Paediatric multiple sclerosis: What it is and what it is not

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What this paper adds

1. **We discuss advances in the diagnosis of MS, highlighting changes to the 2017 revised diagnostic criteria, and advances in our knowledge of antibody-mediated demyelination and the classification of relapsing demyelinating syndromes.**

2. **We compare current and evolving concepts in the approach to the treatment of paediatric MS and summarise important areas of focus for research in order to further improve long-term outcomes for patients with paediatric-onset MS.**

Abstract

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system of autoimmune origin. Demyelination of the brain, optic nerves and spinal cord causes permanent mental and physical disability. The diagnosis of MS in children, as in adults, requires evidence of dissemination of inflammatory activity in more than one central nervous system (CNS) location (i.e., dissemination in space (DIS)) and recurrent disease over time (i.e. dissemination in time (DIT)). When compared at onset, those diagnosed with MS are more likely to have one or more brain lesions, positive oligoclonal bands, have evidence of remote EBV infection and lower levels of Vitamin D as compared to children with monophasic illness.

The identification of myelin oligodendrocyte glycoprotein and aquaporin-4 antibodies and subsequent discovery of their pathogenic mechanisms has led to a paradigm shift in the classification of relapsing demyelinating syndromes. This is reflected in the 2017 revised diagnostic criteria which emphasises the exclusion of MS mimics and aims to enable earlier diagnosis and thus treatment initiation.

The long-term efficacy of individual therapies is hard to evaluate due to small patients numbers and to the relatively high number of patients who switch therapy. Nevertheless, an improvement in prognosis with a globally reduced annual relapse rate is observed compared to pre-treatment era. Given the higher relapse rate and concerning cognitive outcomes in children, there is a question whether more rapid escalation or even using more potent agents earlier should be used in children while considering short and long-term safety profile of these drugs. With the results of the first randomised controlled trial of Fingolimod versus Interferon Beta-1a in paediatric MS published this year and several clinical trials underway there is hope for further progress in the field of paediatric MS.

Introduction

Acquired demyelinating syndromes (ADS) represent acute neurological illnesses characterized by deficits persisting for at least 24 hours and involving the optic nerve, brain or spinal cord, associated with regional areas of increased T2 signal on conventional MRI. Clinical manifestations may be localized to a single CNS site or may be polyfocal. Only 15-46% of children presenting with ADS will be diagnosed with multiple sclerosis (MS)at 5 years[1]. The incidence of paediatric MS range between 0.13-0.66 per 100,000 children per year[1] and up to 10% of all patients with MS have their first demyelinating attack before the age of 18 years[2, 3]. Almost all children progress to a second clinical attack and thus clinically definite MS (RRMS)[1].

The diagnosis of MS requires evidence of dissemination of CNS inflammatory activity distributed in more than one CNS location (dissemination in space, DIS) and over time (dissemination in time, DIT). As new treatment options emerge, the impetus for earlier diagnosis of MS has led to key changes in the diagnostic criteria to gradually be reliant on less stringent imaging criteria and more recently the re-introduction of intrathecal oligoclonal bands as evidence of chronicity of inflammation and hence surrogate evidence for dissemination in time[4]. Additionally, there is a greater emphasis placed on the earlier exclusion of MS mimics to avoid misdiagnosis. Recently, the improved understanding of antibody-mediated demyelination has led to a paradigm shift in the classification of relapsing demyelinating syndromes[5], the importance of which is underlined by recent studies which demonstrate the need for different first-line treatments in myelin oligodendrocyte glycoprotein antibody (MOG-Ab) associated disease compared to MS[6].

The approach to the treatment of MS is also rapidly evolving. A new therapeutic aim of 'no evidence of disease activity (NEDA)', predominantly on neuroimaging, is replacing more conventional targets of utilising relapses and progression of disability to direct disease modifying treatment. Furthermore, the traditional strategy of escalation therapy is being challenged by that of induction therapy[7]. There is increasing promise for paediatric patients with MS; several clinical safety and efficacy trials have been undertaken which may guide the future direction of MS management. An international registry would aid research in this area which is often hindered by small patient numbers. Patient-reported outcomes are being increasingly incorporated.

In this Review, we provide an update on paediatric MS and highlight areas of research that are key priorities for improving clinical management. We outline the clinical features of MS and its mimics, mainly the antibody-mediated disorders, the current approaches to treatment and new approaches in development. We then consider the pathological features, including biomarkers, pathological mechanisms and genetics of MS. Future areas of research are also discussed.

Paediatric relapsing demyelinating syndromes: MS or not MS?

The incidence of ADS is between 0.5 to 1.66 per 100,000 children[1]. A focal or multifocal ADS is the first presentation of MS in 15-45% of children[8-10]. Unlike in adult populations, the majority of paediatric patients who present with an ADS have a monophasic disease and even of those who relapse, approximately 40% have a non-MS course[5, 11]. In a large Canadian cohort of children with ADS, those diagnosed with MS were 38 times more likely to have one or more brain lesions as compared to children with monophasic illness; 45 times more likely if they also had cerebrospinal fluid (CSF) oligoclonal antibodies (OCBs) and 3.3 times more likely to have remote EBV infection as compared to children with monophasic illness. Children with vitamin D sufficiency were 66% less likely to be diagnosed with MS[9].

It is important to exclude both inflammatory and non-inflammatory mimics. The most common differential diagnoses are: the antibody-mediated disorders (MOG and AQP4 antibodies); acute CNS infection (as can be seen in Epstein-Barr Virus, Mycoplasma, enteroviruses); inherited leukodystrophies[12] (including Alexander's disease, mitochondrial cytopathies, metachromatic leukodystrophy) and inflammatory vasculopathies (including systemic lupus erythematosus, primary CNS vasculitis, neurosarcoidosis). Some of the genetic disorders may also follow a relapsing disease course, and share features of brain inflammation such as contrast enhancement, intrathecal oligoclonal bands and an acute response to steroids[13].

The discovery of AQP4-Ab in patients with neuromyelitis optica spectrum disorders (NMOSD) who were previously thought to have opticospinal MS has increased our understanding of the role of antibodies in specific demyelinating syndromes. In clinical practise the identification of these antibodies has led to earlier diagnosis and initiation of specific treatment for this patient cohort. AQP4-Ab are rare in children occurring in 0.7%[9] to 4.5%[14] of children with an ADS.

A key recent development has been the characterisation of MOG-Ab associated demyelination. MOG-Ab are present in one third of children who present with an ADS and approximately half of MOG-Ab patients have a relapsing disease course[15]. Time to relapse is variable and may occur over 10yrs from first presentation. Although initially reported in patients with NMOSD (in both adults[19, 20] and children[21]) or limited forms of the disease such as recurrent idiopathic optic neuritis (RION)[17], these antibodies have been identified in nearly all children with multiphasic disseminated encephalomyelitis (MDEM)[16] and ADEM-ON[18] (ADEM followed by ON). Younger children more typically present with more supratentorial brain lesions, whereas older children and adults more commonly present with optic neuritis. MOG-Ab patients are less likely than MS patients to have intrathecal oligoclonal bands and CSF pleocytosis[5, 11]. Of note, many patients originally diagnosed with paediatric MS have been re-classified as MOG-associated demyelination in recent years. This is an important consideration when

reviewing the literature. MOG-Ab associated demyelination does not respond to first line disease-modifying therapies used in paediatric MS (interferon beta and glatiramer acetate), however azathioprine, mycophenolate mofetil, rituximab and intravenous immunoglobulin have been associated with a reduction in relapse frequency to different extents or degrees[6].

In a recent paper, we have proposed four main relapsing acquired demyelinating syndromes (RDS); multiple sclerosis, AQP4 Ab-associated disease, MOG Ab-associated disease and antibody-negative RDS[5]. In this retrospective study, 98.4% of MS patients had an abnormal MRI with T2-hyperintense lesions at onset; a neuroradiologist blinded to the clinical features and antibody status of each case correctly classifed 93.6% of MS cases and 100% of non-MS cases. All MS patients had evidence of remote EBV infection and 94.6% had CSF OCBs. ADEM presentations were only seen in the non-MS group. All MS patients with spinal involvement had short segment myelitis, whereas longitudinally-extensive transverse myelitis (>3 spinal cord segements) was only seen in the non-MS RDS group. A reason for the MS phenotype seen in this childhood cohort, which resembles significantly the typical phenotype of adult MS, when compared to previous paediatric cohorts, may be the distinction of MOG Ab-associated disease from the MS group (no patients with MOG-Ab were diagnosed with MS). Previous studies have shown that 6%-29% of children initially diagnosed with ADEM progress to a diagnosis of MS[2, 9]. These studies also reported atypical MRI findings such as widespread white matter involvement, increased frequency of longitudinally-extensive transverse myelitis and a lower frequency of intra-thecal OCBs compared to adults[1]; features that are now known to be typical of the MOG Ab-associated disease.

Paediatric MS: Current diagnostics

The diagnosis of MS is dependent on evidence of dissemination of inflammatory activity in more than one CNS location (i.e. dissemination in space (DIS) and recurrent disease over time (i.e. dissemination in time (DIT)) This can be solely based on 2 clinical attacks, each lasting greater than 24hrs and more than 30days apart, however confirmatory MRI is usually a key part of the diagnostic process. Furthermore, the criteria includes the exclusion of alternative diagnoses for which an MRI is crucial. Dissemination in space (DIS) can be demonstrated by one or more T2 lesions that are characteristic for MS in at least 2 of the following areas: periventricular; juxtacortical or cortical; infratentorial; spinal cord. Dissemination in time (DIT) can be demonstrated by the simultaneous presence of gadolinium-enhancing and non-enhancing lesions on a single MRI scan, or by a new T2 and/or gadolinium-enhancing lesion on a follow-up scan.

The McDonald 2010 criteria enable(d) a diagnosis of MS in children over the age of 11 years presenting with a CIS and evidence of DIS and DIT on MRI, provided that the clinical presentation did

not meet the criteria for ADEM[22]. Changes in the revised McDonald 2017 criteria include: (i) the presence of intrathecal OCBs to substitute for DIT in patients presenting with a typical CIS who fulfil the requirements for DIS; (ii) the inclusion of a symptomatic lesion as evidence of DIS or DIT; and (iii) the inclusion of cortical grey matter lesions in DIS, now considered in combination with juxtacortical lesions[4]. The 2017 criteria also highlight the requirement for exclusion of alternative diagnoses and the fact that the criteria should only be applied to patients with typical CIS.

Inclusion of the spinal cord MRI as a routine part of the diagnostic MS work-up may lead to an even higher sensitivity[23] and should be considered and prospectively evaluated. Spinal cord lesions occur preferentially in the cervical region and therefore this is the area with the greatest diagnostic yield[24].

Clinical features and disease course: does the age matter?

Of those presenting with MS before the age of 18, almost all (95-100%) will have relapsing remitting MS (RRMS)[2, 25, 26]. Presentation with progressive neurological symptoms and signs in children and adolescents, should prompt evaluation for an alternative underlying diagnosis, such as hereditary spastic paraparesis, some forms of which may have white matter involvement, or other inherited white matter disorders[27]; on the contrary, the same presentation in adults would be consistent with a diagnosis of primary progressive MS in adults.

There are 2 important considerations which should be kept in mind when discussing the presenting clinical features of paediatric MS. Firstly, the questionable ability of young children to articulate mild sensory or visual deficits. Secondly, previous studies of paediatric MS may have included patients with antibody-positive relapsing demyelinating conditions, which are now recognised as separate clinical entities to MS.

Paediatric MS can present with features similar to those seen in adults; optic neuritis, transverse myelitis, sensory loss, bladder dysfunction. However, cerebellar and brainstem presentations are more common than in adults. Approximately half to two-thirds of paediatric patients overall present with a polysymptomatic presentation[26]. The most common symptoms are sensory; cerebellar; visual; brainstem; pyramidal[28]. Characteristic radiological features are illustrated in **Figure 1**.

Pre-pubertal presentation of MS is less common and is estimated to account for approximately 20%-30% of paediatric MS[29]. The female to male ratio is almost equal in pre-pubertal onset MS in comparison to post-puberty, when it increases to approximately 2:1[30].

Paediatric MS generally has a higher relapse rate in the early years following diagnosis compared to adult cohorts and there is a shorter interval between the incident attack and a second demyelinating

event[31]. These findings were not affected by time spent on disease modifying treatments. When age at onset was treated as a continuous variable, it correlated with relapse rate. A recent German study reported that 41.6% of patients with paediatric onset MS fulfilled criteria for highly active disease[32]. There was no correlation between disease activity and sex or age at presentation. Lesion load at first MRI, and disease activity in the first year, can be suggestive of an highly active disease, and thus aid patient selection for the most effective therapies.

Despite highly active disease, particularly in the initial years, patients with paediatric-onset MS demonstrate a slower rate of accrual of disability compared to adults-onset patients. This is postulated to be due to the greater plasticity of the developing brain and consequently a greater capacity for repair. For example, in one study which followed 59 patients with MS for a median of 5.9 years, 90% continued to have a normal neurological examination at last follow-up[33]. In a German study of 88 children with MS, the median EDSS scores were less than 1 at 2 years, 1.2 at 10 years and 2.5 at 15 years[29]. A seminal paper which compared 394 patients with paediatric-onset MS to 1775 patients with adult-onset MS demonstrated that it took approximately 10 years longer for the paediatric-onset patients to reach irreversible disability and secondary progression; however they reached these landmarks at a biological age approximately 10 years younger than their counterparts with adults-onset disease[25].

Up to 70% of adults with MS exhibit cognitive dysfunction[34]. Unfortunately, it is also a prominent feature of paediatric MS which can occur even at the earliest stage of disease (including first presentation with CIS); data suggest that up to a third of paediatric patients are affected[35]. The domains affected in children are similar to those with adult-onset MS and include memory, information processing speed, executive function and attention. Cognitive disability has been linked to a younger age at onset[36-39]. Putative mechanisms include demyelination of the immature CNS, which may impair subsequent maturation of white matter pathways involved in cognitive functioning; the neurodegenerative component of MS which is postulated to begin at disease onset[40] may lead to loss of relevant neural networks; disease onset during early formative years may disrupt the acquisition of basic building blocks crucial for future learning[41].

A longitudinal study re-evaluated 56 patients 2 years after initial assessment and found the incidence of cognitive impairment increased from 31% to 70%; 75% of patients demonstrated a deterioration in cognitive performance[39]. This study found no association between duration of disease or disability burden and cognitive performance. However another study published results of 231 paediatric patients with either MS (n=187) or CIS (n=44) and EDSS score was the only variable which was significantly independently associated with reduced cognitive function[42].

Environmental and genetic risk factors: the complex interplay

A summary of environmental and genetics risk factor is illustrated in **Table 1** and **Figure 2**. Low vitamin D status has been consistently associated with disease susceptibility in adult onset MS. The association between neonatal levels of vitamin D and future risk of MS is controversial. A Swedish population-based case-control study with 459 cases of MS showed no association, however the results may have been affected by degradation of 25-hydroxyvitamin D due to high storage temperatures of dried blood spot samples[43]. Contrastingly, a similarly designed Danish case-control study which measured 25-hydroxyvitamin D levels on dried blood spot samples showed an association between low concentrations of neonatal vitamin D and increased risk of MS[44]. A Finnish study showed a nearly 2-fold increased risk of development of MS in the offspring of women who were vitamin D deficient during early pregnancy[45]. In a Canadian study, circulating 25-hydroxyvitamin D levels in children at onset of ADS were inversely associated with risk of MS, suggestive of a protective effect of vitamin D[9]. The situation concerning vitamin D levels is somewhat complicated by the fact that obesity, which is also a risk factor for paediatric MS development[46, 47], is itself associated with a low serum concentration of vitamin D. Further proof of the intertwining aspects of these risk factors, has been provided by another study which showed that earlier age at sexual maturity contributed to earlier age at MS onset, particularly in association with obesity, which is known to expedite the advent of puberty[48].

Commonly acquired childhood infections have been implicated in the pathogenesis of paediatric MS; however the interpretation of association is complex and genetic factors are likely to affect this. History of remote Epstein-Barr Virus (EBV) infection was reported in all (62/62) paediatric patients with MS compared to 42% in patients with non-MS relapsing demyelination in one study[5]. In a case-control study comparing 189 paediatric patients with MS to 66 controls, EBV nuclear antigen-1 seropositivity was significantly associated with MS independently of age, sex, race, ethnicity and HLA-DRB1*1501/1503 status[49]. Contrastingly, in the same study, remote infection with cytomegalovirus (CMV) was independently associated with lower odds for development of paediatric MS. The case was more complex for herpes simplex virus-1 (HSV-1) infections and depended on HLA-DRB1 status. In HLA-DRB1-negative patients, the odds ratio for MS associated with HSV-1 positivity was 4.1, compared to 0.07 in HSV-1 positive patients who were HLA-DRB1-postive.

A link has been demonstrated between parental smoking and the development of paediatric MS; of note the increase in risk was significantly associated with the longer duration of exposure in older cases[50]. This is unsurprising considering the link between both active smoking and passive smoking in a dose-dependent manner to adult-onset MS[51, 52].

Genetic susceptibility has long been established in adult-onset MS; the presence of *HLADRB1*15:01* being the strongest genetic predictor. One of the largest case-control studies (569 cases) to date

proved a shared association in paediatric MS with *HLA-DRB1*15:01*, with an odds ratio of 2.95, suggesting similar biological processes regardless of age of onse[53]. Twenty-eight non-MHC variants studied were also significantly associated. Similar results were reported by the first genome-wide association study (GWAS) in paediatric MS[53]. Further studies will be required to further evaluate the relevance of these SNPs but it is likely they will lead to an enhancement of our understanding of the pathophysiology underlying MS. A study comparing 57 novel risk alleles showed that genetic risk scores were significantly different in patients with paediatric MS compared to those with monophasic acquired demyelinating syndromes[54]. As it rarely occurs in first degree relatives, paediatric onset MS is unlikely to be solely due to genetic risk[55]. Epigenetic or environmental interactions are more likely to be responsible.

The association with obesity and vitamin D levels may also have an underlying genetic basis. Obesity risk alleles identified by GWAS[56] demonstrated a causal association with paediatric MS following adjustment for age, sex, ancestry, *HLADRB1*15:01* allele and over 100 non-HLA MS risk variants[57]. The same study used 3 genetic variants known to affect serum concentrations of 25-OH-vitamin D levels to compute a genetic risk score which estimated the effect of each risk variant. The genetic risk score associated with increasing serum concentrations of 25-OH-vitamin D decreased the odds of pediatric-onset MS.

In multivariate models, *HLA-DRB1*15:01*, remote EBV infection and reduced vitamin D concentrations were independently associated with MS. Furthermore when comparing children who had all three risk factors present, to those who had none, there was a significant difference in the percentage who developed MS (57% versus 5%)[9].

Management

Traditionally, acute episodes or relapses were managed with either intravenous methylprednisolone usually at a dose of 20mg-30mg/kg/day (max 1g) for 3-5 days or oral methylprednisoplone 500mg for 5 days. However a recent multi-centre randomised controlled trial and also meta-analysis have shown oral methylprednisolone to be equally effective, well tolerated and safe and there is therefore an increasing shift towards its use[58]. If there is a contra indication to or an inadequate response to steroids, intravenous immunoglobulin (IVIg) or plasma exchange (PLEX) can be used.

A summary of the different disease-modifying therapies (DMT) and their mechanism of action is illustrated in ***Table 2***. Prompt initiation of a first-line DMT following diagnosis is recommended by the International Pediatric Multiple Sclerosis Study Group (IPMSSG), as it is not clear at presentation which patients will go on to have a high relapse rate[59, 60]. Further support for the prompt initiation of therapy is

the high rate of cognitive dysfunction in patients with MS and the fact that a single demyelinating attack appears to affect age-expected brain growth[61]. The majority of data comes from open-label observational or retrospective studies. The efficacy of first line options is roughly equal – an approximately 30-40% reduction in relapse rate[60].

Patients need to be monitored for both tolerability and efficacy. This is usually achieved by clinical review every 3 – 6 months and MRI every 6-12 months. Serial MRI scans are used to monitor response to treatment and to assess for accrual of asymptomatic lesions. The IPMSSG guidelines propose 6 monthly scans and scans 6 months after initiation of a new therapy in order to avoid prematurely defining treatment failure. These should ideally include both brain and spinal cord; however the inclusion of spinal cord MRI for routine monitoring in adult MS is debated, as its value to detect asymptomatic lesion may not be significant, if brain MRI is routinely performed[62]. Whether all the scans need to be gadolinium-enhanced is also being questioned. Gadolinium increases the sensitivity of MRI in detecting disease activity, since some new T2 lesions can only be visually detected after being identified as new gadolinium-enhancing lesions[63] and gadolinium enhancement is a temporary phenomenon, lasting about 3 weeks[64]. The recent concerns regarding the potential accumulation of gadolinium in the CNS and the fact that evaluation of new or enlarging T2 lesions is a robust measure of disease activity, suggest that the use of gadolinium in children may be limited to when there is a specific clinical question, until further data on this issue are provided.

A definition for treatment failure proposed by the IPMSSG is a patient fully compliant and on full-dose therapy for at least 6 months, , with an increase or no reduction in relapse rate, 2 or more new T2 or contrast-enhancing lesions on MRI compared to the pre-treatment period, or two or more clinical or MRI relapses within a 12 month period[60]. It is recommended that rapid cognitive decline should be taken into account. Unfortunately, this definition has not yet been formally applied in a research setting, and so it is uncertain exactly what percentage of patients experience treatment failure.

In case of treatment failure, especially when clinical relapses have occurred and/or increased in number, a patient may consider a second-line therapy. Up to 60% will require escalation to more effective therapy[32]. Second line DMTs are generally more efficacious, but are associated with more significant side-effects. The decision of which treatment to start will depend on a variety of features including the severity and frequency of relapses; the route and mechanism of action of a proposed therapy; the side effect profile of a proposed therapy. Ultimately, the decision is made in collaboration with the patient and their family and guided by their goals.

Problems in the current era of treatment for paediatric MS include adherence and treatment tolerability. Onset during adolescence probably contributes to this, as social pressures make it difficult to be

"different". The fact that many first line medications are injectable is likely to further affect compliance. From 37% to 47% of children self-reported a non-adherence (not taking the medication for >20% of past month)[65, 66]. The FUTURE study evaluated self-administration of IFN-beta-1a with an auto injector in a group of 50 patients aged between 12 and 16 years old and reported an overall significant improvement in self-reported and parent-reported quality of life[67].

The long-term efficacy of individual therapies is hard to evaluate due to small patients numbers and to the relatively high number of patients who switch therapy. However, results from long-term studies have demonstrated a globally reduced annual relapse rate compared to pre-treatment[68, 69] ranging from pre-treatment annualised relapse rates of 1.9-3.2 and declining to 0.04-0.9 after treatment initiation[70].

Prognostic factors have been hard to define. As discussed above, the concept of highly active MS identifies patients who are more likely to require second line therapy. There are conflicting reports in the literature regarding how age at onset of treatment affects prognosis. One recent study found that starting treatment younger than 12 years is the only factor in multivariate analyses to positively affect outcome; however in other studies this has not been the case[29, 69, 71]. Another study found time of less than 1 year between first and second attacks to be a negative prognostic factor[72], but approximately 80% of children with MS will relapse in the first year.

An improvement in prognosis has also been demonstrated compared to the pre-treatment era. Two recent studies in which patients received early therapy showed global disability scores among the lowest thus far reported in the literature. One study included 97 patients with a median follow-up duration of 12.5 years; 89% of patients had an EDSS score </= 3.5 at the end of the study[68]. Another study compared paediatric MS patients treated in 2005 with those treated in 2015 and showed a reduced relapsed rate of 46% and reduced EDSS by 44%[32]. Of note 44% of the 2015 group received second-line therapy. The authors also noted there may have been a longer delay in diagnosis in the earlier cohort. Nevertheless, these are promising improvements and with several clinical trials underway, there is huge hope for further developments in the care of paediatric MS (**Table 3)**.

The goal of treatment in MS has long been considered to halt relapses, disability progression and accrual of new MRI lesions. A relatively recent concept has been proposed as a new therapeutic aim - that of 'no evidence of disease activity' (NEDA)[73], defined by absence of clinical relapses, of new, enlarging or enhancing MRI lesions and of confirmed disability progression[74]. A randomised clinical trial (RCT) of interferon-beta-1b (IFNB-1b) permitted the assessment of different definitions of NEDA for predicting long-term outcome and identified that patients who experienced clinical NEDA for the 2-year period following randomization were less likely to develop negative disability outcome after 16 years follow-up[75].

Future perspectives and areas of research

The key to improving outcomes in MS is making early, accurate diagnosis and ensuring safe remission of inflammation. Future research needs to be based around these two goals.

Diagnostic accuracy and monitoring of remission can be facilitated through developing imaging biomarkers in both aiding in the diagnosis and then monitoring treatment. for example by assessing the role of new imaging biomarkers, such as the central vein sign[76] and grey matter lesion topology[77]to differentiate between MS and NMOSD. **Table 4** describes some of the advanced imaging methods and the relationship between these techniques and the biologic and chemical pathways leading to multiple sclerosis pathology. Magnetization transfer ratio (MTR) and positron emission tomography (PET) markers of remyelination, chronic inflammation and microglial activation could be used as more sensitive markers of disease progression than clinical relapse or conventional MRI parameters. Atrophy of the brain and spinal cord, measured longitudinally, correlates with disability accumulation and could be used as a quantitive outcome measure both clinically and as part of clinical trials.

Another important area of development is that of induction versus escalation therapy[82]. The current approach to treatment of paediatric-onset MS involves initiation of treatment with safer but likely less efficacious first-line therapies and then progression to more efficacious 2nd-line therapies as required ('escalation'). There is increasing debate concerning this approach and initiating therapy with more potent therapies and then de-escalating has been suggested as an alternative ('induction'). In this way there would be potential avoidance of permanent disability or loss of cognition while waiting to be changed to a more efficacious drug. A recent paediatric paper proposed a new treatment strategy termed 'HEET'[83] – highest efficacy early treatment aiming to maintain age-expected brain growth and to age-expected cognitive maturation and function. The hypothesis is that aggressive management during the initial inflammatory phase of MS, with a lower tolerance for any evidence of disease activity, will lead to overall improved outcomes. However, the relationship between subclinical disease activity and disability has yet to be established.

Figure 1: Radiological phenotypes in children with acquired demyelinating syndromes.
Axial FLAIR of a 5-year-old girl who presented with left sided weakness and MRI consistent with MS (A). She continued to have multiple clinical relapses despite treatment with disease modifying therapies. Axial FLAIR 4-years later demonstrating significant atrophy(B). Axial post-contrast T1 (C) and coronal FLAIR (D) of a 15-year-old girl with aggressive MS who had 3 clinical relapses at the first 2months from presentation. MRI showing multiple enhancing and non-enhancing lesions. Axial FLAIR of a 12-year-old girl with AQP4-Ab NMOSD and destructive brain lesions (E,F). Axial FLAIR demonstrating a "Leukodystrophy-like" imaging pattern in a boy with relapsing encephalopathies and MOG-Ab(G). Axial T2 demonstrating middle cerabellar peduncles involvement in a 5year-old girl with relapsing episodes of ataxia and MOG-Ab (H)

Figure 2: Environmental and genetic risk factors in paediatric MS
There are two components to the MS disease pathology; an inflammatory process and a neurodegenerative process. At disease onset the inflammatory process is more prominent. Overtime the neurodegenerative process becomes more prominent with secondary damage and irreversible axonal loss. Clinical heterogeneity and variance in progression are well-recognized properties of MS and are thought to be secondary to a combination of genetic and environmental risk factors. The main genetic risk factor is *HLA DRB1*1501*. In addition to its influence on risk, HLA alleles, specifically the HLA-DRB1*15:01 allele, have been associated with specific disease phenotypes, such as age at disease onset, response to treatment and radiological outcomes. A large part of disease susceptibility is due environmental risk factors such as low vitamin D status, exposure to cigarette smoking, and remote Epstein-Barr virus (EBV) infection; these factors have also been associated with disease course modification. In this figure blue refers to disease activity and the lightning flashes are triggering events.

Table 1: Genetic and environmental risk factors

Authors	Risk factor	Study	Patients with MS (n=)	Risk (95% CI)
Paediatric onset MS				
Mikaeloff et al [50]	Passive smoking	Case-control study versus healthy controls	129	RR 2.12 (1.43-3.15)
Waubant et al [84]	Remote EBV infection	Case-control study versus healthy controls	189	OR 3.78 (1.52-9.38)
Waubant et al [49]	Remote HSV-1 infection and negative HLA-DRB1*15 allele	Case-control study versus healthy controls	189	OR 4.11 (1.17-14.37)
Waubant et al [49]	Remote HSV-1 infection and positive HLA-DRB1*15 allele	Case-control study versus healthy controls	189	OR 0.07 (0.02-0.32)
Banwell et al[49]	Decreased Vitamin D levels	Comparative study of ADS children: MS versus non-MS	63	HR 1.11 per 10nmol/L decrease in 25-OH-VitD concentration (1.00-1.25)
Nielsen et al[44]	Decreased levels of 25(OH)D in neonates	Case-control versus healthy controls	521	OR for top (>48.9nmol/L) versus bottom quintile (<20.7nmol/L): 0.53 (0.37-0.78)
Ued et al [6]	Decreased levels of 25(OH)D in neonates	Case-control versus healthy controls	459	OR 1.0 (0.68-1.44)
Chitnis et al[47]	Obesity	Case-control study versus healthy controls	254	Girls: Premanarcheal: OR 1.48 (0.88-2.51) Postmenarcheal: OR 1.68 (1.21-2.34) Boys: OR 1.42 (1.09-1.86)
Gianfresco et al[57]	Presence of HLA-DRB1*15:01 allele	Case-control study versus healthy controls	569	OR 2.95 (2.33-3.32)
Banwell et al[9]	Combination of HLA-DRB1*15 allele, low 25(OH)Dlevels, remote EBV infection	Prospective cohort study patients presenting with ADS	16	HR 5.27 (1.23-22.6)

Table 2: Disease-Modifying Drugs

Drug	Brand name and dose	Presumed mechanism of action	Adverse events	Pediatric consideration
Interferone β1a Interferone β1b	*Betaferon* 250microrgams alternate days, SC *Rebif* 22 or 44 micrograms 3 times weekly, SC *Avonex* 30micrograms weekly IM *Plegridy* 125micrograms pegylated every 2 weeks, SC	Reduces BBB permeability and modulates T-cell, B-cell, and cytokine functions	Injection site reaction, flu-like symptoms, LFT elevation, leukopenia, (depression)	Younger children AST/ALT elevation more prominent. Titrate more slowly
Glatiramer acetate	*Copaxone* 20mg daily Or 40mg three times a week	Stimulates regulatory T cells	Injection site reaction, hypersensitivity reaction	
Natalizumab	*Tysabri* 3-5mg/kg (max dose 300mg) monthly	Prevents lymphocytes from entering into the CNS	Infusion reaction, PML	Children more likely to be JC negative. Risk of sero-conversion
Fingolimod	*Gylenia* *0.5mg tablet daily*	Interferes with S1P mechanism and prevents lymphocytes exiting the lymph nodes	Bradyarrhythmia, macular edema, herpes viruses infection (VZV)	Thymic maturation Adherence
Terifunomide	*Aubagio* 7mg or 14mg daily	Inhibits pyrimidine synthesis (general immunosuppression)	Hepatotoxicity (potential need for GI washout), teratogenic risk	Teratogenicity
Dimethyl Fumarate	*Tecfidera* 240mg tablet twice a day	Activates the nuclear-related factor 2 transcriptional pathway, modulate nuclear factor kB, which could have anti-inflammatory effects	Flushing, gastrointestinal symptoms, leukopenia	
Alemtuzamab	*Lemtrada* 5day intravenous infusion year 1followed by 3day infusion year 2.	Anti CD52+ Ab; depletes mature circulating B and T cells	Infusion reactions, infection, secondary malignancies, autoimmune disorders, thrombocytopenia	Exclude other mimics such as MOG and AQP4 antibodies prior to treatment
Cladribine	*Mavenclad* 3.75mg/kg tablets, up to 20days a year	Selective depletion of lymphocytes	Lymphopenia, Infection	

Table 3: Therapeutic trials

Name	Study population	Design	Primary objective	ClinicalTrials.gov identifier
PARADIGMS: Safety and Efficacy of Fingolimod in Paediatric Patients With Multiple Sclerosis	215 participants with RR paediatric MS	A 2 Year, Double-blind, Randomized, Multicenter, Active-controlled Core Phase to Evaluate Safety & Efficacy of Daily Fingolimod vs Weekly Interferon β-1a IM in Paediatric Patients With Multiple Sclerosis and 5 Year Fingolimod Extension Phase	To evaluate the safety and efficacy of fingolimod vs. interferon beta-1a IM in paediatric patients	NCT01892722
CONNECT: Phase 3 Efficacy and Safety Study ofdimethyl fumarate in Paediatric Subjects With Relapsing-remitting Multiple Sclerosis (RRMS)	142 participants with RR paediatric MS, aged 10-17 years	Open-Label, Randomized, Multicenter, Multiple-Dose,Active-Controlled, Parallel-Group, Efficacy and Safety Study of dimethyl fumarate in Children With Relapsing-Remitting Multiple Sclerosis, With Optional Open-Label Extension	To evaluate the safety, tolerability, and efficacy of BG00012 in paediatric subjects with RRMS, as compared with a disease-modifying treatment and to assess health outcomes and evolution of disability	NCT02283853
TERIKIDS: Efficacy, Safety and Pharmacokinetics of Teriflunomide in Paediatric Patients With Relapsing Forms of Multiple Sclerosis	166 participants with RR paediatric MS, aged 10-17 years	A Two Year, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Trial to Evaluate Efficacy, Safety, Tolerability, and Pharmacokinetics of Teriflunomide Administered Orally Once Daily in Paediatric Patients With Relapsing Forms of Multiple Sclerosis Followed by an Open-Label Extension	To assess the effect of teriflunomide in comparison to placebo on disease activity measured by time to first clinical relapse	NCT02201108
FOCUS: Study of the Effect of dimethyl fumarate on MRI Lesions and Pharmacokinetics in Paediatric Subjects With RRMS	22 participants with RR paediatric MS, aged 10-17 years	Open-Label, Multicenter, Multiple-Dose Study of the Effect of BG00012 on MRI Lesions and Pharmacokinetics in Paediatric Subjects With Relapsing-Remitting Multiple Sclerosis	Evaluate the effect of BG00012 (dimethyl fumarate) on brain magnetic resonance imaging (MRI) lesions in paediatric participants with relapsing-remitting multiple sclerosis (RRMS)	NCT02410200
LemKids: A Study to Evaluate Efficacy, Safety, and Tolerability of Alemtuzumab in Paediatric Patients With RRMS With Disease Activity on Prior DMT	50 participants with RR paediatric MS, aged 10-17 years	A Multi-center, Open-label, Single-arm, Before and After Switch Study to Evaluate the Efficacy, Safety and Tolerability of Alemtuzumab in Paediatric Patients With Relapsing Remitting Multiple Sclerosis With Disease Activity on Prior Disease Modifying Therapy (DMT)	To evaluate the efficacy, safety, and tolerability of alemtuzumab (IV) in paediatric patients from 10 to <18 years of age with Relapsing Remitting Multiple Sclerosis (RRMS) who have disease activity on prior Disease Modifying Therapy (DMT).	NCT03368664

Table 4: Advanced imaging techniques

Technique	How it works	Uses	Studies to date
Diffuse tensor imaging (DTI)	Non-invasive indirect assessment of axonal structure and myelin integrity by characterizing the diffusion properties of water molecules in the brain; main indices used are white matter fractional anisotropy (FA) and mean diffusivity (MD). Studies of normal white matter maturation using DTI of healthy subjects have demonstrated a progressive increase in white matter FA and a decrease in MD with age, suggesting an increase in axonal size with more efficient axonal transport, and myelin maturation and compaction [1,2]	Assess microscopic tissue damage in the 'normal-appearing white matter' (NAWM) that is not seen by conventional MRI	Reduced FA and MD in MS compared to healthy controls[3] indicative of a failure of age-expected white matter development and also a progressive loss of tissue integrity over time. Children with monophasic ADS with no brain lesions demonstrated indices similar to the healthy controls while those with intracranial lesions had persistently abnormal DTI indices suggesting that NAWM is negatively impacted by a single demyelinating attack if associated with brain lesions.
Cortical imaging: Double inversion recovery sequencing	Simultaneous T1-based suppression of signals from both white matter and CSF yields images in which T2 variations in grey matter are more easily detected	Detect cortical lesions for which standard MRI techniques have a low sensitivity due to their small size and poor contrast against normal-appearing cortical grey matter.	Cortical lesions are seen in 79% of children with paediatric onset MD[85]
Volumetric imaging	T1-weighted MRI pulse sequence with a variety of quantitative techniques such as voxel-based or deformation-based morphometry. In paediatrics, use Z-scores at each brain location to compare to a database of age-matched controls. Z-scores are computed by warping the particular image to a reference image. This overcomes the problem of dynamic brain growth in children compared to adults.	Assess volume loss (or atrophy) over time as a measure of axonal loss and the neurodegenerative aspect of MS.	Reduced head size, brain volume and particularly thalamic volume in patients with paediatric-onset MS compared to age- and sex-matched healthy controls[86].
Magnetic Transfer imaging (MT)	Tissues with altered protein-water interactions are less suppressed by MT radiofrequency pulses causing the lesions to be more easily detectable on T2-weighted imaging. MT ratio (MTR) maps identify neuroaxonal damage and myelin loss as hypointense lesions; remyelinated lesions have a higher MTR than demyelinated lesions	Quantify the level of microstructural damage within visible T2 lesions and normal appearing white and grey matter; Monitor remyelination	Serial imaging has been used to quantify changes in MTR lesions; MTR recovery in acute MS lesions decreases with age in adolescents suggesting that younger children have the greatest capacity for remyelination which gradually decreases with age[87].
Functional MRI (fMRI)	Evaluates the pattern of cerebral blood flow which is indicative of activation and/or of functional connectivity.	Assess resting-state and task based activation of cerebral blood flow and can compare healthy controls to paediatric MS patients	In the resting state, children with MS and preserved cognition show heightened functional connectivity, suggesting increased activation of compensatory networks[88]; In contrast, fMRI studies in cognitively impaired patients have shown decreased activation or functional connectivity in key areas.[89]

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