

# Alphabet soup

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As I reviewed the articles for this Editor's Corner of *Neurology®: Neuroimmunology & Neuroinflammation (N2)*, I was reminded of the childhood treat alphabet soup. I am sure that many of our readers enjoyed, as I did, the challenge of the search for letters to form words that could be scooped up in a spoonful. The complexity of the immune system and its representation in a myriad of abbreviations, acronyms, and initialisms appeared in that moment as a bowl of alphabet soup waiting to be organized and understood. The studies in this edition of *N2*, several of which are summarized below, move us closer to that goal.

Relapsing-remitting multiple sclerosis (RRMS) is a clinically and immunologically heterogeneous disorder and patients have variable responses to interferon- $\beta$  (IFN- $\beta$ ). This heterogeneity can confound biomarker studies. The study by Hegen et al.<sup>1</sup> approaches the issue by measuring serum cytokines from patients with RRMS before initiation and after 3 months of IFN- $\beta$  therapy. Cytokines were compared in responders and nonresponders, defined by relapses and Expanded Disability Status Scale score. The variability of baseline cytokine levels was used to cluster patients into subsets. The authors observed 2 distinct baseline cytokine profiles that correlated with IFN- $\beta$  nonresponsiveness characterized by elevated levels of interleukin (IL)-17F or of IL1 $\beta$ , IL-8, CXCL1/Gro- $\alpha$ , CCL2/MCP1, and IL-17A. They also found 2 distinct profiles that distinguished IFN- $\beta$  responders, characterized by low levels of all cytokines except CD40L or high levels of IL-7. This study, accompanied by an editorial by Wu,<sup>2</sup> provides additional evidence for immunologically distinct subgroups of RRMS that can be informative for prognosis and treatment response.

The study by Bakshi et al.<sup>3</sup> aimed to determine whether serum antibody repertoires are linked to cerebral MRI measures of disease severity in RRMS. The authors probed an antigen array of 420 CNS-related autoantigens, lipids, and heat shock proteins

with the serum of 21 patients for whom normalized compartment-specific global brain volumes were obtained by 3T MRI. They found that atrophy and T2 lesions each associated with increased reactivity to a different set of lipids. These results need to be validated in a larger patient cohort and in patients with nondemyelinating neurodegenerative diseases. However, the study suggests that serum antibody profiles may serve as biomarkers for monitoring disease pathology and progression and raises the possibility of a role of lipid-specific immunity in MS.

Metz et al.<sup>4</sup> assessed whether serum antibody reactivities could distinguish between aquaporin-4 (AQP4) antibody-positive and -negative neuromyelitis optica spectrum disorder (NMOSD) and RRMS. The authors used pooled sera from different patient groups and healthy controls to screen more than 8,700 peptides of potential relevance for inflammatory demyelinating diseases as well as random peptides. Based on the results, they developed a microarray of 700 peptides. The key result was that patients with NMOSD and RRMS have different antibody reactivities to a number of human and viral antigens as well as to random peptides. These reactivities correctly distinguished between NMOSD (AQP4-positive or -negative) and RRMS in approximately 80% of patients. If confirmed, these results could be particularly useful in differentiating AQP4-negative NMOSD and RRMS.

The diagnosis of cerebral vasculitis as the cause of a stroke can be difficult. Biopsy may be negative and ancillary studies such as angiography have high sensitivity but low specificity. Thom et al.<sup>5</sup> sought to determine whether IL-17 could serve as a biomarker for cerebral vasculitis in patients presenting with strokelike symptoms. Because levels of IL-17 in CSF are too low to detect by current methods, the authors expanded cells from CSF and measured intracellular IL-17 in the CD4<sup>+</sup> lymphocytes. The CD4<sup>+</sup> lymphocytes from patients with cerebral vasculitis had significantly higher IL-17 than patients with

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stroke not due to vasculitis or patients with other noninflammatory neurologic diseases. Prior data suggest a role of Th17 cells in the pathogenesis of inflammatory and autoimmune disorders. The results of the current study support IL-17 as a diagnostic biomarker and as a potential target for therapeutic interventions in cerebral vasculitis.

The pathogenesis of giant cell arteritis (GCA) is being revealed. Gildeen et al.<sup>6</sup> evaluated the presence of varicella-zoster virus (VZV) antigen in the temporal arteries of 104 patients with biopsy-positive GCA, 100 patients with biopsy-negative GCA in whom the diagnosis was based on clinical and laboratory features, and 61 age-matched controls. Using an extensive number of thin-cut sections from each biopsy, the results demonstrated VZV antigen in 70% of the GCA biopsy-positive and 58% of the GCA biopsy-negative cases, compared to 18% of the controls. In all 3 groups the VZV antigen was located in multiple arterial layers but most persistently in the adventitia. Of note, adventitial inflammation was seen adjacent to the antigen in more than half of the GCA biopsy-negative cases that had VZV antigen but not in the controls with VZV antigen. These data suggest that GCA may be in many cases a VZV vasculopathy and provide the first evidence linking VZV with pathology in GCA biopsy-negative patients.

The immunopathologic relevance of B cells in MS and other demyelinating disorders is addressed in the study by Lehmann-Horn et al.<sup>7</sup> The authors show that experimental autoimmune encephalomyelitis induced by myelin oligodendrocyte glycoprotein peptide (p)35–55 was more severe in mice with selective deficiency of B cell very late antigen-4 (VLA-4) expression than in controls. In the model, the B cell VLA-4 deficiency reduced the CNS accumulation of B but not T cells and was associated with an almost complete absence of CNS regulatory B cells (Breg). The results demonstrate that CNS accumulation of Breg is VLA-4 dependent and suggest that CNS Breg contribute to the regulation of CNS autoimmunity.

In this issue of *N2* you will also find case reports of a patient with Degos disease mimicking primary CNS vasculitis<sup>8</sup> and IL-7 treatment of progressive multifocal leukoencephalopathy.<sup>9</sup>

I hope this preview has piqued your interest to read each of the excellent articles on a diversity of subjects in this issue of *N2*.

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## DISCLOSURE

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