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Paediatric acquired inflammatory demyelinating disorders of the central nervous system

Manjula Tennakoon

Teaching Hospital Ratnapura, Sri Lanka.

Correspondence
Manjula Tennakoon
Teaching Hospital Ratnapura, Sri Lanka.
Email:
manjulathennakoon170@gmail.com

https://orcid.org/0000-0009-0009-4070-3740

Abstract

Our understanding of paediatric acquired inflammatory demyelinating diseases is continually evolving. By integrating extensive clinical and paraclinical data, we can refine diagnostic accuracy using epidemiological information, clinical presentations, specific antibodies, and radiological abnormalities. Tailored management approaches can then be implemented based on the most congruent clinical picture. The availability of international collaborative research and standardised group protocols facilitates the selection of optimal immunosuppressive drug regimens, ensuring effective management of the disease and its comorbidities. Acute disseminated encephalomyelitis, acute optic neuritis, and acute transverse myelitis are observed in both paediatric and adult populations. However, there are notable differences in their clinical and radiological phenotypes, treatment considerations, and prognoses in the younger group. Understanding these distinctions is crucial for developing age-appropriate diagnostic and therapeutic strategies and predicting long-term outcomes in affected individuals. This article integrates the latest advancements and data to synthesize and critique the literature on acute acquired demyelinating disorders in children.

KEYWORDS

ADEM, optic neuritis, transverse myelitis, multiple sclerosis, NMOSD, MOGAD

INTRODUCTION

Acquired inflammatory demyelinating disorders of the central nervous system are relatively uncommon in the paediatric population, with an estimated annual incidence of 9.8 per million children per year worldwide.[1] However, reported frequencies are higher in tertiary care paediatric neurology referral centres. These disorders primarily cause demyelination of the brain and/or spinal cord. They share some distinct differences in clinical presentation, radiological findings, antibody profiles, treatment strategies, and prognoses from those seen in adult patients.

These disorders can manifest as either monophasic or relapsing illness and distinguishing between these types necessitates ongoing clinical and radiological monitoring. They are classified in various ways: typically based on their location(s) within the central nervous system (CNS), monophasic and polyphasic clinical courses, and the mono-focal or multifocal extent of involvement (Table 1).[1] This review article focuses on current literature and recent advancements in diagnosing and treating acquired demyelinating syndromes in paediatric patients. It explores frequently encountered monophasic demyelinating disorders such as acute disseminated encephalomyelitis (ADEM), acute optic neuritis (AON), acute transverse myelitis (ATM) and myelin oligodendrocyte glycoprotein antibody-associated diseases (MOGADs).

TABLE 1 Paediatric acquired demyelinating disorders classification[1]

Disorder	Definition
Acute disseminated encephalomyelitis (ADEM)	• A first polyfocal CNS event with a presumed inflammatory cause. • Encephalopathy that cannot be explained by fever. • MRI often shows bilateral diffuse, poorly demarcated T2 lesions. • No new symptoms, signs, or MRI findings after the initial three months.
Multiphasic ADEM	• New event of ADEM three months or more after the initial event that can be associated with new or re-emerging clinical and MRI findings. • Frequently associated with the presence of MOG-Ab.
Clinically isolated syndrome (CIS)	• The first mono-focal or multifocal CNS demyelinating event. • Encephalopathy is absent unless caused by fever.
Paediatric multiple sclerosis (MS)	MS can be diagnosed in those for whom there is no better explanation, if both dissemination in time (DIT) and dissemination in space (DIS) can be demonstrated.
Primary progressive MS (PPMS)	PPMS is exceedingly rare in childhood, and therefore one should be extremely attentive in arriving at this diagnosis. Biopsy and/or further genetic investigations can be done to rule out mimics.
MOG-Ab-associated disease (MOGAD)	• MDEM: recurrent ADEM (see earlier). • ADEM-ON: ADEM or MDEM followed by optic neuritis (ON). • NMOSD like phenotype: ON and acute transverse myelitis (ATM), either sequentially or simultaneously. • Relapsing inflammatory ON (RION). • Brainstem demyelination: recurrent episodes of demyelination often involving the posterior fossa and brainstem.
Neuromyelitis optica spectrum disorder (NMOSD)	• If AQP4 – positive, one of the core criteria is required: • If AQP4 – negative or unavailable, two core criteria are needed.

ADEM – acute disseminated encephalomyelitis; CNS– central nervous system; MRI – magnetic resonance imaging; CIS –clinically isolated syndrome; MS – multiple sclerosis; MOG-Ab – myelin oligodendrocyte glycoprotein antibodies; MOGAD – myelin oligodendrocyte glycoprotein antibody associated disease; MDEM - multiphasic disseminated encephalomyelitis; ON – optic neuritis; TM – transverse myelitis; RION – recurrent isolated optic neuritis; NMOSD – neuromyelitis optica spectrum disorder; AQP4 – aquaporin 4

Approach to the acute event of paediatric acquired inflammatory demyelinating disorders

The initial assessment following the first attack should encompass a comprehensive history and thorough examination. A detailed history plays a pivotal role in discerning whether symptoms are acute, hyperacute, or subacute, thereby facilitating accurate diagnosis and ruling out potential differentials. Typically, symptom onset in acquired demyelinating disorders is subacute.

A hyperacute presentation (reaching maximal severity within a few hours of onset) is less common and could suggest a haemorrhagic/ischaemic aetiology. Further, transient neurologic symptoms (e.g., symptoms lasting for seconds, minutes, or hours and then resolving), as opposed to those that are continuous, are more suggestive of paroxysmal disorders (e.g., migraine, seizure).

The history should also identify potential preceding factors, such as infection(s) or vaccine(s), travel outside of the country, insect/tick bites, rashes, or recent trauma/injury.[2] The mono-

focal acquired demyelinating syndromes include ON and ATM; whereas, multifocal acquired demyelinating syndromes include ADEM.[2]

Apart from a thorough neurological examination, the physical examination should be comprehensive, focusing on identifying any infectious foci, a thorough rheumatological assessment, attention to specific dermatological findings, and evaluating for nutritional deficiencies. These steps are essential for determining the possible aetiology and excluding disease mimics.

The laboratory evaluation in a patient with an acquired demyelinating syndrome should include cell counts, protein, glucose, IgG index, and oligoclonal bands (in serum and cerebrospinal fluid (CSF)) as well as serum assessment for myelin oligodendrocyte glycoprotein (MOG) and aquaporin-4 (AQP4) IgG antibodies.[2] The presence of oligoclonal bands and the pattern of distribution (e.g., unique to the intrathecal space versus a mirrored pattern with equivalent numbers in serum and CSF) can assist in diagnosis and prognosis for relapsing disease.[2] Radiological evaluation of the brain, optic nerves, and spine using magnetic resonance imaging (MRI) is essential.

The primary treatment is immunotherapy, though some patients may only require assurance and close observation. The first line of immunotherapy includes intravenous (IV) methylprednisolone (IVMP) followed by oral prednisolone. When there is no response to first-line treatment or when steroids are contraindicated intravenous immunoglobulin (IVIg) or plasma exchange (PLEX) may be considered.

Acute disseminated encephalomyelitis (ADEM)

The clinical hallmark of ADEM is encephalopathy with multifocal neurologic symptoms and signs.[2] ADEM predominantly affects younger prepubescent children and is typically monophasic in over 90% of children, with a median age of onset from 5 to 8 years.[3]

Most give a history of preceding non-specific respiratory or gastrointestinal illness 1-3 weeks before symptom onset. ADEM following vaccination is rare, with less than 5% of reported cases showing a temporal association.[4] Prodromal symptoms of ADEM may include fever, fatigue, malaise, headache, and gastrointestinal symptoms.[2] The typical clinical presentation often involves a subacute onset of encephalopathy accompanied by multifocal neurological deficits corresponding to the affected regions of the central nervous system (CNS). Symptoms may include cranial nerve palsies and seizures.

The differential diagnosis is broad and is listed in Table 2. The definitions of ADEM have historically been an umbrella term for non-infectious acute inflammatory demyelinating events of the CNS, particularly occurring in children. Until recently, the definition of ADEM varied widely, leading to differences in the phenotypes reported. In 2007, the International Paediatric Multiple Sclerosis Study Group (IPMSSG) proposed consensus definitions for paediatric acquired demyelinating disorders of the CNS to improve consistency in terminology.[5] In 2013, the original definitions were updated. ADEM remains a diagnosis of exclusion, always necessitating thorough consideration of alternate diagnoses. The new diagnostic criteria for ADEM[5] require the following:

1. A first polyfocal clinical CNS event with presumed inflammatory demyelinating cause.
2. Encephalopathy (alteration in consciousness or behaviour unexplained by fever, systemic illness, or postictal symptoms).
3. Brain MRI abnormalities consistent with demyelination during the acute 3-month phase.
4. No new clinical or MRI findings 3 months or more after the clinical onset.[5]

Non-monophasic ADEM is a small but important subset of patients with ADEM who will subsequently be diagnosed with relapsing disorders, including neuromyelitis optica spectrum disorders (NMOSD) and multiple sclerosis (MS). We currently have insufficient diagnostic technologies to reliably distinguish this subset from most patients with ADEM for whom the disease course is monophasic.

CSF analysis typically reveals mild to moderate lymphocytic or monocytic pleocytosis. Intrathecal oligoclonal bands are rare but, when present, exhibit a mirrored pattern with the serum (e.g., three bands in the serum and three bands in the CSF), indicating a lack of intrathecally unique bands.[6] MOG antibodies are detected in more than half of all paediatric patients with ADEM and should be tested for in any child with an ADEM phenotype. Rarely, AQP4-positive NMOSD can present with tumefactive demyelination that mimics ADEM in children.[7]

Children with ADEM exhibit bilateral large (>1 to 2 cm) T2/fluid-attenuated inversion recovery (FLAIR) hyperintense lesions on MRI that predominantly involve the cerebral white matter. Grey matter involvement is not infrequent, but T1-hypointense lesions should be absent.[8] Lesions are bilateral, large, poorly demarcated (smudged edge appearance), and diffuse, bright on T2-weighted. Approximately 10% of lesions in ADEM exhibit enhancement with gadolinium (Figure 1).

The main differentiating features of ADEM compared to MS are periventricular sparing and the absence of periventricular ovoid lesions perpendicular to the ventricular edge (Dawson's fingers). There are, however, no absolute imaging criteria to differentiate ADEM from MS.[5]

Treatment approaches for ADEM often include high-dose intravenous steroids followed by an oral prednisolone course taper over 4 to 6 weeks. IVIg may also be tried, either concurrent with or following corticosteroid treatment. Plasma exchange is

used for fulminant ADEM or cases that prove refractory to steroids and/or IVIg (e.g., lack of any clinical improvement within 2 to 3 days or lack of marked improvement within 1 to 2 weeks from treatment.[2]

Most paediatric patients with ADEM experience a monophasic course with good neurologic outcomes. Repeat imaging at least 3 to 6 months following the initial attack is useful to provide a new imaging baseline for the patient and should demonstrate improvement of prior MRI abnormalities.[2]

Acute Optic Neuritis (AON)

Optic neuritis (ON) is a common presenting symptom in paediatric CNS demyelinating disorders and may be associated with dramatic visual loss.[9] The literature indicates that ON constitutes approximately one-quarter of children presenting with demyelinating events. ON in childhood is marked by heterogeneity and may occur as a monophasic illness, recurrent isolated ON, and recurrent ON in the context of multifocal inflammatory CNS diseases such as ADEM, MS, and NMO.

The cardinal features of ON include decreased visual acuity (VA), dyschromatopsia (abnormal colour vision, notably red colour desaturation), and visual field (VF) deficits. Visual loss usually occurs over hours to days, typically reaching a nadir within several days of onset.[9] Unilateral presentation at onset may be followed rapidly by bilateral involvement. Depending on the duration of symptoms it is considered as follows: within 2 weeks: 'bilateral simultaneous ON'; within 2-12 weeks: 'bilateral sequential ON'; after 12 weeks: 'bilateral recurrent ON'.[10]

Neurologic examination may show evidence of reduced visual acuity, visual field loss, red colour desaturation, an afferent pupillary defect, or optic disc oedema in the acute/subacute setting.[2] The studies have shown that younger children (<10 years of age) are more likely to present with bilateral ON and older children with unilateral ON.[9] Paediatric ON is more frequently bilateral compared to its adult counterpart, with greater occurrence of optic disc oedema and more severe visual loss. However, long-term recovery in children tends to be more favourable than in adults.

The differential diagnosis is also wide for acute and subacute vision loss (Table 2). In the child presenting with a first episode of acute or subacute visual loss attributed to the optic nerve, once infectious, genetic, and neoplastic aetiologies have been ruled out, specific clinical and laboratory indicators may assist in predicting the likelihood of ON being the first manifestation of MS, chronic relapsing inflammatory optic neuropathy (CRION), NMOSD or part of an underlying systemic rheumatologic condition such as systemic lupus erythematosus.[9] Pain with eye movement is reported and doesn't consistently differentiate inflammatory from noninflammatory optic neuropathies in children. Children find it difficult to differentiate headache from eye pain and headache becomes a complaint. Physical examination findings include the presence of the relative afferent pupillary defect, with fundoscopic examination often revealing optic nerve abnormalities including papillitis in the acute stage and optic nerve pallor and atrophy in the chronic stage. Papillitis has been noted in 46%-69% of children with ON compared to one-third of those with adult ON.[11]

MOG antibodies are an important component of laboratory evaluation, with approximately 30% of all cases of paediatric MOG-associated disorders manifesting as ON.[12] Although bilateral ON is seen in AQP4-positive NMOSD, this disorder is quite rare in childhood; however, high-titre MOG antibodies are detected in nearly 70% of children with ON.[13]

MRI of the orbits is not required to diagnose ON in children as it is a clinical diagnosis supported by history and examination. It may show focal abnormalities of the anterior visual pathway. Typical MRI findings in dedicated orbital MRI studies consist of thickening of the optic nerves on T1-weighted imaging, bright T2 signal along the optic nerve or chiasm, and post-gadolinium enhancement. Longitudinally extensive lesions of the optic nerve are present in children who are positive for the AQP4 IgG (NMO IgG) and MOG antibodies (Figure 2) and not in children with MS.[14] When myelopathic symptoms are present with ON or if there is a high suspicion of MS or NMOSD, a spinal MRI should also be considered.

Computerized visual field (VF) testing (perimetry) is not routinely done in children with acute optic neuritis unless there is a concern of papillitis from papilloedema. It can usually be performed in children older than 7 years. The rate of VF defects like central and non-central scotoma in acute optic neuritis in children is unknown but they occur in 97.5% of adult cases.[15] The visual evoked potentials are beneficial for assessing acute cases and for identifying prolonged latencies in chronic conditions. Additionally, optical coherence tomography (OCT) is valuable for quantifying retinal structure. OCT can provide an assessment of neuronal injury, including retinal nerve fibre layer thickness, retinal ganglion cell bodies, and axonal layers.

Within the first several weeks of the onset of ON, OCT testing typically shows swelling (i.e., increased thickness) of the retinal nerve fibre layer of the affected eye(s); however, in the chronic setting, OCT demonstrates thinning of the retinal nerve fibre and ganglion cell/inner plexiform layers.[16] In children, prolonged P100 latencies on visual evoked potential (VEP) testing are frequent in the acute phase[17] but it is unclear whether children, who may have excellent recovery from ON[17] are more likely than adults to have normalized VEP waveforms in long-term follow-up.[18] Of importance, although ON may be clinically limited to one eye in many cases, electrophysiologic studies of paediatric MS suggest that bilateral involvement frequently occurs in paediatric MS even in the absence of overt ON in the fellow eye.[19] Visual dysfunction in ON can be measured by other sensitive tools like metrics of low contrast dysfunction, contrast sensitivity and low contrast letter acuity.

TABLE 2 Differential considerations for children presenting with acquired demyelinating syndromes[2]

	Autoimmune-inflammatory	Infectious	Genetic	Toxic/ metabolic	Vascular/ traumatic	Neoplastic
Optic neuritis	Granulomatous (e.g., sarcoidosis); Rheumatologic (e.g., systemic lupus erythematosus [SLE], Sjögren syndrome); Neuroinflammatory (multiple sclerosis [MS], neuromyelitis optica spectrum disorder [NMOSD], myelin oligodendrocyte glycoprotein [MOG]-associated disorders)	Lyme disease, Syphilis, Bartonella, Tuberculosis, viral infection (e.g., human immunodeficiency virus [HIV], Epstein Barr virus [EBV], cytomegalovirus)	Hereditary optic neuropathy (e.g., Leber hereditary optic neuropathy)	Vitamin B12 deficiency. Biotinidase deficiency Folate, copper, or vitamin E deficiency Heroin myelopathy Radiation/ chemotherapy related myelopathy Carbon monoxide poisoning	Vasculitis (polyarteritis nodosa, granulomatosis with polyangiitis); Central nervous system vasculitis; Ischaemic optic neuropathy; Traumatic optic neuropathy	Optic glioma Hemophagocytic lympho-histiocytosis; Gliomatosis cerebri; Central nervous system lymphoma; Infiltrative astrocytoma
Transverse myelitis	Granulomatous (e.g., sarcoidosis); Rheumatologic (e.g., SLE, Sjögren syndrome); Behcet disease, Neuroinflammatory (MS, NMOSD, MOG associated disorders, Guillain-Barré syndrome)	Acute flaccid myelitis: viral (e.g., EBV, varicella-zoster virus, enterovirus, human T-cell lymphotropic virus type 1 [HTLV-1], West Nile virus); bacterial (e.g., Mycoplasma, Bartonella, Lyme disease)	Mitochondrial disorders (e.g., Leigh syndrome, Leukoencepha-lopathy with brainstem and spinal cord involvement and lactate elevation (LBSL))	Vitamin B12 deficiency. Biotinidas deficiency Folate, copper, or vitamin E deficiency Heroin myelopathy Radiation/ chemotherapy-related myelopathy Carbon monoxide poisoning	Vasculitis (polyarteritis nodosa, granulomatosis with polyangiitis); Central nervous system vasculitis; Spinal cord infarction; Fibrocartilaginous embolus; Arteriovenous malformation; Compressive myelopathy	Intramedullary tumor (e.g., astrocytoma); Extramedullary tumour causing cord compression (e.g., meningioma)
ADEM	Granulomatous (e.g., sarcoidosis); Rheumatologic (e.g., SLE, Sjögren syndrome); Neuroinflammatory (MS, NMOSD, MOG-associated disorders)	Lyme disease, tuberculosis, Bartonella, Rickettsia	Mitochondrial disorders (e.g., polymerase gamma [POLG]-related disorders, MELAS); Leukodystrophies; Inborn errors of metabolism	Vitamin B12 deficiency. Biotinidase deficiency Folate, copper, or vitamin E deficiency Carbon monoxide poisoning	Vasculitis (polyarteritis nodosa, granulomatosis with polyangiitis); Central nervous system vasculitis; Posterior reversible encephalopathy syndrome (PRES)	Hemophagocytic lympho-histiocytosis; Gliomatosis cerebri; Central nervous system lymphoma; Infiltrative astrocytoma

SLE – systemic lupus erythematosus; MS – multiple sclerosis; NMOSD – neuromyelitis optica spectrum disorder; MOG – myelin oligodendrocyte glycoprotein; HIV – human immunodeficiency virus; EBV – Epstein-Barr virus; HTLV-1 – human T-lymphotrophic virus; LBSL – Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation; POLG – polymerase gamma; MELAS – mitochondrial encephalopathy, lactic acidosis and stroke-like episodes; PRES – posterior reversible encephalopathy syndrome

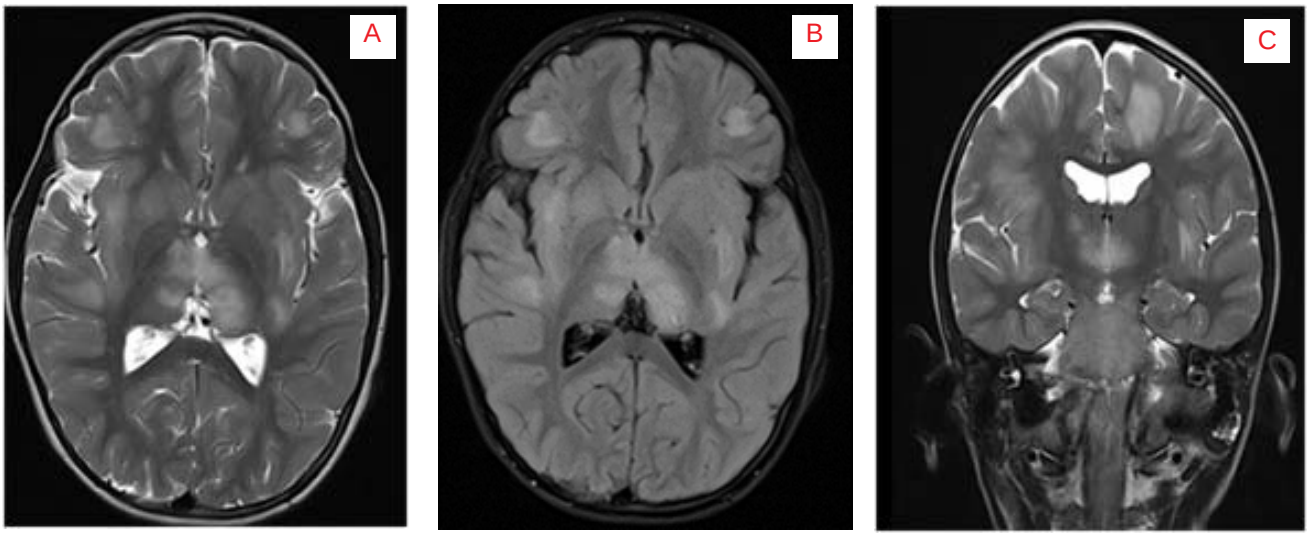

FIGURE 1 MRI images of a 6-year-old boy who presented with ADEM.

A) T2-weighted MRI brain demonstrating high signal intensity areas involving the gray-white junction of both cerebral hemispheres, thalami, and right basal ganglia.

(B) T2-FLAIR axial brain image showing changes in the grey-white junction of both cerebral hemispheres, thalami, and right basal ganglia.

(C) T2 weighted coronal MRI demonstrating high signal intensities in the pons and cerebral peduncle.

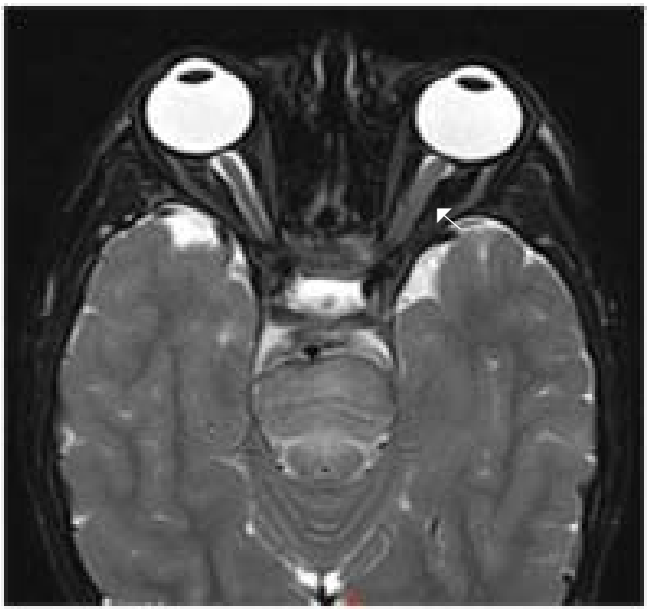

FIGURE 2 MRI image of a 6-year-old boy who presented with left optic neuritis positive MOG antibodies[46]

T2 weighted MRI of B/L optic nerves demonstrating thickening and increased T2 signal in the left optic nerve (white arrow) with normal right optic nerve and chiasma.

Recovery of visual acuity following ON is generally excellent in children, with the majority attaining full high-contrast visual acuity. However, approximately half of the patients may continue to experience deficits in low-contrast visual acuity. Children often report subjective visual abnormalities after ON that high-contrast visual acuity cannot capture. Differentiating ON as a clinically isolated syndrome from a relapsing disease like MS and NMOSD can be achieved through specific imaging and relevant immunological biomarkers.

Simply after an episode of ON, the subsequent diagnosis of MS in children with no brain lesion is infrequent. Children who presented with acute ON were followed up for more than 5 years and 13-36% of them were diagnosed with MS. The presence of white matter lesions in the MRI during an acute episode indicates that the likelihood of MS is higher.[9]

Although young children may have bilateral severe ON without experiencing recurrence, a poor response to steroids, or the presence of brain or spinal cord MRI findings typical of NMOSD should lead to evaluation of serum AQP4 antibodies and concomitant autoantibodies. This is important because of the availability of treatment to prevent visual disability in NMOSD and the high association of serologic markers such as anti-Ro/SSA with NMOSD.

CSF biomarkers can be utilized to establish the relapse risk of ON. The presence of aquaporin or MOG antibodies indicate the future risk of relapse and at the same time the presence of either of these antibodies suggests that the future diagnosis of paediatric MS is unlikely. The likelihood of MS following isolated ON is increasingly higher if the patient is older (e.g., peripubertal/post-pubertal), has at least two oligoclonal bands unique to the intrathecal space, and has concurrent demyelinating lesions within the brain outside of the optic nerve/chiasm.[20,21] CSF oligoclonal bands were found in 80% of paediatric patients with MS and only 15% of children with monophasic ON.[9]

No clinical trials have been performed for the standard treatment of paediatric ON, so clinical practice currently follows evidence gleaned from the Optic Neuritis Treatment Trial (ONTT)[22] in which recovery after intravenous steroid

administration in the first 15 days after onset, was more rapid than after placebo or oral steroids. By 7 weeks after onset, little difference between the groups could be seen.[20] Treatment in the paediatric population consists of 30 mg/kg per day IV methylprednisolone, maximum 1 g daily, for 3-5 days. The need for a prolonged course of oral steroids is unknown: one retrospective study suggested no difference in outcome between shorter (< 2 weeks) and longer (>2 weeks) courses of steroids in children with acute ON.[18]

Treating acute episodes of ON with steroid pulse treatment is particularly important in children as it speeds up recovery and minimizes psychosocial disturbances and functional impairment leading to learning issues. Little evidence for acute therapies beyond steroid treatment exists. However, if improvement does not occur after the administration of steroids, a second course of high-dose steroids, therapeutic plasma exchange (TPE), immunoadsorption, or IVIg may be considered. The case series suggests that plasmapheresis is safe in paediatric demyelination[19] and has potential benefits in steroid-resistant paediatric patients.[23] IVIg usage for acute paediatric ON is limited and only evident in case reports and small case series.

Acute transverse myelitis (ATM)

Paediatric ATM is an immune-mediated CNS disorder and contributes to 20% of first-acquired autoimmune demyelinating syndromes experienced by children.[24] It is categorised as a subgroup of non-compressive transverse myelopathies.[24] In children, ATM exhibits a bimodal distribution, affecting very young children (under 5 years) and prepubertal children (over 10-12 years of age). ATM is more common in adults, but children account for 20% of cases.[25]

ATM can present with back pain as the first symptom followed by motor and sensory deficits. Sensory symptoms can be either positive with burning paraesthesia, hyperaesthesia, and allodynia or negative like numbness. A clear sensory level may not be evident. A complete ATM describes bilateral motor and sensory deficits with bladder dysfunction, whereas, in partial cord syndromes, there are patchy motor or dissociated sensory deficits of at least one spinal segment with occasional bladder involvement.[26-28] The spinal cord involvement usually evolves over 2-4 days and peaks at 5-6 days. ATM patients can develop flaccid paralysis during the early stage of the illness. There are case series describing the acute TM variant termed acute flaccid myelitis (AFM) which has significant involvement within the spinal cord grey matter resulting in flaccid polio-like patterns of weakness.

ATM may occur with ADEM or represent an initial attack of a relapsing demyelinating syndrome, such as MS, NMO, or an autoimmune rheumatologic disorder (e.g., systemic lupus erythematosus [SLE], Sjögren syndrome, and sarcoidosis).

The differential diagnosis list for the acute presentation of transverse myelitis (Table 2) is wide. It should be differentiated from other forms of myelopathy and it can be the sentinel attack of relapsing demyelinating diseases such as NMOSD and MS. The list of investigations is extensive when aiming to detect definitive aetiology and exclude differential diagnosis. The transverse myelitis consortium working group (TMCWG) has formulated the diagnostic criteria for ATM which can be applied to children with appropriate modifications to account for the difficulty in defining a clear sensory level in the younger child (usually under 5 years old).

The proposed diagnostic criteria for ATM by the TMCWG is for idiopathic ATM. A diagnosis of idiopathic ATM should require that all the inclusion criteria and none of the exclusion criteria are fulfilled. A diagnosis of disease-associated ATM should require that all the inclusion criteria be met and that the patient is identified as having an underlying condition listed in the disease-specific exclusions.[29]

When a child presents with myelopathic symptoms it is a neurological emergency because prompt diagnosis and intervention will help to lessen neurological disability. The contrast-enhanced spinal MRI is the investigation of choice, as it aids in excluding differentials that require immediate surgical intervention while providing a detailed assessment of non-compressive myelopathic distribution.

MRI is helpful for the diagnosis and assessment of the prognosis in children. MRI lesions are often centrally located with high T2 signal intensity involving grey and neighbouring white matter. Longitudinally extensive ATM occurs in the majority.[30] The lesions can be contiguous or patchy. Longitudinally extensive transverse myelitis (LETM) defined as >3 vertebral segments, occurs in most children. In ATM gadolinium enhancement is seen frequently but its absence does not rule out ATM. Asymptomatic lesions on brain MRI are seen in more than one-third and predict MS or NMO[24] and isolated LETM is not unique to ATM and can be seen as the first episode of NMO and rarely, of MS. Cervical and cervicothoracic lesions represent most lesions. Spinal nerve root or cauda equina enhancement may be delineated on MRI, suggesting a simultaneous CNS and peripheral nerve inflammatory disorder (i.e., an "ATM-plus syndrome") or a secondary event from cellular damage to the anterior and ventral horn.[24] A patchy axonal motor and sensory polyneuropathy is seen on EMG in ATM-plus syndromes.[31]

CSF analysis and serum investigations are instrumental in delineating specific aetiologies and ruling out alternative (e.g., infectious or neoplastic) aetiologies. CSF protein and white blood cell counts may be normal in 20-50% of children with definite ATM.[25,30,32,33] Qualitative tests for intrathecal oligoclonal bands are positive in up to one-third of children, many of whom will eventually have MS.[25,30,34] It is important to test for MOG and AQP4 antibodies as isolated ATM

(particularly if longitudinally extensive) may be the initial manifestation of either entity.[2] Compared to adult cohorts, the presence of MOG or AQP4 antibodies is less common in paediatric ATM. MOG antibodies are detected in 14% (with a small minority exhibiting relapsing disease),[34] and AQP4 antibodies are found in 3% (with the majority exhibiting relapsing disease) of paediatric ATM cohorts.[35]

Because of the lack of controlled clinical trials, there are no US Food and Drug Administration-approved therapies for ATM. Medications are used based on experience and data from open-label studies and retrospective analyses, primarily from studies involving adults.[24] IV methylprednisolone is the first-line treatment for ATM and likely improves the chances of walking independently in addition to the chances of a full neurologic recovery.[36] For ATM in children that proves refractory to corticosteroids, plasma exchange may lead to additional functional improvement.[37] Data suggest that certain conditions respond preferentially to specific therapeutic interventions. For example, SLE patients with ATM may respond well to cyclophosphamide, whereas patients with NMOSD benefit from plasmapheresis. In patients without a prior history indicative of a systemic condition, the treatment of ATM must be approached empirically. Typically, pain is the first symptom to improve following the initiation of immunotherapy, followed by motor deficits and bladder dysfunction, while sensory deficits may take longer to show improvement.

Most paediatric patients will recover well from TM. However, a minority may experience poor outcomes. Usually, one-half of the patients will fully recover within two years. Potential factors (at onset) that denote a higher risk of poor outcome include female sex, American Spinal Injury Association (ASIA) scale A to C at presentation, gadolinium enhancement of lesions on MRI, absence of CSF pleocytosis, and lack of cervical inflammatory lesions.[34] Approximately 17% to 29% of patients with ATM will relapse in the long term.

The risk for a future diagnosis of MS following ATM is approximately 14% to 22% and is highest in those of female sex with concurrent demyelinating lesions in the brain and the presence of CSF oligoclonal bands.[38] ATM may have a relapsing course, which could be categorized as relapsing ATM, a presentation of MS, part of a systemic autoimmune disease, or NMOSD in the setting of identified antibodies.[39,40]

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD)

MOG is expressed on the surface of the myelin in central and peripheral nerves. Anti-MOG antibodies have been identified in paediatric patients with increased heterogeneity and are detected in one-third of all children at the initial onset of the acquired demyelinating syndrome.[2] The incidence of MOG-associated demyelination is higher in children (0.31 per 100,000) than in adults (0.13 per 100,000). It occurs with a relatively equal sex ratio, particularly in younger children.[12]

The clinical phenotypes associated with MOG antibodies are diverse. The paediatric MOGAD is clinically classified into various subtypes (Table 3). Typical phenotypes of MOGAD are ADEM, ON, LETM, and NMOSD-like phenotypes. ADEM is the most common initial presentation in children. Relapsing phenotypes are multiphasic disseminated encephalomyelitis (MDEM), ADEM-ON, relapsing ON, and relapsing NMOSD-like phenotype. The emerging and atypical clinical phenotypes are encephalitis, overlapping syndromes, seizures, leukodystrophy-like phenotype, combined central and peripheral demyelination in MOGAD, and non-classifiable clinical phenotypes.[12]

The diagnostic criteria for MOGAD were updated in 2023 and the presence of MOG antibody is a core criterion. Cell-based assays are important for the diagnostic accuracy of detecting MOG-IgG (Table 4). The risk of relapse can be estimated with serial testing for MOG antibodies.[41] The studies from animal models suggested that MOG antibodies are pathogenic. In MOGAD particularly in children, detection of oligoclonal bands is rare (7-11%) while it is increased in paediatric MS (40%-88%).[42] Future research is required to find new biomarkers that predict the prognosis.[42]

Imaging of the entire neuroaxis is recommended at the first presentation itself for acute demyelinating syndromes in the paediatric age group. Imaging plays a crucial role in differentiating paediatric MS, and less defined subgroups of NMOSD as well as for excluding disease mimics like infections, vasculitis, malignancies, and mitochondrial diseases. Compared to the imaging characteristics of children with MS, children with MOGAD present with various imaging patterns that correspond often with the respective subtype as well as the age at presentation.[43] Several MRI characteristics in brain, spine, and optic nerve imaging help differentiate MOGAD from paediatric MS and NMOSD . In MOGAD the involvement of grey matter in spinal cord forms the H sign on axial view and thin linear T2 hyperintense signals on sagittal view. The lower cord is often preferentially affected, with the conus medullaris being classically affected.

Brain MRI should be performed using a magnetic field strength of at least 1.5 T, preferably 3.0 T, with a slice thickness of at least 3 mm for 2D sequences. The minimum requirements for clinical routine brain MRI sequences should include (i) T2-weighted spin-echo (SE) sequences in the axial plane, (ii) T2 fluid-attenuated inversion recovery (FLAIR) sequences in another plane than T2-SE or (even better) in three-dimensional (3D) acquisition, (iii) T1-weighted SE sequences in at least axial plane or ideally 3D magnetization prepared rapid acquisition gradient echo before, and (iv) after contrast agent administration, and (v) axial diffusion-weighted imaging.

TABLE 3 Clinical classification of paediatric MOGAD with corresponding key features[12]

Disease course	Classification	Key features
Monophasic MOGAD with:	ADEM phenotype	• Younger patients • Characterized by encephalopathy • Often longitudinal spinal cord involvement, which can be asymptomatic
	ON phenotype	• Adolescents • Severe vision loss at onset, anterior and bilateral optic nerve involvement, with disc oedema • Overall good and often rapid functional recovery, but indication of permanent axonal damage (OCT)
	ON plus phenotype	• ON and optic perineuritis (perineural enhancement and inflammation of orbital tissues)
	TM phenotype	• Adolescents • Severe motor and sensory deficits at onset; subset with conus involvement and following bladder problems • Overall good and often rapid motor recovery, but bowel/bladder residual symptoms are common
	NMOSD-like phenotype	• Adolescents • Simultaneous ON and TM
	Encephalitis-like phenotype	• Seizures and cortical lesions, with adjacent subcortical involvement in a subset of patients
Relapsing* MOGAD with:	ADEM-ON phenotype	• Younger patients • Recurrent episode(s) of ON more than 3 months after start of previous ADEM episode
	MDEM phenotype	• Younger patients • Characterized by encephalopathy • Recurrent episode(s) of ADEM more than 3 months after start of previous ADEM episode
	RON phenotype	• Adolescents • Relapsing ON episodes, often steroid responsive, sometimes steroid-dependent
	NMOSD-like phenotype	• Adolescents • ON followed by subsequent TM or reversed; or simultaneous ON and TM followed by new ON and/or TM episode(s)
	Encephalitis-like phenotype	• Seizures and cortical lesions, with adjacent subcortical involvement in a subset of patients • Subsequently with demyelinating event(s)/lesion(s)
	Leukodystrophy-like phenotype	• Youngest patients • Encephalopathy, ataxia, ON and/or seizures • Extensive brain involvement

*A relapse is defined by the consensus group as a new clinical episode accompanied by radiological evidence depending on the subtype of MOGAD, appearing at least one month subsequently to the last acute attack, while a 'flare-up' is defined as a re-occurrence of symptoms within one month (and up to three months in ADEM patients) after the start of acute treatment and not meeting the definition of a relapse.

MOGAD – myelin oligodendrocyte glycoprotein antibody associated disease; ADEM – acute disseminated encephalomyelitis; MDEM – multiphasic disseminated encephalomyelitis; ON – optic neuritis; OCT – optical coherence tomography; RON – recurrent optic neuritis; TM – transverse myelitis; NMOSD – neuromyelitis optica spectrum disorder.

TABLE 4 Proposed diagnostic criteria for MOGAD[41]

<table>
<tr><th colspan="4">Diagnosis of MOGAD (requires fulfillment of A, B, and C)</th></tr>
<tr><td>A) Core clinical demyelinating event</td><td colspan="3">Optic neuritis
Myelitis
ADEM
Cerebral mono-focal or polyfocal deficits
Brainstem or cerebellar deficits
Cerebral cortical encephalitis often with seizures</td></tr>
<tr><td rowspan="4">(B) Positive MOG-IgG test</td><td rowspan="4">Cell-based assay: serum</td><td>Clear positive</td><td rowspan="4">No additional supporting features required
• AQP4-IgG seronegative AND
• ≥ 1 supporting clinical or MRI feature</td></tr>
<tr><td>Low positive</td></tr>
<tr><td>Positive without a reported titre</td></tr>
<tr><td>Negative but CSF positive</td></tr>
<tr><td rowspan="3">Supporting clinical or MRI features</td><td>Optic neuritis</td><td colspan="2">• Bilateral simultaneous clinical involvement
• Longitudinal optic nerve involvement (> 50% length of the optic nerve)
• Perineural optic sheath enhancement
• Optic disc oedema</td></tr>
<tr><td>Myelitis</td><td colspan="2">• Longitudinally extensive myelitis
• Central cord lesion or H-sign
• Conus lesion</td></tr>
<tr><td>Brain, brainstem, or cerebral syndrome</td><td colspan="2">• Multiple ill-defined T2 hyperintense lesions in supratentorial and often infratentorial white matter
• Deep grey matter involvement
• Ill-defined T2-hyperintensity involving pons, middle cerebellar peduncle, or medulla
• Cortical lesion with or without lesional and overlying meningeal enhancement</td></tr>
<tr><td colspan="4">(C) Exclusion of better diagnoses including multiple sclerosis</td></tr>
</table>

Sequences dedicated to the optic nerves, including sequences with fat saturation in the frontal plane, are important in the event of a clinical picture of ON. Spinal imaging should include sagittal and axial T2-weighted sequences, and sagittal and axial T1-weighted sequences, only after gadolinium administration if combined with brain MRI. The entire spinal cord should be studied. Additional axial images of the spinal cord should be performed in areas affected by lesions.[43]

Acute treatment appears to not affect the disease course in MOGAD, but efficient treatment is mandatory in the acute phase to prevent residual symptoms in the long term. The acute treatment protocols include IV methylprednisolone with or without oral prednisone taper, IVIg, and PLEX. The vast majority of paediatric MOGAD patients were treated with IV methylprednisolone at acute presentation (first episode or relapse), with dosages between 20 and 30 mg/kg/day over 3-5 days. IVIg is usually administered over 1-5 days with a total dosage of 1-2 g/kg (not exceeding 1 g/kg/day). PLEX constitutes an established treatment escalation in adults and paediatric MOGAD patients during the acute phase. Most often, PLEX is administered subsequently or in addition to IV methylprednisolone.[44]

A large mixed adult and paediatric cohort with 252 MOG-positive patients showed that 78% of these patients had a

good (not further specified) or full recovery from the initial attack, with more often a full recovery in paediatric patients and patients presenting with ON and ADEM/ADEM-like phenotypes.[42] In conclusion, children with MOGAD have good outcomes with overall 68-96% making full recovery. However, this depends on the initial clinical phenotype and the number and types of clinical attacks during follow-up.[45]

CONCLUSION

The acquired inflammatory demyelinating diseases with monophasic courses are not uncommon in children. It is important to distinguish monophasic disease from relapsing disease. Longitudinal follow-up of these patients clinically and radiologically with antibody testing helps to define the specific subtypes. A definitive diagnosis necessitates a thorough knowledge of the latest radiological and biochemical diagnostic tools and techniques, coupled with the ability to apply them judiciously in a resource limited setting.

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