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Topical Review

Antibody-Mediated Autoimmune Encephalitis in Childhood

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ABSTRACT

BACKGROUND: The differential diagnosis of encephalitis in childhood is vast, and evaluation for an etiology is often unrevealing. Encephalitis by way of autoimmunity has long been suspected, as in cases of acute disseminated encephalomyelitis; however, researchers have only recently reported evidence of antibody-mediated immune dysregulation resulting in clinical encephalitis. **MAIN FINDINGS:** These pathologic autoantibodies, aimed at specific neuronal targets, can result in a broad spectrum of symptoms including psychosis, catatonia, behavioral changes, memory loss, autonomic dysregulation, seizures, and abnormal movements. Autoimmune encephalitis in childhood is often quite different from adult-onset autoimmune encephalitis in clinical presentation, frequency of tumor association, and ultimate prognosis. As many of the autoimmune encephalitides are sensitive to immunotherapy, prompt diagnosis and initiation of appropriate treatment are paramount. **CONCLUSIONS:** Here we review the currently recognized antibody-mediated encephalitides of childhood and will provide a framework for diagnosis and treatment considerations.

Keywords: autoimmune, encephalitis, pediatric, encephalopathy

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Introduction

Encephalitis is a broad term encompassing any inflammatory disease process of the brain that manifests clinically with alterations of consciousness and/or behavioral changes. Associated signs and symptoms of encephalitis may include (but are not limited to) seizures, movement abnormalities (e.g., dyskinesias, choreoathetosis), ataxia, dysautonomia, and focal neurological deficits. Encephalitis may occur as the result of a primary infection of the central nervous system (CNS) or through an autoimmune process triggered by an infection, vaccine, or occult neoplasm.

Researchers have long presumed that an autoimmune process has the potential to lead to a clinical encephalitis (e.g., acute disseminated encephalomyelitis [ADEM], opsoclonus-myoclonus ataxia, and Rasmussen encephalitis),[1-3] yet the pathogenic immune mechanisms for many of these cases have never been defined. For the adult-onset encephalitides, particularly those with limbic symptomatology, paraneoplastic autoantibodies (i.e., antibodies formed in association with a neoplasm) were described as early as 1992.[4-6] It was not until the early 2000s that disease-causing, nonparaneoplastic autoantibodies (i.e., those formed without an associated neoplasm) to neuronal surface antigens were officially reported.[7-9] When the California Encephalitis Project was initiated in 1998, an infectious etiology was the most commonly identified cause of reported encephalitis cases.[10] Identified autoimmune-mediated encephalitis cases have now surpassed individual viral etiologies[11]; however, the exact prevalence of individual autoimmune encephalitides remains largely unknown.

Presentation with an autoimmune encephalitis in childhood is often subacute, with a varied constellation of symptoms.[12-14] Concurrent inflammatory findings in the cerebrospinal fluid (CSF), including the presence of oligoclonal bands, lymphocytic pleocytosis, and elevated protein, may be present but are relatively nonspecific. Magnetic resonance imaging (MRI) of the CNS may also demonstrate abnormalities that provide clues for diagnosis, particularly on fluid-attenuated inversion recovery (FLAIR) or T2-

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weighted images. The treatment of autoimmune encephalitis consists of immunomodulatory therapy. The duration of therapy depends on the autoimmune encephalitis in question and the patient's clinical response. Outcome in childhood is generally good but may depend on the pathogenic autoantibody and neuronal target involved, in addition to the time from symptom onset to treatment initiation.

This review discusses the spectrum of known autoimmune encephalitides occurring in childhood, with a primary focus on those disorders whose associated autoantibodies target either the neuronal surface or intracellular proteins (Table 1). We will describe the clinical presentation, laboratory and imaging findings, and outcomes for both common and rare autoimmune encephalitides and include a discussion on the use of immunotherapy to treat autoimmune encephalitis.

Unique aspects of autoimmune encephalitis in childhood

Although several aspects of autoimmune-based encephalitis can be generalized across the age spectrum (e.g., symptomatology and acute management), the clinical presentation, disease course, impact of a chosen therapy,

TABLE 1.
Clinical Characteristics of Individual Antibody-Associated Encephalitides in Childhood

Autoimmune Encephalitis	Ages Described*	Clinical Manifestations	Associated Tumor	Risk of Relapse	Long-Term Outcomes
NMDAR	20 mo-17 yr	Seizures, behavioral disturbance, aphasia, psychosis, orofacial dyskinesias, catatonia	30% of females with ovarian teratoma	Up to 25% when causative tumor is not identified and removed	80% or greater have full recovery
VGKC	10 mo-17 yr	Seizures, behavioral disturbance, movement disorders, dysarthria, developmental regression	Neuroblastoma in one case (patient with multiple autoantibodies)	Unknown; reported in single case series as 25% relapse rate in childhood	Unknown, but most reported patients show marked to full recovery
GlyR	1-14 yr	PERM, seizures, ADEM with ON	None currently reported in childhood	Unknown; reported in single case series as 25% relapse rate in childhood	Unknown; generally considered to have good outcomes
$GABA_A$	2-17 yr	Seizures, cognitive and memory alterations, movement abnormalities	Hodgkin's lymphoma predating encephalitis in one patient	Unknown, but reported in a single pediatric case	Unknown; most have good recovery but residual seizures
$GABA_B$	3-18 yr	Seizures, movement disorders, memory loss, delirium, psychosis	None currently reported in childhood	Unknown in childhood	Unknown; majority reported show full recovery
AMPA	7-8 yr	Seizures, memory loss, behavioral changes	None currently reported in childhood	Unknown in childhood	Unknown
D2R	4 mo-15 yr	Seizures, lethargy, psychiatric symptoms, dystonia, parkinsonism, chorea, ataxia	None currently reported in childhood	Unknown; reported in case series as 25% relapse rate in childhood	Unknown; a single case series reports full recovery in 40%
mGluR5 (Ophelia syndrome)	Adolescence	Memory loss, depression, hallucinations, behavior abnormalities	Hodgkin's lymphoma	Uncommon if treated appropriately	Full recovery with appropriate treatment
Hu	1-15 yr	Behavioral changes, seizures, posterior cord syndrome, ataxia	Estimated 25% associated with neuroblastoma	Unknown in childhood	Reported patients with continued seizures despite treatment
Ma1 and *Ma2*	2-14 yr	Seizures, behavioral changes, memory loss, speech changes	None currently reported in childhood	Unknown in childhood	Reported patients with poor outcomes
GAD	2-17 yr	Seizures, cognitive decline, psychosis, memory loss, stiff-person syndrome, progressive developmental delay	None currently reported in childhood	Unknown in childhood	Variable outcome potentially related to rapidity of treatment

Abbreviations:
ADEM = Acute disseminated encephalomyelitis
AMPA = α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
D2R = Dopamine D2 receptor
$GABA_A$ = Gamma-aminobutyric acid type A
$GABA_B$ = Gamma-aminobutyric acid type B
GAD = Glutamic acid decarboxylase
GlyR = Glycine receptor
mGluR5 = metabotropic glutamate receptor 5
NMDAR = N-methyl-D-aspartate receptor
ON = Optic neuritis
PERM = Progressive encephalomyelitis with rigidity and myoclonus
VGKC = Voltage-gated potassium channel

* Ages listed include those age ranges for children and adolescents, although it is important to remember that all disorders in this table have been reported in adulthood as well.