

Commentary on "Autoimmune encephalitis and epilepsy: evolving definition and clinical spectrum"

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Acute encephalitis is neurological syndrome with diverse etiologies that occurs mostly in children, impacting their physical and cognitive development.¹⁾ Its estimated annual incidence in children is a minimum of 10.5/100,000.²⁾ The etiology of acute encephalitis remains unknown in more than half of cases. Herpes simplex virus (HSV) is the main virus found in the cerebrospinal fluid and blood; therefore, most cases of encephalitis might be infectious diseases.³⁾ However, recent advanced molecular technologies revealed that the presence of antibodies against neuronal proteins is associated with acute encephalitis syndromes, so-called autoimmune encephalitis (AIE). AIE reportedly occurred in many children presenting with seizures and behavioral and psychiatric changes that did not respond to conventional encephalitis antiviral or antibacterial medications. However, the overall prevalence of AIE remains unknown and its diagnostic algorithms remain undetermined. The mean incidence of antibody-mediated AIE was recently reported as 1.54 children/million in the Netherlands.⁴⁾

In a review article, Seo et al.⁵⁾ described the most relevant data of the immunologic and clinical characteristics of AIE recognized to date with the aim of assisting clinicians with the differential diagnosis and favoring early and effective treatment.

Autoantibodies found in AIE syndromes are classified into 3 types depending on the locations of their antigens, such as intracellular proteins, plasma membrane and synaptic receptors, and ion channels and/or other cell surface proteins. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, the most common AIE, is predominant in young women and children.⁶⁾ Anti-NMDAR encephalitis may be associated with HSV, *Mycoplasma pneumoniae* infection, measles, mumps, influenza A/H1N1, and group A hemolytic *Streptococcus* infection.⁷⁾ Autoimmune responses to the NR1 subunit of NMDAR were demonstrated to be triggered by various infectious agents in children. Movement disorders and seizures are significantly more common than psychiatric symptoms in children with AIE than in affected adults.

Gamma-aminobutyric acid A receptors (GABA_AR) are ligand-

gated ion channels. Patients with anti-GABA_AR encephalitis develop a rapidly progressive encephalitis with refractory seizures, status epilepticus, and/or epilepsy partialis continua. Nearly half of the reported cases occurred in children.⁸⁾ In the pediatric population, anti-GABA_AR encephalitis may progress as a postviral encephalitis and coexist with NMDAR antibodies.

Patients with suspected AIE should be thoroughly investigated using neuroimaging, electroencephalography, lumbar puncture, and serologic testing for appropriate biomarkers to confirm the diagnosis and exclude alternative etiologies. AIE might be detected in children presenting with multifaceted seizures and unexpected behavioral changes. The spectrum of neuropsychiatric manifestations is less clear in the pediatric than adult population with AIE. Screening for malignancy is mandatory in children to rule out paraneoplastic syndrome. The detection of specific autoantibodies confirms the diagnosis of AIE. Thus, clinical suspicion is important for the diagnosis and early intervention because the earlier immunomodulatory therapy is administered, the better the outcome. However, not all patients with AIE have antibodies; thus, the absence of antibodies does not rule out underlying autoimmune mechanism. Therefore, AIE must be considered a possible cause in patients with progressive sudden-onset sensorimotor deficits and movement disorders of unknown etiology.

The use of immunosuppressive therapy should not be delayed until the confirmation of a cancer diagnosis or the presence of antibodies to neuronal proteins and no definite contraindications for immunosuppressive therapy. Overall, outcomes in children are usually good, although this varies by the underlying tumor type and stage as well as the severity of the initial neurological symptoms and timing of the initial treatments. Abnormal magnetic resonance imaging findings, a clinical presentation with sensorimotor deficits, and a treatment delay exceeding 4 weeks were associated with worse clinical outcomes in 38 children with anti-NMDAR encephalitis.⁹⁾

The central nervous system (CNS) is considered an immune-privileged organ, but recent research revealed that it is an active

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environment that interacts with diverse immune cells in both the disease state and the healthy brain. Immune processes play a vital role in CNS homeostasis, resilience, and brain reserve, and highly sensitive narrow ranges of inflammatory balance seem to be required for health. Crosstalk between the immune and nervous systems has been revealed in a wide spectrum of neurological diseases.¹⁰ Increased levels of proinflammatory cytokines are found in patients with epilepsy, developmental disorders, neurodegenerative diseases, and psychiatric disorders.¹¹⁻¹³ Even antibodies against fetal brain tissues, such as contactin-associated protein-like 2, were detected in the sera of pregnant mothers whose babies were later diagnosed with autism spectrum disorders but not in mothers of healthy children.¹⁴ Therefore, many neurologic and neurodevelopmental disorders in children might be re-evaluated and investigated in terms of immunologic interactions including autoantibodies, cytokines, and microRNAs.¹⁵

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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