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We would like to commend Bulut et al[1] for their investigation of brain MR imaging findings that could potentially be useful in discriminating pediatric-onset neuromyelitis optica spectrum disorder (NMOSD) from acute disseminated encephalomyelitis (ADEM). These 2 entities exist within the broader category of immune-mediated CNS disease, which is so challenging to diagnose prospectively, given the complexity, heterogeneity, and clinical-radiologic overlap between these different immune-mediated conditions. Given the current limitations in our understanding of the underlying pathophysiology of these disorders, we would like to take this opportunity to provide a historical context for this article and highlight a few recent studies from *JAMA Neurology* with larger cohorts that adopt a more granular neuroimaging approach to disease characterization.

In their retrospective study of 10 pediatric patients with NMOSD and 10 pediatric patients with ADEM, Bulut et al identify MR imaging findings that could be potentially used to help differentiate NMOSD and ADEM in clinical practice. However, one must first acknowledge that, under the diagnostic criteria used in the study (2015 Consensus Diagnostic Criteria for NMOSD, https://www.ncbi.nlm.nih.gov/pubmed/26092914 and the 2007 Consensus Diagnostic Criteria for ADEM, https://www.ncbi.nlm.nih.gov/pubmed/17438241), it is possible for a single patient to meet both criteria. This highlights the tremendous clinical and radiologic overlap between these 2 general diagnostic categories and suggests that a NMOSD versus ADEM paradigm does not always allow adequate classification of the diseases. Even the term neuromyelitis optica (NMO) "spectrum disorder" implies that we currently lack an adequate understanding of the underlying pathophysiology to distinguish between specific entities within this 1 category, especially in the absence of antibodies against aquaporin-4 (AQP4), at least until another new causative autoantibody is identified. Similarly, ADEM is an umbrella term for entities often occurring after an infection or vaccination that share similar clinical phenotypes and imaging features, and it remains unclear how much of ADEM can be attributed to underlying autoantibodies such as those against myelin oligodendrocyte glycoprotein (MOG). Given these limitations, we should proceed with caution when drawing conclusions about MR imaging findings in these patients, especially when using small sample sizes and evolving disease classification systems.

In reality, patients in 2019 with new onset of immune-mediated CNS disease within the gray zone of NMOSD versus ADEM by imaging can end up with the clinical designation of ADEM if they meet the criteria for encephalopathy or present after a recent infection, but in some cases further discrimination can be rather arbitrary at initial presentation in the absence of positive anti-AQP4 or anti-MOG antibodies. This ongoing process of "greater discrimination through improved scientific understanding" is exemplified by the historical progression from "NMO is a variant of MS" to "NMO is a distinct antibody-mediated disease targeting AQP4" to "additional CNS antigens such as MOG can also be targeted by autoantibodies and result in a similar disease process."[2]

JAMA Neurology published a series of studies in 2018–2019 that provides additional insight into how best to characterize MR imaging findings in pediatric patients with new onset of immune-mediated CNS disease. For readers interested in exploring this topic in more detail, we specifically want to highlight the work of the following authors: Hacohen et al[3] wrote a prospective study of 102 pediatric patients with MOG antibody-associated disease (MOG Ab)–associated relapsing demyelinating syndromes initially given diagnoses of NMOSD, ADEM with subsequent optic neuritis, and multiphasic disseminated encephalomyelitis with relapsing optic neuritis who did not respond well to disease-modifying drugs but did respond to azathioprine, mycophenolate mofetil, rituximab and intravenous immunoglobulins. Dubey et al[4] wrote a retrospective study of 54 patients, including 16 children and 38 adults with MOG immunoglobulin G–positive (MOG-IgG +) myelitis with various clinical presentations, including isolated transverse myelitis, acute flaccid myelitis, and myelitis in combination with ADEM or optic neuritis who had imaging characteristics distinct from MS and AQP4-IgG myelitis. López-Chiriboga et al[5] wrote a retrospective study of 51 patients, including 31 children and 20 adults, with a clinical diagnosis of ADEM in which patients with persistent MOG Ab seropositivity had significantly higher rates of relapse.

It is always encouraging to see radiology contributing to the field of clinical research on NMOSD and ADEM that has largely been the domain of our neurology and pathology colleagues.

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Neuroimaging will continue to have a tremendous impact in our understanding of these diseases, but further translational research and interdisciplinary collaboration with large cohorts of patients will likely be required before we can reliably distinguish immune-mediated CNS diseases that are currently incompletely characterized but have similar clinical and radiologic phenotypes.

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