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DEMYELINATING DISORDERS (J. BERNARD & M. CAMERON, SECTION EDITORS)

Atypical Pediatric Demyelinating Diseases of the Central Nervous System

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Abstract

Purpose of Review Pediatric central nervous system demyelinating diseases include multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), and acute disseminated encephalomyelitis (ADEM). As diagnostic criteria become more inclusive, the risk of misdiagnosis of atypical demyelinating diseases of rheumatologic, infectious, and autoimmune etiology increases.

Recent Findings We review mimics of multiple sclerosis, neuromyelitis optica spectrum disorder, and acute disseminated encephalomyelitis, including rheumatologic diseases: systemic lupus erythematosus and neuro-Behçet disease; infectious diseases: human immunodeficiency virus, progressive multifocal leukoencephalopathy, and subacute sclerosis panencephalitis; and autoimmune diseases including X-linked Charcot-Marie-Tooth disease, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) and autoimmune glial fibrillary acidic protein (GFAP) encephalopathy.

Summary Atypical demyelinating disease may mimic classic neuroinflammatory diseases of the central nervous system. Imaging may meet criteria for a diagnosis of multiple sclerosis, or patients may present with optic neuritis and transverse myelitis consistent with neuromyelitis optica spectrum or myelin oligodendrocyte glycoprotein (MOG) antibody disorders. Through careful history-taking and review of atypical MRI findings, we may avoid misdiagnosis and mistreatment.

Keywords Pediatric · Demyelination · Multiple sclerosis · Neuromyelitis optica · ADEM · MOG

Introduction

All demyelinating diseases of the central nervous system (CNS) are rare in the pediatric population. Incidence of childhood-onset demyelinating disease is reported between 0.64 and 1.66 per 100,000 individuals in several population-based and observational studies [1, 2]. The most common demyelinating diseases include multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), and acute disseminated encephalomyelitis (ADEM). Myelin oligodendrocyte glycoprotein antibodies (MOG-ab) disorders are now being widely studied and believed to have overlapping presentations as well.

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Since 1965, clinicians have used diagnostic criteria to evaluate dissemination in space and time in MS; however, it was not until 1997 that T2-hyperintense lesions on magnetic resonance imaging (MRI) were included in diagnostic criteria. The Barkhof criteria required the presence of many lesions, including juxtacortical, infratentorial, spinal cord and periventricular lesions, and either one or more gadolinium-enhancing lesions, or nine or more T2-hyperintense lesions [3]. In 2001, the International Panel on Diagnosis of MS created the McDonald criteria, which have been repeatedly revised to increase sensitivity of the criteria and facilitate early diagnosis of MS. [4] Increasing sensitivity can decrease specificity. The current McDonald 2017 criteria have been evaluated in children and have been found to be more sensitive, but less specific, than the McDonald 2010 criteria [5••].

Similarly, the newest criteria for NMOSD are broad, including (in absence of the aquaporin 4 antibody, which is very specific for this disease) a single episode of optic neuritis, acute myelitis, or area postrema syndrome; along with acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome, or symptomatic cerebral

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syndrome with NMOSD-typical brain lesions [6]. These criteria have also been evaluated in the pediatric population [7].

Diagnostic criteria for ADEM include both clinical and radiological features, including a first clinical central nervous system event with presumed inflammatory demyelinating cause, encephalopathy that cannot be explained by other etiologies and improvement, with no new clinical or MRI findings 3 months or more after onset. MRI of the brain should reveal diffuse, large (1–2 cm in size), multifocal lesions primarily involving the white matter, although the basal ganglia and thalamus are frequently involved [8].

Myelin oligodendrocyte glycoprotein (MOG) is a protein expressed in the central nervous system (CNS) in the membrane of oligodendrocytes and on the outer surface of the myelin sheath. Antibodies to this protein can be detected in the cerebrospinal fluid in demyelinating disorders consistent with ON, NMOSD, and ADEM, but more rarely in cases of isolated transverse myelitis [9••, 10]. While no clinical features are definitively associated with MOG-antibody seropositivity, it is more common in younger patients, and children under 9 often present with subcortical and deep white matter brain lesions [11, 12]. The presence of MOG antibodies does not predict whether patients will relapse, even when titers are followed serially [9••], and it is unclear at this time whether the presence of MOG antibodies should change management of pediatric demyelinating disease.

While the increased sensitivity of diagnostic criteria for these CNS demyelinating diseases leads to earlier diagnosis and treatment of potentially devastating diseases, clinicians must be aware of the potential for misdiagnosis. In this review, we discuss atypical demyelinating diseases of children that can mimic and meet diagnostic criteria for MS, NMO, or ADEM.

Rheumatologic

Neuropsychiatric Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune connective tissue disease with a complex etiology, multi-system involvement, and an unpredictable course. Involvement of the central or peripheral nervous system significantly increases mortality and morbidity in patients with SLE [13, 14]. Neurological complications of SLE most commonly include stroke, seizures, and headache. Rarely, myelopathy and demyelination can occur. Both transverse myelitis—often longitudinally extensive—and optic neuritis have been described in the setting of SLE, mimicking NMOSD. Optic neuritis occurs in approximately 1% of people with SLE. Early treatment with steroids is associated with better recovery of vision [15]. Similarly, about 1–2% of people with SLE will experience transverse myelitis, which does not necessarily respond to steroids [16, 17]. Lupoid sclerosis, an SLE-related demyelinating syndrome, leads to multiple lesions in the white matter of the brain, distinct in space and time, and can meet the McDonald criteria for multiple sclerosis (Fig. 1a, b). A history that is more consistent with multi-system involvement, absence of classic ovoid lesions with partial ring-enhancement or T1 hypointense "black holes" on MRI, and elevated anti-nuclear or anti-phospholipid antibodies should raise suspicion for SLE-related demyelinating syndrome [18]. Notably, anti-nuclear antibodies (ANA) and anti-phospholipid antibodies are detected in some patients with multiple sclerosis and do not necessarily correlate with symptoms of SLE [19–21]. .In addition, MOG antibodies have been identified in patients with SLE [22]. History and clinical examination are thus crucial in the distinction between SLE and demyelinating disease.

Neuro-Behçet Disease

Behçet disease is a multisystem vasculitis characterized by uveitis, recurrent orogenital ulcers, erythema nodosum, and skin lesions. It is more common in males, particularly in Western Asia and Southern Europe. It primarily presents in young adults, although neurological manifestations may be more common in children [23, 24]. Like lupoid sclerosis in SLE, demyelination can occur, separated in space in time and can meet the McDonald criteria, but is less likely to meet Barkhof criteria [25]. Patients can develop T1 "black holes" and brainstem atrophy [26], which can predict a progressive disease course [27]. Demyelination associated with MOG antibodies may mimic neurological manifestations of Behçet disease [28].

Sjögren Syndrome

Sjögren syndrome (SS) primary affects and impairs the exocrine glands, but extraglandular organs can be involved. Peripheral neuropathy, particularly sensory neuropathy, is more common than involvement of the central nervous system. Much like SLE, patients can present with optic neuritis or transverse myelitis, or disseminated demyelinating lesions that may be asymptomatic, and may meet the McDonald criteria for a diagnosis of multiple sclerosis. In addition, elevated IgG index and oligoclonal bands have been seen on CSF studies [29]. While primary demyelination can occur in SS, patients with SS also appear to be at increased risk of aquaporin-antibody positive NMOSD [30]. SS with transverse myelitis and MOG antibodies has been reported as well [31].

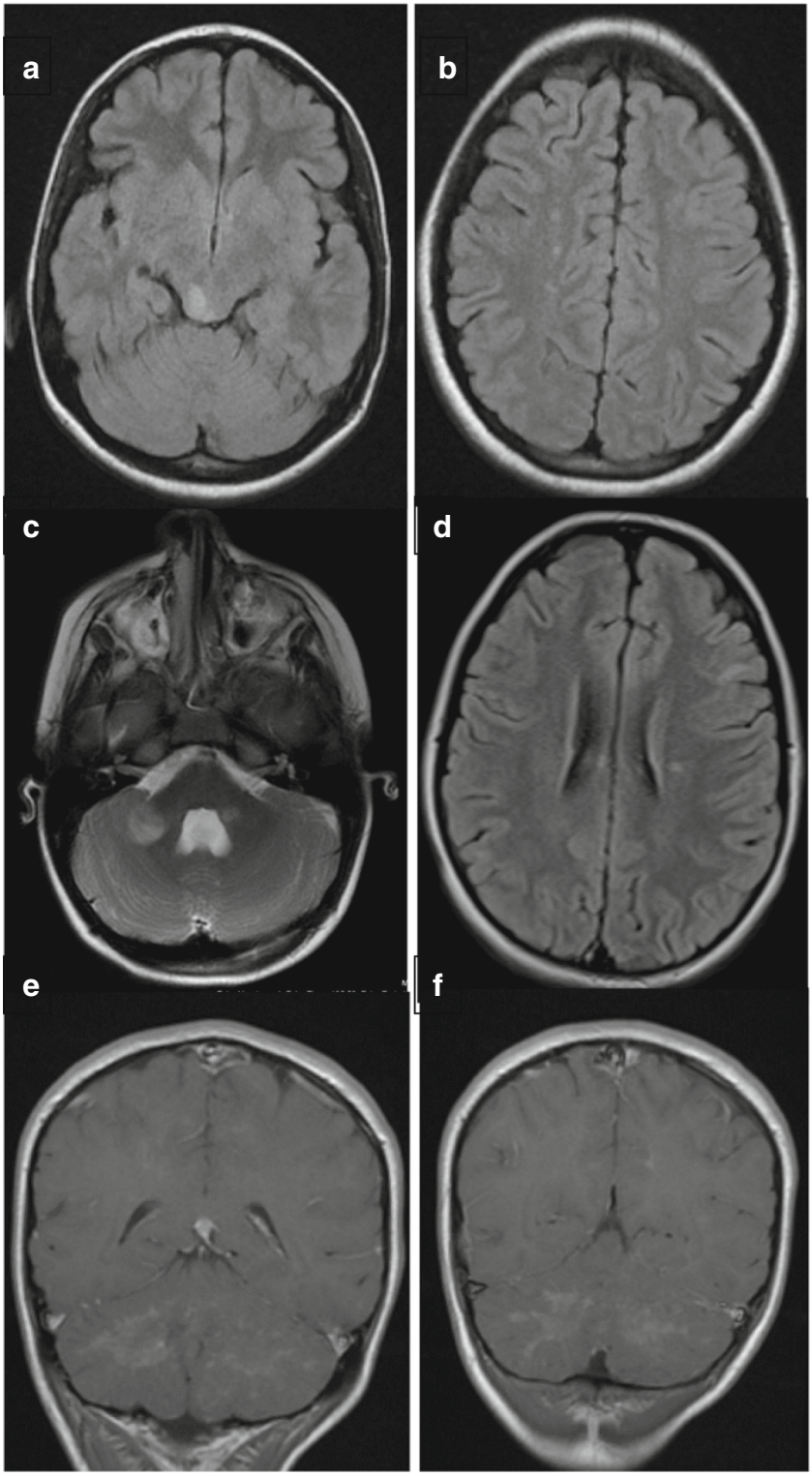

Fig. 1 **a**, **b** Axial T2 FLAIR MRI images of a 13-year-old female patient who presented with decreased color vision in one eye and was diagnosed with SLE. By imaging, she met McDonald criteria with gadolinium enhancement and dissemination in space. She also complained of painful joint swelling, and her mother had a diagnosis of SLE. Her ANA titer was 1:1280; ESR was 107; and anti-DNA antibodies were 1400. C) Axial T2 MRI image of hyperintense white matter lesion in a 6-year-old boy, eventually diagnosed with X-linked Charcot-Marie-Tooth disease, who presented with ataxia, nystagmus, and emesis, which resolved. Two years later, he presented with transient leg weakness and follow-up MRI **d** revealed new hyperintense white matter lesions on T2 FLAIR. Due to foot deformities, nerve conduction studies were done which were consistent with peripheral demyelinating disease and led to the diagnosis of CMT. **e**, **f** Coronal T2 FLAIR imaging of a 15-year-old girl with possible CLIPPERS. Presenting symptoms included vertigo and nausea, ataxia, rotary nystagmus, and action myoclonus. She responded radiographically but not clinically to steroids. Her symptoms did respond to IVIG and she was maintained on rituximab.

Infectious

Human Immunodeficiency Virus

Infection with human immunodeficiency virus (HIV) leads to neurological complications in the majority of both children and adults. Even in absence of opportunistic infections like progressive multifocal leukoencephalopathy (discussed below), malignancies, or clear HIV encephalopathy, children infected perinatally with HIV are at risk for developmental delay. A variety of demyelinating disorders have been reported in the setting of HIV that can mimic classic demyelinating diseases, without clear infectious cause. These include tumefactive demyelinating lesions that may be mistaken for tumefactive MS [32], and combined optic neuritis and transverse myelitis resembling NMO. In children, primary HIV infection can cause asymmetric diffuse white matter lesions, accompanied by encephalopathy, consistent with ADEM [33–35].

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a frequently fatal demyelinating disease of the central nervous system caused by the John Cunningham (JC) virus. While exposure to the virus is common, PML is rare, and occurs exclusively in the setting of immunosuppression from human immunodeficiency virus (HIV), cancer, post-transplantation medications, primary immunodeficiency, or immunomodulation for autoimmune inflammatory diseases, including rheumatologic disease and multiple sclerosis [36]. Children are less likely to test positive for the JC virus, and risk for conversion to JC virus antibody positivity increases with age [37, 38]; however, PML has been identified in prepubescent children in the setting of HIV or primary immunodeficiencies. Even in the presence of seropositivity, the risk of PML in the setting of multiple sclerosis disease–modifying therapies is difficult to estimate in the pediatric population. Demyelination can occur in virtually any area of the brain but affects the frontal and parietooccipital regions most frequently. Hyperintense lesions are seen on T2-weighted MRI images and may enhance with gadolinium [39]. These lesions can be challenging to distinguish from the lesions of multiple sclerosis or HIV.

Subacute Sclerosing Panencephalitis

Measles is a highly contagious disease caused by a paramyxovirus, transmitted through respiratory droplets. Although measles was declared eliminated in the USA in 2000, dropping vaccination rates and international travel led to a resurgence of the disease, with more cases reported in 2019 than in any year since 1992 [40]. Subacute sclerosing panencephalitis (SSPE) can occur approximately 4 to 10 years (median 7 years) following a primary measles infection. Children who contracted measles before 5 years of age and children with human immunodeficiency virus infection are at the greatest risk [41]. An asymptomatic period follows the initial infection. In Stage 1 of SSPE, children experience personality changes, including cognitive decline, mood swings and tantrums, irritability, and depression. After approximately 6 months, symptoms progress to seizures, muscle spasms, and dementia (Stage 2). Stages 3 and 4 involve progressive unresponsiveness leading to coma, autonomic dysregulation, and death [42]. MRI findings are variable and include decreased gray matter volume [43], diffuse symmetric white matter changes, subcortical and juxtacortical T2 hyperintensities [44], pial-gyral enhancement [45], or hyperintensities in the basal ganglia [46]. Involvement of optic nerves, brainstem, and spinal cord could resemble NMOSD [47, 48]. Electroencephalography often reveals periodic high-amplitude complexes [49, 50]. Both serum and cerebrospinal fluid may reveal measles antibody titers that are 10 to 1000 times higher than those seen in primary measles infection. There is no treatment for SSPE and mortality is high. Antiviral and immunomodulatory medications have been tried and may slow progression of the disease if SSPE is detected in the initial stage [51–54]. No cases of SSPE have been associated with vaccination. When vaccination rates increase, cases of SSPE decline [55].

Autoimmune

X-linked Charcot-Marie-Tooth Disease

Charcot-Marie-Tooth disease (CMT) is the most common hereditary peripheral neuropathy, characterized by weakness, muscle wasting, sensory disturbance, hyporeflexia, and pes cavus foot deformity. While CMT is usually inherited in an autosomal dominant pattern, X-linked CMT (CMT-X) is the second most common form of this disease. CMT-X is associated with mutations involving the gap junction protein connexin-32. Cases have been reported of patients, including pediatric patients, with CMT-X, who present with recurrent, transient neurological symptoms associated with transient white matter lesions on MRI (Fig. 1c, d). Patients can present with bulbar symptoms, like dysarthria, hemiplegia, sensory changes, or ataxia. Treatment is usually not indicated, as both neurological symptoms and radiological findings resolve [56–59]. Demyelination mimicking MS has also been reported in an adult patient with genetically confirmed CMT1A [60]. Studies involving diffusion-tensor imaging suggests that white matter abnormalities may be common in CMT variants [61].

Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) was described in 2010. While primarily a disease of adults [62, 63], cases have been reported in several children, as young as 10 [62, 64, 65]. CLIPPERS is characterized by distinctive punctate or curvilinear gadolinium-enhancing MRI lesions that are most prominent in the pons (Fig. 1e, f). Patients present subacutely with neurological symptoms primarily localizing to the rhombencephalon, including gait ataxia, vertigo, dysarthria, and diplopia; however, other cortical and white matter areas can also be involved and symptomatic [63].

Analysis of cerebrospinal fluid can be unremarkable or reveal mildly elevated protein, pleocytosis, or oligoclonal bands [63]. Like NMOSD, a CLIPPERS presentation can be associated with antibodies to myelin oligodendrocyte glycoprotein (MOG) [66, 67] although most cases are seronegative [63]. Rapid clinical and radiological improvement is seen after initiation of either intravenous or oral steroids. Symptoms can worsen, however, when steroids are stopped. Long-term steroid-sparing agents include azathioprine and mycophenolate, but immunomodulatory monoclonal antibodies like tocilizumab [68] and rituximab [69] have been used as well.

Autoimmune GFAP Astrocytopathy

Glial fibrillary acidic protein (GFAP) astrocytopathy was initially described in 1991 but was fully characterized in 2016. While this meningoencephalomyelitis is more common in individuals over 40 years old, with a median age of 54 [70], it has been reported in the pediatric population as well [71, 72]. Patients present with acute or subacute onset of a variety of symptoms, including myelitis, headache, abnormal vision, fever, ataxia, psychosis, dyskinesia, dementia, and seizures. On head imaging, abnormal T2 hyperintensities can be identified in the cortex, white matter, basal ganglia, and spinal cord (sometimes longitudinally extensive). With gadolinium administration, perivascular spaces enhance in a characteristic linear pattern radiating from the ventricle. CSF studies reveal lymphocytic pleocytosis. CSF is more specific than serum for the diagnostic GFAP autoantibody [71]. Clinical improvement occurs after intravenous steroid administration, usually followed by an oral steroid taper. Approximately 20% of patients will relapse and some may need long-term immunosuppression [70, 73••].

Conclusions

The presentation of central nervous system demyelinating diseases can be variable and it can be challenging to accurately diagnosis and treat children with these rare diseases. As diagnostic criteria for classic neuroinflammatory diseases become increasingly inclusive, providers should rely on careful history taking along with the established diagnostic criteria, particularly when considering the vulnerable pediatric population.

Compliance with ethical standards

Conflict of Interest Regina M. Troxell and Alison Christy each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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73.•• Fang B, McKeon A, Hinson SR, Kryzer TJ, Pittock SJ, Aksamit AJ, et al. Autoimmune glial fibrillary acidic protein astrocytopathy: a novel meningoencephalomyelitis. JAMA Neurol. 2016;73:1297–307 **This is the first characterization of the clinical presentation, response to corticosteroids, and associated neoplasms in patients with seropositivity for GFAP immunoglobulin.**