Pediatric Neurology 132 (2022) 56–66

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Topical Review

Autoimmune Encephalitis in Children

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ARTICLE INFO

Article history:
Received 4 February 2022
Accepted 9 May 2022
Available online 13 May 2022

Keywords:
Autoimmune encephalitis
N-methyl-D-aspartate receptor encephalitis
Hashimoto encephalopathy
Myelin oligodendrocyte glycoprotein-associated cortical encephalitis
Antibody-negative autoimmune encephalitis

ABSTRACT

Autoimmune encephalitis is a group of central nervous system (CNS) inflammatory disorders that most commonly affect young adults and children. These disorders are closely associated with antibodies against neuronal cell-surface proteins, receptors, and ion channels; however, some forms of the disorder have no known antibody at this time. In children, neurological manifestations such as seizure, movement disorders, and focal neurological deficits are more prominent at initial presentation than psychiatric or behavioral symptoms. When psychiatric symptoms do occur, they often manifest as temper tantrums, aggression, agitation, and rarely psychosis. Prompt diagnosis and early treatment can lead to improved outcomes and decreased relapses. First-line therapies include intravenous steroids, intravenous immunoglobulin, and plasmapheresis, whereas rituximab and cyclophosphamide are utilized for refractory or relapsing disease. This review highlights the different forms of this disorder, discusses approach to diagnosis and treatment, and reviews the outcome and prognosis of children diagnosed with different forms of autoimmune encephalitis.

Introduction

Autoimmune encephalitis (AE) in children is rare but important to recognize as prompt treatment can lead to better outcomes.[1] In 1968, the first case of suspected immune-mediated limbic encephalitis was reported in an individual with associated small cell lung carcinoma.[2] Since then, numerous antibodies associated with immune-mediated encephalitis have been characterized, including the discovery of antibodies against the *N*-methyl-D-aspartate (NMDA) receptor (NMDA-R) in 2005, which is now the leading known cause of AE in children.[3,4] In children, neurological rather than psychiatric symptoms are often the most prominent initial disease manifestations. Disease severity can range from mild behavioral changes to profound encephalopathy, status epilepticus, and even coma. Diagnosis is made with the identification of antibodies to neuronal cell-surface receptors, ion channels, or proteins; however, in some cases, no antibodies are identified, and the diagnosis is made clinically with the exclusion of alternate diagnoses. Neuroimaging, cerebrospinal fluid (CSF) analysis, and electroencephalography (EEG) are utilized to support a diagnosis of AE. Early initiation of immunotherapy, and in some cases ongoing long-term immunotherapy, can result in promising outcomes. This review discusses the common forms of pediatric AE (Table 1), approach to diagnosis, treatment strategies, and outcomes.

Epidemiology

AE, or immune-mediated encephalitis, accounts for a significant proportion of all cases of encephalitis. The California Encephalitis Project, a study evaluating the epidemiology and etiology of encephalitis in adults and children, reported that more than half of patients with encephalitis have a noninfectious etiology, and of these patients, the most common etiology was immune-mediated.[4,7] In a large, multicenter UK study of patients of all ages with symptoms of encephalitis, 4% had NMDA receptor antibodies, making it the second most common etiology of immune-mediated encephalitis after acute disseminated encephalomyelitis (ADEM).[8] Moreover, NMDA-R encephalitis is now more commonly identified as an etiology of encephalitis in children than any single viral cause.[7] The precise incidence and prevalence of AE is unknown, but recent literature suggests an incidence of 1.54 children/million with a female predominance.[9] AE affects individuals of all ages, with some AE syndromes more commonly affecting young adults and children. Pediatric AE is less commonly associated with an underlying neoplasm.[4,9]

Disclosures: None.
Conflicts of interest: None.

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https://doi.org/10.1016/j.pediatrneurol.2022.05.004
0887-8994/

Autoimmune encephalitis syndromes

Antibodies to extracellular proteins and receptors

N-methyl-D-aspartate (NMDA) receptor

The most common form of known antibody-mediated AE is NMDA-R encephalitis. NMDA-Rs are glutamate-gated ion channels that play significant roles in synaptic transmission and plasticity, which clinically contribute to human memory and cognition.[10] About 40% of NMDA-R encephalitis cases occur in patients younger than 18 years. The incidence of pediatric NMDA-R encephalitis ranges from 0.07 to 0.085 per 100,000 children.[11] Women account for about 80% of pediatric NMDA-R encephalitis.[12] Risk factors for developing NMDA-R encephalitis have not been clearly defined; however, numerous studies have implied an association of NMDA-R encephalitis with viral infections, including herpes simplex virus, Japanese encephalitis virus, and even the 2019 novel coronavirus.[13-15] NMDA-R encephalitis evolves through stages over the course of days to weeks, often beginning with a viral prodrome. About 50% of children with NMDA-R encephalitis have a viral prodrome consisting of fever, malaise, headache, gastrointestinal symptoms, or upper respiratory tract infection symptoms.[12,16] Following the prodrome, initial disease manifestations in children, especially young children, often include prominent neurological symptoms, such as seizure or movement disorders, rather than predominately psychiatric symptoms as commonly seen in adults.[3,4,16,17] In one cohort study of 20 pediatric patients with NMDA-R encephalitis, 60% presented with seizure, movement disorder, or focal neurological deficits rather than psychiatric manifestations. This study also found that patients younger than 12 years were more likely to present with neurological features compared with children older than 12 years.[16] Irrespective of initial presentation, 90% of children will progress to develop at least three symptoms, including psychiatric features, memory disturbance, seizures, dyskinesias, change in level of consciousness, or autonomic dysfunction within the first month of disease onset.[4,12] Tumor is uncommonly identified in children; however, ovarian teratomas occur in about 30% of women younger than 18 years.[12] In men, testicular tumor is exceedingly rare. Only about 30% of children will have abnormal brain magnetic resonance imaging (MRI) compared with 55% of adults with NMDA-R encephalitis.[4] Abnormal CSF in pediatric NMDA-R encephalitis is very common, with up to 94% of patients having lymphocytic pleocytosis (>5 CSF white blood cells per mm^3). CSF NMDA antibody titers have been shown to correlate with disease course and remain present in patients with clinical relapse.[18] EEG is abnormal in over 90% of children with NMDA-R encephalitis.[4,12] Recovery can be slow, but up to 80% will demonstrate near-full recovery up to two years after initial presentation.[17] In patients with near-full recovery, autonomic instability, dyskinesias, encephalopathy, and seizure are typically the first symptoms to improve with immunotherapy, whereas the psychiatric and cognitive symptoms can persist.[4] Some studies report ongoing cognitive symptoms for as long as three years post disease onset in children.[19] Clinical relapse occurs in approximately 20% to 25% of children.[4,12] Acute first-line treatment includes intravenous methylprednisolone (IVMP), intravenous immunoglobulin (IVIG), plasma exchange (PLEX), or a combination of these therapies.[3,4,20] Although antibody testing is utilized to confirm the diagnosis, testing can take days to weeks to result, and therefore empirical treatment is recommended for cases with high index of suspicion. Early and aggressive treatment is associated with better neurological outcomes as measured by improvement in modified Rankin scale (mRS) scores and relapse rate.[17,21] In one large, multi-institutional observational study, 96% of patients who responded to first-line therapies had good outcome (defined as mRS score between 0 and 2) compared with 29% of patients with poorer outcomes (mRS between 3 and 5) who did not receive first-line immunotherapy.[17] Up to 30% to 40% of patients initially treated with first-line therapies will not exhibit adequate recovery (with treatment failure considered to be no clinical improvement or change in mRS score after 10 days to 4 weeks of treatment)[3,4,17] and require second-line therapies such as rituximab, cyclophosphamide, or tocilizumab. Rituximab and cyclophosphamide are the most commonly used second-line therapies. There is increasing evidence to suggest that rituximab is safe and effective for refractory disease and preventing relapse.[22-25] For patients refractory to rituximab, tocilizumab might be a safe and effective option.[26,27]

Leucine-rich, glioma-inactivated 1 (LGI-1) and contactin-associated protein-like 2 encephalitis

Both leucine-rich, glioma-inactivated 1 (LGI-1) and contactin-associated protein-like 2 are auxiliary proteins associated with voltage-gated potassium channels (VGKCs). Disease-causing antibodies are typically found against LGI-1 or contactin-associated protein-like 2 protein rather than the VGKC itself. These antibodies are uncommon in children, and thus data on these disorders is limited. About 2.7% of children being evaluated for central nervous system (CNS) autoimmunity have these antibodies. The most frequently described clinical presentations include subacute cognitive decline, seizures, movement disorders, and psychiatric manifestations.[28-30] In one of the largest case series of children with LGI-1 antibodies, no children were found to have faciobrachial dystonic seizures, hyponatremia, or cancers as commonly seen in adults.[30] CSF profiles are often normal. MRI is abnormal in up to 33% of children with these antibodies with T2 hyperintensities in the temporal lobes being the most common finding.[28,30] Treatment consists of IVMP, IVIG, and/or PLEX with most children improving with immunotherapy.[30] Outcomes are generally favorable. Frequency of associated tumor in VGKC encephalitis is unknown, although no isolated cases of tumor in pediatric VGKC encephalitis have been reported in contrast to adults in whom tumor is identified in about 30%.[28]

Glycine receptor antibody encephalitis

Glycine receptor antibody encephalitis has been reported in a few pediatric cases. Glycine receptor encephalitis most commonly manifests with a “stiff person syndrome (SPS)” phenotype or “progressive encephalomyelitis with rigidity and myoclonus (PERM)” phenotype both characterized by muscle rigidity, debilitating muscle spasms, and myoclonus. Initially, both SPS and PERM were thought to be associated solely with antibodies against the glutamate deoxycarboxylase (GAD) enzyme; however, in 2008, a patient was described with PERM without GAD antibodies but instead with antibodies against the glycine receptor.[31] Since then, additional patients with SPS and PERM have been described with glycine receptor antibodies. GAD antibodies can be identified concurrently with glycine receptor antibodies, however. In one large study of 52 patients with glycine receptor antibodies (aged 1 to 75 years), muscles spasms (69%), excessive startle (42%), and eye movement disorders (40%) were the most frequent clinical features. Limbic encephalitis and epileptic encephalopathy were also recognized manifestations.[31-33] Most patients had normal MRIs. Seventeen of 29 patients in this cohort who had electromyography performed were abnormal. Only about one-third of patients with CSF testing demonstrated a pleocytosis.[32] Treatment with IVMP, IVIG, or PLEX, resulted in clinical improvement; however, relapses did occur.[32] There are reports suggesting efficacy with rituximab for refractory cases.[32,34] Neoplasms are rarely identified.[32]

TABLE 1.
Clinical Features of Autoimmune Encephalitis

Subtype	Typical Presentation	Common CSF Findings	Common Neuroimaging Findings	Common EEG Findings	Tumor Association	Long-Term Treatment	Outcome
NMDA	Seizures, orofacial dyskinesias, behavioral change, psychiatric features	Majority with lymphocytic pleocytosis	30% with abnormal MRI	>90% with abnormal EEG; Extreme delta brush	30% of females with ovarian teratoma	Rituximab, monthly IVIG, cyclophosphamide	Good outcome
LGI-1 and CaspR2	Cognitive decline, seizures, movement disorders	Often normal	Majority normal; can show T2 hyperintensities in the temporal lobes	Variable	None currently reported in children	Unknown	Generally favorable
GlyR	SPS, PERM, muscle rigidity, myoclonus, seizure	~1/3 with pleocytosis	Majority normal	Variable	None currently reported in children	Rituximab for relapsing cases	Variable
GABA-A	Seizure, status epilepticus, alteration in mental status	Variable	Majority with multifocal cortical and subcortical involvement	Often abnormal	Hodgkin lymphoma reported in 1 patient[5]	Unknown	Good recovery
GABA-B	Seizure, alteration in mental status, memory loss, confusion	Often with lymphocytic pleocytosis	Often with T2 hyperintensities in the temporal lobes	Often abnormal	None currently reported in children	Unknown	Good recovery
Ophelia syndrome (mGluR5)	Behavioral change, confusion, memory loss	Can see pleocytosis and elevated protein	MRI may be normal or with nonspecific findings; may also show evidence of diffuse cerebellar hyperintensities or involvement of temporal lobes	Nonspecific abnormalities can be seen	Hodgkin lymphoma	Treatment of Hodgkin lymphoma; unknown response to immunotherapy	Full recovery with appropriate treatment
MOG	Seizure, focal neurologic deficits, alteration in mental status	Often with CSF pleocytosis	Often with multifocal cortical and subcortical white matter changes	Often abnormal	None currently reported in children	Monthly IVIG or rituximab for relapsing patients	Good outcome
GFAP	Encephalopathy, seizures, psychiatric symptoms, tremor, meningeal symptoms (including headache)	Majority with lymphocytic pleocytosis and oligoclonal bands	Characteristic linear, radial perivascular pattern of enhancement in cerebral white matter and perilateral ventricular regions	Nonspecific abnormalities can be seen	Uncommon in children but various tumors have been identified (yolk sac tumor, paraganglioma)	Rituximab, azathioprine, or mycophenolate mofetil for relapsing cases	Good outcome
Hashimoto encephalopathy (TPO, thyroglobulin)	Hallucinations, confusion, encephalopathy, seizure, movement disorder	Elevated CSF protein	Nonspecific white matter changes, but often normal	Nonspecific abnormalities	None currently reported in children	Rituximab	Good outcome
Hu	Refractory seizures, psychiatric symptoms, alteration in mental status	Often normal	Majority with T2 hyperintensities in the medial temporal lobes	Often abnormal	25% associated with neuroblastoma	Consider T-cell-targeted therapies; poor response to immunotherapy	Poor outcome with cognitive decline and refractory seizures
Ma	Seizures, behavioral change, speech disturbance, dystonia	Variable	T2 hyperintensities in the temporal lobes, hypothalamus, and midbrain	Often abnormal	One report of an adolescent with mediastinal seminoma[6]	Consider T-cell-targeted therapies; poor response to immunotherapy	Poor outcome with refractory seizures
GAD	SPS, seizure, cognitive decline, memory loss, cerebellar ataxia, psychosis	Variable	Often with T2 abnormalities in the temporal lobe	Often abnormal	None currently reported in children	Consider rituximab	Variable outcome Variable outcome

Rasmussen encephalitis	Focal seizures, hemiparesis, cognitive decline	50% with normal CSF profile	EEG often with unihemispheric slowing with or without epileptiform activity	MRI with unihemispheric focal cortical atrophy	None currently reported in children	Hemispherectomy, AEDs	
Antibody-negative encephalitis	Seizure, movement disorders, behavioral change, psychosis	Lymphocytic pleocytosis	Can be similar to NMDA or normal	Can be similar to NMDA or normal	None currently reported in children	Unknown	Good outcome

Abbreviations:
AEDs = Antiepilepsy drugs
CaspR2 = Contactin-associated protein like 2
CSF = Cerebrospinal fluid
GABA-A = Gamma-aminobutyric acid type A
GABA-B = Gamma-aminobutyric acid type B
GAD = Glutamate deoxycarboxylase
GFAP = Glial fibrillary acidic protein astrocytopathy
GlyR = Glycine receptor
Hu = antineuronal nuclear antibody type 1
LGI-1 = Leucine-rich glioma inactivated 1
mGluR5 = Metabotropic glutamate receptor 5
MOG = Myelin oligodendrocyte glycoprotein
MRI = Magnetic resonance imaging
NMDA = *N*-methyl-D-aspartate
PERM = Progressive encephalomyelitis with rigidity and myoclonus
SPS = Stiff person syndrome
TPO = Thyroid peroxidase

Gamma-aminobutyric acid type A receptor encephalitis

Gamma-aminobutyric acid type A receptor encephalitis has been rarely reported in children. The primary manifestations of gamma-aminobutyric acid type A receptor encephalitis are seizure, refractory status epilepticus, and altered mental status. Neuroimaging often demonstrates multifocal cortical and subcortical involvement.[35] EEG is often abnormal with diffuse abnormalities or seizure. Treatment with immunotherapy appears to be effective in most; however, treatment approaches are ill-defined.[35]

Gamma-aminobutyric acid type B (GABA-B) receptor encephalitis

Gamma-aminobutyric acid type B (GABA-B) receptor encephalitis is also exceedingly rare in children and typically occurs in adults with a median age of 62 years.[36] The clinical presentations are commonly seizure, memory loss, confusion, and altered mental status. Neuroimaging of the brain is often abnormal with the most common finding being T2 hyperintense lesions within the temporal lobes. CSF can demonstrate lymphocytic pleocytosis. About 50% of adult cases are associated with tumor, the most common being small cell lung carcinoma.[36,37] Patients treated with immunotherapy and/or tumor removal have good recovery.[37,38] In one study of 20 children and adults with GABA-B antibodies, 15 of 19 patients with outcome data showed complete or partial neurological recovery after IVMP, IVIG, or PLEX and tumor removal when indicated.[37]

Ophelia syndrome

Ophelia syndrome was first described by Ian Carr in his daughter at age 15 years when she developed symptoms of limbic encephalitis. A Hodgkin lymphoma was detected, and she was treated resulting in significant neurological improvement. Dr. Carr suspected a humoral-mediated process causing this disorder, which he named “Ophelia syndrome.” Since this time, there have been additional patients with similar presentations (symptoms of limbic encephalitis in the setting of Hodgkin lymphoma), and some have been found to have antibodies against the metabotropic glutamate receptor 5. In a case series written in 2011 by Lancaster et al., two patients were described who presented with limbic encephalopathy and were found to have antibodies against the metabotropic glutamate receptor 5. Neuroimaging in both of these patients was abnormal, one with mesial temporal lobe involvement and the second with bilateral posterior parietal-occipital cortex involvement. CSF demonstrated pleocytosis in both patients. Both patients had good outcomes with tumor treatment.[39] The role of immunotherapy in these patients is unknown.

Myelin oligodendrocyte glycoprotein (MOG)

Myelin oligodendrocyte glycoprotein (MOG) is a myelin protein exclusively expressed in the CNS that is believed to play roles in myelin protein integrity, oligodendrocyte maturation, and cell-mediated and humoral immune responses.[40] Antibodies to MOG have been identified in up to one-third of children with an acquired demyelinating syndrome with the common presenting phenotypes being ADEM, optic neuritis, and transverse myelitis.[41,42] Children with MOG antibodies commonly follow a monophasic disease course with approximately 20% to 34% of children having relapsing disease.[43,44] Encephalitis, distinct from ADEM, is another phenotype that has recently expanded the spectrum of MOG disorders. A large prospective observational study performed between 2013 and 2018 investigated and described MOG encephalitis other than ADEM in children. This study identified MOG antibodies in 34% of children with an encephalitis phenotype and demonstrated that MOG antibodies were more commonly identified than all other neuronal antibodies combined; this confirms the importance of MOG antibody testing in all children presenting with features of AE.[45] In general, MOG disorders affect children more frequently than adults, and MOG encephalitis is more common in younger children. The most common clinical manifestations of MOG encephalitis are altered mental status, seizure, abnormal behaviors and abnormal movements. The cerebral cortex and deep gray structures including the basal ganglia and thalamus are most commonly affected on brain MRI.[42,46] CSF profile typically shows pleocytosis with lymphocytic predominance. Unique CSF oligoclonal bands are rare.[42] Roughly 20% of these patients had relapse with the most common relapsing phenotype being optic neuritis.[45] Overlap syndromes, with concurrent NMDA-R antibodies and MOG antibodies, have been reported. In one study, about 4% of patients with NMDA-R antibodies had concurrent glial antibodies with half of these patients having MOG antibodies.[47] In another study, MOG antibodies were identified in nine of 23 (~40%) patients with NMDA-R encephalitis with these patients all demonstrating evidence of CNS demyelination.[11] The majority of patients with MOG encephalitis are treated with steroids, IVIG, or PLEX.[42,45] Generally, long-term immunotherapy is only initiated in children with relapsing MOG disease as most MOG-positive children will have a monophasic disease course.[44] For relapsing disease, monthly IVIG and/or rituximab have been shown to be most effective at reducing relapse rate with monthly IVIG also showing improvement in expanded disability status score.[42,45,48] Larger studies are needed to confirm these findings. Up to 85% of children respond to immunotherapy with favorable outcomes.[44,45]

Autoimmune glial fibrillary acidic protein astrocytopathy

Glial fibrillary acidic protein is an intermediate filament protein in astrocytes that is often used as a biomarker for astrocytes. Antibodies against this protein have been identified in both children and adults presenting with features of encephalitis, meningoencephalomyelitis, meningitis, and myelitis.[49,50] The median age of onset is around 44 years with men and women being affected equally.[49] The most common presenting features include meningeal symptoms (headache, photophobia, neck stiffness), encephalopathy, seizure, symptoms of myelopathy (paresthesias or weakness), symptoms of papillitis, cognitive impairment, and psychiatric disturbance.[49-51] MRI of the brain is frequently abnormal with the characteristic linear perivascular enhancement extending radially from the ventricles. CSF is also commonly abnormal with profound lymphocytic pleocytosis, elevated protein, and often positive oligoclonal bands.[49-51] Coexisting autoimmunity is common with concurrent NMDA-R antibodies being the most commonly identified.[49,50] Children with autoimmune glial fibrillary acidic protein astrocytopathy are generally steroid-responsive and ultimately have favorable outcomes.[49,51]

Hashimoto encephalopathy

The first case of Hashimoto encephalopathy (HE) was described by Lord Brain and colleagues in 1966. The patient described in this report presented with tremor, hallucinations, altered mental status, and agitation in the setting of elevated thyroid antibodies.[52] More than 200 cases have now been reported in adults and children, and HE has a prevalence of about 2.1 per 100,000. In children, the disorder is even more rare, with only a little over 60 cases being reported.[53,54] Similar to the first described case of HE, the most common presenting symptoms in children include psychosis, confusion, abnormal movements, cognitive deterioration, and seizure.[54] Diagnostic criteria for HE in adults proposed by Graus et al. was based on clinical presentation; the presence of elevated anti-thyroid antibodies, namely, thyroid peroxidase antibodies and/or thyroglobulin antibodies; MRI findings; absence of well-characterized neuronal antibodies in the serum or CSF; and presence of subclinical or mild overt thyroid disease.[55] However, more

recently, a study with 17 pediatric patients with HE revealed that adult diagnostic criteria lacked sensitivity when applied to children, given that the majority of children in this study did not have thyroid disease.[56] Moreover, in the largest meta-analysis of HE, only 32% of patients had evidence of thyroid disease at the time of diagnosis.[57] In children, thyroid peroxidase antibodies are elevated in about 80% to 100% of patients and thyroglobulin antibodies are elevated in 60% to 70%.[54] However, elevated thyroid peroxidase antibodies have been found in up to 10% to 13% of asymptomatic children.[4,58] Brain MRI is often normal in patients with HE; however, nonspecific white matter changes or meningeal enhancement can be seen.[4,53] CSF protein is often elevated in HE, but the CSF profile can also be normal.[53] Initially, HE was thought to be particularly responsive to steroids, and thus it was referred to as "steroid-responsive encephalopathy associated with autoimmune thyroiditis." However, only 30% to 55% of patients have a complete response to steroids.[4,58] In children, a review performed in 2008 showed that of 25 pediatric patients with HE, about 55% had complete response to steroids.[59] Patients refractory to steroids or patients unable to receive steroids are often treated with IVIG or PLEX with good effect.[60-62] Rituximab therapy is also used in patients with relapsing HE.[63] Most patients have favorable outcomes with a relapse rate ranging from 12.5% to 50%.[53,58,63]

Antibodies to intracellular proteins

Anti-Hu encephalitis

Antineuronal nuclear antibody type 1 antibodies, also known as anti-Hu antibodies, have been associated with paraneoplastic limbic encephalitis (PLE) mostly affecting adults; however, there have been few reports of children with these antibodies. PLE is characterized by alteration in mental status, seizure, and psychiatric symptoms. In the largest series of PLE, which included children and adults, 60% of patients had antineuronal antibodies, with anti-Hu antibodies being most common.[64] In this series, the majority of patients had associated small cell lung carcinoma and poor neurological outcomes.[64] In children, the most common presentation is also with progressive memory loss, confusion, and seizure. Unlike adults, children less likely have associated cancer. When a tumor is identified in these children, it is most commonly neuroblastoma.[65,66] In a large series of eight children with anti-Hu antibodies, only 25% had associated tumor (neuroblastoma), whereas the remaining 75% presented with limbic encephalitis without neoplasm. Two-thirds of the children who presented with limbic encephalitis in this series had abnormal brain MRIs that most commonly revealed T2 hyperintensities in the medial temporal lobes. CSF cell counts and protein were normal in all of the children.[66] The majority of the children had refractory seizures, poor response to immunotherapy, and poor outcomes consistent with other reports of pediatric and adult anti-Hu encephalitis.[29,64,66]

Anti-Ma2 encephalitis

Anti-Ma2 encephalitis is a rare PLE that is associated with testicular tumors in adult men. Anti-Ma2 encephalitis has also been associated with non–small cell lung carcinoma, breast cancer, and lymphoma. Anti-Ma2 encephalitis is believed to be mediated by a T-cell cytotoxic process rather than being antibody-meditated as seen with other forms of AE that are associated with extracellular proteins and receptors.[64,67] Only a few cases of anti-Ma2 encephalitis have been described in children, and in these reports, the clinical manifestations include seizures, behavioral change, speech disturbance, and dystonia.[29,67] Tumor is rarely seen in these children, but there is one report of an adolescent with anti-Ma2 antibodies with a mediastinal seminoma.[6] MRI typically demonstrates abnormalities in the temporal lobes, hypothalamus, and midbrain.[6,29,64,67] Like anti-Hu encephalitis, most patients have poor response to immunotherapy and poor outcomes.[6,29,64,67]

Anti-glutamate decarboxylase encephalitis

Glutamate decarboxylase (GAD) antibodies are most commonly identified in patients with SPS, limbic encephalitis, autoimmune epilepsy, and cerebellar ataxia.[68] In children, these antibodies are uncommon, but when present these children manifest with seizure, memory loss, confusion, and psychiatric symptoms.[69-71] GAD antibodies are also identified in non-neurological conditions such as type I diabetes, as well as in up to 1% of healthy individuals at low titers,[55,72] and thus it is important to take caution when interpreting positive GAD antibodies. Most studies suggest that high serum titers of GAD antibodies (often 100 to 1000 times higher than found in patients with diabetes) and/or confirmation of intrathecal production of GAD antibodies in the appropriate clinical setting (e.g., patients with SPS, cerebellar ataxia, or refractory epilepsy) are required to support the association of these antibodies with neurological syndromes.[55,68,72] Neuroimaging most commonly shows abnormalities within the hippocampus, and EEG is often abnormal.[69-71] Treatment with IVMP, IVIG, and PLEX has shown mixed results,[68-71] but there is growing evidence that rituximab might be effective.[69,70]

Other autoimmune encephalitides

Rasmussen encephalitis

Rasmussen encephalitis was first described in the 1950s by Dr. Theodore Rasmussen and colleagues.[73] This disorder is characterized by progressive refractory focal seizures, focal neurological disability (usually hemiparesis), and cognitive decline in the setting of gradual atrophy of one hemisphere of the brain.[4,74] The disorder predominantly affects children between the ages six and eight years. The estimated incidence of Rasmussen encephalitis is 2.4 per 10 million people aged 18 years or younger.[74] The pathogenesis of Rasmussen encephalitis is unclear, although it is postulated to be secondary to a T-cell-mediated process based on pathologic studies. In 1994, Dr. Roger and colleagues identified antibodies to the metabotropic glutamate receptor 3 suggesting an antibody-mediated process; however, these findings have not been reproduced.[75] MRI findings include unilateral ventricular enlargement and unilateral cortical and/or subcortical T2-hyperintense signal.[74,76] CSF profiles are variable with about 50% of cases having normal CSF profiles.[76] In 2005, a European consensus panel proposed formal diagnostic criteria that requires all three of the following: (1) clinical focal seizures, (2) EEG demonstrating unihemispheric slowing with or without epileptiform activity, and (3) MRI with unihemispheric focal cortical atrophy or two of the following: (1) epilepsia partialis continua or progressive unilateral cortical deficits, (2) MRI with unihemispheric focal cortical atrophy, or (3) histopathology demonstrating T-cell-dominated encephalitis.[74,76] Treatment for Rasmussen encephalitis includes steroids and IVIG with benefit in some cases, but definitive treatment remains surgical hemispherectomy.[76] There have been cases of Rasmussen encephalitis treated with rituximab and tacrolimus with some effect, but this is limited to case report data.[76,77]

Antibody-negative autoimmune encephalitis

One of the more difficult types of AE to diagnose is antibody-negative AE given that there is no identified antibody or known AE syndrome to explain the presentation. Nonetheless, a significant number of children presenting with features of AE have no identified serum or CSF autoantibody. In one study of 48 patients with probable AE, only 44% of these children had an identified

autoantibody.[78] In this study, clinical features were similar between both antibody-negative and antibody-positive patients.[78] Children categorized as antibody-negative AE include patients who present with clinical features of AE but do not meet criteria for a defined AE syndrome, such as ADEM or Rasmussen encephalitis, and who also have negative AE antibody testing.[55] Diagnostic criteria to help guide our approach to diagnosing these patients was proposed by Graus et al. requiring the following 4 criteria be met: (1) rapid progression (over less than three months) of alteration in mental status, psychiatric symptoms, or memory loss; (2) exclusion of well-defined AE syndromes (ex-Bickerstaff encephalitis, ADEM); (3) absence of well-known autoantibodies in the serum and CSF; and at least two of the following: (a) MRI findings suggestive of AE, (b) CSF with pleocytosis or oligoclonal bands, (c) brain biopsy showing CNS inflammation; and (4) exclusion of alternate diagnoses.[55]

Treatment of these children relies on the same immunotherapies that are utilized in antibody-positive AE. Response to immunotherapy in antibody-negative children is similar to that in antibody-positive patients in most reports.[78] However, one cohort study that evaluated cognitive outcomes of antibody-negative AE showed that children with antibody-negative AE had poorer cognitive outcomes at 1-year follow-up compared with children with NMDA-R encephalitis.[79] This study also demonstrated that postencephalitic epilepsy was more common in antibody-negative AE.[79] Larger studies will be required to better understand treatment response and optimal treatment approaches.

Diagnostic approach

General approach to diagnosis and acute management

The diagnosis of AE in children can be challenging due to the variety of presenting features and extensive differential diagnosis.[4] A multidisciplinary approach is essential including discussions between neurologists, rheumatologists, psychiatrists, and infectious disease physicians. In children, the differential diagnosis includes infection, vascular etiologies, demyelinating disorders, metabolic and/or mitochondrial disorders, malignancies, drug intoxications, neurorheumatologic disorders, genetic leukoencephalopathies, and psychiatric disorders. Infection should be specifically ruled out promptly as immunotherapies used in AE could worsen an infectious process.

An additional challenge with the diagnosis of AE is that autoantibody testing can take days to weeks to result. Definitive antibody testing should not prevent the initiation of immunotherapy in children where there is a high index of suspicion for AE as early treatment leads to better outcomes and a reduction in relapse rate.[1,17,20] A proposed diagnostic approach to children presenting with features of AE is outlined in Figure. Concepts proposed in this figure are derived from previously proposed diagnostic criteria, observed clinical features, and described treatment approaches.[3,4,12,55,80,81] For children with high clinical suspicion of AE (children presenting with all three of the major clinical features of AE), full workup including serologic, CSF, neuroimaging, and EEG (if indicated) evaluation is recommended. EEG may be considered clinically indicated in patients with profound encephalopathy, abnormal movements, or paroxysmal events or behaviors suggestive of seizure activity. As long as alternate diagnoses are ruled out, empirical treatment with IVMP, IVIG, or PLEX should be started (Fig). Children presenting with severe neurological deficits or profound encephalopathy should receive PLEX and IVMP, whereas children with mild symptoms can receive IVMP ± IVIG. Children who may not present with all of the typical features of AE, but present with moderate clinical suspicion, noninvasive testing including neuroimaging ± EEG (if indicated), and serologic evaluation can be pursued. Consultation with psychiatric, rheumatology, and infectious disease colleagues can be particularly helpful in these cases. If there is evidence of neuroinflammation or neurological dysfunction based on initial testing and alternate diagnoses have been excluded, further testing with CSF analysis should be pursued and empirical treatment can be considered (Fig). For children with low clinical suspicion of AE, noninvasive evaluation (EEG, MRI, serology); consultation with rheumatology, infectious disease, and psychiatry to rule out alternate diagnoses; and further observation for the development of features consistent with AE is recommended. If these patients develop features of AE or if antibodies return positive during observation, treatment should be initiated (Fig). This approach allows for discretion as to who gets more invasive testing and empirical treatment and therefore can prevent invasive testing (i.e. lumbar puncture) and potentially harmful therapy when clinical suspicion for AE is moderate or low.

Serum laboratory evaluation and cerebrospinal fluid (CSF) analysis

Systemic infection, neuroinflammatory and neurorheumatologic conditions, metabolic and mitochondrial conditions, and drug ingestion/toxic exposures can all mimic AE and should be ruled out with appropriate laboratory testing (Table 2). In particular, serum MOG and AQP-4 antibody testing should be performed as these antibodies can coexist with NMDA-R antibodies. Table 2 outlines studies to consider during evaluation; however, evaluation should be tailored specifically to the patient. For definitive diagnosis, both serum and CSF AE antibody panels should be sent. CSF testing is more sensitive than serum testing, except in the case of MOG and LGI-1 antibodies where serum is more sensitive. Up to 14% of patients with AE have evidence of antibodies in the CSF but not in the serum.[18] With CSF testing, pleocytosis and elevated CSF protein can be seen, commonly with a lymphocytic predominance; however, normal CSF does not exclude a diagnosis of AE.[78] CSF oligoclonal bands can be positive and are commonly identified in certain subtypes of AE (NMDA, GABA-B, and GAD encephalitis).[82]

Neuroimaging and EEG

Neuroimaging is often normal in AE, but if abnormalities are identified, they are generally nonspecific. More than 50% of children with AE will have normal neuroimaging.[81] GABA-B encephalitis and MOG encephalitis are more likely to have abnormal MRI findings than other forms of AE.[5,45] Neuroimaging is often helpful to rule out AE mimics such as vasculitis, demyelinating syndromes, stroke, or malignancy. EEG findings in pediatric AE are often abnormal, although nonspecific. In children, EEG findings are more likely to be generalized rather than focal compared with adults.[81] In children with AE, extreme delta brush, characterized by rhythmic delta activity with overriding fast beta frequencies, can be seen in up to half of children with NMDA-R encephalitis.[83]

Tumor evaluation

Although tumors are rarely identified in children with AE, tumor evaluation should be performed in all children with a diagnosis of AE given that approximately one-third of female children 18 years or younger are found to have an ovarian teratoma.[12] Evaluation with MRI of the chest, abdomen, and pelvis or ultrasound of the ovaries or testes is generally recommended at the time of diagnosis, and biannual focused surveillance imaging (i.e., ultrasound of the ovaries or testes) is recommended for at least two years post diagnosis.[3,12]

Symptomatic therapies for children with autoimmune encephalitis

Children with AE often develop symptoms that require specific treatments in addition to immunotherapy. The most common

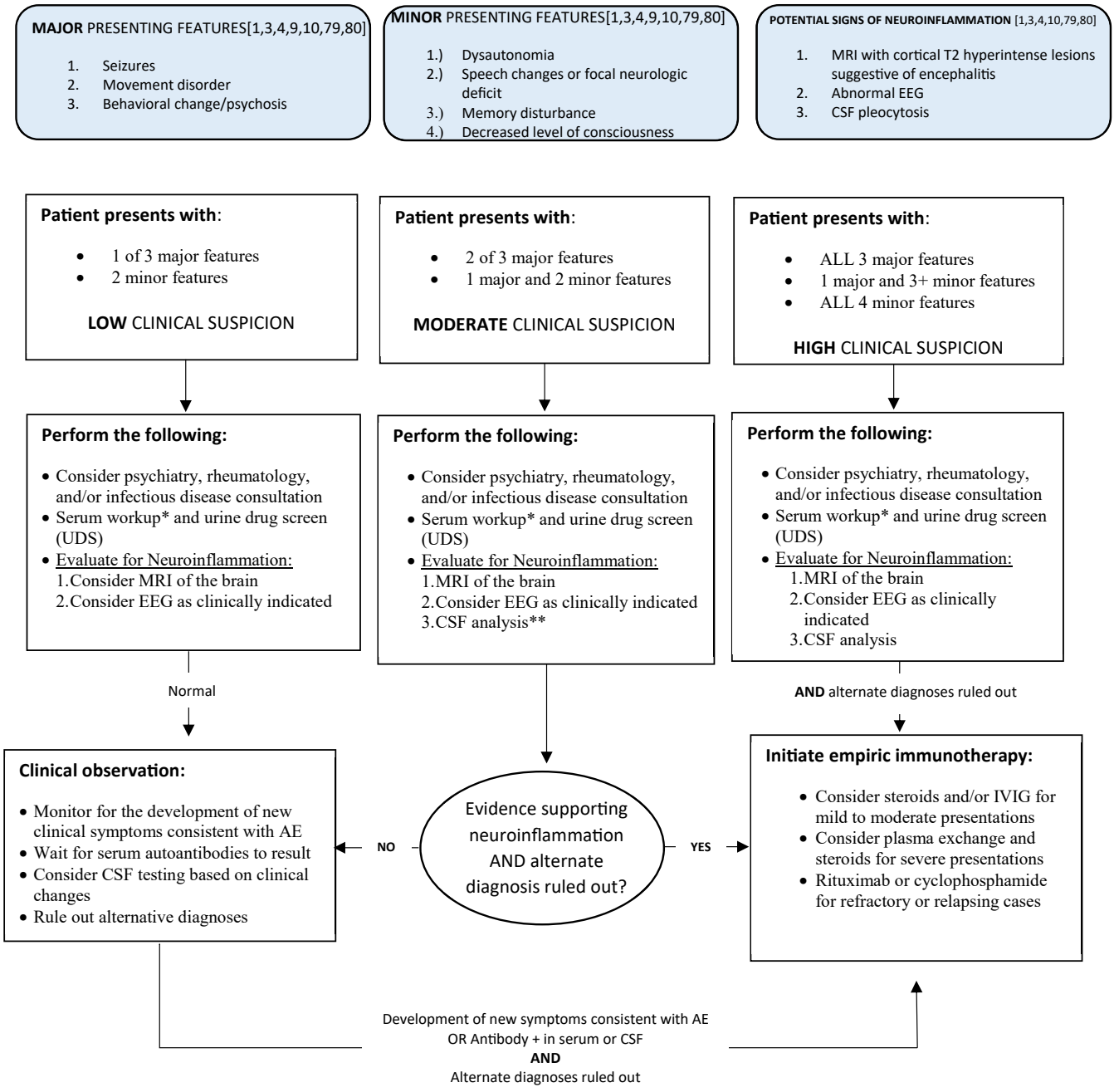

FIGURE. Proposed diagnostic approach and acute management. This algorithm describes a general approach to a child presenting with signs and symptoms of autoimmune encephalitis (AE). This algorithm is based on previously proposed criteria, observational data, and described treatment approaches.[1,3,4,11,12,80,81] Treatment should be initiated before the return of autoantibodies in cases with moderate to high clinical suspicion. First-line therapies include intravenous steroids, intravenous immunoglobulin (IVIG), and/or plasma exchange based on severity of symptoms. Immunotherapy should be escalated to second-line therapies such as rituximab or cyclophosphamide in refractory cases.[17] Cases with low clinical suspicion require further observation, thorough investigation for alternate causes, and the development of further evidence to support an AE diagnosis (i.e., positive autoantibodies). *Serum workup could include infectious studies (erythrocyte sedimentation rate, C-reactive protein, complete blood cell count, herpes simplex virus testing, human immunodeficiency virus testing, varicella zoster testing, and viral encephalitis panel), neuroinflammatory studies (autoimmune encephalopathy panel, myelin oligodendrocyte glycoprotein antibodies, aquaporin-4 antibodies, oligoclonal bands), neurorheumatologic studies (angiotensin converting enzyme, anti-nuclear antibody testing, anti-neutrophil cytoplasmic antibody testing, double-stranded DNA testing), metabolic and mitochondrial testing (lactate/pyruvate ratio, comprehensive metabolic panel, plasma amino acids, ammonia level, copper, ceruloplasmin, vitamin B_{12}, vitamin B_1), thyroid studies (thyroid stimulating hormone, thyroxine, thyroglobulin antibodies, thyroid peroxidase antibodies), and serum drug screens. **Cerebrospinal fluid (CSF) analysis should be pursued based on results of initial serologic and neuroimaging results. The color version of this figure is available in the online edition.

symptoms associated with pediatric AE include seizures, movement disorders, psychosis and behavioral abnormalities, dysautonomia, sleep dysfunction, and physical and cognitive impairment. The most common antiseizure medications utilized in pediatric AE include levetiracetam, valproic acid, oxcarbazepine, carbamazepine, and lacosamide.[84,85] Valproic acid has also shown to be useful

TABLE 2.
Serum Laboratory Evaluation and Cerebrospinal Fluid Analysis

Diagnostic Study Categories	Serum Studies	Cerebrospinal Fluid Studies	Urine Studies
Infectious studies	• CBC • ESR • CRP • HSV • HIV • VZV • Viral encephalitis panel/meningitis panel	• Routine studies (WBC, protein, glucose) • HSV	• Urinalysis • Urine culture
Neuroinflammatory studies	• MOG antibodies • AQP-4 antibodies • Autoimmune encephalopathy panel • Paraneoplastic panel • Oligoclonal bands	• Oligoclonal bands	• None
Neurorheumatologic studies	• ACE • ESR • ANCA • ANA antibody panel • dsDNA	• ACE	• None
Mitochondrial, metabolic, & malignancy studies	• Comprehensive metabolic panel • Lactate/pyruvate ratio • Plasma amino acids • Acylcarnitine profile • Ammonia • Copper • Ceruloplasmin • Vitamin B_{12} • Vitamin B_1	• Cytology • Flow cytometry	• Urine organic acids
Thyroid studies	• TSH • T4 • Thyroglobulin antibodies • Thyroid peroxidase antibodies	• None	• None
Toxicology screens	• Serum drug screen	• None	• Urine drug screen

Abbreviations:
ACE = Angiotensin-converting enzyme
ANA = Anti-nuclear antibody panel
ANCA = Antineutrophil cytoplasmic antibodies
AQP-4 = Aquaporin-4
CBC = Complete blood cell count
CRP = C-reactive protein
dsDNA = Double-stranded DNA
ESR = Erythrocyte sedimentation rate
HIV = Human immunodeficiency virus
HSV = Herpes simplex virus
MOG = Myelin oligodendrocyte glycoprotein
T4 = Thyroxine
TSH = Thyroid-stimulating hormone
VZV = Varicella zoster virus
WBC = White blood cell

for mood stabilization. Beta-blockers and alpha agonists are commonly used for dysautonomia management,[84,86] whereas benzodiazepines are the mainstays of treatment for movement disorders and sleep dysfunction.[84,86,87] Intensive rehabilitation leads to significant functional improvements and even complete recovery, although ongoing cognitive impairment and memory deficits are common.[88-90] Neuropsychologic evaluation and rehabilitation is strongly encouraged. It is important to reiterate that these therapies are “adjunctive therapies” as immunotherapy is the primary treatment for AE.

Summary

Pediatric AE diagnosis and treatment approaches have evolved tremendously since the initial discovery of antibodies to the NMDA-R. With advances in reliable antibody detection methods, the field can more confidently identify autoantibodies in patients with corresponding symptoms of AE. Here we reviewed the most common autoantibodies found in children presenting with features of AE. NMDA-R encephalitis is the most common form of known antibody-mediated AE; however, many other AE syndromes can occur in children. In particular, MOG-positive AE is increasingly more recognized in children. Associated tumors are uncommon in pediatric AE, but it is recommended that all children undergo tumor evaluation as tumor removal can lead to complete recovery. All children presenting with symptoms of AE should undergo evaluation for not only the most common autoantibodies associated with AE but also alternate etiologies that can mimic AE. Empirical treatment should be initiated in children with high clinical suspicion of AE to achieve the best possible outcomes. Symptomatic therapies and intensive rehabilitation should be tailored to the individual patient to allow for the most optimal recovery.

Future research, ideally in the form of randomized clinical trials, will be essential to determine the most effective treatment approaches for AE in children. This will require multicenter collaborations given the rarity of these disorders. Physical and cognitive rehabilitation, crucial components to management of AE, will need to be studied to enhance overall recovery. Further research will be required to identify novel disease-causing autoantibodies, which will ultimately help elucidate the underlying pathogenesis of the disease and broaden the scope of our understanding of pediatric AE.

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