

Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient

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Abstract

Objective

Autoimmune encephalitis (AE) is an important and treatable cause of acute encephalitis. Diagnosis of AE in a developing child is challenging because of overlap in clinical presentations with other diseases and complexity of normal behavior changes. Existing diagnostic criteria for adult AE require modification to be applied to children, who differ from adults in their clinical presentations, paraclinical findings, autoantibody profiles, treatment response, and long-term outcomes.

Methods

A subcommittee of the Autoimmune Encephalitis International Working Group collaborated through conference calls and email correspondence to consider the pediatric-specific approach to AE. The subcommittee reviewed the literature of relevant AE studies and sought additional input from other expert clinicians and researchers.

Results

Existing consensus criteria for adult AE were refined for use in children. Provisional pediatric AE classification criteria and an algorithm to facilitate early diagnosis are proposed. There is also discussion about how to distinguish pediatric AE from conditions within the differential diagnosis.

Conclusions

Diagnosing AE is based on the combination of a clinical history consistent with pediatric AE and supportive diagnostic testing, which includes but is not dependent on antibody testing. The proposed criteria and algorithm require validation in prospective pediatric cohorts.

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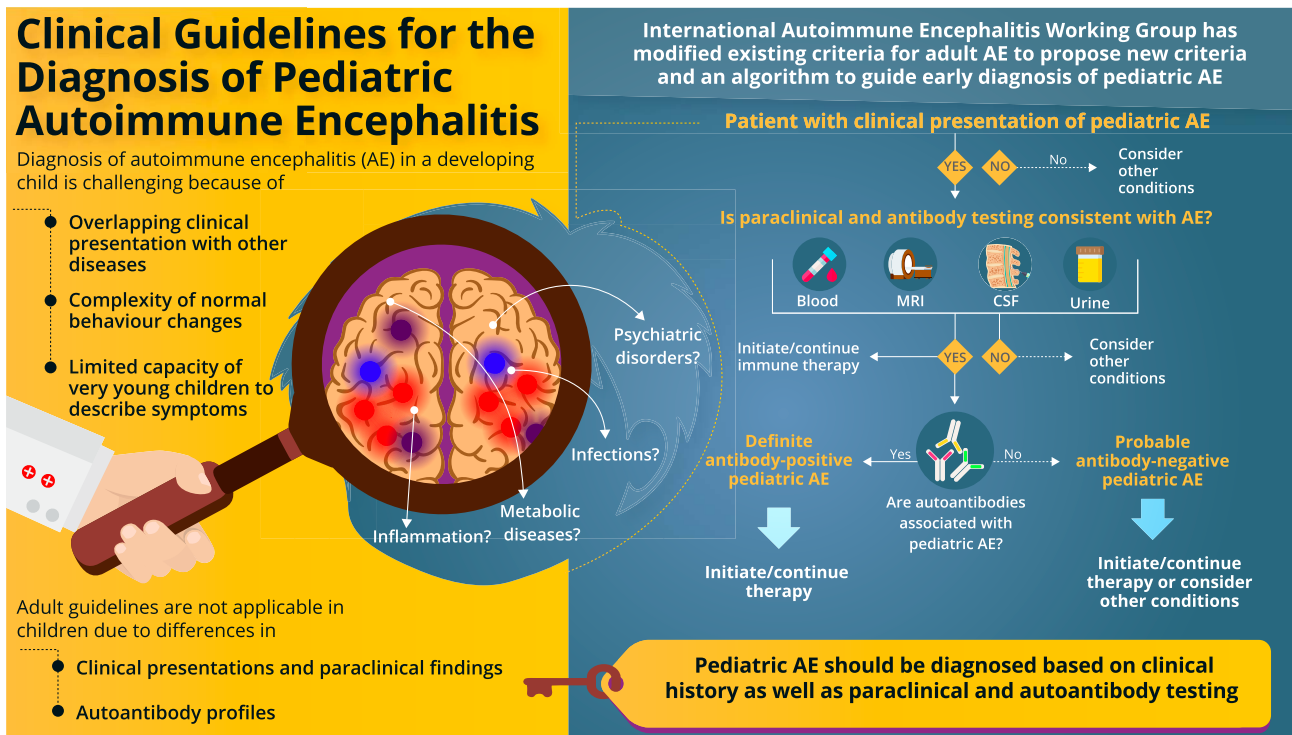
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Glossary

AE = autoimmune encephalitis; Caspr2 = contactin-associated protein-like 2; FIRES = febrile infection-related epilepsy syndrome; GABA_AR = gamma-aminobutyric acid A receptor; GAD65 = glutamic acid decarboxylase 65; HE = Hashimoto encephalopathy; LGI1 = leucine-rich glioma-inactivated protein 1; MOG = myelin oligodendrocyte glycoprotein; NMDAR = N-methyl-D-aspartate receptor; PANDAS = pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANS = pediatric acute-onset neuropsychiatric syndrome; VGKCC = voltage-gated potassium channel complex.



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Neurology
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Autoimmune encephalitis (AE) refers to an increasingly recognized group of inflammatory brain diseases. Children with AE present with acute or subacute onset of neuropsychiatric symptoms due to an underlying abnormal immune response to the CNS.^{1,2} Many AE associate with antibodies directed toward extracellular antigens, such as synaptic receptors and ion channels.^{2,3} Autoantibodies that bind to extracellular antigens are generally pathogenic, whereas antibodies that bind intracellular antigens are not considered pathogenic, instead general markers of autoimmunity.

A number of different antibodies have been described in children with AE.^{4–21} Currently, the most common autoantibodies in children target the N-methyl-D-aspartate receptor (NMDAR), myelin oligodendrocyte glycoprotein (MOG), and glutamic acid decarboxylase 65 (GAD65).^{5–12} It is also recognized that not all children with a clinical phenotype of AE have a known autoantibody.^{1,4}

Diagnosing AE is challenging because of overlap in clinical presentations between the types of AE, other inflammatory brain diseases, infections, metabolic diseases, and psychiatric disorders.¹ It is especially difficult in children because of the complexity of

normal behavioral changes during childhood and the limited capacity of younger children to describe their symptoms.¹ Compared to adults with AE, children may manifest important differences in symptoms, paraclinical findings, comorbidities, treatment response, and prognosis.^{4–7,22–24} There is an urgent need to recognize pediatric AE because treatment delays worsen prognosis and increase the risk of permanent neurocognitive deficits.^{6,25,26}

In this article, we build on existing consensus criteria for adult AE by refining them for use in children.²⁷ We propose provisional pediatric AE classification criteria and an algorithm to facilitate early diagnosis. Diagnosing AE is based on the combination of a clinical history consistent with the disease and supportive diagnostic testing, which includes but is not dependent on antibody testing. We also discuss the differential diagnosis in children with suspected AE.

Methodology

At the 2014 Autoimmune Encephalitis Alliance (AEalliance.org) conference in North Carolina, the Autoimmune Encephalitis International Working Group was formed and initiated discussions around developing diagnostic criteria for AE. A subcommittee of pediatric neurologists and rheumatologists

identified that adult-focused criteria may not apply well to children. As a result, this subcommittee collaborated through conference calls and email correspondence to consider the pediatric-specific approach to AE. The subcommittee reviewed the literature on relevant AE studies and sought additional input from other experts. The first author (T.C.) developed a draft based on the preceding discussions that was subsequently reviewed and modified by all authors.

Existing diagnostic criteria for AE

The International Encephalitis Consortium 2013 diagnostic criteria for encephalitis of presumed infectious or autoimmune etiology require patients to have altered mental status lasting more than 24 hours with no alternative cause identified.²⁸ Confirmation of this diagnosis requires at least 3 minor criteria, including fever within 72 hours of presentation; new onset focal neurologic findings; CSF leukocytosis; acute new neuroimaging abnormality suggestive of encephalitis; or EEG abnormalities consistent with encephalitis.²⁸ These criteria do not differentiate autoimmune from infectious encephalitis.

More recently, an international group developed diagnostic criteria for early diagnosis of AE in adults, which require (1) subacute onset over less than 3 months of working memory deficits, altered mental status, or psychiatric symptoms; (2) at least one of the following: new focal CNS findings, seizures not explained by a preexisting disorder, CSF pleocytosis, and/or MRI features suggestive of encephalitis; and (3) reasonable exclusion of alternative causes.²⁷ Specific neurologic syndromes were given criteria, including limbic encephalitis, anti-NMDAR encephalitis, and autoantibody-negative AE.²⁷

These AE criteria required modification to be applied to children. For example, deficits in working memory are challenging to identify in younger children. Also, children are less likely to present with a well-defined neurologic syndrome and, even in anti-NMDAR encephalitis, the sequence of symptom development may differ from adults.⁵⁻⁷ Furthermore, the differential diagnosis for a child presenting with temporal lobe seizures and cognitive slowing is broad, whereas this presentation in adults suggests limbic encephalitis or acquired temporal pathology.

Clinical features distinguishing adults and children with AE

Typically, children with AE are previously healthy and present with rapid onset of neuropsychiatric symptoms. Prodromal symptoms including fever occur in over 50% of patients.^{2,4-6} Between disease onset and initiation of therapy, symptoms typically persist over time. This distinguishes AE from pediatric acute-onset neuropsychiatric syndrome (PANS), where patients often experience a relapsing-remitting course with rapid progression to maximum symptom severity and rapid return to previous function over hours or days, sometimes without therapy.

Neurologic manifestations of AE include altered level of consciousness, confusion, disturbed sleep, movement disorders and seizures. Seizures are the most common feature in AE and may be the predominant manifestation.^{4-7,10-21} Seizures may be focal or generalized and are often multifocal.^{4-7,10-21} Over one third of patients with AE have abnormal movements, such as ataxia, chorea, dystonia, myoclonus, or tremor.^{4-7,13,15} Both seizures and movement disorders can be highly refractory to standard treatments in children with AE.^{10,14,16,24} Some degree of cognitive impairment is seen in the overwhelming majority of AE patients and is considered a cardinal symptom.^{4,5,13,14,16,19,21} As such, a diagnosis of AE would be highly questionable in patients with documented normal cognition, again differentiating AE from PANS where cognition is often preserved. Assessing memory deficits in young children may be challenging; however, developmental regression, language loss or speech impairments may be presenting features of pediatric AE.^{5-7,29}

Behavioral changes, such as repetitive or stereotypical behaviors, irritability, hyperactivity, hypersexuality, insomnia and anger outbursts, are common in pediatric AE.⁴⁻⁷ Psychiatric symptoms may range from mood swings and mild personality changes to fulminant psychosis and occur in over 50% of AE patients.⁴⁻⁷ New-onset psychosis in children younger than 13 years is uncommon and considered a red flag for an underlying medical, rather than primary psychiatric, condition. It is critical to assess for cognitive changes, seizures, movement abnormalities, or other neurologic symptoms in children with acute psychiatric symptoms, as these symptoms are suggestive of AE.

Children with AE likely differ from adults in their clinical presentations due to evolution of neuronal circuits, neuroreceptor densities and myelination during normal development. Children with AE are more likely to present with multifocal neuropsychiatric symptoms, rather than isolated clinical syndromes. For example, children with GAD65 antibodies may not present with the classic stiff-person syndrome or cerebellar degeneration seen in adults.^{11,12,22} Children with anti-NMDAR-associated encephalitis are more likely to present with movement abnormalities, agitation, insomnia, seizures, speech deficits, ataxia, and/or hemiparesis, whereas memory deficits, psychiatric manifestations, and central hypoventilation are more common in adults with the same antibody.⁵⁻⁷ Pediatric AE is less associated with tumors compared with adults.⁴⁻⁷

Diagnostic evaluation of children and teenagers with suspected AE

Although no single investigation is diagnostic of pediatric AE, the presence of a suggestive clinical phenotype and supportive paraclinical testing is essential to diagnose an underlying inflammatory process and to exclude alternative diagnoses. Initial investigations to be considered for any child with suspected AE are listed in table 1, although diagnostic workup should be tailored to the individual.

Table 1 Recommended investigations for children with suspected AE

A. Initial investigations for patients with possible AE	
Diagnostic imaging	Brain MRI with gadolinium (including T1, T2, FLAIR, and diffusion-weighted sequences) Consider adding spine MRI if neurologic abnormalities potentially mediated by spinal cord involvement
Blood tests	Complete blood cell count and differential Erythrocyte sedimentation rate, C-reactive protein, and ferritin Vitamin B12 level and vitamin D level Serum lactate Thyroid-stimulating hormone, free thyroxine, and thyroid autoantibodies (e.g., antithyroid peroxidase, antithyroglobulin, and anti-thyroid-stimulating hormone receptor) Serologic testing for infectious causes (dependent on regional epidemiology) Consider antinuclear antibodies and specific antinuclear antibodies (e.g., anti-double-stranded DNA and anti-Smith) if indicated by clinical presentation Consider serum complement and immunoglobulin levels if personal or family history of autoimmunity or immune deficiency
Urine tests	Testing for recreational drugs (e.g., marijuana, cocaine, and opioids)
Lumbar puncture	Opening pressure CSF cell counts, protein, lactate, oligoclonal bands, and neopterin (if available) Infectious testing dependent on regional epidemiology, but often includes PCR for enterovirus, herpes simplex virus, and varicella zoster viruses Save 5–10 mL of CSF for future testing
Respiratory tests	Nasopharyngeal swab for respiratory viruses and mycoplasma PCR
EEG	Assess for focal or generalized seizures, epileptiform discharges, and changes in background activity
B. More specific investigations for patients with possible AE	
Blood tests	Serum testing for antibodies associated with AE ^a
Lumbar puncture	CSF testing for antibodies associated with AE ^a
Neurocognitive tests	Assess for cognitive deficits affecting memory, attention, problem solving, language, and cognitive processing Consider using symbol digit modalities test to screen for cognitive dysfunction
Other tests	Consider if available and/or if required based on initial investigations: PET and SPECT

Abbreviations: AE = autoimmune encephalitis; FLAIR = fluid-attenuated inversion recovery.

^a See tables 2 and 3 for details regarding neural antibodies identified in children.

Blood tests are helpful to assess for systemic inflammatory changes, autoantibodies associated with systemic autoimmune diseases, vitamin B12 deficiency, markers of infection, elevated lactate due to metabolic conditions, and recreational drug use. Erythrocyte sedimentation rate, C-reactive protein, leukocyte counts, and platelet counts may be normal in children with AE.^{1,4–21}

CSF pleocytosis and/or elevated protein levels may be seen at diagnosis or during disease course, but are not uniformly present.^{1,4–21} Recommended tests to assess for infectious encephalitis were based on population-based studies in California and England (table 1).^{30,31} However, workup for infectious

etiologies varies depending on the season and region where the patient lives or has traveled. A recent report suggests that anti-NMDAR encephalitis may be more common in children than any specific infectious encephalitis, further highlighting the importance of considering AE when evaluating for infectious encephalitis.³² CSF neopterin is a useful but not rapidly accessible biomarker that is frequently elevated in anti-NMDAR encephalitis and other encephalitides, but normal in PANS.³³ There is evidence that AE (particularly anti-NMDAR encephalitis) may be triggered by herpes simplex virus encephalitis and Japanese encephalitis.³⁴

All patients should have a brain MRI with and without gadolinium. Over half of patients with AE will have a normal

Table 2 Antibodies that are commonly identified in pediatric AE

Antibody target (localization)	Typical clinical features in children	
GAD65 ^{10–12} (intracellular)	Frequency	Common in AE, but only pathologic if high titers in serum and present in CSF
	Clinical	Encephalitis with memory loss, cognitive impairment, cerebellar ataxia, and temporal lobe seizures
	MRI	May be normal initially often progresses to lesions in the limbic system, cerebellum, and cortices with possible atrophy
	EEG	Epileptiform discharges may be multifocal
	Other	CSF leukocytosis may be mild with oligoclonal bands Associated personal or family history of autoimmunity Often resistant to immunotherapy
MOG ^{8,9,42,45–47} (extracellular)	Frequency	Common in AE
	Clinical	Acute disseminated encephalomyelitis including encephalopathy, optic neuritis, or transverse myelitis (but not typical MS); cortical encephalitis with seizures; brainstem encephalitis; and meningoencephalitis without demyelination
	MRI	Focal or multifocal white matter lesions, longitudinally extensive myelitis and optic neuritis
	EEG	Nonspecific slowing
	Other	Serum antibody testing preferable to CSF Higher titers of antibodies in younger children Persistent antibodies in relapsing disease
NMDAR ^{5–7} (extracellular)	Frequency	Most common antibody target in pediatric AE
	Clinical	Encephalitis with movement disorder, seizures, psychiatric symptoms, reduced verbal output/mutism, developmental regression (in younger children), sleep dysfunction (mainly insomnia), and autonomic instability
	MRI	Normal in at least 65% of patients; T2/FLAIR lesions may be identified in the cortex, white matter, cerebellum, or basal ganglia; reversible cerebral atrophy is a late finding
	EEG	Abnormal in over 90% of patients—most have generalized slowing, but may see focal epileptic activity, focal slowing, or “prolonged spindles/delta brush pattern”
	Other	CSF antibody testing preferable to serum Increased association with tumors in females and in patients older than 12 y

Abbreviations: AE = autoimmune encephalitis; FLAIR = fluid-attenuated inversion recovery; GAD65 = glutamic acid decarboxylase 65; MOG = myelin oligodendrocyte glycoprotein; NMDAR = NMDA receptor.

brain and spine MRI at diagnosis.^{4–7,16,21,22} Inflammatory lesions (high signal on T2 and fluid-attenuated inversion recovery sequences) may develop over time, and cerebral atrophy may occur months later.^{4,6,7,15} MRI lesions are most likely to be present in those with antibodies to MOG or the gamma-aminobutyric acid-A receptor (GABA_AR).^{9,14,15} Neuroimaging findings are not limited to the temporal lobe or cortex.^{1,5–21} A normal MRI lessens suspicion for CNS vasculitis, demyelinating diseases, infections, and malignancies.¹ In contrast, restriction on diffusion-weighted imaging reduces the likelihood of pediatric AE and should prompt consideration of other etiologies, such as infection-associated encephalopathies and vasculitis.¹ Small retrospective adult AE studies have proposed that functional PET and SPECT studies may demonstrate brain dysfunction, but experience is limited in pediatric AE.^{35,36}

A normal EEG is unusual in children with AE during active disease, although prolonged EEG may be needed for

improved sensitivity. Therefore, focal or generalized seizures, epileptiform discharges, and encephalopathic changes, such as diffuse or focal slowing, may help to distinguish AE from primary psychiatric disorders or PANS. Adults with AE are more likely to have EEG changes predominantly involving the temporal lobes, whereas EEG findings in children may be more generalized.^{4–7,14–21} Specific EEG features, such as the “delta brush” pattern and extreme spindles, have been linked to anti-NMDAR encephalitis, but sensitivity is low.^{6,22,23}

Neurocognitive testing may identify deficits in memory, attention, problem solving, language, and processing speed, particularly in younger children. A change in neurocognitive function supports a diagnosis of pediatric AE and may differentiate these patients from those with primary psychiatric disorders. However, interpretation of neurocognitive testing at diagnosis should be undertaken with caution, as there is often no premorbid testing for comparison.

Table 3 Antibodies that are identified less frequently in pediatric autoimmune encephalitis

Antibody target (localization)	Typical clinical features in children	
Dopamine-2 receptor¹³ (extracellular)	Frequency	Very uncommon
	Clinical	Encephalitis with predominant movement disorders, psychiatric symptoms, sleep disturbance, mutism, and decreased consciousness
	MRI	Abnormal in 50% of patients, usually symmetric selective involvement of basal ganglia
	EEG	No consistent pattern reported
	Other	Variable CSF findings, sometimes lymphocytic pleocytosis or oligoclonal bands
GABA_A receptor^{14,15} (extracellular)	Frequency	Uncommon
	Clinical	Encephalitis with refractory seizures, status epilepticus, or epilepsy partialis continua
	MRI	Multifocal T2/FLAIR lesions in cortical/subcortical areas
	EEG	Epileptiform activity and generalized slowing
	Other	Most patients have CSF leukocytosis Often associated with GAD or thyroid autoantibodies
GABA-B receptor^{16,17} (extracellular)	Frequency	Very uncommon
	Clinical	Encephalitis with focal or generalized seizures and mixed movement disorder
	MRI	Abnormal in over 50% with increased T2/FLAIR signal in the medial temporal lobe (may be multifocal and may be associated with changes on diffusion-weighted imaging)
	EEG	Diffuse slowing and epileptiform discharges
	Other	CSF abnormal in up to 90% with lymphocytic pleocytosis Pediatric cases not linked to infection or tumor
Glycine receptor^{18,19} (extracellular)	Frequency	Uncommon
	Clinical	Progressive encephalomyelitis with rigidity and myoclonus; encephalitis; and other brainstem syndromes
	MRI	Frequently normal (70% reported cases)
	EEG	Abnormal in approximately 70%, usually slowing
	Other	Variable CSF findings of lymphocytosis, elevated protein, and oligoclonal bands May be associated with antibodies to other targets (e.g., GAD)
m-GluR5^{20,21} (extracellular)	Frequency	Very uncommon
	Clinical	Encephalitis with psychiatric symptoms
	MRI	Variable MRI findings, often T2/FLAIR
	EEG	Variable EEG findings, typically absent epileptiform discharges
	Other	CSF lymphocytic pleocytosis

Abbreviations: FLAIR = fluid-attenuated inversion recovery; GABA = gamma-aminobutyric acid; GAD = glutamic acid decarboxylase; m-GluR5 = metabotropic glutamate receptor 5.

Other diagnostic tests may be considered. Most children with AE do not require brain biopsy. However, a targeted brain biopsy of MRI abnormalities may be needed when the diagnosis remains uncertain after initial workup. The diagnostic yield of brain biopsy is higher in pediatric patients than in adults.³⁷

Antibody testing and interpretation in children and teenagers with suspected AE

Antibodies associated with pediatric AE are listed in tables 2 and 3. Each antibody is associated with characteristic

Table 4 Proposed classification criteria for possible, definite antibody-positive and probable antibody-negative pediatric AE

Categorical features of AE	Specific diagnostic features	Diagnostic categories		
		Possible AE	Probable antibody-negative AE	Definite antibody-positive AE
1. Evidence of acute or subacute symptom onset	Onset of neurologic and/or psychiatric symptoms over ≤ 3 mo in a previously healthy child	Yes	Yes	Yes
2. Clinical evidence of neurologic dysfunction	Features include: Altered mental status/level of consciousness or EEG with slowing or epileptiform activity (focal or generalized) Focal neurologic deficits Cognitive difficulties ^a Acute developmental regression Movement disorder (except tics) Psychiatric symptoms Seizures not explained by a previously known seizure disorder or other condition	≥ 2 features present	≥ 2 features present	≥ 2 features present
3. Paraclinical evidence of neuroinflammation	Features include: CSF inflammatory changes (leukocytosis >5 cells/mm ³ and/or oligoclonal banding) MRI features of encephalitis Brain biopsy showing inflammatory infiltrates and excluding other disorders	Not available	≥ 1 features present	$\geq 1^b$ features present
4. AE serology	Presence in serum and/or CSF of well-characterized autoantibodies associated with AE	Not available	No	Yes
5. Exclusion of other etiologies	Reasonable exclusion of alternative causes, including other causes of CNS inflammation	Yes	Yes	Yes

Abbreviation: AE = autoimmune encephalitis.

^a Severe cognitive dysfunction that is not attributable to a primary psychiatric syndrome as documented by a qualified clinician (e.g., neurologist, psychiatrist, and neuropsychologist) or a significant drop in IQ (>20 points).

^b When antibodies against NMDA receptor, gamma-aminobutyric acid A receptor, or glutamic acid decarboxylase 65 are present in CSF, further paraclinical markers of neuroinflammation are not required to diagnose definite AE. When only serum antibodies are present, one or more paraclinical marker(s) of neuroinflammation is required.

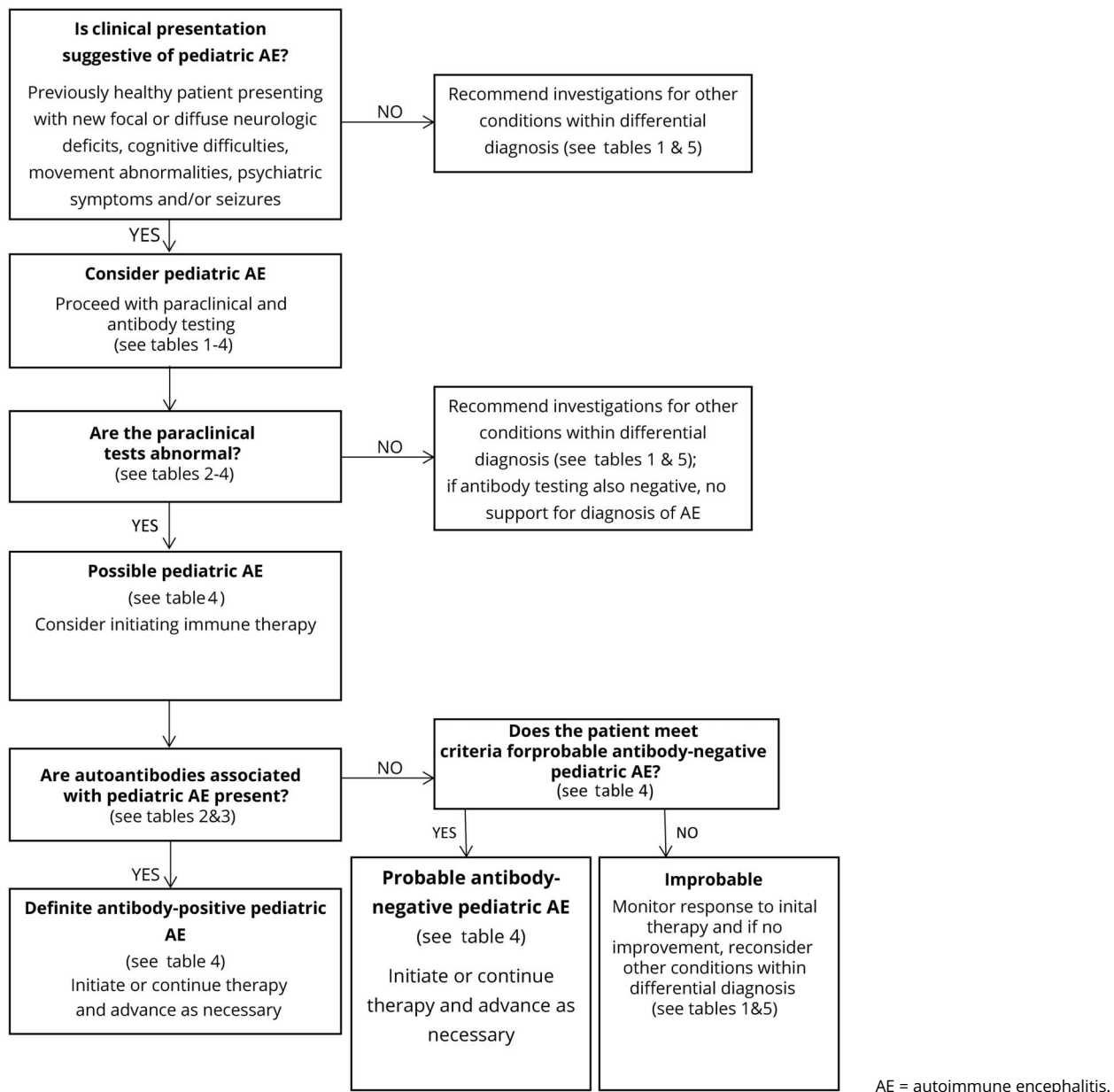
symptoms, seizure types, and other clinical findings. However, there is significant overlap between the different disorders and so testing a panel of neural autoantibodies is recommended for any child with suspected AE. The most common autoantibodies identified in children target NMDAR, MOG, GAD65, and GABA_A R. Given the rarity of other autoantibodies, further testing should be considered only if antibodies to these targets are negative and suspicion of AE persists (table 3).

Antibody testing should be performed in both CSF and serum to avoid false-negative and false-positive results. For example, testing for NMDAR antibodies typically has higher sensitivity in CSF compared with serum, with up to 15% of patients having negative serum results.⁵⁻⁷ In contrast, MOG autoantibodies have higher sensitivity in serum.⁹

Interpretation of antibody test results should carefully consider the child's clinical presentation, especially when more than 1 antibody is identified. For example, GAD65 antibodies tend to be associated with personal or familial autoimmunity and low titers, such as those seen in type 1 diabetes mellitus, are not neurologically relevant.²² The presence of more than 1 antibody in some patients with AE has been recognized and may be associated with overlapping syndromes. Antibody specificity is also important when interpreting antibody test results. For instance, only IgG isotype antibodies to the GluN1 subunit of the NMDAR on a cell-based assay are specifically associated with AE.^{5,38}

In adults with AE, most antibodies to the voltage-gated potassium channel complex (VGKCC) do not bind to the channel, but to proteins in the complex, particularly leucine-rich glioma-inactivated protein 1 (LG11) and contactin-

Figure Algorithm for diagnostic workup of children with suspected AE using provisional criteria



associated protein-like 2 (Caspr2).³⁹ In children, VGKCC antibodies rarely target LGI1 or Caspr2.^{40,41} It has been argued that VGKCC antibodies without specific binding to LGI1 or Caspr2 have limited clinical significance.⁴⁰

Proposed classification criteria and algorithm for diagnosis of pediatric AE

We modified the criteria for adult AE and propose provisional classification criteria for possible pediatric AE, probable antibody-negative pediatric AE, and definite antibody-positive pediatric AE in table 4.²⁷ A diagnostic algorithm is also provided in figure. The provisional criteria and algorithm should be assessed prospectively in future cohorts.

A diagnosis of pediatric AE should be considered in previously healthy children who present with acute or subacute (less than 3 months) onset of new focal or diffuse neurologic deficits, cognitive difficulties, developmental regression, movement abnormalities, psychiatric symptoms, and/or seizures. Although children with preexisting developmental delay or chronic behavior/psychiatric abnormalities may develop AE, alternative diagnoses, such as genetic, metabolic, or neurodegenerative etiologies, should be considered in these patients.

Children with a clinical presentation suggestive of AE should have serum and CSF examined for neuronal antibodies, undergo paraclinical testing for neuroinflammation, and have disease mimics excluded (tables 1 and 4). EEG is not included

Table 5 Differential diagnosis of AE in children and adolescents

Primary CNS inflammatory	AE, including HE
	Primary or secondary CNS vasculitis
	Demyelinating diseases: acute disseminated encephalomyelitis, MS, and neuromyelitis optica
	Rasmussen encephalitis
Systemic inflammatory	Autoimmune diseases: antiphospholipid syndrome, celiac disease, Behçet disease, sarcoidosis, systemic lupus erythematosus, and Sjögren syndrome
	Autoinflammatory diseases: interferonopathies and hemophagocytic lymphohistiocytosis
Infectious	Bacteria: <i>Borrelia burgdorferi</i> , <i>Listeria monocytogenes</i> , <i>Mycoplasma pneumoniae</i> , <i>Mycobacterium tuberculosis</i> , and <i>Treponema pallidum</i>
	Viruses: adenovirus, enterovirus, Epstein-Barr virus, HSV, HIV, influenza, JC virus, measles, rabies, varicella zoster virus, and West Nile virus
	Parasites: malaria
Postinfectious or infection-associated encephalopathy	Postmycoplasma basal ganglia encephalitis
	Post-HSV encephalitis movement disorder
	Poststreptococcal neuropsychiatric disorders (including Sydenham chorea)
	Encephalitis lethargica
Diseases with immune mechanisms under review	FIRES
	ANE
	AESD
	PANDAS
	PANS
Metabolic	Genetic/inherited diseases: leukodystrophies, mitochondrial diseases, mucopolysaccharidoses, organic acidurias, and Wilson disease
	Hepatic encephalopathy
Neoplastic	Primary CNS tumors (e.g., lymphoma, glioma, and astrocytoma)
	Metastatic disease (e.g., neuroblastoma and leukemia)
Nutritional	Vitamin B12 deficiency
Psychiatric	New onset schizophrenia, bipolar disorder, conversion disorder, childhood disintegrative disorder, and psychogenic seizures
Toxic	Recreational drugs (e.g., alcohol, marijuana, synthetic cannabinoids, cocaine, opioids, and methamphetamines)
	Ingestions (e.g., ethylene glycol, methanol, and inhalants)
	Medications, such as metronidazole and cyclosporine
Other	Child abuse and neglect

Abbreviations: AE = autoimmune encephalitis; AESD = acute encephalopathy with biphasic seizures and diffusion restriction; ANE = acute necrotizing encephalopathy; FIRES = febrile infection-related epilepsy syndrome; HE = Hashimoto encephalopathy; HSV = herpes simplex virus; PANDAS = pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANS = pediatric acute-onset neuropsychiatric syndrome.

as paraclinical evidence of neuroinflammation because EEG cannot differentiate AE from other encephalopathies. However, EEG encephalopathic features are allowable as an alternative for clinical features of encephalopathy. If a patient fulfills criteria for possible pediatric AE (table 4) and is functionally impaired, therapy may be started while awaiting the results of

antibody and other testing, given the importance of early treatment to improve outcomes.^{4,25,26} If a patient with possible AE subsequently does not have positive antibodies or paraclinical testing for neuroinflammation, a diagnosis of AE is not supported. For these children, careful further consideration of the differential diagnosis is warranted, and additional immune

therapy should only be undertaken with caution (table 5, figure).

Children may have AE caused by antibodies that have not yet been identified and may meet criteria for probable antibody-negative pediatric AE (table 4). These patients will have 1 or more positive paraclinical tests for neuroinflammation, but negative antibody testing. Children who meet the criteria for definite antibody-positive pediatric AE will have positive antibody testing. If CSF antibodies are present (e.g., NMDAR and GAD65), no other paraclinical evidence of neuroinflammation is required for a diagnosis of definite AE (table 4). If only serum antibodies are present, 1 or more paraclinical tests of neuroinflammation must be abnormal. There should be caution in diagnosing AE when only serum antibodies (particularly NMDAR, GABA_AR, and glycine receptor) are found in the absence of paraclinical evidence of neuroinflammation.

The proposed pediatric AE criteria differ from the adult criteria in several ways (table 4, table e-5, [links.lww.com/nxi/A184](https://www.lww.com/nxi/A184)).²⁷ First, the pediatric criteria include both acute and subacute time frames for symptom onset, reflecting the range in disease course observed in children. Adult AE criteria were developed for several well-defined syndromes (i.e., limbic encephalitis, acute disseminated encephalomyelitis [ADEM], and anti-NMDAR encephalitis) and the associated algorithm focuses on whether patients meet criteria for these syndromes.²⁷ In contrast, many pediatric patients with AE do not present with a well-defined syndrome and so the pediatric criteria were devised to capture the breadth of clinical and paraclinical findings reported in children. Similarly, the pediatric AE algorithm (figure) does not focus on syndrome identification, but is intended to guide a clinician in assessing clinical features and in paraclinical and antibody testing, so as to determine whether an AE diagnosis is appropriate. The adult AE criteria group clinical and paraclinical markers together, whereas the pediatric criteria distinguish clinical evidence of neurologic dysfunction from paraclinical evidence of neuroinflammation.

Patients with definite AE may benefit from continued or advanced immunosuppressive therapy, although specific protocols are not yet validated. Identification of an antibody associated with AE may facilitate counseling regarding expected course and outcomes. Timing of clinical responses to immunotherapy in children with AE may vary from immediate to months after starting.^{5-7,24,42} Therefore, using response to therapy as confirmatory support for a diagnosis of AE may be misleading.

Approach to clinically recognizable syndromes

Anti-NMDAR encephalitis

Anti-NMDAR encephalitis is the most common pediatric AE. The current adult diagnostic criteria for anti-NMDAR-associated encephalitis have been tested and apply well in

children.⁴³ However, children are more likely to present with neurologic symptoms, instead of psychiatric symptoms, and may not present with the classic sequence of symptoms described in adults—for example, movement disorders and autonomic dysfunction occur earlier in children.⁵⁻⁷

AE associated with antibodies to MOG, including acute disseminated encephalomyelitis

The most common autoantibody associated with autoimmune demyelination targets MOG.^{8,9,42} Patients who have ADEM associated with MOG autoantibodies are more likely to exhibit large globular lesions and long segment myelitis compared with those without these antibodies.⁴⁴ Children with MOG antibodies are also less likely to have oligoclonal bands than those with MS.^{42,44} However, the spectrum of brain disease associated with MOG antibodies in adults and children has broadened to include ADEM, meningoencephalitis, cortical encephalitis with seizures, brainstem encephalitis, and mimics of vasculitis.⁴⁵⁻⁴⁷ Some of these patients will evolve into more typical demyelinating phenotypes, such as ADEM; therefore, MOG antibodies should be considered in pediatric AE presentations beyond ADEM.⁴⁵⁻⁴⁷ MOG autoantibodies are typically transient in monophasic ADEM, but remain positive in relapsing phenotypes.^{8,9,42}

Limbic encephalitis

The clinical, EEG, and radiologic features of limbic encephalitis are uncommon in children.⁴⁸ Autoantibodies associated with adult limbic encephalitis include those that target LGI1, GAD65, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, gamma-aminobutyric acid-B receptor, Caspr2, Hu, and Ma2.³ With the exception of GAD65, these specific antibodies are rare in children.⁴⁸

Hashimoto encephalopathy

Hashimoto encephalopathy (HE) presents with nonspecific neuropsychiatric symptoms accompanied by antithyroid antibodies, which are considered markers of autoimmunity, rather than pathogenic. Patients may develop seizures, altered mental status, cognitive decline, psychosis, paranoia, focal neurologic defects, and movement disorders.^{49,50} Over 70% of children with HE have a normal brain MRI, CSF rarely shows pleocytosis, and EEG often shows generalized or focal slowing without seizures.^{49,50} Most children have normal thyroid function despite having antithyroid antibodies.^{49,50} Thoughtful interpretation is required because serum thyroid autoantibodies have been identified in healthy children.^{49,50}

Approach to probable antibody-negative pediatric AE

Children with a clinical phenotype of AE and paraclinical findings of neuroinflammation, but negative testing for neural antibodies, may meet criteria for probable antibody-negative pediatric AE (table 4). It is well recognized that not all neural autoantibodies have been identified. Having CSF and serum

testing in a research laboratory may identify patients who have antibodies against neural cell surface antigens of yet unknown identity and who may respond to immunotherapy.

Probable antibody-negative AE is one of the most challenging clinical scenarios. It is appropriate that a child presenting with new onset encephalopathy, neuropsychiatric features, and changes in function be investigated for possible AE. However, the differential diagnosis in children is arguably broader than in adults, and so it is important to ensure that other diagnoses have been excluded before giving an AE diagnosis. Pathologic entities that often cause diagnostic difficulty are cortical dysplasias and genetic epilepsies presenting with fever-provoked symptomatic focal seizures, infection-provoked encephalopathy and PANS. In these syndromes, CSF pleocytosis or oligoclonal bands are usually absent, and MRI is either normal or demonstrates alternative pathology. Therefore, critical examination of paraclinical tests for evidence of CNS inflammation is mandatory to avoid unnecessary immune suppression. A diagnosis of probable antibody-negative pediatric AE should also be reassessed in children with atypical features.

Differential diagnosis of AE

The spectrum of inflammatory brain diseases in children has rapidly expanded as new diseases and new etiologies for existing conditions have been described. The underlying pathogenic mechanisms that lead to CNS inflammation may involve vessel wall inflammation, demyelination, or an immune response directed against neurons and supporting structures.^{1,3} Inflammation may also occur secondary to infection, malignancy, or a systemic inflammatory disease. Diagnosing pediatric AE is especially challenging because of the clinical overlap between conditions in the differential diagnosis (table 5) and the clinical heterogeneity within patients having the same disease.

Specific conditions within the differential diagnosis of AE

Comprehensive evaluation is required to distinguish children with AE from those who have other inflammatory brain diseases. For example, children with large-vessel CNS vasculitis typically demonstrate a stroke phenotype, including paresis and speech deficits, and may be distinguished by the presence of ischemic changes on MRI and angiographic abnormalities, such as aneurysm and beading.⁵¹ In contrast, children with small-vessel CNS vasculitis present with cognitive dysfunction, seizures, vision abnormalities, and bilateral nonischemic lesions on MRI and have inflammatory vessel wall changes identified on brain biopsy.⁵¹

Infection-associated encephalopathy disorders include febrile infection-related epilepsy syndrome (FIREs), acute necrotizing encephalopathy, mild encephalopathy with reversible splenium lesion, and acute encephalopathy with biphasic seizures and diffusion restriction.⁵² These syndromes have typical clinical and radiologic features, often with diffusion restriction on imaging, which may infer cytotoxicity and distinguish these patients from those with AE. For example, children with FIREs develop

a nonspecific febrile illness followed by sustained refractory status and then progress to chronic, drug-resistant epilepsy with neuropsychological impairment.⁵² Neuroimaging and brain biopsy in FIREs are usually normal.⁵² The pathogenesis of these diseases is unresolved, but may include genetic vulnerability leading to an infection-triggered “cytokine storm.”⁵²

Other diagnoses within the differential are PANS and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). These conditions describe an idiopathic or postinfectious onset of obsessive-compulsive disorder, eating restriction, other emotional syndromes, tics, loss of skills, or personality change.⁵³ Both clinical phenotypes lack robust biomarkers, and pathogenesis remains disputed; however, there is some evidence of immune mediation and immunotherapy responsiveness.^{53,54} Although patients may appear to have an acquired brain syndrome, most children with PANDAS or PANS would not fulfill the proposed pediatric AE criteria.

Also, monogenic autoinflammatory syndromes may involve the brain, such as the genetic interferonopathies, vasculopathies, and hemophagocytic lymphohistiocytosis.⁵⁵ These disorders typically present in early childhood, result in chronic progressive disease, often involving increasing spasticity, intracranial calcifications and microcephaly, and are associated with persistent CSF immune activation.⁵⁵ These syndromes are distinguished from AE by the presence of non-neurologic features, such as skin lesions, cytopenias, hepatosplenomegaly, and lung disease.⁵⁵

Finally, neuropsychiatric symptoms are common in pediatric AE and are also the hallmark of primary psychiatric disorders. Delusions, hallucinations, reduced speech, sleep disturbance, and cognitive difficulties may be seen in both disease groups. Features that distinguish patients with AE from those with psychiatric disease include autonomic instability, hyperkinesia, dyskinesia, rapid progression of psychosis despite therapy, seizures, slowing or epileptic activity on EEG, CSF pleocytosis, CSF oligoclonal bands, and MRI abnormalities.⁵⁶

Discussion

Proposed pediatric AE criteria are intended to address differences in clinical presentations, paraclinical findings, and autoantibody profiles between children and adults. The accompanying algorithm aims to guide diagnostic workup and facilitate earlier initiation of therapy.

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Appendix (continued)

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