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## N2 year in review

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## N2 year in review

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2019 has been a very good year for our journal. N2 was included in MEDLINE and in June received its first impact factor, a competitive 7.353. We have been fortunate to recruit Dr. Marinos Dalakas to our team of International Associate Editors. Dr. Dalakas is Professor of Neurology at the University of Athens (Greece) and Jefferson University (Philadelphia, PA). His remarkable knowledge on inflammatory and autoimmune neuromuscular diseases will be a great asset to the journal. These accomplishments and successes would not have been possible without the growing number of readers, the increasing number of manuscript submissions, and the generosity of our reviewers who freely give their time to the journal. To all, we send our appreciation.

In the 2018 N2 Year in Review,<sup>1</sup> I wrote some comments related to how the immune checkpoint inhibitors (ICIs) had revolutionized the treatment of cancer. I noted the concern of several investigators about the immune-related adverse effects (irAEs) of these drugs, potentially leading to an increase in patients with autoimmune or paraneoplastic neurologic syndromes. This concern still exists, although a recent review indicated a relatively low number of irAEs that fulfilled criteria of paraneoplastic syndromes, including the presence of immune responses specifically directed against antigens expressed by the tumor and the nervous system (onconeural antigens).<sup>2</sup> Indeed, the authors identified only 14 reported cases (2 with Ma2 antibody-associated syndromes) that fulfilled these criteria. Much more frequent, however, were neurologic irAEs unrelated to these mechanisms (e.g., without onconeural antibodies) and mediated by other inflammatory or autoimmune responses, including polyneuropathy, Guillain-Barré syndrome, myasthenia gravis, aseptic meningitis, myelitis, or myositis.<sup>2,3</sup>

During this past year, several studies on ICIs have shown “adverse effects” (e.g., facilitating the occurrence of paraneoplastic syndromes), whereas other studies have shown “beneficial effects” such as the use of ICIs as potential treatments for progressive multifocal leukoencephalopathy (PML). In the November issue of N2, Vogrig et al.<sup>4</sup> retrospectively reviewed a cohort of 50 patients with Ma2 antibody-associated paraneoplastic syndromes and identified 6 who developed the syndrome after treatment with ICIs. None of these 6 patients had seminoma or testicular germ cell tumors, which were found in 25% of the rest of the cohort. The authors did not find differences between the neurologic features of the ICI-associated cases compared with the other anti-Ma2 cases. All 6 patients were treated with steroids and removal of the ICI, and some received plasmapheresis or rituximab. Four of the patients died (3 from the neurologic disease and associated complications), and the other 2 had moderate to severe disability. During the 12-month period in which the 6 patients with ICI-associated anti-Ma2 syndromes were identified, a total of 17 patients were diagnosed with anti-Ma2 syndrome. Before this, the annual number of patients with anti-Ma2 syndromes diagnosed in this reference center was relatively stable with a median of 4 cases per year. Although the reason for the overall increase in the number of patients with anti-Ma2 syndrome is unclear, it is remarkable that almost 1/3 had



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From the ICREA-IDIBAPS Hospital Clínic, University of Barcelona (J.D.), Spain; University of Pennsylvania (J.D., D.L.K.), Philadelphia; University of Athens Medical School (M.C.D.), Athens, Greece; Jefferson University (M.C.D.), Philadelphia, PA; Charite University Hospital (F.P.), Berlin, Germany; and Department of Neurology (S.S.Z.), University of California, San Francisco.

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received ICIs. Overall, the finding suggested that we should remain vigilant for an increase of other paraneoplastic neurologic syndromes as ICIs are increasingly available for a wide variety of cancers. Given that low titers of paraneoplastic antibodies (e.g., Hu, Ri, or Yo, among others) occur in some patients with cancer without paraneoplastic syndromes,<sup>5–7</sup> several investigators have suggested that testing for these antibodies before treating patients with ICIs may help to identify those that are at risk of developing paraneoplastic syndromes. This can be particularly useful for patients with tumors that have propensity to associate with paraneoplastic syndromes, such as small-cell lung cancer.<sup>2</sup>

PML is a severe disease of the brain that usually affects immunosuppressed patients and results from reactivation of the polyomavirus JC (JCV) and infection of oligodendrocytes and, to a lesser extent, astrocytes. Because there are no specific anti-JCV drugs, the only treatment strategy is to restore the function of the immunologic system. Although ICIs were initially designed to enhance tumor cell-specific responses, anti-program cell death-1 monoclonal antibodies (PD1-abs) have recently been used to treat PML. In the first group of publications that included a total of 10 patients treated with a PD1-ab, 7 showed mild to substantial improvement, 1 who was stable before initiating the treatment remained stable, and 2 deteriorated.<sup>8–10</sup> Two additional patients were recently reported in N2, and both showed no improvement with PD1-ab. One was considered to be a good candidate for the drug (young age, with a primary immunodeficiency syndrome, not previously treated with immunosuppression, limited MRI lesions, and low CSF viral load), was treated with PD1-ab at very early stage of the PML, and received more doses than those reported in patients who improved, but had relentless progression to death.<sup>11</sup> The second case had several immunosuppressive disorders, a very high viral load, and died after 2 infusions of the PD1-ab. An interesting observation was that this patient had fewer progenitor-exhausted T cells and more terminally exhausted T cells compared with a previously reported patient who had a favorable outcome.<sup>12</sup> Thus, the authors postulated that patients with PML deprived of progenitor-exhausted T cells (which have the ability to revert from exhausted to active) may be those who do not respond to PD1-ab. In addition, preliminary data from both patients suggested that JCV-specific CD4<sup>+</sup> T cells may be more important than CD8<sup>+</sup> T cells in keeping JCV on check.<sup>12</sup>

Moving to a different topic, a study of a series of 17 patients with serum glycine receptor (GlyR) antibodies was published this year in N2. Thirteen of these patients developed stiff-person syndrome accompanied by parkinsonism or cerebellar signs. In addition, 10 patients had various visual symptoms (spider web-like images, palinopsia, photophobia, hallucinations, and synesthesia, among others), and another 3 presented with primarily autoimmune epilepsy with psychiatric symptoms.<sup>13</sup> These findings are in contrast with a series of 14 patients in which the most prevalent symptoms were seizures and epilepsy in 8 cases and progressive encephalomyelitis with

rigidity and myoclonus (PERM) in only 3. Among the remaining 3 patients, 1 had global fatigable weakness with sustained clonus, another had laryngeal dystonia, and the other had hemiballismus with tics.<sup>14</sup> Of interest, the frequency of the symptoms in this study is actually different from that reported in a review by the same authors of 187 previously reported patients, in which 48% had PERM, 22% epilepsy, and the remaining 30% mixed phenotypes (cerebellar ataxia, movement disorders, demyelination, encephalitis, and cognitive dysfunction).<sup>14</sup> To understand the discrepancies of these 2 studies,<sup>13,14</sup> we need to examine the features they have in common. For example, neither of them examined systematically patients' CSF; in one study, the CSF was not examined,<sup>13</sup> and in the other, only 3 of 14 patients had the CSF examined (2 of them without antibodies).<sup>14</sup> Moreover, as soon as the GlyR antibodies were identified in the patients, both studies took at face value that the symptoms were linked to the antibodies. There was little consideration for the fact that GlyR antibodies can be detected in serum of patients with many different disorders (e.g., AQP4 or MOG autoimmunity, MS, patients with cancer without neurologic diseases, opsoclonus-myoclonus, or cerebellar ataxia).<sup>15–17</sup> Thus, it is not surprising that if enough patients with the same disorder are investigated, a small percentage of seropositive cases will be identified. For example, in another series of 238 patients with epilepsy, 13 (5%) had GlyR antibodies in serum.<sup>18</sup>

These considerations are applicable to most autoimmune encephalitides associated with neuronal surface antibodies. Indeed, bearing in mind that (1) antibodies against neuronal cell-surface antigens associate with autoimmune encephalitis or myelitis, (2) patients may harbor antibodies only in CSF, and (3) CSF neuronal antibodies are more disease specific than serum antibodies, it is remarkable that in 2019, there are still studies on autoimmune encephalitis in which CSF testing is not considered. The lack of comprehensive studies (e.g., study of serum and CSF and use of appropriate controls) interferes with the assessment of true associations between antibodies and diseases, promotes uncertainty (any antibody can cause any symptom), and may have important consequences in the diagnosis and treatment of patients. These may include not treating patients who should be treated (e.g., patients in whom antibodies are present in CSF but missed with serum only testing<sup>19</sup>) or using immunotherapy in patients who may not have an autoimmune disease (e.g., patients with antibodies only in serum and unrelated neurologic symptoms). This is reminiscent of the history of VGKC complex antibodies and its ever increasing “expansion of the phenotype” due to resistance to accept that their utility was more than questionable, leading to frequent misdiagnosis and exposure of patients to unwarranted therapies.

In recent years, several autoimmune, multisystemic, or fibroinflammatory disorders have been identified based on the presence of antigen-specific autoantibodies of the IgG4 subclass.<sup>20</sup> In Neurology, IgG4 antibodies are largely represented by 2 immunologically distinct neuromuscular diseases, MuSK

antibody-positive myasthenia gravis (MuSK-MG) and antinodal/paranodal antibody-mediated CIDP. These disorders are clinically important because they exhibit poor response to IVIg or plasmapheresis, and they are immunologically unique because IgG4 antibodies cannot bind complement or many Fc receptors on immune cells, and they are able to exchange Fab-arms with other IgG4 molecules. As a result, IgG4 antibodies are viewed as functionally bispecific and monovalent, unable to engage in antigen cross-linking and internalization. Although their immunopathogenicity is not completely understood, there is convincing evidence, mostly from autoimmune neuromuscular diseases studies, that IgG4 antibodies function by blocking enzymatic activity or protein-protein interactions of their target antigens. The past year, the field has further advanced with new information regarding the association of Ig4 antibodies with distinct neurologic phenotypes and their effect on antigenic targets.

Huijbers et al.<sup>21</sup> in the May issue provide new insights on the function of IgG4 antibodies in MuSK-MG. They generated monovalent Fab fragments from patient-derived recombinant IgG4-MuSK antibodies and investigated the functional effects of bispecificity and monovalency of Fab-arm-exchanged antibodies in a tissue culture model. They report that recombinant monovalent MuSK IgG4 engages in bivalent monospecific antibody-antigen interactions. Although the monovalent anti-MuSK blocks MuSK signaling and AChR clustering, the bivalent anti-MuSK stimulates MuSK phosphorylation and partially induces AChR clustering. It seems that the IgG4 MuSK antibodies require Fab-arm exchange of IgG4 to be more functionally monovalent to become pathogenic; in other words, depending on the number of MuSK binding sites, MuSK antibodies can either act as MuSK agonist or antagonist. The work has practical implications in antibody-mediated autoimmunity because inhibition of Fab-arm exchange might have therapeutic potential not only in MuSK MG but also in other IgG4-mediated autoimmune disorders.

A breakthrough in CIDP autoimmunity has been the remarkable observation that some patients, especially with an atypical CIDP phenotype highlighted by severe subacute neuropathy, tremor, and sensory ataxia, do not respond to IVIg or plasmapheresis and have IgG4 antibodies to nodal/paranodal antigens directed against neurofascin-155 (Nfasc155), neurofascin-140/186 (Nfasc140/186), contactin-1 (CNTN1), and contactin-associated protein-1 (Caspr1).<sup>22</sup> These major observations were now confirmed in a larger multicenter study providing further data on the IgG4 phenotypes and their pathogenicity. Cortese et al.<sup>23</sup> in the January issue found the incidence of these antibodies in 5.5% among 342 Italian patients with CIDP; of those, 9 had antibodies against the paranodal Nfasc155, 1 against both the nodal Nfasc140/186 and the paranodal Nfasc155, 3 against CNTN1, and 6 against Caspr1. Anti-Caspr1 IgG4 was shown to penetrate paranodal regions and disrupt the integrity of the Nfasc155/CNTN1/Caspr1 complex, consistent with the effect of IgG4 in disrupting protein-protein interactions of the targeted antigens.<sup>21–23</sup> A

useful observation that emerged from this study is that IgG4 antinodal/paranodal antibodies were not only restricted to patients with the originally described atypical CIDP phenotype,<sup>24,25</sup> but they are relevant to all patients with CIDP fulfilling the EFNS/PNS criteria. The same message was reiterated in the September issue by Carrera-Garcia et al.<sup>26</sup> who reported the first child with relapsing CIDP and IgG-4 antibodies against contactin-1, poorly responding to IVIg. Both studies strengthen the view that testing for antibodies against nodo-paranodal proteins is needed for all adults and pediatric patients with CIDP refractory to conventional therapies.

The complexity of nodal/paranodal antibodies was further highlighted in 2 patients with autoantibodies against 2 different neurofascin (NF) isoforms.<sup>27</sup> In contrast to the aforementioned characteristic phenotype associated with antibodies against the paranodal NF-155-specific Fn3Fn4 domain, a different phenotype was identified in patients who had IgG3 antibodies against all the NF isoforms. The anti-pan-NF-associated CIDP was characterized by a more aggressive course, tetraplegia and cranial nerve involvement indicating that IgG3 antibodies directed against both NF epitopes, the paranodal NF-155 and the nodal NF-140/186, define a different clinical phenotype. In contrast to IgG4, IgG3 autoantibodies activate complement and have a strong proinflammatory effect, hence their association with more severe disease. Although the underlying mechanism of multiple epitopes remains unclear, intramolecular epitope spreading could be an explanation, as seen in other autoimmune diseases. Collectively, these studies strengthen the clinical importance of antinodal/paranodal proteins not only in defining phenotypes but also in highlighting that these patients have a severe disease poorly responding to IVIg and plasmapheresis necessitating early intervention with more effective therapies aiming at downregulating the humoral immune response. Rituximab is currently the preferred agent for all IgG4-related diseases,<sup>20,28</sup> and it is likely effective by depleting the Nfasc155, Nfasc140/186, CNTN1, Caspr1, and MuSK-reactive B cells.

At least 12 other autoimmune multisystemic or lymphoproliferative diseases are hallmarked by the prototypic IgG4-related syndrome (IgG4-RD).<sup>20</sup> Neurologic manifestations can be seen as part of the multiorgan fibroinflammatory involvement, mostly represented by meningeal and spinal cord disease and often presented as hypertrophic pachymeningitis and hypophysitis. In this context, Levraut et al.<sup>29</sup> in the July issue report on 2 cases of hypertrophic pachymeningitis and suggest that PET imaging increased intrathecal IgG4 levels, and histopathologic studies are essential in arriving at proper diagnosis and early therapy initiation.

In persons living with HIV (PLWH), the persistence of the virus within the CNS and in lymphoid tissues continues to be a major challenge in the effort to “cure” HIV infection and to prevent complications such as HIV-associated neurocognitive disorders.<sup>30</sup> Although suppressive antiretroviral therapy (ART) effectively prevents the development of CNS

opportunistic infections and fulminant HIV encephalitis, it does not fully protect against the development of neurocognitive dysfunction.<sup>31</sup> Therefore, neuroprotective therapies to use in conjunction with ART are being sought, as are plasma and CSF biomarkers that might identify patients at risk of HIV-driven neurocognitive dysfunction.

In the May 2019 issue of *N2*, a review by Ambrosius et al.<sup>32</sup> discusses the potential use for anti-neuroinflammatory drugs as adjunctive agents for treatment and/or prevention of HIV-associated neurocognitive disorders in PLWH. Evidence suggests that even during effective ART suppression of HIV infection (i.e., undetectable plasma and CSF HIV RNA), immune activation, oxidative stress, and inflammation persist to some degree within the CNS and also within peripheral tissue compartments.<sup>33</sup> In this sense, the neuropathogenic mechanisms that characterize virally suppressed HIV infection of the CNS resemble those of MS, and drugs that target these pathways and that can be used in conjunction with ART are being investigated. Furthermore, such drugs might be expected to have beneficial effects not only within the CNS but also within other tissue compartments (e.g., cardiovascular system) affected by immune activation, oxidative stress, and inflammation in PLWH. Among those MS drugs discussed by Ambrosius et al. as potential candidates are several developed for the treatment of MS, including dimethyl fumarate (anti-inflammatory, antioxidant; use in PLWH also discussed in reference 34), fingolimod (inhibitor of T-lymphocyte trafficking), teriflunomide (inhibitor of T- and B-lymphocyte proliferation), and natalizumab (inhibitor of T-lymphocyte trafficking). Each of these drugs indeed targets critical points in the HIV neuropathogenesis cycle, including the trafficking of infected T lymphocytes out of lymph nodes and across the blood-brain barrier, proinflammatory signaling (NF- $\kappa$ B and others), and production of reactive oxygen species, among others. The ability of fingolimod to retain antiviral T lymphocytes in lymphoid tissues in the simian immunodeficiency virus (SIV) rhesus macaque model of HIV pathogenesis has generated interest in its potential to limit SIV/HIV persistence in situ.<sup>35</sup> Additional studies are certain to follow.

However, resistance to the use of such immunomodulating and/or immunosuppressive MS drugs associated with lymphocytopenia for treatment in PLWH appears to be common among neurologists, and concerns about possible complications deserve robust discussion. It should be noted, however, that PLWH who are virally suppressed by ART sustain CD4<sup>+</sup> T-lymphocyte counts with long-standing immunosuppressive therapy after kidney and liver transplantation, without increased risk of opportunistic infections or premature death (reviewed in Ref. 36). As chronic inflammation in PLWH and associated end-organ effects become more aggressively targeted, one may anticipate that immunomodulating MS drugs will receive more and more attention for use in PLWH.

Attending to the need for identification of associative and predictive biomarkers for the development of HIV-associated

neurocognitive disorders, Gisslen et al.<sup>37</sup> (January 2019 *N2* issue) have correlated CSF levels of soluble TREM2 (a specific macrophage/microglia activation marker) with CSF levels of NFL in PLWH. Archived CSF samples from 112 adult PLWH and 11 HIV-negative controls (all collected between 1999 and 2014, irrespective of neurocognitive status and ART suppression) were analyzed for sTREM2, neopterin (a marker of activation of macrophages, microglia, and astrocytes), and NFL. CSF sTREM2 levels correlated strongly with neopterin and even more strongly with NFL. The correlation of CSF sTREM2 with severe neurocognitive dysfunction, seen typically in uncontrolled CNS HIV infection and not in ART-suppressed infection, suggests that it will not be a sensitive biomarker for neurocognitive dysfunction in ART-suppressed patients. Furthermore, although 36% of patients on suppressive ART had elevated CSF neopterin compared with controls, none of those patients had elevated sTREM2. Because TREM2 is considered specific to cells of monocyte lineage, the investigators concluded that a significant component of the residual CNS inflammation present in ART-suppressed PLWH may result from activation of cells (astrocytes and lymphocytes) other than macrophages and microglia. This study has specific value in providing evidence for multiple cellular contributors to chronic CNS inflammation in PLWH, and it suggests that assessing multiple CSF biomarkers (sTREM2, neopterin, NFL, and others) may be necessary for accurately profiling disease progression, clinical risk, and response to neuroprotective therapies.

Finally, in the March 2019 issue of *N2*, Kamtchum-Tatuene et al.<sup>38</sup> presented an interesting study of ischemic stroke risk in PLWH in sub-Saharan Africa, which linked elevated plasma levels of ICAM-1 (activation of endothelia) with HIV infection independently of stroke and other risk factors (ART use, diabetes, and hypercholesterolemia). Because this study involved only 61 stroke cases (19 PLWH) and 168 nonstroke controls (32 PLWH), it might be underpowered to detect the expected association between HIV and stroke risk, but the detection of significantly elevated plasma ICAM-1 in individuals receiving ART suggests persistent endothelial activation in ART-treated PLWH. However, this study adds to growing evidence supporting the potential pathogenic effects of chronic inflammation and activation of multiple CNS-relevant cell lineages (endothelia, macrophages, microglia, and astrocytes) in ART-suppressed PLWH, and it also supports the importance of studying of HIV-associated CNS disease risks as a worldwide issue.

In 2019, several articles published in *N2* have made relevant contributions to the areas of pathogenesis, biomarkers, and treatment of MS. Individual MS risk is influenced both by genetic susceptibility and environmental factors, such as EBV infection, low vitamin D, smoking, obesity, and others.<sup>39–42</sup> Recently, alterations of the gut microbiome in MS through dietary habits have received increasing attention as possible link between potentially modifiable environmental factors and the immune system.<sup>43–46</sup> However, previous human studies

were limited by small sample sizes, enrollment of patients with longer disease duration, and confounding effects of immunomodulatory therapy, thus precluding conclusions regarding the causal influence of the gut microbiome on the MS immune system, or in other words, leaving the “chicken or egg dilemma” unresolved.<sup>47</sup> Katz Sand et al.<sup>48</sup> investigated in a cross-sectional study the effects of 2 widely used disease-modifying drugs, glatiramer acetate (GA) and dimethyl fumarate (DMF), on gut microbial composition. Stool samples from 168 participants with MS from 2 MS centers (75 treatment naive, 33 on DMF, and 60 on GA) were collected, and 16S rRNA amplicon sequencing was performed in parallel with immunophenotyping from patients’ whole blood (at 1 center only) to validate the expected effects of DMF and GA. Both drugs were associated with alterations of the fecal microbiota composition, namely a decreased relative abundance of the Lachnospiraceae and Veillonellaceae families. Moreover, in patients treated with DMF, there was a decreased relative abundance of the phyla Firmicutes and Fusobacteria and the order Clostridiales and an increase in the phylum Bacteroidetes. Both drugs differentially affected metabolic pathways with some overlap. This study demonstrates that DMDs may have a profound impact on the gut microbiome in MS, which has to be taken into account for future studies.

Two other studies have dealt with therapeutic modulation of environmental factors in MS. Modulation of diet was proposed to have beneficial impact on tissue damage and disease severity in animal models of MS.<sup>49,50</sup> Brenton et al.<sup>51</sup> have now conducted a pilot study to assess the safety and tolerability of a type of ketogenic diet in patients with relapsing-remitting MS (RRMS). Of 20 patients enrolled into this single-arm, open-label 6-month trial, 19 adhered to the dietary regimen for 3 months and 15 for 6 months. Body mass index, total fat mass, fatigue, and depression scores were significantly improved at the end of the study, and the proinflammatory adipokine leptin was reduced after 3 months on diet. Although this study was not designed to prove a beneficial effect of a dietary intervention on MS disease course, it has shown that nutrition interventions are feasible in MS with good adherence, thus warranting subsequent larger, randomized trials.

The second study by Camu et al.<sup>52</sup> adds to the contentious issue as to whether vitamin D supplementation is able to modify MS disease course.<sup>53–55</sup> The CHOLINE trial was a randomized, double-blind, placebo-controlled, parallel-group study in 181 patients with RRMS on stable immunomodulatory treatment with interferon beta-1a 44 µg SC 3 times weekly and at least 1 documented relapse during the previous 2 years.<sup>52</sup> Patients with low serum vitamin D (<75 nmol/L 25-hydroxy vitamin D) were eligible and were randomized 1:1 to either 100,000 IU of high-dose oral cholecalciferol or placebo every other week add-on to interferon beta over 96 weeks. The primary end point (change in the annualized relapse rate [ARR] at 96 weeks) was not met. However, in 90 patients (45 per group) who completed the 2-year follow-up, efficacy parameters (ARR, new T1 hypointense lesions, volume of T1

hypointense lesions on brain MRI, and EDSS progression) significantly favored the active intervention, whereas there was no difference between both completer groups with regard to new T2 and gadolinium-enhancing lesions and brain gray and white matter volumes. The rate of adverse events was similar between groups. Although the study was negative in respect to the primary end point, presumably due to lack of statistical power, and is therefore not able to provide an unambiguous answer to the question whether high-dose vitamin D supplementation beneficially modifies MS disease course, it backs current clinical management now adopted by many MS neurologists who supplement low vitamin D levels in their patients.

The year 2019 in *N2* has also provided us with some new insights into biomarkers to monitor disease course and immunotherapy in MS. Brain atrophy that is believed to reflect at least in part also the neurodegenerative component of MS and is detectable on a group level from earliest disease stages<sup>56</sup> has long been proposed as marker to measure progressive tissue loss over the course of the disease. Azevedo et al.<sup>57</sup> in a longitudinal study have now investigated the effect of normal aging on brain atrophy in MS. Brain MRIs from 520 patients with relapse onset MS and from 130 healthy controls, most of them with more than 1 measurement time point, were investigated. The rate of whole-brain atrophy attributable to MS changed significantly with age and decreased from –0.38% per year at age 30 years to –0.12% per year at age 60 years, whereas the slope of normal aging atrophy increased from 0.01% per year at age 30 years to –0.31% per year at age 60 years. Of interest, the rate of MS-specific thalamic atrophy decreased from –0.59% per year at age 30 years to –0.05% per year at age 60 years, whereas the rate of normal aging atrophy increased from –0.15% per year at age 30 years to –0.62% at age 60 years. By contrast, in the putamen and the caudate nucleus, the contributions of MS-specific atrophy and normal age did not change substantially over the age span. This study suggests that the trajectories of tissue loss attributable to MS and normal aging, respectively, may differ across brain regions, which has implications for the interpretation of brain volume changes in clinical trials and with immunotherapy.

Another emerging imaging technique to visualize and quantify neuroaxonal degeneration in autoimmune neuroinflammation is retinal optical coherence tomography that seems to be in closer proximity to clinical use in individual patients than brain atrophy measurements.<sup>58–60</sup> Cordano et al.<sup>61</sup> have now investigated the value of OCT-derived measures of retinal neurodegeneration to predict disability worsening in patients with MS. This retrospective study in 305 patients with various subforms of MS and a median follow-up time of 7.9 years between OCT scan and most recent EDSS grading evaluated the association of the baseline peripapillary retinal nerve fiber layer thickness (pRNFL) and the subsequent EDSS score. The authors report an increase in the EDSS score of 0.024 points, with each 1-µm decrease in the baseline pRNFL. Similar results were obtained when adjusting for the presence of previous optic neuritis episodes. In line with a previous report,<sup>62</sup> this

study shows that a pRNFL measurement may be useful to prognosticate disability as long as 6–9 years later. Despite some obvious limitations such as the use of the older time-domain OCT technology, the retrospective nature of the study, and the lack of a baseline EDSS score in all study participants, this work supports the use of OCT in clinical patient management as long as acquisition procedures comply with established quality criteria.<sup>63</sup>

Initial investigations leading to the development of the anti-VLA4 monoclonal antibody natalizumab (Tysabri) in MS therapy focused on its role in inhibiting CNS recruitment of T cells through the blood-brain barrier (BBB).<sup>64</sup> Because VLA4 is also expressed on B cells and monocytes, natalizumab treatment may affect function of those cells and possibly contribute to its therapeutic benefit. It is known that natalizumab treatment of patients with MS reduces accumulation of B cells in CSF.<sup>65</sup> Selective genetic deficiency of B-cell VLA-4 expression reduces CNS accumulation of B cells, proinflammatory Th17 cells, and monocytes in experimental autoimmune encephalomyelitis (EAE) induced by MOG protein, a model that requires B cells and leads to antigen-specific B-cell activation.<sup>66</sup> In the July issue of *N2*, Hussain et al.<sup>67</sup> reported on selective B-cell VLA-4 deficiency in a model of EAE that is dependent on T cells, but not B cells, and observed that although the absence of VLA-4 on B cells reduced CNS B-cell accumulation, it did not alter EAE susceptibility. Their exciting findings are consistent with previous work indicating that VLA-4 expression on B cells is important in regulatory B-cell (Breg) control of EAE<sup>68,69</sup> and collectively highlight how B-cell VLA-4 expression may promote pathogenic and regulatory roles of different B-cell subsets in CNS autoimmune disease, including MS. In the same issue of *N2*, Sucksdorff et al.<sup>70</sup> evaluated how natalizumab treatment of patients with MS influenced activation of microglia, resident CNS innate immune cells. Microglial activation was measured in 10 patients with MS using the 18-kDa translocator protein (TSPO)-binding radioligand [<sup>11</sup>C]PK11195 and PET imaging before and after 1-year treatment with natalizumab. Natalizumab treatment was associated with reduced microglial activation in normal-appearing white matter and at the rim of chronic MS lesions. Thus, their study demonstrated how natalizumab treatment of MS may reduce activation of resident CNS innate immune cells and established how TSPO-PET imaging can be used as a tool to assess longitudinal changes in microglial activation in NAWM and in perilesional areas in the MS brain in vivo.

Although natalizumab is recognized as a very effective MS therapy, its use can be associated with PML, a CNS infection caused by the opportunistic JCV. Serum antibodies to JCV serve as a surrogate marker for exposure to JCV, and the risk of PML is increased with elevated titers. In the November issue of *N2*, Largey et al.<sup>71</sup> conducted a longitudinal observational study analyzing serum and CSF samples before and during natalizumab treatment of 15 patients with MS for antibodies to JCV and other viruses, including measles, mumps, rubella, and

influenza, as well as certain bacteria. When comparing serum and CSF antibody levels, they detected evidence of intrathecal synthesis of anti-JCV antibodies in 20% of patients with MS before natalizumab treatment. During natalizumab treatment, intrathecal production of JCV antibodies was lost more frequently in comparison to antigen-specific antibodies to other neurotropic viruses and bacteria tested. Thus, their data suggest that there is intrathecal production of JCV-specific antibodies in a minority of patients and that there may be selective reduction of intrathecal JCV-specific humoral immunity during natalizumab treatment. Previous clinical investigations, and recent experimental evidence from Hussain et al.<sup>67</sup> and Lehmann-Horn et al.,<sup>66,68</sup> demonstrating that CNS penetration of B cells, like T cells, is VLA-4 dependent, raise the possibility that reduction of intrathecal production of JCV-specific antibodies could reflect decreased CNS recruitment of JCV-specific B cells and/or T cells (i.e., T follicular helper), which are required for B-cell differentiation into antibody-producing plasmablasts and plasma cells. Further studies including replication of these findings by Largey et al.<sup>71</sup> in a larger cohort will be important to determine whether reduction of intrathecal humoral JCV-specific immunity translates to higher risk of PML.

For several years, MOG antibodies have been well recognized in acute disseminated encephalomyelitis and bilateral optic neuritis. In 2014 and 2015, several groups described patients with opticospinal disease mimicking NMOSD that had MOG-specific antibodies, but not AQP4-specific antibodies.<sup>72–74</sup> At that time, there was concern in classifying MOG antibody-associated disease as a form of NMOSD, as the pathophysiology of MOG-targeted and AQP4-targeted diseases is distinct, the clinical course of these conditions may not be identical, and patients with these 2 disorders may not respond to therapeutics in the same manner.<sup>75,76</sup> Since that time, the number of MOG antibody-associated diseases has increased. In the March issue of *N2*, 2 groups described cases of patients with additional clinical conditions associated with MOG antibodies.<sup>77,78</sup> In 1 study, Patterson et al.<sup>77</sup> reported on 2 patients exhibiting signs of small vessel CNS vasculitis. Both patients presented with fever, headaches, and mental status changes, and 1 had cranial nerve palsies. They had abnormal brain MRIs and brain biopsies demonstrating lymphocytic infiltration of small vessels. With presumed diagnosis of small vessel primary vasculitis, these patients initially received cyclophosphamide and steroids. While on that regimen, 1 patient developed optic neuritis. MOG antibodies were detected in stored serum samples from both patients, and rereview of the biopsies revealed absence of fibrinoid necrosis, a pathologic requirement for the diagnosis of small vessel primary vasculitis. Treatment was changed upon recognition these patients had a MOG antibody-associated disease. One patient had no more relapses on treatment with rituximab, azathioprine, and low-dose prednisone, whereas the other patient stabilized on a slow prednisone taper. In the same issue of *N2*, Cobo-Calvo et al.<sup>78</sup> identified 3 MOG antibody-positive patients with radiologic and/or clinical

involvement of their cranial nerves. One patient had involvement at the root exit of the oculomotor nerve with gadolinium enhancement that extended beyond the transition between the CNS and the peripheral myelin. Labeled purified serum IgG from each patient was tested on tissue specimens from nonhuman primates (NHPs) (*Cynomolgus macaques*), a species that expresses MOG protein that is highly homologous with human MOG. The serum IgG samples reacted to myelin in the NHP brain tissue with the same pattern as a MOG-specific monoclonal antibody used as a positive control and did not react with cranial nerves. As MOG is produced by oligodendrocytes within the CNS, absence of staining of cranial nerves was not surprising. However, at this time, the pathophysiologic mechanism(s) responsible for the cranial nerve involvement in these patients with anti-MOG antibodies is puzzling. Further studies are needed to determine whether the MOG antibodies are pathogenic or if such antibodies are a surrogate for a humoral or cellular immune response targeting an antigen expressed in cranial nerves. Regardless, it is important to be aware that the spectrum of conditions associated with anti-MOG antibodies has grown, some of those conditions may mimic other neurologic disorders, and treatments may differ.

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

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