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PEDIATRIC OPTIC NEURITIS

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Pediatric Optic Neuritis

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ABBREVIATION LIST

ADEM – acute disseminated encephalomyelitis

AQP4 – aquaporin-4

AQP4-IgG – antibodies against aquaporin-4

AQP4-NMOSD – neuromyelitis optica spectrum disorder with antibodies against aquaporin-4

BCG – bacillus Calmette-Guérin

CBC – complete blood cell count

CNS – central nervous system

CSF – cerebrospinal fluid

DMD – disease-modifying drug

EBV – Epstein-Barr virus

ECG – electrocardiogram

EDSS – Expanded Disability Status Scale

GCIP – ganglion cell and inner plexiform layer

GCL – ganglion cell layer

GFAP – glial fibrillary acidic protein

GI – gastrointestinal

IM – intramuscular administration

IPMSSG – International Pediatric Multiple Sclerosis Study Group

IV – intravenous administration

IVIG – intravenous immunoglobulin

IVMP – intravenous methylprednisolone

JCV – John Cunningham virus

LETM – longitudinally extensive transverse myelitis

LFT – liver function tests

MHC – major histocompatibility complex

MOG – myelin oligodendrocyte glycoprotein

MOG-Ab – antibodies against myelin oligodendrocyte glycoprotein

MOG-AD – myelin oligodendrocyte glycoprotein antibody disease

MRI – magnetic resonance imaging

MS – multiple sclerosis

NMO – neuromyelitis optica

NMOSD – neuromyelitis optica spectrum disorder

NORDIC – Neuro-Ophthalmology Research Disease Investigator Consortium

OCB – oligoclonal band

OCT – ocular coherence tomography

ON – optic neuritis

ONTT – Optic Neuritis Treatment Trial

PCR – polymerase chain reaction

PEDIG – Pediatric Eye Disease Investigator Group

PLEX – plasma exchange

PML – progressive multifocal leukoencephalopathy

PO – per os

PON – pediatric optic neuritis

PON1 – Pediatric Optic Neuritis Prospective Data Collection Study

RNFL – retinal nerve fiber layer

SC – subcutaneous administration

SD-OCT – spectral domain ocular coherence tomography

SLE – systemic lupus erythematosus

VA – visual acuity

VEP – visual evoked potentials

VZV – varicella-zoster virus

ABSTRACT

Optic neuritis is defined as an inflammation of the optic nerve, presenting with visual acuity loss, visual field defects, color vision impairment and relative afferent pupillary defect, if unilateral.

It is a rare entity in children in comparison with adults, but occurs in approximately 25% of demyelinating acute syndromes at pediatric age. Pediatric optic neuritis may occur as an idiopathic isolated event, following a viral infection or vaccination or in association with a central nervous system demyelinating disease, such as multiple sclerosis, neuromyelitis optica spectrum disorder or myelin oligodendrocyte glycoprotein antibody disease.

Current clinical practice is guided by clinical investigation of optic neuritis occurring in adults; however, significant differences in presentation and evolution exist between both age groups, making optic neuritis challenging to diagnose and treat in pediatric age. Compared to adults, children present higher rate of bilateral involvement, of papillitis and more severe loss of visual acuity at presentation.

Diagnostic work-up includes brain magnetic resonance imaging, lumbar puncture and blood tests; testing modalities such as ocular coherence tomography, visual evoked potentials and serologic testing of antibodies against aquaporin-4 and myelin oligodendrocyte glycoprotein can provide key information for the understanding of specific disease mechanisms and directed treatment.

Standard of care suggests the use of intravenous steroid therapy during the acute episode, eventually followed by oral steroid treatment; immunosuppressive drugs are reserved for cases of treatment failure.

Regarding prognosis, most children experience significant recovery; however, the risk of developing a neuroinflammatory or demyelinating disease varies among studies.

In the past decade, there was an exponential growth of knowledge regarding this entity, mostly due to the identification of said autoimmunity serologic markers. Hence, with this review article the authors intend to expose the current state of knowledge regarding pediatric optic neuritis, establishing bridges with the various neuroinflammatory and demyelinating diseases that present with this condition, as well as summarize the most recent advances concerning diagnosis, treatment and prognosis, pointing future directions for research on this entity.

Keywords: optic neuritis, pediatrics, infant, child, adolescent

RESUMO

A nevrite óptica é definida como uma inflamação do nervo óptico, manifestando-se por diminuição da acuidade visual, defeitos do campo visual, discromatópsia e defeito pupilar aferente relativo, se unilateral.

Trata-se de uma entidade rara na criança comparativamente ao adulto, no entanto corresponde a aproximadamente 25% das síndromes desmielinizantes agudas nesta faixa etária. Pode ocorrer como um evento isolado idiopático, após uma infeção viral ou vacinação ou associado a uma doença desmielinizante do sistema nervoso central, como a esclerose múltipla, a neuromielite óptica e a doença associada ao anticorpo anti-glicoproteína oligodendrocítica da mielina.

A prática clínica corrente tem por base orientadora a investigação realizada em adultos; contudo, existem diferenças significativas no que toca à apresentação clínica e evolução da doença nos dois grupos etários, podendo tornar desafiante o seu diagnóstico e tratamento em idade pediátrica. Comparativamente ao adulto, constata-se uma maior prevalência de envolvimento bilateral, papilite e diminuição da acuidade visual mais grave à apresentação.

A avaliação diagnóstica inclui a realização de ressonância magnética crânio-encefálica, punção lombar e análises sanguíneas; testes como a tomografia de coerência óptica, potenciais evocados visuais e marcadores serológicos (anticorpos anti-aquaporina-4 e anti-glicoproteína oligodendrocítica da mielina) podem fornecer informação preponderante para a compreensão do mecanismo específico da doença e orientação do tratamento.

O tratamento baseia-se fundamentalmente na administração de corticoterapia endovenosa durante os surtos, associando eventualmente corticoterapia oral; a terapêutica imunossupressora é reservada para os casos de falência terapêutica prévia.

No que toca ao prognóstico, a maioria das crianças experiencia recuperação significativa, mas o risco de desenvolver uma doença neuroinflamatória ou desmielinizante varia entre estudos.

Ao longo da última década, assistimos a um crescimento exponencial do conhecimento acerca desta entidade, muito à custa da identificação dos referidos marcadores serológicos de autoimunidade. Assim, com este artigo de revisão, os autores pretendem expor o estado de conhecimento atual relativamente à nevrite óptica em idade pediátrica, estabelecendo as pontes necessárias com várias doenças neuroinflamatórias e desmielinizantes que têm na nevrite óptica uma das suas manifestações clínicas, bem como sistematizar os mais recentes avanços no que toca ao diagnóstico, tratamento e prognóstico, apontando futuras direções para a investigação acerca desta entidade.

Palavras-chave: nevrite óptica, pediatria, criança, adolescente

1. INTRODUCTION

Pediatric optic neuritis (PON) is an inflammatory disorder of the optic nerve in children,[1–5] firstly described by Hierons and Lyle, in 1959.[6]

It is an important cause of dramatic unilateral or bilateral visual loss of acute onset, in pediatric age.[2,4,5] It is a common presenting symptom in pediatric central nervous system (CNS) demyelinating disorders,[1–5,7] although rare in comparison to adults.[5,8] Despite similarities between childhood and adult-onset varieties, PON and adult optic neuritis (ON) are considered different clinical entities.[2,6]

The pathophysiology of this disorder is thought to be based on peripheral activation of T-cells that may cross the blood brain barrier causing a delayed type IV hypersensitivity reaction; this causes destruction of myelin, also involving the axon. This process leads to visual dysfunction, with loss of visual acuity (VA) and pain. These symptoms are limited to the acute PON episode; soon after, it begins the process of remyelination and proliferation of sodium channels in the neuronal segments and the reorganization of the cortical activation, often lasting for more than two years.[2–4] However, in general, PON entails good visual prognosis.[5]

Although knowledge regarding clinical features, associated diseases, treatment and outcomes of PON has increased over the past years, limited case series and retrospective reviews constitute most of the information available due to the rarity of this condition.[1,4,5] Hence, further well-designed prospective research on diagnosis and prognosis is needed, especially in order to keep up with recent advances on disease-specific treatments.[1,5,6]

This review aims to provide an update on current knowledge about PON, with close attention to its relationship with neuroinflammatory diseases. Clinical presentation, approach to the evaluation of children with suspected PON, treatment and outcomes will be discussed, pointing future directions for research.

2. METHODS

A literature search of PubMed database was conducted using the following search terms: (pediatrics OR child OR adolescent OR infant) AND (optic neuritis). Review articles published between January 2014 and December 2019 were considered. Only studies written in English and for which the full text was available were included. Articles unrelated to pediatric age (between 0 and 17 years and 364 days) were excluded.

The original search identified 40 studies, of which 30 fulfilled the eligibility criteria. The reference lists of these papers were also screened, and 19 additional articles were included in the review (Fig.1).

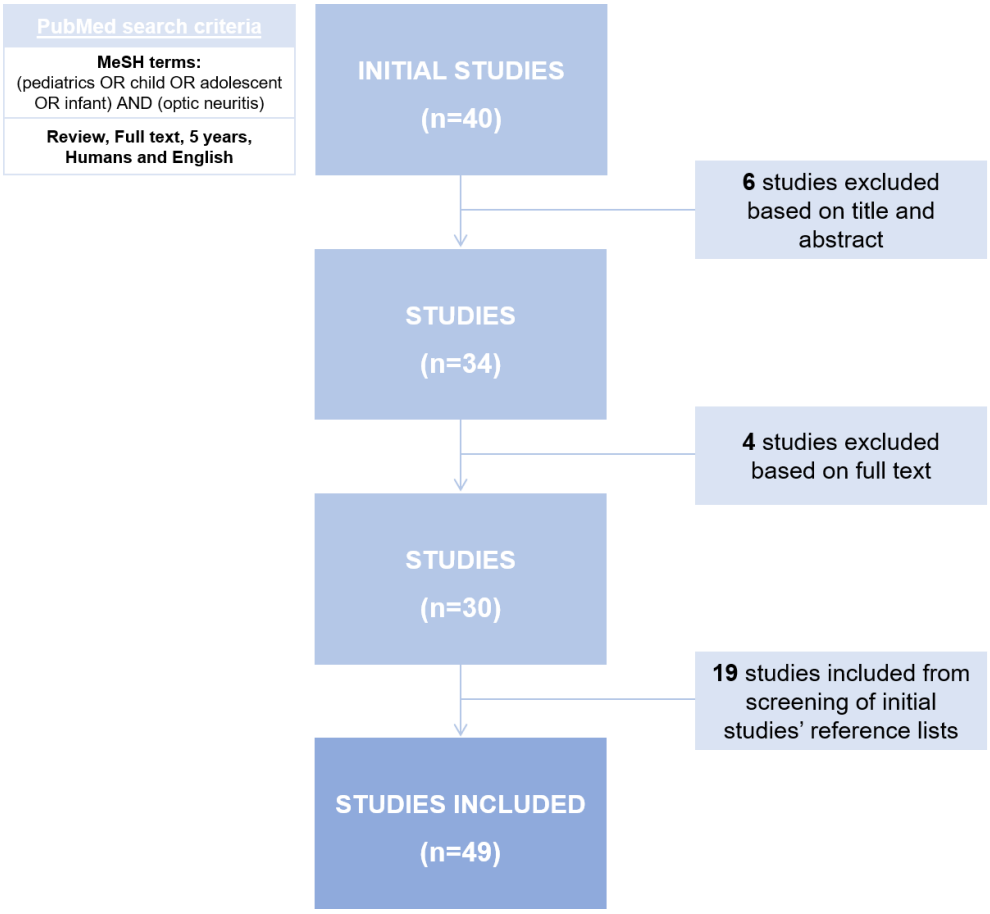

Figure 1. Flowchart showing the selection of published studies.

3. RESULTS

3.1. EPIDEMIOLOGY

ON is much less common in children than in adults, with an annual incidence rate of 0.15–0.57 per 100.000 person-years compared with 5.1 per 100.000 person-years in adults;[2,4,5,8] nevertheless, it accounts for approximately 25% of pediatric acute demyelinating syndromes.[8]

The average age at presentation ranges from 8.6 to 11.8 years.[2,8] Studies have also shown that younger children (<10 years of age) are more likely to present with bilateral PON.[2,4]

Regarding the gender prevalence, PON affects prepubertal girls and boys equally;[8] however, in postpubertal children, it is more common in females (female:male ratio ranging from 1.42:1 to 2.7:1), similarly to adults.[5,8]

When it comes to race, its influence on the development of ON in children is not well understood.[8] Some studies report a racial disparity, with higher incidence of ON in non-white children than non-white adults,[5] and others suggest ethnicity may influence the risk of developing a systemic demyelinating disorder after an episode of acute PON.[8]

3.2. CLINICAL PRESENTATION

The common clinical presentation of ON includes acute or subacute loss of VA associated with visual field deficits, impaired color vision, decreased contrast sensitivity, photopsia, relative afferent pupillary defect if unilateral, pain with eye movement and optic disk swelling.[1–4,8–10] Uhthoff's phenomenon (decreased VA in presence of a high body temperature or during physical exercise), a mild to moderate Tyndall effect in the anterior chamber or in the vitreous and a peripheral retinal periphlebitis may be also seen in some patients.[3]

However, there are significant differences in the presentation and course of the disease in children, in comparison to adults. In fact, most common signs and symptoms of PON are an atypical presentation in adults with ON, in whom it justifies a thorough investigation.[5]

Children are more likely to present a more severe visual impairment, with most studies reporting a VA at presentation of 20/200 or worse in more than half of pediatric patients.[1,2,4–6,8] The evolution of visual loss usually ranges from hours to days, reaching its lowest point within several days of onset.[4]

Furthermore, children present a higher rate of bilateral involvement, which may occur simultaneously or sequentially.[1–6,8,10,11] Younger children are more likely to have bilateral ON; approximately two thirds of children less than 10 years of age present with bilateral visual loss, whereas the majority of cases were unilateral in children older than 10 years of age.[4,10] A relative afferent pupillary defect may be present in unilateral cases.[8]

Additionally, unlike adult cases which are mostly retrobulbar, children are more likely to present with optic nerve swelling.[1–5,8] Papillitis may be seen in up to 74% of children with optic neuritis.[5,8]

Moreover, pain with eye movement is less reported by children in contrast to adults with ON, in whom it is almost universal; it occurs in only approximately half of pediatric cases.[5,8,10] It is important to notice, however, that it may be difficult for children to distinguish pain behind the eyes from headache.[4]

Children are also more likely to report a prodromal viral illness, such as measles, mumps, chicken pox and infectious mononucleosis, or immunizations.[1,3,6] A history of preceding upper respiratory tract infection has been referred in 30-70% of pediatric cases.[2]

Other clinical features in PON include visual field defects, of which a central or cecocentral scotoma is the most common;[1–4,8] dyschromatopsia (color perception deficits, namely red color desaturation);[1–4,8] low-contrast vision deficits (however central high-contrast VA may remain relatively preserved in some children);[1–4,8] and photopsia.[2,3]

3.3. DIAGNOSTIC WORK-UP

The diagnosis of PON should be based, in the first instance, on detailed clinical history and physical examination.[1,6] In some children, the difficulty in providing accurate information and the tendency to simulate vision loss (in order to obtain glasses, as an example) make diagnosis challenging.[1] In spite of that, a thorough review of systems and neurologic examination searching for signs of polyfocal or systemic disease (involvement of other areas of the CNS or including ocular, dermatologic, joint, renal and hepatic involvement) should be performed in all children with suspected PON.[4,6]

Once the diagnosis is supposed, the diagnostic work-up should be directed toward ruling out other causes of optic disc edema in children, namely underlying infectious, neoplastic, metabolic and autoimmune diseases for which delay in treatment can result in permanent vision loss or other neurologic impairment.[1,6,8]

A full work-up including magnetic resonance imaging (MRI) of the brain and orbits and lumbar puncture is recommended in all cases.[2,3,5,6,8] Further imaging and laboratory tests for infectious and inflammatory disorders must be performed according to the child's clinical context: complete blood count (CBC), tests for sarcoidosis (angiotensin converting enzyme, chest X-ray), tuberculosis (interferon-gamma release assay, purified protein derivative skin test), syphilis (fluorescent treponemal antibody absorption test, rapid plasma regain test), Lyme disease (*Borrelia burgdorferi* serology), cat scratch disease (*Bartonella henselae* serology), vasculitis and systemic lupus erythematosus (SLE).[2,3,6,8] Serologic testing, namely identifying antibodies against aquaporin-4 (AQP4-IgG) and myelin oligodendrocyte glycoprotein (MOG-Ab), ocular coherence tomography (OCT) and visual evoked potentials (VEP) may also be helpful in clarifying specific disease processes, allowing timely directed treatment.[1–3,5]

3.3.1. MAGNETIC RESONANCE IMAGING

Although not required to diagnose ON in children (once it is considered a clinical diagnosis), brain and orbits MRI is the imaging test of choice in the approach of these children; it should be performed during the following two weeks after the initial symptoms,[3,4] not only to confirm optic nerve enhancement but also to assess for other intracranial pathology: sphenoid sinusitis, compressive lesions, meningeal enhancement and inflammatory or demyelinating lesions elsewhere in the brain.[2,6] Spinal cord MRI may also be useful for the differential diagnosis.

Typical orbits MRI findings include thickening of the optic nerves on T1-weighted imaging, bright T2 signal along the optic nerve or chiasm and post-gadolinium enhancement.[4]

3.3.2. LUMBAR PUNCTURE

A lumbar puncture should be included in the diagnostic work-up of PON, since children are more likely to present a secondary cause of optic disc edema, particularly in bilateral cases.[8]

Cerebrospinal fluid (CSF) should be analyzed for protein, glucose and cell count, as well as oligoclonal bands (OCBs) and IgG index, particularly in cases of polyfocal white matter disease in anticipation of multiple sclerosis (MS). If an infectious disease is suspected, viral polymerase chain reaction (PCR) and cultures for bacteria and fungi should also be performed.[2,8]

Routine measurements also include an evaluation of CSF opening pressure, which is elevated in nearly one third of children with acute disseminated encephalomyelitis (ADEM), MS or isolated ON.[6] However, this parameter has limitations; for instance, it cannot be used to differentiate bilateral disc edema due to pseudotumor cerebri syndrome from that due to bilateral ON.[6]

3.3.3. SEROLOGIC MARKERS

Serologic testing identifying AQP4-IgG and MOG-Ab may be helpful in diagnosing and treating the disease in a timely and disease-specific method.[1,12]

AQP4-IgG is an antibody to the astrocytic water channel aquaporin-4 (AQP4), considered to be a specific serologic marker for neuromyelitis optica spectrum disorder (NMOSD).[5,12–23] It is thought to cause direct astrocytopathy and neuronal necrosis with secondary oligodendrocyte loss and demyelination.[5,10,24,25] AQP4-IgG can be present in both serum and CSF; however, serum testing is more sensitive than if it is done in the CSF.[16,26] The more recent tests, cell-based assays for AQP4-IgG, present specificities of nearly 100% and sensitivities ranging from 70-100%;[5,12,16,18,19,21,23,24,27,28] however, studies revealed that AQP4-IgG testing could remain negative up to four years after disease onset, therefore it should be repeated in patients with high suspicion even if the test is initially negative.[10,16,27] Seropositivity for these antibodies suggests a non-MS clinical course, predicting a poorer prognosis and a probable relapsing course.[1,5,12,16,19,20,23,26]

In its turn, MOG-Ab is an antibody primarily of the IgG1 subtype[24] directed against a glycoprotein of the myelin sheath outer layer, involved in myelin adhesion, regulating oligodendrocyte microtubule stability and mediating the complement cascade.[1,2,5,12,15,24,26,29,30] This antibody is thought to cause inflammation and myelin destruction without direct astrocyte damage.[5,16,24] There has been an increasing interest in this biomarker, and recent studies provided significant advances in the assessment and categorization of PON, with myelin

oligodendrocyte glycoprotein antibody disease (MOG-AD) being recognized as a specific nosological entity.[5,10,26] MOG-Abs are much more common in the pediatric population, being present in at least one third of children with an acute demyelinating syndrome,[5,10,24,31] with the highest seropositivity rates found in very young children;[9,28] international 2018 guidelines for MOG-Ab serology in children should be strictly followed, in order to avoid false positives and overdiagnosis of MOG-AD.[5] The most recommended MOG-Ab testing relies upon cell-based assays, using full length human myelin oligodendrocyte glycoprotein (MOG) as the target antigen.[5,10,12,24,26,28,31,32] In these assays, it is rare to present simultaneously MOG-Ab and AQP4-IgG seropositivity;[5,10,19,26] therefore, it is preferable to test the most probable autoantibody with reflex testing to the other than to test for both at the same time.[5]

Initially, MOG-Ab was thought to be most commonly associated with ADEM in young children;[5,24,28] however, it was recently demonstrated that ON is the most common presenting phenotype.[5] MOG-Ab seropositivity predicts a non-MS disease course,[1,9,10,15,21,24,28,29,31,33] and has been identified in many patients with NMOSD who are AQP4-IgG negative;[5,6,24,31] however, a patient may also be seronegative for both.[1]

3.3.4. VISUAL EVOKED POTENTIALS

VEP are electrophysiologic tests that provide information on the integrity of axons and their surrounding myelin; they may be particularly useful in nonverbal patients.[8] VEP testing abnormalities in patients with PON include prolonged P100 latency and/or reduced amplitudes in the acute phase. However, it is still uncertain whether children with ON are more likely than adults to show normalized VEP waveforms in long-term follow-up.[1,4]

3.3.5. OCULAR COHERENCE TOMOGRAPHY

OCT is a noninvasive, inexpensive and reproducible imaging exam used to assess the severity of optic nerve disease qualitatively and quantitatively, as it provides characterization of the optic nerve head, peripapillary retinal nerve fiber layer (RNFL) and cellular layers of the macula with high, near-histological resolution.[11,34] This is particularly useful since unmyelinated tissue layers offer a window into global CNS inflammation and neurodegeneration.[35]

This technology creates optical cross-sections that may be reconstructed into three-dimensional maps, allowing to outline and measure the thickness of the different tissue layers;[1,11,14,34,35] of importance, quantitative analysis of RNFL thickness is a useful way of assessing optic neuropathies over time.[11] Furthermore, OCT evaluates microscopic ocular pathology that may not be apparent on clinical examination.[11]

OCT can have an important role in the evaluation of ON in younger pediatric patients unable to reliably perform VA, visual field or color vision testing, also allowing to assess the progression of the disease without the need for a sedated MRI scan of the brain and its associated risks.[1,5,11] Nevertheless, OCT use is still sparse in most pediatric ophthalmology practices, since it requires appropriate positioning and cooperation that may be difficult to obtain from young children; however, newer developed technologies such as spectral domain OCT (SD-OCT)[11,14,34] and handheld OCT unit have made it possible to obtain high-quality images in pediatric patients.[11,34]

OCT findings in ON and other demyelinating diseases in adults and children include thickening of RNFL in the acute phase[11] followed by thinning of RNFL,[1,4,11,14,34] which is a manifestation of optic atrophy that develops 4-6 weeks later and correlates to the final visual outcome.[11] Reduced macular volumes and microcystic macular edema are also commonly found.[1,4,11,14,34]

More recent methods of OCT can assess with more accuracy the ganglion cell and inner plexiform layers, which is technically challenging in traditional OCT – ganglion cell layer thickness is estimated as a combination of ganglion cell layer and inner plexiform layer (GCIP). The thickness of the latter is proven to be associated with MRI changes, low contrast visual acuity and disability outcome in MS.[1,11]

3.4. DIFFERENTIAL DIAGNOSIS

PON may occur in a wide spectrum of conditions: as an idiopathic, monophasic illness; as an autoimmune response to viral infection or immunization; as recurrent isolated episodes or as a sentinel attack or relapse of a primary demyelinating disorder such as MS, NMOSD or MOG-AD.[2–6,8,11] Of notice, 25% of children with an initial demyelinating event present with ON.[4] Table I summarizes the common presentations and diagnostic considerations of primary demyelinating disorders with PON as a clinical feature.

Significant alternative diagnoses include sarcoidosis,[36] SLE,[37] small vessel CNS vasculitis, idiopathic granulomatous optic neuropathy, infectious neuroretinitis, papilledema and leukemia.[4,5]

3.4.1. POST-INFECTIOUS / POST-VACCINATION

Up to two thirds of younger children with ON report a preceding viral infection, namely adenovirus, measles, mumps, chickenpox, rubella and infectious mononucleosis.[8] A systemic demyelinating process stimulated by the virus is believed to be involved.[8] Non-viral infections may also be implicated, including Lyme disease,[8] brucellosis[8] and pneumonia secondary to *Mycoplasma pneumoniae.*[8,38,39]

Vaccination against hepatitis B, diphtheria, tetanus, pertussis, measles, mumps, rubella, influenza, rabies, smallpox and bacillus Calmette-Guérin (BCG) have also been reported in association with PON.[8]

3.4.2. MULTIPLE SCLEROSIS

MS is a primary inflammatory demyelinating disorder of the CNS, characterized by both sensory and motor symptoms at onset and predominantly monosymptomatic presentation with a relapsing-remitting pattern.[3,5,8,12,21,24,29,35,40]

The immune-mediated pathophysiology is still unclear,[5,20,29] but it is known that neuro-axonal degeneration, as a consequence of inflammation and demyelination, represents the principal substrate of disability.[35]

3.4.2.1. Epidemiology

About 2–10% of all patients with MS present clinical onset before the age of 18 years,[7,10,17,21,30,32,35,40–43] with a mean age at onset between 12 and 16 years.[10,30,44] The reported ratio of girls to boys increases with age, being nearly equal in children younger than 6 years old and 3:1 in adolescents, similarly to adults.[17,21,43,44]

Table I. Common presentations and diagnostic considerations of primary demyelinating disorders with pediatric optic neuritis as a clinical presentation

		MS	NMOSD	MOG-AD
Epidemiology	**Mean age at onset**	12 -16 years[10,30,44]	10 - 12 years[10,27]	13 - 18 years[5,24,31]
	Female:male ratio	Nearly 1:1 if < 6 years old 3:1 in adolescents[17,21,43,44]	3:1[10,27]	Slight female majority[5,24,31]
Clinical features	**PON**	Severe VA impairment at presentation	Greater VA impairment at presentation[8,19]	Severity of VA impairment at presentation similar to NMOSD-PON[5]
		Sequential or recurrent[3,8]	Bilateral simultaneous involvement, recurrent[2,27]	Bilateral involvement[5,15,24]
		Absence of optic disc swelling[5]	Altitudinal visual field defects[2,27]	Equal prevalence of optic disc edema[5]
		Poor visual prognosis[5]	Severe residual visual loss[2,27]	Good visual recovery[5,6,33]
	Other	Sensory and motor symptoms at onset with a relapsing-remitting pattern[3,5,8,35,40]	Acute myelitis (specifically LETM) Area postrema syndrome Acute brainstem syndrome Symptomatic narcolepsy or acute diencephalic clinical syndrome Symptomatic cerebral syndrome[10,27]	Encephalopathy Seizures Weakness Fever Headache Meningeal signs Gait abnormalities Paresthesias[6,8,29]
Laboratory findings	**Serum**	MOG-Ab rarely present[24,28] Absence of OCBs[7,21,30] Elevated IL-10, IL-21, IL-23 and IL-27 titers[29]	Elevated AQP4-IgG titer[10,25-27] **OR** Elevated MOG-Ab titer[10,23-27]	Elevated MOG-Ab titer[5,10,24]
	CSF	OCBs (2/3 of patients) or increased CSF IgG index[7,21,30]	OCBs or increased CSF IgG index (1/3 of patients)[10,16,21]	OCBs rarely present[16,33]
		Pleocytosis (< 60 cells/mm^3)[9,21] (lymphocytic predominance)[10,16]	Pleocytosis (> 50-100 cells/mm^3)[18] (lymphocytic predominance)[16,27]	Mild to moderate pleocytosis (lymphocytic predominance)[21,33]

			Increased proteins (sometimes >1g/L)[18] High levels of GFAP (acute phase)[13,27]	Increased proteins (up to 1.1g/L)[33] elevated CXCL13, APRIL, BAFF, CCL19, IL-6, G-CSF[29,31]
Imaging	**MRI**	**Orbits** T2 hyperintense or T1-weighted gadolinium enhancing short-length lesions of the optic nerve[13]	**Orbits** T2 hyperintense or T1-weighted gadolinium enhancing lesions of both posterior optic nerves (extending over half of its length), optic chiasm or optic tract[5,8,27]	**Orbits** Bilateral, anterior optic nerve lesions with longitudinally extensive and nerve sheath enhancement and relatively preserved chiasm and optic tracts[5,26,31]
		Brain and spine Well-defined, high-signal ovoid-shaped T2-weighted and T2-FLAIR images spread throughout the white matter in different areas: [9,17,22,29] periventricular juxtacortical infratentorial spinal cord (usually involving less than two cord segments, namely in the cervical cord)[22,27,31] Dawson fingers[12,17,20] Reduced brain, thalamic and corpus callosum volumes[17,30]	**Brain** T2-weighted lesions involving the hypothalamus, thalamus or periependymal surfaces of the third and fourth ventricle in the brainstem/cerebellum[15-17,27] Large, confluent, unilateral or bilateral subcortical or deep white matter lesions[15-17,27]	**Brain** T2 and FLAIR hyperintense, poorly defined and large (greater than 1-2 cm) brain or brainstem lesions[5,24,33] If isolated PON: small, nonspecific brain lesions[5,24]
			Spine Acute: LETM lesion[8,15,27] Chronic: longitudinally extensive cord atrophy[27]	**Spine** More involvement of the conus and thoracolumbar region[26,31]
	OCT	Thinner RNFL, mainly in the temporal quadrant[1] Lower macular volumes[35] Subclinical PON[4,6,34,35]	More significant and diffuse thinning of the peripapillary RNFL, particularly the superior and inferior quadrant[1,2,14] More pronounced macular thinning[1,2,14] Microcystic macular edema[2,5,14]	Inconclusive[5]

AQP4-IgG – antibodies against aquaporin-4; CSF – cerebrospinal fluid; GFAP – glial fibrillary acidic protein; LETM – longitudinally extensive transverse myelitis; MOG-Ab – antibodies against myelin oligodendrocyte glycoprotein; MOG-AD – myelin oligodendrocyte glycoprotein antibody disease; MRI – magnetic resonance imaging; MS – multiple sclerosis; NMOSD – neuromyelitis optica spectrum disorder; OCB – oligoclonal band; OCT – ocular coherence tomography; PON – Pediatric optic neuritis; RNFL – retinal nerve fiber layer; VA – visual acuity

MS is thought to be the result of a combination of genetic and environmental factors;[9,12,20,29,30] specific haplotypes in the HLA-DR allele of the major histocompatibility complex (MHC), namely HLA-DRB1*1501 allele, represent the major genetic risk factor,[7,9,10,21,23,29,30,32] while geographical distribution further away from the equator,[10,29] low serum vitamin D levels,[7,10,20,21,29,30,32] Epstein-Barr virus (EBV) seropositivity,[7,10,12,21,29,30,32] salt intake,[29] obesity,[7,10,20,21,29,30,32] head trauma[29] and smoke exposure[7,10,12,20,21,29,32] are potential childhood environmental risk factors for MS.

3.4.2.2. Clinical presentation

Regarding clinical features, most pediatric patients present with visual loss, diplopia, paresthesias, weakness, ataxia or urinary symptoms.[44] The phenotype at presentation of pediatric MS may be a clinically monofocal event (all the findings related to a single CNS location); a clinically polyfocal event without encephalopathy (findings related to more than one CNS site); or polyfocal deficits identified in the context of an acute encephalopathy.[17]

Younger children are more likely to present with polyfocal features and more severe acute deficits than older patients;[17,30,44] in contrast, adolescents tend to resemble adult-onset MS manifestations, typically with discrete neurologic findings, such as focal motor or sensory deficits, not only at presentation but also at relapses.[17,45]

Ninety-seven percent of children with MS experience a relapsing-remitting disease course;[7,10,17,20,21,30,32,42–44] hence, primary progressive MS is extremely rare in pediatric age and should always motivate assessment for alternative diagnosis.[21,30,42,44]

3.4.2.2.1. PON in pediatric MS

Optic neuritis is the first manifestation of pediatric MS in 10 to 22% of children.[8,12]

The risk of progression to MS after the first episode of PON is still uncertain.[1,3,5,8,9,17,30] Recent studies have reported rates of conversion in children from 22–29% over varied follow-up periods, significantly lower than in adults, with 50% of patients diagnosed with MS over 15 years.[5,9]

Certain clinical presentations of PON seem to be associated with a higher probability for MS, namely absence of optic disc swelling,[5] preferential involvement of temporal quadrant of RNFL,[2] and sequential (with a difference between both eyes of more than two weeks) or recurrent ON.[3,8] Unilateral or bilateral involvement is not an independent risk factor for MS.[3,6,8,9]

The risk of progression to MS increases with age, probably as a result of differential factors in the immune system.[3,5,8,9,20] In a meta-analysis, the median age of presentation of

PON in children diagnosed with MS was 14.7 years;[46] it also reported that every one year increase in age of presentation of PON was associated with a 32% increased risk of progression to MS.[46]

Ethnical or geographic factors may also be implicated in this risk, with several studies reporting a lower rate of MS conversion in certain Asian populations, namely in Taiwanese children.[3,8] Gender does not seem to be a factor to be considered in the progression of PON to MS.[6,9]

3.4.2.3. Diagnostic work-up

Regarding diagnostic tests, MRI findings in pediatric MS patients include T2 hyperintense or T1-weighted gadolinium enhancing short-length lesions of the optic nerve[13] and well-defined, high-signal ovoid-shaped T2-weighted and T2-FLAIR images spread throughout the white matter in different areas, namely periventricular, juxtacortical, infratentorial and in the spinal cord.[9,17,22,29] Dawson fingers are typical lesions, corresponding to linear and ovoid T2 hyperintense lesions emanating upright from the corpus callosum.[12,17,20] The so-called black holes, which are chronic T1-hypointense lesions, were shown not to help in the determination of dissemination in time; this is assessed by the presence or absence of gadolinium enhancement.[47] Younger children present with atypical initial brain MRI features compared with adolescents, whose MRI findings resemble adult MS;[17] prepubertal patients tend to show large undefined lesions that may resolve over time, more brainstem and cerebellar lesions and a higher lesion volume early in the disease.[17,21,45] Furthermore, global brain volume is typically lower than age-expected values,[17,24,30,32,41] as well as thalamic volume[17,30,32] and callosal area.[30]

Spinal cord MRI seems to be less useful in the diagnosis of MS in children than in adults.[45,47] The typical pattern of spinal cord involvement on MRI is usually less than two cord segments,[22,27,31] with the cervical cord being more affected than the thoracic cord,[22,45] and the dorsal aspect of the cord more often involved than the ventral, rarely traversing the full cross-sectional diameter of the cord;[27,31] however, longitudinally extensive transverse myelitis (LETM) with lesions spanning at least three contiguous segments may also occur in pediatric MS.[8,12,16,19–21,27,45]

CSF analysis typically shows evidence for inflammation, characterized by pleocytosis (usually <60 cells/mm^3,[9,21] mainly consisting of lymphocytes)[10,16] and for a humoral immune response with OCBs not present in serum or increased CSF IgG index.[7,9,12,20,21,24,26,29,30,42]

Characteristic periventricular white matter lesions on initial brain MRI and positive OCBs in the CSF are two consistent risk factors for MS following an episode of PON,

particularly if combined.[2,5,8,9,24,32,43] On the other hand, a normal brain MRI and absence of OCBs in CSF cannot exclude the possibility of MS development in the future, even though there is low probability of that.[6,9,30]

Serum cytokine profiles seem to predict relapse in pediatric-onset MS;[29] studies have shown that elevation of IL-10, IL-21, IL-23 and IL-27 titers (values greater than 5 times the mean of one of these markers) had a positive predictive value of 44% for relapse, whilst the absence of this elevation yielded a negative predictive value of 80%.[29] MOG-Abs can be rarely found in children with MS[24,28] and, when present, decline to undetectable levels over the course of the disease.[24]

In contrast with adult-onset MS, the role of OCT in children with MS is not well defined, despite growing evidence of its value in the assessment of neurodegeneration in this age group; validation through large-scale longitudinal studies is crucial.[35] Limited studies on OCT findings in pediatric MS reported that eyes with a previous history of PON showed 10 to 20% thinner RNFL, mainly located temporally,[1] and 26% lower macular volumes than MS non-PON eyes or control eyes;[35] however, MS non-PON eyes also presented lower temporal RNFL and ganglion cell layer (GCL) volumes than control eyes, pointing to a pattern of subclinical retinal damage.[4,6,34,35] RNFL and GCL atrophy is thought to be a consequence of retrograde degeneration of the constituent fibers of the optic nerves caused by inflammatory axonal transection and/or chronic demyelination.[35]

VEPs, in their turn, may also be useful in identifying subclinical disease;[1] electrophysiologic studies of pediatric MS have shown that bilateral optic neuropathy is common as part of the disease process, regardless of having a history of PON or not.[1,4,35]

3.4.2.4. Diagnostic criteria

McDonald criteria from the International Panel on Diagnosis of Multiple Sclerosis, updated in 2017, combine clinical, imaging and laboratory evidence in order to demonstrate dissemination of lesions in both space and time, which is the core requirement for the diagnosis of MS (See Appendix I).[7,12,47] These came to provide the possibility to establish the diagnosis at the time of a first clinical demyelinating event.[5,7,29,32,42,47]

These criteria were considered most applicable to patients with 11 years of age or older;[7,42,47] in patients younger than 11 years old, the likelihood of MS is lower, therefore caution is recommended when applying these criteria.[7,42,45,47]

Also of notice, ADEM, even though typically following a monophasic course, in some cases may present with recurrent clinical episodes or MRI evidence of new lesions, leading to a misdiagnosis of MS.[47] For this reason, the 2017 revised McDonald criteria should not be

applied to children at the time of ADEM presentation and a following episode characteristic of MS is necessary to make the diagnosis;[42,44,47] furthermore, alternative diagnoses, including NMOSD and ADEM, need to be excluded in all children.[12,47]

Hence, the diagnosis of pediatric MS can be obtained by fulfilling any one of the following diagnostic criteria: two or more non-encephalopathic clinical CNS events with presumed inflammatory cause, separated by more than 30 days and involving more than one area of the CNS; one non-encephalopathic episode typical of MS which is associated with MRI findings consistent with 2017 McDonald criteria for dissemination in space and in which a follow-up MRI shows at least one new enhancing or non-enhancing lesion consistent with criteria for dissemination in time; one ADEM attack followed by a non-encephalopathic clinical event, three or more months after symptom onset, that is associated with new MRI lesions that fulfill the 2017 McDonald dissemination in space criteria; or a first, single, acute event that does not meet ADEM criteria and whose MRI findings are consistent with the 2017 McDonald criteria for dissemination in space and dissemination in time (applies only to children ≥11 years old).[12,43,47]

The 2017 McDonald diagnostic criteria consider OCB as evidence of dissemination in time and does not require for MRI lesions to be clinically silent.[5,32,47] Optic nerve lesions, however, are still not considered evidence of dissemination in space, since they commonly occur in other demyelinating disorders.[5,47]

3.4.2.5. Treatment

Current treatment recommendations for children derive from the optic neuritis treatment trial (ONTT), which is in line with the international consensus for treatment of other demyelinating attacks happening in pediatric MS.[5,7,21] The accepted protocol for acute therapy consists of intravenous methylprednisolone (IVMP) that can be followed by oral prednisolone tapered over 1 to 4 weeks, if incomplete symptomatic resolution is observed.[5,7,10,20,43] Plasma exchange (PLEX) or intravenous immunoglobulin (IVIG) are alternative therapies when steroids are contraindicated or caused insufficient improvement.[5,10,20,29,43]

Regarding chronic immunomodulation, disease-modifying drugs (DMDs) should be initiated as soon as the diagnosis is made (Table II).[5,30] First-line therapies in children include DMDs used for adult MS, such as interferon-beta and glatiramer acetate,[6–8,10,12,20,21,29,30,32,40–43,48] although there is little evidence for their use in the pediatric population.[1,10,29,41–43,48] Other agents have been the subject of many studies, with promising results for natalizumab,[5–8,10,20,21,30,40–43,48] rituximab[5–8,10,41,43,48] and fingolimod[5–8,10,20,32,40,41,43,48] in reducing relapse rates;

these are considered second-line medications.[5,6,8] Peginterferon beta-1a, dimethyl fumarate, teriflunomide and alemtuzumab are being evaluated in ongoing studies.[5,7,10,29,32,41,42]

The first-line therapy fails in almost half of the children.[7,8,20,30,42,43] According to the 2012 International Pediatric Multiple Sclerosis Study Group (IPMSSG) statement, inadequate treatment response is defined as: a minimum time on full-dose therapy of at least six months; being fully compliant with treatment; and at least one of two or more relapses (clinical or MRI) within a 12-month period or an increase or no reduction in relapse rate, new T2 lesions, or new contrast-enhancing lesions on MRI from the pre-treatment period.[7,10,29,30,41,42,48] Twenty percent of pediatric MS patients require escalation to second-line therapies, but the majority responds to a switch to a different first-line drug.[7,8] Recommendations for therapy escalation in pediatric population are based in adult-MS guidelines, and include gradual escalation from therapies with less potential toxicity to higher potency therapies;[29] however, some studies suggest that early intervention with high potency therapies might lead to better future disability outcomes.[29,42,48]

3.4.2.6. Prognosis

MS in children presents higher relapse rates (2-3 fold) than in adults,[5,7,8,10,12,17,21,30,34,35,40–42] with a more significant accumulation of MRI lesions, impaired brain growth and cognitive disability. Despite presenting a slower progression, as measured by the Expanded Disability Status Scale (EDSS),[10,29,44] irreversible damage occurs within an average of two decades from diagnosis, 10 years earlier than in adults with MS.[5,7,10,12,17,20,21,30,32,35,40–42,48]

Motor disability, cognitive impairment, fatigue, psychiatric symptoms, bladder and bowel dysfunction, neuropathic pain and psychosocial dysfunction are common sequelae in pediatric MS and may drastically reduce the quality of life of these patients;[7,10,12,20,21,29,30,32,40,42,44] regarding cognitive impairment, executive function, processing speed, visuomotor integration and attention are the most affected domains.[29,30]

The visual prognosis is poorer when MS is diagnosed, with only 27% of children with MS-ON experiencing complete visual recovery after a year and 68% presenting persistent visual field deficits, in comparison with 90% and 22%, respectively, of children with isolated PON.[5]

Relapses and progression of disability can be minimized with early treatment.[5,8,12]

Table II. Immunomodulating therapies in pediatric multiple sclerosis

Drugs		Mechanism	Dose	Side effects	Recommended monitoring
Injectable agents	Interferon-beta[7,29,42]	Promotion of anti-inflammatory cytokines Decrease in pro-inflammatory cytokines Reduction of leukocyte migration across the blood-brain barrier	**IFNβ-1a** 44µg SC three times weekly **OR** 30µg IM weekly **Pegylated-IFNβ-1a** 125µg SC every 2 weeks **IFNβ-1b** 250µg SC every other day	Injection site reactions Flu-like symptoms Elevated liver enzymes Hematologic abnormalities Thyroid dysfunction	CBCs and LFTs (monthly for the first 6 months, then every 6 months) Thyroid function (at baseline then every 6 months)
	Glatiramer acetate[7,29,42]	Copolymer of myelin basic protein Immunomodulatory and neuroprotective effects	40mg SC three times weekly	Injection site reactions Post-injection systemic reaction	None
Oral agents	Fingolimod[7,29,42]	Sphingosine-1-phosphate inhibitor Prevention of egress of lymphocytes from lymph nodes Additional potential effects on the blood-brain barrier and on differentiation and protection of oligodendrocyte precursor cells Possible role in remyelination	0.5mg PO daily	First-dose bradycardia Elevated liver enzymes Lymphopenia Macular edema Infection (including herpes viruses) Basal cell carcinoma PML (rare)	ECG (at baseline and close monitoring for 6 hours after first dose) VZV antibody status (at baseline) CBC (at baseline) LFTs (at baseline and every 3 months for first year) Ophthalmologic exam (at baseline and 3-4 months after initiation)
	Dimethyl fumarate[7,29]	Inhibition of lymphocyte proliferation Promotion of an anti-inflammatory cytokine profile Antioxidant effects	240mg PO twice daily	Flushing GI upset Eosinophilia Lymphopenia Elevated liver enzymes Rare cases PML	CBC (at baseline, then every 3 months) LFTs (at baseline, after 6 months, then every 6-12 months)
	Teriflunomide[29,42]	Inhibition of pyrimidine synthesis, thus inhibiting lymphocyte proliferation	14mg PO daily	GI upset Alopecia Headache Hypertension	CBC (at baseline) LFTs (at baseline, then monthly for 6 months)

				Infection Elevated liver enzymes Hematologic abnormalities Teratogenic	Blood pressure (at baseline, then periodically) Pregnancy test and tuberculosis screening (at baseline)
Biologic agents	**Natalizumab**[7,29,42]	Monoclonal antibody against α4-integrin Prevention of migration of leukocytes across the blood-brain barrier	300mg IV every 4 weeks	Infusion reactions Hypersensitivity reactions Infection (including herpes viruses) PML	Anti-JCV antibody (at baseline and every 6 months if negative) MRI monitoring in patients with high risk of PML (eg. every 6 months) CBCs and LFTs (periodically)
	Rituximab[7,29]	Anti-CD20 chimeric monoclonal antibody Depletion of B-cells	500mg/m^2 IV x 2 doses 14 days apart **OR** 375mg/m^2 IV x 4 doses 7 days apart	Infusion reactions (including anaphylaxis) Infection Hematologic abnormalities PML (rare)	CBC (at baseline and periodically during therapy) B-cell levels (as clinically indicated)
	Alemtuzumab[7,29]	Monoclonal antibody to CD52 Prolonged lymphocyte depletion	12mg IV daily x 5 days, then 12mg IV daily x 3 days one year later	Infusion reactions Infection (including herpes viruses) Autoimmune thyroid disease Immune thrombocytopenia purpura Antiglomerular basement membrane disease	ECG (prior to each treatment course) CBC, creatinine, urinalysis (at baseline and then monthly until at least 48 months after last treatment course) Thyroid function (every 3 months until at least 48 months after last treatment course)
	Ocrelizumab[29]	Humanized monoclonal antibody to CD20 Depletion of B-cells	600mg IV every 24 weeks	Infusion reactions Infection	

CBC – complete blood count; ECG – electrocardiogram; GI – gastrointestinal; IM – intramuscular administration; IV – intravenous administration; JCV – John Cunningham virus; LFT – liver function tests; PML – progressive multifocal leukoencephalopathy; PO – per os; SC – subcutaneous administration; VZV – varicella-zoster virus

3.4.3. NEUROMYELITIS OPTICA SPECTRUM DISORDER

Neuromyelitis optica (NMO), initially termed Devic's disease,[3,16,22,27] is an autoimmune inflammatory disorder characterized by acute, severe episodes of ON and transverse myelitis.[1,3,6,8,10,13–19,21–23,25–27,29,49] This disease is further categorized by AQP4-IgG status;[5,27,29] the severity of NMO episodes, compared with MS and MOG-AD, may be explained by the mechanism of action of these autoantibodies.[5,26]

The term NMOSD was adopted in 2007 to include patients with limited forms of the disease, such as first-attack LETM or recurrent or bilateral ON, who are likely to develop a relapse course;[5,12–14,18,19,24,27,29] it also included the cerebral, diencephalic and brainstem lesions that occur in a minority of patients with otherwise typical NMO,[13,19,27] as well as AQP4-IgG-seropositive patients with coexisting autoimmune disorders.[13,19,27]

3.4.3.1. Epidemiology

NMOSD is uncommon in children;[17,19,50] pediatric-onset NMOSD accounts for 3 to 5% of all NMOSD cases.[10,15–17,19] Pediatric NMOSD usually develops in children around 10-12 years old, although it was reported in ages as young as 16 months; females are more likely to be affected than males, with a ratio of 3:1.[10,15,16,19,27]

It is typically a sporadic disease, but reports suggest about 3% of cases are familial; however, few genetic risk factors are connected to NMOSD.[16] NMOSD has been associated with other autoimmune diseases including Sjogren's syndrome,[50] SLE, juvenile dermatomyositis, celiac disease, autoimmune hepatitis, Hashimoto's and Graves' diseases, childhood onset diabetes, atopic dermatitis, panserositis and juvenile rheumatoid arthritis.[5,10,15,16,18,19,23,50]

3.4.3.2. Clinical presentation

The most frequent initial presentation of pediatric NMOSD includes motor, visual and constitutional (namely fever) symptoms.[16] The core clinical characteristics include ON, acute myelitis (specifically LETM), area postrema syndrome (with vomiting and intractable hiccups), acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome with typical MRI diencephalic lesions and symptomatic cerebral syndrome.[3,8,10,15,16,19,21,27,40]

In comparison to adults, a greater proportion of children may have monophasic disease.[15,21,27]

3.4.3.2.1. PON in pediatric NMOSD

In approximately 60% of children, isolated PON without transverse myelitis is the initial presentation of NMOSD.[5,6,8,19] The estimated risk of progression to NMOSD after an episode of PON ranges from 1 to 7%.[8]

NMOSD-PON is more severe, occurs more frequently and is more commonly associated with brain lesions than ON in adults with NMOSD.[8,19] In comparison with MS-PON, NMOSD-PON causes a much greater impairment;[2,3,5,15,18,27] it is more often recurrent, presents more frequently with bilateral simultaneous optic nerve involvement and affects the chiasm with altitudinal visual field defects.[2,14,18,27]

3.4.3.3. Diagnostic work-up

In clinically suspicious cases of NMOSD, brain, orbital and full spine MRI with and without contrast is recommended.[5,16] MRI characteristics of PON in NMOSD include T2 hyperintense or T1-weighted gadolinium enhancing lesions of both posterior optic nerves (extending over half of its length), optic chiasm or optic tract, usually without brain lesions.[5,8,13-15,18,19,27,31] When present, brain MRI findings include T2 hyperintense diencephalic lesions around the third ventricle and aqueduct, dorsal brainstem lesions adjacent to the fourth ventricle and periependymal lesions around the lateral ventricles; white matter lesions in the hemispheres can be large and tumefactive or fusiform following white matter tracts.[13,15–17,19,27]

Full spine MRI may show LETM, with lesions spanning at least three contiguous segments;[8,12,13,15,18,19,22,25,27] these lesions typically involve the central gray matter, characteristically extend into the brainstem if cervical, and may be associated with cord swelling, central hypointensity on T1-weighted sequences and gadolinium enhancement.[13,15,19,27,31] LETM, however, as previously mentioned, is less specific in children as it can occur in ADEM and MS as well as NMOSD.[8,12,13,15,16,19–21,27] Chronic spinal lesions appear in MRI as longitudinally extensive cord atrophy, with or without focal or diffuse T2 signal change involving the atrophic segment.[27]

Lumbar puncture should also be performed.[16] CSF from NMOSD patients generally presents higher white blood cell counts when compared to MS,[10,16,18,21,22,27] (>50-100 cells/mm^3)[18] usually lymphocytic-predominant.[16,21,22,27] OCBs are positive in one third of patients, compared to two thirds of MS children.[10,16,18,21] Protein increase is also found (sometimes >1g/L);[18] CSF glial fibrillary acidic protein (GFAP) also has the potential to be a diagnostic and prognostic biomarker, but is raised only for days to weeks following an attack.[13,27]

Recent studies with OCT showed that, in comparison with MS-ON, NMOSD-ON presents with a more significant and diffuse thinning of the peripapillary RNFL, and that this may be an early phenomenon.[1,2,5,14] Also, in NMOSD-ON the entire peripapillary RNFL is involved, particularly the superior and inferior quadrant.[1,2,14] Macular thinning is more pronounced in NMOSD-ON than in MS-ON as well, which is consistent with the more severe residual visual impairment in the first.[1,2,14] Microcystic macular edema is more likely to occur in NMOSD-ON, however, it is uncertain whether OCT can provide reliable RNFL measurements when disc edema is present.[2,5,14] Unlike in MS, subclinical PON in NMOSD is uncommon; NMOSD eyes without a history of PON usually have normal RNFLs.[14]

As previously noted, AQP4-IgG positivity should be assessed in all children with PON, since not only it predicts a high risk for NMOSD,[2,7,10,12,14,16,18–21,23,25–27,40,49] but also is the basis of diagnosis stratification in the 2015 revised international consensus diagnostic criteria.[8,12,23,26,50] AQP4-IgG titers increase just before an episode, while treatment with steroids or PLEX as well as remission may be associated with lower values;[5,27] however, this biomarker does not seem to accurately reflect disease activity or prognosis.[5,23] Furthermore, it was recently identified a group of children with ON, recurrent ON and NMOSD syndrome who are negative for AQP4-IgG but MOG-Ab positive.[2,8,10,13,16,18,19,23–27,31,40] It is still unclear the predictive value of these antibodies, however these patients, usually younger and with a lower female:male ratio,[16,24,26,27,31] seem to present fewer severe episodes and faster recovery from ON and myelitis when compared to AQP4-IgG positive patients.[2,8,13,16,18,19,21,24,25,27,31]

3.4.3.4. Diagnostic criteria

The 2015 international criteria were stratified into NMOSD with AQP4-IgG (AQP4-NMOSD) and NMOSD without AQP4-IgG (See Appendix II).[5,10,15,16,18,19,26] The latter allows to include not only the MOG-Ab positive patients, that represent over 20% of AQP4-IgG-negative NMOSD cases, but also seronegative patients who meet clinical diagnostic criteria.[5] Further update of these criteria may exclude MOG-Ab positive patients and include them in MOG-AD disease spectrum.[5]

Of notice, the 2015 diagnostic criteria were proposed for adult NMOSD; however, the consensus group considered it to be applicable in children, since most clinical, radiological and laboratory characteristics of pediatric NMOSD are similar to adult disease.[5,6,8,10,15,19,27,29]

Hence, diagnosis of AQP4-NMOSD requires at least one core clinical characteristic and exclusion of alternative diagnoses.[15–19,21,27,40] In its turn, diagnostic criteria for NMOSD with either negative or unknown AQP4 status also include exclusion of alternative diagnosis and at least two core clinical characteristics that meet all the following requirements: one core clinical

characteristic must include ON, acute myelitis with LETM or area postrema syndrome; dissemination in space of at least two core characteristics; and fulfillment of MRI requirements.[15–19,21,27,40]

3.4.3.5. Treatment

Acute treatment recommendations for suspected NMOSD are similar to the ones for MS, also beginning with IVMP but rapidly escalating to second-line therapy with PLEX and/or IVIG, since each attack has the potential to cause severe, cumulative disability.[5,10,15,16,18,19,21,40] In these children, oral prednisolone is usually tapered over 2-6 months, more slowly than in MS;[5,15] however, switching to steroid-sparing agents should be done as quickly as possible, given its side effects in the pediatric population, namely hypothalamic–adrenal axis disruption and growth suppression.[5] Regarding second-line therapy, PLEX is the first choice due to its mechanism of autoantibody clearance, and IVIG should be administered if PLEX is unavailable; however, there is a lack of evidence of success with these therapies, which indications are based on treatment guidelines for adults.[5,15,16,18,23]

Early chronic immunosuppression is required, and it is often continued even if sustained clinical remission (Table III).[5,16,18,21] In children, first-line agents for chronic immunotherapy include rituximab, azathioprine and mycophenolate mofetil, with evidence of reducing relapse rate.[5,6,8,10,12,15,16,18,19,21,29] An alternative option is methotrexate.[8,15,19] According to recent studies, interferon-beta, glatiramer acetate, dimethyl fumarate, alemtuzumab, fingolimod and natalizumab, agents prescribed to MS, may exacerbate NMOSD, thus early-stage diagnostic specific is critical.[1,5,10,12,13,15–18,20,26,27,29,47] Cyclophosphamide and mitoxantrone are also not recommended in children due to important side effects, namely hemorrhagic cystitis, secondary malignancy and infertility with the first[8,16,19] and cardiotoxicity and leukemia with the latter.[8,15,16,19] Anti-IL-6R-antibodies and eculizumab represent potential future treatments.[16,18,19]

3.4.3.6. Prognosis

A relapse course is seen in over 90% of children with NMOSD, with cumulative disability;[1,5,10,15–19,21] relapses are unpredictable and possibly life-threatening. In comparison to MS pediatric patients, children with NMOSD reach a higher EDSS score within two years of disease onset.[16]

Children with NMOSD-ON present with severe residual visual loss (VA 20/200 or worse) despite high-dose steroids;[2,3,5,15,18,27] the median time from onset of NMOSD to permanent vision loss (<20/200) is 1.3 years.[8,16]

Table III. Immunomodulating therapies in pediatric neuromyelitis optica spectrum disorder

	Drugs	Mechanism	Dose	Side effects
Injectable agents	**Rituximab**[10,15,16,18,19]	Anti-CD20 chimeric monoclonal antibody Depletion of B-cells	375 mg/m^2 IV every week (maximum total loading dose of 2 g) for 4 weeks **and then** 750 mg/m^2 IV (maximum total dose of 1 g) at approximately 6 months or earlier upon B-cell return	Infusion reactions (including anaphylaxis) Infection Hematologic abnormalities PML (rare)
Oral agents	**Azathioprine**[10,15,16,19]	Purine analogue Interference with DNA synthesis in proliferating cells, including T and B-cells	2–3 mg/kg/day PO	Fever Malaise Myalgia Nausea Diarrhea Elevated LFTs Severe leukopenia Rash Hypersensitivity reactions Lymphoma
	Mycophenolate mofetil[10,15,16,18,19]	Immunosuppressant drug Block of proliferation and clonal expansion of T and B-cells	600 mg/m^2 PO twice a day for a total of 1200 mg/m^2 in a day (with a maximum of 1000 mg twice a day for a total of 2000 mg in a day) (slow up titration - start at a quarter dose up to 250 mg twice a day for 14 days, then half dose up to 500 mg twice a day for 14 days and then goal dose after that)	Nausea, Abdominal pain Diarrhea Constipation Headache Fatigue Hair loss Anxiety Dizziness Rash Bruising Leucopenia PML Abortive effects
Biologic agents	**Tocilizumab**[16]	Monoclonal antibody targeting the IL-6 receptor		Infections (especially respiratory) Liver function abnormalities Neutropenia Elevated cholesterol
	Eculizumab[16]	Humanized monoclonal IgG targeting the complement protein C5 Inhibition of the complement cascade and the endpoint destruction of astrocytes		Infusion reactions Increased risk of meningococcal infections

IV – intravenous administration; LFT – liver function tests; PML – progressive multifocal leukoencephalopathy; PO – per os

3.4.4. MYELIN OLIGODENDROCYTE GLYCOPROTEIN ANTIBODY DISEASE

MOG-AD is as a newly recognized disease entity that comprises isolated ON (a single episode of unilateral or bilateral ON without evidence of other CNS involvement),[6] relapsing ON (an episode of ON and at least 1 relapse, without any other manifestations),[6] monophasic ADEM (single polyfocal CNS event with encephalopathy and presumed inflammatory demyelination and no new disease activity, clinical or radiological, >3 months after onset),[33] multiphasic disseminated encephalitis (ADEM followed at >3 months by second ADEM episode, but no further ADEM or non-ADEM demyelinating events)[12,33] and ADEM followed by recurrent ON (frequent ON attacks ranging from one to nine episodes during a follow-up of up to 5 years, occasionally in combination with further ADEM like attacks).[5,10,17,19,24,28,29,31,33]

3.4.4.1. Epidemiology and clinical presentation

MOG-AD was initially thought to be monophasic, however several studies reported a relapsing course with cumulative disability.[5,7,23,24,26,28,32,33,43] There seems to exist an history of prodromal illness in many patients, even though it has not been found an association with a specific virus;[5,7,8,21–23,25,29,31,33,43] in contrast, there is no evidence that MOG-AD is associated with autoimmune disorders.[5,31]

PON is the most common phenotype of MOG-AD,[5] but encephalopathy, seizures, weakness, fever, headache, meningeal signs, gait abnormalities and paresthesias may also occur.[6,8,29] MOG-PON occurs more frequently in female teenagers (13-18 years);[5,15,24,28,31] encephalitis, however, is more prevalent among younger children (4-8 years).[5,8,15,21,24,28,31] This suggests that clinical presentation of MOG-AD may be age dependent,[5,10] and progressively more similar to the clinical phenotype observed in adults as the child's age increases.[28]

Furthermore, recent studies concluded that there may not be a higher prevalence in white population as previously thought.[5]

3.4.4.1.1. PON in pediatric MOG-AD

MOG-ON represents 17 to 57% of PON cases. It is bilateral in more than 80% of children,[5,15,24,26] being more commonly unilateral in patients with recurrent PON.[24] The prevalence of optic disc edema is similar when compared with other forms of PON.[5] The severity of VA impairment at presentation is also similar to the one occurring in AQP4-PON.[5]

3.4.4.2. Diagnostic work-up

MRI findings include bilateral, anterior optic nerve lesions with longitudinally extensive and nerve sheath enhancement and relatively preserved chiasm and optic tracts, in contrast with NMOSD-ON.[5,26,31] Other features may help to differentiate MOG-AD from MS, namely the presence of T2 and FLAIR hyperintense, bilateral, poorly defined and large (greater than 1-2 cm) brain or brainstem lesions[5,7,8,12,17,22,24,26,29,31,33] in the absence of T1 hypointense demarcated periventricular ovoid lesions and Dawson's fingers;[5–8,21,31,33] additionally, MOG-AD lesions enhance at the same time, contrarily to MS, which presents with lesions disseminated in time and space.[5,6,8] Patients with isolated MOG-ON, however, most commonly present with small, nonspecific brain lesions, if any at all.[5,24] Spinal imaging shows more involvement of the conus and thoracolumbar region in MOG-Ab positive patients, unlike AQP4-IgG positive patients who present more commonly with cervicothoracic involvement.[26,31]

Recent studies with OCT reported conflicting results in MOG-ON compared with AQP4-ON, with some showing much more discrete thinning of RNFL and GCL,[5,26] whereas others describe pronounced thinning similar to AQP4-ON.[5] This may be explained by MOG-Ab mechanism; since it does not cause direct astrocytopathy, some ganglion cell axons may be preserved in the optic nerve demyelination.[5]

CSF OCBs are rarely present in MOG-ON,[16,33] whereas mild to moderate pleocytosis is frequently found,[5,7,21,24,26,33] with a high percentage of lymphocytes.[21,33] CSF protein is also commonly mildly increased (up to 1.1g/L).[33] CSF cytokine profiles show elevations in B-cell related cytokines and chemokines, including CXCL13, APRIL, BAFF and CCL19, but also to Th17 related cytokines (IL-6 and G-CSF).[29,31]

Routine evaluation of MOG-Ab titers may be useful in determining the risk of relapse.[5] MOG-Ab titer at inaugural episode is not predictive of a relapsing course;[5,10,24,31] it is, however, thought to be associated with a persistently elevated MOG-Ab titer.[5,10,24,28] On the other hand, some MOG-Ab positive children later present negative titers, usually following a non-relapsing course from that moment on;[5,24] the time interval between the initial episode and decreasing MOG-Abs levels is highly variable and probably influenced by age, sex and genetic factors.[24]

3.4.4.3. Diagnostic criteria

Diagnostic criteria for MOG-AD have been suggested by several groups, but have not been fully validated.[10]

3.4.4.4. Treatment

Currently, acute treatment recommendations for MOG-AD are similar to MS and NMOSD guidelines.[5,24] In the acute phase, the majority of children respond well to IVMP.[10,21,24,26,31,33,43] Oral steroid therapy is usually then carried for 4 to 6 weeks, with fast recovery in most patients.[5,10,21,24,31,33,43] The tapering pace should be adjusted according to the severity of the episode,[5,31] since during this period children are more prone to relapse – nearly 70% of patients, once oral prednisolone dose is lowered under 10 mg per day or after two months of steroid withdrawal.[5] IVIG and PLEX are also acute treatment options in children who had not responded to initial therapy.[10,21,24,26,31,33,43]

MOG-AD does not usually require long-term treatment since it is most commonly a monophasic disorder;[6,10,12,15,29] however, chronic immunotherapy should be considered given the response to initial steroid treatment and the prospect of relapse, despite the lack of studies to support drug choice.[5,12,24,26] Mycophenolate mofetil and rituximab are the most commonly used, with approximately 50% efficacy;[10] however, recent studies report conflicting results, with IVIG and maintenance prednisolone achieving the best results regarding relapse rates.[5,24] Therefore, steroid therapy should be resumed at the first evidence of recurrence.[5] Cyclophosphamide, azathioprine and methotrexate were generally not well tolerated.[5] Withdrawal of immunotherapy after a long period of remission is controversial.[5,26]

Of notice, some agents used in the treatment of MS, such as alemtuzumab, show deleterious effects when prescribed in MOG-AD or are ineffective, namely interferon-beta and glatiramer acetate; hence, it is mandatory to exclude MS.[5,24,26,31,32]

3.4.4.5. Prognosis

MOG-AD presents as a relapsing disorder in only one third of children.[5] When following a relapsing course, the most common presentation is recurrent ON, particularly in children older than 9 years.[5,24,28]

The visual prognosis of MOG-PON is typically favorable, with better recovery than adult MOG-ON and AQP4-PON (89–98% versus 33% attaining visual acuity of 20/25 or better after 6 months).[5,6,26,33]

3.5. TREATMENT

The first treatment recommendations for ON resulted from the ONTT, in 1992.[1,8] This study aimed to evaluate the efficacy of steroid therapy in adults with ON, showing that treatment protocols with IVMP followed by oral prednisone provided quicker resolution of visual impairment (from 7 to 2 weeks),[1,3,4,6] unlike oral steroid therapy alone, that was ineffective and associated with higher relapse rates.[1,3] However, the study also concluded that, despite accelerating visual recovery, steroid therapy does not have any impact in visual and neurological long-term outcomes, except in cases of NMOSD.[4–6] ONTT did not include pediatric patients and, so far, there are no similar studies regarding children with PON; for that reason, although controversial, ONTT recommendations are considered the standard of care in PON.[1–4,6,8]

Many children, however, recover VA without any treatment.[6] Therefore, current clinical practice oscillates between a conservative, wait and watch approach for unilateral and mild bilateral cases, and treatment with short dosages of intravenous corticosteroids in bilateral cases with severe loss of VA.[2,3] Age (prepubertal vs postpubertal) and gender also influence clinician's individual decision to begin treatment.[6] Essentially, treatment protocols are not consensual, but most practitioners prescribe steroid therapy as the first-line approach.[6,8]

The most recommended protocol consists of a 3–5-day course of IVMP (30 mg/kg/day; maximum dose of 1 g daily),[2–8,10,15,16,18–21,24,31,33,43] followed by oral prednisolone at a starting dose of 1 mg/kg/day and tapered over variable periods that range from 1 week to 6 months, depending on the underlying disorder.[2,4-8,10,15,16,18,20,33,43] It is uncommon to use superdoses of oral prednisolone in children since dosing is undefined, despite evidence that are equivalent to IVMP in adults,[1,5,7] with the advantage of being less expensive and avoiding the placement of an intravenous line; further studies are needed on this.[1]

Of notice, there has been a paradigm shift concerning the timing to begin steroid therapy, motivated by the growing awareness of the irreversible optic nerve damage associated with NMOSD, which diagnosis is difficult to make since it can present uniquely with unilateral ON. Hence, current practice leans towards initiating IVMP at disease onset instead of waiting for the etiology establishment, in order to prevent optic nerve injury while the evaluation is ongoing.[6]

IVIG (2 g/kg divided over 2–5 days) and PLEX (five to seven exchanges over 10–14 days) are alternative therapies in the acute treatment of PON when unresponsive to steroids.[1,3-8,10,15,16,18-20,31,33,43,49] Of notice, PLEX must precede IVIG administration to prevent the removal of IVIG from the blood stream.[5,31] These therapies entail side effects, such as headache, myalgia, fever and allergic reaction in the case of IVIG, and risk of infection (especially catheter related infections), electrolyte and coagulation disturbances and hypersensitivity reactions

when it comes to PLEX.[7,8,15,49] There is, however, a lack of evidence in pediatric population to support these treatments.[1,4,8]

Additionally, the accurate diagnosis of underlying CNS demyelinating diseases enables timely immunomodulation, crucial to prevent cumulative disability associated with a relapsing course.[1,3–6] Choice of prophylactic therapy for recurrent disease associated with MS, NMOSD and MOG-AD associated PON were discussed in detail above.

3.6. PROGNOSIS

Several studies evaluating prognosis of PON have been conducted in the last decade, assessing clinical outcomes, frequency, risk of recurrence and severity of residual functional and structural deficits.[4]

PON has better visual prognosis than ON in adulthood, with the majority (70-85%) of children experiencing full visual recovery (VA 20/20) in contrast with only half of the adults, at one year after diagnosis.[2–6,8] Visual outcome is also more favorable in younger children (less than 10 years).[1–3]

Visual recovery spontaneously begins 2–3 weeks after onset and can last up to 2 years.[2,3] A study reported a mean time to visual recovery of 61 days, with considerably longer periods according to the severity of the initial VA loss;[51] final VA is dependent on VA loss at presentation.[3]

However, even when VA recovers to 20/20, residual functional and structural defects may persist.[2–4,8] Even though recovery of high contrast VA is excellent in most children, low contrast VA is usually reduced.[4,8] Persistent visual field[4] and color defects[2] are also common, as well as relative afferent pupillary defect, mild pallor in the temporal optic disc and perception of Uhtoffs' and Pullfrich's phenomenon;[2,3] the latter is the result of an unequal conduction speed between both optic nerves, and is demonstrated with a pendulum seeming to describe an ellipse despite moving in a single plane.[3] OCT also shows persistent thinning of the RNFL and of the GCL in children with history of PON.[8]

Thus, poor visual outcome is associated with older age and severe vision impairment at presentation, but also with bilateral involvement at presentation,[1,4] presence of optic atrophy[1] and diagnosis of an underlying neurological disorder.[1,5,8] A significant proportion of children with PON are ultimately diagnosed with a recurrent demyelinating disease, which leads to cumulative impairment;[5] hence, children presenting an episode of PON should be submitted to follow-up with serial examinations, although there is no standard schedule.[8]

3.7. FUTURE DIRECTIONS

The need of prospective studies to assess outcomes and optimal treatment of PON has motivated the launch of Pediatric Optic Neuritis Prospective Data Collection Study (PON1) in July 2016, as a result of a collaboration between the Pediatric Eye Disease Investigator Group (PEDIG) and the Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC).[1,6,8] This prospective study aims to estimate visual outcomes six months after the initial presentation of PON and it is designed to test the potential of enrolling enough PON patients for a prospective treatment trial.[1,6,8]

Data on visual acuity, low-contrast VA, OCT, MRIs, quality of life, puberty status and AQP4-IgG status will also be collected at five study visits over the two year study duration and analyzed to estimate the risk of recurrence and development of MS.[6,8] The study includes 45 sites throughout North America, aiming to recruit 100 patients over a two year enrollment period; if the goal is achieved, a PON treatment trial will be considered.[6,8] Similarly to ONTT for ON in adults, such a study has the potential to deeply impact the approach of PON.[8]

Hence, prospective studies are necessary to overcome the lack of evidence-based research concerning diagnosis and management of PON.[1,6] Future research should aim at a deepening of knowledge regarding progressive change in optic nerve head, retinal GCL and RNFL thickness in PON, as well as the link between functional and patient-related outcomes, optic nerve lesion and structural changes in other areas of the CNS in children with demyelinating disorders.[4]

4. CONCLUSION

PON is a rare condition when compared to adult ON, but usually presents a better visual prognosis, particularly when monophasic. However, an important proportion of PON cases has an underlying neuroinflammatory or demyelinating recurrent disease, which entails cumulative impairment and, therefore, poorer visual outcomes. Hence, these entities, namely MS, AQP4-NMOSD and MOG-AD must be recognized as early as possible. Due to significant similarities between these disorders, the diagnosis may be challenging; however, diagnostic work-up with MRI of the brain and orbits (and, in addition, of the spine), CSF analysis, serology for AQP4-IgG and MOG-Ab and OCT is a key strategy to risk stratification. This allows clinicians to initiate proper, timely treatment with steroid therapy, PLEX and/or IVIG as well as chronic immunotherapy if indicated, in order to avoid recurrence and consequent cumulative disability.

Despite the substantial increase in studies of PON in the past decade, this condition remains enigmatic; thus, prospective studies are needed, and PON1 is expected to provide further major developments in the upcoming years.

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APPENDIX I

Diagnostic criteria for Multiple Sclerosis

Table IV. The 2017 McDonald criteria for diagnosis of multiple sclerosis

Number of clinical attacks*	Number of lesions with objective clinical evidence	Additional data needed for a diagnosis of MS
≥2	≥2	None
≥2	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location)	None
≥2	1	**Dissemination in space** an additional clinical attack implicating a different CNS site OR by MRI
1	≥2	**Dissemination in time** an additional clinical attack OR by MRI OR demonstration of CSF-specific oligoclonal bands
1	1	**Dissemination in space** an additional clinical attack implicating a different CNS site OR by MRI **AND** **Dissemination in time** demonstrated by an additional clinical attack OR by MRI OR demonstration of CSF-specific oligoclonal bands
0 (progression from onset - **primary progressive MS**)		**1 year of disability progression** (retrospectively or prospectively determined) independent of clinical relapse **AND** **two of the following criteria:** • One or more T2-hyperintense lesions characteristic of MS in one or more of the following brain regions: periventricular, cortical or juxtacortical, or infratentorial • Two or more T2-hyperintense lesions in the spinal cord • Presence of CSF-specific oligoclonal bands

Adapted from: Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162–73.

***Attack** - Attack, relapse, exacerbation, and (when it is the first episode) clinically isolated syndrome; A monophasic clinical episode with patient-reported symptoms and objective findings typical of multiple sclerosis, reflecting a focal or multifocal inflammatory demyelinating event in the CNS, developing acutely or subacutely, with a duration of at least 24 hours, with or without recovery, and in the absence of fever or infection.

CNS – central nervous system; CSF – cerebrospinal fluid; MRI – magnetic resonance imaging; MS – multiple sclerosis

Table V. 2017 McDonald criteria for demonstration of dissemination in space and time by MRI

Dissemination in space	Dissemination in time
≥1 T2-hyperintense lesions characteristic of MS in ≥2 of 4 areas of the CNS: periventricular cortical or juxtacortical infratentorial brain regions spinal cord	simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time **OR** a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI

Adapted from: Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162–73.

CNS – central nervous system; MRI – magnetic resonance imaging; MS – multiple sclerosis

Table VI. Diagnostic consensus for pediatric multiple sclerosis

Number of clinical CNS events with presumed inflammatory cause	1st clinical CNS event	Time gap	2nd clinical CNS event	MRI requirements
≥ 2	non-encephalopathic	≥ 30 days	non-encephalopathic	involving ≥1 area of the CNS
1	non-encephalopathic	-	-	**dissemination in space** **AND** 2nd MRI consistent with **dissemination in time**
≥ 2	ADEM	≥ 3 months	non-encephalopathic	new MRI lesions consistent with **dissemination in space**
1 (applies only to children ≥11 years old)	does not meet ADEM criteria	-	-	**dissemination in space** **AND** **dissemination in time**

Adapted from: Chou IJ, Whitehouse WP, Wang HS, Tanasescu R, Constantinescu CS. Diagnostic modalities in multiple sclerosis: perspectives in children. Biomed J. 2014;37(2):50–9.

ADEM – acute disseminated encephalomyelitis; CNS – central nervous system; MRI – magnetic resonance imaging

APPENDIX II

Diagnostic criteria for Neuromyelitis Optica Spectrum Disorder

Table VII. Diagnostic criteria for Neuromyelitis Optica Spectrum Disorder from the 2015 International Panel for Neuromyelitis Optica Diagnosis

NMOSD with AQP4-IgG	NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status
1. At least 1 core clinical characteristic **2.** Positive test for AQP4-IgG using best available detection method **3.** Exclusion of alternative diagnoses	**1.** At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all the following requirements: a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM or area postrema syndrome b. Dissemination in space (2 or more different core clinical characteristics) c. Fulfillment of additional MRI requirements, as applicable **2.** Negative tests for AQP4-IgG using best available detection method, or testing unavailable **3.** Exclusion of alternative diagnoses
Core clinical characteristics 1. Optic neuritis 2. Acute myelitis 3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting 4. Acute brainstem syndrome 5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions 6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions **Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status** 1. Acute optic neuritis: requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over >1/2 optic nerve length or involving optic chiasm 2. Acute myelitis: requires associated intramedullary MRI lesion extending over ≥3 contiguous segments (LETM) OR ≥3 contiguous segments of focal 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	

Adapted from: Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015;85(2):177–89

AQP4-IgG – antibodies against aquaporin-4; LETM – longitudinally extensive transverse myelitis; MRI – magnetic resonance imaging; NMOSD – neuromyelitis optica spectrum disorder