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Finding NMO

Neuromyelitis optica in children

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Since the discovery in 2004 of NMO-IgG, the autoantibody associated with neuromyelitis optica (NMO),¹ neurologists are increasingly relying on the NMO-IgG test to rule in or rule out NMO. Related disorders like optic neuritis (ON), transverse myelitis (TM), acute disseminated encephalomyelitis (ADEM), and longitudinally extensive TM (LETM; ≥ 3 spinal cord vertebral segments) can all be monophasic or multiphasic, can occur together or individually, and can occur in adults or children. Similarly, multiple sclerosis (MS) is often confused with these disorders, especially early in the disease. But little is known about the prevalence of NMO-IgG in children presenting with these disorders. In the current issue of *Neurology*®, Dr. Banwell at the Hospital for Sick Children in Toronto, Canada, along with colleagues in Argentina and Montreal, and Dr. Pittock and colleagues at the Mayo Clinic in Rochester, Minnesota, aim to determine the seroprevalence of NMO-IgG in children with NMO and related disorders.²

This is the first published characterization of NMO-IgG seroprevalence in children and includes 87 patients with NMO, TM, ON, ADEM + TM, and MS from two centers, Toronto and Buenos Aires. Diagnoses were based on well-established clinical and radiologic criteria, and clinicians were blinded to the NMO-IgG status for the purpose of this study. The results show that 8 out of 17 children with NMO were seropositive for NMO-IgG, largely in those with recurrent disease (7 out of 9). In children with TM, NMO-IgG status absolutely correlated with recurrence in that 12 out of 12 with first episode TM were seronegative and 1 out of 1 with recurrent TM was seropositive. Out of 5 patients with relapsing optic neuritis, only one was NMO-IgG positive. TM in the context of ADEM and MS is not associated with NMO-IgG seropositivity. The authors conclude, therefore, that the prevalence of NMO-IgG seropositivity in NMO, re-

lapsing ON and TM, and the prevalence of NMO-seronegativity in MS, are similar to those in adults.

So, where are we then in understanding the nosology of NMO and its cousins, and in understanding the role of NMO-IgG in diagnosis and in pathogenesis? In adults, the most recently revised 2007 diagnostic criteria for NMO,³ as well as prior suggested criteria,^{4,5} have emphasized that the myelitis component of NMO has important distinguishing clinical and radiographic features from MS and that these features may reflect unique mechanisms of disease. The myelitis of NMO is defined by a longitudinal inflammation spanning more than three vertebral segments.⁶ Such a pattern of myelitis is likely to be associated with loss of antigravity strength and sphincteric deficits at attack peak severity. In comparison, the myelitis seen in relapsing-remitting MS exhibits sharply marginated, perivenular, T-cell-mediated demyelination with much less severe clinical manifestations. The NMO-IgG test is specific in that a very small percentage of patients with MS or idiopathic TM demonstrate NMO-IgG seropositivity while a substantial percentage of patients with NMO or recurrent LETM do.

Recently, the NMO-IgG autoantibody test has been incorporated into the updated 2006 diagnostic criteria for NMO.³ The target of the NMO-IgG autoantibody is the aquaporin-4 (Aqp4) water-pump channel⁷ localized on the abluminal side of blood vessels and astrocytic foot processes.⁸ The spinal cord pathology in NMO features hyalinized small vessels, intense perivascular neutrophilic and eosinophilic infiltration, and deposition of immunoglobulin and neocomplement C9.⁹ These changes suggest that there is humorally mediated microangiopathy leading to cylindrical spinal cord necrosis and cavitation.¹⁰ Appreciation that the myelitis of NMO may be initially characterized by a transient inflammatory phase has led to suggestions that early use of

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B-cell targeted or depleting treatments, such as rituximab,¹¹ may prevent the grim prognostic features of wheelchair dependence, blindness, or premature death associated in more than 50% of adult patients within 10 years.¹²

Significant advances have been made in understanding both the clinical and basic science of NMO. We have gone beyond the questions of whether NMO is distinct from MS or from idiopathic TM: it is. We have gone beyond the question as to whether NMO spectrum disorders, like LETM and ON, can behave like NMO in terms of recurrence: they do. And whether the NMO-IgG is a specific marker for NMO and for disorders that behave and have pathologic similarities to NMO: it is. These are important steps forward.

There is still a lot we do not know. The role of NMO-IgG in the pathogenesis of NMO has yet to be worked out. We do not yet know whether NMO-IgG is simply a valuable biomarker for a primary autoimmune disease underlying the NMO spectrum disorders, or whether the autoantibody causes the damage that defines it. Further, this study emphasizes that 100% of children who tested positive for NMO-IgG had recurrent disease of some variety along the NMO spectrum and the authors suggest that the NMO antibody may play a role in the pathogenesis of recurrence. We do not know if NMO-IgG is positive in these children at their first attack. If so, NMO-IgG defines a group of patients who are likely to have recurrent disease and therefore might benefit from immunomodulatory therapy to prevent subsequent disability. Some data exist to suggest that the NMO-IgG test may distinguish monophasic from recurrent patients at first attack¹³ but we need more data both in adults and in children in this area. It remains possible that the children with recurrent disease in this study became NMO-IgG positive only after they have had several attacks as a result of recurrent “immunization.” In this scenario, repeated inflammation and CNS injury unrelated to NMO-IgG present Aqp-4 or a breakdown product in the context of inflammation to the immune system leading to the generation of autoantibodies against it. The NMO-IgG test, in this scenario, would not be helpful until after the patient has presented with recurrent disease by clinical criteria.

Nonetheless, we are learning progressively more about NMO, driven by good science and good clinical neurology. This study provides an excellent addition to the growing literature of NMO as it is the first study in children and serves as a foundation for other studies to more precisely define the prevalence of NMO-seropositivity in NMO and NMO spectrum diseases in children.

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