The earlier the better

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In autoimmune and other inflammatory diseases of the nervous system, as in most diseases, the earlier the diagnosis is made, the better the outcome. In the current issue of *Neurology® Neuroimmunology & Neuroinflammation*, there are several articles that revolve around this theme, mostly representing patients with radiologically isolated syndrome (RIS), clinically isolated syndrome (CIS), or assessment of integrity of corticospinal tracts (CSTs) in normal-appearing white matter in patients with MS.

Makhani et al.[1] describe the clinical and radiologic outcomes of 38 children with incidental findings on MRI suggestive of RIS. The rationale for the study was based on data from adults with RIS, showing that they have a 34% risk of developing a first episode of CNS demyelination within 5 years of RIS presentation.[2] The current study focuses on a historical cohort of children aged <18 years with incidental MRI findings consistent with demyelination that met the 2010 criteria for dissemination in space for MS. Sixteen patients (42%) developed a first clinical event consistent with demyelination in a median of 2.0 years. When the authors considered the children who fulfilled the RIS criteria used for adults, 10/19 children (53%) developed a first clinical event. The presence of ≥2 oligoclonal bands in the CSF and spinal cord abnormalities on MRI were associated with an increased risk of a first clinical event after appropriate adjustments for sex and age. Results of this study highlight the importance of the detection of RIS in children; whether these children should be treated with disease-modifying agents is a question that can only be answered with prospective studies with larger number of patients.

Pawlitzki et al.[3] investigated CST integrity in the absence of white matter lesions using diffusion tensor imaging (DTI) in early MS disease stages, including 19 patients with CIS, 11 relapsing-remitting MS (RRMS), and 32 age- and sex-matched healthy participants without a history of neuropsychiatric disease. Patients with CIS and RRMS had significantly lower CST fractional anisotropy (FA) and higher mean diffusivity (MD) values compared with controls. The findings suggest that corticospinal motor system axonal integrity loss can be detected at very early disease stages, even in the absence of white matter lesions and before brain volume loss is identified. The authors acknowledge the small sample size as a limitation of the study and suggest that DTI can be useful to guide treatment decisions in patients with few inflammatory lesions, or without lesions, in the face of just 1 clinical event. Future studies will need to combine DTI with other advanced imaging techniques and CSF biomarkers such as neurofilament studies to better understand the pathogenic mechanisms underlying early FA and MD changes in normal-appearing white matter of patients with MS.

Recent studies showed that clearance of myelin debris after CNS tissue injury in MS is required for subsequent tissue repair.[4] In MS lesions, myeloid cells involved in phagocytosis include both microglia and macrophages that are derived from circulating monocytes.[5] In this issue of *Neurology: Neuroimmunology & Neuroinflammation*, Healy et al.[6] investigated a molecular mechanism that underlies a defect in myelin phagocytosis by macrophages generated from patients with MS. The same authors had previously reported that MerTK, which is a member of the TAM (Tyro3, Ax1, and MerTK) family of tyrosine kinase receptors, is important in mediating myelin phagocytosis by human myeloid cells. The expression of the TAM family of receptors was found to be increased by transforming growth factor β (TGFβ) and decreased by proinflammatory cytokines.[7] In the current study, the authors used several techniques to assess phagocytosis and expression of TAM family molecules in monocyte-derived macrophages (MDMs) from peripheral blood monocytes of 25 untreated RRMS and secondary progressive MS patients and age- and sex-matched healthy controls. The findings showed that MDMs from patients with MS had a reduced ability to phagocytose human myelin but not red blood cells compared with healthy participants. Patients' cells had lower levels of MerTK and its natural

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ligand, Gas6, independent of the activation state of the cells. Moreover, different from healthy participants' MDMs which showed increased expression of IL-10 after myelin uptake, patients' MDMs did not show increased IL-10. These deficits were restored when patients' cells were treated with TGFβ. Of interest, MerTK has been identified as a gene associated with increased MS susceptibility in 2 large, independent discovery and replication cohorts. The current study was not powered to resolve whether differences in myelin phagocytic activity reflect MerTK gene polymorphisms, but the authors provide an interesting hypothesis on why alterations of TAM expression may play a role in defective T-cell tolerance and expansion of self-reactive T cells. The importance of this article is that it provides a mechanism that underlies a defect in myelin phagocytosis by macrophages of patients with MS, which is amenable to therapeutic intervention.

In another study, Iizuka et al.[8] retrospectively reviewed the information of 136 patients with clinically suspected autoimmune encephalitis and identified 11 who were eventually diagnosed with cryptogenic new-onset refractory status epilepticus (cNORSE). All 11 patients were negative for antibodies against neuronal surface proteins. Given that the clinical presentation of these patients often resembles that of patients with antibody-mediated encephalitis, the authors compared the clinical features of these 11 patients with those of 32 patients with anti-NMDA receptor encephalitis. The findings showed that patients with cNORSE more frequently had prodromal fever, status epilepticus, need for ventilatory support, and symmetric MRI abnormalities and less frequently had dyskinesias, psychobehavioral symptoms, CSF oligoclonal bands, and a tumor association than patients with anti-NMDAR encephalitis. Whereas 72% of patients with anti-NMDAR encephalitis had a good outcome (defined as a modified Rankin scale score of 0–2), only 27% of patients with cNORSE had a good outcome. However, an interesting observation was that 4 of the 5 patients with cNORSE treated with cyclophosphamide showed partial response to the treatment.

In addition to these studies, the November issue of *Neurology: Neuroimmunology & Neuroinflammation* contains a comprehensive review on B-cell–targeted therapies in relapsing forms of MS by Dubey et al.,[9] and other interesting original articles that I hope will catch your attention.

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