Pediatric multiple sclerosis and antibody-associated demyelination: clinical, imaging and biological considerations for diagnosis and care

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Abstract

The field of acquired central nervous system neuroimmune demyelination in children is transforming. Recent advances in assay development, refinement of diagnostic criteria, increased biological insights provided by advanced neuroimaging techniques, and level 1A evidence for therapeutic efficacy of biological agents are re-defining diagnosis and care. Three distinct neuroimmune conditions—multiple sclerosis (MS), anti-myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD) and anti-aquaporin-4 antibody neuromyelitis optica spectrum disorder (AQP4-NMOSD)—can now be distinguished, with human and animal model evidence supporting distinct pathobiological disease mechanisms. Development of highly effective therapies for adult-onset MS and NMOSD, with relapse rate suppression of greater than 90%, motivate advocacy for trials in children. However, clinical trials are challenged by the rarity of these conditions in the pediatric age group, necessitating new approaches to trial design including age-based trajectory modeling based on Phase 3 adult studies. Despite these

limitations, the future for children and adolescents living with MS, MOGAD or NMOSD is far brighter than in years past, and will be brighter still if successful therapies to promote remyelination, enhance neuroprotection, and remediate cognitive deficits can be further accelerated.

Introduction

[A: I have suggested moving the epidemiology to here to provide some initial context. OK?] The first attack of CNS demyelination in children (termed, acquired demyelinating syndromes (ADS)) represents the initial clinical presentation of multiple sclerosis (MS), anti- myelin oligodendrocyte glycoprotein associated disease (MOGAD), anti-AQP4 associated neuromyelitis optica spectrum disorder (AQP4-NMOSD), or can occur as a monophasic illness **[A: in adults or children, or both?]**. Global incidence of pediatric ADS is estimated as 0.87 (95% CI: 0.35–1.40) per 100,000 children per year [1]. Approximately 20% of children with ADS will be confirmed to have MS [2,3], although these pediatric-onset MS patients represent fewer than 5% of all MS patients [4]. Anti-MOG antibodies are detected in approximately 30% of children with ADS (50% of those presenting under the age 11 years)[5], while a diagnosis of AQP4-NMOSD is made in fewer than 5% of children with ADS [6,7]. In North American and European cohorts, approximately 60% of incident ADS patients will remain monophasic (30% of whom have anti-MOG antibodies at onset), and relapses almost never occur in patient who do not meet MS criteria and are seronegative for anti-MOG and anti-AQP4 antibodies [5,8].

In the past, pediatric demyelinating syndromes were classified based on a monophasic or relapsing course, with MS being the predominant diagnosis for relapsing cases. Over the last two decades **[A: How recently? Can you be more specific?]**, the recognition of disease entities characterized by the presence of circulating antibodies toward central nervous system (CNS) antigens, namely AQP4 and MOG, has led to a frameshift in diagnosis. These disorders share a neuroimmune biology and the risk for relapsing course, but the fundamental biological underpinnings and the optimal therapies differ.first pediatric clinical trials provided robust evidence on safety and efficacy of MS therapies in children, and insights into disease pathophysiology availed the development of high-efficacy treatments for NMOSD. While much remains unknown about the biological mechanisms behind MOGAD, data from retrospective studies guide the current considerations on the most appropriate management approach. **[A: In your abstract, you mention a shift in care of this disorders as well as diagnosis. Can you provide a brief introduction to the developments here to clarify for readers why this review is timely?]**

In this Review, we focus on the current knowledge on biological and clinical features of MS, MOGAD, and AQP4-NMOSD in children, and discuss latest diagnostic criteria and neuroimaging insights **[A: further details added to reflect your heading structure. OK?]**. We propose an investigational and management algorithm to guide pediatric providers navigating the expanding landscape of diagnostic and therapeutic opportunities. We emphasize the exciting reality of highly effective therapies for pediatric MS and AQP4-NMOSD, and the emerging guidelines for the management of MOGAD. We focus on recommendations based on level 1A evidence whenever available, then discuss evidence based on consensus guidelines, and provide

our recommendations for scenarios for which higher-level evidence are awaited **[A: is this an accurate description of your approach?]**. We end by highlighting future opportunities for collaborative research, the imperative of evidence- and safety-based therapies, and the next steps priorities for the advancements that will meaningfully alter the projected outcome of these diseases.

Clinical features in children

Incident acute neurological deficits referable to the localization of a demyelinating lesion are similar in MS, MOGAD and AQP4-NMOSD, and monophasic ADS. Qualitative differences between these three conditions are summarized in Table 1, and key pathology features are summarized in Panel 1.

Relapsing Remitting MS: Over 98% of children and adolescents diagnosed with MS experience a relapsing-remitting course. While a primary-progressive MS course, defined by progressive neurological impairment from disease onset, has been reported in pediatric cases, it is exceedingly rare in childhood, and a diagnosis of primary-progressive MS should only be considered after exhaustive search for alternative etiologies [4,9].

Compared to adults, children with MS experience a higher frequency of relapses in the first years after clinical onset (annualized relapse rate 1·13 vs 0·40 [10]), as well as larger number and volume of new T2 lesions on brain MRI [10,11]. Despite having a highly active inflammatory disease, the recovery from each clinical episode is often remarkable, and pediatric MS patients rarely develop permanent disability during childhood or adolescence [12]. Based on retrospective data accumulated largely prior to the advent of most MS therapies, the average time from first attack to development of progressive disability (secondary-progressive MS) is 20 years, with onset at 30-40 years of age [4,13]. The risk for secondary disease progression and disability accrual may be mitigated by current increasingly effective MS therapies.

While pediatric MS patients rarely experience permanent physical neurological impairment during childhood, fatigue, depression, and cognitive impairment do occur and have a negative impact on quality of life. Up to 30-50% of pediatric MS patients report that their fatigue interferes with enjoyable activities[14-16]. Elevated depression and anxiety scores are observed in approximately 25% of patients [16]. Cognitive impairment is more prevalent with increasing disease duration, and pediatric-onset MS patients are more likely to experience cognitive deficits in adulthood compared to adult-onset patients [17-20].

Monophasic and relapsing MOGAD: Many children with MOGAD will have only a single demyelinating attack. Two prospective incident cohorts from Canada and Spain demonstrated that 80-83% of children with anti-MOG antibodies at presentation (median age 6·2- 7·31 years) did not experience further attacks after an observation period of 3·5-6·9 years [5,21]. A greater likelihood of monophasic disease course was associated with younger age at presentation, a presenting phenotype of ADEM and conversion to seronegative status over time [5]. In relapsing patients, the median time to the second clinical attack is between 5 and 12 months [5,21,22]. In a pediatric cohort of 50 children with relapsing MOGAD who were not treated, 58% had only one

relapse over a median of 5 years [23]. Importantly, the inter-attack interval can be highly variable, and relapses can occur even decades after the initial events in childhood [24], suggesting that the true likelihood of relapses may be higher than appreciated in cohorts observed for brief periods of time.

Relapse severity is also variable, with most children with MOGAD recovering promptly and nearly completely from the presenting episode. A prospective study on 82 children with MOGAD followed from first clinical presentation found a median EDSS score at four years of follow-up of 0 (IQR 0-1) [5]. Similarly, in a Spanish study on 116 children with ADS or encephalitis positive for MOG antibodies, 78 experienced a complete neurological recovery, 21 improved markedly but did not return to entirely normal neurological function, 16 were left with moderate to severe neurological deficits, and one child died [21]. Poor outcome was predicted by recurrent ADEM-like attacks culminating in a leukodystrophy-like MRI pattern, or by cortical encephalitis with cerebral atrophy. In other case series, approximately 10% of MOGAD patients experienced an aggressive disease course characterized by multiple ADEM attacks, MRI findings of wide-spread leukodystrophy-like T2 bright lesions, and by progressive cognitive decline, cerebellar deficits and visual loss [23].

Relapsing AQP4-NMOSD: A relapsing disease course is observed in over 80% of children with AQP4-NMOSD [25-29]. Recovery from attacks can be poor, particularly with repeated attacks in the optic nerves and spinal cord. In adults with AQP4-NMOSD, only 25% of long-term disability was related to the onset attack, indicating the importance of prompt initiation of relapse-preventing therapies [30].

In a recent multicenter, multinational study of 67 children with AQP4-NMOSD [31], 29 (43·2%) children had EDSS scores of 3 or greater after a median of 4 years (IQR 2-10). Visual impairment was seen in 32 (47·8%) patients (20 of whom were registered blind), motor deficits were found in 14 (21·2%, of which 5 were wheelchair-bound and 2 used a walker) and cognitive impairment was detected in 17 (25·4%) patients. A more severe disease course was seen in non-whites with both shorter time to first relapse and higher EDSS at last follow-up. Optic neuritis at onset was associated with poor visual outcome (OR 8·67, 95% CI = 1·76-42·62, p=0·008) and a younger age at onset was associated with cognitive impairment (OR 0·79; 95% CI = 0·64-0·96, p=0·018).

Diagnosis and diagnostic criteria for pediatric MS, MOGAD and AQP4-NMOSD

Table 1 includes the current international diagnostic criteria for MS and AQP4-NMOSD. Formal criteria for MOGAD are under development, and at present, the diagnosis is largely based on the presence of positive antibody testing in the appropriate clinical context. Testing recommendations for anti-MOG and anti-AQP4 antibodies are summarized in Panel 2.

The international McDonald panel criteria for MS [32]notes the following caveats: (i) particular caution should be applied in children presenting before the age of 11 years, where the incidence of MS is particularly low; and (ii) the criteria should not be applied at the time of an incident attack with phenotype of ADEM. In children with ADEM presentation, a future diagnosis of MS must be supported by the occurrence of additional clinical attacks typical for MS.

With these caveats, the 2017 McDonald MS criteria perform well in the pediatric population, including in children younger than 12 years with non-ADEM presentation, with comparable sensitivity to adult-onset diagnostics, and high specificity [3,33,34]. The 2017 criteria re-emphasize the contribution of CSF oligoclonal bands (OCBs) to MS diagnosis, with has been affirmed in pediatric cohorts [3]. The increased ability to confirm an MS diagnosis at presentation has immediate implications for prompt initiation of disease modifying therapy (DMT).

Pediatric patients currently diagnosed with MS for whom clinical and MRI evolution strongly suggest MOGAD should be tested for anti-MOG antibodies. Children with typical MS features at onset and over time are highly unlikely to test positive for MOG antibodies [35].

The most recent criteria for NMOSD [36] provide guidance for children and adults with and without anti-AQP4 antibodies (Table). Of note, longitudinally extensive transverse myelitis (LETM) is not specific for NMOSD in children, and can be observed in pediatric MS, monophasic myelitis and monophasic ADEM [37].

Neuroimaging insights

Characteristic imaging features of MS, MOGAD and AQP4-NMOSD are illustrated in Figure 1.

Multifocal T2 hyperintense lesions, with a predilection for specific CNS locations (as outlined in Table 1 and Figure 1) is the hallmark of MS. The presence, at first attack, of T1 hypointense lesions, and persistence of these "black holes", assist in identifying children with MS, given that the presence of established focal tissue injury supports a chronic disease process [3]. Accrual of new and newly enlarging T2 lesions, some of which enhance after administration of gadolinium, provides MRI evidence of active disease. Despite the accrual of, on average, 9 new lesions within 6 months of onset [38], children demonstrate better recovery of T1 intensity in acute lesions as compared to adults with MS, as well as greater lesional repair capacity (as inferred by magnetization transfer imaging analyses), which is lost by adolescence [39,40].

Non-lesional brain tissue is also negatively impacted by MS, as demonstrated by abnormal diffusion tensor imaging (DTI) values (reflective of damage to fibre bundles and demyelination) in the normal-appearing white matter [41-44].

Pediatric MS patients show reduced brain and skull sizes compared to age- and sex-matched healthy children [45,46], already detectable at the time of clinical presentation [47]. Longitudinal studies demonstrate failure of age- and sex-expected rates of brain growth during childhood, failure to achieve maximal brain volumes, and development of atrophy during adolescence [45,47].

Focal cortical lesions are present in pediatric MS patients, and it remains to be determined whether pediatric-onset patients have the extensive subpial demyelination observed in adult-onset disease [48,49]. Gray matter structures, particularly the thalamus, demonstrate early and prominent impact in both adults and children [45,50]. Such disproportional thalamic involvement is likely to be at least in part secondary to the disruption of thalamic connections by focal white matter lesions[50]. However, an additional mechanism of damage, possibly involving the diffusion

of toxic soluble factor/s from CSF, is suggested by the recent finding of a 'surface-in' pattern of thalamic injury, more pronounced in proximity to the CSF interface observed in children with MS, but not in children with monophasic ADS [51]. Other brain regions, such as the hippocampus and the cerebellum, have been also reported as negatively impacted in children with MS [50,52,53].

The imaging features associated with MOGAD differ by the age at presentation and the associated clinical phenotype. Younger children and those presenting with ADEM typically manifest with large, ill-defined lesions involving both the gray and white matter, which can show dramatic resolution over follow-up [54 5]. In some cases, white matter lesions can converge into a "leukodystrophy-like" pattern [55]. Prominent cortical involvement can be observed, particularly in children with encephalitic features [21,56]. The involvement of the optic nerve, when present, is often longitudinally extensive, can be bilateral and associated with optic-disc swelling [5,57-60]. Spinal cord lesions can also be longitudinally extensive [58], may involve the conus, and in some cases demonstrate a predominant T2-hyperintensity of the gray matter which gives an H-shape appearance on axial views [61](Figure 1K).

Brain lesions are observed at presentation in over 30% of children with AQP4-NMOSD [25]. Lesions are often large (>2cm), and typically located in regions adjacent to the third and fourth ventricles, including diencephalon, hypothalamus and area postrema. Optic nerve lesions are often bilateral, longitudinally extensive and involving the posterior segments, including the optic chiasm [37]. Spinal cord lesions are also typically longitudinally extensive, mainly centrally located and often associated with spinal cord swelling. Characteristic spotty areas within lesions of T2-signal intensity equal to the surrounding CSF ("bright spotty lesions") can be observed (Figure 1 P) [62].

Treatment

Care of children with CNS demyelinating attacks require a comprehensive approach, led by providers experienced in the care of neuroimmune disorders, nursing expertise in medication education, social work support for children and their families, neuropsychologists to aid in the evaluation and management of cognitive and academic challenges, and psychologists and psychiatrists to address mood disorders. Healthy weight, vitamin D supplementation, avoidance of exposure to cigarette smoke, and physical activity are important facets of wellness that should be emphasized.

Management of an acute demyelinating attack: Management of an acute attack, whether an incident event or relapse, is fundamentally the same irrespective of whether the child has MS, MOGAD, AQP4-NMOSD, or is experiencing their sole attack of ADS.

The initial treatment is intended to rapidly decrease inflammation and promote symptom recovery. It typically consists of intravenous corticosteroids (30 mg/kg/day, maximum 1 g for 3–5 days). Recent trials in adults suggested that equivalent dose of oral corticosteroid might have similar efficacy of intravenous administrations, while improving the accessibility to treatment and the comfort of both patients and families [63]. Oral corticosteroid taper is controversial, and is often not required for children who have experienced marked recovery after the intravenous corticosteroid dosing. In a recent international survey, protracted (> 3 months) steroid treatment

following the first episode of MOGAD was endorsed by most adult neurologist but only a minority of pediatric providers, mainly due to concerns for metabolic complications [64].

Patients who fail to demonstrate prompt clinical improvement, or those for whom symptoms worsen despite corticosteroids may gain improvement with intravenous immunoglobulins (IVIG, total of 2 g/kg over 2-5 days), or plasma exchange (PLEX, typically 5-7 exchanges over 2 weeks). PLEX is preferred in the context of severe attacks, such as those in the brainstem or spinal cord [65,66], and showed superiority over corticosteroids in inducing recovery in adults with NMOSD [67]. In these circumstances, prompt initiation of PLEX treatment is of paramount importance, given the detrimental impact of treatment delays on clinical outcome [67]. A recent retrospective study on 65 children with severe demyelinating events, showed marked clinical improvement after PLEX in 72% of patients at the end of treatment, and in 88% at 6 months of follow-up [68].

Chronic Immunomodulation: Early initiation of immunomodulation is now considered the standard of care for children with MS, relapsing MOGAD and AQP4-NMOSD [69]. Treatment of pediatric MS focuses on prevention of relapses, as well as reducing the risk for secondary disease progression. The accumulation of disability in patients with MOGAD and AQP4-NMOSD is thought to be largely attack-related, making relapse prevention and adherence to treatment of utmost importance.

Supplementary Figure 1 outlines the timeline, approved doses (largely approved for adults) and summarizes the presumed mechanisms of action for currently available disease modifying therapies (DMTs) for MS and AQP4-NMOSD. Several recent comprehensive reviews of therapeutic strategies are available for pediatric MS [70,71] and AQP4-NMOSD [37], and while treatment reviews are not yet available for MOGAD, a recent international survey summarizes current considerations [64,72].

Most of the data contributing to these therapeutic reviews is based on case series and consensus, with very few clinical trials available to inform. A comprehensive review of the challenges and priorities for clinical trial efforts in pediatric MS has recently been published and is summarized in Panel 3 [69]. The key constructs apply also to relapsing MOGAD and AQP4-NMOSD.

Safety of Chronic Immunomodulation: Several general principles apply for DMTs, as modulation of the human immune system both acutely and over years poses risks for opportunistic infections and malignancy, and challenges the ability to effectively and safely vaccinate.

Varicella zoster (VZV) vaccination or evidence of immunity to VZV (history of clinical infection and positive serology) is required prior to initiating fingolimod, and hepatitis B vaccination is required for patients prescribed anti-CD20 therapy. Pneumococcal and meningococcal vaccinations are required for anti-C5b9 therapy specifically. In addition to mandatory vaccinations related to individuals DMTs, it is strongly advised to complete the full pediatric vaccination schedule prior to initiation of any chronic immunomodulation.

During active treatment, administration of inactivated vaccines is safe, but possibly less immunogenic. Administration of live and live-attenuated vaccines should be avoided in patients

receiving immunosuppressive therapies, while it can be considered after treatment discontinuation, following an interval from last treatment proportional to the half-life of the specific therapy [73] and documentation of immune cell repopulation, when indicated.

Patients on immunomodulatory therapies should receive the influenza vaccination annually, although vaccine responsiveness could be reduced [73]. Ensuring vaccination of their families will also reduce patient exposure risk. Vaccination against human papilloma virus is also encouraged for females and males.

Data on infection rates for individual therapies in pediatric demyelinating disease cohorts is limited, but extrapolation from adult data indicates an increased risk associated with most DMTs, which tends to be higher for newer agents as compared to injectable therapies [74]. A specific risk for progressive multifocal leukoencephalopathy (PML) has been reported following treatment with natalizumab, and less commonly for fingolimod, dimethyl fumarate and anti-CD20 therapy. Since only 10% of 10 years-old children and 50% of adolescents would test positive for remote JC virus infection [75], the use of these therapies carries lower risk of PML in pediatrics, provided periodic monitoring for seroconversion while on therapy. All patients should be screened for tuberculosis prior to commencement of immunosuppressive therapies.

Treatment of Pediatric Multiple Sclerosis: There are now more than 15 DMTs approved for adult-onset MS with only one therapy being formally approved for pediatric MS, based on Phase 3 clinical trial evidence (Supplementary Figure 1). Selection of DMTs is an individualized decision that balances therapeutic potency, time to reach maximal efficacy, putative mechanism of action, mode of delivery, and short and long-term safety and tolerability.

Injectable therapies: Conventional first-line options include injectable interferon-beta preparations and glatiramer acetate (GA). Case series support modest efficacy of interferons and GA, with overall favorable safety profiles. The BETAPAEDITRIC study, an open label observational study of 67 pediatric MS patients (median disease duration at onset of therapy 11 months) demonstrated a reduction in annualized relapse rate (ARR) from 2·4 (pre-treatment) to 1·6 on therapy, although 49% continued to experience relapses, 66% developed new T2 and 49% new gadolinium-enhancing lesions [76]. A retrospective study of 741 children demonstrated superiority of newer (oral and infusion) DMTs over interferon and GA in controlling disease activity, with reduction of ARR (rate ratio 0·45, 95% CI 0·29-0·70), of new/enlarging T2 lesions (HR 0·51, 0·36-0·72) and of gadolinium-enhancing lesions (HR 0·38, 0·23-0·63) [77].

Oral therapies: Five oral therapies have been approved for adult MS: fingolimod, dimethyl fumarate, teriflunimode, cladribine and siponimod (reviewed in [78]), with additional oral therapies with similar mechanisms in clinical trial.

In the phase 3, double blind, double dummy design PARADIGMS trial [79] 215 pediatric MS patients were randomized to either interferon-beta-1a or fingolimod (0·5 mg daily; 0·25 mg daily for patients < 40 kg). The study showed clear superiority of fingolimod on reducing relapse rate (0·12 vs 0·67, p<0·001), accumulation of brain MRI lesions (4·39 vs 9·27, p<0·001) and annualized rate of brain atrophy (-0·48% vs -0·80%, p=0·014) [79,80]. VZV infection has been specifically associated with fingolimod exposure in adults [81]. Although none of the children

recruited in the PARADIGMS trial developed VZV, other infections were reported in 3·7% of patients in the fingolimod arm *vs* 1·9% of patients on interferon beta-1a [79]. A small proportion (5·6%) of patients receiving fingolimod experienced seizures during the trial, and physicians should be aware of this potential complication.

An open label 6 months trial of dimethyl fumarate focused on pharmacokinetic analyses was completed in 2016, followed by a phase 2 open label comparator trial (FOCUS). The FOCUS trial consisted of an 8 weeks baseline and 24 weeks treatment period, with the primary endpoint being change in accrual of T2 lesions (mean 7·5 new T2 lesions during the 8 weeks pre-baseline and 2·5 new lesions in the final 8 weeks of the treatment period) [82].

A phase 3, placebo-controlled trial on Teriflunomide on 152 pediatric MS patients has recently reached completion and published data is awaited. Cladribine and siponimod have not yet been studied in pediatric MS.

Infusion based therapies: Infusion therapies include anti-CD20 (rituximab, ocrelizumab), anti-CD52 (alemtuzumab) and anti-alpha4 integrin (natalizumab) treatments.

Data from a Phase 2 dose-finding study of ocrelizumab (OPERETTA) in pediatric MS is not yet available. Case series have reported clinical efficacy and tolerability of rituximab in pediatric MS cohorts (reviewed in [83]). Protracted anti-CD20 therapies might be associated to development of hypogammaglobulinemia and a risk of infection [74,83].

Alemtuzumab is associated with risks for secondary autoimmunity including thyroiditis, thrombocytopenia, and hemophagocytic lymphohistiocytosis and there exists a black box warning against use in pediatrics.

Bone marrow transplant: Autologous hematopoietic stem cell transplantation (aHSCT) in adults with MS has shown dramatic reduction in relapse rate, although toxicity from the conditioning regimen has limited wide-spread adoption. The European Society for Bone and Marrow Transplant reviewed outcomes and safety of aHSCT in 21 pediatric MS patients from multiple centers [84]. Only one child required intensive care, infectious complications occurred in 4, and fever in a further 12 children. After a median of approximately three years, none of children deteriorated neurologically, only two experienced clinical relapses and one had evidence of new MRI activity.

Therapeutic recommendations for MOGAD: Currently, no consensus exists on the appropriate timing for initiation of chronic immunotherapy in patients with MOGAD, with the estimation of the risk/benefit ratio being challenged by the absence of reliable predictors of risk of relapses and long-term outcome. Given that a substantial proportion of children with MOG antibodies are likely to remain monophasic [2,5,21], most clinicians initiate chronic immunomotherapy only after a second event [64].

Data from the seven largest retrospective studies of treatments for relapsing MOGAD, revealed that at a median of 9-16 month, 16/23(70%) pediatric patients remained relapse free on monthly

IVIG; 16/31(51.6%) remained relapse free on mycophenolate mofetil (MMF); 14/32 (43.8%) remained relapse free on azathioprine and 18/38 (47.4%) remained relapse free on rituximab [23,85-89]. No benefit in relapse prevention was associated with the use of conventional MS treatments (interferon-beta and GA). Despite the reported efficacy of rituximab in a proportion of patients with MOGAD, there are now increasing reports of adult patients who continued to relapse despite B-cell depletion while on rituximab [85,90], with a recent multicenter/multinational study reporting circulating CD19+ B-cells suppressed to <1% of total lymphocytes at the time of 45/57 (78.9%) relapses [91]. Formal clinical trials are highly needed to ultimately define the most effective therapies and duration of treatment for relapsing MOGAD.

Treatment of NMOSD: The high risk of relapse in patients with AQP4-NMOSD, as well as the risk of residual disability associated with each clinical episode, dictate to initiate long-term relapse-preventing treatments after the first attack. With the rarity of the disease in pediatrics, treatment protocols are derived from international adult guidelines. Most commonly used treatments, such as azathioprine, MMF and rituximab have not been formerly approved for NMOSD and rated as class IV by the American Academy of Neurology. In a recent study of 67 children from 13 European centers and one center in Brazil [31], AZA, MMF and rituximab reduced relapses, with rituximab associating with the lowest annualized relapse rate. The benefit of early treatment with rituximab, is also supported by retrospective pediatric studies (class IV evidence)[92]. Patients treated with rituximab are more likely to relapse if B-cells repopulation occurs, emphasizing careful monitoring of B cell counts and timing of infusions [90,92].

Recently, unprecedented advancements in the therapeutic strategies for NMOSD have been made possible by improved understanding of the role of complement activation, interleukin-6 receptor signaling, and of CD19-positive B cells. In a randomized double-blind trial of Eculizumab compared to placebo (as add-on therapies to standard treatment), only 3/96 patients exposed to eculizumab experienced a relapse, compared to 20/47 patients in the placebo group ($p<0{\cdot}001$) [93]. One patient treated with Eculizumab died of a pulmonary complication. In N-Momentum, a randomized 2:1 trial of inebilizumab compared to placebo, clear superiority of inebilizumab (21/172 treated experienced relapses compared to 22/56 in the placebo group) led to early study closure [94]. Finally, in a double-blind placebo-controlled study of 41 patients treated with satralizumab and 42 placebo controls, relapse reduction favored satralizumab [95]. Importantly, these studies were either conducted exclusively in AQP4-IgG positive NMOSD (eculizumab) or showed significant disease suppression primarily in AQP4-IgG positive participants (satralizumab and inebilizumab). Enrolment of patients age less than 18 years occurred in the satralizumab trial and may be considered in future trials.

In Figure 2, we propose an algorithm to aide in the diagnosis and management of children presenting with the first clinical episode of ADS.

Conclusions and future directions

Diagnosing pediatric MS, MOGAD and AQP4-NMOSD is now more accurately conferred owing to improved diagnostic criteria and high-quality assays for antibody detection. With increased diagnostic certainly, a fuller appreciation of the breadth of clinical expression of these

diseases has emerged and evidence-based treatment options are expanding. There remain, however, many unmet needs.

MS, MOGAD and AQP4-NMOSD are only three of the many neuroimmune disorders (reviewed in [96]). The development of assays to detect immune responses to other CNS antigens, peripheral blood interrogation to define disease-specific circulating immune responses, CSF analyses capable of defining intracerebral immune signatures, and more advanced MRI techniques may aid in identification of as yet unrecognized neuroimmune diseases.

A key unmet need is to define the determinants of the inter-subject variability in disease course, response to treatment and outcome observed within MS, MOGAD and AQP4-NMOSD populations. Race, sex, genetic variability in immune regulation, medication metabolism, mitochondrial bioenergetics, gut microbiome composition, prior infections, nutritional status and social determinants of health, are all important considerations. **[A: figure 1 is very complicated and little context was provided for the figure citation in the epidemiology section. I suggest moving the figure citation here to illustrate your conclusions and moving the figure to the appendix] Supplementary** Figure 2 summarizes putative genetic and environmental factors implicated in MS, MOGAD and AQP4-NMOSD, and illustrates our current understanding of the typical clinical and radiological trajectories.

Can personalized medicine, or even just improved access and prompt initiation of DMTs mitigate the risk for secondary-progressive MS reported in untreated pediatric MS populations of the past? [13] Is relapsing MOGAD ultimately a self-limited illness, in some or all patients? Will the therapeutic advances in AQP4-NMOSD translate safely and effectively to children? With the escalating growth of insights into the mechanisms behind neuro-inflammatory diseases and the accelerated pace of drug discovery, the next years hold promise for answers to many of these questions.

Declaration of interests:
G.F. has no relevant conflict of interest.
T.A. received speaker honoraria from Novartis and Biogen, and travel expenses for scientific meeting participation from Roche.
Y.H. has no relevant conflict of interest.
T.C. serves as a consultant to Novartis, Sanofi Genzyme and Genentech-Roche. Dr. Chitnis serves on clinical trial advisory boards for Novartis and Sanofi Genzyme. Dr. Chitnis receives grant funding from Novartis, Mallinckrodt, National Multiple Sclerosis Society, National Institutes of Health, and the Department of Defense.
B.B. serves as a consultant to Novartis, UCB pharmaceuticals and Roche. Dr. Banwell serves as a non-remunerated advisor on clinical trial safety for Novartis, Biogen, Teva Neuroscience and Genentech. Dr. Banwell receives grant funding from the National Multiple Sclerosis Society, National Institutes of Health, and the Canadian Multiple Sclerosis Society.

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in in the writing of the report or in the decision to submit the paper for publication. **[A: is this addition accurate?]**

Authors contributions:
GF and BB designed and wrote the core content of the manuscript and reviewed all referenced articles. TA, YH, TC contributed to content and edited the final manuscript.

Search strategy and selection criteria:
Publications in English were identified by searches of PubMed (January 1, 1975 to May 30, 2020; with a prioritization for publications from 2015 to 2020 and inclusion of older material if seminal to the field) and review of their respective bibliographies. Search terms used were "multiple sclerosis", "myelin oligodendrocyte glycoprotein", "acute disseminated encephalomyelitis", "optic neuritis", "transverse myelitis", or "demyelinating diseases" and combined with "children" or "pediatric" or "paediatric" or "adolescent." Single case reports and data only published in abstract form were excluded. The final reference list was generated on the basis of relevance to the topics covered in this Review.

References **[A: if additional references are added to this list from the table, please remove some. Ideally we need to aim for no more than 100 references, but we certainly cannot exceed 120 Hacohen]**

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Panel 1: Key Pathological Findings in MS, MOGAD and AQP4-NMOSD[1]

MS [97]:

- Focal areas of confluent demyelination, inflammation, and glial reaction, often with inflammation centered around a vein
- Predominant CD8+ T-cells infiltration
- Extensive axonal injury in acute lesions, with axonal demyelination and transection
- Frequent cortical involvement, including focal leukocortical and intracortical lesions, as well as subpial demyelination that can be extensive (adult studies [98])

MOGAD [99]:

- Coexistence of both peri-venous and confluent white matter demyelination
- Predominant CD4+ T-cells and granulocyte infiltration, complement deposition within lesions
- Relative axonal preservation
- Frequent cortical involvement, predominantly intracortical, with subpial demyelination also reported

AQP4-NMOSD [100]:

- Extensive loss of immunoreactivity for astrocytic proteins, extending beyond areas of demyelination
- Perivascular deposition of immunoglobulins and activation of complement
- Perivascular and parenchymal eosinophils and neutrophils infiltrates; axonal loss, necrosis, and cavitation in destructive regions
- Absence of cortical demyelination

[1]Most data on pathology features of these three disorders described in the panel are results of studies conducted mainly or exclusively in adult patients.

Panel 2: Key laboratory investigations for acquired demyelinating syndromes

Assay selection

The testing of anti-MOG and anti-AQP4 antibodies should be performed with cell-based assays (CBA)[101,102]. To assess the presence of anti-MOG antibodies, assays should use the full-length human MOG as target antigen. Although Fc- or IgG1- specific secondary antibodies were initially considered to provide greater specificity in MOGAD, a recent multicenter study showed

comparable results for assays applying anti-IgG(H+L), anti-IgG1 and anti-IgG-Fc secondary antibodies [103,104]. Live immunofluorescence CBA (CBA-IF) and flow cytometry CBA have been showed similar sensitivity and specificity results, and although the threshold for positivity varies according to the specific assay, the most commonly used live MOG-IgG CBAs show high level of agreement for high positive and negative samples [104]. Nonetheless, inter-assay agreement is variable in the context of low MOG-IgG titers, and false positive may occur in this context. Importantly, commercially available assays employing fixed-cells are subject to higher risk of false positive and negative anti-MOG antibodies results compared to live cell-based assays [102,104,105].

An additional key investigation for children with ADS is the CSF analysis for oligoclonal bands (OCBs). Intrathecal immunoglobulin synthesis is supported by the presence of two or more OCBs not observed in the corresponding serum sample run simultaneously.

Specimen selection

Serum should be the specimen of choice for testing the presence of both anti-MOG and anti-AQP4 antibodies, given greater sensitivity compared to CSF [103,106]. When detected in CSF, antibodies are usually found at lower concentration, suggesting a peripheral origin. Rarely, MOG antibodies are detected exclusively in the CSF [21,107], but the clinical implications of this finding is still unclear.

Role of antibody titres

Anti-MOG antibodies: antibody titres are higher in proximity to a clinical attack and decrease during remission [2,5,108]. The initial titres of serum anti-MOG antibody have poor utility in predicting the likelihood of clinical relapses or relapse severity, but can be of diagnostic relevance, since low titers of MOG antibodies (i.e. ≥1:160-1:1,280 by CBA-IF) have been occasionally detected pediatric patients with typical MS, while detection of high anti-MOG titres (i.e. ≥1:1,280 by CBA-IF) strongly pleads against an MS diagnosis [2,5,21,105].

Anti-AQP4 antibodies: although some studies reported increase of anti-AQP4 antibody titres in proximity to clinical attacks [109], anti-AQP4 antibody titres have low utility in predicting relapses, relapse severity, or disability (class II evidence)[109-112].

Test timing and longitudinal serological evaluation

Anti-MOG antibodies: whenever possible, anti-MOG serology should be obtained in proximity to a clinical episode, since up to 50% of children initially positive for anti-MOG antibodies convert to seronegative status after a median of 12 months [5]. Younger patients, and those presenting with ADEM, have greater likelihood of becoming seronegative over time. Therefore, in the presence of a suggestive clinical phenotype and delayed serological evaluation, the possibility of MOGAD can still be considered in patients with negative anti-MOG antibody results, and testing should be repeated in proximity to any subsequent attack. The detection of conversion to MOG-antibody seronegative status can have some prognostic value, as patients who become seronegative are on average less likely to develop relapses than those who remain seropositive [5,21,22]. Nonetheless, many patients will remain monophasic despite persistent

seropositivity, and conversion to anti-MOG antibody negative status can be transient, not entirely excluding the possibility of further clinical attacks [5,8].

Anti-AQP4 antibodies: in contrast to anti-MOG antibodies, anti-AQP4 antibodies remain detectable over time in most patients, including those who received immunotherapy [110,113]. Although conversion to seronegative status has been reported in some cases, it is unclear if these patients are less likely to experience further attacks [110,113]

Impact of treatment on antibody titres: The frequency of anti-MOG or anti-AQP4 antibodies in the general population is extremely low, and thus treatment with intravenous immunoglobulins is unlikely to result in false positive results. Conversely, the possibility of detecting exogenous anti-JC virus antibodies after intravenous immunoglobulins treatment should be considered in the risk-stratification for treatment with Natalizumab. Since treatment with plasma-exchange would remove circulating antibodies, any serology testing in close proximity to apheresis could potentially lead to false negative antibody results.

Panel 3: Challenges facing clinical trial design and implementation in pediatric MS, relapsing MOGAD and AQP4-NMOSD

- **Diseases rarity**: given the low incidence and prevalence of pediatric demyelinating syndromes, clinical trial recruitment invariably requires numerous participating sites across multiple countries. Clinical trial initiation across such a broad network is inherently beholden to multisite institutional ethics approvals, which are often less facile than in adult centers more familiar with clinical trials in these diseases. The PARADIGMS trial, for example, required 87 centers in 26 countries to screen 348 children and enroll 215 eligible participants [79]. Seven centers were unable to enroll a single patient, and most centers enrolled fewer than 10 children- posing fiscal challenges for the study sponsor and remunerative challenges for single sites.
- **Diseases impact:** pediatric MS is associated with high relapse rate and early brain atrophy, AQP4-NMOSD with risk for relapse-related disability, and MOGAD with highly variable severity of relapses and unknown long-term chronicity. These critically important variables must be balanced against treatment benefit and risk. For pediatric MS, clinical trial designs that compare a DMT shown efficacy for adult-onset disease to placebo does not currently meet the standard of equipoise, even though such design has the highest power to prove efficacy in the smallest sample size. For MOGAD, should trials enroll patients at first attack, or only after clear evidence of relapsing disease and for what treatment duration? In AQP4-NMOSD, given the high risk for morbidity and early blindness, is it ethical to delay access (as will be inherent if formal trials for this rare disease are mandated) to new therapies proven to markedly improve outcome in adult NMOSD?
- **Long term Safety:** children and adolescents diagnosed with MS and AQP4-NMOSD are likely to require DMT treatment for decades, posing the need for evaluation of the long-term risks of DMT exposure, particularly when initiated during developmental ages. Identifying such risks requires data collection through childhood and into adulthood, spanning pediatric and adult health care systems, and requires vigilance for toxicities

reasonably expected (infection risks, malignancy) but also unexpected. Phase 4 extension of all clinical trials will provide several years of rigorous safety and clinical data, but establishing registries for decades of data is what is truly required.

- **Impact of clinical trial participation:** participation of children in clinical trials requires absenteeism from school, parental leaves from work, sibling care considerations, and surrogate consent from parents worried about whether they are making the best choice for their child. Clinical trial protocols that minimize in person visits, utilize video-based visits, streamline laboratory, imaging and in person visits, and provide financial recompense for families are essential.
- **Sustained access to effective therapies and care:** all clinical trials should be required to provide participants access to the proven new therapy in perpetuity. After a new therapy is proven effective in pediatric patients, advocacy is essential to ensure that the treatment is approved by regulatory authorities. Advocacy must also address the annual cost of therapy, which can vary widely between different countries. Advocacy efforts through the Multiple Sclerosis International Federation, petitions to the World Health Organization's essential medicines list, and efforts of national MS societies are underway to increase access to effective treatments for children worldwide.

Figure legends:

Figure 1: Characteristic imaging features of MS, MOGAD and NMOSD
Typical MS features (top panel): ovoid T2 bright lesions perpendicular to the major axis of the corpus callosum ("Dawson's fingers", A); areas of T1 hypointensity corresponding to hyperintense lesions in T2 weighted images ("black holes", B); focal well-defined pontine lesion adjacent the CSF interface (C); short lesion mainly involving the posterior columns of the spinal cord (D-E); short lesion in the anterior portion of the left optic nerve (F).
Common imaging features of MOGAD (middle panel): large ill-defined lesions in the supra- and infra-tentorial white matter, with bilateral involvement of the middle cerebellar peduncles (G-H); confluent white matter lesions configuring a "leukodystrophy-like" pattern (I); bilateral hyperintensity of the cortical grey matter on T2 weighted images (J); spinal cord lesion with prominent grey matter involvement ("H sign", K); although this finding has been reported mainly in adults, it is also present in children (Authors' experience); longitudinally extensive left optic nerve lesion (L).
Typical MRI features of AQP4-NMOSD (bottom panel): T2 hyperintense lesions involving the diencephalon (M) and area postrema (N). Longitudinally extensive transverse myelitis (LETM, involving more than three consecutive vertebral segments) associated with spinal cord swelling (O). Spotty area of strong hyperintensity on corresponding axial T2 weighted images ("bright spotty lesions", P); posterior optic nerve lesion with involvement of the optic chiasm (Q-R, images kindly provided by Dr. Cesar Augusto P. Alves).

Figure 2: Proposed diagnostic and therapeutic algorithm for pediatric ADS

Key investigations for the evaluation of children with ADS include acquisition of AQP4-IgG and MOG-IgG serology, brain and spinal cord MRI, and evaluation of CSF OCBs. The results of paraclinical exams (particularly antibody testing) should be interpreted in the context of the associated clinical profile.

If AQP4-IgG are detected and diagnostic criteria for AQP4+ NMOSD **[A: for AQP4+ NMOSD?]** are met, prompt initiation of chronic immunotherapy is recommended.

If MOG-IgG antibodies are detected in the context of a clinical profile suggestive for MOGAD, a diagnosis of MOGAD can be conferred. At least 50-70% of children with MOG antibodies will experience a monophasic disease course, which argues against initiation of chronic immunomodulatory therapy at onset. Children with a severe first attack, with residual visual loss or spinal cord insult, may be offered immunotherapy at onset given that a second attack could result in blindness or marked impairment in motor, sensory or bladder function. In all patients, longitudinal clinical monitoring is recommended. Repeat measurements of antibody titres at 6-12 months can be of certain utility in estimating the future risk of relapses (with patients becoming seronegative being less likely to experience relapses), although with important limitations (see Panel 2). Chronic immunotherapy is commonly initiated in children who experience a second attack. The optimal duration of chronic immunotherapy in MOGAD is unknown, as it remains to be determined whether MOGAD is a life-long disease.

In seronegative patients, clinical and imaging features guide the distinction between MS, NMOSD or ADEM. If the clinical and imaging profile is suggestive for MS and diagnostic criteria are met at baseline, therapy with MS DMT should be promptly initiated. If criteria are not fulfilled at baseline, close clinical and MRI monitoring should be performed to enable detection of clinical or MRI evidence for dissemination in space and time of disease activity, which will confirm the diagnosis of MS.

For children meeting diagnostic criteria for ADEM (polyfocal deficits and encephalopathy), and who are seronegative for MOG and AQP4, the likelihood of monophasic course is high (>90%) provided that new deficits that arise within 90 days of onset are considered as part of the inciting event, and chronic immunomodulatory therapy is not advised. Longitudinal clinical observation, and annual MRI scans to confirm absence of new lesions and resolution of initial T2 bright lesions is advised. Serial imaging once imaging has returned to normal, particularly in young children with ADEM and who are negative for MOG antibodies has low yield given the very low risk for further relapses and can reasonably be deferred.. In children who experience new relapses >90 days post onset, it is appropriate to re-evaluate MOG-IgG and AQP4-IgG antibodies (although if serologies were negative when tested in close proximity to the incident attack, it would be rare to detect antibodies later in the disease course of MOGAD or AQP4-NMOSD), and to consider application of MS diagnostic criteria (if the relapse is a non-ADEM event).

[A: would it be more logical to swap the flow diagram for ADEM presentation with that of seronegative NMOSD in the figure to match the order discussed in the legend?] Similar considerations for withholding chronic immunotherapy until evidence of clinical relapses, and re-evaluation of serology at the time of new clinical attacks, apply to children who meet criteria

for seronegative-NMOSD or who do not fall in any of the previous categories. In consideration of paucity of data to guide treatment recommendations, the final decision on the management of these patients is left to discretion of the treating physicians.

For all patients, diagnoses in the differential of ADS must always be excluded and should be re-evaluated when clinical, laboratory or MRI features at onset or over time diverge from features expected for MS, MOGAD or AQP4-NMOSD.

[1]A dedicated orbital MRI should be acquired in patients with features of optic neuritis.
[2]Caution should be used in the interpretation of low MOG-IgG titres, as false positives can occur. Patients with clinical, laboratory and imaging features typical for MS in whom low titre of MOG-IgG antibodies are detected, should be diagnosed with MS.
[3] MS diagnostic criteria should not be applied at presentation in children with an ADEM phenotype. Application of 2017 McDonald criteria in these children require a subsequent non-ADEM attack (>90 days from incident ADEM), as well as MRI features typical of MS.
[4]Additional MRI requirements in support of a diagnosis of seronegative NMOSD are: optic neuritis associated with a) normal brain MRI or only nonspecific white matter lesions, or b) T2-hyperintense or T1 gadolinium-enhancing optic nerve lesion extending for >1/2 of optic nerve length or involving optic chiasm; myelitis with a) MRI lesion extending at least 3 contiguous segments, or b) focal spinal cord atrophy extending at least 3 contiguous segments in patients with history compatible with transverse myelitis. Area postrema syndrome: T2-hyperintense lesion in area postrema/dorsal medulla. Brainstem syndrome: periependymal brainstem T2-hyperintense lesion.

[A: please ensure abbreviations are clearly defined] ADS=acquired demyelinating syndrome; OCBs=oligoclonal bands; ON=Optic Neuritis; TM=Transverse Myelitis; AQP4= anti-aquaporin-4 antibody; NMOSD= neuromyelitis optica spectrum disorder; MOG= anti-myelin oligodendrocyte glycoprotein antibody; ADEM=Acute Disseminated Encephalomyelitis; DIS=Dissemination in Space; DIT=Dissemination in Time; LETM=longitudinally extensive transverse myelitis; DMT=disease modifying therapy; MS=multiple sclerosis.