

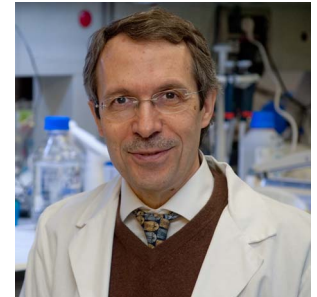
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N2 Year in Review

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Two thousand twenty-two has been the year in which the COVID-19 pandemic has receded leaving us with a substantial number of important investigations on the disease and the interactions between neuroinflammatory disorders and SARS-CoV-2 infection or vaccinations. This Year in Review, which in fact covers 2021 and 2022, includes many of these studies and others focused on different topics that have attracted the attention of *N2* readers. These studies have been selected by the editors and reflect the broad range of topics covered in *N2*. That our contributors accomplished these studies while facing the challenges presented by the pandemic demonstrates their commitment to the continued advancement of knowledge that will surely lead to improving the lives of our patients and to a healthier community in general. We have grouped the studies in 6 general themes including paraneoplastic and autoimmune encephalitis, MOG antibody-associated disease (MOGAD), neurologic diseases associated with IgG4 autoantibodies, COVID-19-related studies in the context of neurologic autoimmunity, other infectious diseases of the nervous system, and inflammatory mechanisms in neurodegenerative diseases.

The first international diagnostic criteria for paraneoplastic neurologic syndromes (PNSs) were published in 2004.¹ Over the ensuing 17 years, the identification of new disorders and pathogenic mechanisms led an international panel of investigators to report an update on those criteria that were published in July 2021.² The current criteria are important because they are broad and comprehensive and include the paraneoplastic disorders associated with antibodies to neural intracellular antigens and those associated with antibodies against neural surface antigens. The panel proposed to substitute the term classical PNS for high-risk phenotypes and introduced the concept of intermediate-risk phenotypes for those disorders that are less frequently associated with cancer. A similar risk stratification is used for the classification of neural antibodies, considering high risk those antibodies with a >70% probability of occurring with cancer and intermediate risk those with a 30%–70% probability of a cancer association. These changes in terminology serve to clarify several erroneous concepts derived from the previously used nomenclature for syndromes and antibodies. For example, although limbic encephalitis is a classical immune-mediated syndrome, it can occur with or without cancer depending of the type of antibody. On the other hand, not all intracellular neuronal autoantibodies are necessarily paraneoplastic or onconeurological (e.g., GAD65 antibodies rarely associate with cancer), and some cell surface neuronal antibodies can be paraneoplastic or onconeurological (e.g., GABA_BR antibodies frequently associate with cancer). Overall, based on the type of syndrome, antibody, and presence or absence of a clinically detected tumor, the panel developed a PNS score that allows classification of PNS in 3 levels of evidence: definite, probable, and possible. Thus, with the exception of opsoclonus-myoclonus (which in most patients does not associate with an autoantibody), the diagnosis of definite PNS requires the presence of high- or intermediate-risk antibodies in combination with the appropriate syndromes. The panel emphasized that errors in antibody testing are common, and therefore, a positive antibody test should not override clinical



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judgment, which is a concern recently addressed by other studies.^{3,4} In addition, the panelists suggested that for patients with high-risk syndromes and high-risk antibodies, if the initial tumor screening is negative, this should be repeated every 4–6 months for 2 years. Specific recommendations for similar PNS in the context of immune checkpoint inhibitors were also provided.

Among the high-risk antibodies for paraneoplastic syndromes, the testing for Yo (PCA) antibodies is a frequent cause of misdiagnosis.^{5,6} The syndrome that associates with these antibodies is a paraneoplastic cerebellar degeneration (PCD) in the context of breast and ovarian cancer and much less frequently other tumors. For many years, the main target antigen of these antibodies was considered to be an intracellular (nuclear) protein called cerebellar degeneration-related protein 2 (CDR2).⁷ However, recent studies by Vedeler et al. showed that CDR2 is recognized by the antibodies of a subset of patients with cancer with or without PCD, whereas a homolog called CDR2-like (CDR2L) that is predominantly expressed in the cytoplasm of Purkinje cells is the target of those antibodies specifically associated with PCD.⁸ The importance of this finding is that it clarifies the extraordinary number of false-positive clinical tests for anti-Yo-associated PCD. Indeed, currently commercialized immunoblot (or line blot) diagnostic tests only include the CDR2 antigen and thus do not discriminate between patients with breast or ovarian cancer with or without PCD. In the March 2021 issue of *N2*, this problem was further examined by Herdlevær et al.⁹ using sera and CSF samples of 24 patients with suspected PCD (6 in the context of gynecologic or breast cancer), who were considered anti-Yo positive using 2 different commercial diagnostic tests based on the CDR2 antigen. Using one of the commercial line blots, all 24 cases (100%) were positive, and using the other line blot, 20 of 24 (83%) were positive. Moreover, 13/24 (54%) were also positive in a commercial cell-based assay (CBA) that expresses CDR2. In contrast, when the authors used an in-house immunoblot or CBA that specifically expressed CDR2L, only the 6 patients with anti-Yo-associated PCD were positive, confirming the high sensitivity and specificity of CDR2L for this type of PCD.

Until recently, the reason why only a very small number of patients with tumors expressing neuronal proteins develop PNS was unknown. There is now mounting evidence that distinct genetic tumor alterations may predispose (in the context of specific HLA haplotypes) to develop PNS.¹⁰ In the September 2022 issue of *N2*, Peter et al.¹¹ examined the genetic profiles of 22 breast cancers from patients with anti-Yo-associated PCD. The tumors were invasive but of no special histologic type and occurred with early metastases to local lymph nodes. They overexpressed human epidermal growth factor receptor 2 (HER2) but were hormone negative. Of interest, all paraneoplastic breast cancers carried at least 1 genetic alteration (variation or gain in copy number) of the *CDR2L* gene. Analysis of differentially expressed genes

found 615 upregulated and 54 downregulated in the paraneoplastic tumors compared with HER2-positive tumors without PCD. The findings supports the role of genetic alterations of *CDR2L* in triggering the immune tolerance breakdown and suggest a distinct biomolecular profile in the tumors of anti-Yo-associated PCD.

Regarding anti-NMDA receptor encephalitis (NMDARe), 2 studies assessed the prognosis of this disease in the young- and late-onset patients.^{12,13} In an article published in September 2022, Yeshokumar et al.¹² performed an analysis of cross-sectional informant-reported data of 41 patients/caregivers of patients with NMDARe treated at 3 major academic hospitals. Neurologic disability was assessed with the modified Rankin Scale (mRS) and functional outcomes with the Adaptive Behavior Assessment System, 3rd edition (ABAS-3). They found that patients younger than 12 years ($n = 17$) were more likely to have lower mean ABAS-3 scores and were in the below-average range compared with older patients. On the other hand, no differences in mRS scores were identified between age groups. The authors concluded that although NMDARe is associated with an overall favorable outcome, younger age at onset associates with worse long-term adaptive behavior despite no differences in neurologic disability. These divergent chronologic outcomes (good and earlier functional neurologic outcomes, compared with more protracted cognitive-psychiatric improvement) are a typical feature of NMDARe, which has been meticulously described recently and resembles the cognitive-psychiatric alterations of patients with schizophrenia.

In a study published in March 2022, Bastiaansen et al.¹³ performed a nationwide observational study in patients diagnosed with NMDARe between 2007 and 2019. A total of 126 patients were included (median age, 24 years, range 1–86 years), representing a mean annual incidence of 1/million. Patients aged 45 years or older (19%) were more likely to have fewer seizures (46% vs 71%), fewer symptoms during the disease course (3 vs 6), and more often did not have antibodies detectable in serum than younger patients. Moreover, in the late-onset group, the outcome was worse, and among the patients with tumors (9/24, 38%), all tumors were carcinomas. Irrespective of patients' age, CSF was more accurate than serum to diagnose NMDARe. The authors emphasize that NMDARe occurs at all ages and is less rare in the elderly than initially expected. In older patients, the clinical phenotype is less stereotypic, has different tumor association (carcinomas instead of teratomas), and a less favorable recovery compared with that of younger patients, confirming findings of a previous study.¹⁴

The neonatal Fc receptor (FcRn) is responsible for the transport of IgG through the placenta and for extending serum IgG half-life after birth. In the July and November 2021 issues of *N2*, 2 experimental animal models of antibody-mediated diseases examined whether blockade of the FcRn to prevent the placental transfer of pathogenic antibodies decreased the

likelihood of maternal antibody-mediated neonatal disease in the offspring.^{15,16} One of the studies examined the effect of FcRn blockade in a model of maternal-to-fetal transfer of AChR antibody-mediated arthrogyrosis multiplex congenita, and the other model was focused on the placental transfer of NMDAR antibody-mediated synaptic and behavioral alterations.¹⁶ Although each model used a different antibody to block FcRn function, both studies showed that FcRn blockade prevents placental transfer of pathogenic antibodies and therefore the corresponding peripheral or CNS alterations. These models have potential therapeutic implications for all antibody-mediated diseases during pregnancy.

In addition to the above-selected articles, over 60 interesting articles on paraneoplastic and autoimmune encephalitis were published during 2021–2022 in *N2*, one of them focused on international consensus recommendations for the treatment of pediatric anti-NMDAR encephalitis¹⁷ and another on the diagnosis and management of pediatric opsoclonus-myoclonus-ataxia syndrome.¹⁸

Our knowledge and understanding of MOGAD, a disorder recognized only for several years, is advancing at a remarkable pace. Initially, acute disseminated encephalomyelitis (ADEM), unilateral and bilateral optic neuritis, and transverse myelitis were described as 3 separate, and sometimes overlapping, presentations of MOG antibody-associated CNS demyelinating disease. Although less common clinical presentations had been recognized, the number of MOGAD clinical patterns and associations described has expanded.¹⁹ In this regard, clinicoradiologic reports have suggested an association of seizures and meningoencephalitis-like presentations of MOGAD with the presence of cortical lesions and leptomeningeal involvement.^{19–22} Temporal association of ADEM with prior infection or vaccination is well recognized. There are now case reports associating rare cases of MOGAD with prior SARS-CoV-2 infection or SARS-CoV-2 vaccination.^{23,24} Although these findings might suggest molecular mimicry between MOG and SARS-CoV-2 spike protein used for vaccination, this possibility has not been substantiated. The risk, if one exists, of eliciting MOGAD after SARS-CoV2 vaccination is likely exceptionally low.

As clinical manifestations of MOGAD are diverse, it is logical to ask whether there is differential antibody binding to MOG and, if so, might those patterns associate with individual clinical phenotypes or severity. Full-length MOG contains an extracellular domain, which is the predominant target of MOG-specific antibodies in MOGAD, and transmembrane and cytoplasmic domains. Oligodendrocytes may express different MOG isoforms, some that are missing certain cytoplasmic amino acid sequences (exons), including a second hydrophobic membrane-associated domain that may stabilize expression of the proximal extracellular domain.²⁵ In a study reported in *N2*, Schanda et al.²⁶ expressed several different isoforms of MOG and evaluated MOG-specific antibody binding of a large number of serum samples from individuals who had MOGAD

or MS and samples from healthy controls. Antibodies within serum samples from individuals who had MOGAD reacted to MOG. Differential binding was observed, and the strongest antibody responses targeted the full-length MOG isoform. However, the recognition of different isoforms did not associate with clinical presentation, disease course, or neuropathology.

Like aquaporin-4 (AQP4)-specific antibodies in NMOSD, MOG-specific antibodies are IgG1. Unlike AQP4-specific antibodies, which activate complement and contribute to NMOSD pathogenesis, the extent that MOG-specific antibodies contribute to MOGAD is still unknown. IgG1 is a T cell-dependent isotype, and in animal models, MOG-specific antibodies only cause disease in association with CNS inflammation, typically induced by MOG-specific T cells.²⁷ In general, MOGAD is considered to have an outside-in pathogenesis where antibody levels are highest in serum,²⁸ supporting the testing of serum specimens for diagnosis of MOGAD. However, intrathecal MOG-specific antibodies have been detected in a small percentage of patients with MOG-seronegative ADEM^{19,29} and patients with AQP4-seronegative NMOSD,²⁹ indicating that in some MOGAD cases, there is de novo CNS production of MOG-specific IgG. In a study published in *N2*, Kwon et al.³⁰ evaluated paired serum-CSF samples from 474 patients with suspected inflammatory demyelinating disease (IDD). CSF MOG-IgG was positive in 19 patients with seropositive MOGAD, 9 with other IDD, 4 with MS, but none with AQP4-seropositive NMOSD nor non-IDDs. Of those 32, 19 were seropositive patients with MOGAD, and 13 were uniquely CSF MOG-IgG positive. Both CSF MOG-IgG titer and CSF/serum MOG-IgG index, but not serum MOG-IgG titer, were associated with disability. Collectively, these findings provide a key message for neurologists; when there is a high clinical suspicion of MOGAD in an MOG-IgG-seronegative patient, one should strongly consider evaluating CSF for MOG-IgG. Furthermore, these recent findings of CSF MOG-IgG in the absence of serum MOG-IgG indicate that an outside-in only view is not entirely correct. There may be more than 1 pathogenic mechanism for generation of MOG-specific IgG in MOGAD.

Considerable effort is being devoted to the development of therapies for MOGAD, but none have yet been approved. IV and oral steroids, other oral immunosuppressive treatments, plasmapheresis, IV IgG, and anti-CD20 B-cell depletion are commonly used, although with variable levels of success. In contrast, 3 different treatments, inebilizumab (anti-CD19 B-cell depletion), eculizumab (complement C5 convertase inhibition), and satralizumab (anti-IL6 receptor) have been approved for AQP4-seropositive NMOSD. Thus far, anti-CD20 B-cell depletion has not proven reliably beneficial in MOGAD.³¹ Eculizumab may not be successful in MOGAD. Organized clusters of AQP4 on astrocytes permit efficient AQP4-specific antibody binding and complement activation, likely accounting for the exquisite sensitivity of AQP4-seropositive NMOSD to complement inhibition. MOG

expression on oligodendrocytes does not occur in such fashion. Second, complement deposition has not been consistently identified in CNS lesions of patients with MOGAD. However, preclinical and clinical studies both support advancing IL-6 antagonism in MOGAD treatment. In this context, Ringelstein et al.³² reported in *N2* an open-label treatment trial with tocilizumab, an anti-IL6 receptor antibody. Tocilizumab was safe and reduced the probability of relapse in patients with MOGAD and AQP4-seropositive NMOSD. Currently, satralizumab is being tested in MOGAD in larger studies. In addition, MOG-specific tolerogenic approaches, which may be devoid of complications of systemic immunosuppression, are being considered. If candidate therapeutics can be developed and tested as quickly as was achieved in NMOSD, it may not take long before therapies become approved for MOGAD.

The last year, several articles, at least 5 in *N2*, have focused on IgG4 neurologic diseases (IgG4-ND) expanding on their clinical and immunopathogenic characteristics, shedding light in understanding the mechanism of IgG4 antibodies, especially in connection with autoimmune nodopathies/paranodopathies, clarifying how the IgG4 valency modulates pathogenicity and explaining the rationale of why patients with IgG4-ND, in contrast to their disease counterparts associated with IgG1-3 antibody subclass, do not adequately respond to conventional immunotherapies with IVIg and steroids. The information is important because the IgG4-ND comprise an expanding, immunopathologically distinct disease spectrum³³ that now includes (1) CIPD with paranodal antibodies to neurofascin-155, contactin-1, CASPR, and nodal/paranodal pan-neurofascins (NF140/NF186/NF155); (2) MuSK myasthenia; (3) LGI1 and CASPR2-associated autoimmune CNS and PNS disorders presenting as encephalitis, autoimmune epilepsy, Morvan syndrome, and neuromyotonia. Because these 2 antigens, LGI1 and CASPR2, are also expressed in the peripheral nerves and dorsal root ganglia, their clinical heterogeneity was recently expanded further. Ramanathan et al.³⁴ described in an important large series of 147 patients that 52% with anti-CASPR2 and 19% with anti-LGI1 antibodies experienced neuropathic pain with reduced intraepidermal nerve fiber densities, as seen in small fiber sensory neuropathy, and autonomic nervous system features like POTS. Serum CASPR2 antibodies, but not LGI1 antibodies, bound in vitro to unmyelinated human sensory neurons and rodent dorsal root ganglia.³⁴ The patients' pain symptoms responded to immunotherapies, highlighting a new subset of antibody-mediated autoimmune pain syndrome; (4) anti-IgLON5 disease spectrum presenting with a complex symptomatology of bulbar dysfunction, ataxia, movement disorders, sleep alterations, and abnormal eye movements^{33,35,36}; and (5) anti-DPPX encephalitis, characterized by gastrointestinal symptoms, cognitive dysfunction, and neuronal excitability, where in a patient subset, the antibodies are also of IgG4 subclass.^{33,37}

In a subset of these patients, the antibodies are of IgG4 subclass, which is of significance in determining response to

immunotherapies, as explained below. Of major clinicopathologic importance has been the observations that the aforementioned IgG4 antibodies do not cause an inflammatory-mediated tissue destruction, as the antibodies of the IgG1-3 subclass do, but they inhibit cellular adhesion, block enzymatic activity, or disrupt protein-protein interactions,³⁷ all functions of therapeutic relevance that explain why these patients do not adequately respond to IVIg and steroids.³³

The new information on IgG4-ND published in *N2* last year, started in the January issue with a multicenter study lead by Martín-Aguilar et al. on the largest series of patients with autoimmune nodo/paranodopathies and IgG4 antibodies to neurofascin-155, that highlighted the distinct clinical, laboratory, and therapeutic profile of these patients.³⁸ In a large series of 40 patients fulfilling the CIDP criteria, the patients had a distinct clinical profile characterized by progressive sensorimotor, distal more than proximal weakness of upper and lower extremities, an intention or action tremor, sensory ataxia in 75%, and cranial nerve involvement (mostly facial palsies and bilateral optic neuritis) in 30%. Importantly, more than 80% of the patients did not respond to IVIg or steroids but responded only to rituximab, confirming the original observation by Querol et al.³⁹ In all rituximab-treated patients, the IgG4 antibody titers substantially decreased correlating with clinical response, suggesting that specific antibody titers may serve as a guide for reinfusion decisions. Because NF155 is expressed in the central and peripheral nervous systems, Pegat et al.⁴⁰ showed in an important case report that anti-NF155 antibodies can be also associated with a demyelinating disease concurrently affecting both the CNS and the PNS. Furthermore, in a large series of patients with nodo-paranodopathy, Appeltshauer et al.⁴¹ showed a higher incidence (33%) of diabetes and a 3.4-fold higher risk of diabetes mellitus in these patients compared with the general population. Because IgG4-related diseases occur after chronic antigenic exposure³³ and diabetes may expose paranodal targets to the adaptive immune response, it was proposed that diabetes mellitus might be a potential risk factor predisposing to developing nodo-paranodopathy, especially since diabetes preceded the onset of neuropathy.⁴¹ The information is of relevance not only to patients with nodopathy but also to all IgG4-ND where it is now important to examine whether they are also connected with a higher incidence of diabetes mellitus.

A major dilemma has been the reasoning of why the IgG4-ND, not only the patients with nodopathy but also MuSK-MG, in contrast to their IgG1-3-associated counterparts, exhibit most of the times poor response to IVIg and inadequate response to steroids or plasmapheresis, but excellent response to anti-B-cell therapies, like rituximab.^{33,38,39} As pointed out by Dalakas,³³ this is of major importance to clinical neurologists to initiate the proper immunotherapy from the outset because most patients with IgG4-ND clinically present similarly to their IgG1-3-associated identical syndromes, and they are almost always treated with conventional immunotherapies of steroids,

IVIg, plasmapheresis, and oral immunosuppressants until recognized in retrospect that they do not adequately respond, questioning not only the diagnosis but also the associated autoimmunity.

The reasoning and consequences of the IgG4 in inducing dysfunction of the target antigens not responding to commonly used IVIg were elaborated by Dalakas in the January issue⁴² who pointed out that the IgG4s have a unique structure because their 2 heavy and light chains are joined by non-covalent bonds. As a result, the IgG4s cannot cross-link identical antigens, but they continuously undergo half-antibody Fab-arm exchange recognizing the antigen only with 1 arm, being functionally monovalent and bispecific^{33,42}; this is in contrast to the IgG1-3 antibody subclasses, which are monospecific and bivalent, because they bind the same antigen with 2 identical antigen-binding sites. Consequently, the IgG4s, by recognizing the antigen only with 1 Fab arm, cannot cause high concentration of antigen-bound molecules at their targets, being unable to engage in cross-linking and internalization of targeted antigen.^{33,42} These IgG4 effects are reflected in their 2 unique binding peculiarities; first, they cannot bind to C1q complement component to activate the complement cascade, and second, they bind to Fc receptors deferentially having reduced capacity to bind the inhibitory Fc γ receptor (Fc γ RIIB).^{33,42} In contrast to IgG1-3 subclass, therefore, the IgG4 antibodies have noninflammatory properties being unable to form cross-linked immune complexes to degrade their targeted antigen and inadequate to activate cellular or complement-mediated immune responses.^{33,42} Because complement inhibition and upregulation of Fc γ RIIB expression are the 2 main functions by which IVIg exerts its benefits,^{42,43} IVIg is ineffective in IgG4-ND because these key immunoinflammatory functions are irrelevant to the mechanistic effects of IgG4 antibodies. Furthermore, in patients with IgG1-3 antibody subclasses, IVIg exerts additional beneficial effects via idiotypic antibodies, an action also irrelevant to IgG4-ND because IVIg contains only 0.7%–2.6% IgG4 and its idiotypes, being of IgG1-3 subclass, cannot effectively neutralize IgG4 antibodies.^{42,43} In contrast, rituximab, by targeting memory B cells and IgG4-producing CD20-positive short-lived plasma cells, induces long-lasting clinical benefits. Rituximab is therefore, the preferred treatment in IgG4-ND because it effectively targets the production of pathogenic IgG4 antibodies.^{33,42,44} The impressive efficacy of anti-B-cell therapies has been shown in large series of patients with nodopathies^{38,39} and myasthenia gravis with anti-MuSK antibodies,⁴⁴ but also in several patients with LGII and CASPR2-associated autoimmune disorders.^{33,34}

Valency and the need to identify an insidious IgG4 subclass switch have been also pointed out by Dalakas to explain a change in response to therapies.^{33,42} Immunoglobulin subclass switch can often occur late in the immune response, but suspecting an insidious subclass switch from IgG1-3 to IgG4 may be of clinical consequence regarding response to therapies, especially to IVIg because a patient previously responding to IVIg

becomes IVIg unresponsive.^{33,42} This has been noted in patients with nodal CIDP who stopped responding to IVIg when switched from IgG3 antibody subclass against CNTN1/CASPR1 to IgG4 against CASPR1⁴⁵; the reverse has also occurred in MuSK-MG where a subclass switch from IgG4 anti-MuSK antibodies to IgG1 was associated with stable remission and response to steroids, as commonly seen in AChR-MG.^{33,44} As pointed out,^{33,42} vigilance is especially needed in LGII and CASPR2 and in IgLON5 and DPPX autoimmunities because these patients have antibodies either of the IgG1-3 or of the IgG4 subclass, and a subclass switch may be more likely to occur due to chronic antigenic stimulation. Finally, the IgG4 valency may also play a role on the pathogenicity of these antibodies, as explored by Jentzer et al.,⁴⁶ who studied the in vitro potency of monovalent IgG4 anti-neurofascin-155 (Nfasc155) antibodies into becoming functionally bispecific and monovalent via the Fab-arm exchange process. It was demonstrated that a proportion, from 7% to 78%, of anti-Nfasc155 IgG4 antibodies can become monospecific and bivalent exerting pathogenicity while their transformation into functionally monovalent form can decrease paranodal alterations. Although these in vitro observations were not explored in a clinical setting to substantiate their clinical value for prognosis or response to treatment, the observations strengthen the view that not only a subclass switch to IgG4 but the IgG4 valency via Fab-arm exchange can also dictate pathogenicity, which is applicable to the immunotherapeutic responses observed in all IgG4-ND.

The global COVID-19 pandemic that emerged in late 2019/early 2020 has caused unprecedented challenges for individuals and societies as a whole while individual burden might have been perceived as higher by people with a compromised immune system. In particular, there was (and still is) anxiety among patients with autoimmune neurologic conditions, many of whom are on immunomodulatory or immunosuppressive therapy, regarding a potential increased risk for developing COVID-19 or a more severe clinical course of the disease. There is also concern among physicians regarding whether immunotherapy should be continued due to the COVID-19 threat. The advent of several efficacious vaccines against SARS-CoV2 raised questions about the efficacy of these vaccines in immunocompromised people.

Numerous studies have addressed these questions over the past 2 years, some of which were published in *N2*. Although these studies were mostly nonrandomized uncontrolled case series or registry studies, they nonetheless have provided us with a relatively consistent picture of the risk of SARS-CoV2 infection and severe disease course in patients with MS, neuromyelitis optica spectrum disorders (NMOSD), and others.

In the January 2022 issue of *N2*, Olivé-Cirera et al.⁴⁷ examined whether children receiving immunotherapy for neuro-immunologic disorders had (1) increased susceptibility to SARS-CoV2 infection or to develop more severe forms of COVID, (2) increased relapses or autoimmune complications

if COVID infected, and (3) changes in health care delivery during the pandemic. Overall, 153 children were retrospectively assessed using a survey that covered the period from March 2020 to March 2021. Among the 153 children, 79 (52%) were on immunosuppressive treatment. COVID-19 was suspected or confirmed in 17 (11%) patients (all with mild symptoms), with a frequency similar in patients treated with or without immunosuppressants (14% vs 8%). The frequency of neurologic relapses was also similar in patients with and without COVID-19 (18% vs 21%). Factors associated with COVID-19 included having cohabitants with the infection and lower blood levels of vitamin D. Return to face-to-face schooling or mask type did not influence the risk of infection. Most patients/families (92%) were satisfied with the change of clinical visits from face to face to remote. Overall, in this cohort of children with neuroimmunologic disorders, the frequency of COVID-19 was low and not affected by immunotherapy.

A systematic review⁴⁸ published in May 2021 comprising 87 studies with 4310 patients with MS and confirmed/suspected COVID-19 suggests that although the overall mortality rate from COVID-19 did not appear to be increased in people with MS, higher hospitalization and mortality rates occurred in patients with no disease-modifying therapies, followed by patients on B-cell depletion. A single-center retrospective study from Barcelona with 407 patients found almost 2-fold higher incidence rates of COVID-19 in persons with MS (pwMS) compared with the general population, although disease courses were mostly mild despite comorbidities and the use of disease-modifying therapies.⁴⁹ A retrospective multicenter registry study from Spain with 326 patients with MS with confirmed or suspected COVID-19 showed that older male patients with MS with comorbidities, longer disease course, higher disability, and progressive disease were more likely to have severe SARS-CoV2 infections.⁵⁰ However, the mortality rate of 2.1% in this cohort was lower than in other registries and what was reported from the general European population at that time.⁵¹ A large case-control study from Italy matching 779 pwMS with confirmed COVID-19 and 1,558 pwMS without COVID-19 assessed risk factors for getting COVID-19 in pwMS.⁵² In several statistical models, comorbidities, female sex, and younger age were found to associate with a higher risk of contracting COVID-19, as also occurred in patients receiving natalizumab (OR 2.38). In line with these studies, registry data from the United States (New England) reported a case fatality rate of 4.4% and identified age and comorbidities as independent risk factors for hospitalization with COVID-19 in 91 patients with CNS demyelinating diseases, the majority of them pwMS.⁵³ In a retrospective case-cohort study, Sormani et al.⁵⁴ compared COVID-19-related outcomes in 1,362 pwMS with the age- and sex-matched Italian population. In this study, risk ratios for severe events (hospitalization, intensive care unit admission and death after COVID-19) in pwMS with an EDSS >3 and ≥1 comorbidity were about twice as high as in the general population, while in pwMS with an EDSS ≤ 3 and no comorbidity an increased

hospitalization rate was found in patients who were on B cell-depleting therapies.

The COVID-19 in MS Global Data Sharing Initiative in an impressive sample size of 5,648 pwMS with confirmed (83.4%) or suspected COVID-19 corroborated the findings of previous smaller or single-center studies; again, male sex, older age, progressive MS, and higher disability, as well as the use of ocrelizumab and rituximab, were associated with COVID-19 severity.⁵⁵

A few studies have dealt with immune responses to SARS-CoV2 in convalescent COVID-19 pwMS. In a retrospective study from Spain in 145 convalescent COVID-19 pwMS, 121 were positive for SARS-CoV2 antibodies,⁵⁶ and 25 of 42 patients presented a cellular response (interferon gamma) to SARS-CoV2 up to 13 months after COVID-19 infection. Although pwMS treated with B cell-depleting agents had lower antibody titers than those on other immunotherapies, severe COVID-19 and a longer interval from last infusion raised the likelihood of a humoral response. Five of 7 B cell-depleted patients without antibody response to SARS-CoV2 were able to mount cellular responses. Another study from France⁵⁷ that included 61 pwMS on different immunotherapies and with available SARS-CoV2 serology after COVID-19 showed lower anti-SARS-CoV2 immunoglobulin G indices in patients on fingolimod or B cell-depleting agents compared with patients on other immunotherapies and untreated patients. To address concerns of blunted immune responses to SARS-CoV2 in patients on B-cell depletion, Rolfe et al.⁵⁸ in a multicenter retrospective study from Germany compared patients with RRMS on extended-interval dosing of ocrelizumab (EID, defined as ≥4-week delay of dose interval) with a standard-interval dosing (SID) during the same period. Of 318 pwMS enrolled, 116 were treated with an EID (median delay 8.68 weeks). The rate of relapse-free patients at 3 months after last infusion was comparable between groups (90.1% SID; 90.5 EID), as were the proportion of patients with 3-month confirmed disability progression (8.9% SID; 9.5% EID) and with MRI progression (4.5% SID; 6.9% EID). A multivariate logistic regression revealed no association between treatment regimen (EID or SID) and a no evidence of disease activity status at follow-up. The authors conclude that deployment of EID for ocrelizumab-treated patients could serve as potential risk mitigation strategy in the era of the COVID-19 pandemic.

In light of the emerging individual and societal burden related to long-term sequelae of COVID-19,⁵⁹ a study by Garjani et al.⁶⁰ is insightful by assessing this burden in pwMS from the United Kingdom. Of almost 8,000 patients who participated in an online study by the UK MS Register, 599 reported COVID-19. Nearly 30% had long-lasting COVID-19 symptoms for ≥ 4 weeks and 12.4% for ≥12 weeks. Risk factors for lower likelihood of recovery from COVID-19 were female sex, pre-COVID EDSS ≥7, and probable anxiety/depression before COVID-19.

Other neuroimmunologic disorders have also been investigated in the context of COVID-19. Newsome et al.⁶¹ reported data from the COViMS Registry comprising 77 patients with NMOSD and 20 patients with myelin oligodendrocyte glycoprotein–associated disease (MOGAD) and COVID-19. The majority of patients with NMOSD were on rituximab when diagnosed with COVID-19, 9.1% were admitted to the ICU, and 8 (10.4%) died. The only risk factor for a poorer COVID-19 outcome was the presence of ≥ 1 comorbidity (OR 6.0, 95% CI 1.79–19.98). By contrast, there were no deaths in the MOGAD cohort and no risk factors for ICU admission or ventilation emerged. However, the authors acknowledged the small sample size in the MOGAD cohort. A Brazilian multicenter study⁶² with 2,061 persons with NMOSD documented by neurologists using a web-based case report form found only 34 COVID-19 cases (18 confirmed and 16 probable). In this study, the odds of hospitalization and ICU admission were higher than in the general Brazilian population, whereas the death rates were not substantially different; only 1 patient with NMOSD died. NMOSD-related disability, type of immunotherapy, and comorbidities were not associated with COVID-19 outcome; however, 5 of 34 patients (15%) developed relapse or pseudorelapse during or after SARS-CoV2 infection.

Fortunately, vaccines against COVID-19 were available from late 2020/early 2021 and particularly recommended for pwMS and other neuroinflammatory disorders.⁶³ However, concerns arose as to the efficacy of the vaccines in immunocompromised patients, especially those on B cell–depleting agents. Several articles in *N2* have dealt with COVID-19 vaccinations. A single-center study from Spain investigated immune responses to the full schedule of mRNA vaccines in a cohort of 99 patients with myasthenia gravis, 87 of whom mounted a humoral response and 72 a T-cell response to SARS-CoV2.⁶⁴ The combination of prednisone with other immunosuppressants was associated with lower seroconversion ratios and lower T-cell response ratios. Another multicenter study from the Netherlands included immune responses after the 3rd vaccination with mRNA vaccines.⁶⁵ In a small sample of ocrelizumab-treated pwMS, a third vaccination ($N = 8$) boosted T-cell responses, although there was no additive effect on the maximal T-cell response. By contrast, patients treated with fingolimod failed to mount T-cell responses to SARS-CoV2 after the second ($N = 12$) and third ($N = 9$) vaccinations, a finding in line with another study from Germany.⁶⁶ Not surprisingly, the timing of vaccination against SARS-CoV2 in relation to B-cell depletion in pwMS has an effect on cellular and humoral immune responses to the vaccine as shown in a study that included 133 pwMS on anti-CD20 monoclonal antibodies.⁶⁷ Vaccination reactogenicity was reported by 719 pwMS who received the AstraZeneca, Pfizer-BioNTech, or Moderna vaccines, using an online people-powered research network (iConquerMS).⁶⁸ The most common reactions after the first dose were pain at the injection site (54%), fever (34%), headache (28%), and malaise (21%); the frequency of these

reactions was comparable to that of the general population, and they were mostly self-limiting.

COVID-19 is associated with a broad range of acute and post-acute vascular, inflammatory, and metabolic CNS complications; in addition, direct neurotoxic effects of SARS-CoV2 have been proposed. Several studies published in *N2* in the past 2 years have contributed to a mechanistic understanding of these still largely unknown pathomechanisms. Bodro et al.⁶⁹ reviewed the presentations and mechanisms of CNS disorders related to COVID-19 in the January 2021 issue, whereas Hanson et al.⁷⁰ in the 2022 March issue reported an array of plasma biomarkers of neuropathogenesis in hospitalized and nonhospitalized patients and those with postacute sequelae. Plasma neurofilament light chain (NfL) and GFAP values were higher in patients with COVID encephalopathy than in the other cases investigated (hospitalized and nonhospitalized patients with neuro-PASC [neurologic symptoms as part of postacute sequelae of SARS-CoV2 infection]), and plasma SARS-CoV2 nucleocapsid antigen was detectable in some nonhospitalized patients 3 weeks after symptom onset, suggesting possible prolonged antigenic stimulation or latent infection as one mechanism of SARS-CoV2 neuropathogenesis.⁷⁰ In an intriguing autopsy study, Fuchs et al.⁷¹ found SARS-CoV 2 and ACE2 transcripts in epithelial cells of the choroid plexus and ependymal cells of the CSF-brain interface in a patient with MS who died of COVID-19 and a deceased non-MS COVID-19 control patient pointing to the choroid plexus as a critical CNS entry point for SARS-CoV2.

Although emerging infectious diseases such as COVID-19 that are associated with neuroinflammation and neurologic complications have generated enormous interest in recent years, there remains a critical need for predicting outcomes and managing neurologic complications from other globally pervasive infectious diseases.

Among these, bacterial meningitis is a global health burden with wide geographic differences in incidence (1–1,000/100,000) that is complicated by the emergence of multidrug-resistant bacterial strains.⁷² The disease burden is particularly high in under-resourced countries with limited access to childhood immunization and other health care resources. Acute and subacute neurologic complications of bacterial meningitis (hearing loss, hydrocephalus, cerebral edema, seizures, or stroke) are well recognized. Nonetheless, longer-term complications such as cognitive impairment, which may be associated with inapparent neuronal injury, are unpredictable and poorly understood mechanistically.⁷³ Robust neuroinflammation is considered to be a major driver of the hearing loss associated with bacterial meningitis, and adjuvant corticosteroids (but not noncorticosteroid adjuvants) in combination with antibiotics have proved to reduce the risk of hearing loss and some other neurologic deficits in adults and children.^{74–76} Predictive markers for neurologic outcomes,

including cognitive impairment, in bacterial meningitis are clearly needed.

In the December 2021 issue, Chekrouni et al.⁷⁷ examined levels of NFL in CSF obtained from 425 adult patients in The Netherlands with community-acquired bacterial meningitis and associated their Glasgow Outcome Scale (GOS) performance scores as a primary outcome measure of the predictive value of CSF NFL.⁷⁸ These patients were participants of the MeninGene study of outcomes of community-acquired bacterial meningitis in adults (\geq age 16 years) in the Netherlands, which began in 2006. An unfavorable outcome was broadly defined as a GOS score from 1 to 4, and a favorable outcome was defined as a score of 5.⁷⁸ Seventy-three percent of patients had either *Streptococcus pneumoniae* or *Neisseria meningitidis*, and neurologic sequelae (not directly assessed by the GOS) at the time of discharge included hearing impairment (29%), cognitive impairment (23%), cranial nerve palsies (15%), and focal cerebral deficits (14%). Notably, CSF NFL levels were higher in patients with unfavorable GOS scores (1–4) at discharge or in patients discharged with focal cerebral deficits, cranial neuropathies, or an admission Glasgow Coma Scale <14 . CSF NFL levels were higher in patients with pneumococcal meningitis compared with nonpneumococcal meningitis, indicating more severe injury in pneumococcal meningitis. The area under the curve (AUC) for predicting an unfavorable outcome was moderately robust (AUC = 0.69 (95% CI 0.64–0.74), with a cutoff value for CSF NFL of 681 pg/mL and a sensitivity and specificity of 63% and 67%, respectively. These levels of sensitivity and specificity are modest, and further study of NFL as an outcome predictor is necessary.

This study is important in linking neuronal injury in bacterial meningitis with clinical outcomes by assessing CSF NFL levels, a validated neuronal injury biomarker. The results are not surprising, and the implications are apparent. It potentially represents a first step in further defining the extent of inapparent neuronal injury that may escape detection by neuroimaging assessments (as in COVID-19), but it is only a first step. The Glasgow Outcome Scale estimates functional impairment in daily independence and social recovery commonly associated with traumatic brain injury,⁷⁹ and so other more appropriate neurocognitive assessment tools used in cognitive outcome studies should be applied. CSF sampling is impractical in routine clinical practice, and so confirming an association between plasma (or serum) NFL levels and outcomes in patients with bacterial meningitis is clearly a worthy goal for advancing additional research studies and future clinical applications. Notably, previous studies demonstrate strong associations between elevated plasma NFL levels and the diagnosis of amnesic mild cognitive impairment or Alzheimer disease (AD) and between plasma NFL and cognitive decline in older individuals without dementia.^{80,81} In addition, higher plasma (or serum) NFL levels associate with poorer short-term clinical outcomes in patients with severe COVID-19 without overt neurologic manifestations at the time of hospital discharge, although as of

now, there appears to be no predictive value for long-term neurologic deficits in patients with COVID-19.^{82–84} Longitudinal assessments of cognitive functioning and associations with plasma or serum NFL in patients surviving bacterial meningitis will be the next step in developing sensitive indicators of current and future adjuvant therapeutic approaches for reducing long-term neurologic complications.

It is now broadly accepted that inflammation plays a central role in neurodegenerative disorders. However, there are still relevant open questions about the implication of the innate and adaptive immune systems, the chronology of these responses (early vs late in the neurodegenerative process), and especially a need to disentangle beneficial from harmful signals in each disorder. In this sense, Wang and collaborators,⁸⁵ using the radiotracer [11C]PK11195, showed that microglial activation was increased in individuals with brain amyloidosis who progressed clinically within the AD continuum. Rocha et al.⁸⁶ used another radioligand, [11C]-ER176, to investigate microglial activation in Huntington disease (HD), demonstrating that only clinically manifest HD showed significant tracer uptake in the globus pallidus and putamen, associated with decreased volume in the same areas, which suggests a relative late phenomenon in the course of the disease, associated with disease progression. Even if the signal-to-noise ratios are different between tracers and AD and HD, both studies support the concept that activated microglia in key areas of the brain may be associated with clinical progression. Regarding the involvement of the adaptive immune system in neurodegenerative disorders, a study by Joshi et al.⁸⁷ showed CSF alterations in patients with Alzheimer disease, indicating that CD4⁺ T cell-mediated adaptive immune responses were altered. Li et al.⁸⁸ also showed dysregulation of peripheral CD4⁺ T cells, CD8⁺ T cells, and CD19⁺ B cells in patients with Parkinson disease, partially associated with motor severity. These findings suggest that several alterations in the immune system might be associated with clinical symptoms and support the investigation of immunomodulators in neurodegenerative diseases.

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