Neuroinflammatory and Demyelinating Disorders of Childhood

20

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20.1 Introduction

In this chapter, we will review monophasic and recurrent demyelinating disorders in children. We will first review consensus definitions and provide an approach to the evaluation of children with first episode of acquired demyelinating disorder. We will discuss typical clinical and radiological features of these syndromes. In the second section, we will review features of recurrent demyelinating syndromes in children, focusing on clinical presentation and treatment options.

20.2 Definitions and Classification

Acquired demyelinating syndromes (ADS) can be defined as syndromes resulting in single (monofocal) or multiple (polyfocal) lesions originating in the central nervous system (CNS) caused by inflammatory demyelination. Monophasic events may be classified as (1) clinically isolated syndrome (CIS), characterized by monofocal or polyfocal deficits without encephalopathy, or (2) acute disseminated encephalomyelitis (ADEM), characterized by polyfocal deficits and encephalopathy. Recurrent disorders include pediatric multiple sclerosis (MS), neuromyelitis optica spectrum

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Table 20.1   Acute demyelinating syndrome (ADS) classification

Monophasic ADS:
• Clinically isolated syndrome (CIS): monofocal or polyfocal deficits without encephalopathy
– Optic neuritis (ON)
– Transverse myelitis (TM)
– Other clinically monofocal or polyfocal ADS
• Acute disseminated encephalomyelitis (ADEM)
Recurrent ADS:
• Neuromyelitis optica (NMO)
• Serum antibodies to myelin oligodendrocyte glycoprotein (MOG)
• Pediatric multiple sclerosis
• Recurrent demyelinating disease not otherwise specified [DD-NOS]

disorders (NMOSD), and serum antibodies to myelin oligodendrocyte glycoprotein (MOG)-associated demyelination (see Table 20.1) [1].

20.3   Approach to a Child with Suspected Demyelination

Any patient with new, subacute focal neurologic deficits occurring after a known infection, and in the absence of trauma, metabolic derangements, or known underlying structural abnormalities, should be suspected of having acquired CNS demyelination. In addition to detailed history and physical examination, the suggested workup for these children includes cerebrospinal fluid (CSF) and serum analysis as well as neuroimaging (Fig. 20.1). Laboratory features, suggestive of acquired demyelination, include mild to moderate CSF pleocytosis, elevated CSF protein, presence of oligoclonal bands (OCBs), and increased immunoglobulin G (IgG) index. Magnetic resonance imaging (MRI) features may include the presence of multifocal white and gray matter abnormalities, presence of spinal cord lesions, optic nerve thickening or hyperintensity on T2-weighted imaging, and the presence of enhancement of lesions after the administration of gadolinium. Specific features associated with each of the disorders will be discussed below.

20.4   Section 1: Monophasic Demyelinating Syndromes

Clinically isolated syndromes (CIS) include optic neuritis (ON), transverse myelitis (TM), and other isolated syndromes including those with isolated cerebellar and brainstem lesions. These disorders may be monophasic in many cases, but could also be the first presentation of a relapsing syndrome such as NMOSD or MS (see Clinical course and risk of recurrence after the first demyelinating episode). Below we review each entity separately.
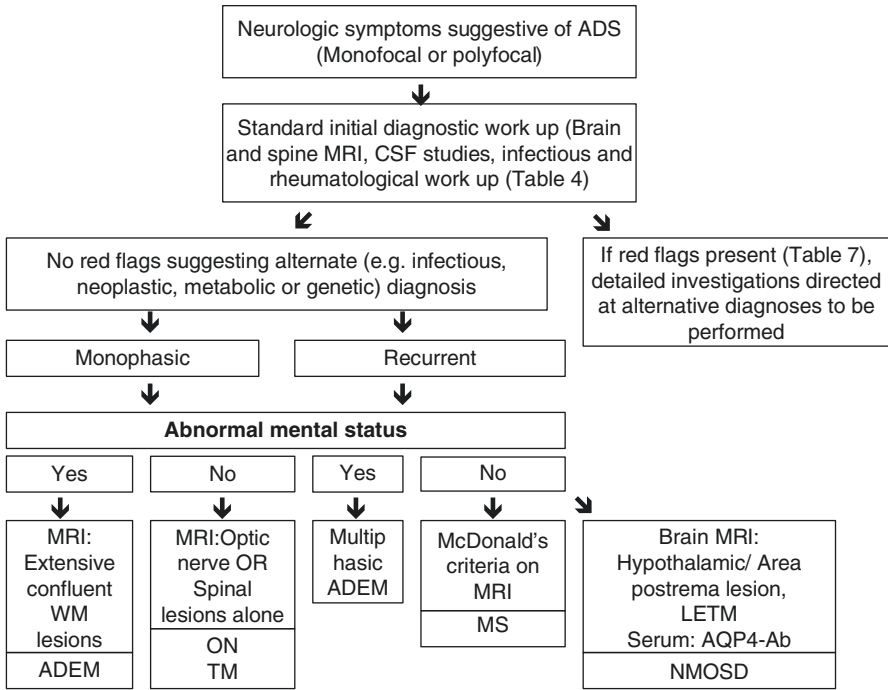
Neurologic symptoms suggestive of ADS
(Monofocal or polyfocal)

↓

Standard initial diagnostic work up (Brain
and spine MRI, CSF studies, infectious and
rheumatological work up (Table 4)

No red flags suggesting alternate (e.g. infectious,
neoplastic, metabolic or genetic) diagnosis

If red flags present (Table 7),
detailed investigations directed
at alternative diagnoses to be
performed

Monophasic	Recurrent

Abnormal mental status

Yes	No	Yes	No

MRI: Extensive confluent WM lesions	MRI:Optic nerve OR Spinal lesions alone	Multip hasic ADEM	McDonald's criteria on MRI	Brain MRI: Hypothalamic/ Area postrema lesion, LETM Serum: AQP4-Ab
			MS	
ADEM	ON TM			NMOSD

Fig. 20.1 Diagnostic approach to acquired demyelinating syndromes (ADS)

20.4.1   Optic Neuritis

Optic neuritis (ON) is characterized by inflammation of the optic nerve. It may present as an isolated condition or can be associated with variety of other immune-mediated CNS or systemic disorders [2]. Mean age of onset ranges from 9 to 12 years of age with an approximate 1.5:1 female-to-male ratio [3]. Its incidence is 1–5 per 100,000/year [3]. Between 13% and 36% of children with an initial episode of ON are eventually diagnosed with MS [4].

20.4.1.1   Clinical Features

Common clinical features of ON include periorbital pain or headache made worse by eye movement, subacute decrease in visual acuity (VA), abnormal color vision, reduced low-contrast letter acuity, and visual field (VF) defects. Physical examination at the time of an acute event will reveal a relative afferent pupillary defect (RAPD) in unilateral cases. Initial visual acuity can range from 20/40 or better to no light perception. Close to 60% of children have a VA of 20/200 or worse [5].

Inflammation of the optic nerve head (papillitis) is reported in up to 64% of cases of ON in children [6]. Bilateral ON and papillitis at onset are seen in 72% of children younger than 10 years of age, in comparison to older children [5]. The absence of pain and presence of retinal exudates, retinal hemorrhages, severe disk swelling, and lack of response to treatment suggest alternative diagnosis (Table 20.2).

Table 20.2 Differential diagnosis of pediatric inflammatory demyelinating disorders

Endocrine:
• Steroid-responsive encephalopathy associated with autoimmune thyroiditis
Nutritional:
• Vitamin B12, vitamin E, or folate deficiency
• Celiac disease
• Wernike–Korsakoff
Inflammatory/autoimmune:
• Systemic lupus erythematosus (SLE)
• Acute encephalopathy with autoantibodies
• Neurosarcoidosis
• Sjögren syndrome
• Antiphospholipid antibody syndrome (APLAS)
• Behçet disease
• Isolated or primary angiitis of CNS
• Hemophagocytic lymphohistiocytosis (HLH)
• Guillain–Barré syndrome and Bickerstaff brainstem encephalitis
• Susac syndrome
• Postinfection cerebellitis
Infections:
• Neuroborreliosis (Lyme disease)
• HSV encephalitis
• HIV infection
• Tuberculosis
• Neurocysticercosis
• Neurosyphilis
• Progressive multifocal leukoencephalopathy (PML)
• Whipple disease
• Thrombotic thrombocytopenic purpura/hemolytic–uremic syndrome (TTP/HUS)
• HTLV-1
Mitochondrial:
• Myoclonic epilepsy with ragged red fibers (MERRF)
• Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)
• Leber hereditary optic neuropathy (LHON)
• Leigh syndrome
• Kearns–Sayre syndrome
• DNA polymerase gamma (POLG)-related disorders

Table 20.2 (continued)

Genetic/metabolic:
• Inborn errors of metabolism
• Amino acid and organic aciduria
• GM2 gangliosidosis
Leukodystrophy:
• Metachromatic leukodystrophy
• Adrenoleukodystrophy
• Krabbe disease
• Pelizaeus–Merzbacher disease
• Refsum disease
• Vanishing white matter
• Leukoencephalopathy with brainstem and spinal cord involvement and elevated lactate levels
• Biotin-responsive basal ganglia disease
• Wilson disease
• Fabry disease
• Alexander disease
Toxic:
• Radiation
• Chemotherapy (methotrexate, cyclosporine, cytosine-arabinoside)
• Extrapontine myelinolysis
Neoplastic:
• Lymphoma
• Astrocytoma
• Medulloblastoma
• Metastases
• Langerhans cell histiocytosis
Others:
• Migraine
• CADASIL

20.4.1.2 Laboratory and Neuroimaging Features

For optic neuritis, a basic inflammatory and infectious workup is recommended. A summary of recommended CSF and serological investigations for first-time ADS in children is listed in Table 20.3. Brain MRI is helpful for MS risk stratification. MRI features in ON consist of thickening of the optic nerves on T1-weighted imaging, bright T2 signal along the optic nerve or chiasm, and postgadolinium enhancement on T1-weighted imaging. Visual evoked potentials (VEPs) will show prolongation of the P100 in the acute phase. Visual field (VF) testing can be performed in children older than 7 years of age and may show an enlarged central, paracentral, or altitudinal scotoma. Optical coherence tomography (OCT) will show increased retinal nerve fiber layer thickness (RNLFT) at onset of ON if papillitis is present. In

the chronic phase, reductions in the RNLFT will be seen, with an average reduction in RNFLT of around 25% after one episode [7]. In cases of bilateral optic neuritis or MRI features suggestive of NMOSD, aquaporin-4 (AQP4) antibody should be tested (see Sect. 20.7). A proposed relationship between serum anti-MOG antibodies and recurrent ON in children has also been reported [8].

Patients who present with ON and no lesions on MRI typically have a monophasic course and a favorable prognosis. A retrospective multicenter cohort study of 357

Table 20.3 Investigations for a child with suspected demyelinating disorder

Investigation	Diagnostic purpose
Neuroimaging	
Full spine MRI with gadolinium	MS, LETM in NMO, nerve root enhancement in Guillain–Barré syndrome (GBS) Vertebral body compression, disk herniation, epidural hematoma, tumors, arteriovenous malformation, ischemic myelopathy, atlantoaxial subluxation
Brain and orbits MRI	MS, NMO, ADEM, leukodystrophy
CSF studies	
CSF cell count and cytology	Inflammation, infection, and tumor
CSF protein and glucose	Guillain–Barré syndrome, meningitis, encephalitis
IgG index, oligoclonal bands (paired with serum)	MS, NMO, and TM
Fungal and bacterial CSF cultures	Infections
CSF viral serology: • Polymerase chain reaction (PCR) for HSV, CMV, EBV, VZV, human herpesvirus 6–7 (HHV6–7) • Enterovirus**,** Parechovirus, West Nile virus • Human T-cell leukemia virus type 1 (HTLV-1)	Viral and bacterial infections
Mycoplasma pneumoniae *Borrelia burgdorferi* Acid-fast Bacilli (AFB) VDRL	Lyme disease (seasonal) Tuberculosis (TB) Syphilis
Serology—infectious workup	
Serum viral serologies: • PCR for HSV, CMV, EBV, VZV • West Nile virus • HTLV (based on travel to endemic areas only) Mycoplasma pneumoniae PCR and titers	Viral and bacterial infections
VDRL *Borrelia burgdorferi* titers Cysticercoids	Syphilis Lyme disease (seasonal) Cysticercosis
Throat swab and stool for enterovirus PCR	Acute flaccid myelitis

Table 20.3   (continued)

Serology—autoimmune workup	
Serum aquaporin-4 IgG	NMOSD
Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibody (ANA), extractable nuclear antigen (ENA), double-stranded DNA, antineutrophil cytoplasmic antibody (ANCA), antiphospholipid antibodies, lupus anticoagulant, Anti-Ro, Anti-La, Thyroid-stimulating hormone, Antithyroid peroxidase (Anti-TPO)	Systemic lupus erythematosus, Sjögren syndrome, antiphospholipid antibody syndrome (APLAS), Behçet disease, Hashimoto encephalopathy
MOG antibodies	MOG antibody-associated disease
Angiotensin-converting enzyme level and chest X-ray	Sarcoidosis
Serology—nutritional workup	
Vitamin B12, folate, vitamin E, Biotinidase, vitamin D, copper, plasma amino acids, ammonia, lactate	Nutritional and metabolic causes of myelopathy
Special tests	
Visual evoked potentials (VEPs)	Silent demyelinating lesions

children with ON, followed for a median of 4 years, showed that the two strongest predictors of developing MS were the presence of CSF oligoclonal bands (seen in 80% of patients with MS and only in 15% of children with monophasic ON) and abnormal cranial MRI [9].

20.4.2   Transverse Myelitis

Twenty percent of children with a first episode of demyelination experience transverse myelitis. The mean age of presentation is 8 years, with a bimodal distribution (children under 5 and children 10–12 years) [10, 11]. Approximately 50% of patients report a preceding infection, typically a nonspecific upper respiratory tract infection in the previous month [12]. Close to 10% of patients with acute transverse myelitis (ATM) develop MS [13].

20.4.2.1   Clinical Features

Acute transverse myelitis (ATM) is characterized clinically by acute or subacute development of neurologic dysfunction in motor, sensory, and autonomic nerves and may be accompanied by bowel and bladder dysfunction. Children may present with complete or partial cord syndromes, manifesting as patchy motor or sensory deficits with occasional bladder involvement. One of the most common initial symptoms in children is pain, which is seen in up to 60% of children at presentation [14]. Sensory findings may include positive symptoms, such as burning, paresthesias, hyperesthesia, or negative symptoms, such as numbness. Importantly, a clearly

defined sensory level may not be evident in up to 40% of children [15]. Sphincter involvement is reported in up to 72% of children with ATM [10]. Motor symptoms are predominantly in keeping with upper motor neuron (UMN) findings, such as weakness, increased tone, and hyperreflexia in the lower extremities. Signs of spinal shock, manifesting as flaccid paresis and absent reflexes, are reported in the initial phase and may last up to 12 weeks [14]. Acute and hyperacute deficits, suggestive of a spinal cord lesion, warrant urgent spinal imaging, as an earlier intervention for vascular disorders and spinal cord compression may improve the outcome. The presence of a sensory level, radicular pain, areflexia, and failure to respond to anti-inflammatory therapies raises concern for an alternative diagnosis (Table 20.2). Diagnostic criteria have been established by the Transverse Myelitis Consortium Working Group (TMCWG) to define idiopathic ATM (Table 20.4). The utility of the TMCWG definitions in younger children is limited, as the presence of a clear sensory level is difficult to discern on physical examination and gadolinium-enhancing lesions may not be present in this age group [16].

20.4.2.2 Laboratory and Neuroimaging Features

In ATM, MRI lesions reveal T1-isointense and T2-hyperintense signals involving the gray matter and neighboring white matter (WM) and may enhance with gadolinium. Lesions may be contiguous or patchy. Longitudinally extensive TM (LETM), defined as expanding across greater than three vertebral segments, occurs in 66–85% of ATM in children. In some patients with suggestive clinical features, the initial spine MRI may be normal and should be repeated in 24–48 h after presentation [11]. While CSF pleocytosis (>5 WBC/mm^3) provides supporting evidence for ATM, normal CSF results have been reported in up to 50% of pediatric patients with ATM [12]. A complete recommended workup for ADS is reviewed in Table 20.3. In patients with ATM, a higher risk of MS is seen in those with longitudinal lesions between 1 and 3 spinal segments. Similarly, the presence of CSF oligoclonal bands increases the risk for MS [17].

Table 20.4 Transverse Myelitis Consortium Working Group (TMCWG) definition of acute transverse myelitis (ATM) [16]

1.	Sensory, motor, or autonomic dysfunction attributable to the spinal cord
2.	Bilateral signs or symptoms but not necessarily symmetric
3.	Clearly defined sensory level
4.	Exclusion of extra-axial compressive etiology by neuroimaging (MRI or pyelography; CT of spine not adequate)
5.	Inflammation within the spinal cord demonstrated by CSF pleocytosis or elevated IgG index or spinal gadolinium enhancement
6.	Progression to nadir less than 21 days following the onset of symptoms

If none of the inflammatory criteria is met at symptom onset, repeat the MRI and lumbar puncture evaluation between 2 and 7 days following symptom onset to meet criteria

20.4.3 Acute Disseminated Encephalomyelitis (ADEM)

ADEM is monophasic in 70–90% of cases. Encephalopathy and multifocal brain lesions on MRI affecting the gray and white matter of the brain and spinal cord are characteristic of ADEM. Estimated incidence is 0.2/100,000 in Canada [18]. The mean age of onset of ADEM in the pediatric population is reported to be 7.4 ± 1.3 years of age [19]. A preceding triggering event is reported in the majority of children (69%) receiving a diagnosis of ADEM [19]. In addition, ADEM has been reported following vaccinations (postimmunization encephalomyelitis). Vaccination-associated ADEM has been observed after the measles/mumps/rubella vaccinations [20, 21]. Two prospective studies of children with ADEM showed that 5–18% had a second attack suggesting MS [22, 23].

20.4.3.1 Clinical Features

Children with ADEM present with encephalopathy in association with multifocal neurologic deficits, which reach a nadir 4–7 days after presentation. Encephalopathy may include irritability, confusion, lethargy, and coma [24]. Prodromal symptoms can include fever, malaise, headache, nausea, and vomiting. Neurologic signs and symptoms in ADEM include long-tract signs (60–95%), acute hemiparesis (76%), cerebellar ataxia (20–65%), visual loss due to optic neuritis (7–23%), cranial nerve involvement (22–45%), seizures (13–35%), spinal cord involvement (24%), and slurred speech (5–12%) [19, 22]. Viruses that have been described in single case reports in relation to ADEM include coronavirus, coxsackie, cytomegalovirus (CMV), Epstein-Barr (EBV), herpes simplex (HSV), hepatitis A, HIV, influenza, measles, rubella, varicella zoster (VZV), West Nile, and more recently Zika [25–29].Typically, there is a latency period of 7–14 days between a febrile illness and the onset of neurologic symptoms. More aggressive variants of ADEM have been described in the literature, including acute hemorrhagic leukoencephalitis and acute necrotizing encephalopathy of childhood (ANEC).

Clinical features can often help differentiate between ADEM and MS [26]. ADEM usually follows a prodromal viral illness and can be associated with fever. ADEM usually produces widespread central nervous system disturbance with impaired consciousness and/or encephalopathy, while MS typically has a relapsing-remitting course. Disease activity more than 3 months after ADEM onset is suggestive of a more chronic disorder like MS. CSF oligoclonal bands are seen most consistently in patients with MS. ADEM has a monophasic course in a majority of patients; however, multiphasic cases have been reported. As such, the International Pediatric Multiple Sclerosis Study Group (IPMSSG) proposed a consensus definition for multiphasic ADEM (Table 20.5). It is defined as two episodes consistent with ADEM separated by 3 months that can be associated with new or reemergence of prior clinical and MRI findings [22, 30–32]. Diagnosis of MS in children with prior diagnosis of ADEM requires a second non-ADEM attack together with either further MRI findings suggestive of new lesions or a third attack not meeting the criteria for ADEM.

Table 20.5 Summary of 2012 International Pediatric Multiple Sclerosis Study Group (IPMSSG) definitions for clinically isolated syndrome, pediatric multiple sclerosis (MS), and other CNS demyelinating disorders

Pediatric clinically isolated syndrome (CIS) (all are required)
• A clinical CNS event with presumed inflammatory demyelinating cause
• Absence of a clinical history of CNS demyelinating disease (if any, see pediatric MS)
• No encephalopathy, except as readily explained by fever
• Does not meet baseline MRI criteria for MS
Pediatric acute disseminated encephalomyelitis (ADEM) (all are required)
• A first polyfocal, clinical CNS event with presumed inflammatory demyelinating cause
• An encephalopathy that cannot be explained by fever
• No new clinical or MRI findings 3 months or more after onset
• Brain MRI is abnormal during the acute (3 months) phase with typically diffuse, poorly demarcated large lesions involving predominantly the cerebral white matter
Multiphasic acute disseminated encephalomyelitis
• New event of ADEM 3 months or more after the initial event that can be associated with new or reemergence of prior clinical and MRI findings
• Timing in relation to steroids is no longer pertinent
Pediatric MS (any of the following)
• Two or more CIS separated by more than 30 days involving more than one area of brain, optic nerves, or spinal cord
• One CIS associated with MRI findings consistent with the 2010 McDonald MRI dissemination in space (DIS) (≥1 T2 lesion in two of the four following locations: periventricular, juxtacortical, infratentorial, or spinal cord) and in which a follow-up MRI shows at least one new lesion consistent with dissemination in time (DIT) (simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions) criteria
• One clinical event (CIS) whose MRI findings are consistent with criteria for DIS and DIT
• One ADEM attack followed by one CIS 3 or more months after symptom onset that is associated with new MRI findings consistent with criteria for DIS
Pediatric neuromyelitis optica (revised—see Sect. 20.7)

20.4.3.2 Laboratory and Neuroimaging Features

Initial diagnostic workup includes MRI of the brain and spine, serologic and CSF testing for infections in suspicious cases (Table 20.3). Lesions seen on MRI in ADEM include extensive, bilateral, asymmetric patchy areas of T2-weighted hyperintensity within the white matter, deep gray nuclei, and spinal cord. Lesions in the deep gray matter involve areas of the thalamus or the basal ganglia, which often occur bilaterally and are located at the gray–white junction [22]. Any two of the following MRI features such as (1) absence of diffuse bilateral lesion pattern, (2) presence of black holes, or (3) presence of two or more periventricular lesions can help distinguish ADEM from MS with a sensitivity of 81% and specificity of 95% [20]. CSF can be normal in up to 61% of patients with ADEM [19, 33]. The CSF examination is characterized by normal opening pressure, moderate lymphocytic pleocytosis (between 50 and 180 cells/mm^2) and may show elevated protein (40–100 mg/dL) [19, 27]. Oligoclonal bands are infrequently seen in the CSF (10%) [34]. Despite ADEM patients commonly reporting a recent infection before their neurologic presentation, testing for viral etiologies is rarely positive (17%) [19].

20.5 Workup: First-Time Demyelination

The differential diagnosis for children with suspected first-time demyelination is broad (Table 20.2). The workup includes neuroimaging, CSF studies, laboratory testing, and special tests (Table 20.3).

20.6 Treatment: Acute Demyelinating Events

In the absence of evidence-based data for the pediatric population with demyelinating disorders, most treatment recommendations are extrapolated from adult studies, case reports, case series, and retrospective analyses. There are no studies to date comparing the efficacy of the different immunomodulatory therapies in children with ADS. Acute management of patients with ADS is reviewed here.

20.6.1 Corticosteroids

Corticosteroids are the mainstay of treatment in demyelinating conditions, particularly in an acute relapse. High-dose corticosteroids suppress the immunologic activation associated with ADS and MS relapses via several mechanisms such as hindering the cytokine cascade, inhibiting the activation of T cells, facilitating the apoptosis of activated immune cells, among others [35]. The standard empiric therapy for ADS consists of high-dose corticosteroids, with 30 mg/kg/dose (maximum 1000 mg) of methylprednisolone intravenously (IV MP) once a day for 3–5 days. In adults with optic neuritis, the optic neuritis treatment trial (ONTT) showed that IV MP hastened the recovery of vision when administered in a timely manner, and decrease in recurrence rate in the first 2 years [36]. A multicenter open-label study of 12 children and 17 historical controls with severe ATM treated with IV MP showed a significant difference in the proportion of patients treated with steroids walking independently within 1 month and achieving full recovery at 1 year compared to historical controls, with no difference in the frequency of complications between the treatment group and historical controls [37].

20.6.2 Intravenous Immunoglobulin (IVIg)

IVIg has an impact on inflammation by decreasing levels of cytokines, binding to antibodies against myelin, and blocking fragment crystallizable (Fc) receptors. Additionally, it may promote remyelination. IVIg use has been reported to be of benefit in small case series in steroid-refractory acute ON and ATM cases [19]. A total of 2 g/kg is administered, divided in one to five equal consecutive daily doses. Advantages include ease of administration, safety profile, and high tolerability [38]. Frequently reported side effects include headache and allergic reaction. Risk of thrombosis is increased with IVIg and should be considered and watched for.

20.6.3 Plasma Exchange (PLEX)/Plasmapheresis

Benefits of plasma exchange occur through the elimination of pathogenic inflammatory mediators, including autoantibodies, complement components, and cytokines [39]. Case series suggest that plasmapheresis is safe in pediatric demyelinating disorders. Furthermore, in a double-blinded randomized-controlled trial of PLEX in CNS demyelinating disease where 22 patients refractory to steroids were randomized to PLEX or sham therapy, PLEX was found to have statistically significant benefits [40]. As per the American Academy of Neurology (AAN) updated guidelines, plasmapheresis may be considered in the treatment of fulminant CNS demyelinating diseases (NMODS included) that fail to respond to high-dose corticosteroid treatment (Level C) [41].

20.6.4 Cyclophosphamide

ATM in the context of rheumatological conditions such as systemic lupus erythematosus (SLE) has been treated with cyclophosphamide [42].

20.7 Section 2: Recurrent Demyelinating Syndromes

Risk of recurrence after a single demyelinating event in youth can be stratified according to the age of presentation, CSF composition, presence of antibodies such as astrocytic water channel aquaporin-4 (AQP4) antibodies, and MRI manifestations. Children under the age of 12 presenting with an ADEM phenotype and those with CIS and no brain lesions have a low risk of developing MS (1.9–3.3%). On the other hand, children over the age of 12 presenting with multifocal lesions on brain MRI are at high risk of an eventual diagnosis of MS (60.6%) [43]. Below, we outline clinical features of the two most recognized recurrent demyelinating syndromes.

20.7.1 Neuromyelitis Optica Spectrum Disorders (NMOSD)

Neuromyelitis optica spectrum disorders (NMOSD) are an increasingly recognized group of disorders characterized by the presence of AQP4 antibodies [44]. The mean age at presentation ranges from 32 to 45 years in most case series [45]. Pediatric onset of the disease is relatively rare and accounts for 3–5% of all NMOSD cases. The frequency of AQP4 in children with inflammatory disorders of the CNS is 78% for relapsing neuromyelitis optica (NMO) and 20% for partial forms of NMO [46].

While AQP4 antibodies are seen in two-thirds of pediatric patients with clinical manifestations satisfying diagnostic criteria for NMOSD [44], more recently, antibodies to myelin oligodendrocyte glycoprotein (MOG) have been implicated as potentially pathological in individuals with clinical syndromes suggestive of NMOSD. Anti-MOG

antibodies have been found to be present in children with recurrent disease who are AQP4 negative with a clinical phenotype, which includes optic neuritis, longitudinally extensive transverse myelitis, and multifocal brain lesions [47, 48]. The relevance of these antibodies for clinical practice is currently under investigation.

20.7.1.1 Diagnosis

In 2015, the International Panel for NMOSD Diagnosis (IPND) proposed revised criteria (Table 20.6), which addressed distinctive features of pediatric NMOSD [44]. The current diagnostic criteria divide NMOSD into two major subtypes based on the serum AQP4-IgG status. The IPND recommended the current criteria also be applied

Table 20.6 2015 NMOSD diagnostic criteria [44]

A. NMOSD with AQP4-IgG	1. 1 Core clinical characteristic 2. Positive AQP4-IgG testing using the best available method 3. Exclusion of alternative diagnoses

B. NMOSD without AQP4-IgG or with unknown AQP4-IgG status	1. ≥2 Core clinical characteristics occurring as a result of ≥1 clinical attacks and meeting all of the following:
	  (a) At least one clinical characteristic: Must be optic neuritis, LETM, or area postrema syndrome
	  (b) Dissemination in space (≥2 different core clinical characteristics)
	  (c) Fulfillment of additional MRI requirements
	2. Negative tests for AQP4-IgG using the best available method or testing unavailable
	3. Exclusion of alternative diagnoses

C. Core clinical characteristics	1. Optic neuritis 2. Acute myelitis 3. Area postrema syndrome 4. Acute brainstem syndrome 5. Symptomatic narcolepsy or acute diencephalic syndrome with typical diencephalic MRI lesions 6. Symptomatic cerebral syndrome with typical brain lesions
D. Additional MRI requirements	
1. Acute optic neuritis	(a) Brain MRI normal or showing nonspecific white matter lesions (b) Optic nerve MRI with T2-hyperintense or T1-weighted gadolinium-enhancing lesion extending over 0.1/2 optic nerve length or involving optic chiasm
2. Acute myelitis	Requires intramedullary MRI lesion extending over three contiguous segments (LETM) or ≥3 contiguous segments of spinal cord atrophy in patients with history compatible with acute myelitis
3. Area postrema syndrome	Requires associated dorsal medulla/area postrema lesions
4. Acute brainstem syndrome	Requires associated periependymal brainstem lesions

to the pediatric population, but with some minor modifications. This includes less specificity of LETM, as this can also be observed in pediatric patients with MS and ADEM, also acknowledging that AQP4-IgG is rarely positive in monophasic LETM in children. The new criteria aim to facilitate earlier and more accurate diagnosis of patients with NMOSD. This is especially important for AQP4-IgG-seronegative cases where detailed clinical, neuroimaging, and laboratory descriptions of patients will be necessary to better characterize this heterogeneous population.

20.7.1.2 Clinical Features and Outcome

Clinical features at onset include ON (most often bilateral), LETM, area postrema syndrome (intractable hiccups, nausea/vomiting), brainstem and diencephalic syndromes such as narcolepsy/hypersomnolence (Table 20.6). In a study from the Mayo Clinic with 48 children with AQP4-IgG-positive NMOSD, at least one episode of ON or transverse myelitis was seen in 83% and 78% of children, respectively. Additionally, 45% of the cohort had other symptoms such as encephalopathy, seizures, ophthalmoparesis, ataxia, or area postrema syndrome [49]. This study also reported coexisting autoimmune disorders in 42% of their pediatric cohort (SLE, Sjögren syndrome, juvenile rheumatoid arthritis, Graves' disease).

A recent prospective multicenter study compared the clinical features of pediatric NMOSD to other pediatric demyelinating diseases and validated the new 2015 IPND diagnostic criteria in children [50]. Of 38 pediatric NMO cases, 97% met the revised 2015 IPND diagnostic criteria. The mean age at onset was 10.2 ± 4.7 years. Serum or CSF NMO IgG was positive in 65% of NMO cases on initial presentation; however, a few cases became seropositive within 3 years of disease onset, supporting the notion that repeat testing up to 3–4 years should be considered in patients with a high likelihood of NMOSD. Moreover, there were no distinctive clinical features that set apart seropositive versus seronegative NMOSD patients besides a predominance of seropositivity in African-Americans compared to Caucasians.

The course of NMO is characterized by a high relapse rate with accumulation of neurologic disability [46]. One study comparing 12 individuals with pediatric-onset NMOSD to those with adult onset NMOSD demonstrated a longer time to irreversible disability in those with pediatric onset disease but greater levels of visual impairment [51].

20.7.1.3 Preventative Therapy for NMOSD in Children

Acute treatment follows the same algorithm discussed in Sect. 20.6. Additionally, information on three agents has been published in relation to pediatric-onset NMOSD.

- Azathioprine (AZA): Recommended dose: 2–3 mg/kg/day. AZA is a prodrug form of 6-mercaptopurine (6-MP), which works as a purine antagonist that gives negative feedback on purine metabolism and inhibits DNA and RNA synthesis. Its use is associated with relapse rate reduction in children, with 60% remaining relapse-free for 18 months [52].

- Rituximab (RTX): Recommended dose: 375 mg/m^2 once weekly for 4 weeks or 500 mg/m^2 once, then 2 weeks later. RTX is a monoclonal antibody directed against the CD20 antigen. Use in the pediatric population is well described. A multicenter retrospective study of 16 children with NMOSD receiving more than two rituximab courses and followed for 6 years showed significant reduction of annualized relapse rate pre- and post-rituximab ($p = 0.003$). A close monitoring of CD19 (+) B cells is suggested, as B cell repopulation creates a risk of relapse [53]. A case series of youth with NMOSD receiving rituximab as a first-line therapy experienced complete cessation of disease activity and stabilization of neurologic disability [54].

Mycophenolate Mofetil (MMF): Recommended dose: 2000 mg/day. MMF is a pro-drug that inhibits the proliferation of B and T lymphocytes. Retrospective studies including children have shown that MMF is effective in reducing relapse frequency and improving disability [55].

20.7.2   Pediatric Multiple Sclerosis

Pediatric MS, defined as the onset of MS before the age of 18, is seen in 5% of MS patients, with almost three-quarters (72%) experiencing their first symptoms after the age of 12 [56–58]. The prevalence of pediatric MS is 1.35–2.5 per 100,000 children [57] and the female-to-male ratio is 2.8:1.

20.7.2.1   Diagnosis

Diagnostic criteria for pediatric MS, based on clinical and MRI features, which support the presence of dissemination of MS events in time and space, are outlined below [32]:

- Two or more nonencephalopathic (i.e., unlike acute disseminated encephalomyelitis or ADEM), clinical central nervous system (CNS) events with presumed inflammatory cause, separated by more than 30 days and involving more than one area of the CNS.
- One nonencephalopathic episode typical of MS, which is associated with MRI findings consistent with the 2010 McDonald criteria (Table 20.5) for dissemination in space (DIS) and in which a follow-up MRI shows at least one new enhancing or nonenhancing lesion consistent with criteria for dissemination in time (DIT).
- One ADEM attack followed by a nonencephalopathic clinical event, 3 or more months after symptom onset, which is associated with new MRI lesions that fulfill the 2010 McDonald dissemination in space criteria.
- A first, single, acute event that does not meet the ADEM criteria and where MRI findings are consistent with the 2010 McDonald criteria for dissemination in space and dissemination in time (applies only to children ≥12 years).

MRI is an important tool in the diagnosis of demyelinating syndromes [59] (Table 20.5). The criterion of dissemination in space (DIS) in both pediatric and adult patients with MS can be met by the presence of at least one lesion in at least two of four typical white matter locations, including juxtacortical, periventricular, infratentorial, and spinal cord. In patients presenting with a spinal cord or brain-stem syndrome, these symptomatic lesions do not count toward the MRI lesions. Dissemination in time (DIT) in older patients (older than 12 years of age) can be met at the time of a baseline scan, provided that there is evidence of both a gadolinium-enhancing and nonenhancing clinically silent lesion. Radiologically isolated syn-drome (RIS) symptoms in which MRI features consistent with MS are present in the absence of clinical symptoms do not satisfy the diagnostic criteria for MS.

20.7.2.2 Clinical Features and Course of Pediatric MS

Clinical features of MS include visual loss, ataxia, diplopia, long-tract signs (par-esthesias, weakness), urinary symptoms, and cranial nerve palsies. Older children mostly present with monofocal symptoms, whereas in younger children demyelin-ating events are mostly polyfocal and can be associated with encephalopathy, as described earlier in Sect. 20.7. A European observational study of 394 children with pediatric-onset MS found that children were more likely than adults to present with isolated optic neuritis, an isolated brainstem syndrome, or symptoms of encepha-lopathy (i.e., headache, vomiting, seizure, or altered consciousness) [60].

A relapsing course is seen in 98% of pediatric MS cases. As in the adult popula-tion, individuals with pediatric-onset MS with a relapsing course eventually reach a stage of irreversible disability. The median time from diagnosis to this (EDSS = 4) is 20 years or at 34 years of age [61]. Children who demonstrate progressive disease at onset should be investigated for alternative diagnoses (Table 20.2). Relapse rates are significantly higher in pediatric-onset MS than adult onset disease (0.8 in pediatric-onset MS vs. 0.3 in adult onset MS, $p < 0.001$) [62]. A short interval between the first two demyelinating episodes and incomplete recovery after the first attack have been associated with increased risk of further attacks and/or reaching a higher disability score [63, 64]. Disease severity is currently measured by the Expanded Disability Status Scale (EDSS) that scores the disability based on the functional system scores [65]. Up to 35% of pediatric MS patients have some identifiable cognitive dysfunc-tion at the time of diagnosis. Younger age at onset, higher EDSS score, and number of relapses together with low scores on measures of intellectual function predict greater impairment across cognitive domains [66].

20.7.2.3 Laboratory Investigations

Specific CSF findings are not required for MS diagnosis. CSF pleocytosis (lympho-cytic) has been described in 52–66% of pediatric MS patients, with a white blood cell (WBC) count of <60 cells/mL. Oligoclonal bands and elevated IgG index may be seen in approximately two-thirds (63% and 68%, respectively) of children older than 11 with MS, and fewer younger children (43% and 35%) [67]. Notably, how-ever, OCBs are nonspecific markers and may be detected in 8–15% of children with monophasic demyelinating syndromes [65].

20.7.2.4   Treatment in Pediatric MS

Lifestyle Modifications
Low vitamin D has been associated with increased risk of MS and an increased relapse rate [23, 68]. Patients usually require 800–3000 IU oral vitamin D per day to achieve normal serum levels. In children, second hand smoke has been associated with an increased risk for MS [69].

Disease-Modifying Therapies
The United States Food and Drug Administration (FDA) has not approved any of the disease-modifying therapies approved for use in adult MS and for use in pediatric MS. However, a number of treatments are currently being used off-label in these children. We have provided details regarding these therapies below.

First-Line Disease-Modifying Therapy
Glatiramer acetate (GA) and interferon beta (IFN-b) have been routinely used in adults with MS for the past 15–20 years. These treatments are associated with a decrease in relapse rate of 30% [70]. There have been no randomized trials in children; however, two position papers have reported on expert consensus on the use of IFN-b and GA in pediatric patients [71, 72]. The International Pediatric Multiple Sclerosis Study Group (IPMSSG) recommends that all pediatric patients with MS should be considered for treatment with either an IFN-b or GA as first-line therapy. In the presence of inadequate treatment response or persistent side effects, transition to a different first-line therapy or escalation to a second-line therapy should be considered.

Following the IPMSSG consensus criteria, inadequate treatment response in pediatric MS is defined as [71]:

(a) Minimum time on full-dose therapy 6 months
(b) Fully compliant on treatment
(c) At least one of the following:
  • Increase or no reduction in relapse rate, or new T2 or contrast-enhancing lesions on MRI from pretreatment period
  • ≥Two confirmed relapses (clinical or MRI relapses) within a 12-month period or less

Second-Line Disease-Modifying Therapies
At this time, there is limited information on the use of second-line MS disease-modifying therapies for pediatric-onset multiple sclerosis (POMS). However, multiple case series have suggested safety and efficacy comparable to that seen in adult MS [73]. Fortunately, ongoing clinical trials in pediatric patients with MS evaluating newer therapies such as fingolimod, dimethyl fumarate, and teriflunomide are underway [74] (Table 20.7). Below, we have provided a summary table (Table 20.7) of currently available treatments, their side effects, and the current evidence in pediatric population.

Table 20.7 Disease-modifying therapies (DMT) in pediatric MS

Name of the drug	Mechanism of action	Side effects	Studies in pediatric MS			Dose
			Study	No. of pts	Design	
First-line therapy						
Interferon-Beta [75, 76] –1a (Avonex)- Intramuscular (IM) once per week –1a (Rebif)- Subcutaneous (SC) Three times per week –1b (Betaseron)- SC every other day	Shift pro-inflammatory T-helper 1 to T-helper 2 responses	Flu-like symptoms, leukopenia, thrombocytopenia, anemia, transaminases Injection site reaction Neutralizing antibodies (NAbs)	Ghezzi et al. [77] Tenembaum and Segura [78] Tenembaum et al. [79]	130 pts 24 pts 307 pts	Retrospective single center Retrospective single center Retrospective, multicenter, Phase 4	IFN-b-1a 30 mg IM weekly IFN-b-1a 22 or 44 mg SC 3 times weekly IFN-b-1a 22/44 mg SC 3 times weekly
Glatiramer acetate (Copaxone) [80] SC, daily, or 3 times a week (40 mg SC TIW)	Shifts Th1 to Th2 responses, promotes "bystander cells," i.e., T regulatory cells	Injection site Lipoatrophy, Acute chest syndrome (anxiety, palpitation, flushing)	Kornek et al. [81] Ghezzi et al. [77]	7 pts 14 pts	Retrospective single center	Copaxone 20 mg SC daily

Teriflunomide (Aubagio) [82] Oral, once daily	Reversible inhibition of dihydroorotate dehydrogenase, mitochondrial enzyme involved in pyrimidine synthesis for DNA replication	Hair thinning, alopecia Liver function abnormalities Gastrointestinal (GI) events (nausea, vomiting, cramping, diarrhea) Leukopenia Hypertension Reactivation of TB	TERIKIDS (Sanofi NCT02201108)	165 pts—estimated, ongoing	Randomized, double-blind, placebo-controlled clinical trial—Phase 3	3.5, 7, or 14 mg oral
Dimethyl fumarate (Tecfidera) [83, 84] Oral, twice daily	Nrf2 antioxidant pathway modulator	Flushing after dosing GI upset Lymphopenia Dermatitis Progressive multifocal leukoencephalopathy (PML) risk factors: (1) Lymphocyte count ≤500 (2) Age > 50 (3) Hx of immunosuppressant or Natalizumab use	CONNECT (Biogen-NCT02283853) FOCUS (Biogen-NCT02410200) Makhani et al. [85]	142 pts—estimated 18 pts—estimated 13 pts	Open-label, randomized active-controlled clinical trial—Phase 3 Open-label, prospective study Retrospective, Dual center study	120 mg oral Not available 120–240 mg oral

(continued)

Table 20.7 (continued)

Name of the drug	Mechanism of action	Side effects	Study	No. of pts	Design	Dose
			Studies in pediatric MS			
Second-line therapy [73]						
Natalizumab [86] (Tysabri) IV every 3 months	Humanized monoclonal antibody targeting the a4 subunit of a4b1 integrin	Hypersensitivity reaction: hives, rash Infusion-related side effects (headache, flushing, dizziness) Pharyngitis/sinusitis Peripheral edema Hepatotoxicity PML Risk factors for PML [87]: (1) Seropositive for anti-JC virus (JCV) antibodies (2) Prior use of immunosuppressant (3) Duration of Natalizumab therapy	Biogen (NCT01884935) Ghezzi et al. [88] Kornek et al. [89]	13 pts—estimated 101 pts 11 pts	Open-label, prospective study Multicenter registry Retrospective single center	300 mg intravenously (IV) every 4 weeks 300 mg every 28 days 300 mg every 28 days
Fingolimod [90, 91] (Galina) Oral once daily	Sphingosine-1-phosphate receptor modulator	Bradycardia at first dose Varicella and herpetic infections Macular edema Cutaneous malignancy Lymphopenia PML (Rare)	Novartis (NCT01892722) Fragoso et al. [92]	190 pts—estimated 17 pts	Randomized-controlled, double-blind, double dummy masked Retrospective single center	Once daily at a dose of either 0.5 or 0.25 mg Not available

Drug	Mechanism	Adverse effects	Reference	Patients	Study type	Dose
Mitoxantrone [93, 94] IV infusion every 3 months	DNA topoisomerase inhibitor	Cardiotoxicity, Leukemia, Secondary lymphoid cancer, Leukopenia, Discoloration of urine, Alopecia	Kornek et al. [95]	4 pts	Retrospective single center	36, 68, 84, and 120 mg/m
Rituximab IV infusion 2 weeks apart	Monoclonal antibody directed against the CD20 antigen	Infusion reactions, Hepatitis B activation, Bowel obstruction/perforation, PML	Dale et al. [96], Beres et al. [97], Salzer et al. [97]	4 pts, 3 pts, 14 pts	Multicenter retrospective study, Retrospective case series, Retrospective case series	375 mg/m^2 weekly for 4 weeks
Cyclophosphamide [98] IV infusion	Alkylating agent	Bladder cancer, Sterility, Secondary leukemia	Makhani et al. [99]	17 pts	Retrospective multicenter	$600–1000 \text{ mg/m}^2$/dose
Ocrelizumab IV infusion	Monoclonal antibody directed against the CD20 antigen	Infusion-related adverse events	None	None	None	None
Daclizumab IV infusion	Humanized monoclonal antibody specific for the interleukin 2 receptor α chain	Headache, Leukopenia, Transaminitis	Gorman et al. [100]	7 pts	Case series	1 mg/kg monthly

20.8 Conclusions

Knowledge about pediatric demyelinating disorders has grown significantly in recent years. Above, we have provided a summary of clinical features, investigations, and both acute and prophylactic therapies in these conditions. Future multi-institutional, international collaborative studies are needed to advance knowledge regarding therapies and outcomes of these disorders.

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