# White matter changes in childhood NMDA receptor encephalitis

## Bringing new light to an old phenotype

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Landmark work from the first decade of the 21st century describing specific antibodies associated with inflammatory disorders of the CNS has revolutionized child neurology. Of particular interest has been NMDA receptor antibody–related encephalitis (NMDAR-encephalitis), which was originally described in a small cohort of women with ovarian teratoma.[1] It is now recognized that children represent more than one-third of reported cases of NMDAR-encephalitis.[2] The prevalence of this disorder is unknown, but growing literature on this phenomenon has expanded the spectrum of the clinical phenotype with which NMDAR antibodies are associated and suggests that it may be more common than previously thought.

The clinical characteristics of NMDAR-encephalitis include a distinctive triad of seizures, psychiatric manifestations, and abnormal movements.[3] Key clinical features of the presentation of NMDAR-encephalitis in children comprise high rates of seizure at onset and a relatively low rate of associated neoplasm (9%–30%).[4] Until recently, MRI of the brain was expected to be normal in childhood NMDAR-encephalitis, thus setting this disorder apart from the widely described phenomena of acute disseminated encephalomyelitis (ADEM) and other acute inflammatory CNS syndromes of childhood.

Hacohen et al.[5] describe a cohort of 10 children with antibody-positive NMDAR-encephalitis who presented with white matter changes on MRI. The authors describe 3 distinct syndromes, also recently described by other investigators,[6,7] including brain stem encephalitis, post–herpes simplex virus encephalitis, and what they describe as "acquired demyelinating syndromes" (ADS). These 10 patients were drawn from a cohort of 46 NMDAR-positive patients, constituting more than one-fifth of the cohort: a surprising finding, and one that gives pause to those who deal with children presenting acutely with inflammatory disorders of the CNS. It highlights the potential for a higher level of biological specificity in the diagnosis of children who might have otherwise received the diagnosis of an ADS.

Whether the NMDAR antibody plays a specific role in pathogenesis and clinical presentation of these conditions is unclear from this study. Of interest, 3 of the 5 children that Hacohen et al. classified in the ADS category were found to have concomitant anti–myelin oligodendrocyte glycoprotein (MOG) antibodies, a finding also recently reported in another study.[7] Others have reported the presence of MOG antibodies in children with similar clinical phenotypes to those described by Hacohen et al., namely ADEM and recurrent optic neuritis with brain lesions.[8] But previous studies suggesting the transient nature of MOG antibodies in pediatric monophasic ADS[9] emphasize the need to carefully consider the pathogenic significance of any antibody found in association with acute inflammatory CNS conditions in children. This topic constitutes an important area of future investigation.

The cohort of children studied by Hacohen et al. represents a distinct and unusual subgroup not only because of their white matter abnormalities but also because of the high number experiencing relapse. Whereas in other large published series of children with NMDAR-encephalitis 25% experience relapses,[4] the majority of the patients in this series (7 of 10 patients) experienced relapses. Because the authors do not describe whether the rate of relapse was equally high in the remaining 35 patients in their series, it is unknown whether relapse rate was unusually high in their cohort or only in the group with white matter abnormalities. The high relapse rate is consistent with a recent study showing that approximately 50% of patients with anti-NMDAR-encephalitis and demyelinating features (n = 23) experienced relapses, in contrast to 12% of the entire series (n = 691).[7]

Given the high rate of relapse in comparison to other populations that have been described, it is possible that the presence of NMDAR antibodies in this group of patients may have different implications than in children with monophasic illness. The authors point out that the NMDAR antibodies may be a product of the underlying demyelination, but NMDAR antibodies were not seen in another study evaluating NMDAR antibodies in a large cohort of patients with neuromyelitis optica or multiple

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sclerosis.[7] The relationship of NMDAR antibodies to demyelination is therefore unclear. Nonetheless, the presence of these antibodies in this cohort is intriguing. With further investigation, it may be possible to use presence of NMDAR antibodies to help rationalize therapy decisions in children with varied clinical presentations, white matter abnormalities, and NMDAR antibodies who, until now, received diagnoses and treatment recommendations based on MRI appearance and clinical course. A high priority is to determine as best as possible whether the NMDAR antibodies are directly pathogenic. Faced with a patient with recurrent and potentially devastating disease, the ability to offer targeted B-cell therapy brings promise: early diagnosis and treatment may help to reduce morbidity and improve both functional and physical outcomes in this population. This hypothesis remains to be tested in further studies.

Although longitudinal analysis of NMDAR titers was not available for all patients, fluctuating antibody titers were reported by Hacohen et al. to be associated with variable intensity of symptoms. This finding is significant for 2 reasons: (1) it highlights the potential pathogenic significance of NMDAR antibodies in these cases, and (2) it suggests a possible role for evaluating antibody titers to follow disease activity. This approach is supported by recent findings in a large cohort of NMDAR antibody–positive adults, which suggest that high antibody titers in CSF and serum may correlate with poor outcome early on, that titers fall regardless of disease severity, and, finally, that changes in titers occur in relation to relapses.[10] Whether this relationship between disease activity and antibody titers will hold true in the pediatric population will require further investigation using serum and CSF. If antibody titers and clinical activity are linked, repeated testing, and testing performed early on in the face of possible recurrence, may assist in selection and timing of therapeutic interventions.

This study offers hope and raises questions for the future. It highlights the possibility that specific biomarkers carrying pathologic significance might be found in children with inflammatory CNS disorders. The results may provide rationale for the administration of targeted therapy in children with recurrent inflammatory CNS disease who presently defy biologically specific categorization. Further longitudinal analysis of the course of the MRI abnormalities in these children is needed, as are further studies documenting natural history, outcomes, and response to therapies in this population. In an era of big science, the important observations highlighted in this study remind us that many key lessons can be learned by carefully thinking about the patients we care for.


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