Pediatric inflammatory brain diseases: a diagnostic approach

Heather Van Mater

Purpose of review
Autoimmune-mediated inflammatory brain diseases represent a rapidly evolving area of medicine. The expanding spectrum of disease challenges providers as they strive to accurately diagnosis and treat children presenting with new onset neuropsychiatric deficits. This review examines recently published studies on primary central nervous system vasculitis and autoimmune encephalitis and utilizes key distinguishing features to guide a diagnostic approach.

Recent findings
The spectrum of inflammatory brain disease continues to expand with the recognition of variable disease phenotypes and targets of the immune system. Providers are often overwhelmed by the heterogeneity in clinical features and the lack of sensitivity and specificity of diagnostic testing. Recent scientific advances have enhanced our ability to diagnose these conditions and provide great promise for successful treatment in even severely affected children.

Summary
We are beginning to recognize the brain's susceptibility to autoimmunity and the broad spectrum of phenotypes associated with these conditions. Differentiating the various types of inflammatory brain disease remains challenging and benefits from a systematic approach.

Keywords
autoimmune encephalitis, central nervous system vasculitis, diagnostic approach, limbic encephalitis, *N*-methyl-D-aspartate receptor encephalitis

INTRODUCTION

Pediatric inflammatory brain diseases encompass a broad range of conditions characterized by brain dysfunction due to an autoimmune process. The recognition of both primary central nervous system (CNS) vasculitis and autoimmune encephalitis as the cause of new onset neurologic and psychiatric symptoms in children creates a diagnostic challenge that requires a multidisciplinary approach. Heterogeneity in disease manifestations and diagnostic test results can make accurate diagnosis difficult, but prompt diagnosis and treatment are critical because even severely affected children can have profound improvement when treated early and aggressively. This review utilizes recently published studies to create a conceptual framework and outline a diagnostic approach, highlighting the key distinguishing features of childhood inflammatory brain diseases.

SPECTRUM OF PEDIATRIC INFLAMMATORY BRAIN DISEASE

Autoimmune-mediated pediatric inflammatory brain disease is an umbrella term encompassing a broad range of diseases secondary to vasculitis, encephalitis or encephalomyelitis (Fig. 1). Although there is growing recognition that inflammatory brain diseases should be considered in children with acute or subacute onset of neurologic and/or psychiatric symptoms, the heterogeneity in clinical features and the lack of sensitivity and specificity of standard laboratory and imaging studies create significant diagnostic uncertainty. The complexity in diagnosis is further complicated by the broad differential diagnosis, including metabolic, infectious and oncologic disease, in addition to other primary neurologic and psychiatric diseases. Ideally, there would be a tailored approach to evaluation

Division of Pediatric Rheumatology, Department of Pediatrics, Duke University, Durham, North Carolina, USA

Correspondence to Heather Van Mater, Division of Pediatric Rheumatology, Duke University Medical Center, 2301 Erwin Road, DUMC Box 3212, Durham, NC 27710, USA. Tel: +1 919 684 6575; fax: +919 684 6616; e-mail: heather.vanmater@duke.edu

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KEY POINTS

- Autoimmune-mediated inflammatory brain diseases should be considered as a potential cause for children presenting with acute or subacute onset of neuropsychiatric deficits.
- There is significant heterogeneity in the clinical and diagnostic manifestations both within and across various inflammatory brain diseases, necessitating a thorough and thoughtful diagnostic approach.
- Standard imaging and diagnostic testing can be normal in many forms of inflammatory brain disease and should not dissuade one from fully evaluating children with a clinical course consistent with an inflammatory brain disease.
- Inflammatory brain diseases have the potential for dramatic recovery with early and aggressive treatment.

based on clinical features, but this is not feasible at this time. Children with various forms of inflammatory brain disease were found to have significant overlap in their presentations, and the standard imaging and laboratory studies did not clearly distinguish patients with CNS vasculitis and antibody-mediated encephalitis [1]. Efforts should be made to determine a definitive diagnosis whenever possible to provide targeted therapy. Although some patients will require initiation of therapy at presentation because of the severity of their disease, therapy should not be initiated without concurrently performing a complete evaluation. Diagnostic testing can be compromised the longer patients are treated, impeding the ability to make a correct diagnosis.

DIAGNOSTIC EVALUATION

The evaluation of children with suspected inflammatory brain disease should be guided by the clinical and diagnostic findings (Table 1) [2,3–5,6▪,7,8,9▪▪,10▪▪,11–25,26▪▪,27–30]. Patients should have an MRI with and without contrast, as well as diffusion-weighted imaging, to evaluate for ischemic changes [4]. A normal MRI greatly reduces the possibility of primary CNS vasculitis, especially angiographic positive disease, as over 98% of primary CNS vasculitis cases have an abnormality on MRI (Fig. 2). In the setting of a normal MRI, the diagnostic yield of further vessel imaging [magnetic resonance angiography (MRA), computed tomography angiogram, conventional angiogram] is low. If the MRI is abnormal, the child could have either CNS vasculitis or autoimmune encephalitis, and obtaining vessel imaging may be warranted. Patients should have a lumbar puncture as well as extensive blood work to evaluate for evidence of inflammation, infection and other systemic diseases. Although basic testing for infectious processes, metabolic, hematologic and oncologic diseases may be performed, the extent of testing will vary on the basis of the clinical features and initial diagnostic testing.

CENTRAL NERVOUS SYSTEM VASCULITIS

CNS vasculitis can be a primary diagnosis or secondary to other underlying diseases such as systemic vasculitis and systemic lupus erythematosus. Because neurologic manifestations can be the initial presenting features of rheumatic disease, children should be evaluated for these conditions [31–34]. The diagnostic criteria for pediatric primary CNS vasculitis are similar to the adult criteria with the addition of new

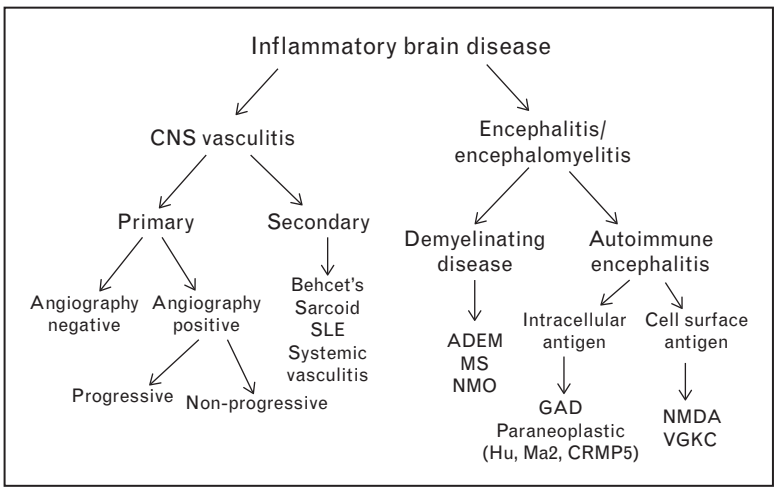

FIGURE 1. Autoimmune-mediated inflammatory brain diseases.

Table 1. Key features of inflammatory brain disease

	Clinical features	Typical laboratories	Radiographic findings	Important notes	Treatment
Vasculitis					
Non-progressive angiography positive [2,3]	Focal neurologic deficit (motor or sensory)	Normal CSF	Abnormal MRI (100%)	Test for VZV given similar clinical picture [5,6▪]	Anticoagulation
		Normal inflammatory markers	Ischemic lesions (89%) [1]	No progression of disease at 3 months	+/− Steroids
			Unilateral disease [3,4]	MRA misses 30% of cases detected on conventional angiogram [6▪]	
Progressive angiography positive [2,3]	Focal deficits plus	May have elevated inflammatory markers	Abnormal MRI (100%)	Bilateral disease hallmark, can be multifocal unilateral	Anticoagulation
	Diffuse deficits		Ischemic lesions common	Progression of disease (if untreated) at 3 months	Steroids, Cyclophosphomide (induction)
	Cognitive decline		Angiography with multiple vascular beds, can be bilateral		MMF (initial and/or maintenance)
	Headache				
	Seizure (30%)				
Angiography negative [2]	Focal deficits plus	Elevated inflammatory markers (75%) and abnormal CSF studies (90%) [7]	Abnormal MRI (92%)	By definition negative angiography	Cyclophosphomide (induction)
	Diffuse deficits	Brain biopsy with lymphocytic infiltrate	Ischemic lesions rare (8%)	Brain biopsy required for definitive diagnosis	Steroids
	Cognitive decline		Normal angiography (100%) [3,4]	Can have a normal MRI (8%)	MMF (maintenance)
	Behavior changes				Infliximab (refractory disease) [8]
	Seizures				
	Prominent headache [4,7]				
Autoimmune encephalitis					
NMDA [9▪▪,10▪▪,11]	Classic progression of symptoms	CSF abnormal in 79%	1/3 with abnormal MRI	Associated with ovarian teratoma	IVIG
	Autonomic dysfunction		Electroencephalogram abnormal in 90%		Pheresis
					Steroids
					Rituximab
Limbic encephalitis (LE)	Amnesia, Seizure, Psychiatric disease			Memory loss a key feature	IVIG
					Pheresis
					Rituximab
					Steroids

(*Continued*)

Table 1 (*Continued*)

	Clinical features	Typical laboratories	Radiographic findings	Important notes	Treatment
VGKC [12,13]	Seizures (72%), Behavioral changes (64%)	CSF usually normal	MRI usually abnormal, Increased FLAIR Medial temporal lobe	Unique faciobrachial dystonic seizures [14]	
	Less cognitive/memory decline (present in 1/3)	LG_1antibody		Neuromyotonia	
		Caspr2 antibody		Association with thymoma	
AMPA	LE + with prominent psychosis	CSF leukocytosis	Increased FLAIR of medial temporal lobe		
GABA [12,15–17]	LE + with prominent seizures [15]	CSF leukocytosis	Increased FLAIR of medial temporal lobe	Behavior changes and altered consciousness predate seizures	
		$GABA_B$ or $GABA_A$ positive	Abnormal MRI		
GAD [18–20]	Temporal lobe epilepsy with cognitive deficits [21]		Mesial temporal lobe abnormalities	Tumors rare	
	Stiff man syndrome			Ataxia can be prominent	
	Cerebellar ataxia			Stiff man syndrome	
				Relatively resistant to therapy	
Encephalomyelitis					
NMO [22–24]	Optic neuritis	AQP4 antibody	Optic neuritis (bilateral or sequential)	Less responsive to therapy	Aggressive therapy
	Transverse myelitis	MOG antibody [26▪▪]	Parenchymal lesions	Transverse myelitis can be silent	Pheresis, IVIG, Steroids, Rituximab [23,27]
			Long segment transverse myelitis (>3 segments)	MOG antibody more common in children, milder disease course [25,26▪▪]	Tocilizumab (refractory cases) [28]
ADEM [22,29,30]	Encephalopathy	CSF normal in up to 65%	Multifocal demyelinating lesions (bilateral, typically asymmetric)	Classically presents 2–4 weeks after illness	IVIG
	Multifocal neurologic symptoms		Rarely unilateral	Optic neuritis rare (6%)	Steroids
	Fever			Recurrent ADEM is rare and should prompt consideration of alternative diagnosis	
	Headache				
	Seizure (30%)				
	Postviral				

ADEM, acute disseminated encephalomyelitis; AMPA, alpha-amino-3-hydroxy-5-methyl-4 isoxazelepropionic acid; AQP4, aquaporin-4; CSF, cerebrospinal fluid; FLAIR, fluid attenuated inversion recovery; GABA, gamma-amniobutyric acid; GAD, glutamic acid decarboxylase 65; IVIG, intravenous immunoglobulin; MMF, mycophenolate mofetil; MOG, myelin-oligodendrocyte glycoprotein; MRA, magnetic resonance angiography; NMDA, *N*-methyl-D-aspartate receptor encephalitis; NMO, neuromyelitis optica; VGKC, voltage-gated potassium channel; VZV, varicella zoster virus.

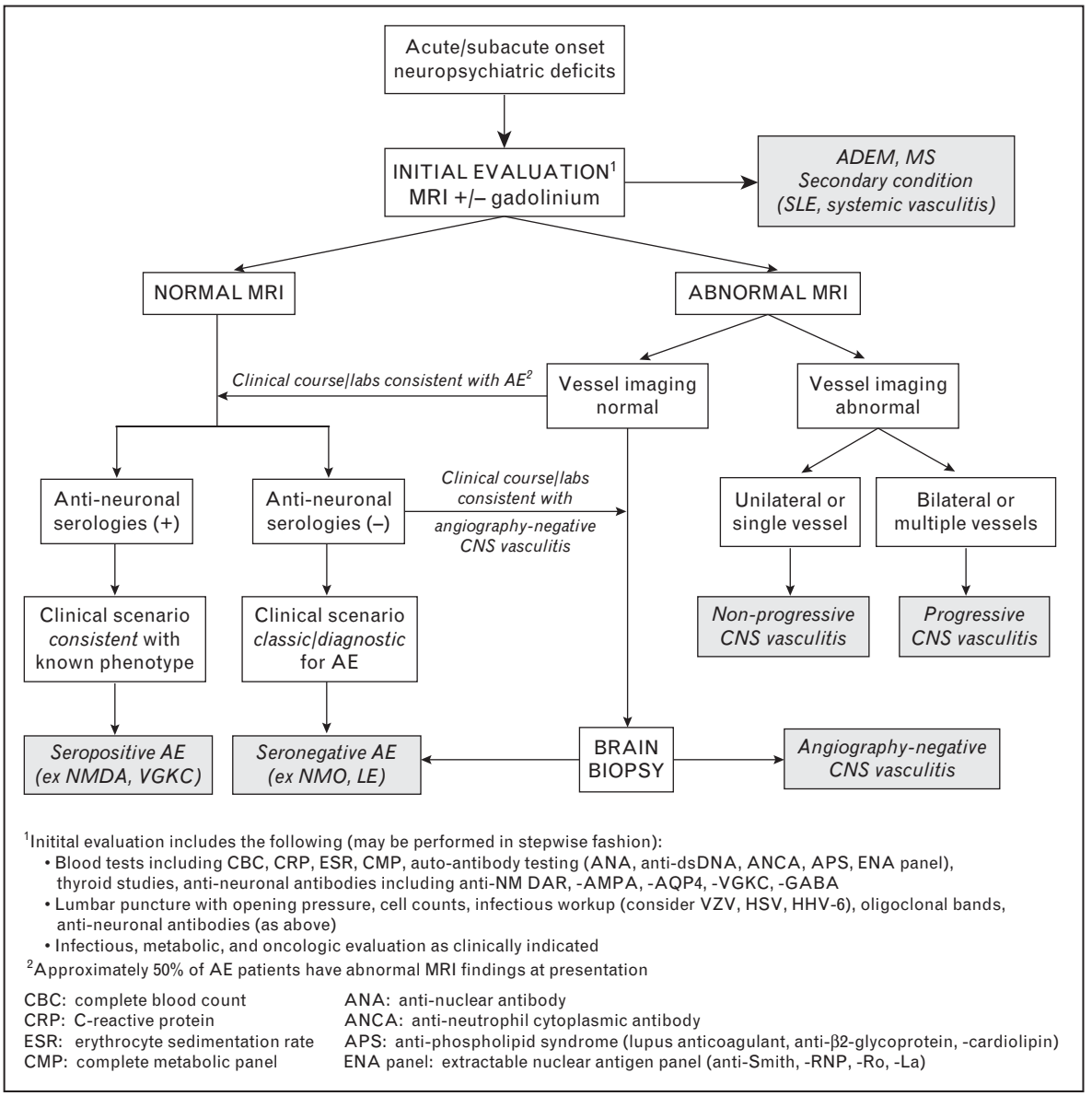

FIGURE 2. Diagnostic approach to the evaluation of pediatric inflammatory brain disease. Inflammatory brain diseases should be considered in patients presenting with new onset neuropsychiatric deficits. The imaging and laboratory studies will vary on the basis of the clinical presentation, and although those with 'classic' findings may have a more limited evaluation (ex neuromyelitis optica, *N*-methyl-D-aspartate receptor encephalitis), all patients should have an MRI with and without gadolinium and basic laboratory studies. Given the overlap in symptomatology and diagnostic testing between angiographic negative central nervous system vasculitis and autoimmune encephalitis, children with these conditions often require similar evaluations.

onset psychiatric disease along with newly acquired neurologic deficits, angiographic and/or histologic features of vasculitis and no evidence of systemic disease [35,36]. Three subtypes of pediatric primary CNS vasculitis have been identified, including angiographic positive nonprogressive disease, angiographic positive progressive disease and angiographic negative disease [2,3]. The term angiographic positive disease is often used interchangeably with large vessel CNS vasculitis and angiographic negative with small vessel vasculitis, but this can create confusion because this classification differs from the conventional description of vessel size for systemic vasculitis. In particular, neuroradiologists may describe angiographic positive disease that affects the smaller more distal vessels as 'small vessel' vasculitis despite the angiography abnormality. We therefore prefer the terms angiographic positive and angiographic negative disease as they reduce misunderstandings (author's experience).

The preferred vessel imaging technique may vary by institution. MRA/V may be sufficient in

children with the clinical presentation of acute stroke with classic MRA findings such as stenosis, occlusion or beading. However, MRA failed to detect 30% of cases that were detected on conventional angiogram [6▪]. Conventional angiogram is the gold standard and is best for evaluating the smaller vessels, but may not be necessary in all children [4].

ANGIOGRAPHIC POSITIVE DISEASE

In CNS vasculitis, the vessels have a unique angiographic appearance with a focus of segmental stenosis or occlusion alternating with areas of dilation, producing a banding or striated pattern. It is important to recognize that childhood CNS vasculitis is a dynamic process, which may appear as a fluctuating course clinically and radiologically in the first several days to weeks [6▪]. Hemorrhage is rare in primary CNS vasculitis of childhood, seen in only 7 of 110 children in one case series, and should make one consider alternative diagnoses [37]. Angiographic positive disease includes progressive and nonprogressive disease. This distinction is based on several important characteristics, including the radiologic patterns at diagnosis and evidence of progression 3 months after diagnosis [2,4,7]. Given the differences in treatment recommendations for these two entities, it is essential to use laboratory testing and radiologic features to distinguish them.

Nonprogressive angiography positive central nervous system vasculitis

Nonprogressive disease is characterized by more focal findings of hemiparesis and sensory deficits. Headaches occur but less commonly than in other categories. Diffuse neurologic deficits such as cognitive decline, seizures and psychiatric symptoms are much less common, as are constitutional symptoms such as fever and fatigue. Inflammatory and cerebrospinal fluid (CSF) studies are often normal [2,4,7].

Radiographic features include ischemic lesions on MRI and large vessel involvement, classically of the anterior circulation, including the distal internal carotid, anterior cerebral and the middle cerebral artery [4,6▪,38,39]. In nonprogressive disease, the vessel involvement is usually limited to one vascular bed and should be unilateral. A thorough infectious evaluation should be considered, given the similar findings between nonprogressive CNS vasculitis and postvaricella vasculopathy, which has been associated with arterial strokes in children [5].

Progressive angiographic positive central nervous system vasculitis

Children with progressive disease present with headaches and more diffuse brain dysfunction (cognitive impairment, behavior changes and altered levels of consciousness) in addition to focal neurologic deficits (hemiparesis and sensory deficits). Headaches are seen in this population and can be quite debilitating. Seizures occur in about a third of cases and predict more severe disease activity over time. Although they are more likely to have evidence of systemic inflammation, constitutional symptoms and CSF changes, many continue to have limited evidence of inflammation [2,4,7].

Radiologic changes in these children are similar to that described for nonprogressive disease, but the lesions tend to be more extensive, often with multiple vascular beds involved. Bilateral disease is seen and is helpful to distinguish progressive disease from nonprogressive disease at diagnosis.

Angiographic negative primary central nervous system vasculitis

When angiography is negative, the diagnosis of angiographic negative primary CNS vasculitis should be considered. This presents with more severe encephalopathy with prominent headaches, cognitive decline, seizures and behavior changes. These children usually have abnormalities seen on MRI, but 8% have been reported with normal MRI findings. Ischemic lesions are uncommon in this population (8%), compared with angiography-positive disease (89%) [7]. Evidence of inflammation is common with 75% of patients having at least one elevated inflammatory parameter and 90% having an abnormality on CSF studies [4,7]. Despite a high frequency of laboratory abnormalities, they are often subtle and may not trigger a concern for significant inflammation. Furthermore, small but notable subsets of patients do not have an abnormal finding in the blood or CSF.

By definition, angiographic negative disease has no evidence of vessel involvement on imaging studies [3,4] and requires a brain biopsy to verify small vessel inflammation. This population can be one of the most challenging to diagnose as there is a broad differential diagnosis including demyelinating diseases [acute disseminated encephalomyelitis (ADEM)], antineuronal antibody-mediated encephalitis and infections, and they may have limited abnormalities present to prompt a brain biopsy. However, if there is a high suspicion for CNS vasculitis based on clinical manifestations, a brain biopsy should be performed to make a definitive diagnosis. Ideally, the biopsy is obtained prior to initiating therapy or at least within 10 days of starting immunosuppressive therapy. Lesional biopsies are preferred, but nonlesional biopsies in the nondominant frontal lobe should be considered as a

suitable alternative when a lesional biopsy is not possible [4]. Brain biopsies in children have a higher diagnostic yield than in adults, with 69% resulting in a diagnosis, as well as ruling out other important mimickers of CNS vasculitis. The histology of pediatric CNS vasculitis differs from adult findings. Children often present with lymphocytic infiltrates without the typical vessel destruction, granulomas or necrosis considered 'classic' of adult CNS vasculitis and a discussion with pathology may be helpful [4,6▪,40].

AUTOIMMUNE ENCEPHALITIS

The recent discovery that autoimmune encephalitis, an inflammatory disease of the brain that results in altered mental status, focal neurologic deficits and seizures, can be due to a primary autoimmune process has changed the approach to diagnosis and treatment of children presenting with new onset neuropsychiatric symptoms. One of the challenges in diagnosing these conditions lies in the heterogeneity both within and between different disease entities in symptomatology, pathology and response to therapy. The cellular location of the antigenic target is an important factor that impacts prognosis, the likelihood of associated cancer and therapy recommendations. Intracellular targets tend to elicit a T-cell response with neuronal injury and are poorly responsive to therapy. In contrast, cell surface antigens involved in cell signaling predominantly elicit a B-cell response with less neuronal injury and often marked response to immunotherapy [10▪▪,41]. There are varying locations in which a breach in the blood brain barrier can occur, including the choroid plexus, leptomeninges and parenchymal vessels, which may also explain the variability attributed to a single antibody [11,42]. Although there are several classic autoimmune encephalitis syndromes now recognized, there is considerable overlap in many of their features, in addition to overlap with CNS vasculitis, necessitating that both conditions be evaluated in parallel.

Laboratory testing is now available for several antineuronal antibodies associated with autoimmune encephalitis, but it is recognized that there are likely to be other antineuronal antibodies yet to be discovered. In addition, as MRI and CSF studies are often unremarkable, efforts are being made to develop diagnostic criteria that are not dependent on a positive antibody or abnormal test, but rather focus on the clinical manifestations [43]. The MRI is normal in half the cases of autoimmune encephalitis, especially in children [9▪▪,44,45]. In a study [46▪] of 69 patients with limbic encephalitis with various antineuronal antibodies, only 11 out of 69 had an elevated CSF cell count (more than five), 16 out of 69 had elevated protein (>500 mg/l) and 25 out of 69 had oligoclonal bands. PET scans have been suggested as a useful adjunct for evaluation, especially when the MRI is normal. However, a small study [47] showed that PET scan is also imperfect as it detected abnormalities in only 6 out of 13 patients with autoimmune encephalitis (four out of four with intracellular antigens and two out of nine with cell surface antibodies). Response to immunotherapy has also been discussed as a diagnostic criterion, although the threshold of when to initiate therapy is unclear. Furthermore, as up to half of patients with known antibody positive disease fail first-line therapy, determining whether a lack of response is due to a nonautoimmune process, nonreversible injury or inadequate duration or drug choice will continue to be limiting [48].

Anti-*N*-methyl-D-aspartate receptor encephalitis

Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis is now recognized as a common cause of encephalitis, affecting young adults and children as young as 8 months [9▪▪]. The classic features include a characteristic sequence of clinical features, progressing through several stages of disease related to an antibody titer-dependent decrease in synaptic NMDA receptor clusters. Patients classically have a prodromal illness with flu-like symptoms before developing psychiatric manifestations, including psychosis and paranoia, with subsequent neurologic findings including seizures, cognitive decline, autonomic dysfunction, loss of consciousness and central hypoventilation. All children develop cognitive and behavioral changes over the course of their disease. Children over 12 years old often present with psychiatric or behavioral symptoms first, whereas those less than 12 tend to present with neurologic findings including seizures and movement disorders [9▪▪,10▪▪]. Similarly to the titer-dependent escalation in symptoms and clinical findings, the recovery progresses backwards, with improvements first in autonomic instability, dyskinesias, level of consciousness and seizures. The psychiatric manifestations can actually reemerge as the patient continues to improve, with escalating impulsivity and disinhibition. It is essential to recognize this is part of the recovery process and not evidence of a flare of the disease. Over time, memory and social interactions improve, but difficulty with executive functioning and memory deficits can take months to years to resolve [9▪▪,10▪▪,44].

Evaluation reveals a normal MRI in most cases (55–66%), but electroencephalograms are abnormal in 90% and CSF studies in 79%. Although the anti-NMDA antibody can be detected in serum, CSF testing is more sensitive as serologic testing can miss up to 10% of cases and CSF titers correlate better with disease activity [9▪▪,44,46▪,49]. Given the association with teratomas, women should be screened with a pelvic MRI to evaluate for an ovarian mass [44]. The risk of cancer is much lower in younger children and in males, with no reported men less than 18 with an associated cancer or teratoma [10▪▪].

The role of infection as a trigger has been highlighted with the recent association of herpes simplex virus (HSV) encephalitis and NMDA receptor encephalitis. Following an episode of HSV encephalitis, anti-NMDA receptor antibody synthesis was seen 1 to 4 weeks after the initial HSV infection, but not during the initial illness. These patients did not improve with acyclovir, but they did improve with immunosuppression [50▪,51]. This heightens the need for clinicians to consider infectious triggers of autoimmunity, and not overlook an evolving autoimmune process.

Half of the patients with NMDA receptor encephalitis treated with first-line therapy [intravenous immunoglobulin (IVIG), steroids and/or pheresis] had symptomatic improvement within 4 weeks of initiation, whereas the other half required escalation to second-line therapy (cyclophosphomide, rituximab) [9▪▪]. In children, the median time from the start of therapy to the first sign of improvement was 11.5 days [10▪▪].

Limbic encephalitis

Although often used as a synonym for autoimmune encephalitis, limbic encephalitis refers to a particular clinical syndrome of encephalitis associated with rapidly progressive short-term memory deficits, psychiatric symptoms (depression, irritability, hallucinations, paranoia) and seizures. Subacute onset of short-term memory loss is considered a hallmark of the disorder. Classically associated with a paraneoplastic process, limbic encephalitis is increasingly recognized outside of oncologic disease [11,21,52]. Limbic encephalitis has now been associated with antibodies targeting voltage-gated potassium channel proteins, alpha-amino-3-hydroxy-5-methyl-4 isoxazelepropionic acid, gamma-amniobutyric acid and glutamic acid decarboxylase, each of which is associated with various clinical phenotypes (Table 1) [15,17,21,45]. The role of thyroid antibodies in limbic encephalitis is unclear and may only reflect autoimmunity rather than being directly pathogenic.

ENCEPHALOMYELITIS

Encephalomyelitis includes inflammatory conditions that affect the brain and the spinal cord. This category includes ADEM and neuromyelitis optica (NMO).

Neuromyelitis optica

Initially thought to represent an aggressive variant of multiple sclerosis, NMO is recognized as a distinct entity associated with aquaporin-4 (AQP4) antibody. The criteria for diagnosis have evolved over time but classically include optic neuritis (bilateral or sequential) and long segment transverse myelitis (more than three segments). This is a clinical syndrome, and although a positive AQP4 immunoglobulin G is helpful to make a diagnosis, it is not required [22–24]. Antibodies to myelin-oligodendrocyte glycoprotein (MOG) have recently been described in sero-negative NMO. This antibody is seen more commonly in children and may be associated with a higher rate of recovery [26▪▪].

Acute disseminated encephalomyelitis

The most common immune-mediated inflammatory brain disease in children, ADEM, is classically a mono-phasic illness with an acute or subacute onset of encephalopathy with multifocal symptoms and MRI lesions following an infection [22,29,30]. ADEM is frequently the initial presumed diagnosis in children presenting with various inflammatory brain diseases given its frequency in pediatrics. However, given recurrent ADEM is rare, recurrent episodes or atypical presentations should prompt consideration of other inflammatory conditions that may require more aggressive or chronic immunotherapy.

CONCLUSION

Inflammatory brain diseases are increasingly recognized as the cause of new onset neurologic and psychiatric symptoms in children. Although providers are challenged by the heterogeneity in disease manifestations and broad differential diagnosis, the potential for dramatic recovery with prompt initiation of immunotherapy emphasizes the importance of a thorough and thoughtful diagnostic approach.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

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