From brain to brawn

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After a subspecialized work day, when I opened the list of articles for the December issue of *N2* I was reminded of how fascinating neurology is. There is an interesting group of studies that range from the CNS to the muscle and from acquired to innate immunity. For this corner, I selected only a few that represent the wide spectrum of topics. Alemtuzumab is a humanized monoclonal antibody that targets the membrane glycoprotein CD52, providing long-lasting suppression of disease activity in patients with relapsing-remitting multiple sclerosis (RRMS). The underlying mechanisms resulting in these effects include complement-dependent cell lysis, antibody-dependent cellular cytotoxicity, and apoptosis leading to elimination of T cells. However, the effect of alemtuzumab on innate cells has been less investigated in patients with RRMS, and this is the main goal of the study of Gross et al.¹ Innate immune cells comprise myeloid cells such as dendritic cells (DCs) and macrophages and lymphoid cells (ILCs), which include cytotoxic natural killer (NK) cells and 3 noncytotoxic tissue-resident subsets: ILC1, ILC2, and group 3 ILC (ILC3 and tissue-induced cells). The authors studied 12 patients with RRMS before and during alemtuzumab treatment and examined the effects on several of the above innate cell populations. They found that in comparison with CD4⁺ T lymphocytes, myeloid and lymphoid innate cell subsets expressed lower amounts of CD52 on their surface. Interestingly, conventional DCs and plasmacytoid DCs that usually reconstitute rapidly in other immunosuppressive settings (e.g., allogeneic stem cell transplantation and immune conditioning) were found to be reduced 6 months after alemtuzumab treatment, although the interleukin (IL)-23 production in DCs was unchanged. In addition, within the ILC compartment, the subset of CD56^{bright} NK cells expanded under alemtuzumab treatment but their cytolytic activity did not change. Interestingly, beneficial effects of daclizumab (a human monoclonal antibody against IL-2 receptor chain) are also associated with increasing numbers and function of the CD56^{bright}

NK cells in patients with RRMS, but different from alemtuzumab, daclizumab has effects on the cytolytic activity of NK cells. The authors acknowledge the limited number of patients and lack of functional assays in their study, but the findings are in line with the long-term efficacy of alemtuzumab, suggesting a remodeling of the innate immune system with preservation of immune competence in patients with RRMS.

Blood-brain barrier (BBB) impairment is considered a critical event in CNS injury in HIV infection, but the characterization of this impairment has not been fully defined. In this issue of *N2*, Anesten et al.² aimed to determine the prevalence of BBB disruption in 631 HIV-infected individuals and 71 controls. HIV-infected patients were classified as untreated neuroasymptomatic, untreated HIV-associated dementia (HAD), and patients on suppressive antiretroviral treatment (ART). The study shows that BBB integrity was mainly affected in patients with HAD, and the BBB damage correlated with CNS immunoactivation (measured by neopterin levels). Notably, almost one fifth of the untreated neuroasymptomatic participants had signs of BBB impairment. These patients had normal neurologic examinations and no complaints of cognitive function, but neuropsychological testing was not performed in all participants. Whereas untreated neuroasymptomatic patients with impaired BBB had significantly higher levels of both CSF neopterin and CSF neurofilament (an indicator of neuronal injury) compared with patients without BBB dysfunction, no such difference was identified in participants on antiretroviral therapy or in healthy controls. These findings led the authors to formulate 2 hypotheses that await testing: (1) albumin ratio elevation in neuroasymptomatic patients may predict the subsequent development of HIV-associated cognitive deficits and (2) there is no need for antiretroviral drugs that penetrate the brain if the albumin ratio is normal.

Some forms of inflammatory myopathies, such as dermatomyositis, often associate with cancer. Recent

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studies have shown that patients with necrotizing autoimmune myopathies without autoantibodies or with antibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) are more likely to have an underlying malignancy than those with a similar syndrome but with antibodies against signal recognition particle.³ In this issue of *N2*, Kadoya et al.⁴ investigated the risk of cancer in 33 patients with antibodies against HMGCR identified among a cohort of 621 patients with idiopathic inflammatory myopathies. Twelve of the 33 patients (36%) had cancer, 4 of them with history of statin exposure, and another 3 patients without cancer also had statin exposure. Four of the 12 patients with cancer had non-necrotizing myopathies (3 nonspecific myositis and 1 dermatomyositis). Compared with patients without cancer, those with cancer were older and had more frequent myalgia, higher C-reactive protein and erythrocyte sedimentation rate, and higher mortality. The findings suggest that myopathy with HMGCR antibodies may occur with myositis without necrotizing features, and confirm that these antibodies not only occur with statin exposure but also as a paraneoplastic manifestation of cancer.¹

In another study, Miller et al.⁵ investigated the prevalence of autoimmune disease in symptomatic *C9ORF72* (C9) mutation carriers and frontotemporal dementia with motor neuron disease (FTD/MND) cohorts. The authors previously reported a relationship between systemic autoimmune inflammation in FTD progranulin (PGRN) mutation carriers and semantic variant primary progressive aphasia (svPPA) patients.⁶ However, the co-occurrence of autoimmune disease in C9 and FTD/MND patients was unknown. This combined cohort (C9 and FTD/MND) showed 12% prevalence of nonthyroid autoimmune disorders that clustered within the same 3 categories previously known for PGRN and svPPA including inflammatory arthritides, cutaneous conditions, and gastrointestinal disorders. Interestingly, 75% of the C9 and FTD/MND cohort were male and had male-predominant autoimmune disease (ankylosing spondylitis, ulcerative colitis, and sarcoidosis), whereas 60% of the previously reported PGRN and svPPA patients with autoimmune disease were female and only 15% possessed one of these male-predominant autoimmune disorders. Given that pathologically PGRN and svPPA typically display

frontotemporal lobar degeneration (FTLD) with abnormal TDP-43 positive aggregates (FTLD-TDP) and this pathology is also present in patients with FTD/MND or C9 mutation carriers, the current findings provide evidence that select autoimmune inflammation may be linked to FTLD-TDP pathophysiology.

In addition to these studies, this December issue of *N2* contains a review on the immunology of neuromyelitis optica during pregnancy and a curious case of Rosai-Dorfman syndrome among other interesting articles.^{7,8}

DISCLOSURE

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