that can become very large, contain bone, and perforate into the bowel and vagina. This historical finding is remarkable; it probably represents the first description of a paraneoplastic syndrome given that the case predates by 35 years the description of Trousseau syndrome, which is considered the first paraneoplastic syndrome reported.[30]

During the last year, the SARS-CoV-2 pandemic not only dominated our lives and affected direct interactions with our patients but also had a prominent presence in neurology journals. In *N2*, 11 published articles were centered on whether SARS-CoV-2 infects the CNS or PNS, triggers neuro-autoimmunity, or increases susceptibility to infection in patients on immunotherapies, shedding light on the challenging concerns of neuroinvasion and autoimmunity.

COVID-19–associated neurologic events, including strokes, hypercoagulable state, hypoxic-ischemic, and toxic-metabolic encephalopathies, were reported early this year,[31] but evidence that COVID-19 can trigger neuro-autoimmunity emerged when GBS, the prototypic viral-triggered autoimmune disease, was recognized almost concurrently in several worldwide hotspots.[11,12,32–34] A review in *N2* by Dalakas[10] synthesized these cases pointing out that 2 early clinical and laboratory signs, anosmia/ageusia, and lymphocytopenia/thrombocytopenia are red flags in suspecting COVID-19 in asymptomatically infected individuals that present not only with GBS but with any acute neurologic event. GBS peaks 5–10 days after the first COVID-19 symptoms and can present with multiple cranial neuropathies or Miller Fisher syndrome (MFS).[10,35] Other evolving COVID-19–triggered autoimmunities were pointed out, including acute necrotizing autoimmune myositis, evidenced by high CK levels (>10,000) in 10% of COVID-19–infected patients[31] responding, whenever treated, to immunotherapy[10,36]; acute necrotizing encephalopathy or brainstem encephalitis with MRI-enhancing white matter lesions[14,16]; encephalitis with increased CSF interleukin (IL)-1β, IL-6, and rapid recovery[13]; and endothelial inflammation (endothelialitis) with encephalopathy and meningeal enhancement responding to immunotherapy.[37]

Because SARS-CoV-2 RNA shares 75%–80% genomic sequence with its 2 neurovirulent coronavirus predecessors, Middle East respiratory syndrome coronavirus and SARS-CoV, neuroinvasion was suspected considering its high virulence and lethality. The sudden loss of smell and taste not only in GBS but in up to 60% of COVID-19 carriers early in the infection[38] strengthened the view of viral entry into the brain. In contrast to commonly reversible anosmia when the non-neural olfactory epithelial cells are virally infected, persistent anosmia/ageusia was suggestive of neurotropism targeting olfactory neurons.[38] In mice, oronasal infection with SARS-CoV infects olfactory receptor neurons in the neuroepithelium gaining access to the olfactory bulb and brainstem.[39] SARS-CoV may also enter the CNS via retrograde axonal transport through the trigeminal nerve nociceptive receptors in the nasal cavity and the sensory fibers of glossopharyngeal nerves.[39] The MRI-enhanced oculomotor, trigeminal, and facial nerves observed in patients with brainstem encephalitis or MFS strengthened the notion of neuroinvasion or edematous neuroinflammation.[35] SARS-CoV-2 invades cells by binding to angiotensin-converting enzyme-2 (ACE2) receptors, reportedly expressed—although not fully substantiated—in endothelial cells of brain vessels, nerves, and muscles, facilitating potential CNS and PNS entry.[38] Macrophages also express ACE2 receptors that may carry the virus into neural tissues, like HIV (Trojan horse phenomenon), augmenting neuroinflammation and tissue injury.[40] Notwithstanding its

neuroinvasive potential however, most published data point to COVID-19–triggered autoimmunity,[10,35] as also summarized by Bodro et al.[13]

A step toward clarifying the above was a pivotal study by Alexopoulos et al.,[19] who assessed in 8 patients with encephalopathy whether anti–SARS-CoV-2 antibodies are intrathecally produced in response to locally persisting viral antigens or are passively transferred into the CSF from the circulation due to the impaired BBB. Anti–SARS-CoV-2 antibodies were detected in the CSF of all patients, but 4/8 had high titers comparable to their serum values denoting BBB disruption; only 1/8 had anti–SARS-CoV-2 immunoglobulin G (IgG) intrathecal synthesis.[19] A disrupted BBB allows passive entry into the CNS not only of antibodies but also circulating cytokines and inflammatory mediators, which may affect endothelial cells, a structural part of the BBB, resulting in endothelialitis and further BBB disruption. Anti–SARS-CoV-2 antibodies entering the CNS can, by mobilizing complement or guiding SARS-CoV-2–infected macrophages, lead to activation of microglia or resident macrophages enhancing neuroinflammation and neurodegeneration, as supported by the presence of 14-3-3 protein in 4/8 patients with poor outcome.[19] These observations highlight the need for prospective CSF studies to determine the pathogenic role of anti–SARS-CoV-2 antibodies or other neuroinflammatory molecules, explore markers of neurodegeneration, and guide early initiation of proper therapeutic interventions.[19] Considering that the CSF from most published patients, not only with encephalopathies but also with GBS and cranial neuropathies, has been acellular and SARS-CoV-2–PCR negative,[10,13,19] the possibility of intrathecal viral replication driven by locally persisting viral antigens appears unlikely, except if there is rapid viral clearance or unique compartmentalized immune response within the CNS.

That SARS-CoV-2 triggers neuro-autoimmunity is additionally supported by the data from COVID-19–triggered GBS where many treated patients responded fast to IVIg, whereas at least 2 examined patients harbored antibodies to GD1b ganglioside,[34,41] as seen in other postviral-induced GBS.[10] As pointed out,[10] these antibodies are of significance because the attachment of COVID-19 spike S protein to respiratory cells is mediated not only by ACE2 receptors, but also by binding to sialic acid–containing glycoproteins and gangliosides on cell surfaces.[42] Because in GBS and other autoimmune neuropathies, gangliosides containing disialosyl moieties can serve as antigens and anti-GD1b gangliosides are pathogenic,[43] cross-reactivity between epitopes within the COVID-19 spike–bearing gangliosides and signature sugar moieties on nerve glycolipids may represent molecular mimicry similar to the one observed between nerve glycolipids and *Campylobacter jejuni* or Zika virus–triggered GBS.[10,35]

Regarding common autoimmune neurologic disorders, like MS, neuromyelitis optica spectrum disorder (NMOSD), chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, or inflammatory myopathies, there is convincing evidence that neither the disease itself nor the maintenance therapies they receive with steroids, mycophenolate, or azathioprine increase susceptibility to COVID-19 or place them into an immunosuppressed or immunocompromised category; if clinically stable and not lymphopenic, there is no need to alter therapies.[10] The same applies to disease-modifying therapies in patients with MS,[1,3] especially because these therapies target mostly adaptive immunity with insignificant effect on innate immunity that facilitates infection of macrophages and viral spread,[10] as also summarized by Berger et al.[1] For patients on monthly IVIg, there may be even a theoretical advantage of IVIg offering natural protective autoantibodies. The anticomplement agent eculizumab, approved for NMOSD and myasthenia gravis, should not be withheld as it may have an added protective benefit.[10,44] Complement, being an integral component of the innate immune response to viruses and an instigator of proinflammatory responses, exacerbates SARS-CoV–associated respiratory distress[44,45]; eculizumab, currently tested for the inflammatory complications of COVID-19, already shows early benefits.[46] Postponing or suspending cladribine, alemtuzumab, mitoxantrone, and hematopoietic stem cell transplantation is highly advisable.[47] For patients on rituximab (RTX) and ocrelizumab, infusion intervals can be prolonged to more than 6 months, as both B-cell reduction and clinical benefit persist longer.[1,10,47]

Notwithstanding the need to further explore the COVID-19–driven acute events of neuro-autoimmunity or neurovirulence, there is an urgent need to assess post-neuroinflammatory effects in COVID-19 survivors. In analogy to postviral fatigue syndromes associated with less invasive viruses, the post–COVID-19 neurologic sequelae are expected to be profound considering the multisystemic effects of COVID-19, even if many acute events are not directly caused by the virus, as argued by Bodro et al.[13] Many discharged patients, as pointed out,[10] are left with muscle weakness, atrophy, and gait imbalance; several have lost smell and taste; and still others exhibit cognitive and mental issues, even after short-term illness, compounded by social isolation, anxiety, and fears. A systematic study of neurologic, cognitive, and neuropsychological assessments is needed to help all recovered patients return to normalcy.

T-helper 17 (Th17) cells are considered a hallmark proinflammatory T-cell subset that participates in pathogenesis of several organ-targeted autoimmune diseases, including MS. IL-26, a member of the IL-10 cytokine family, has been identified as a human Th17-associated cytokine that is regulated by IL-1β, IL-23, and RAR-related orphan receptor γt, the master regulator in Th17 differentiation. IL-26 appears to have a proinflammatory role in inflammatory bowel disease[48] and rheumatoid arthritis.[49] In the November issue of *N2*, Broux et al.[50] investigated the potential role of IL-26 in MS. Based on the earlier observations in Th differentiation and other autoimmune diseases, these authors hypothesized that IL-26, like IL-17, would have a

proinflammatory role and promote BBB disruption.[51] Indeed, they observed that IL-26 is preferentially expressed by Th17 cells. However, when examining the transcriptome of IL-26–treated human BBB endothelial cells, they observed that IL-26 downregulated expression of proinflammatory cytokines, tumor necrosis factor α, interferon (IFN)-γ, and IL-6. Furthermore, IL-26 promoted expression of certain BBB tight junction (TJ) molecules, including JAM-1, and this effect was inhibited by antibodies that prevented binding to the IL-26 receptor (R), a heterodimer composed of IL-10R2 and IL-20R1. Although mice do not express IL-26, they do express the IL-26R, which permitted the authors to examine the influence of IL-26 treatment in mice. IL-26 treatment of mouse BBB endothelial cells promoted expression of certain TJ proteins, including JAM-1 and CLDN5. IL-26 treatment in vivo was associated with reduced severity of clinical EAE, decreased CNS extravasation of blood proteins, and reduced CNS infiltration of Th17 cells. Conversely, IL-26 treatment was associated with an increased CNS accumulation of Treg and Th10 cells, a well-known regulatory T-cell subset. Thus, although IL-26 is expressed by Th17 cells, this cytokine exhibits anti-inflammatory characteristics, promoting BBB integrity and CNS accumulation of regulatory T cells. The authors' observations are exciting and raise additional questions. In further studies, it will be important to determine whether all activities of IL-26 are mediated through IL-10R2. It will also be important to determine how this cytokine influences antigen-presenting cell (APC) function of myeloid cells and other APC subpopulations. Given that IL-26 exerted proinflammatory responses in 2 other organ-specific autoimmune diseases,[48,49] one will need to be cautious in advancing IL-26 therapeutically in MS. Clearly, more work is needed to further elucidate the role of IL-26 in CNS autoimmune diseases.

Several disease-modifying therapies (DMTs) used for treatment of MS cause alterations in cellular or humoral immunity that may be sustained after treatment discontinuation. This is a particular concern when a patient has breakthrough MS activity or develops medication intolerance, leading one to consider subsequent alternate therapy. Fingolimod (Gilenya), one of the S1P modulators, traps lymphocytes in secondary lymphoid tissues, resulting in reduced lymphocyte counts within peripheral blood.[52] Fingolimod is immunosuppressive, predisposing to viral infections, including herpes simplex and varicella, and less commonly may be associated with progressive multifocal leukoencephalopathy in JC virus–seropositive patients.[53] In a recent study published in *N2*, Nagy et al. investigated the dynamics of immune cell recovery in 58 patients after discontinuation of fingolimod treatment.[54] Surprisingly, 22% remained lymphopenic 1 year later. Risk factors for sustained lymphopenia included low baseline lymphocyte counts, prior treatment with mitoxantrone, and subsequent treatment with the anti-CD20, RTX. Sustained lymphopenia in association with RTX may not be surprising, as RTX can cause a near complete elimination of peripheral blood B cells, which may account for approximately 15% of circulating lymphocytes. Regardless, the study by Nagy underscores the concern for sustained immune suppression when using certain DMTS sequentially and the need for careful monitoring.

The MS DMT, alemtuzumab (Campath, Lemtrada), a monoclonal antibody that targets CD52 and depletes mature B and T cells, is highly effective in relapsing-remitting MS. In contrast with fingolimod and other DMTs that pose greater risk for viral infections or other consequences from immune suppression, alemtuzumab is associated with risk for secondary (iatrogenic) humoral autoimmunity in up to 40% of patients. Signs or symptoms of 3 secondary autoimmune conditions, Graves' disease, immune thrombocytopenia, or, more rarely, antiglomerular basement membrane disease are delayed, occurring more than 18 months after the first treatment course, a time when there is B-cell hyperrepopulation and reduced thymic T-cell reconstitution. Independent of alemtuzumab treatment, the corresponding primary (idiopathic) humoral autoimmune conditions are sometimes treated with anti-CD20 B-cell depletion. Meltzer et al.[55] therefore hypothesized that scheduled anti-CD20 B-cell depletion could mitigate against the risk for alemtuzumab-induced secondary autoimmunity. In a 10-patient pilot study, they administered low-dose (50–100 mg/m^2) RTX after the first or second cycle of alemtuzumab. Some of their patients were followed for a mean of 41 months. They did not observe evidence of secondary autoimmunity in any of their patients. Although their results are provocative, additional studies are needed to confirm their findings, establish how effectively low-dose RTX depletes B cells, and determine whether concomitant treatment of anti-CD52 and anti-CD20 provides greater benefit than approved dosing with anti-CD20 alone. Of additional interest, cases of paradoxical MS disease activation after alemtuzumab treatment have also been reported.[56,57] In these rare instances, RTX has been administered and has been effective in stabilizing those patients.

Whether MS and NMO influence susceptibility to COVID-19 infection are questions that have concerned patients and their treating neurologists. Reports published in *N2* early in the COVID-19 pandemic have indicated that MS or NMO alone does not confer greater susceptibility to either disease.[3–5] However, a large study of patients with MS with confirmed COVID-19 identified age, obesity, and Expanded Disability Severity Score as independent risk factors for more severe COVID-19 outcome.[58] How individual DMTs alter risk of COVID-19 is not clear. Because of the antiviral properties of type I IFNs α and β, it has been suggested that IFN-β therapy in MS could be protective against COVID-19.[7] Whether anti-CD20 B cell–depleting antibodies pose greater risk of COVID-19 is not clear. A large study of patients with MS in Italy identified a higher risk of severe outcome of COVID-19 infection in patients with MS treated with ocrelizumab or RTX.[59] In contrast, report of a pharmacovigilance case series conducted by the manufacturer of ocrelizumab indicated that there was no greater risk of severe COVID-19 outcome in ocrelizumab-treated patients with MS. As B cells serve as the source of antibody-secreting plasmablasts and plasma cells, one

is also concerned whether anti–CD20-treated patients will mount protective antibody responses to COVID-19 vaccines that may soon become available. In this context, a recent study observed that humoral responses to several nonlive vaccinations were attenuated in patients with MS treated with ocrelizumab.[60] It is clear that additional studies are needed before considering recommendations regarding use of MS therapeutics and COVID-19 risk.

In recent years, myelin oligodendrocyte glycoprotein (MOG)-associated disease (MOGAD) has emerged as immune-mediated nosologic entity distinct from typical aquaporin-4 (AQP4) ab–positive NMOSD.[61–63] Moreover, MOG seropositivity is rarely found in patients with classic MS.[64] Availability of reliable assays to test for antibodies to MOG is important for managing these patients. Here, an international consortium examined several MOG antibody assays in a multicenter approach.[65] Thirty-nine clearly MOG-IgG–positive sera, 39 low-positive sera, 13 borderline-negative sera, 40 clearly negative sera, and 30 sera from healthy blood donors were distributed to 5 testing centers where several live and fixed immunofluorescence cell-based assays, live flow cytometry cell-based assays, and ELISA assays were performed. Eighteen replicates (9 MOG-IgG positive and 9 negative) served as technical controls. Agreement was excellent (96%) between live cell-based assays for MOG-IgG in samples previously clearly identified as positive or negative, whereas agreement was not as good for the fixed cell-based assay (90%). Cell-based assays showed an excellent interassay reproducibility, whereas ELISA failed to show concordance with cell-based assays for detecting MOG-IgG. In contrast, the agreement of cell-based assays for borderline negative and low positive samples was much lower (77% and 33%, respectively). This work has important implications for MOG-IgG testing and interpretation of test results in clinical practice: (1) commercially available fixed cell-based assays are useful when live cell-based assays are not available; however, the former will miss approximately 10%–15% of positive cases. This underscores the recommendation to retest patients with a typical clinical presentation of MOGAD in a center offering live cell-based assays when the fixed cell-based assay is negative; (2) ELISAs are not adequate for the detection of MOG-IgG and should therefore not be used; (3) the interpretation of borderline seropositivity remains an unresolved issue until the most useful cutoff for clinical purposes will have been established. In the meantime, low-positive MOG-IgG is probably only meaningful in conjunction with the suitable clinical presentation (in patients with ON, ADEM, myelitis, and some forms of encephalitis) but not classic MS.

Another study from Korea reported a different biomarker profile between AQP4 ab–positive NMOSD and MOGAD.[66] AQP4 ab–positive patients with NMOSD had higher serum levels of glial fibrillary acidic protein than patients with MOGAD, and levels of this biomarker of astrocyte damage were higher in relapse than remission in NMOSD but not in MOGAD. Serum levels of another widely researched marker of neuroaxonal damage, neurofilament light chain (NfL), were comparable in both conditions, but only patients with NMOSD had higher NfL values in relapse than in remission. By contrast, only patients with MOGAD had higher serum tau levels in relapse as compared to remission. These findings emphasize distinct mechanisms of tissue damage in AQP4 ab–positive NMOSD and MOGAD and moreover propose that tau, a microtubule-associated protein in neurons, could be further investigated as clinically applicable biomarker in patients with MOGAD.

The question as to whether MOGAD should be treated with immunotherapy right after the first clinical event is still contentious owing to a presumably high proportion of monophasic cases and an on average more favorable prognosis than AQP4 ab–positive NMOSD. However, most experts would advocate relapse-preventive immunotherapy after 2 or more attacks.[67] Unfortunately, data on the appropriate drugs for treating MOGAD are still scarce. Although larger case series have demonstrated good efficacy of oral corticosteroids and generic immunosuppressants such as azathioprine and mycophenolate mofetil (MMF), the situation seems to be less clear for RTX, and classic MS drugs were reported to be of no effect or even harmful as in AQP4 ab–positive NMOSD.[68,69] Against this background, a prospective observational cohort study from China, although not a randomized trial, provides valuable clinical evidence on the effect of MMF on relapse rates in MOGAD.[70] Seventy-nine patients with MOGAD (children and adults, 54 on MMF and 25 without MMF; both groups had an additional and comparable steroid taper) were followed over a median of 261 days (without MMF) and 472.5 days (with MMF). Relapse rates were 7.4% in the w/ MMF group and 44% in the w/o MMF group. MMF treatment was associated with a profoundly reduced risk of relapse, even after adjusting for covariates such as age group (children vs adults), sex, disease course, and initial MOG-IgG titer (HR 0.08, 95% CI 0.02–0.28, $p < 0.001$). Only 1 patient discontinued MMF owing to side effects. Despite inherent limitations of this noncontrolled trial, the results show that MMF might confer effective attack prevention in patients with MOGAD.

Treatment with monoclonal antibodies (mAbs) is a therapeutic mainstay in many autoimmune diseases, which often affect young females in child-bearing age.[71–73] As disease activity may be increased in the peripartum period in some conditions, withholding immunotherapy may be hazardous for the mother. On the other hand, women are often advised to forego breastfeeding because of scant safety data on the use of mAbs during this period, although both the mother and the neonate may benefit from it. LaHue and colleagues conducted a review of the medical literature and extracted data from 30 studies on breast milk concentrations of 19 mAbs (among them natalizumab, RTX, tocilizumab, and eculizumab), which were generally low.[74] The relative infant dose, a parameter comparing infant with maternal drug dose, was assessed for some mAbs including RTX and natalizumab and was below 10%, which is generally considered safe. None of 368 infants

followed for 6 or more months after exposure to breast milk of mothers treated with mAbs had overt developmental delay or serious infections. Despite some limitations, this work suggests low mAb transfer into breast milk and may help inform individual treatment decisions as to mAb treatment during the postpartum and lactation period. However, the authors rightly call for registries to substantiate these findings. This review is paralleled by another study in 9 women with MS who received RTX while breastfeeding.[75] In serial samples collected between hours to several weeks from RTX infusion, maximum concentrations were attained 1–7 days after infusion and yielded a relative infant dose of 0.08%. The authors conclude that RTX therapy may confer an acceptable risk-to-benefit ratio, supporting both maternal treatment and breastfeeding, in women with severe neurologic autoimmune diseases.

Neuroinflammation, oxidative stress, and aging are linked to cognitive risk in persons living with HIV (PLWH), even in individuals achieving suppression of virus replication with antiretroviral therapy.[76] Several studies in the May 2020 issue addressed the potential impact of these factors in PLWH. Certain populations (distinguished by genetic background, age, or other factors) may be more vulnerable to effects of neuroinflammation and oxidative stress. In a study of 528 PLWH (276 African Americans and 252 European Americans), Garza et al.[77] showed that a common genetic regulatory variation [(GT)n dinucleotide repeat length] in the promoter region of the antioxidant enzyme, heme oxygenase-1 (HO-1), is a unique risk factor for cognitive impairment in PLWH. The presence of at least 1 short (GT)n repeat allele, which associates with higher HO-1 expression, associated with a 2-fold reduction in an individual's cognitive impairment risk. Furthermore, this reduced risk effect appears to be linked to neuroinflammation, particularly in individuals of African ancestry. The implications are important. Because HO-1 is therapeutically targetable (e.g., dimethyl fumarate), neurologic complications of virus infections associated with neuroinflammation and oxidative stress (HIV, SARS-CoV-2, and others) may potentially be preventable with HO-1–inducing drugs.[78]

Also, in the May 2020 issue, Groff et al.[79] used magnetoencephalography (MEG) and neuropsychological testing to compare 77 PLWH with 93 HIV-negative controls to assess the effects of HIV infection on the integrity of occipital-parietal visual-spatial responses, which this group had shown before to vary predictably with aging.[80] Cognitively impaired PLWH differed from unimpaired PLWH in age-dependent responses. Although not specifically examined in this study, biomarkers of neuroinflammation and oxidative stress increase with age in the HIV-infected brain, which suggests that studies linking MEG responses with biomarkers of neuroinflammation linked to cognitive impairment are warranted.

Neuroinflammation and the use of the recreational drug cannabis (once considered a drug of abuse) in PLWH were the subject of study by Ellis et al.[81] in the September 2020 issue. In this study, plasma and CSF samples from 35 PLWH and 21 HIV-negative controls matched for cannabis use (recency, density, cumulative months, and grams) were analyzed. The investigators found that recent cannabis use associated with reduced neuroinflammation (indicated by reduced CSF expression of IL-16, C-reactive protein, and soluble receptor for TNF type II). This is not necessarily surprising, as CB2 receptors (CB2Rs) are expressed in microglia and astrocytes, and CB2R activators have anti-inflammatory effects.[82] This study builds upon a body of literature that suggests some potential neuroprotective effects of cannabis use and thus defining specific effects of these is increasingly important as the use of medical marijuana rises in PLWH.[83]

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Disclosure

J. Dalmau is Editor of *N2*; he holds patents for the use of Ma2, NMDAR, GABABR, GABAAR, DPPX, and IgLON5 as autoantibody tests and receives royalties from the use of these tests. M.C. Dalakas, D.L. Kolson, and F. Paul are Associate Editors of *N2*. S.S. Zamvil is Deputy Editor of *N2*. Go to Neurology.org/NN for full disclosures.

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N2 year in review

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