Inflammatory Diseases of the Central Nervous System

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KEYWORDS

• Pediatric neuroinflammatory diseases • Pediatric neuroimmunology
• Pediatric demyelinating disease • Pediatric autoimmune encephalitis

KEY POINTS

- Pediatric neuroinflammatory disorders encompass demyelinating diseases, immune-mediated epilepsies, rheumatologic conditions with neurologic manifestations, and certain genetic disorders with inflammatory pathophysiology.
- Each disorder has a distinct pathophysiology that guides treatment and determines prognosis.
- Neuroinflammatory diseases should be considered in any child that presents with encephalopathy, focal neurologic deficits, seizures, or movement disorders.

INTRODUCTION

Pediatric neuroinflammatory conditions are a complex group of immune-mediated disorders with a wide range of clinical presentations, including focal neurologic deficits, encephalopathy, seizures, movement disorders, and psychiatric manifestations. Initial evaluation often involves multiple disciplines, including neurology, rheumatology, and psychiatry, as well as extensive investigation including MRI of the brain and spine, serum and cerebrospinal fluid (CSF) studies, electroencephalography (EEG), ophthalmologic examination, and neuropsychological assessment.

Pediatric neuroinflammatory conditions can be classified according to clinical presentation, pathophysiologic mechanism (ie, antibody-mediated vs innate immunity-mediated) or imaging and laboratory findings. In this article, we group these conditions into acquired demyelinating diseases, immune-mediated epilepsies/encephalopathies, primary rheumatologic conditions with central nervous system (CNS) manifestations, CNS vasculitis, and neurodegenerative/genetic conditions with immune-mediated pathophysiology.

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ACQUIRED DEMYELINATING CONDITIONS

There has been significant progress in understanding pediatric demyelinating diseases over the past 10 years, including elucidating pathophysiologic mechanisms, discovery of antibody markers, and development of targeted treatments depending on the specific demyelinating condition.[1] These disorders can be divided into monophasic and multiphasic diseases, although it can be difficult to predict the risk of further demyelinating events at first presentation.

MONOPHASIC DEMYELINATING DISEASE
Acute Disseminated Encephalomyelitis

Definition
Acute disseminated encephalomyelitis (ADEM) is defined as a first polyfocal CNS event with presumed inflammatory demyelinating cause. The presence of encephalopathy and MRI abnormalities consistent with demyelination are required to meet diagnostic criteria.

Epidemiology
ADEM is the most common demyelinating disease in children, and its incidence is estimated to be 0.3 to 0.6 per 100,000 per year. The median age of presentation is 5 to 8 years old and it occurs more frequently in male patients.[2]

Pathophysiology
ADEM typically occurs in the postinfectious period (2–3 weeks following a viral infection); however, a causal relationship has not been established. It is histopathologically characterized by macrophage and lymphocyte infiltration of the perivascular regions.[3]

Clinical presentation
Patients present with acute onset of encephalopathy and polyfocal neurologic deficits, which can include ataxia, dysarthria, focal weakness, vision loss due to optic neuritis (ON), and weakness or sensory changes due to spinal cord syndrome. Seizures occur more frequently in patients with ADEM compared with other acquired demyelinating diseases. These symptoms can be preceded by a prodromal phase of fever, headache, nausea, and vomiting. ADEM progresses rapidly, with a clinical nadir at approximately 2 to 5 days.[2]

Typically, ADEM is a monophasic event with no new disease activity after 3 months of disease onset; however multiphasic ADEM (MDEM) does occur and is defined as a second ADEM event more than 3 months after the initial event. ADEM also can be followed by ON (ADEM-ON) or be the first presentation of a neuromyelitis optica spectrum disorder (NMO-SD). In 2% to 3% of patients, ADEM can be followed by a non-ADEM event that then meets criteria for diagnosis of multiple sclerosis.[2]

Fulminant forms of ADEM can require admission to the intensive care unit (ICU), mechanical ventilation for airway protection, and invasive monitoring of intracranial pressure due to cerebral edema. A hemorrhagic form of ADEM, acute hemorrhagic leukoencephalopathy, has also been reported.

Diagnostic laboratory tests and imaging
Infectious workup, including herpes simplex virus polymerase chain reaction, should be initiated in cases of suspected ADEM. Other serum studies include complete blood count, erythrocyte sedimentation rate, C-reactive protein, anti-aquaporin-4 (AQP-4) antibodies, and anti-myelin oligodendrocyte protein (MOG) antibodies.

CSF is usually notable for an elevated white count with lymphocytic predominance and elevated protein levels. Elevated immunoglobulin (Ig)G Index has also been

reported; however, CSF-specific oligoclonal bands (OCBs) are not typically found in patients with ADEM.[2]

MRI brain and spine demonstrate multiple T2 fluid-attenuated inversion recovery (FLAIR) lesions that are bilateral, asymmetric, and poorly marginated, involving both the gray and white matter. Spinal cord involvement is seen in around 30% of patients. Contrast-enhancing lesions are present in around 30% of patients (**Fig. 1**).[1,2]

Treatment

Treatment of acute attacks of demyelinating disease, including ADEM, is based on consensus guidelines and expert opinion and discussed in **Box 1**.[1,2] Longer-term treatments such as monthly high-dose steroids or monthly intravenous immunoglobulin (IVIg) can be used in patients with MDEM or ADEM-ON.

Outcome

Most children with monophasic ADEM are reported to have full recovery. There are, however, studies that show that even one demyelinating event leads to decreased white matter growth and long-term neurocognitive deficits such as learning difficulties and attention problems.[4]

Clinically Isolated Syndrome

Clinically isolated syndrome (CIS) is an umbrella term that is used for a first-time demyelinating event other than ADEM. Estimated incidence is 0.5 to 1.66 per 100,000 children.[5] Clinical phenotypes include ON, transverse myelitis, brainstem syndrome, and any other monofocal or multifocal first-time event (without associated

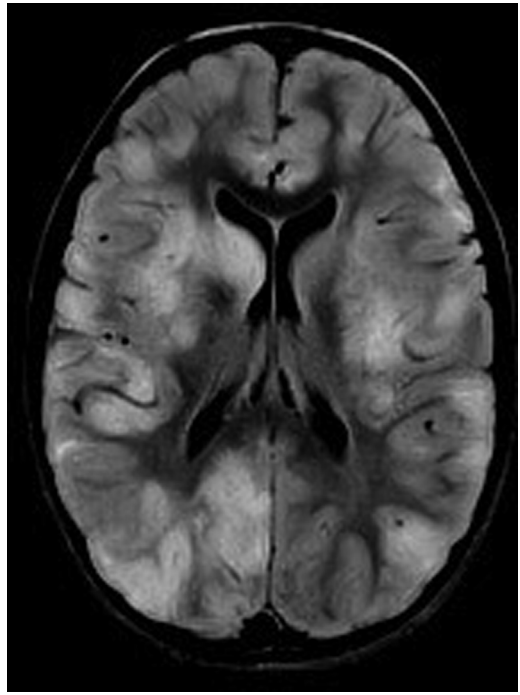

Fig. 1. T2 Axial FLAIR image showing extensive demyelinating lesions involving both the gray and white matter in ADEM.

Box 1
Treatment of acute attacks of demyelinating disease

- High-dose corticosteroids (usually intravenous [IV] methylprednisolone 30 mg/kg/d) followed by oral steroid taper over 4 to 6 weeks.
- IVIg in cases that do not fully respond to steroids.
- Plasmapheresis in severe cases

encephalopathy). Studies have shown that approximately 80% of patients go on to have a second attack in a median time of 0.7 years (range between 0.3 and 2.2 years).[6]

Evaluation of patients presenting with CIS should include MRI of the brain and spine. Ophthalmologic examination should be performed, including optical coherence tomography, where available. Visual evoked potentials can be useful to identify subclinical ON in some patients. Serum studies include anti-MOG antibodies, AQP-4 antibodies, and vitamin D levels, as well as antinuclear antibody and antiphospholipid antibodies to evaluate for systemic autoimmune mimickers of demyelinating disease. Obtaining CSF is recommended, as the presence of OCBs can assist in making an earlier diagnosis of multiple sclerosis. **Box 2** lists predictors of progression to multiple sclerosis after CIS. Recent infection preceding the CIS event suggests lower risk of evolution into MS.[5,7]

Acute treatment of CIS is discussed in **Box 1**, although in patients with suspected NMO-SD or fulminate transverse myelitis, plasmapheresis should be initiated more promptly given improved outcomes in this subset of patients.[10]

MULTIPHASIC DEMYELINATING DISEASE

Multiple Sclerosis

Definition

Pediatric-onset multiple sclerosis (POMS) is defined as MS with onset before 18 years of age, using the 2017 McDonald Criteria. To meet criteria for diagnosis, patients must prove dissemination in space (DIS) and dissemination in time (DIT). DIS is proven by lesions in 2 or more of the MS-typical areas. DIT can be proven by more than 1 attack, new lesions on serial MRIs, presence of contrast-enhancing and non–contrast-enhancing lesions on one MRI, or presence of OCBs in CSF.[1]

Box 2
Predictors of progression to multiple sclerosis after clinically isolated syndrome

- Female gender[6]
- Age>10 y[1]
- Postpubertal status in female patients[1]
- Positive cerebrospinal fluid oligoclonal bands[6]
- MRI brain lesions[6]
- Multifocal/polyfocal symptoms at onset[6]
- Low vitamin D levels[1]
- Remote Epstein-Barr virus infection[1]

Epidemiology

Three percent to 5% of all MS cases have pediatric onset. Mean age of onset in POMS is 11 years; however, most patients are older than 15.[1] There is a known female predilection for MS, although not in the younger than 11 years age group.[3]

Pathophysiology

MS is an autoimmune disease in which T and B lymphocytes are activated and in turn activate the CNS microglia and astrocytes, creating an inflammatory environment.[1] The characteristic pathologic finding in MS is a confluent, sharply demarcated white matter lesion with demyelination, inflammation, and gliosis. In comparison with adult MS, POMS is found to be more inflammatory and cause more axonal damage.[3]

Clinical presentation

Patients with POMS present with a relapsing-remitting subtype of MS. In fact, the diagnosis of a progressive form of MS in the pediatric population should raise suspicion for a leukodystrophy or mitochondrial disease.

Patients can present with ON, transverse myelitis, cerebral attacks, and brainstem attacks affecting vision, strength, bowel/bladder control, extraocular movements, and sensation.

In addition to acute attacks, up to a third of patients with POMS report cognitive difficulties that interfere with their school performance, and depression and anxiety are prevalent in this patient population.[11]

Diagnostic laboratory tests and imaging

Pertinent laboratory tests and workup are the same as those for CIS.

Classic MS lesions on MRI are larger than 3 mm, ovoid, sharply demarcated, and homogeneous in signal intensity. Lesions should be asymmetric and present in the MS-typical areas: periventricular, cortical/juxtacortical, infratentorial, and spinal cord (**Fig. 2**).

Neuropsychological evaluation is important to assess any cognitive issues that may arise.

Treatment

Treatment of acute attacks in POMS is discussed in **Box 1**.

There has been tremendous development in the disease-modifying treatments (DMTs) for preventing disease progression in MS, which has led to a shift in treatment paradigm from a stepwise escalation approach to initiation of treatment with higher efficacy medications.[12]

Currently, only fingolimod, an oral sphingosine-1-phosphate immunomodulator, is approved by the Food and Drug Administration for use in patients with POMS; however, glatiramer acetate (injectable), dimethyl fumarate (oral), natalizumab (infusion), and rituximab (infusion) are commonly used in clinical practice. Decision on which DMT to start is based on patient and parent preference, availability of medications, tolerability of side effects, and disease severity. The goal of therapy is to achieve no evidence of disease activity (NEDA), which is defined as no relapses, no new MRI lesions, and no increase in disability.[13]

Outcome

Disability accrual in POMS is measured by the Expanded Disability Status Scale (EDSS). Although patients with POMS tend to recover from relapses better than their adult counterparts, their long disease duration and more active disease can lead to significant disability over time. Prognosis is worse in patients with highly active disease or in those who do not fully recover from relapses.[14]

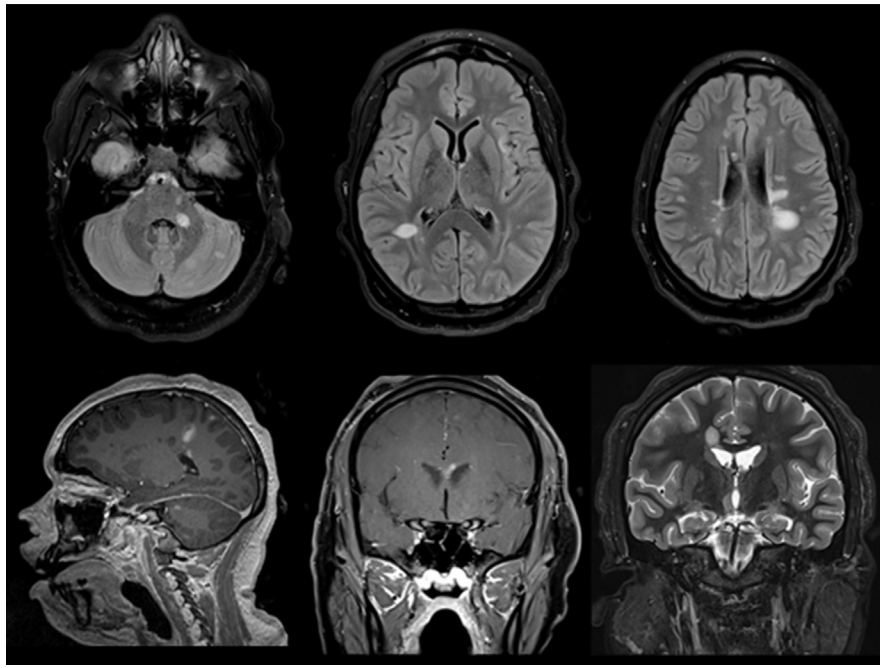

Fig. 2. Axial FLAIR (*top row*) and coronal FLAIR (*bottom row, right*) images from a patient with confirmed POMS show multiple ovoid, hyperintense lesions within the white matter. On the contrast-enhanced sequence (*bottom row*), several lesions show ill-defined contrast enhancement.

Neuromyelitis Optica Spectrum Disorder

Definition

NMO-SD is a spectrum of demyelinating disease with prominent features of ON and longitudinally extensive transverse myelitis (LETM). Diagnostic criteria (**Table 1**) for NMO-SD classify patients based on presence or absence of AQP-4 antibodies, with most patients being AQP-4 IgG positive.[1] Anti-MOG antibodies are also found in patients with NMO-SD with a reported frequency of approximately 10%. Dual seropositivity has not yet been reported. Approximately 15% of pediatric NMO-SD cases are seronegative for both antibodies.[15,16]

Epidemiology

Three percent to 5% of all NMO-SD cases have pediatric onset with a typical age of onset of 10 to 12 years. Girls are more likely to be affected than boys.[16]

Pathophysiology

Pathology shows demyelination due to AQP-4 antibodies activating the complement system after binding to the AQP-4 water channel on astrocyte foot processes. This autoimmune astrocytopathic picture is distinct from the inflammation seen in MS.[3]

Clinical presentation

Pediatric NMO-SD is a relapsing disease and common relapses include vision loss due to ON, weakness, sensory changes, or bowel/bladder issues due to LETM and intractable nausea/vomiting due to area postrema syndrome.

Table 1
Diagnostic criteria of Neuromyelitis Optica Spectrum Disorder

Antibody Status	Needed for Diagnosis
Aquaporin-4 positive	1 Core clinical characteristic, exclusion of alternative diagnosis
Aquaporin-4 negative	2 Core clinical characteristics with the following criteria: a One characteristic must be either ON, LETM, or area postrema syndrome b Dissemination in space of 2 core characteristics c Fulfillment of MRI criteria, which includes involvement of more than one-half of the optic nerve in ON, LETM extending of $\geq$3 segments, and additional requirements for area postrema and brainstem syndrome

Abbreviations: LETM, longitudinally extensive transverse myelitis; ON, optic neuritis.

Of note, patients with pediatric NMO-SD are more likely to have coexisting autoimmune conditions, such as autoimmune thyroid disease, systemic lupus erythematosus, and Sjogren's syndrome (**Fig. 3**).[1]

Diagnostic laboratory tests and imaging

Serum studies should include testing for AQP-4 antibodies and anti-MOG antibodies.

CSF testing shows lymphocytic pleocytosis, often with a higher white count (>50 cells) than seen in CIS or multiple sclerosis. Elevated IgG index and oligoclonal banding can be seen in up to 30% of patients.[1]

Treatment

Treatment of acute attacks is discussed in **Box 1**. Of note, plasmapheresis is often initiated before IVIg in children with NMO-SD, as early initiation has shown improved outcomes in severe attacks in adult NMO-SD.[10]

Azathioprine, mycophenolate mofetil, and rituximab are commonly used first-line DMTs in NMO-SD and all have been found to reduce the rate of relapse in children.[15,16] New monoclonal antibody treatments such as tocilizumab, satralizumab, and eculizumab have shown efficacy in adult patients with NMO-SD and are sometimes used off-label in pediatric patients.

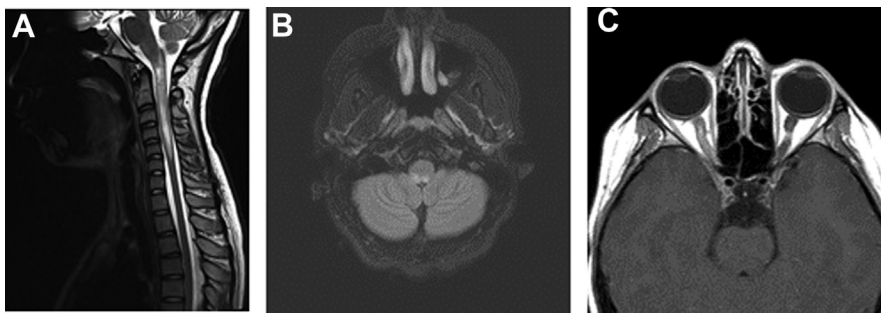

Fig. 3. Imaging from a patient with confirmed AQP-4 positive NMO-SD. (*A*) Sagittal FLAIR image shows LETM extending over greater than 3 segments in the cervical spinal cord. (*B*) Axial T2 FLAIR image shows a brainstem lesion associated with area postrema syndrome. (*C*) Sagittal T2 FLAIR image shows increased signal in the right optic nerve, consistent with ON.

Outcome

Pediatric NMO-SD is more active than POMS with a mean of 1.8 attacks in the first 2 years of disease and higher EDSS within 2 years of disease onset.[1]

MOG-RELATED DEMYELINATION

Anti-MOG antibodies are found in both monophasic and multiphasic demyelinating syndromes and commonly seen in patients with MDEM, ADEM-ON, relapsing ON, relapsing TM, and NMO-SD. Since anti-MOG testing has become available, positivity has been reported in 18% to 35% of children with acute demyelinating syndromes.[1,17]

The presence of anti-MOG antibodies suggests a non-MS disease course but otherwise offers limited insight into risk of relapse. Approximately 50% of patients found to have MOG antibodies follow a relapsing course and these relapses can occur within a few months or more than 10 years after the initial attack.[1]

Acute attacks are treated as discussed in **Box 1**.

Longer-term treatment in MOG-positive patients is typically initiated after the second attack or if patients meet criteria for NMO-SD. Treatment regimens include monthly IVIg, monthly high-dose steroids, mycophenolate mofetil, azathioprine, and rituximab. Optimal duration of treatment is unclear, however many centers suggest 2 years of treatment.[18]

IMMUNE-MEDIATED EPILEPSIES AND ENCEPHALOPATHIES

The link between epilepsy and neuroinflammation is one that has been studied for many years in the context of Rasmussen encephalitis (RE). More recently, epilepsy caused by antibody-mediated conditions (such as NMDA receptor encephalitis) and innate immunity-driven disorders such as FIRES has also been described. Of note, elevation in inflammatory markers has also been found in infantile spasms, suggesting that neuroinflammation plays some part in either the development or propagation of some epilepsy syndromes that were previously considered solely "genetic" in etiology.[19]

Autoimmune Encephalitis (Anti-NMDA Receptor Encephalitis)

Definition

Autoimmune encephalitis (AIE) is a group of disorders in which brain inflammation and dysfunction is caused by antibodies against neuronal receptors and cell surface proteins that are involved in neuronal excitability. Anti-NMDA receptor encephalitis is the most frequent form of AIE in the pediatric population and is the focus of this section.[20] AIE associated with other antibodies (such as anti-GAD and anti-VGKC) is exceedingly rare in the pediatric population and mostly found as a paraneoplastic disorder in adults.[20] Of note, Hashimoto encephalopathy, also known as steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT), can have a similar clinical presentation and should be evaluated for in all suspected cases of AIE.[20]

Epidemiology

The California Encephalitis Project found that the frequency of anti-NMDA receptor encephalitis was greater than any single viral encephalitis, especially in younger patients, and more recent studies have confirmed a comparable prevalence to viral encephalitis.[21,22] Forty percent of all patients with anti-NMDA receptor encephalitis are younger than 18 years old.[9,20]

Pathophysiology

Anti-NMDA receptor antibodies are directed at the NR1 subunit of the NMDA receptor and cause selective crosslinking and internalization of NMDA receptors, leading to reduction in NMDA-mediated synaptic currents. In contrast to T-cell mediated processes, this does not lead to cell death and effects can be reversed once the antibody is no longer present.[8]

Clinical presentation

Clinical presentation varies based on the age of the patient. In older children, a prodromal phase of fever and headache is followed by onset of psychiatric and behavioral changes. This then progresses to decreased level of consciousness, seizures, movement disorders, and autonomic and vital sign instability. Children younger than 12 years tend to present with seizures, movement disorders, behavioral changes, and loss of speech or mutism.[20,23]

Anti-NMDA receptor encephalitis is associated with benign ovarian teratomas in up to 40% of young women. Testicular tumors are rarely found in male patients younger than 18 years. Anti-NMDA receptor encephalitis has also been reported to occur weeks or months after herpes simplex encephalitis.[24]

Diagnostic laboratory tests and imaging

Diagnosis is confirmed by demonstrating anti-NMDA receptor antibodies in the serum or CSF. MRI can be normal in 50% of patients. EEG typically shows diffuse background slowing and some may show prominent delta brush activity (faster frequencies admixed onto slower frequencies); the EEG can may also show electrographic seizures in approximately 60% of patients.[20]

Treatment

No definitive standard of treatment has been established, thus treatment is based on expert consensus. When teratoma is present, there is evidence that removal of the tumor and prompt immunotherapy leads to improved outcome. Children typically receive IV steroids and IVIg as first-line therapy with plasmapheresis reserved in most centers for cases with severe autonomic or vital sign instability. Increasingly, rituximab is being used after these treatments due to reports of efficacy and improved outcomes.[20,23]

Outcome

Patients with AIE often have prolonged hospital stays and need intensive inpatient rehabilitation. Eighty percent of patients are reported to have substantial or full recovery, although this recovery can take up to 2 years after initial presentation. Neurocognitive and psychiatric symptoms often linger, thus a multidisciplinary approach involving neurology, psychiatry, and cognitive rehabilitation is key to improving outcomes.

Clinical relapses occur in 12% of children and the efficacy of long-term immunosuppression in preventing relapses is not established.[20,25]

Challenge of seronegative autoimmune encephalitis

In patients with suspected AIE in whom no disease-causing antibody is found, the diagnosis of seronegative AIE can be made. Diagnostic criteria for seronegative AIE have been proposed and include presentation consistent with AIE, exclusion of other disorders, and evidence of CNS inflammation (ie, signal changes on MRI or CSF pleocytosis) (**Box 3**).[8,23]

Box 3
Challenges of antibody testing in neuroinflammatory conditions[8]

The detection of specific antibodies has become more clinically relevant as more antibodies associated with neuroinflammatory conditions have been elucidated. However, it is equally important to be aware of the limitations of using the presence of an antibody to establish a definitive diagnosis. Anti-GAD antibodies, for example, can be found at lower titers in 1% of healthy people and up to 80% of those with type 1 diabetes. Only at high titers are anti-GAD antibodies associated with neurologic symptoms. Furthermore, the target antigens of these antibodies can have more than 1 subunit and antibodies against each of the subunits can have different clinical significance. For example, antibodies against the voltage-gated potassium channel complex (VGKC) itself are nonspecific and cannot be used to diagnose neuroinflammatory conditions. However, antibodies against 2 of its subunits, LGI and CASPR2 are pathogenic and associated with well-defined syndromes. Furthermore, patients can be dual seropositive for anti-NMDA receptor antibodies and either anti-myelin oligodendrocyte or anti-aquaporin-4 antibodies. Clinicians should be aware that overlapping demyelinating and autoimmune encephalitis syndromes can occur in these cases, and in patients with atypical features for either disease, one should consider evaluation for the other.[9]

Febrile Infection-Related Epilepsy Syndrome

Definition

Febrile infection-related epilepsy syndrome (FIRES) is a rare condition characterized by onset of refractory status epilepticus in a previously healthy child following a febrile illness.

Epidemiology

The estimated prevalence of FIRES is 1:1,000,000 and it occurs primarily in school-aged children with a median age of onset of 8 years.[26]

Clinical presentation

Children with FIRES have a routine febrile illness that is followed by new onset of seizures without any concomitant neurologic changes. The seizures evolve into status epilepticus, refractory to even anesthetic agents. Patients universally require ICU level care due to need for airway management secondary to status epilepticus and the large doses of anti-epileptics and sedatives that are used to treat the seizures. After this acute phase of refractory status epilepticus resolves, patients enter the chronic phase of FIRES, which is characterized by severe neurocognitive impairment and drug-resistant epilepsy.[26]

Pathophysiology

Given the close temporal relationship to febrile illness, FIRES is presumed to be an innate immune disorder triggered by infection. An intrathecal overproduction of proinflammatory and proconvulsant cytokines (such as interleukin-6) has been found in the CSF of children with FIRES, which likely elicits an explosive onset of epilepsy.[26,27]

Diagnostic laboratory tests and imaging

The diagnosis of FIRES is one of exclusion and initial workup should include infectious studies in both the serum and CSF, testing for autoimmune encephalitis including thyroid antibodies, metabolic studies, and consideration of whole-exome sequencing and mitochondrial next generation sequencing. CSF neopterin and cytokines can also be sent to aid in diagnosis, although their exact significant is unclear.[26]

Continuous EEG is used to guide therapeutic interventions, as well as to recognize nonconvulsive seizures.

MRI is often normal during the acute phase of FIRES but typically shows brain atrophy with hippocampal sclerosis within a month of seizure onset.[26]

Treatment

Following the failure of common anticonvulsants, IV pentobarbital and IV midazolam are used to obtain seizure control and often place patients in burst-suppression. The optimal length of burst-suppression is unknown and long periods of burst-suppression are associated with poorer neurocognitive outcomes (although this is likely also reflective of more severe disease).

Treatment with IV Steroids, IVIg, and plasmapheresis is often initiated due to concern for autoimmune encephalitis, although with limited response.[28]

Ketogenic diet has shown improved seizure control and improved neurocognitive outcomes in small groups of patients, thus is often initiated very quickly after the diagnosis of FIRES is suspected. Anakinra, an interleukin-1 receptor antagonist, has shown safety and efficacy in case reports and is being studied further in multicenter retrospective studies.[28]

Outcome

The acute phase of FIRES has a reported mortality rate of up to 60%. In reports of patients who did survive this acute phase, all were left with drug-resistant epilepsy and most with severe neurocognitive impairment. Ketogenic diet and potentially treatment with anakinra have shown some promise in improving neurocognitive outcomes.[26–28]

Rasmussen Encephalitis

Definition

RE is a progressive condition characterized by unihemispheric brain inflammation and eventual atrophy with resultant focal epilepsy, progressive hemiplegia, and cognitive decline.[29]

Epidemiology

RE is a rare condition with estimated incidence in studies ranging from 1.7 to 2.4 cases per 10 million people. The median age of onset is 6 years with no reported gender predominance.[29]

Pathophysiology

Histopathology in patients with RE shows unihemispheric cortical inflammation with neuronal loss and eventual gliosis. The trigger for the onset of inflammation has not been found despite extensive research into infectious agents and genetic changes that may predispose one to this type of immune response.[29]

Clinical presentation

Patients typically present with frequent focal seizures arising from one cerebral hemisphere and many have epilepsia partialis continua (EPC). If left untreated, children develop contralateral hemiparesis and cognitive decline within a year of onset of seizures. After this acute phase, there is a residual chronic phase of stable but severe motor and cognitive issues with refractory epilepsy.[29]

Diagnostic laboratory tests and imaging

No specific serum or CSF laboratory tests can make the diagnosis of RE; however, autoimmune encephalitis, CNS vasculitis, and neurologic manifestations of primary rheumatologic diseases should be ruled out to the best of the clinician's ability.

MRI is the mainstay for diagnosis of RE and typically within months of disease onset shows unilateral enlargement of the ventricular system with T2 FLAIR signal in the

affected cortical or subcortical regions. Serial MRIs show progressive signal change and continued atrophy. Functional studies using fludeoxyglucose F-PET can show unilateral cerebral hypometabolism before MRI changes and can be helpful in making an early diagnosis.

EEG can show persistent high amplitude delta activity over the affected hemisphere within months of seizure onset. Epileptiform activity and seizures can be captured; however, EPC may not always have recognizable ictal EEG abnormalities.[29]

Treatment

Functional hemispherectomy remains the only curative option for the seizures associated with RE with studies showing improved cognitive outcomes with early intervention. Without surgical intervention, seizures, especially EPC, are refractory to medical management.

Case reports have shown positive outcomes with long-term corticosteroids, IVIg, tacrolimus, and rituximab; however, these treatments need to be studied in larger groups of patients to assess outcomes more effectively.[29]

Outcome

Outcome in RE depends on several factors, including severity of initial presentation, involvement of dominant versus nondominant hemisphere, and time to definitive treatment with surgical intervention.[29]

Opsoclonus Myoclonus Ataxia Syndrome

Definition

Opsoclonus myoclonus ataxia (OMA) is an immune-mediated encephalopathy with acute onset of neurologic deficits, often in the setting of neuroblastoma.

Epidemiology

In children, OMA typically develops in the first 2 years of life, with a mean age at presentation of 20 months.[30]

Pathophysiology

OMA is presumed to be an autoimmune condition due to rapid development of symptoms, findings of B-cell activation in the CSF, and response to immunotherapy, although no specific antibody has been found.[20] Fifty percent of pediatric patients with OMA have an underlying neural crest tumor, and it is postulated that there may be a common brain/neuroblastoma antigen that leads to CNS inflammation.[30]

Clinical presentation

Previously healthy, typically developing children present with new-onset ataxia, myoclonus, and opsoclonus, although presence of all 3 is not required for diagnosis. Children can develop gait failure and lose the ability to sit up due to ataxia. Speech regression and severe irritability with sleep disturbances are reported.[20,30]

Diagnostic laboratory tests and imaging

Although there is no specific marker for OMA, antibody panel testing for autoimmune encephalitis in the serum and CSF as well as routine CSF studies should be performed. In patients with suspected OMA, investigation for underlying neuroblastoma should include MRI of the chest/abdomen/pelvis, urinary catecholamine metabolites, and radiolabeled iodine scintigraphy (MIBG scan). If tumor is not identified at time of diagnosis, it is recommended to repeat testing for neuroblastoma in 6 months.[30]

Treatment and outcome

Early diagnosis and combination therapy with corticosteroid, IVIg, and rituximab has showed improvement in developmental outcome. Treatment often improves opsoclonus, myoclonus, and ataxia symptoms; however, patients can be left with residual cognitive, speech/language, and behavioral deficits, especially if treatment is delayed. Relapses are reported to occur in approximately 50% of patients, often in the setting of infections or tapering immunosuppression.[20,30,31]

CENTRAL NERVOUS SYSTEM MANIFESTATIONS OF RHEUMATOLOGIC DISEASE

Many primary rheumatologic diseases have associated neurologic complications, the most prevalent being systemic lupus erythematosus (SLE). SLE is an autoimmune condition that affects the joints, kidneys, skin, and bone marrow. Neuropsychiatric SLE syndromes (NPSLE) are reported in 20% to 95% of pediatric patients with SLE (15%–81% with neuropsychiatric manifestations at diagnosis) and are associated with higher morbidity and mortality.[32,33] Common neurologic issues include seizures, ischemic stroke, and psychosis. Subacute headaches, mood changes, and cognitive issues are also reported.[32] The pathophysiology of NPSLE involves small-vessel vasculopathy and thrombosis as well as parenchymal damage related to antineuronal antibodies and complement/cytokine mediated inflammation. Antiphospholipid antibodies (APL), which are found in most children with SLE, are associated with small-vessel vasculopathy, ischemic strokes, and focal CNS inflammation.[32] Treatment of pediatric NPSLE typically involves escalating immunosuppression for treatment of underlying SLE. Medications used include monthly cyclophosphamide for 6 months, rituximab, and oral steroids. Anticoagulation is added in cases complicated by thromboses.[33,34]

CNS infection and posterior reversible encephalopathy syndrome should also be considered in pediatric patients with SLE with neurologic dysfunction, given the use of immunosuppressive medications and chronic steroid use.[33,34]

Other less common pediatric rheumatologic conditions, such as Behcet syndrome, sarcoidosis, Sjogren syndrome, macrophage activation syndrome related to juvenile idiopathic arthritis, and monogenic autoinflammatory syndromes (such as periodic fever syndromes), also can present with neurologic complications and should be considered in patients with systemic symptoms, multi-organic involvement, and neurologic disease.

CENTRAL NERVOUS SYSTEM VASCULITIS

CNS vasculitis is an inflammatory disease involving the cerebral vasculature that can cause neurologic deficits and psychiatric disease in previously healthy children. CNS vasculitis can occur secondary to an underlying systemic illness, such as infection (mycobacterium tuberculosis, varicella zoster), rheumatologic disease (SLE, systemic vasculidities), or related to malignancy/radiation treatment of malignancy. CNS vasculitis in which no systemic illness or condition that can cause vasculitis is found is called childhood primary angiitis of the central nervous system (cPACNS).[35] Diagnostic criteria for primary angiitis were first proposed by Calabrese in adult patients and these have since been adapted for pediatric patients. cPACNS can be further classified into 3 subtypes, which are discussed in **Table 2**. There have been no large clinical trials to guide the care of children with cPACNS, thus treatment regimens are based on expert opinion (**Fig. 4**).[35–37]

Table 2
Classification of childhood primary angiitis of the central nervous system

Subtype/ Vessel Involvement	Clinical Presentation	Diagnostic Studies	Disease Course	Treatment
Nonprogressive large-medium vessel	Sudden-onset focal neurologic deficits Male>female	MRI with unilateral ischemic lesions in large vessel territories MRA with enhancement of vessels Angiography with unilateral stenoses, dilatations of the proximal segments of ACA, MCA, ICA	No progression/new vascular territory involvement after 3 mo (reclassified as progressive if this occurs)	Anti-thrombotic therapy-heparin X 3–6 mo followed by long-term aspirin Use of steroids is controversial
Progressive large-medium vessel	Focal and diffuse (headaches, cognitive dysfunction, mood changes) deficits Male > female	Increased inflammatory markers (ESR, CRP, WBC) MRI lesions in more than 1 vascular territory, some bilateral Anterior >posterior circulation involvement Angiography with stenoses, dilatations of the proximal segments of ACA, MCA, ICA	New stenoses on angiography beyond 3 mo of disease Patients typically have residual focal neurologic deficits	High-dose IV steroids × 3–5 d followed by oral steroids IV monthly cyclophosphamide pulses × 6 mo followed by mycophenolate mofetil or azathioprine
Small vessel	Seizures, movement disorders, diffuse neurologic and psychiatric deficits Female>male	Increased CSF cell count/protein MRI with inflammatory lesions (less commonly ischemic), leptomeningeal enhancement Normal MRA and angiography, brain biopsy with evidence of vascular inflammation often needed for diagnosis	Most with good recovery of neurologic deficits, can have continued seizures with need for long-term anti-epileptics	High-dose IV steroids × 3–5 d followed by oral steroids IV monthly cyclophosphamide pulses × 6 mo followed by mycophenolate mofetil or azathioprine

Abbreviations: ACA, anterior cerebral artery; CRP, C-reactive protein; CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate; ICA, internal carotid artery; IV, intravenous; MCA, middle cerebral artery; WBC, white blood cells.

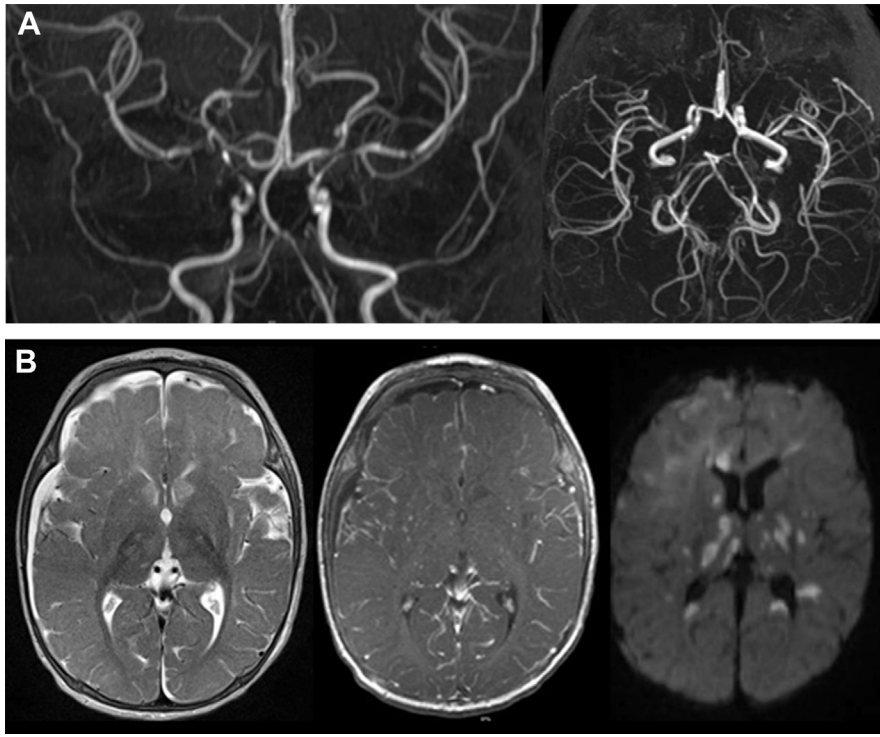

Fig. 4. (*A*) Coronal and axial MRA in a case of CNS vasculitis. A significant narrowing and irregularity is noted, affecting the distal internal carotid arteries bilaterally as well as the M1 and M2-segments of both middle cerebral arteries. (*B*) Axial T2 images show multifocal, ill-defined T2-hyperintense lesions within the central gray matter, hemispheric white matter, and cortical gray matter bilaterally. Most of the T2-hyperintense lesions are more conspicuous on diffusion-weighted imaging (DWI) and reveal imaging characteristics compatible with cytotoxic edema (DWI-hyperintense). On the contrast-enhanced sequence, mild diffuse leptomeningeal enhancement is noted as well as an increased vessel enhancement.

GENETIC CONDITIONS WITH IMMUNE-MEDIATED PATHOPHYSIOLOGY

As the genetic basis of more neurologic disorders is found, many are found to have inflammatory pathophysiology with potential for treatment with immunomodulators. Aicardi-Goutieres, for example, is a monogenic type 1 interferonopathy with causative genetic mutations in the intracellular signaling machinery (TREX1 and RNASEH2A/2B/2C). This leads to overproduction of interferon, which in turn causes progressive encephalopathy characterized by intracranial calcifications, white matter disease, and CSF lymphocytosis. Systemic interferon overproduction causes skin lesions, glaucoma, hypothyroidism, and lupuslike disease. Patients can present with neurologic abnormalities at birth or in early childhood and severity of disease varies based on gene involvement, though phenotype can vary even within families.[38] JAK kinase inhibitors are useful in blocking interferon activation in these patients and an open-label study with baricitinib showed decreased skin inflammation and improved developmental abilities in a small group of patients (**Fig. 5**).[39]

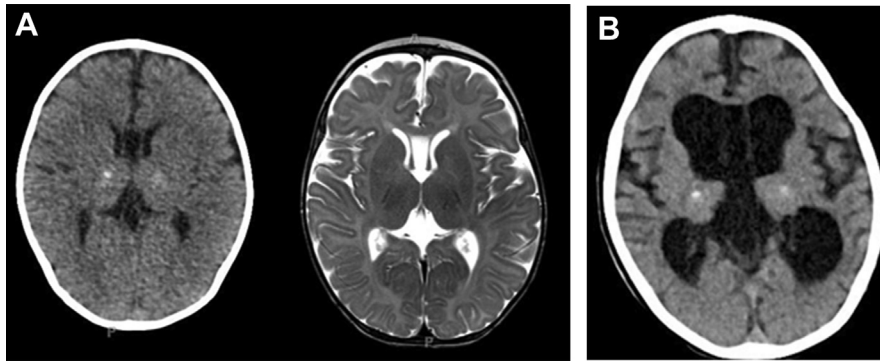

Fig. 5. (*A*) Axial non–contrast-enhanced computed tomography (CT) and matching axial T2-weighted MR images of a 5-year-old boy with confirmed Aicardi-Goutieres syndrome. Subtle hyperdense calcifications are noted within the bilateral thalami. The calcifications are barely visible as T2-signal alterations on the matching MRI. (*B*) Follow-up non–contrast-enhanced CT 2 years later shows progressive, global white matter volume loss with ex vacuo widening of the ventricular system and mild widening of the subarachnoid space.

SUMMARY

In conclusion, pediatric neuroinflammatory diseases encompass a wide range of disorders with varying clinical presentations, underlying pathophysiology, and treatments. Prompt evaluation for these conditions, with multidisciplinary involvement, should be initiated when neuroinflammation is suspected, as many are treatable with immunomodulating medications.

CLINICS CARE POINTS

- Clinical presentation of neuroinflammatory diseases can include encephalopathy/behavioral changes, seizures, focal neurologic deficits, or movement disorders.
- A multidisciplinary approach involving neurology, rheumatology, ophthalmology, psychiatry, and neuropsychology is critical to the diagnosis and management of children with neuroinflammatory conditions.
- Clinicians must exercise caution when interpreting results of antibody testing and should be aware of the possibility of overlapping neuroinflammatory syndromes.

DISCLOSURE

The authors have nothing to disclose.

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