Imaging Biomarkers in Paediatric Acquired Demyelinating Syndromes

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Declaration

I, Omar Abdel-Mannan, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Dr Carmen Tur assisted with statistical analysis for Chapter 3.

Dr Dimitrios Champsas assisted with statistical analysis for Chapter 4.

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Dr Thomas Rossor, Dr Ming Lim, Dr Evangeline Wassmer and Dr Cheryl Hemingway contributed to the recruitment of patients for the prospective cohort in Chapter 3.

Abstract

The overall aim of this thesis is to improve understanding of paediatric multiple sclerosis (MS) and other acquired demyelinating syndromes (ADS) through epidemiological, clinical, and imaging studies. I investigated how clinical and radiological data can: (i) determine the long-term outcomes and incidence of ADS phenotypes in children, (ii) evaluate the real-world effectiveness of disease-modifying therapies (DMTs) in paediatric MS, and (iii) differentiate between paediatric myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) and MS to improve diagnostic accuracy and treatment decision-making.

Paediatric ADS represent a spectrum of heterogeneous disorders affecting the central nervous system, with paediatric MS, aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder (AQP4-NMOSD), and MOGAD being the most defined forms. While clinical and paraclinical investigations are key in diagnosing children suspected of having MS, differentiation among disease phenotypes remains challenging due to overlapping features. This distinction is crucial because treatment strategies differ significantly, influencing both short- and long-term outcomes.

I first used long-term follow-up data from a UK-wide prospective surveillance study to determine the incidence and outcomes of ADS in children.

To address the evolving MS treatment landscape, I then conducted a large-scale, multicentre retrospective study evaluating the real-world effectiveness of newer DMTs versus injectables in paediatric MS. This provided key insights into treatment efficacy, relapse reduction, and its impact on clinical and radiological outcomes. I prospectively investigated the efficacy and safety of ocrelizumab, a newer monoclonal antibody, in

paediatric MS within a real-world setting, contributing to understanding high-efficacy therapies in disease management and long-term safety.

Finally, using multicentre retrospective MS and MOGAD cohorts, I identified lesion dynamics distinguishing the two diseases and explored MRI biomarkers for disease monitoring, prognostic assessment, and treatment response evaluation.

These studies collectively aim to enhance our ability to diagnose and manage paediatric demyelinating disorders effectively, inform treatment decisions, and improve long-term neurological outcomes for affected children.

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Impact statement

This thesis advances the understanding, diagnosis, and management of paediatric acquired demyelinating syndromes (ADS), particularly paediatric multiple sclerosis (MS) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). Using real-world data, MRI analysis, and longitudinal studies, this research addresses key gaps in these conditions, with implications for clinical practice, healthcare policy, and future research.

Impact on Clinical Practice

The findings highlight the superior efficacy of newer disease-modifying therapies (DMTs) over traditional injectables in paediatric MS. The study provides strong real-world evidence supporting early use of high-efficacy treatments to prevent disability. Timely intervention is crucial, as it helps preserve cognitive function and reduce disease burden. The prospective study on ocrelizumab shows promising efficacy in paediatric MS, with 93% of patients achieving no evidence of disease activity (NEDA-3) at 12 months, suggesting it could become a key treatment option.

A key finding is the distinct lesion dynamics in paediatric MS versus MOGAD. Lesion resolution is more common in MOGAD, whereas asymptomatic lesions and disease progression are more frequent in MS. These results support the need for tailored imaging criteria to improve diagnosis and guide treatment.

Impact on Research and Scientific Advancements

During my PhD, I have published this research in three first-author papers and presented findings at multiple international conferences. This work provides valuable long-term follow-up data on paediatric MS and MOGAD, contributing to a better

understanding of disease progression and treatment outcomes. It also identifies cases initially diagnosed as ADS but later reclassified, underscoring the need for ongoing diagnostic vigilance. Imaging biomarkers explored in this thesis enhance knowledge of lesion repair, demyelination, and axonal damage, supporting the development of prognostic markers for future clinical trials. Moreover, the findings emphasize the need for further prospective research to refine treatment algorithms. By identifying risk factors for relapse and disease progression, this work informs future trials aimed at optimizing paediatric MS and MOGAD management.

Impact on Policy and Healthcare Systems

The findings have implications for healthcare policy and treatment access. The demonstrated effectiveness of newer DMTs highlights the need for early access to high-efficacy therapies for children with MS. Standardising MRI protocols is also crucial for improving diagnosis and disease monitoring. This research advocates for a multidisciplinary approach to paediatric MS and MOGAD, emphasising collaboration among neurologists, radiologists, and immunologists. By informing policy discussions on treatment guidelines, this work contributes to improving healthcare delivery and patient outcomes.

Impact on Patients and Families

Beyond academic and clinical implications, this research directly benefits patients and families. By improving diagnostic accuracy and promoting more effective treatments, the findings contribute to better disease management, reduced relapse rates, and improved long-term quality of life. The study underscores the importance of patient education and shared decision-making, empowering families to advocate for the best possible care.

Conclusion

This thesis advances knowledge of paediatric demyelinating diseases, providing critical insights into disease mechanisms, treatment efficacy, and clinical outcomes. The findings have the potential to influence clinical practice, shape future research, guide policy recommendations, and ultimately improve the lives of children affected by MS and MOGAD.

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List of abbreviations

MS: Multiple Sclerosis

POMS: Paediatric-onset Multiple Sclerosis

ADS: Acquired Demyelinating Syndromes

RRMS: Relapsing-Remitting Multiple Sclerosis

DMT: Disease-Modifying Therapy

CNS: Central Nervous System

MRI: Magnetic Resonance Imaging

EDSS: Expanded Disability Status Scale

ARR: Annualised Relapse Rate

NEDA: No Evidence of Disease Activity

MOGAD: Myelin Oligodendrocyte Glycoprotein Antibody-associated Disease

AQP4-Ab NMOSD: Aquaporin-4 Antibody-positive Neuromyelitis Optica Spectrum Disorder

ADEM: Acute Disseminated Encephalomyelitis

ON: Optic Neuritis

TM: Transverse Myelitis

CIS: Clinically Isolated Syndrome

DIS: Dissemination in Space

DIT: Dissemination in Time

OCB: Oligoclonal Bands

CSF: Cerebrospinal Fluid

IVIg: Intravenous Immunoglobulin

PLEX: Plasma Exchange

BICAMS: Brief International Cognitive Assessment for Multiple Sclerosis

EBV: Epstein-Barr Virus

HLA: Human Leukocyte Antigen

LETM: Longitudinally Extensive Transverse Myelitis

MDEM: Multiphasic Disseminated Encephalomyelitis

PPMS: Primary Progressive Multiple Sclerosis

RDS: Relapsing Demyelinating Syndromes

ANEC: Acute Necrotizing Encephalopathy

HLH: Hemophagocytic Lymphohistiocytosis

Publications associated with this thesis

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Abdel-Mannan OA, Manchoon C, Rossor T, Southin JC, Tur C, Brownlee W, Byrne S, Chitre M, Coles A, Forsyth R, Kneen R. Use of disease-modifying therapies in pediatric relapsing-remitting multiple sclerosis in the United Kingdom. Neurology: Neuroimmunology & Neuroinflammation. 2021 May 21;8(4):e1008.

Abdel-Mannan O, Ciccarelli O, Hacohen Y. Considering the future of pediatric multiple sclerosis trials after the CONNECT open-label randomized trial. JAMA Network Open. 2022 Sep 1;5(9):e2230451-.

Abdel-Mannan O, Champsas D, Tur C, Lee V, Manivannan S, Usman H, Skippen A, Desai I, Chitre M, Forsyth R, Kneen R. Evolution of brain MRI lesions in paediatric myelin-oligodendrocyte glycoprotein antibody-associated disease (MOGAD) and its relevance to disease course. Journal of Neurology, Neurosurgery & Psychiatry. 2024 May 1;95(5):426-33.

Abdel-Mannan O, Eshaghi A, Champsas D, Mankad K, Brownlee W, Rossor T, Wright S, Wassmer E, Hemingway C, Lim M, Ciccarelli O. Real-World Effectiveness of Ocrelizumab in a Multi-Centre Pediatric-Onset Multiple Sclerosis (POMS) Cohort in the United Kingdom (S31. 007). Neurology. 2023 Apr 25;100(17_supplement_2):2585.

Abdel-Mannan O, Eshaghi A, Mankad K, Wright S, Wassmer E, Lim M, Rossor T, Hemingway C, Ciccarelli O, Hacohen Y. Real-world effectiveness of Ocrelizumab in a UK Multi-centre Paediatric-Onset multiple sclerosis cohort. Multiple Sclerosis and Related Disorders. 2023 Dec 1;80:105266.

Wassmer E, Billaud C, Absoud M, Abdel-Mannan O, Benetou C, Cummins C, Forrest K, De Goede C, Eltantawi N, Hickson H, Hussain N. Long term outcome in non-multiple sclerosis paediatric acquired demyelinating syndromes. European Journal of Paediatric Neurology. 2024 Sep 1;52:52-8.

Eyre M, Absoud M, Abdel-Mannan O, Crichton S, Hacohen Y, Rossor T, Rudebeck S, Giovannoni G, Lim M, Hemingway C. Academic outcomes before and after clinical onset of acquired demyelinating syndromes in children: a matched cohort data linkage study. Annals of Clinical and Translational Neurology. 2024 Nov;11(11):3025-30.

Chapter 1: Introduction to Acquired Demyelinating Syndromes in Children

This thesis concerns real-world observational studies (RWS) of children and young people (under 18 years of age) presenting with multiple sclerosis (MS) and other acquired demyelinating syndromes, with a focus on imaging biomarkers. In this chapter, I will review the different presentations of paediatric acquired demyelinating syndromes, followed by the epidemiology, pathobiology and risk factors associated with paediatric MS and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), in addition to the clinical presentations, diagnostic criteria, imaging features, management (including disease modifying and preventative therapies), and expected prognosis for these conditions. Finally, I will review important mimics of acquired demyelinating syndromes.

1.1 Paediatric Acquired Demyelinating Syndromes (ADS)

Acquired demyelinating syndromes (ADS) denote acute neurological disorders characterised by deficits enduring for a minimum of 24 hours and implicating the optic nerve, cerebral structures, or spinal cord, correlated with localized regions of augmented signal on T2-weighted imaging. ADS may manifest as a monophasic disorder, exemplified by optic neuritis (ON), transverse myelitis (TM), and acute disseminated encephalomyelitis (ADEM), typically associated with a generally favourable prognosis[1] or as a chronic relapsing condition, such as Multiple Sclerosis (MS) and Neuromyelitis Optica Spectrum Disorder (NMOSD), culminating in progressive disabilities[2].

The incidence of ADS in children and adolescents ranges from 0.6 to 1.66 per 100,000 annually, with varied presentations. ON occurs in 22–36%, ADEM in 19–24%, and TM

in 3–22%[3-6]. A UK-wide prospective study reported an incidence of 9.83 per million per year for childhood CNS inflammatory demyelination[3]. Ten-year follow-up data showed that 68% of cases remained monophasic, while less than a third developed relapsing demyelinating syndromes (RDS)[7].

These diseases are thought to be triggered by environmental factors in genetically susceptible individuals and have increased in incidence in children in the past few years. It remains unclear whether this is due to heightened clinical awareness or increased exposure to environmental triggers during childhood [8, 9].

Studies indicate that 15% to 46% of children with ADS will be diagnosed with multiple sclerosis (MS) within five years [2]. An MS diagnosis requires evidence of CNS inflammation in multiple locations (dissemination in space, DIS) and occurring over time (dissemination in time, DIT)[10]. Nearly all young people with MS present with a relapsing-remitting course, with relapses typically manifesting as optic neuritis (ON), transverse myelitis (TM), or polysymptomatic episodes[11].

Significant progress has been made in distinguishing multiple sclerosis (MS) from other acquired demyelinating syndromes (ADS). Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) and aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder (AQP4-NMOSD) were previously considered MS variants[11-14]. Although there are clinical phenotypic overlaps between MOGAD, AQP4-NMOSD and MS, cumulative biological, clinical, and pathological evidence allows discrimination between these conditions.

NMOSD is an inflammatory condition with clinical manifestations involving mainly the optic nerve and spinal cord, associated with specific antibodies to aquaporin-4 water channels (AQP4-Abs). Since it is an antibody-mediated disease, immunomodulatory

therapy effectively reduces relapses, which are the main cause of disability and morbidity[15]. In addition, one-third of paediatric patients with ADS are Myelin oligodendrocyte glycoprotein antibody (MOG-Ab) positive, with the frequency of relapsing paediatric MOG-Ab positive patients ranging widely between studies. Younger children with MOGAD often present with acute disseminated encephalomyelitis (ADEM), whereas older children and adults are more likely to develop optic neuritis (ON) and transverse myelitis (TM)[13].

Given this thesis includes paediatric MS and MOGAD cohorts, I will now focus on these two important conditions for the remainder of the chapter.

1.2 Paediatric Multiple Sclerosis

Multiple sclerosis (MS) is a chronic disabling and costly neurodegenerative disorder. Incidence of MS appears to be increasing worldwide with a rising female-to-male sex ratio [16, 17] and with around 5% of adults who develop MS having first symptoms in childhood [18, 19]. Some epidemiological evidence suggests early environmental exposures may influence MS risk [20]. Hence, any epidemiological change in MS may be evident first in the paediatric population.

1.2.1 Pathobiology

The concept of plaque-like sclerosis in multiple sclerosis (MS) was first identified nearly 150 years ago, with evidence of dissemination across multiple CNS regions (DIS) and over time (DIT) forming the foundation of modern diagnostic criteria. Advances in MRI and histological techniques, such as immunohistochemistry, have significantly enhanced our understanding of MS pathology.

Pathological and genetic studies confirm that B and T cells of the adaptive immune system play a crucial role in MS pathogenesis[21, 22]. Since MS is CNS-specific, it is believed that certain autoantigens, uniquely expressed in the CNS, may selectively recruit B and T cells, though no specific candidate antigens have been identified[23]. Autoreactive lymphocytes, which exist naturally in the immune system, have the potential to trigger CNS autoimmunity. There are two main theories explaining how immune responses to CNS autoantigens are initiated.

- *CNS intrinsic model,* in which an initial event in the CNS leads to peripheral release of CNS antigens creating a proinflammatory environment with an autoimmune response subsequently targeting the CNS.
- *CNS extrinsic model,* in which the initiating event is outside the CNS (e.g., systemic infection) and results in an aberrant immune response targeting the CNS.

In both hypotheses, a self-perpetuating cycle of tissue damage leads to the release of peripheral antigens, further priming immune responses in lymphoid tissue and promoting CNS lymphocyte infiltration. Beyond the adaptive immune system, the innate immune system, particularly phagocytes, plays a key role in MS initiation and progression. Macrophages actively promote the proinflammatory B and T cell response, driving tissue damage. Microglial activation is likely an early event in MS lesion development, contributing to pathology through cytokine secretion, chemokines, and free radicals. As the disease progresses, the immune response shifts from being peripheral to CNS-confined, altering disease pathology. White matter injury becomes more diffuse due to microglial activation and immune infiltrates[24], while cortical involvement increases, accompanied by meningeal lymphoid-like follicles[25].

Multiple sclerosis (MS) is characterised by demyelination, axonal and neuronal loss, and astrocytic gliosis. While axonal damage occurs acutely in new inflammatory lesions, neurodegeneration is the primary driver of permanent disability. The mechanisms of axonal loss differ between acute and chronic phases, contributing to disease progression. These pathogenic processes are increasingly studied in vivo using conventional and advanced imaging techniques. Axonal and neuronal loss is reflected in brain atrophy, observed on volumetric MRI at an annual rate of 0.5–1.5%[26]. Ongoing research aims to identify molecular, metabolic, and imaging biomarkers that correlate with clinical progression, improving treatment monitoring and clinical trial outcomes[27].

How does this pathology translate into clinical symptoms? In MS, acute neurological deficits, or relapses, occur due to inflammatory demyelinating lesions affecting different CNS regions. For example, a lesion in the optic nerve leads to optic neuritis, presenting as blurred vision and visual impairment[28]. In optic neuritis, proinflammatory cytokines and demyelination within the lesion lead to a conduction block, causing visual loss. Alongside these negative symptoms, demyelinated axons may generate spontaneous impulses, resulting in positive symptoms, such as flashing lights. Crucially, MRI and optic coherence tomography (OCT) studies show that persistent optic nerve demyelination increases axonal vulnerability, predicting axonal loss within six months post-event. This process contributes to irreversible disability in the progressive phase of MS.

1.2.2 Demographics and epidemiology

Paediatric-onset multiple sclerosis (MS) is rare, with 3-5% of cases presenting before 18 years of age [19, 29]. A recent meta-analysis estimated a global incidence of 0.87 per 100,000 children annually (ranging from 0.05 to 2.85). The global prevalence is

approximately 8.11 per 100,000, though this varies across regions (Table 1.1) [2]. A recent international study using data from 53 countries estimated a lower adjusted global prevalence of paediatric MS at 1.48 per 100,000, reflecting significant under-ascertainment in lower-income regions[30].

A large prospective cohort of paediatric MS patients in North America described the demographic features of 490 children and adolescents [31]. Among these patients, 66% were female, 67% were White, and 20.6% were African American. In younger children, the sex ratio was nearly equal, but a female predominance emerged with age, particularly during adolescence.

This study found that 17% of patients experienced their first demyelinating attack before age 10, compared to 7.6% in previous reports[19]. A notable finding was the greater ethnic diversity, with higher proportions of African American and Hispanic/Latino cases, along with a significant number of second-generation Americans. This contrasts with the predominantly White ethnic distribution observed in adult MS.

In addition to demographic insights, recent evidence supports a prodromal phase in paediatric MS. A 2024 population-based case-control found that, in the five years before diagnosis, children with MS had significantly higher rates of obesity, visual disturbances, gastrointestinal symptoms, cardiac irregularities, and especially skin sensation disturbances (AOR 12.93), compared to controls[32]. These findings suggest a diverse range of early, non-specific symptoms that may precede MS onset in children and adolescents.

1.2.3 Risk factors (Table 1.2)

Recent research has identified multiple genetic and environmental risk factors for paediatric MS, many of which are also observed in adult-onset MS. These include vitamin D deficiency, Epstein-Barr Virus (EBV) infection, and smoking [8].

Table 1.1: Paediatric vs Adult MS incidence across different countries

Country	**Incidence – paediatric (per 100,000/year)**	**Incidence – adults (per 100,000/year)**
Germany	0.64 [33]	0.33 [34]
Netherlands	0.8 [35]	5.9 [34]
UK	0.98 [5]	4.7 [34]
Italy (Sardinia)	2.85 [36]	6.6 [34]
USA	1.66 [37]	5.1 [34]
Iran (Fars)	0.19 [37]	5.2 [38]
Kuwait	2.1 [37]	2.6 [34]
Taiwan	0.52 [39]	6.69 [40]

The strongest genetic risk factor for MS in both adults and children is the HLA-DRB1*1501 allele of the major histocompatibility complex (MHC) on chromosome 6. Children with ADS who carry at least one copy of HLA-DRB1*1501, particularly white children, have a higher likelihood of developing MS[41]. Genome-wide association studies (GWAS) have identified several single nucleotide polymorphisms (SNPs) linked to MS risk in adults, with early evidence suggesting a similar genetic burden in paediatric and adult MS[42]. Initial studies suggest that children and adults with MS share a similar genetic burden [43]. In adults, non-HLA risk SNPs are often located near T cell-regulating genes, potentially altering gene expression and promoting proinflammatory immune responses[44].

Lower serum levels of 25-hydroxyvitamin D has been linked to an increased risk of paediatric MS[45]. Additionally, low vitamin D levels may interact with obesity, further influencing MS susceptibility. Obesity itself is a risk factor for paediatric MS, particularly in females[46], potentially due to proinflammatory adipokines released by adipose tissue and the association between obesity and earlier puberty, another known MS risk factor. Before puberty, MS incidence is equal between males and females (1:1), but after puberty, the female-to-male ratio increases to 2.7:1[47]. This shift suggests that female sex hormones may contribute to MS risk, while male sex hormones may have a protective effect[48].

Epstein-Barr Virus (EBV) exposure has been strongly associated with both adult and paediatric MS risk [49]. A study of 110 children with relapsing demyelinating syndromes found 100% of MS patients had evidence of prior EBV infection, compared to 42.9% in non-MS relapsing demyelination [11]. A more recent multicentre study confirmed this association, showing that over 90% of children diagnosed with MS were EBV-seropositive, while EBV exposure was not elevated in children with Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) or monophasic demyelination[50]. These findings emphasise that prior reports of lower EBV prevalence in paediatric MS likely reflected inclusion of MOGAD cases and further support EBV's specific role in MS pathogenesis across the age spectrum. However, no significant interaction has been identified between EBV seropositivity and the HLA-DRB*1501 allele [45].

Vaccinations, as antigenic challenges in a developing immune system, have been hypothetically considered a potential MS risk factor. However, a case-control study of 143 paediatric MS patients and 1,122 healthy controls found no association between vaccination and MS risk[51]. A follow-up study[52], expanding the cohort to 163 MS or ADS cases and 892 controls, observed a higher odds ratio (OR: 1.74, 95% CI: 1.03–2.95)

for ADS or MS diagnosis in those fully compliant with the vaccination schedule. Concerns have also been raised about increased ADS risk following HPV vaccination, but a large study (780 cases, 3,885 controls) found no evidence of increased risk[53].

Other possible MS risk factors include exposure to parental smoking and gut microbiome differences [54] In multivariate models, HLA-DRB1*15:01, EBV infection, and low vitamin D levels were independently associated with paediatric MS risk [45]. Notably, children with all three risk factors had a significantly higher likelihood of developing MS (57% vs. 5%) compared to those with none [45].

The genetic and environmental factors influencing MS risk may also impact disease course and activity. Mendelian Randomisation studies have shown that genetically lower vitamin D levels are significantly linked to a higher MS risk in both white, non-Hispanic patients[9]. Similarly, genetic risk scores from GWAS studies confirm a strong association between obesity and MS, suggesting a causal relationship in both paediatric and adult MS[55]. Regarding disease progression, recent large-scale genome-wide association studies, including those conducted by the International Multiple Sclerosis Genetics Consortium (IMSGC)[56] and MSBase[57], have identified associations between genetic burden scores and disability outcomes in MS. While genetic susceptibility genes do not appear to determine MS phenotype, some evidence suggests HLA and non-HLA risk factors may influence relapse rates and MRI lesions[9]. A genome-wide search identified a SNP in the LRP2 gene, which was associated with a twofold increased relapse risk in paediatric and adult MS cohorts[58].

1.2.4 Clinical features

Nearly all children and adolescents diagnosed with multiple sclerosis (MS) have a relapsing-remitting disease course [19, 59], while primary progressive MS is exceptionally

rare in this age group and should only be considered after ruling out alternative diagnoses [59, 60]. The initial presentation of paediatric MS resembles that of adults, often manifesting as optic neuritis, transverse myelitis, sensory disturbances, or bladder dysfunction. Notably, 30–60% of paediatric patients present with polysymptomatic symptoms [6], most commonly involving sensory, cerebellar, visual, brainstem, and pyramidal dysfunction [61].

Paediatric MS tends to have a more active disease course initially with a higher relapse rate in the early years after diagnosis, and a shorter interval between the first and second demyelinating event, compared to adults [62]. Nevertheless, paediatric patients have a slower rate of accrual of disability compared to adults e.g. median scores on the Expanded Disability Status Scale (EDSS) score were < 1 at 2 years, 1.2 at 10 years, and 2.5 at 15 years in a German cohort of 88 paediatric MS patients [47].

Paediatric 'highly active' MS refers to patients fulfilling the following criteria: 1) At diagnosis: 2 or more attacks coupled with EDSS progression within the last 12 months and the presence of ≥ 1 gadolinium-enhancing lesion or a significant increase in T2 lesions within the past 6-12 months, or; 2) ≥1 attack within the previous twelve months and ≥ 9 T2 lesions or ≥1 gadolinium-enhancing lesion while under disease modifying therapy with interferon-Beta, glatiramer acetate or dimethyl fumarate.

In the German cohort referenced above[63], 41.6% of patients met these criteria, supporting the idea that paediatric MS is more inflammatory than adult MS. No correlation was found between disease activity and age or gender at presentation.

Table 1.2: Risk factors in MS vs AQP4-NMO vs MOGAD

	Risk Factor	MS Risk (95% CI)	AQP4-NMOSD Risk (95% CI)	MOGAD Risk (95% CI)
Demographic	Ethnicity – Black	+ [15]	+ [64]	-
	Ethnicity - East Asian	-	+ [64]	-
	Gender (Female)>11 years old	+ [35]	-	-
Genetic	HLA-DRB1*15:01	OR 2.95 (2.33-3.32)[42]	OR 1.67conditioned on HLA-DRB1*03:01 (1.13-2.47) [65]	-
	HLA-DRB1*03:01	-	OR 4.09 (2.98-5.99) [65]	-
	HLA-DQB1*05:02	-	-	OR 1.95 (1.25-3.00) [66]
	HLA-DRB1*16:02	-	-	OR 2.21 (1.15-4.08) [66]
Environmental	Low serum 25-hydroxyvitamin D	HR 1.11 (1.00-1.25) per 10nmol/L decrease in 25-OH-vitD [45]	-	-
	Obesity	Females premenarcheal OR 1.48 (0.88-2.51) Females post-menarche OR 1.68 (1.21-2.34) Males OR 1.42 (1.09-1.86) [67]	-	-
	EBV exposure	OR 3.78 (1.52-9.38) [68]	-	-
	HSV-1 exposure, HLA-DRB1*15 neg	OR 4.11 (1.17-14.37) [68]	-	-
	HSV-1 exposure, HLA-DRB1*15 pos	OR 0.07 (0.02-0.32) [68]	-	-
	Low serum 25-OH-vitD combined with HLA-DRB*15 and EBV exposure	HR 5.27 (1.23-22.6)		
	Exposure to smoking	RR 2.12 (1.43-3.15) [69]	-	-
	Caesarean delivery	-	OR 1.95 (0.81-4.71) [70]	-

\+ association between risk factor and disease

\- no association found between risk factor and disease

Despite its high inflammatory activity, paediatric MS is often followed by remarkable recovery, with permanent disability during childhood or adolescence being rare[1].

1.2.5 Diagnosis

The diagnosis of MS requires evidence of dissemination in space (DIS) and dissemination in time (DIT) while excluding alternative diagnoses, often through neuroimaging. Testing for AQP4-Ab and MOG-Ab is essential in atypical cases, as these antibody-associated relapsing demyelinating conditions follow different disease courses and require distinct treatments. DIS is confirmed by the presence of one or more T2 lesions in at least two of the following regions: periventricular; juxtacortical, or cortical; infratentorial; spinal cord. DIT is demonstrated by the presence of both gadolinium-enhancing and non-enhancing lesions on a single MRI scan or by identifying a new T2 and/or gadolinium-enhancing lesion on a follow-up scan.
The 2017 revised McDonald criteria further refine MS diagnosis[10], incorporating these requirements, include:

- Intrathecal oligoclonal bands (OCBs) substituting for DIT in patients presenting with a typical CIS and fulfilling DIS requirements.
- Symptomatic lesions as counting as evidence of DIS or DIT
- Cortical grey matter lesions included in DIS, considered in combination with juxtacortical lesions

The 2017 revised McDonald criteria have improved diagnostic accuracy at disease onset in paediatric MS, primarily due to the substitution of oligoclonal bands (OCBs) for dissemination in time (DIT) [71, 72]. Studies show that 71–84% of children with MS meet the criteria at onset, regardless of age. In a UK-wide prospective cohort of 125 children with ADS, 96% (23/24) of MS cases met the 2017 McDonald criteria at presentation.
CSF analysis remains a key diagnostic tool in paediatric MS. CSF pleocytosis, mainly monocytic, is found in 52–66% of cases[73, 74]. The presence of OCBs in CSF but not in serum strongly supports MS diagnosis, with detection rates of up to 90%[35, 47, 75]. Studies have shown OCBs in 43–60% of children under 11 years old[47, 75] and 63–73% in older children. Serial CSF analysis improves OCB detection rates[47].

1.2.6 Neuroimaging

Over the past 10-15 years, magnetic resonance imaging (MRI) has become a fundamental MS biomarker. MRI plays a key role in many aspects of the disease including diagnosis, disease monitoring, prognosis, and treatment response evaluation.

1.2.6.1 MRI for MS diagnosis

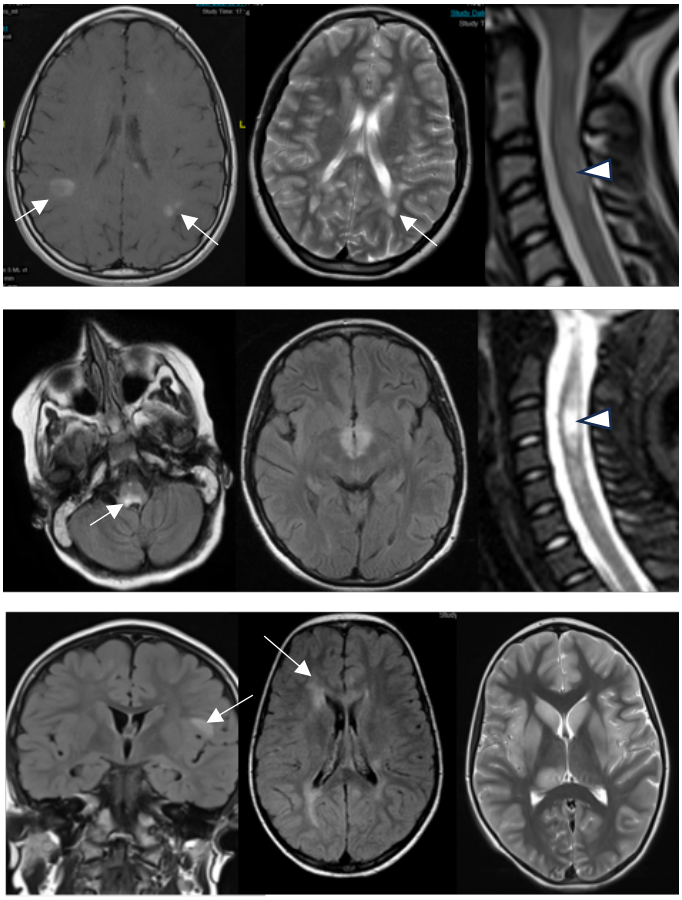
MRI plays a crucial role in the early diagnosis of MS in both adults and children, with dissemination in space (DIS) and dissemination in time (DIT) being essential criteria. The 2017 revised McDonald criteria introduced key updates, including combining cortical and juxtacortical lesions and removing the distinction between symptomatic and asymptomatic lesions. Additionally, oligoclonal bands (OCBs) can now substitute for DIT, improving the criteria's diagnostic performance in paediatric MS compared to the 2010 version[71]. Neuroimaging hallmarks of MS include multifocal T2 hyperintense lesions in characteristic CNS locations. The presence of T1 hypointense lesions ("black holes") at first presentation, particularly if they persist, can further indicate a chronic disease process, aiding in paediatric MS identification[72].

Several studies have evaluated MRI markers that help differentiate paediatric MS from monophasic demyelination:

- KIDMUS Study: Lesions perpendicular to the corpus callosum and the presence of well-defined, MRI-visible demyelinating lesions had 100% specificity and PPV but low sensitivity (21%) for MS diagnosis [76].
- Differentiation from ADEM: The presence of two out of three features; (1) lack of diffuse bilateral lesions, (2) black holes, or (3) two or more periventricular lesions—had 81% sensitivity, 95% specificity, and 95% PPV for MS vs ADEM[77].

- One or more periventricular T2 bright lesions and one or more T1-hypointense lesions had 84% sensitivity, 93% specificity, 76% PPV, and 96% NPV for distinguishing MS from monophasic ADS[78].
- Predictive MRI Markers: T2 hyperintense brain lesions strongly predict MS, while longitudinally extensive myelitis and diencephalic lesions suggest NMOSD. A normal MRI at presentation with ON or TM indicates a low MS risk[79].
- Cortical Lesions: Increasingly identified in paediatric MS, these findings support early cortical involvement in the disease process[79].

Figure 1.1: Neuroimaging features of MS, AQP4-Ab NMOSD and MOGAD



Examples of MRI features in acquired demyelinating syndromes.

Top row: periventricular and juxtacortical lesions or plaques on the left (arrows) and short segment transverse myelitis on the right (arrowheads), typical of relapsing remitting multiple sclerosis (RRMS);

Middle row: hypothalamic lesion on the left (arrows), and a longitudinally extensive transverse myelitis indicated by hyperintensity in the spinal cord on the right (arrowheads), in a child with AQP4-Ab NMOSD;

Bottom row: confluent, enhancing and poorly marginated lesions of the cortical grey matter (arrows) in a patient with MOG-Ab associated disease (MOGAD).

1.2.6.2 MRI for understanding pathobiology

Advanced MRI techniques provide greater pathological specificity than conventional imaging, offering insight into inflammation, demyelination, and neuro-axonal loss (neurodegeneration) in MS. These methods help track disease progression, revealing how different pathological processes interact and relate to clinical outcomes. Neurodegeneration begins early in MS and correlates closely with disability progression.[80]. Brain and spinal cord atrophy can be quantified using MRI, but these measures are not yet widely used in clinical practice for monitoring disease progression or treatment response. However, increasing evidence suggests they can be valuable complementary tools alongside lesion assessment.

Early changes in brain volume (as early as 1 year) predict disability status in both RRMS and primary progressive MS (PPMS) in adults [81, 82]. In addition, higher rates of cervical spinal cord atrophy have been associated with disability progression independent of other clinical and radiological parameters [83, 84]. In adults, whole brain atrophy is driven mainly by grey matter (GM) atrophy, with some regions involved more extensively than others. A longitudinal study of 1,417 MS patients (MAGNIMS network) demonstrated a consistent sequence of GM atrophy across MS subtypes, reinforcing its role in disease progression[85].

Brain volume is reduced in paediatric MS compared to healthy controls, with this atrophy evident at first clinical presentation[86, 87]. Alarmingly, brain atrophy accelerates within the first two years and is strongly linked to disease activity[87]. Grey matter structures (e.g., thalamus) are particularly affected early after disease onset in children as well [86, 87]. Despite these structural changes, physical and cognitive deficits are often absent in early disease stages, likely due to the greater neuroplasticity of the developing brain. This suggests a therapeutic window where early intervention may help prevent long-term disability[88].

Beyond high-resolution anatomical imaging (MPRAGE, T2, FLAIR), advanced imaging techniques are increasingly used to track MS-related brain pathology, including:

- Microstructural imaging: Assesses neurite density, fibre orientation, and brain connectivity using multi-shell diffusion imaging[89]
- Quantitative magnetization transfer (qMT): Strongly correlates with myelin integrity[90]
- Myelin water imaging (MWI): Measures myelin water fraction, providing a sensitive marker of demyelination[91].

These advanced imaging techniques offer superior sensitivity compared to conventional methods, providing biologically meaningful metrics. They can reveal subtle brain abnormalities that may appear normal on standard imaging, offering deeper insights into the extent of MS-related pathology.

1.2.6.3 MRI for monitoring disease course and treatment response

MRI plays a crucial role in monitoring MS progression and treatment response, particularly in prognostication[92]. In adults, the presence of new T2 or gadolinium-enhancing lesions signals ongoing inflammation, with a higher lesion load at onset predicting greater disability progression[93]. In paediatric MS, new or enlarging T2 lesions, with or without gadolinium enhancement, serve as key indicators of disease activity. On average, children develop nine new lesions within six months of onset[94], though advanced imaging suggests they have a greater capacity for lesion repair compared to adults[95].

Although as mentioned earlier, brain atrophy occurs in both adult and paediatric patients, a recent study demonstrated that atrophy does not follow the same spatiotemporal pattern in all MS phenotypes [85]. Deep grey matter nuclei demyelination,

a hallmark of the disease, has been shown to be the main driver of disability progression in adult patients [26].

Spinal cord MRI imaging should be considered and prospectively evaluated as a routine part of the diagnostic workup in children as it may lead to an even higher sensitivity. In fact, spinal cord lesions occur preferentially in the cervical region in MS, representing an area with the greatest diagnostic yield[96]. In adults, spinal cord lesions at onset are linked to a more aggressive disease course[97], but their prognostic significance in paediatric MS remains to be fully explored.

1.2.6.4 MRI for clinical trials and research

In the majority of randomised controlled trials for DMTs, lesion-based metrics are the primary outcome measures. Phase 2 and 3 trials typically assess treatment response using the number of new or enlarging T2 lesions and T1 gadolinium-enhancing lesions. Phase 2 and 3 trials typically assess treatment response using the number of new or enlarging T2 lesions and T1 gadolinium-enhancing lesions[98]. However, T2 white matter lesions are not exclusive to inflammation, as they may also reflect demyelination, axonal loss, and remyelination. While brain atrophy measures are not yet implemented in routine clinical practice, they remain key biomarkers for neurodegeneration in DMT trials. Metrics such as percent brain volume change (PBVC) and regional atrophy assessments (white and grey matter volumes) are increasingly used. Inflammation and brain oedema can however also influence these metrics, limiting their specificity to neurodegeneration[99]. Recent clinical trials have begun incorporating advanced MRI techniques, including proton Magnetic Resonance Spectroscopy (MRS) and Neurite Orientation Dispersion and Density Imaging (NODDI), as potential biomarkers for neurodegeneration.

1.2.7 Management

For paediatric MS, acute relapses are managed by either intravenous or oral methylprednisolone, usually at a dose of 30mg/kg/day for 3-5 days. This can be followed by an oral taper of prednisolone if symptoms do not completely resolve. In the case of inadequate steroid response, intravenous immunoglobulin (IVIg) or plasma exchange (PLEX) can also be used acutely.

In terms of long-term preventative treatment, there are now at least 20 disease-modifying therapies (DMTs) approved for adult MS patients (Table 1.3). In children, only one therapy, fingolimod, has been formally approved for paediatric-onset multiple sclerosis on the basis of phase 3 clinical trial evidence (Table 1.4). Rapid initiation of DMTs in paediatric MS is influenced by evidence of a less favourable long-term prognosis compared to adults, despite the relative paucity of overt physical or cognitive deficits in early childhood, as irreversible damage can still accrue at a younger age [19]. More significantly, the large proportion of highly active disease [63], the high rates of cognitive dysfunction in paediatric MS and the fact that brain atrophy is occurring at a time when it should be growing, all argue in favour prompt initiation of therapy.

Most of our current treatment data is based on open-label observational or retrospective studies. The efficacy of first-line DMTs is roughly equal: around 30% to 40% reduction in annualised relapse rate (ARR) [100]. Tolerability and efficacy of treatment are monitored by clinical review every 3 to 6 months and repeat MRI every 6 to 12 months. In cases of treatment failure (defined by ongoing clinical activity and MRI activity in fully compliant patients for a sufficient period), second-line therapies, including oral agents and infusions, may be considered. In fact, up to 60% require escalation to more effective therapy [101]. Although these drugs are more efficacious, they are also associated with a more significant risk profile.

Various factors will inform the decision of choice of therapy including severity and frequency of relapses, the route and mechanism of action of a proposed therapy, and the side-effect profile of a proposed therapy. The first randomised controlled trial in paediatric MS compared fingolimod versus interferon beta 1a injections in children with relapsing remitting MS [102], recruiting 190 patients from 101 centres in 26 countries. At 2-years follow up, the relapse rate was 80% lower in the fingolimod than in the interferon group, indicating a greater anti-inflammatory impact on the disease in comparison to adult fingolimod trials. Two further RCTs in paediatric MS were recently published; TERIKIDS[103] and CONNECT[104]. Further trials are currently underway on the plethora of newer DMTs that have become available on the last 5 years.

Long term efficacy of each DMT is difficult to evaluate owing to small paediatric patient numbers and high number of patients switching therapy. Nevertheless, long-term studies have demonstrated reduced annualised relapse rates compared with pre-treatment [29, 105]. The established approach to treating paediatric onset MS initially with the safer but less efficacious injectables and subsequently escalating to more efficacious newer agents with evidence of disease activity is being superseded by an 'induction' approach [101]. Increasingly both clinical trial data [102] and real-world observational data in children [106, 107] is demonstrating the advantage of initiating treatment with more potent infusions/oral agents in the first instance, given our knowledge of the impact of disease activity on brain atrophy, cognitive impairment and development of secondary progressive MS at a younger age.

For clarity, in this thesis I refer to first-generation parenteral therapies—interferon-β (various formulations) and glatiramer acetate—as *injectables*, reflecting their route of administration and historically moderate efficacy with well-established safety. I use newer DMTs to denote higher-efficacy agents introduced more recently, comprising oral therapies (dimethyl fumarate, fingolimod, teriflunomide) and infusions

(natalizumab, ocrelizumab, alemtuzumab). Although these drugs differ in mechanisms, monitoring requirements, and long-term safety, grouping them reflects how treatment choices are made in practice and supports the comparative analyses presented later in this thesis (Chapter 3), which examine outcomes for injectables versus newer DMTs in paediatric MS.

Table 1.3: Summary of the different disease-modifying therapies and their mechanism of action

Drug	**Brand name and dose**	**Presumed mechanism of action**	**Adverse events**	**Paediatric consideration**
Interferon β1a Interferoneβ1b	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 Extavia 250 microgram alternate days, 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 oedema, herpes viruses infection (VZV)	Thymic maturation Adherence. No live vaccine while on treatment and reduce vaccine efficacy
Teriflunomide	Aubagio 7mg or 14mg daily	Inhibits pyrimidine synthesis (general immunosuppression)	Hepatotoxicity (potential need for GI washout), teratogenic risk, hair loss	Teratogenicity

Dimethylfumarate	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. Small problem cases	Compliance with twice daily dosing
Alemtuzamab	Lemtrada 5 day intravenous infusion year 1 followed by 3 day 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 No live vaccine for first 6 months after each infusion reduce vaccine efficacy
Cladribine	Mavenclad 3.75mg/kg tablets, up to 20days a year	Selective depletion of lymphocytes	Lymphopenia, Infection	Weight based dosing with no data under 40kg. No live vaccine for 6 month after each course treatment and reduce vaccine efficacy
Ocrelizumab	Ocrevus 1st dose split into 2 doses Intravenous infusion 2 weeks apart Followed by 1 infusion every 6 months	Monoclonal antibody targeting CD20-positive B cells	Infections and infusion reaction	Data from Rituximab may suggest increase risk of hypogammaglobulinemia in children
Ofatumumab	Kesimpta 20mg subcut injection – initially 1 injection/week for 3 weeks and then 1 injection every month	Monoclonal antibody targeting CD20-positive B cells	Infection and injection site reaction	Data from Rituximab may suggest increase risk of hypogammaglobulinemia in children

A major focus of multiple sclerosis (MS) research is treating disease progression. Bruton's tyrosine kinase (BTK) inhibitors, which target B cells and innate immune cells[108], are under phase 3 trials for both relapsing and progressive MS. However, results from trials on evobrutinib showed no superiority over teriflunomide in reducing relapse rates, disability progression, new MRI lesions, or neurofilament light levels[109]. Notably, T1 gadolinium-enhancing lesions were more frequent with evobrutinib, though it slightly reduced slowly expanding lesions, suggesting potential efficacy in smouldering MS. Given these findings, BTK inhibitors may be more effective in progressive MS, with ongoing trials expected to provide further insight. Supporting this,

a recent RCT, the HERCULES trial demonstrated that the BTK inhibitor tolebrutinib significantly reduced 6-month confirmed disability progression in non-relapsing secondary progressive MS compared to placebo (HR 0.69)[110], highlighting its potential as the first effective therapy for this population. A parallel research theme is remyelination therapy. Targeting the M1 muscarinic acetylcholine receptor, PIPE-307, a highly selective oral antagonist, has demonstrated efficacy in promoting oligodendrocyte differentiation and myelination in animal models[111]. Unlike previous muscarinic inhibitors, its selectivity may reduce cognitive side effects, as shown in phase 1 studies. These findings support PIPE-307 as a promising remyelination strategy, warranting further clinical investigation.

1.2.8 Disease course and prognosis

As discussed above, a large proportion of paediatric MS patients fulfil 'highly active' MS criteria, with frequent clinical and/or radiological relapses. Although some studies have shown early initiation of treatment (<12 years old) can positively affect outcome in multivariate analyses, there have been conflicting data [47, 112, 113]. In addition, 80% of children with MS will relapse in the first year. There has been an improvement in prognosis demonstrated compared to the pre-treatment era with studies demonstrating patients receiving early therapy having the lowest reported disability score. For instance, in a cohort of 97 patients with median follow up of 12 years, 89% of patients had an EDSS score of <3.5 [105]. In addition, compared with those treated in 2005, patients treated in 2015 had 46% lower relapse rates and a 44% greater reduction in EDSS[63].

Despite, highly active disease, paediatric MS patients demonstrate a slower rate of disability accrual compared to their adult counterparts, which may be due to greater

brain plasticity and 'brain reserve' allowing a greater capacity for repair after relapses. A seminal study comparing 394 patients with paediatric-onset multiple sclerosis and 1775 patients with adult-onset multiple sclerosis demonstrated that it took approximately 10 years longer for the patients with paediatric-onset disease to reach irreversible disability and secondary progression; nevertheless, they did in fact reach these landmarks at a biological age 10 years younger than their counterparts with the adult-onset disease [114].

A more recent longitudinal study of 5,224 individuals with paediatric-onset multiple sclerosis from MSBase registry (151 centres across 41 countries) and the Italian Multiple Sclerosis and Related Disorders Register (178 centres in Italy), found that high-efficacy therapies significantly reduced disability progression[115]. The greatest benefit was seen when treatment began early in the minimal disability state (HR 0.41, 95% CI 0.31–0.53), compared to untreated individuals. Those receiving low-efficacy therapy in the minimal disability state also had a lower risk of progressing to mild disability (HR 0.65, 95% CI 0.54–0.77) compared to untreated patients.

MS treatment has long aimed to reduce relapses, disability progression, and new MRI lesions. In adults, a therapeutic aim of 'no evidence of disease activity' has become widespread both clinically and in trials, defined as absence of clinical relapses, of new, enlarging, or enhancing MRI lesions, or of confirmed disability progression [116]. However, in children 'minimal evidence of disease activity' is likely to be a more achievable target of treatment, given their more active disease.

Table 1.4: Randomised control trials in paediatric MS

Cognitive impairment is also more prominent in paediatric MS compared to adult patients [117]. This is linked to a younger age at onset [118, 119] and is reported in up to 30%

Clinical trial short name	Patients recruited	NCT number	Status
Safety and efficacy of fingolimod in paediatric patients with multiple sclerosis (PARADIGMS)	220 participants with paediatric RRMS	NCT01892722	Completed
Study of the effect of dimethyl fumarate on MRI lesions and pharmacokinetics in paediatric patients with RRMS (FOCUS)	22 participants with RRMS, aged 10–17y	NCT02410200	Completed
Efficacy, safety, and pharmacokinetics of teriflunomide in paediatric patients with elapsing forms of multiple sclerosis (TERIKIDS)	166 participants with RRMS, aged 10–17y	NCT02201108	Completed
Efficacy and safety study of dimethyl fumarate in paediatric patients with RRMS CONNECT	142 participants with RRMS, aged 10–17y	NCT02283853	Completed
Study to Evaluate the Safety, Tolerability, and Efficacy of BIIB017 (Peginterferon Beta-1a) in Paediatric Participants for the Treatment of RRMS	142 paediatric Subjects Aged 10 to Less Than 18 Years with RRMS	NCT03958877	Active, not recruiting, phase 3
Study to evaluate efficacy, safety, and tolerability of alemtuzumab in paediatric patients with RRMS with disease activity on previous disease-modifying therapies (LemKids)	50 participants with RRMS, aged 10–17y	NCT03368664	Active, not recruiting, phase 3
Study to Evaluate the Efficacy and Safety of Dimethyl Fumarate (Tecfidera) and Peginterferon Beta-1a (Plegridy) for the Treatment of RRMS Paediatric Participants	260 participants with RRMS, aged 10–17y	NCT03870763	Recruiting, phase 3
Efficacy and Safety of Ofatumumab and Siponimod Compared to Fingolimod in Pediatric Patients With Multiple Sclerosis (NEOS)	Planned 120 participants with RRMS, aged 10-18y	NCT04926818	Recruiting, phase 3
Study to Evaluate Safety and Efficacy of Ocrelizumab in Comparison With Fingolimod in Children and Adolescents With Relapsing-Remitting Multiple Sclerosis (RRMS) (OPERATA II)	Planned 117 children and adolescents ages ≥ 10 to ≤ 18 years with RRMS	NCT05123703	Active, recruiting, phase 3

of paediatric patients, even at the earliest disease stage [120]. Data from population-based longitudinal cohort study from Swedish MS Registry evaluating cognitive outcome of 5704 patients (300 with paediatric-onset disease) [121] revealed that

paediatric-onset patients had greater deficits in information processing compared to their counterparts with adult-onset disease, independent of age or disease duration.

In terms of longer term outcomes, a nationwide register-based cohort study of 485 patients with paediatric-onset MS and 4850 persons without MS, matched from the general population showed that patients with paediatric-onset MS were less likely to attend university, earned a lower salary, and were more reliant on disability benefits than persons without MS [122]. It should be noted that being a historical cohort, many of these patients may have been diagnosed in a pre-treatment era and one without higher efficacy treatment available. With increasing clinical trials underway, there remains hope for continued improvement in both short- and long-term outcomes for paediatric MS.

1.3 Measuring treatment response in Paediatric MS

The approach to treatment of relapsing-remitting multiple sclerosis (RRMS) is rapidly evolving, with over 20 disease-modifying therapies (DMTs) currently licensed for adults. Current treatment algorithms in children with MS remain heavily reliant on adult MS protocols, and the majority of DMTs in children are prescribed off-label. Convincing evidence has increasingly emerged to support the biological rationale that effective DMTs in adult MS patients are equally efficacious in children[123]. A number of clinical trials have been published in paediatric MS [102-104]. This is partly as a result of major recruitment challenges due to the low incidence and prevalence of paediatric MS, in addition to challenges of MS diagnosis in children, with an emphasis on exclusion of other mimics, particularly antibody-mediated diseases such as myelin oligodendrocyte glycoprotein (MOG) and aquaporin-4 (AQP-4) antibodies.

1.3.1 Randomised controls trials (RCTs)

Both previously published clinical trials in paediatric MS compared newer oral agents (teriflunomide and fingolimod) to either older injectables or placebo. In the TERIKIDS trial, conducted at 57 clinical centres in 22 countries, 109 patients (<18 years old) were randomly assigned to teriflunomide and 57 to placebo. The study demonstrated similar efficacy of teriflunomide in a paediatric cohort compared with previous adult data, with a reduction in the adjusted number of new or enlarging T2 lesions per MRI scan by 55% and the hazard of relapse by 34% over 2 years. In the open label extension[124], treatment with teriflunomide compared to placebo followed by teriflunomide was associated with a 38% reduction in clinical relapse risk (HR 0.62; 95% CI 0.39–0.98; p = 0.11). Additionally, the number of gadolinium-enhancing T1 lesions decreased by 43% (RR 0.570; 95% CI 0.33–0.98; p = 0.043), while new or enlarging T2 lesions were reduced by 49% (RR 0.511; 95% CI 0.34–0.76; p = 0.001) during the combined double-blind and open-label study periods.

The PARADIGMS trial, meanwhile, enrolled 215 patients (<18 years old) across 80 centres worldwide, with 107 patients assigned to fingolimod, and 108 to interferon β-1a. This study demonstrated superiority of fingolimod with a lower rate of relapse (0.12 vs 0.67, $p < 0.001$), lower accumulation of lesions on MRI (4.39 vs 9.27, $p < 0.001$) and a lower annualised rate of brain atrophy over a 2-year period than interferon β-1a. These randomized trials, however, were limited by small sample sizes (underpowered), protracted enrolment times (3 years in PARADIGMS and 3.5 years in TERIKIDS), a failure to recruit enough pre-pubertal patients (minimising evaluation of dose-dependent responses), and a lack of long-term safety data (e.g., effects on fertility in young females) given the 2-year endpoint. Nevertheless, both studies used MRI as a key secondary endpoint (both lesion load and atrophy) to overcome some of these limitations. Given the validated robust relationship between clinical efficacy and

MRI endpoints[125], this has important implications for the design of paediatric trials testing drugs already studied in adult MS.

In the recent CONNECT study[126], Vermersch et al. conducted a multi-centre active-controlled, open-label, rater-blinded randomized trial of dimethyl fumarate (DMF, an oral DMT) vs interferon β-1a in paediatric MS patients across 63 sites. In total, the study included 150 patients with a median (range) age of 15.0 years (10-17); 78 were randomized to DMF and 72 to interferon β-1a. Sixty-two (79%) patients on DMF completed 96 weeks follow-up, and 41 (57%) of patients on interferon β-1a completed the trial. In the completed population, 16% of patients on DMF had no new or newly enlarging T2 hyperintense lesions at 96 weeks relative to baseline compared to 5% in the interferon β-1a group. In addition, 66% of patients on DMF remained relapse-free compared to 52% on interferon β-1a, with no significant difference in adjusted annualised relapse rate between the two groups: 0.24 (95% CI, 0.15-0.39) for DMF vs 0.53 (0.33-0.84) for interferon β-1a. Overall safety profile between groups was comparable; number of adverse events was 74 (95%) vs 69 (96%), and serious adverse events was 8 (23%) vs 21 (29%) between DMF and interferon β-1a, respectively.

This open label study has several limitations. In particular, the large drop-out rate, 42% in interferon β-1a group and 21% in the DMF group, which may have led to a marginal difference in the adjusted ARR between the two arms. Similarly, follow-up MRIs were only available in 42/72 for the DMF arm and 62/78 for the interferon β-1a arm, which is surprising in the context of a clinical trial. The addition of other imaging outcome measures including whole brain volume and percentage change in brain volume, as reported in PARADIGMS, would also have been of interest in this study when comparing the two treatment arms. Nevertheless, the use of MRI measures as primary outcome and the long-term safety data which will be available from the on-going

extension of this study are valuable information in a rare condition such as paediatric MS.

1.3.2 Real world studies (RWS)

Children included in randomised trials may not be representative of real-world populations, due to the various restrictions required when recruiting eligible patients in RCTs. In addition, RCTs are limited by short follow-up periods, making real world studies (RWS) more suitable for evaluating long-term efficacy and safety. Real-world observational studies include large populations of patients who might benefit from a given treatment, in addition to subgroups that are not typically included in RCTs. Comparisons of effectiveness and safety amongst a growing armamentarium of DMTs are easier in RWS, in addition to the characterisation of prognostic subgroups of patients with a view to developing personalised therapeutic strategies. Nevertheless, RWS are subject to biases that need to be accounted for (Table 1.5). Advanced statistical methodologies are able mitigate the impacts of these biases, however, and the findings of rigorous RWS correspond well with those of clinical trials across the literature.

Table 1.5: Methods to adjust for bias in real-world studies

Type of bias	Phase of study	Description	Strategies to minimise bias
Selection bias	Patient selection	An error when choosing participants of a study that causes systematic differences between comparison groups in prognosis or responsiveness to treatment	Adjustment for baseline covariates (multivariate regression analyses, propensity score adjustments; Bayesian approach; Broader inclusion criteria Subgroup and/or sensitivity analyses
Indication bias	Patient selection	Can arise when patient characteristics influence drug prescription and relate to outcome, thereby acting as confounding Factors	Adjustment for baseline covariates: (multivariate regression analyses, propensity score adjustments, Bayesian approach); Broader inclusion criteria; Subgroup

			and/or sensitivity analyses
Will Rogers phenomenon	Patient selection	Can arise when modifications are made over time to diagnostic criteria for classifying patients; new diagnostic criteria typically enable earlier diagnosis	Use of contemporary cohorts; Sensitivity analysis excluding historical subcohorts
Indication bias	Patient selection	Can arise when patient characteristics influence drug prescription and relate to outcome, thereby acting as confounding Factors	Adjustment for baseline covariates: (multivariate regression analyses, propensity score adjustments, Bayesian approach); Broader inclusion criteria; Subgroup and/or sensitivity analyses
Immortal time bias	Patient selection	Can arise when the period between cohort entry and the date of first exposure to a drug, during which the event of interest has not occurred, is either misclassified or excluded and not accounted for in the analysis	Treatment start date can be defined as a time-dependent variable in analysis
Hidden bias	Patient selection	Results from a lack of information about variables that could influence treatment outcome (for example, a lack of MRI data)	Sensitivity analyses to estimate the robustness of the main analysis (for example, Rosenbaum bounds)
Informative censoring	Follow-up	Patients are most likely to be lost to follow-up if they are doing poorly; if more patients are lost from one study arm than from the other, the results could be biased	Sensitivity analyses
Detection bias	Follow-up	Patients who are receiving any treatment tend to be seen by health professionals more frequently than other people, so earlier detection of various outcomes is more likely	Adjustment of analysis to account for the interval duration between visits of standardized visit frequency (for example, the number of visits per year); Marginal structural modelling
Attrition bias	Follow-up	Can result in a difference in the probability of reaching study outcomes; typically occurs when the duration of follow-up differs in the two treatment arms	Pairwise censoring; Marginal structural modelling

It is clear that the rapidly evolving landscape of MS therapeutics comes with significant challenges including: (i) recruiting a sufficiently high number of children to take part in randomised trials; (ii) the time and cost involved in conducting trials; and (iii) trials conducted based on old medications which become obsolete by the time trials have been completed[127]. Our question is whether we can use a different approach to provide evidence of the efficacy and safety of DMTs in children. It would be attractive to rely on the efficacy of the DMTs from the adult cohorts (MS in adults and children MS is biologically the same disease), and provide safety data from large-scale multi-centre, real-world observational cohorts, which may provide larger sample sizes, which could be used to confirm the efficacy of the medication. In parallel to this effort, factors affecting treatment response and predicting prognosis in clinical practice should be investigated in the real world of paediatric MS. Furthermore, a shift towards using MRI outcome measures as a valid surrogate endpoint for clinical relapses in paediatric trials may help reduce study times when evaluating DMT efficacy, and the above trials have successfully demonstrated that this may be successful. A shift from a focusing on short-term DMT safety profiles to longer-term safety assessment (including in pre-pubescent patients) is recommended, so to ensure that treatment early in life does not expose patients to future risk.

1.3.3 No evidence of disease activity (NEDA)

No evidence of disease activity (NEDA) is widely used as an assessment of treatment outcome in MS trials. NEDA-3 combines MRI activity and clinical progression [128]; defined as no relapses, no sustained disability progression (measured with the EDSS), and no new or enlarging T2-weighted or T1 gadolinium-enhancing lesions detected with MRI. As an increasingly realistic treatment goal with the introduction of highly effective DMTs, the definition of NEDA-3 is evolving to include brain atrophy (NEDA-4) [129], although this remains in the realm of trials and not clinical practice. Indeed, a

recent meta-analysis demonstrated that combining T2 lesion load over 2 years and whole brain volume loss in the second year explained 75% of the variance of disability progression among patients who were on DMTs over a period of 2 years. This was a greater proportion than that produced by each of these measures alone). [130]. In fact, future definitions of NEDA may start to include other metrics, such as patient-reported outcome measures or fluid biomarkers (e.g. serum neurofilament levels)[131]. Predicting response to treatment in MS patients and achieving NEDA is much needed. With so many different DMTs available to reduce clinical relapses, these have different efficacy and safety profiles. In addition, individual patients respond to DMTs differently and up to 60% of them have a new relapse within 2 years which may lead to accumulation of disability and poor compliance to therapy. [132]

However, it is important to also note that whether NEDA-3 persists in patients who achieve it, and whether it accurately predicts long-term prognosis, remains controversial[133]. This may allude to the importance of brain atrophy as an MS imaging outcome measure beyond conventional neuroimaging measures (T2 lesion load). MS, though pathological studies, has been shown to cause significant tissue loss in the brain and spinal cord, more obvious in the progressive types of MS [134]. Brain and spinal cord atrophy on T1 weighted MRI sequences is used to investigate the impact of atrophy on future disability. Higher rates of cerebral atrophy are seen in MS patients when compared to healthy controls (HCs) [135]. At the earliest stages of MS, CIS patients have shown to develop more brain atrophy in those who develop MS after 1-3 years in comparison to those who did not develop MS [136]. Improvements in MRI post-processing have allowed segmentation of WM and GM (both cortical and deep) separately, allowing an improved association with clinical features[26, 137]. Studies have shown that MS patients with higher disease progression have a tendency towards higher central cerebral atrophy, regional atrophy and whole brain atrophy [138-140]. In fact, regional volumes allow a higher sensitivity and smaller sample size when compared

with global measures [141]. Significantly, brain atrophy is not associated with relapse risk in RRMS, which suggests that atrophy is probably driven more by (or independent) neurodegenerative changes rather than neuroinflammatory lesions.

1.4 Paediatric myelin-oligodendrocyte glycoprotein antibody-associated disease (MOGAD)

Myelin-oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is a recently discovered autoimmune disorder affecting both adult and paediatric patients. One-third of children who present with ADS are MOG-Ab positive, and approximately half of patients with MOG-Ab have a relapsing disease course [142]. There is definite clinical overlap with the previously discussed AQP4-NMOSD and MS, but cumulative evidence has allowed clear discrimination between these conditions. Several unanswered questions remain related to MOGAD clinical characterisation and the pathogenetic role of anti-MOG antibodies given the recent discovery of this disease entity.

1.4.1 Pathobiology

Myelin-oligodendrocyte glycoprotein (MOG) is a minor component of CNS myelin, located on the outer lamella of the myelin sheath[143]. The development of anti-MOG antibody (MOG-Ab) detection assays over the past decade has led to the identification of distinct CNS demyelination phenotypes in both adults and children.

The trigger for anti-MOG antibody production remains unclear, but it is hypothesized to arise peripherally in response to infections. Potential mechanisms for post-infectious autoimmunity include molecular mimicry, epitope spreading, and polyclonal B-cell activation, though no specific pathogens have been identified. Anti-MOG antibodies

likely enter the CNS when the blood–brain barrier is compromised, binding to MOG on myelin, leading to demyelination and myelin injury[144, 145]. Elevated levels of proinflammatory cytokines (e.g., IL-6, TNFα), B-cell cytokines, and chemokines in the CSF of MOGAD patients further suggest the involvement of MOG-specific CD4+ T cells, myelin basic protein-specific T cells, and macrophages in disease pathology[146].

From a histopathological perspective, MOGAD lesions are characterised by inflammatory demyelination, in contrast to astrocytopathy in AQP4-NMOSD. Unlike MS, perivascular immunoglobulin and activated complement deposits are rarely present. Instead, MOGAD lesions display perivascular macrophage infiltration and CD4+ T-cell predominance, whereas MS lesions are dominated by CD8+ T cells[147].

1.4.2 Demographics, epidemiology and risk factors

MOGAD shows no significant ethnic or gender predominance, particularly in children under 10 years, which contrasts with the female and non-white predominance observed in MS and AQP4-NMOSD. A mild female predominance is seen in older post-pubertal children and adults, though it is less pronounced than in AQP4-NMOSD[148-150]. Paediatric MOG-Ab-positive patients tend to be younger, have a lower EDSS at two years after disease onset, and experience a longer time to relapse compared to AQP4-NMOSD [71]. MOGAD is more common in children than adults, unlike AQP4-NMOSD, with approximately 34% of paediatric ADS cases being MOG-Ab positive[65].

Research on environmental and genetic risk factors in MOGAD remains limited, similar to NMOSD. There is currently no definitive evidence linking MOGAD to other autoimmune diseases or malignancies. Certain HLA class II alleles, specifically

DQB105:02 and DRB116:02 haplotypes, have been associated with paediatric-onset MOGAD in Chinese patients, [151], but this association was not observed in adult-onset MOGAD, MS, or NMOSD [152]. While HLA involvement is expected, a recent study of 43 Dutch MOGAD patients found no significant HLA association, highlighting the need for further investigation. [153].

1.4.3 Clinical features

1.4.3.1 Monophasic phenotypes

Acute disseminated encephalomyelitis (ADEM) is the most common initial presentation of MOGAD, with up to 50% of paediatric ADEM cases testing MOG-Ab positive. MOGAD-associated ADEM primarily occurs in childhood, typically presenting with encephalopathy, polyfocal neurological deficits, and characteristic MRI abnormalities, which may fluctuate during the acute phase [154, 155]. Children with MOG-Ab-positive ADEM are less likely to experience emotional or behavioural issues compared to seronegative ADEM cases [156]. Additionally, spinal cord involvement on MRI is more frequent in MOG-Ab-positive patients (93%) compared to MOG-Ab-negative cases (33%). While ADEM is generally monophasic, MOG-Ab-positive ADEM patients have a higher risk of relapse, cognitive impairment, and post-ADEM epilepsy.

In older children and adolescents, optic neuritis (ON) is a more common presentation of MOGAD, often causing severe visual loss at onset, similar to AQP4-NMOSD, seronegative ON, and MS-associated ON [157, 158]. However, MOG-Ab-positive patients show significantly better visual recovery at six months compared to AQP4-Ab-positive cases. More than 50% of children with MOGAD-ON present with bilateral optic nerve involvement [159], which is uncommon in MS [160]. Additionally, optic disc oedema is a frequent feature in MOG-Ab-positive ON[161], whereas AQP4-ON is more likely to

involve the optic chiasm and optic tract [160]. Despite good functional visual recovery, OCT findings suggest permanent axonal damage. Isolated transverse myelitis (TM) is rare in MOGAD but can lead to severe motor, sensory, and bowel/bladder dysfunction. Unlike MS-associated TM, MOGAD-TM is typically longitudinally extensive (LETM) and often involves the conus, similar to AQP4-NMOSD [162]. Despite severe initial symptoms, most MOGAD-TM patients experience good motor recovery [163]. Notably, ON and LETM can occur simultaneously in MOGAD, resembling an NMOSD-like phenotype.

1.4.3.2 Relapsing phenotypes

A subset of MOGAD patients experience a relapsing disease course, with phenotypes including multiphasic disseminated encephalomyelitis (MDEM), ADEM followed by one or more ON episode(s) (ADEM-ON), relapsing ON and relapsing NMOSD [164]:

- Multiphasic disseminated encephalomyelitis (MDEM): A relapsing form of ADEM, with new episodes occurring at least one month after the initial attack[155].
- ADEM followed by optic neuritis (ADEM-ON): Some children initially presenting with ADEM later develop isolated optic nerve involvement [164], with 60–70% experiencing residual visual deficits[165].
- Relapsing ON: While more common in adults, MOG-Ab-positive children have higher ON relapse rates than seronegative or MS patients [166, 167], and often meet criteria for chronic relapsing inflammatory optic neuropathy (CRION)[161, 168].
- Relapsing NMOSD-like phenotype: Patients with ON or LETM at onset may continue to relapse with either isolated ON, LETM, or both, leading to a chronic NMOSD-like course. Additionally, some children initially presenting with

isolated ON, TM, or ADEM may later develop a relapsing NMOSD-like phenotype[169].

1.4.3.3 Atypical phenotypes

The phenotypic spectrum of MOGAD continues to expand, now including rarer and atypical presentations. One such manifestation is cortical MOG or cortical encephalitis, observed in both adults and children. This phenotype is characterised by encephalitis with MOG-Ab positivity, presenting with seizures, headache, and/or fever, alongside unilateral or bilateral cortical lesions on brain MRI [170, 171]. In a large multicentre observational cohort of children with definite or possible encephalitis (n=296), 7% tested positive for MOG-Abs. Within the autoimmune encephalitis subgroup (n=64), 34% were MOG-Ab positive [172]. MOG-Ab positive patients most commonly presented with impaired consciousness (100%), seizures (64%), fever (59%), and behavioural deterioration (50%) and abnormal movements (36%). Our group's recent study of 235 paediatric MOG-Ab-positive patients compared 33 (14%) with an encephalitis presentation to 74 (31%) with ADEM [173], showing the encephalitis group were older, required more ICU admissions, received steroids later, and had a higher risk of epilepsy. It recommends testing for MOG-antibodies in all suspected encephalitis cases, even with a normal initial MRI, as 24% of paediatric patients had normal scans. However, it remains difficult to determine if the MOG-Abs are pathogenic in causing the encephalitis with additional pathological studies in these patients showing inconsistent results. In addition, although seizures normally occur in the context of encephalitis, there have been several reports of isolated seizure presentations in MOGA-Ab positive patients [161, 174, 175], often with unremarkable imaging initially. The subsequent demyelinating episode can occur months to years later, suggestive of an underlying immune pathogenesis that may have already been present at seizure onset.

A leukodystrophy-like phenotype has been identified in paediatric MOGAD, characterized by symmetrical, extensive, and confluent MRI abnormalities that progress over time, mimicking genetic or metabolic leukodystrophies [164, 172, 176]. This phenotype is primarily seen in younger children (mean age 3.7 years), presenting with encephalopathy, ataxia, optic neuritis, and/or seizures [177]. Compared to non-leukodystrophy MOGAD patients, these children have worse outcomes (EDSS 3 vs. 0), with a high prevalence of persistent cognitive/behavioral impairments (57%) and seizures (43%) at follow-up.

1.4.4 Diagnosis

Significant progress has been made in MOG-Ab detection assays, with live cell-based assays (CBA) now providing more consistent and reliable results compared to enzyme-linked immunosorbent assays (ELISA) and western blotting [178-183]. The role of CSF MOG-Ab testing remains under investigation. While most CSF-positive patients are also seropositive, not all seropositive patients have CSF positivity, and only a small subset are CSF-positive but seronegative [184, 185]. To enhance diagnostic accuracy, the international MOGAD diagnostic panel (see more details below) included CSF-only MOG-IgG positivity in its criteria but recommended serum testing as the primary approach, with CSF analysis reserved for strong clinical suspicion[186]. Studies report a CSF-only positivity prevalence of 8–17%[187-189], more commonly seen in adults and often associated with cortical encephalitis [188]. However, clinical differences between CSF-only and serum-positive cases remain unclear.

Approximately half of MOGAD patients present with CSF pleocytosis, predominantly lymphocytic or monocytic, with higher white cell counts than typically seen in MS. In a UK cohort, the average CSF white cell count was 251 cells/μL [190]. More extensive disease phenotypes such as ADEM or LETM tend to show higher pleocytosis

compared to optic neuritis (ON) [191, 192]. Unlike MS, MOG-Ab-positive patients are less likely to have intrathecal OCBs, with OCBs and an elevated IgG index detected in fewer than 15% of cases, primarily during attacks [193, 194]. Additionally, CSF cytokine profiles in MOGAD attacks more closely resemble AQP4-NMOSD than MS [195, 196].

The recently proposed 2023 diagnostic criteria for MOGAD[186] provide a standardised approach to diagnosis, with specific considerations for children. These criteria, developed by an international panel of experts, are particularly relevant for paediatric cases due to the distinct presentation and course of MOGAD in children compared to adults. The key components of the criteria are shown in Figure 1.2. The current diagnostic approach follows a three-step process. First, clinicians identify a suggestive clinical and imaging phenotype, classifying cases into six core demyelinating syndromes. Next, MOG-IgG detection is performed, with results categorised based on a defined hierarchy that distinguishes clear positives from less definitive cases. The third and most critical step involves the exclusion of alternative diagnoses, particularly multiple sclerosis (MS). If MOG-IgG results are not clearly positive, additional clinical and imaging supportive features are required, along with a negative AQP4-IgG test. To further refine diagnosis, the criteria include a list of “red flags” that help differentiate MOGAD from MS.

The 2023 diagnostic criteria are particularly significant for paediatric MOGAD cases due to several key factors. First, they recognise the age-specific presentations, acknowledging that children are more likely than adults to present with ADEM-like symptoms. Additionally, the criteria incorporate the distinct MRI patterns often seen in paediatric MOGAD, including large, bilateral cerebral lesions that differ from those in adults. Beyond diagnosis, the criteria also play a vital role in long-term prognosis by enabling early identification and management, which is essential for reducing relapses and preventing long-term disability. Lastly, they assist in differentiating MOGAD from

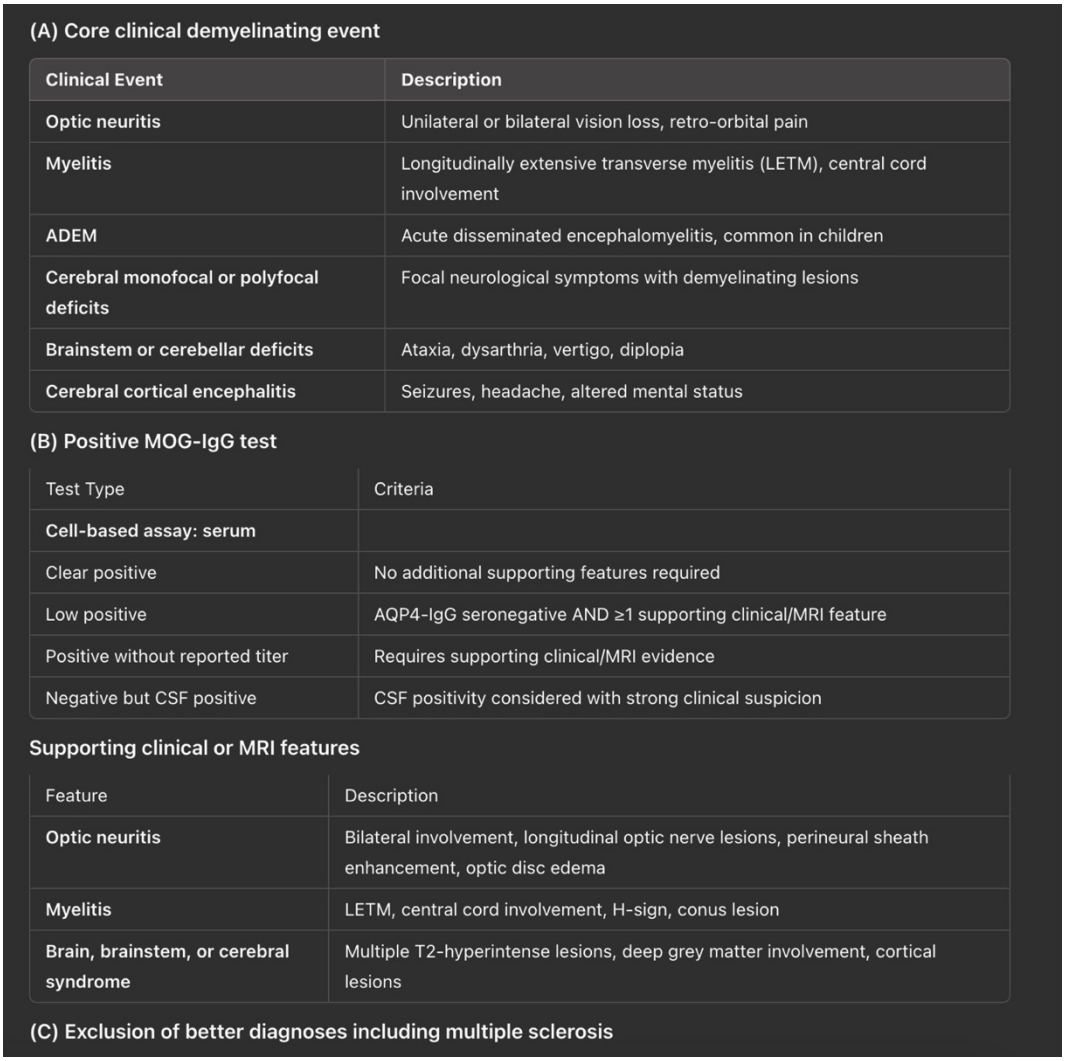
other paediatric demyelinating disorders, such as multiple sclerosis and AQP4-NMOSD, ensuring that children receive the most appropriate treatment strategies.

These standardised criteria enhance the accuracy of MOGAD diagnosis in children, potentially leading to more timely and targeted interventions, and improved long-term outcomes for paediatric patients.

1.4.5 Neuroimaging

Over 50% of MOGAD patients present with abnormal neuroimaging[192], with children showing more extensive brain lesions compared to adults. In ADEM-like MOGAD, deep white and grey matter lesions are common, with brainstem involvement in approximately 40% of cases [11, 197-199]. After resolution of symptoms, follow up scans often remarkably show complete resolution or significant reduction in these lesions. However, a subset of very young children may develop an aggressive leukodystrophy-like phenotype, characterized by confluent, highly enhancing MRI lesions and significant brain atrophy [200]. In MOGAD-associated cortical encephalitis with seizures, MRI findings range from normal scans to reversible cortical changes with leptomeningeal enhancement [201-203]. Rare presentations include isolated seizures [201] and pseudotumor cerebri-like syndromes [204], where contrast-enhanced imaging may improve diagnostic accuracy.

Figure 1.2: MOGAD diagnostic criteria from international panel of experts consensus requires fulfilment of A, B and C[186]



(A) Core clinical demyelinating event

Clinical Event	Description
Optic neuritis	Unilateral or bilateral vision loss, retro-orbital pain
Myelitis	Longitudinally extensive transverse myelitis (LETM), central cord involvement
ADEM	Acute disseminated encephalomyelitis, common in children
Cerebral monofocal or polyfocal deficits	Focal neurological symptoms with demyelinating lesions
Brainstem or cerebellar deficits	Ataxia, dysarthria, vertigo, diplopia
Cerebral cortical encephalitis	Seizures, headache, altered mental status

(B) Positive MOG-IgG test

Test Type	Criteria
Cell-based assay: serum	
Clear positive	No additional supporting features required
Low positive	AQP4-IgG seronegative AND ≥1 supporting clinical/MRI feature
Positive without reported titer	Requires supporting clinical/MRI evidence
Negative but CSF positive	CSF positivity considered with strong clinical suspicion

Supporting clinical or MRI features

Feature	Description
Optic neuritis	Bilateral involvement, longitudinal optic nerve lesions, perineural sheath enhancement, optic disc edema
Myelitis	LETM, central cord involvement, H-sign, conus lesion
Brain, brainstem, or cerebral syndrome	Multiple T2-hyperintense lesions, deep grey matter involvement, cortical lesions

(C) Exclusion of better diagnoses including multiple sclerosis

In acute MOGAD optic neuritis (ON), MRI typically reveals longitudinally extensive optic nerve hyperintensity on T2-weighted images with contrast enhancement[160], affecting over 90% of the intra-orbital segment. Lesions may extend to the optic chiasm but rarely occur in isolation at this site[205]. Characteristic imaging features include; Optic nerve sheath enhancement, often with perineural extension into orbital fat (50% of cases) [206]; Optic disc oedema (53%), frequently visible on imaging [206]. Unlike MS, optic disc oedema is often more pronounced in MOGAD, while MS-associated oedema tends to be mild and less detectable on orbital imaging [207]. The combination of longitudinally extensive optic nerve involvement and the absence of

typical MS brain lesions can help distinguish MOGAD from MS and should prompt MOG-IgG testing [206].

Longitudinally extensive transverse myelitis (LETM), involving three or more vertebral segments, occurs in over 70% of MOGAD cases[208]. More than 70% of MOGAD myelitis affects both the cervical and thoracic spinal cord, often with multiple lesions that combine short and longitudinally extensive segments, a pattern more common than in AQP4-NMOSD[209]. Conus medullaris involvement is also more frequent in MOGAD (30–40%) compared to MS (≤30%)[210]. Key distinguishing features of MOGAD myelitis:

- Central lesion location on axial T2-weighted imaging, often affecting grey matter, creating the H-sign (30–60% of cases vs. 8% in AQP4-NMOSD and rare in MS).
- Pseudo-expansion of the central canal, seen in 29% of MOGAD cases, but rare in MS (4%)[211].
- Contrast enhancement patterns vary, with 26–67% showing enhancement, which may be patchy, cloud-like, or nodular.
- Leptomeningeal and spinal root enhancement occurs in >30% of MOGAD cases, a feature rarely seen in MS[212].

There are definite similarities between AQP4-NMOSD and MOGAD in terms of spinal cord findings (LETM). Involvement of the conus medullaris, abnormalities confined to grey matter and nerve roots, and lack of or minimal gadolinium enhancement favour MOGAD over AQP4-NMOSD or MS [213]. Of note, a clinical-radiological paradox is particularly observed in children, with minor clinical disability despite extensive lesions. Furthermore, MRI of optic nerves in ON demonstrates extensive T2-hyperintensity and T1-gadolinium enhancement that predominates in the anterior portion of the nerve.

Perineural oedema is also a further finding seen in up to half of MOGAD patients presenting with an ON phenotype [214-216].

Post-attack studies show that T2 lesions persist in MS, rarely resolve in AQP4+NMOSD, but disappear in 60–83% of MOGAD cases[217, 218]. A study by our group in collaboration with Mayo Clinic (US), analysed 55 MOGAD patients (median age 14 years, 53% female) across 58 attacks, comparing them with 38 MS and 19 AQP4+NMOSD patients[219]. 10% of MOGAD attacks had a normal initial MRI despite cerebral symptoms, indicating radiologic lag. On repeat MRI (median 8 days later), 47% developed new T2 lesions, 41% remained stable, and 7% showed lesion resolution. Steroid treatment was linked to greater lesion resolution (21% vs. 3%, $p = 0.048$) and fewer new T2 lesions ($p = 0.03$). MRI changes were more frequent in MOGAD (59%) compared to MS (26%) and AQP4+NMOSD (21%), with lesion resolution unique to MOGAD (12%). These findings emphasise MOGAD's dynamic lesion evolution, distinguishing it from MS and AQP4+NMOSD, and support repeat MRI for better disease monitoring.

1.4.6 Management

1.4.6.1 Acute relapse treatment

Currently, no randomised controlled trials or evidence-based guidelines exist for the acute treatment of paediatric MOGAD relapses. Due to delays in obtaining MOG-Ab results, clinicians typically base treatment on clinical phenotype, similar to MS and AQP4-NMOSD management. Corticosteroids remain the first-line therapy, with intravenous methylprednisolone (IVMP) (30 mg/kg/day, max 1g for 3–5 days) often leading to complete symptom remission [220-223]. Therefore, intravenous methylprednisolone (IVMP) (30mg/kg/day or max. 1g for 3-5 days) is used as first line therapy. In cases of severe relapses with inadequate response, escalation therapy is

required, including plasma exchange (PLEX, 5 cycles on alternate days), immunoadsorption, or intravenous immunoglobulins (IVIg, 2g/kg over 2–5 days). PLEX may also be followed by IVIg for additional therapeutic benefit.

The optimal duration and tapering regimen for steroids after initial intravenous treatment in paediatric MOGAD remains unclear and widely debated, often varying by clinician and centre. Some adult centres recommend 1 mg/kg/day for 3 months, followed by a gradual taper over another 3 months. A study of 59 MOGAD patients found that many relapses occurred near the end of the taper or soon after stopping steroids [220]. In children with complete recovery, an oral taper may not be necessary, while those with incomplete recovery may benefit from a longer course, though the risk-benefit balance should be carefully considered.

Although no phase III trials have evaluated acute treatments for MOGAD or NMOSD, retrospective studies emphasize the importance of early intervention. Delayed steroid treatment in MOGAD optic neuritis has been linked to worse visual outcomes, while early immunotherapy reduces relapse risk [224]. High-dose corticosteroids, apheresis, and IVIG are widely used with positive effects. Emerging therapies such as eculizumab (anti-complement)[225] and tocilizumab (anti-IL6)[226] have shown promise in treatment-resistant cases and could be repurposed for acute attacks, though larger controlled trials are needed to confirm their efficacy.

1.4.6.2 Long term relapse prevention treatment (Table 1.6)

Disability accrual in MOGAD is primarily relapse-related, making early identification and treatment of high-risk patients a key therapeutic goal. However, differentiating between true relapses, steroid rebound, and pseudo-relapses due to intercurrent illness is often challenging. In paediatric MOGAD, long-term immunosuppressive

therapy is typically initiated after a second event, as nearly 75% of children follow a monophasic course. Clinicians rely on real-world clinical data, often not optimal for treatment efficacy assessment. Decisions on long-term immune therapy depend on factors such as age, severity of the initial attack, treatment response, risk of disability, and potential adverse effects

Second-line immunosuppressive treatments for MOGAD include mycophenolate mofetil (MMF), azathioprine, and rituximab. In contrast, first-line therapies used in MS (e.g., interferon-β and glatiramer acetate) are ineffective in MOGAD in both adults and children. Among relapsing MOGAD patients in six large retrospective studies [191, 220, 223, 227-229], IVIg monotherapy had the highest relapse-free rate (69%), followed by MMF (47%), rituximab (50%), and azathioprine (39%). However, anti-CD20 therapies (e.g., rituximab) appear less effective in MOGAD than in AQP4-NMOSD.[230]. Importantly, first-line MS therapies (e.g., interferon-β and glatiramer acetate) are ineffective in MOGAD in both adults [229] and children [191]. Second-line MS treatments show little benefit, with natalizumab linked to severe relapses and only anecdotal reports on the use of alemtuzumab, dimethyl fumarate, and fingolimod. Tocilizumab has demonstrated efficacy in reducing relapses in MOGAD patients resistant to standard therapies. Currently, randomised controlled trials are investigating Satralizumab (a subcutaneously administered humanized monoclonal antibody that targets the soluble and membrane-bound IL-6 receptor) and the anti-neonatal Fc receptor antibody Rozanolixizumab in MOGAD, with results expected in 2025–2026.

Table 1.6: Different maintenance treatments in paediatric MOGAD

Drug	Dose	Frequency	Route	Monitoring
Azathioprine (AZA)	2-3mg/kg/day	Daily	Oral	Thiopurine methyltransferase (TPMMT) genotype and activity prior to initiation
Mycophenolate Mofetil (MMF)	600-1200 mg/m^2/day (max 2g/day)	Daily	Oral	
Rituximab	Induction: 2-4 x 375mg/m^2 with 2-week interval OR 2 x 375-500 mg/m^2 with 2-week interval (max 1g/infusion); Reinfusion: 1 x 375-500mg/m^2 (max 1g/infusion)	Every 6 months	IV	CD19+ B cells at 3,4 and 5 months
IV immunoglobulin (IVIg)	1-2 g/kg	Monthly	IV	
Prednisolone: add on 3-6 months (AZA/MMF)	0.5mg/kg/day (min 10mg/day, max 20mg/day)	Daily/alternate days	Oral	

1.4.7 Disease course and prognosis

The disease course of MOGAD is highly heterogeneous, with relapse frequency not directly predicting disability in individual patients. Children under 9 years tend to have more severe brain pathology and higher lesion loads than older children, yet they often show faster recovery from acute attacks [164]. In MS, studies suggest that EDSS recovery declines by 0.15 for every decade of age post-relapse [231]. Approximately 30% of children with MOGAD experience a second attack within five years [142], and 50% of those with relapsing MOGAD and brain involvement develop cognitive difficulties [164]. However, predicting long-term disease course remains challenging. High anti-MOG antibody titres were initially thought to indicate a higher relapse risk, but recent findings suggest patients can remain seropositive without relapsing, while some who serorevert still experience future relapses [232].

Like MS, MOGAD is linked to cognitive impairment in both children and adults [233, 234]. However, it remains unclear whether cognitive deficits precede the clinical onset of paediatric acquired demyelinating syndromes (ADS). A matched cohort study from our group analysed prospectively collected educational data in MS and MOGAD patients (n = 60) compared to controls (n = 449,553)[235]. At ages 10–11, academic performance was significantly lower in MOGAD (-1.27 adjusted z-score; 95% CI: -1.81 to -0.73, P < 0.001) and preclinical MS (-0.40; 95% CI: -0.80 to -0.0003, P = 0.0498). Moderate/high-efficacy MS treatment was linked to better final academic performance (0.92; 95% CI: 0.28–1.57, P = 0.005). After diagnosis, MS patients missed 8.7% of school (controls: 2.9%, P < 0.001) and MOGAD patients missed 11.9% (controls: 2.0%, P < 0.001), highlighting the impact of these conditions on education and school attendance.

1.5 Mimics of Acquired Demyelinating Syndromes

Several inflammatory and non-inflammatory conditions can mimic paediatric ADS, leading to potential misdiagnosis and inappropriate management. A Canadian study identified vascular disorders as a major ADS mimic in 6% of cases[236]. There are some important red flags which should raise concern for ADS mimics, including; a very young age, relevant, family history, atypical presentation and progressive decline, multi-system involvement, symmetrical MRI lesions and lack of response to immunosuppression [237]. We will now cover some important ADS mimics of specific interest.

Infections

Infections account for a large proportion of possible ADS and MS mimics. Extensive clinical history and laboratory investigations are crucial to distinguish infectious/para-infectious diseases from demyelinating disorders. Imaging features that can point towards an infectious aetiology include meningeal enhancement, ring enhancement with restricted diffusion, venous sinus thrombosis, calcification and bilateral striatal and thalamic involvement commonly in viral encephalitis.

An important mimic of demyelination presenting with transverse myelitis is an infective myelitis. This will often present with constitutional symptoms and the pathogenic cause may be viral, bacterial, fungal or parasitic. Acute flaccid myelitis (AFM), essentially a polio-like illness mainly affecting children, is seen in the picornavirus family (enterovirus 71, poliovirus, and, less commonly, coxsackievirus A and B) and in some flaviviruses. Outbreaks of AFM have occurred across multiple global regions since 2012 as seen in example from US enterovirus D68 outbreak. Typically, the clinical presentation is of flaccid and often profound muscle weakness (which can invoke respiratory failure and other critical complications) and it can mimic several other acute neurological illnesses. Imaging demonstrates unilateral or bilateral high signal on T2 sequences in the anterior horns of the spinal cord across multiple segments with variable enhancement.

Systemic autoimmune conditions

Systemic autoimmune diseases with CNS involvement, such as vasculitis, systemic lupus erythematosus (SLE), Sjögren's syndrome, sarcoidosis, and Behçet's disease, can mimic MS and ADS. CNS vasculitis often presents with a relapsing-remitting course, optic neuropathy, and brainstem involvement, sometimes accompanied by systemic symptoms like night sweats and skin changes. MRI may show punctate or tumefactive lesions, basal ganglia involvement, and leptomeningeal enhancement[237]. Brain biopsy is often required for confirmation.

SLE-related neuroinflammation affects 50% of cases but is clinically apparent in only 3%. It presents with ataxia, optic neuropathy, and transverse myelopathy[238], but unlike MS, can include seizures, psychiatric symptoms, and peripheral neuropathy. Diagnosis relies on systemic signs (malar rash, photosensitivity, arthritis) and serological markers (antinuclear antibodies, anti-double-stranded DNA antibodies, and antibodies to extractable nuclear antigens). Sjogren's syndrome can mimic MS with optic neuritis and myelitis, often accompanied by seizures, stroke-like episodes, and encephalopathy. Sarcoidosis can involve the optic nerves, hypothalamus, or cranial nerves, with MRI often showing white matter hyperintensities and leptomeningeal enhancement. Behçet's disease, a multisystem inflammatory disorder, can present with cerebral venous sinus thrombosis, encephalopathy, and psychiatric symptoms. Brainstem and posterior fossa involvement are common, but MRI findings are often non-specific.

Inherited Leukodystrophies and mitochondriopathies

Leukodystrophies, genetically determined leukoencephalopathies, can resemble demyelinating disorders on MRI. An MRI pattern recognition algorithm was developed to allow faster recognition and prompt diagnosis [239] Most present with bilateral, symmetric white matter abnormalities, whereas acquired demyelination tends to be multifocal and asymmetric. Additional MRI findings such as white matter rarefaction, cysts, contrast enhancement, and calcifications help refine diagnosis.

X-linked adrenoleukodystrophy (ALD) can show contrast enhancement, similar to acute MS relapses, while Hypomyelination with Brainstem and Spinal Cord Abnormalities and Leg Spasticity (HSBL) mimics MS but responds to steroids[240]. Similarly, mitochondrial leukoencephalopathies can present with steroid-responsive demyelination[241], further complicating diagnosis.

In addition, demyelinating conditions have been shown to co-exist in patients with mitochondriopathies. Mitochondrial disorders, such as Leber's Hereditary Optic Neuropathy (LHON), can mimic optic neuritis, presenting with severe bilateral vision loss and characteristic vascular changes on fundoscopy. LHON has been reported in cases of MOGAD[242] and AQP4-NMOSD[243], suggesting possible dual pathology.

POLG-related disorders and small-vessel diseases (e.g., CADASIL, CARASIL, FOXC1/PITX2 mutations) can also mimic MS [244], though paediatric-onset cases are rare. Biotinidase deficiency (BD), a metabolic disorder, has been misdiagnosed as NMOSD, with optic neuritis, LETM, and steroid responsiveness further complicating differentiation[245].

Haemophagocytic lymphohistiocytosis (HLH)

Haemophagocytic lymphohistiocytosis (HLH) is a systemic inflammatory disorder caused by genetic mutations (familial HLH) or secondary triggers like infection, autoimmune disease, or malignancy. Recently, isolated CNS HLH has been reported in both adults and children[246, 247], mimicking MS and NMOSD with relapsing demyelination and steroid responsiveness, making diagnosis challenging. Neuroimaging typically shows asymmetric confluent white matter lesions with subcortical and deep white matter involvement and sometimes a nodular perivascular enhancement pattern. The exact mechanism of CNS-restricted neuroinflammation remains unclear but may involve defective T-cell and NK-cell cytotoxicity, leading to impaired antigen clearance[248].

RANPB2 mutation and acute necrotizing encephalopathy

An important ADS mimic is Acute necrotizing encephalopathy (ANEC), a rapidly progressive encephalopathy seen mainly in previously healthy young children (typically

East Asian), normally with a prodromal febrile illness (linked to influenza A epidemics) followed by CNS involvement with encephalopathy and seizures. Haemorrhagic lesions are typically seen in the deep grey matter on brain MRI, and it has been associated with mutations in RANBP2. The risk of ANEC is 40% in patients with this autosomal dominant mutation (which has incomplete penetrance) and the disease is also steroid responsive.

1.6 Rationale for this thesis

Paediatric multiple sclerosis and other relapsing demyelinating conditions present unique diagnostic and management challenges compared to adult-onset multiple sclerosis (MS). Despite significant advancements in understanding the disease course in adults, paediatric MS remains under-researched, particularly in terms of long-term outcomes and optimal treatment strategies. The landscape of disease-modifying therapies (DMTs) for paediatric MS is rapidly evolving, with newer, high-efficacy treatments demonstrating superior outcomes compared to traditional injectable therapies. However, the real-world effectiveness, safety, and long-term impact of these treatments in paediatric populations remain unclear.

While many children with acquired demyelinating syndromes (ADS) experience a monophasic disease course, a subset develops relapsing conditions such as MS, MOGAD, or AQP4-NMOSD. Differentiating between these disorders is challenging due to overlapping clinical and radiological features, yet early and accurate diagnosis is critical as each condition requires a distinct treatment approach. Furthermore, although MOGAD is now recognised as a distinct entity, its long-term prognosis, optimal treatment strategies, and underlying pathophysiology remain incompletely understood.

Against this background, the overarching aim of this thesis is to improve the understanding of disease course, diagnosis, and treatment strategies for paediatric acquired demyelinating disorders, with a focus on imaging biomarkers for diagnosis and treatment response. To address this, I conducted three epidemiological, clinical and imaging real-world observational studies on paediatric MS and MOGAD, which are described in the experimental chapters (Chapters 2 - 4). Ultimately, this research aims to inform clinical decision-making, improve prognostic accuracy, and guide future therapeutic approaches for children with MS and related demyelinating conditions. By leveraging large, well-characterised cohorts with long-term follow-up, this thesis contributes to a growing body of evidence supporting more individualised, evidence-based management of paediatric demyelinating diseases.

Chapter 2: Incidence of Paediatric-Onset Multiple Sclerosis and Other Relapsing Demyelination Conditions

2.1 Summary

In this chapter, I aimed to describe the long-term outcomes of children under 16 years of age diagnosed with acquired demyelinating syndromes (ADS) through a UK-wide prospective surveillance study. Over a 10-year follow-up period, clinical and diagnostic data were collected to determine disease progression and final diagnoses.

Patient diagnoses were obtained from patients' records via the patients' paediatric or adult neurologist using a questionnaire. An expert review panel classified demyelinating phenotypes at follow-up based on established diagnostic criteria. Among the 125 children included in the original study, 24 (19.2%) were ultimately diagnosed with multiple sclerosis (MS), corresponding to an incidence rate of 2.04 per million children per year. Of these, 23 met the 2017 McDonald criteria at disease onset. Additionally, three children (1.6%, 0.26 per million children per year) were diagnosed with aquaporin-4 antibody-positive neuromyelitis optica spectrum disorders (AQP4-Ab NMOSD), while five (4%, 0.43 per million children per year) were diagnosed with relapsing myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). Three seronegative patients who did not meet the criteria for MS experienced relapses, while the majority of children (85 out of 125, or 68%) had a monophasic disease course over the 10-year period.

Notably, 5/125 (4%) originally diagnosed with ADS were reclassified during follow-up: three children diagnosed initially with acute disseminated encephalomyelitis were subsequently diagnosed with acute necrotising encephalopathy (RANBP2 mutation), primary hemophagocytic lymph histiocytosis (Munc 13-4 gene inversion) and anti-NMDA-R encephalitis. One child initially diagnosed with optic neuritis was later diagnosed with vitamin B12 deficiency, and one presenting with transverse myelitis was subsequently diagnosed with Sjögren's syndrome.

Overall, these findings indicate that most paediatric ADS cases follow a monophasic course. However, given the potential for misclassification and the implications for treatment, thorough investigations are essential to differentiate MS from other central nervous system autoimmune disorders.

2.2 Introduction

Paediatric multiple sclerosis (MS) and other acquired demyelinating syndromes (ADS) represent a spectrum of central nervous system (CNS) inflammatory disorders in children. These conditions are associated with significant morbidity and can have long-term implications for neurological function, cognitive development, and quality of life. Despite increased awareness of paediatric MS and related demyelinating diseases, challenges remain in accurately diagnosing and managing affected children due to overlapping clinical, radiological, and immunological features between different disease phenotypes.

Acquired demyelinating syndromes in children encompass a range of clinical presentations, including monophasic conditions such as acute disseminated encephalomyelitis (ADEM), optic neuritis (ON), and transverse myelitis (TM), as well as relapsing disorders like multiple sclerosis (MS), myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), and aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder (AQP4-Ab NMOSD). Distinguishing between these conditions is critical, as each follows a distinct disease trajectory and requires tailored therapeutic strategies. Early and accurate diagnosis is essential to guide treatment decisions and prevent long-term neurological disability, yet it remains a challenge due to the dynamic nature of disease evolution in paediatric patients.

Over the past decade, there has been a growing recognition of the role of CNS autoantibodies, particularly MOG and AQP4 antibodies, in delineating distinct demyelinating syndromes. These biomarkers have revolutionized the classification of paediatric demyelinating diseases, allowing for better differentiation from MS, which remains the most common relapsing disorder in this population However, given the relatively recent clinical availability of MOG-Ab and AQP4-Ab testing, there remains a need for long-term epidemiological studies assessing the incidence and outcomes of these conditions over time.

In a UK-wide prospective surveillance study of children under the age of 16 years (September 2009–September 2010), the incidence of childhood CNS inflammatory demyelination was calculated as 9.83 per million per year[3].

2.3 Aims

Here, we conducted 10-year follow-up evaluations of the above mentioned 2009-2010 cohort (UK-wide prospective surveillance study of children under the age of 16 years), to ascertain the incidence of multiple sclerosis and other relapsing demyelinating syndromes.

2.4 Methodology

Children under 16 years with a first episode of acquired demyelinating syndrome (ADS), who underwent brain and/or spinal MRI, were identified from a prospective UK-wide surveillance study conducted between 2009–2010. Case ascertainment was achieved through two parallel reporting systems: the British Paediatric Surveillance Unit (BPSU) and the British Ophthalmological Surveillance Unit (BOSU). Monthly BPSU reporting cards were sent to over 3,000 consultant paediatricians and paediatric

neurologists across the UK and Ireland, asking whether they had seen a new case of ADS. Positive responders were then sent a structured initial questionnaire to collect standardised data on demographics, clinical presentation, imaging, CSF findings, treatment, and short-term outcomes. A follow-up questionnaire was sent at 12 months to obtain further outcome and diagnostic information.

In parallel, clinicians were encouraged to collect and store acute serum samples (within three months of presentation), which were cryopreserved at –80°C for potential retrospective antibody testing. At the time of the initial study, routine MOG-IgG and AQP4-IgG testing was not available; AQP4-Ab testing was performed only when NMOSD was clinically suspected. Subsequent MOG-Ab testing was carried out in two batches: the first in 2014 on stored samples (n=49), and a second batch when the test became clinically available (n=27).

Demyelinating phenotypes were reviewed and classified by an expert panel (Dr Evangeline Wassmer, Dr Yael Hacohen, Dr Ming Lim, and Dr Sukhvir Wright) at both initial presentation and final follow-up, based on International Paediatric Multiple Sclerosis Study Group criteria, the 2017 revised McDonald Criteria, and the International Consensus Diagnostic Criteria for NMOSD. Clinical and paraclinical data were retrieved from patients' medical records by contacting the responsible paediatric or adult neurologist using a structured follow-up questionnaire.

Ethical approval for the surveillance study was granted by the UK Multicentre Research Ethics Committee (09/H1202/92).

2.5 Statistical Analysis

I used descriptive statistics to summarize the key components of the data set. I used non-parametric statistical tests (Kruskal–Wallis tests) for continuous distributions, as appropriate, given the lack of normality and v2 or Fisher's exact tests were used for nominal data. Estimates of national incidence with confidence intervals (Byar's approximation of the exact Poisson) for the 13-month study were annualised using mid-2010 UK and 2010 Republic of Ireland population estimates[249]. Analyses were performed using GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA).

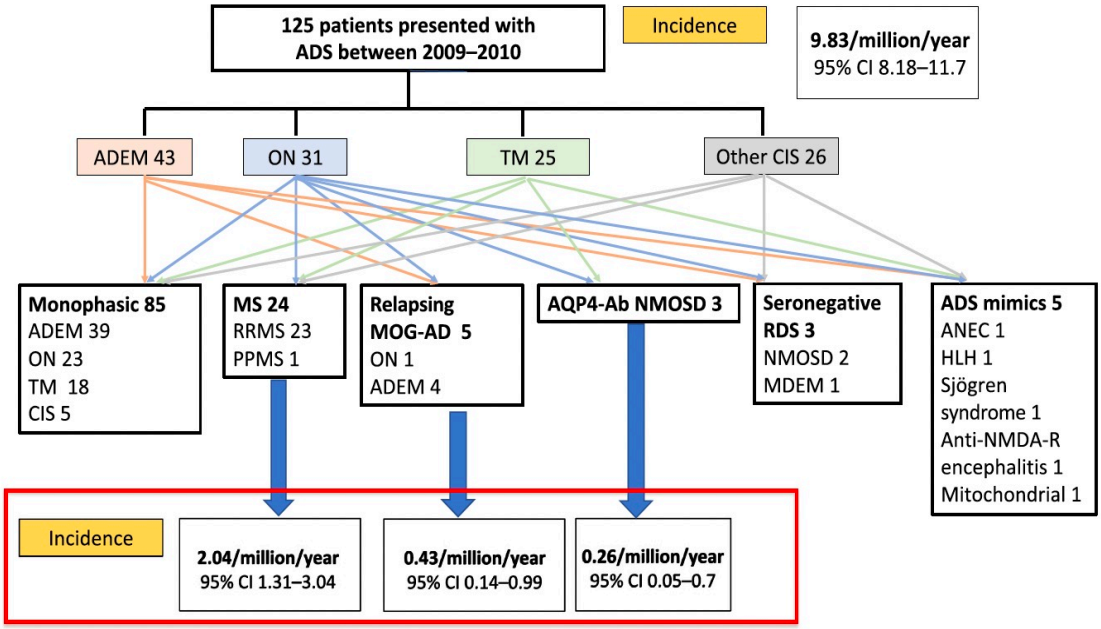
2.6 Results

A total of 125 children were included in the original cohort (64 males, 61 females; median age 10 years, range 1year 4months–15years 11months); follow-up data on diagnosis at 10 years were collected. Paediatric and adult neurologists responded with completed questionnaires for 113/125 patients (90%). Of the 12 patients who did not have 10-year follow-up data (ON n=6, TM n=3, ADEM n=3), all had remained monophasic at 3 years. Eighty-five (68%) of the 125 children included had a monophasic ADS of which 39/85 (45.8%) presented with ADEM, 23/85 (27.1%) with ON, 18/85 (21.2%) with TM (4 with short TM and 14 with longitudinally extensive TM) and 5/85 (5.9%) with other clinically isolated syndrome (CIS) presentations (Figure 2.1).

Thirty-five children (28%) had relapsing demyelinating syndromes (RDS). Twenty-four children (19.2%) had a final diagnosis of MS, including 23 with relapsing remitting MS (RRMS), and one had a primary progressive phenotype. Therefore, the incidence of MS under the age of 16 years in the UK and ROI was calculated as 2.04 per million children per year (95% confidence interval [CI] 1.31,3.04). Of these 4/24 (16.7%) presented under the age of 12 years, with a UK incidence of 0.34 per million children

per year (95% CI 0.09,0.87). When retrospectively applied, the revised 2017 McDonald's diagnostic criteria diagnosis of MS could be made at presentation in 23/24 (95.8%). The remaining patient met the dissemination in space (DIS) criterion at presentation (did not have a contrasted scan or a lumbar puncture) and had a clinical relapse within 1 year of disease onset.

Figure 2.1: Flowchart of 125 children included in the original cohort and the final diagnoses and their incidence



A total of 125 children were included in the original cohort. Initial presentations were acute disseminated encephalomyelitis (ADEM) in 43 (34.4%), optic neuritis (ON) in 31 (24.8%), transverse myelitis (TM) in 25 (20%), and other clinically isolated syndrome (CIS) presentations in 26 patients (20.1%). At 10-year follow-up, 85 (68%) of the 125 children included had a monophasic acquired demyelinating syndrome. Thirty-five children (28%) had a relapsing demyelinating syndrome (RDS); 24 had a final diagnosis of multiple sclerosis (MS), four had relapsing myelin oligodendrocyte

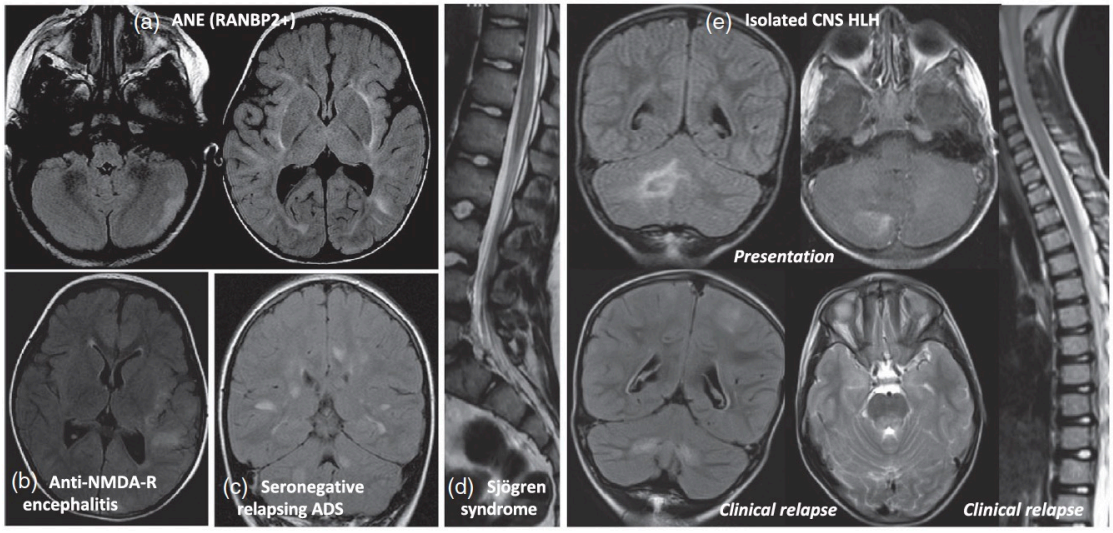
glycoprotein antibody-associated disease (MOG-AD), three had aquaporin-4 antibody (AQP4-Ab) positive neuromyelitis optica spectrum disorder (NMOSD), and three had seronegative RDS. Incidence was calculated for MS, relapsing MOG-AD, and AQP4-Ab NMOSD and is shown below the relevant diagnoses. ANEC, acute necrotising encephalopathy; HLH, haemophagocytic lymphohistiocytosis; MDEM, multiphasic disseminated encephalomyelitis; RRMS, relapsing remitting multiple sclerosis; PPMS, primary progressive multiple sclerosis; NMDA-R, N-methyl-D-aspartate receptor.

Only 76/125 (60.8%) had MOG-Ab and AQP4-Ab tested of which 20/76 (26.3%) were positive for MOG-Ab and 2/76 (2.6%) for AQP4-Ab. All 24 patients with a diagnosis of MS, including the four patients with disease onset under the age of 12 years were negative for both autoantibodies. Antibodies were tested in 41/85 patients with monophasic disease compared to 35/35 patients with relapsing disease. Of the 41 patients with a monophasic disease who had antibody testing, 37/41 (90.2%) were tested at onset, and a further four were tested at follow up. Only 14/43 (32.6%) patients presenting with ADEM had antibody testing at onset, and a further three at follow up. 19/35 (54.3%) of the patients with a relapsing disease course who had antibody testing, were tested at onset and a further 16 were tested at follow up. 5/20 (25%) of the MOG-Ab positive patients had a relapsing disease course. Therefore, the incidence of relapsing MOG-Ab Associated Disease (MOGAD) in children was calculated as 0.43 per million children per year (95% CI 0.14,0.99) and that of AQP4-Ab NMOSD as 0.26 per million children per year (95% CI 0.05,0.7).

Five patients originally diagnosed with an ADS had alternative diagnoses at 10-year follow-up (Figure 2.2). Three patients originally diagnosed as ADEM were found to have the following three final diagnoses: acute necrotising encephalopathy (ANEC) with a confirmed mutation in RANBP2, primary hemophagocytic lymphohistiocytosis (HLH) with an inversion of the Munc 13-4 gene, and Anti-NMDA-R encephalitis (with

white matter involvement on neuroimaging) (Figure 2.2). One patient initially diagnosed with ON did not respond to immunotherapy and was diagnosed with vitamin B12 deficiency (with a concurrent mitochondrial ND5 variant). Finally, one patient who presented with transverse myelitis was subsequently diagnosed with Sjögren's syndrome.

Figure 2.2: Five cases with alternative diagnoses at 10-year follow-up as below



a) Female patient presented at 16 months of age with encephalopathy, generalised seizures, abnormal eye movements and hypotonia. Her sister also presented previously with ADEM at a similar age. Axial T2-weighted FLAIR MRI brain imaging showed abnormal hyperintensity of the left cerebellar grey matter and fairly symmetrical hyperintensity of the cerebral white matter, including the external capsules. Genetic screening confirmed RANBP2 mutation in both siblings.

b) Female patient presented at 2 years of age with severe encephalopathy, seizures and a complex movement disorder. She was noted to have a right sided hemiplegia on clinical examination. She was positive for serum Anti-NMDA-R antibodies, and negative for MOG-antibodies. Axial T2-weighted FLAIR MRI brain imaging showed an asymmetric distribution of multiple hyperintense grey and white matter lesions, with a notable grey matter predominance.

c) Female patient presented at 14 years of age with encephalopathy, bilateral weakness, sensory loss with CSF protein elevation (2.6g/L) and positive oligoclonal bands. Axial T2-weighted MRI brain imaging showed extensive bilateral asymmetrical patchy parenchymal signal abnormality involving the deep white matter, brainstem, internal capsules and cerebellar peduncles. She also had longitudinally extensive transverse myelitis (LETM) from C1-T4 (not shown here). She went on to have two further relapses with a similar presentation within the first year.

d) Female patient presented at 12 years of age with bilateral weakness of upper and lower limbs in addition to sphincter dysfunction. Sagittal T2-weighted MRI imaging of the spinal cord showed a lesion in the conus medullaris.

e) Male patient presented at 8 years of age with left convergent squint, ataxia, seizures in addition to lung infiltrates, cycling cytopenia and hepatosplenomegaly. Coronal T2-weighted FLAIR and contrast enhanced T1-weighted brain MRI imaging at presentation showed a heterogeneously enhancing lesion in the right cerebellar hemisphere bearing some localised oedema and leptomeningeal enhancement. Follow-up imaging on relapse showed symmetrical hyperintense lesions on T2-weighted images in the cerebellum and dorsal pons, symmetrical lesions in the cerebral hemispheres as well as an LETM. He underwent bone marrow transplant with an unsuccessful CNS response with clinical and neurological evidence of progression that led to his demise.

Table 2.1 includes clinical and paraclinical information for this cohort. Children with monophasic ADS group were younger than the MS cohort (median age 8.7 yrs vs 13.9 yrs, $p<0.0001$) and were more likely to present with ADEM; none of the children presenting with ADEM were subsequently diagnosed with MS. Abnormalities in brain MRI at presentation were seen in 23/24 (95.8%) of MS patients compared to 50/83 (60.2%) of patients in the monophasic group ($p=0.0007$). Intrathecal oligoclonal bands were reported in 24/24 (100%) of the MS group compared to only 4/53 (7.5%) of the monophasic ADS group ($p<0.0001$).

Table 2.1: Clinical and paraclinical features of monophasic ADS, MS and all patients

	All patients (*n*=125)	Monophasic ADS (*n*=85)	Multiple Sclerosis (*n*=24)	p value (Monophasic ADS vs MS)
Age at presentation; median (IQR)	10.3 (6.4, 13.9)	8.7 (5.9, 12.2)	13.9 (12.8, 14.7)	<0.0001
Sex (Male: Female)	64:61 (1.05:1)	43:42 (1.02:1)	9:15 (1:1.7)	0.35
Ethnicity (White: Other)	102:23 (4.4:1)	71:14 (5.1:1)	16:8 (2:1)	0.06
Presentation				
ADEM (%)	43 (34.4)	39 (45.9)	0 (0)	<0.0001
TM (%)	25 (20)	18 (21.2)	4 (16.7)	0.57
ON (%)	31 (24.8)	23 (27.1)	7 (29.2)	0.93
CIS –Other (%)	26 (20.1)	5 (5.9)	13 (54.2)	<0.0001
CSF OCB (%)	24/80 (30)	4/53 (7.5)	17/17 (100)	<0.0001
Abnormal brain MRI at onset (%)	83/121 (68.6)	50/83 (60.2)	23/24 (95.8)	0.0007
Abnormal spine MRI at onset (%)	29/58 (50)	26/41 (63.4)	8/11 (72.7)	0.63

Three children (2.4%) died during follow up; one patient during acute presentation of ADEM from acute fulminant inflammation inducing cerebral oedema, one with AQP4-Ab NMOSD 10 years after initial presentation during relapse following a hyperkalaemic cardiac arrest; and the patient with primary HLH died following an unsuccessful bone marrow transplant with further CNS relapses.

2.7 Discussion

In this long-term (up to 10 years) follow-up of a UK population-based active surveillance study on children with acquired demyelinating syndromes (ADS), findings

confirm that most children followed a monophasic disease course. A key observation was that 95.8% of children diagnosed with multiple sclerosis (MS) met the 2017 revised McDonald criteria at presentation. The only child who did not fulfill the criteria lacked oligoclonal band analysis and a contrast-enhanced MRI scan. At the time of the original study, the 2006 McDonald criteria were in use, later replaced by the 2010 and 2017 criteria, which have demonstrated improved sensitivity in both adults[36] and children [71] [250]. Notably, 42% (10/24) of cases met the 2010 criteria at the time of the study. The annual incidence of paediatric MS in children under 16 years (2.04 per million) in this cohort aligns with international reports, which range from 0.13 to 2.85 per 100,000 children per year[135] [232] [164, 251].

Since the initial surveillance period in 2009–2010, there has been a paradigm shift in the diagnosis and management of childhood relapsing demyelinating syndromes (RDS), largely due to the discovery of CNS autoantibodies. Both AQP4-Ab-associated disease and MOGAD are now widely recognised as distinct entities [252]. The low incidence of MOG-Ab positivity and relapsing MOGAD in this cohort is likely attributed to MOG-Ab testing only becoming clinically available in 2014. Despite MOG-Ab positivity being most prevalent across ADS phenotypes [253], only 17 out of 43 (39.5%) children with ADEM had MOG-Ab tested, likely leading to underestimation of MOGAD cases. Additionally, patients tested in 2009–2010 were more likely to have relapsing disease, while monophasic cases may have already become seronegative by the time of testing [254]. Recent data indicates that up to one-third of children with ADS are MOG-Ab positive [255], and the proportion of MOGAD patients with a relapsing disease course in this cohort aligns with findings from other prospective studies [236].

My reported paediatric incidence of AQP4-Ab NMOSD (0.26 per million children per year) is similar to that reported in paediatric studies worldwide (ranging from 0.01 to

0.06 per 100,000/year); however, data remains scarce in this group. NMOSD has global variations in both prevalence and incidence among different geographic areas and ethnicities. In two UK studies in small areas of England and Wales[254, 255], the prevalence of NMO/NMOSD was calculated as 19.6 per million (95% CI: 1.22,2.97), with 21% of the reported prevalent cases under age 20 years, resulting in a higher prevalence in the age group from 0 to 19 years.

Five children initially included in the ADS cohort were later found to have alternative inflammatory aetiologies, highlighting the critical importance of thorough diagnostic evaluation due to significant treatment implications. Traditionally, monogenetic disorders were thought to present in younger children with developmental delay, symmetrical MRI findings, and a lack of response to immunosuppression. However, an increasing number of conditions now mimic ADS, making diagnosis more complex. Notably, one patient with primary HLH exhibited a relapsing disease course, responded well to steroids, and met diagnostic criteria for both MS and NMOSD, further illustrating the overlap between these conditions. A study of 322 ADS patients from the Canadian Paediatric Demyelinating Disease Network found that 20 children (6%) were ultimately diagnosed with alternative conditions[236]. Unlike our findings, vascular disorders were the most frequently reported alternative diagnoses (11 out of 20 cases), including primary or secondary CNS vasculitis, vasculopathy, stroke, and migraine. Additionally, while rare, malignant brain tumours remain an important differential diagnosis to consider [30].

The study has some limitations, including the potential under-reporting of cases, a common issue in epidemiological research. However, this was mitigated by using clear consensus case definitions and multiple case ascertainment sources. Loss of follow-up due to patient migration was another challenge, though the UK national healthcare system enabled the identification of 90% of patients through clinician responses.

It is also unlikely that patients initially diagnosed with monophasic ADS would experience relapses without being referred to the NHS England Highly Specialised Service for Paediatric Multiple Sclerosis, which manages MS and other recurrent demyelinating syndromes. Another limitation was the lack of systematic antibody testing at onset and long-term disability follow-up, such as Expanded Disability Status Scale (EDSS) assessments. Nevertheless, our study clearly demonstrates that (i) the majority of ADS presentations in children are monophasic; and (ii) the diagnosis of MS can be made at onset in the majority of cases when CSF and/or contrasted scans are available. These findings are clinically relevant when counselling children and families at diagnosis, helping to guide expectations and early management.

2.8 Conclusions

A comprehensive understanding of the real-world burden of individual demyelinating conditions across geographic regions, age groups, sex, and ethnicities is crucial for improving diagnostics, treatment strategies, resource allocation, and service development. Given the therapeutic implications, thorough investigations are essential to exclude both MS and CNS autoantibody-associated mimics during the diagnostic process, ensuring accurate diagnosis and appropriate management.

After describing the 10-year follow-up of children with acquired demyelinating syndromes (ADS) from UK-wide prospective surveillance, in Chapter 3, I will focus on paediatric MS and test the real-world effectiveness of treatment with disease modifying therapies (DMTs) both clinically and radiologically, comparing newer DMTs with injectables in children with relapsing remitting multiple sclerosis (RRMS).

Chapter 3: Real-world effectiveness of Disease-Modifying Therapies in Paediatric Relapsing Remitting Multiple Sclerosis in the UK

3.1 Summary

In this chapter, I aimed to evaluate the real-world effectiveness of newer disease-modifying therapies (DMTs) compared to traditional injectable treatments in children with relapsing-remitting multiple sclerosis (RRMS). Additionally, I assessed the efficacy

and safety of ocrelizumab, a newer DMT, in a paediatric MS population within a real-world clinical setting.

I used two separate cohorts in this chapter:

a) In a retrospective, multicentre study, run within the UK childhood neuroinflammatory disorders network, I identified children with RRMS receiving DMTs in the period of January 2012-December 2018. Clinical and paraclinical data were retrieved from patient medical records. I used the following outcome measures: annualised relapse rates (ARR) prior to and on treatment, time to clinical relapse, switching DMT and development of new radiological activity from treatment initiation, in addition to change in EDSS score from baseline to last follow-up.
b) In a prospective study, I recruited consecutive paediatric MS patients (<18 years) from three UK tertiary paediatric neurosciences centres who received ocrelizumab. I assessed patients at baseline and measured outcomes at 6 monthly follow-up intervals. Recruitment is ongoing with 5-year follow-up planned per patient.

In the retrospective cohort, 103 children with RRMS were followed up for a median of 3.8 years. Relapses occurred in 59.5% (53/89) of patients on injectables compared to 15% (8/54) of those on newer DMTs. The ARR decreased from 1.9 to 1.1 in patients receiving injectables ($p < 0.001$) and from 1.6 to 0.3 in those on newer DMTs ($p = 0.002$). New MRI lesions were observed in 86.5% (77/89) of patients on injectables compared to 47% (26/54) of those on newer DMTs. At two years post-treatment initiation, 37% (38/103) of patients exhibited MRI activity without clinical relapses. No significant changes in EDSS scores were observed, and only two patients showed signs of cognitive impairment. Patients on newer DMTs demonstrated significantly longer times to relapse, treatment switching, and new radiological activity compared to those on injectables (log-rank $p < 0.01$). Multivariable analysis indicated that injectables were associated with a twelvefold increase in the risk of clinical relapse

(adjusted HR = 12.12, 95% CI = 1.64-89.87, p = 0.015) and a twofold increase in the risk of new radiological activity (adjusted HR = 2.78, 95% CI = 1.08-7.13, p = 0.034) compared to newer DMTs.

In the prospective cohort, 60 paediatric RRMS patients were included, with a median age of 14.6 years (IQR 13.3–15.5). The majority were female (81.7%) and non-white (68.0%). The median follow-up period was 2 years (range: 1.0–3.6). Of the 43 patients who completed the 24-month follow-up, 93% (40/43) achieved no evidence of disease activity (NEDA-3). The median EDSS score remained stable, from 1.5 at baseline to 1.0 at follow-up (p = 0.21). Serious adverse events were recorded in one patient with enterovirus meningitis, who made a full recovery.

These findings suggest that newer DMTs offer significantly greater effectiveness in reducing both clinical relapses and radiological disease activity compared to traditional injectables. The results support a shift in treatment strategies towards early initiation of higher-efficacy therapies in paediatric RRMS to optimise disease control and long-term outcomes.

3.2 Introduction

The approach to treatment of relapsing remitting (RRMS) is rapidly evolving, with over 20 disease-modifying therapies (DMTs) currently licensed for adults, that target the immune system peripherally and reduce MS relapse risk[101]. DMTs vary in efficacy and risk profile, ranging from older injectables (interferon-β and glatiramer acetate), which offer moderate efficacy with favourable safety, to newer oral and infusion therapies, which provide greater clinical effectiveness but come with a higher risk of adverse effects [63]. To date, only three clinical trials have been published in paediatric MS [102-104].

This is partly as a result of major recruitment challenges due to the low incidence and prevalence of paediatric MS, in addition to challenges of MS diagnosis in children, with an emphasis on exclusion of other mimics, particularly antibody-mediated diseases such as myelin oligodendrocyte glycoprotein (MOG) and aquaporin-4 (AQP-4) antibodies[256].

Current treatment strategies for paediatric MS vary across centres and are largely adapted from adult protocols. The key challenge lies in balancing under-treatment, which risks poor disease control and accumulating disability, against over-treatment, which may expose children to unnecessary toxicity, infertility risks, malignancy, and premature immune senescence [127]. Despite these concerns, paediatric MS prognosis has improved, with a global decline in annual relapse rates compared to the pre-treatment era [61], suggesting that current therapies may positively influence long-term disease progression.

The first randomised controlled trial in paediatric MS comparing fingolimod, a newer oral disease-modifying therapy (DMT), to interferon-β, an older injectable DMT, demonstrated the superior efficacy of fingolimod. The study showed a significantly lower relapse rate, reduced lesion accumulation on MRI, and a slower rate of brain atrophy over a two-year period[102, 257]. Additionally, a multicentre study involving 741 paediatric MS patients from the US Network of Paediatric MS Centers found that those receiving newer DMTs had a substantially lower relapse rate compared to those on older injectable therapies (rate ratio 0.45, 95% CI 0.29-0.70, $p < 0.001$; rate difference 0.27, 0.14-0.40, $p = 0.004$), further supporting the growing evidence of the effectiveness of newer therapies in this population.[258]. Further real-world studies have demonstrated similar results[259, 260].

More recently, ocrelizumab, a humanised monoclonal antibody that selectively depletes CD20+ B cells, shown to be highly effective in adult RRMS and PPMS[261, 262]. Real-world effectiveness data on ocrelizumab in paediatric MS are limited.

3.3 Aims

There are very few studies to guide optimal initial DMT choice for paediatric MS. In the first part of this chapter, my aim was to evaluate real-world effectiveness of treatment with newer compared to older injectable DMTs in children with relapsing remitting multiple sclerosis (RRMS). In addition, I aimed to compare the different clinical (annualised relapse rate), imaging (≥ 2 new T2 hyperintense and/or ≥ 1 gadolinium-enhancing lesions) and disability parameters (Expanded Disability Status Scale, EDSS) pre- and on treatment. In the second part, my aim was to evaluate the efficacy and safety of ocrelizumab for children with MS in a real-world clinical setting with a prospective cohort.

3.4 Methodology

3.4.1 Retrospective cohort

This project was a multi-institutional, retrospective study run within the UK Childhood Neuroinflammatory Disorders (UKCNID) network, involving 7 paediatric neuroscience centres commissioned to manage paediatric-onset MS: Great Ormond Street Hospital (London), Evelina London Children's Hospital (London), Birmingham Children's Hospital, Addenbrooke's Hospital (Cambridge), Alder Hey Children's Hospital (Liverpool), Royal Manchester Children's Hospital and Great North Children's Hospital

(Newcastle). Centres were asked to identify patients <18 years old with RRMS receiving disease-modifying therapies (DMTs) in the period of January 2012 to December 2018, using Blueteq records of DMT prescriptions (drug management system used by NHS England for high-cost drugs including DMTs)[263]. Patients who entered a clinical trial with a DMT were excluded. I retrospectively reviewed clinical data including demographics, clinical findings and laboratory results, first and subsequent relapse characteristics, and treatment information, from electronic medical records of patients and I entered them into a standardized database. Ethical approval for the surveillance study was given by the UK Multicentre Research Ethics Committee (09/H1202/92).

All patients had undergone brain imaging according to local MRI protocols every 6 months. Spinal cord imaging was only performed when clinically indicated and was not done routinely. The patient's age at DMT start, year the DMT was prescribed, duration of use, side effects and reasons for discontinuation or switching therapies were included. The NCI Common Terminology Criteria for Adverse Events (v.5), was used for reporting of adverse events using a grading (severity) scale[264]. Markers of disease severity included first relapse characteristics (polysymptomatic, transverse myelitis, optic neuritis), number of relapses and presence of new T2 hyperintense or gadolinium-enhancing lesions on brain MRI prior to treatment and on-treatment, and Expanded Disability Status Scale (EDSS) scores at baseline and last follow-up.

For the purpose of this thesis, DMTs were categorised into two main groups to reflect historical treatment paradigms and current NHS clinical practice:

- **Older injectables**: This term refers to first-generation, moderately effective treatments administered via subcutaneous or intramuscular injection. These included **interferon beta-1a**, **interferon beta-1b**, and **glatiramer acetate**. These therapies have been in use for over two decades, with well-established

safety profiles but relatively modest efficacy in reducing relapse rates or MRI activity.

- **Newer DMTs**: This term refers to more recently introduced DMTs with higher efficacy profiles, often associated with more targeted mechanisms of action. These include oral DMTs(dimethyl fumarate, fingolimod and teriflunomide), or infusions (natalizumab, ocrelizumab and alemtuzumab). For simplicity and statistical power, this group is referred to throughout the chapter as "newer DMTs" although within this category there is variation in mechanisms, monitoring requirements, and long-term safety data.

This classification mirrors the treatment escalation framework historically used in UK paediatric MS practice, where children often began with older injectable therapies and escalated to newer agents only after breakthrough disease activity The primary comparison was between patients on older injectables and those who were started on or escalated to newer DMTs (oral and infusions). All patients had undergone brain and spinal cord MRI according to local MRI protocols.

I calculated the following outcome measures: i) annualised relapse rates (ARR) prior to and on treatment, ii) time to clinical relapse from treatment initiation (relapses are defined as new/worsening neurologic symptoms lasting at least 24 hours in the absence of fever or infection, as determined by the treating neurologist), iii) time to switching DMT from treatment initiation, iv) time to development of ≥ 2 new T2 hyperintense, and/or ≥ 1 gadolinium-enhancing lesions on brain MRI from treatment imitation, and v) change in EDSS score from baseline to last follow-up on treatment.

I calculated annualised relapse rates (ARRs) as the number of relapses per year before treatment (excluding index event) and during treatment only in patients with at least 6 months of follow-up after initiation of treatment. An attack was defined as

“definitely new neurological symptom” or “clear acute worsening of previous neurological deficits” with objective clinical signs, lasting for at least 24 hours and attributed to an inflammatory CNS event, confirmed by the treating physician. Relapses were analysed for up to 2 years before initiation of therapy and for the duration of the time undergoing therapy.

3.4.2 Prospective cohort

I conducted a prospective study including consecutive paediatric MS patients (<18 years) from three UK tertiary paediatric neurosciences centres who received ocrelizumab (Great Ormond Street Hospital for Children and Evelina Children’s Hospital in London and Birmingham Children’s Hospital). I recruited patients as part of the ‘Predicting Individual Treatment responses towards personalised medicine in Multiple Sclerosis (PITMS)’ study, a large NIHR-funded prospective observational cohort (recruitment target of 800 adults and 80 children). I assessed patients at baseline and measured outcomes at 6 monthly follow-up intervals. I collected data on demographics, clinical variables, MRI, Brief International Cognitive Assessment for MS (BICAMS) and patient reported outcome measures. Recruitment is ongoing with up to 5-year follow-up planned per patient. Ethical approval for the prospective cohort was granted by the Wales Research Ethics Committee (REC reference: 19/WA/0157) as part of the PITMS study.

3.5 Statistical Analysis

I performed descriptive statistics on the demographic and clinical variables. Mean, median, SD and interquartile range were reported as appropriate. A paired 2-tailed t test was used to compare ARRs pre and on treatment. I used Kaplan-Meier survival analyses to estimate the cumulative risk of clinical relapses on treatment, of switching

treatment and of the development of ≥2 new T2 hyperintense and/or ≥1 gadolinium-enhancing lesions on brain MRI, using the log-rank test to compare patients starting older injectables (n=89) and those starting newer DMTs (n=14). I also used Kaplan-Meier survival analyses to estimate the cumulative risk of clinical relapses, ≥ 2 new MRI lesions and EDSS score worsening for all 103 children in our cohort. Additionally, we built Cox Proportional Hazards models in order to investigate the impact of DMT choice (newer DMTs vs older injectables) on the risk of clinical relapses, risk of switching treatment and risk of the development of ≥2 new T2 hyperintense and/or ≥1 gadolinium-enhancing lesions on brain MRI, after adjusting for potential confounders including sex, ethnicity, age at presentation and DMT initiation, relapse characteristics at presentation (optic neuritis, transverse myelitis, polysymptomatic), number of relapses in the prior 6 months, and EDSS at baseline prior to treatment. For each analysis performed, adjusted hazard ratios (HR) are reported for DMT type.

For MRI outcomes, I used midpoint survival analyses due to the fact that there is variation in the timing of MRI scans in clinical practice and the actual time of a new lesion developing is not known. Therefore, I used the midpoint of time between the MRI with a new lesion and previous MRI to estimate when the new lesion developed. For time to ≥2 new T2 hyperintense and/or ≥1 gadolinium-enhancing lesions analysis, I included patients if they had a baseline brain MRI within the 6 months before starting a DMT, as well as ≥1 MRI midpoint during treatment on that DMT. Results associated with a value of $p < 0.05$ were considered significant. Data were analysed with GraphPad Prism 8 (GraphPad Software) and StataSE version 14 (StataCorp LLC, College Station, Texas). This study was approved by Great Ormond Street Hospital Research and Development Department (reference: 16NC10).

3.6 Results

3.6.1 Retrospective cohort

I identified a total of 103 children with a diagnosis of RRMS who received treatment with a DMT. Median age at symptom onset was 14.0 years (IQR 12.0-14.8). Clinical features and patient demographics are summarized in Table 3.1. The median length of follow-up from first clinical presentation was 3.8 years (IQR 3-7 years) and from DMT initiation was 2.8 years (IQR 2.1-3.6 years).

Sixty-three (61%) patients were treated with 1 DMT, 37 (36%) were treated with 2 DMTs and 3 (3%) were treated with 3 or more DMTs. Figure 3 describes the DMT pathway for all 103 patients included. Patients had a median of 2 relapses (range 1-5) prior to starting treatment. The median time from initial presentation to starting older injectables was 1.0 years (IQR 0.6-1.9), whilst from initial presentation to starting a newer DMT was 1.8 years (IQR 1.4, 2.5). Of the 305 clinical relapses reported in the cohort, 113 of these (37%) occurred whilst patients were on treatment.

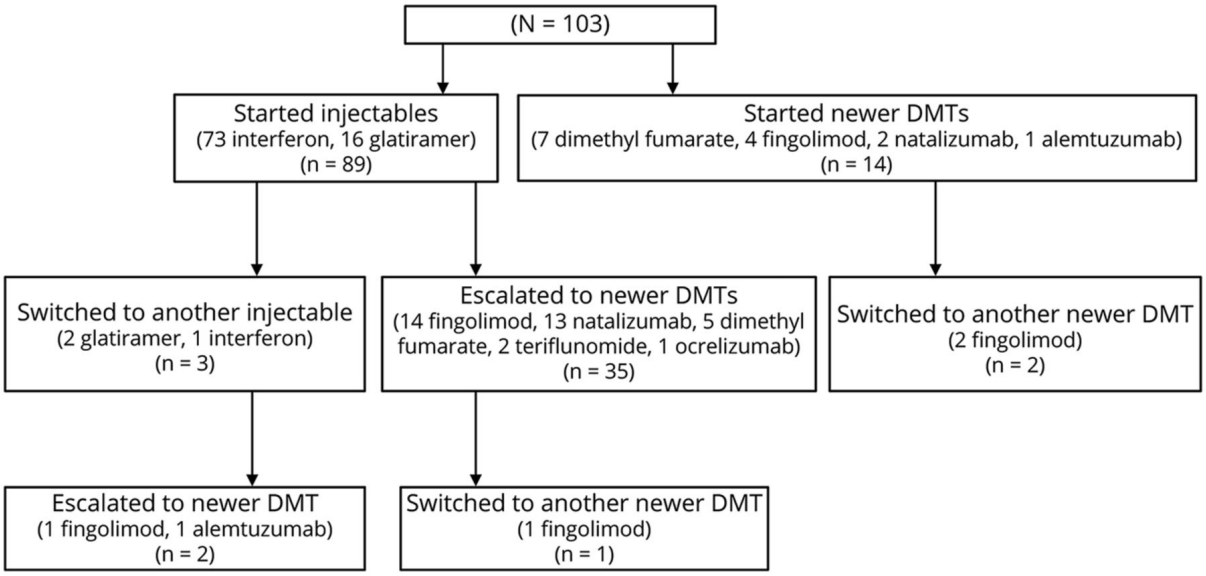
Table 3.1: Demographics, and baseline and follow-up clinical and radiological features of all children with multiple sclerosis included in the retrospective cohort

	All MS patients (*N*=103)	**Patients starting older injectables (n=89)**	**Patients starting newer DMTs (n=14)**	**P value***
Age at presentation (yrs), median (IQR)	14.0 (12.0-14.8)	13.9 (11.9-14.6)	14.3 (12.9-15.1)	0.42
Sex (M:F)	1 : 2.7	24:64 (1:2.7)	3:11 (1;3.7)	0.65
Ethnicity (white: other)	1 : 1.1	49:40 (1.3:1)	2:12 (1:6)	**<0.005**
CIS phenotype at onset				
Optic neuritis	27 (26%)	26 (29%)	1 (7%)	

Transverse Myelitis	4 (4%)	4 (45%)	0 (0%)	
*Polysymptomatic**	72 (70%)	61 (69%)	11 (79%)	
Intrathecal oligoclonal bands	87/93 (95%)	79/83 (95%)	8/10 (80%)	0.06
Abnormal MRI at onset	102 (99%)	88 (99%)	14 (100%)	0.69
Locations of MRI lesions at onset				
Periventricular	95 (94%)	81 (91%)	14 (100%)	
Infratentorial	76 (74%)	66 (74%)	10 (71%)	
Cortical/Juxtacortical	75 (73%)	67 (75%)	8 (57%)	
Spinal cord	60 (59%)	51 (57%)	9 (64%)	
New MRI lesions over time	92 (89%)	86 (97%)	6 (43%)	**<0.0001**
Locations of new MRI lesions				
Periventricular	100 (97%)	87 (98%)	13 (93%)	
Infratentorial	96 (93%)	82 (92%)	14 (100%)	
Cortical/Juxtacortical	89 (86%)	79 (89%)	10 (71%)	
Spinal cord	81 (79%)	75 (84%)	6 (43%)	
No of relapses prior to DMT, median (IQR)	2 (1-3)	2 (1-3)	1 (1.5-2)	0.67
Time from initial presentation to DMT, median (IQR)	1.2 (0.7-2.0)	1.0 (0.6-1.9)	1.8 (1.4, 2.5)	0.50
Baseline EDSS score prior to DMT, median (IQR)	1.0 (0,1.5)	1.0 (0,1.5)	1.0 (0.25-1.5)	0.94
EDSS score at last follow up, median (IQR)	1.0 (1,1.5)	1.0 (1,1.5)	1.0 (1-1.5)	0.83

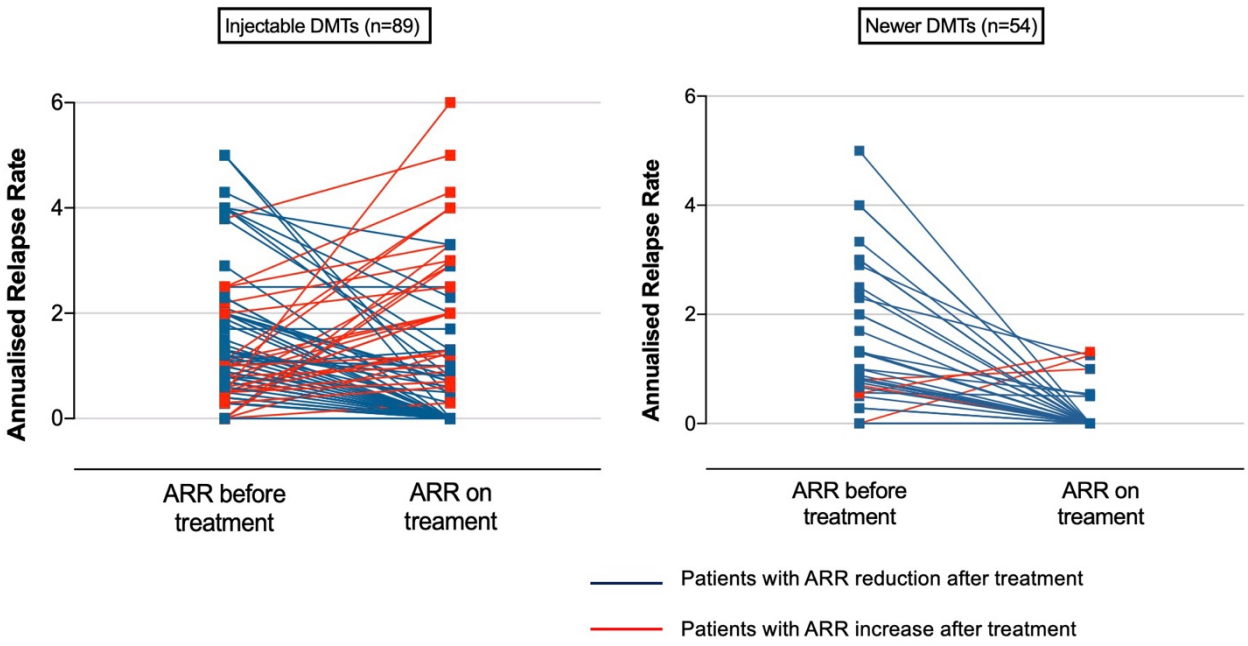
*Descriptive statistics were used to summarise the key components of the dataset. Non-parametric statistical tests (Kruskal–Wallis tests) were used for continuous distributions as appropriate given normality, and χ^2 or Fisher exact tests were used for nominal data

Figure 3.1: Patient Disease-Modifying Therapy (DMT) Pathway



Patients were distributed across treatment centres as follows; 45 (44%) at Great Ormond Street Hospital, 25 (24%) at Evelina Children's Hospital, 18 (18%) at Birmingham Children's Hospital, 5 (5%) at Royal Manchester Children's hospital, 4 (4%) at Great North Children's Hospital, 3 (3%) at Addenbrooke's Hospital, and 3 (3%) at Alder Hey Children's Hospital. Of the 103 children included, 89 patients (86%) were started on an older injectable as their first DMT (interferon-β [n = 73] and glatiramer acetate [n = 14]), and 14 (14%) were started on a newer DMT (dimethyl fumarate [n = 7], fingolimod [n = 4], natalizumab [n = 2], and alemtuzumab [n = 1]). Three of the 89 patients (3%) on older injectables switched to another older injectable (interferon-β [n = 1] and glatiramer acetate [n = 2]), of which 2 were then escalated to a newer DMT (fingolimod [n = 1] and alemtuzumab [n = 1]). Thirty five of 89 (39%) children who started on older injectables were escalated to a newer DMT (fingolimod [n = 14], natalizumab [n = 13], dimethyl fumarate [n = 5], teriflunomide [n = 2], and ocrelizumab (n = 1)), of which 1 switched to another newer DMT (fingolimod [n = 1]). Two of the 14 patients who were started on a newer DMT as their first drug switched to another newer DMT (fingolimod [n = 2]).

Figure 3.2: Annualised Relapse Rates Before and on Treatment



Annualised relapse rates (ARRs) for patients starting older injectables (A) and for patients starting or escalating to newer DMTs (B) before and on treatment: Each line corresponds to a single patient, blue lines correspond to responders (ARR reduction after treatment), and red lines correspond to non-responders (ARR increase after treatment). Overall, the ARR was reduced from 1.9 to 1.1 while on interferon-β and glatiramer acetate (n = 92, p < 0.001). The ARR was reduced from 1.7 to 0.4 for newer DMTs when used as first medication (n = 14, p = 0.02). For newer DMTs used as 2nd- and 3rd-line treatment, the ARR was reduced from 1.6 to 0.2 (n = 40, p = 0.003). DMT = disease-modifying therapy.

The annualised relapse rate (ARR) reduced from 1.9 to 1.1 while on interferon-β and glatiramer acetate (n=89, p<0.001). ARR was reduced from 1.7 to 0.4 for newer DMTs when used as first medication (n= 14, p = 0.02). For newer DMTs used as 2nd and 3rd line treatment, ARR was reduced from 1.6 to 0.2 (n= 40, p = 0.003). Overall, when considering all patients on newer DMTs (either starting on, or escalating to newer DMTs), ARR was reduced from 1.6 to 0.3 (n=54, p = 0.002). For individual newer

DMTs, ARR reduction pre and on treatment was as follows: 1.1 to 0.7 with dimethyl fumarate (n=12, p = 0.3), 1.9 to 0.3 with fingolimod (n=21, p = 0.01), 1.7 to 0.3 with natalizumab (n=15, p = 0.04), 0.5 to 0.5 with teriflunomide (n=2, p = 0.5), 1.2 to 0 alemtuzumab (n=2, p = 0.1) (Figure 3.2). For the 40 patients who escalated from older injectables to newer DMTs there was an overall reduction of ARR from 1.7 to 0.2 (p = 0.0001).

Relapses on treatment were recorded in 53/89 (59.6%) of patients who had an older injectable compared to 8/54 (15%) children who started on or escalated to newer DMTs. Of note, 20 patients (19.4%) who relapsed on treatment were not escalated; of these 13 were on older injectables and 7 were on newer DMTs. Kaplan-Meier survival analysis showed longer time to first relapse in children on newer DMTs compared to older injectables (log-rank p <0.001) (Figure 3.3A) and a longer time to switching treatment in children on newer DMTs compared to older injectables (log-rank p = 0.0016) (Figure 3.3C). Median time to new event (relapse) was 0.9 years (IQR 0.6, 1.3) on newer DMTs compared to 0.4 years (IQR 0.2, 0.8) on older injectables.

During the period, a median of 4 (range 3-10) repeated MRI scans were performed. Radiological activity occurred in 77/89 (86.5%) of patients who had an older injectable, compared to 26/54 (47%) who started on or escalated to newer DMTs. Kaplan-Meier survival analysis showed children on newer DMTs had longer time to developing of ≥2 new T2 hyperintense and/or ≥1 gadolinium-enhancing lesions compared to those on older injectables (log-rank p =0.002) (3.3B). Median time to new radiological activity was 2.8 years (IQR 0.5, 2.0) on newer DMTs compared to 1.8 years (IQR 0.8, 3.2) on older injectables. Overall, treatment failure, as evidenced by clinical relapses occurred in in 53/103 (51%) patients and by new MRI lesions occurred in 91/103 (88%) patients at 2 years from treatment initiation. In fact, at 2 years, 38/103 (37%) patients had ≥2

new T2 hyperintense and/or ≥1 gadolinium-enhancing lesions in the absence of clinical relapses.

Baseline and follow-up EDSS scores during treatment were available for all children; median EDSS at baseline prior to treatment initiation was 1.0 (IQR 0,1.5), and at last follow-up on treatment was 1.0 (IQR 1,1.5). In total, only 10 children (9.7%) had an EDSS ≥2 prior to treatment initiation and this increased to 12 (11.7%) children at last follow-up. EDSS worsening ≥1.0 point was observed in 12 children (13%) on older injectables compared to seven children (13%) who were started or escalated to newer DMTs. Out of 88 children with cognitive assessments reported, only 2 (2%) had cognitive impairment; as defined by impairment in 3 separate domains on testing[265].

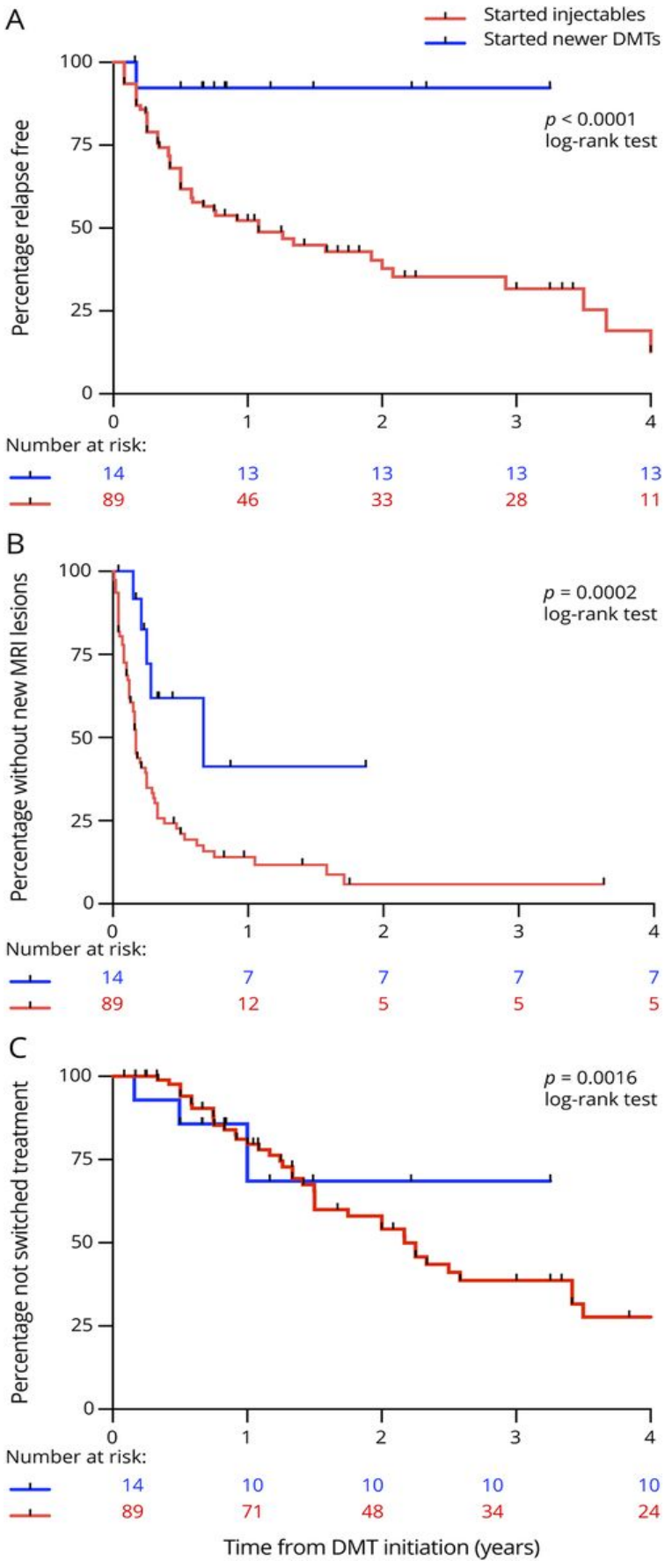
I performed multivariable analysis and adjusted our results for the variables that have been identified as potential confounders, showing that starting on older injectables was associated with a twelvefold increased risk of clinical relapse (adjusted HR=12.12, 95% CI=1.64-89.87, p=0.015) and a twofold increased risk of new radiological activity (adjusted HR=2.78, 95% CI=1.08-7.13, p=0.034) compared to starting on newer DMTs. For patients starting older injectables there was no increased risk of switching treatment (adjusted HR=0.96, 95% CI=0.28-3.29, p=0.94) compared to those starting on newer DMTs.

Kaplan-Meier survival analysis demonstrated that the proportion of patients with ≥2 new T2 hyperintense and/or ≥1 gadolinium-enhancing lesions was higher than the proportion who had clinical relapses and EDSS score increase ≥ 1 throughout follow-up (Figure 3.4).

Side effects were reported by 55/89 patients (61.8%) on older injectables, of which 50 were grade 1 adverse events on the CTCAE grading scale[264], and 5 were grade 2.

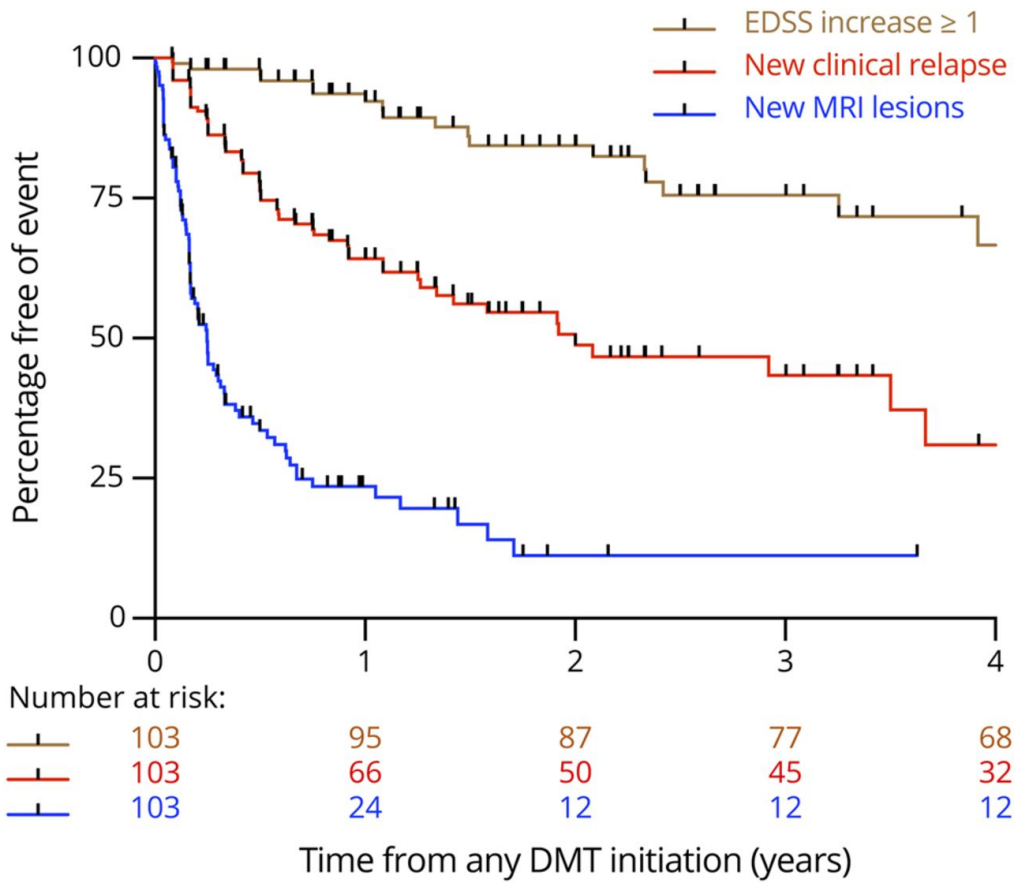
Side effects were reported for 18/54 (33%) who started or were escalated to newer DMTs, of which 14 were grade 1 adverse-events, and 4 were grade 2. The most commonly reported side effects for older injectables were flu-like symptoms (n=19), injection site reaction (n=16), headaches (n=7), myalgia and fatigue (n=5), gastrointestinal disturbance (n=3) and derangements in liver function tests and full blood count (n=5). The most commonly reported side effects for newer DMTs were derangements in liver function tests and full blood count (n=2), gastrointestinal disturbance (n=2), myalgia and fatigue (n=2), headaches (n=1). In 5 patients, DMTs were discontinued (n=2) or switched (n=3) due to side effects (blood derangements n=3, severe myalgia/flu like symptoms n=2).

Figure 3.3: Kaplan-Meier survival analyses for older injectables and newer DMTs


A
Started injectables
Started newer DMTs
Percentage relapse free
100
75
50
25
0
p < 0.0001
log-rank test
0
1
2
3
4
Number at risk:
14 13 13 13 13
89 46 33 28 11
B
Percentage without new MRI lesions
p = 0.0002
log-rank test
Number at risk:
14 7 7 7 7
89 12 5 5 5
C
Percentage not switched treatment
p = 0.0016
log-rank test
Number at risk:
14 10 10 10 10
89 71 48 34 24
Time from DMT initiation (years)

Kaplan-Meier survival analyses estimating the cumulative risk over 24 months of clinical relapses on treatment (A), the cumulative risk of the development of ≥2 new T2 hyperintense and/or ≥1 gadolinium-enhancing lesions on brain MRI (B), and the cumulative risk of switching treatment (C) for older injectables and newer disease-modifying therapies (DMTs).

Figure 3.4: Kaplan-Meier Survival Analysis for all RRMS Patients



Kaplan-Meier survival analysis estimating the cumulative risk over 24 months of clinical relapses, ≥ 2 new MRI lesions, and Expanded Disability Status Scale score worsening for all 103 children in our cohort.

3.6.2 Prospective cohort

In the prospective cohort, I recruited and included a total of 60 paediatric MS patients (all relapsing remitting); 49 female (81.7%), 41 non-white (68.0%), with a median age of 14.6 yrs (IQR 13.3, 15.5) (Table 3.2). Over 2/3 of patients presented with polyfocal CIS with 23% presenting with optic neuritis and 5% with transverse myelitis.

All children had a positive EBV IgG serology, abnormal MRI at onset and positive intrathecal OCBs. Median follow-up period so far was 1.0 yrs (range, 0.1-2.6). Forty-three patients (71.7%) had ocrelizumab as their first-line DMT.

The median number of relapses per patient pre-treatment was 2 (range 1-5).

Two patients relapsed within 1 month of starting ocrelizumab. During the follow-up period, a median of 4 (range 2-8) repeated MRI scans were performed (total scans, n=280).

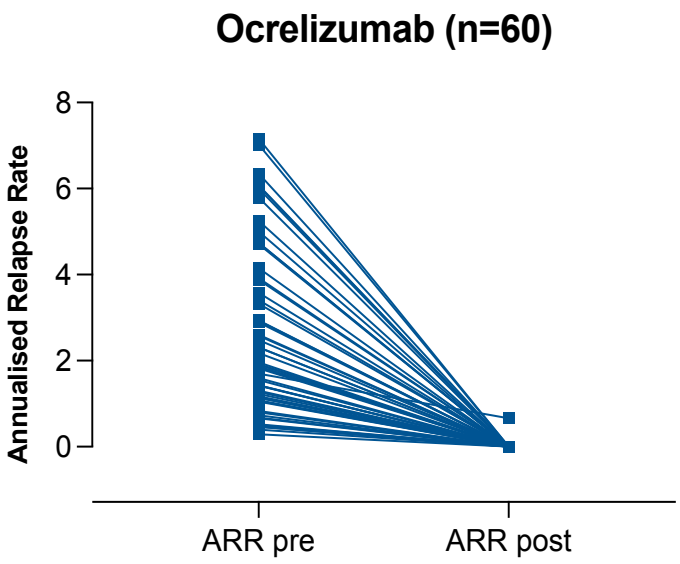
Table 3.2: Baseline demographic, clinical and paraclinical data for prospective Ocrelizumab cohort

	N= 60
Age at presentation, Median yrs (IQR)	14.6 (13.3-15.5)
Sex (M : F)	11:49 (1:4.5)
Ethnicity (white : other)	19:41 (1:2.2)
CIS phenotype at onset	
Polysymptomatic (Involvement of brainstem or cerebellum; cerebral hemisphere)	43 (71.7%)
Optic neuritis	14 (23.3%)
Transverse Myelitis	3 (5%)
Vitamin D, mean (nmol/L)	45
Immunoglobulin G/ A / M, mean (g/L)	11.0 / 1.8 / 1.3
EBV IgG positive	60 (100%)
Intrathecal oligoclonal bands	60 (100%)
Abnormal brain MRI at onset	60 (100%)

Forty out of 43 (93.0%) patients achieved no evidence of disease activity (NEDA-3) at 12-months follow-up. Two patients had one new brain lesion each at 6-months and a different patient had a relapse (optic neuritis) without new brain lesions at 6

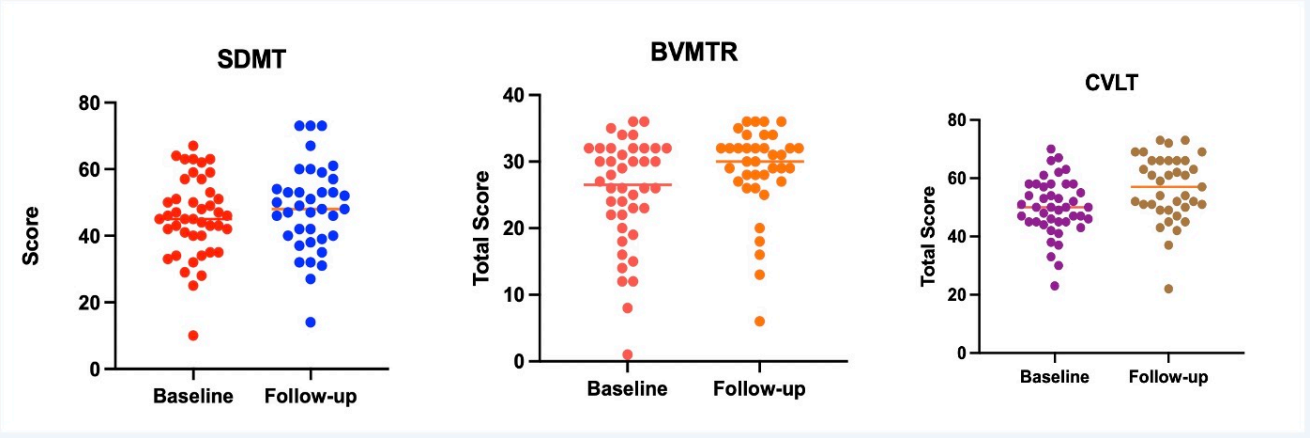
months. Annualised relapse rate (ARR) was reduced from 2.54 pre-treatment to 0.001 post-treatment (p<0.0001). Median EDSS score remained stable during follow-up; 1.0 at baseline and at follow-up (p=0.21) (Figure 3.5). There was no change in BICAMS scores at follow-up; baseline SDMT mean score 46 vs follow-up SDMT mean score 48 (p=0.39) (Figure 3.6). The most common adverse events reported were infusion-related reactions (33/60, 55%), all of which were grade 1 or 2. Serious adverse events were recorded in one patient with enterovirus meningitis, who made a full recovery and decided to continue ocrelizumab.

Figure 3.5: Annualised Relapse Rates before and on ocrelizumab



Annualised Relapse Rate (ARR) was reduced in our cohort from 2.54 pre-treatment to 0.001 on treatment. Each blue line corresponds to an individual patient from the 60 included so far.

Figure 3.6: Brief International Cognitive Assessment for MS (BICAMS) before and on treatment



BICAMS scores for our cohort at baseline vs last follow-up for all 60 patients. This demonstrates no significant difference between the two timepoints for all 3 measures.

3.7 Discussion

3.7.1 Retrospective cohort

In the first and largest UK-wide observational study of DMTs in children with MS, I demonstrated that treatment with newer DMTs (oral or infusions) was more effective in preventing relapses and new or gadolinium-enhancing T2 lesions compared to older injectable therapies.

My results are in keeping with the first randomized control trial of fingolimod versus interferon-β in children[102, 266]. A high rate of treatment failure with older injectables has been previously reported in children, ranging from 25% to 64% across studies[267]. In a multicentre observational study from the US Network of Paediatric MS Centers those on newer DMTs had lower relapse rates (rate difference = 0.27, p = 0.004), lower rate of new/enlarging T2 (HR = 0.51, p < 0.001) and gadolinium-enhancing lesions (HR =

0.38, $p < 0.001$) than those on older injectables[258]. In a follow-up study of 736 girls enrolled in the US network, relapse rates were significantly higher during the peri-menarche period compared to pre- and post-menarche, suggesting puberty is a time of increased disease activity[268]. Use of oral and infusion disease-modifying therapies reduced relapse risk, highlighting the need for closer monitoring and possible therapeutic adjustments around puberty. A French paediatric cohort study showed significantly lower mean annualised relapse rates (ARR) for patients treated with fingolimod, teriflunomide, dimethyl fumarate, or natalizumab compared to those on interferon[259]. Furthermore, a study of 530 paediatric multiple sclerosis (MS) patients from a multi-centre French cohort found that high-efficacy therapy (alemtuzumab, fingolimod, mitoxantrone, natalizumab, ocrelizumab, ofatumumab, and rituximab) was more effective than moderate-efficacy therapy (including dimethyl fumarate, glatiramer acetate, interferon and teriflunomide), reducing relapse risk by 54% (HR 0.46; $P < 0.001$) over five years and MRI activity (OR 0.34; $P = 0.001$).[269] High-efficacy therapy was better tolerated, with moderate-efficacy therapy patients six times more likely to discontinue treatment (HR 5.97) due to lack of efficacy and intolerance. Treatment choice had no significant impact on disability progression or education (OR 0.51; $P = 0.09$).

Graves et al. conducted a meta-analysis of 19 studies involving participants from various global regions, revealing that ARR was significantly higher in patients treated with interferon (IFN) compared to those receiving fingolimod or natalizumab[270]. Similarly, a large multinational retrospective study recently published analysed 1,218 paediatric MS patients treated with fingolimod, natalizumab, or an older injectable[260]. At the five-year follow-up, the highest percentage of relapse-free patients was observed in the natalizumab group (90%), followed by those on fingolimod (72%), while only 36% of patients receiving older injectables remained relapse-free.

Over recent decades, MRI-based measures of inflammatory activity (focal brain lesions) have become the primary efficacy outcomes in adult MS clinical trials. These lesion-related MRI markers provide an objective assessment of MS pathology and correlate with clinical outcomes in RRMS, particularly with relapse risk in the short and medium term[93]. In paediatric MS, newer DMTs delayed the onset of new radiological activity compared to older injectables. However, at 2 years post-treatment initiation, while only 51% of patients experienced a relapse, 88% developed new MRI lesions, highlighting the disconnect between clinical and radiological disease activity in this highly inflammatory paediatric MS phenotype

With regards to measures of disability, in this cohort, children had a median EDSS of 1.0 both at baseline prior to treatment initiation and at last follow-up on treatment. Only 9.7% of patients had EDSS ≥2 prior to treatment, which increased to 11.7% at last follow-up on treatment. Only a minority of children had evidence of disability progression (defined as EDSS worsening ≥1.0 point) on both older injectables (13%) and newer DMTs (13%). A recent North American study demonstrated that children recover better from relapses than adults with MS[271]; for every 10 years of age, there was reduced EDSS recovery by 0.15 points ($p < 0.0001$). In addition, improvement in EDSS following a relapse was seen in a larger proportion of children compared to adults ($p = 0.006$) with every 10 years of age, increasing the odds of EDSS not improving by 1.33 times. The effects of age-related heightened inflammation and neuronal plasticity influence the clinical course in paediatric MS, leading to faster and more complete recovery from relapses (even without treatment) [272]. At the same time, frequent radiological activity is often seen in the absence of clinical relapse, even during treatment, highlighting a disconnect between clinical and subclinical disease activity.

This underscores the limitations of clinical outcome measures such as EDSS and ARR in accurately capturing disease activity in paediatric MS. Relying on relapse occurrence to guide treatment initiation or escalation is inadequate. A study of 1555 adult RRMS patients demonstrated that early treatment with fingolimod, natalizumab, or alemtuzumab reduced the risk of conversion to secondary progressive MS compared to older injectables[273]. Given that brain atrophy is already present at diagnosis in paediatric MS [87, 274] and correlates with disease activity [86], there is an urgent need for more sensitive, paediatric-specific outcome measures—either as alternatives to or in conjunction with clinical metrics—to better assess disease impact on the developing brain.

In this real-world clinical cohort, no paediatric-specific side effects were reported, and newer DMTs demonstrated comparable short-term safety and tolerability to adults [275]. Only 5 patients required discontinuation or switching due to adverse events. Side effects were noted in 60% of children on older injectables compared to 33% on newer DMTs, which is reassuring, particularly given high non-compliance rates with older injectables in adolescents (up to 47%) [276, 277]. While the short-term safety profile appears favourable over a median follow-up of 3.8 years, the long-term effects of infusion and oral DMTs (e.g., alemtuzumab, ocrelizumab, cladribine) on the developing immune system remain uncertain, necessitating long-term longitudinal studies.

Fewer patients on newer DMTs switched treatment in this study. Beyond the improved disease control, this is also important for reduction of cumulative risk from multiple DMTs particularly as it is likely that some patients who are diagnosed with MS as teenagers will require treatment for decades. Interestingly, despite ongoing clinical relapses, 20 patients (19.4%) continued on the same treatment without escalation. This was likely due to access and availability of DMTs at the time.

In this cohort, only 2 out of 88 children (2%) had cognitive impairment identified through neuropsychology testing. This is notably lower than the 30% prevalence reported in the literature [278, 279], which may be due to the short follow-up period, as cognitive decline may manifest later in early adulthood. A population-based longitudinal study from the Swedish MS Registry involving 5704 MS patients found that paediatric-onset MS patients exhibited greater impairments in information processing compared to adult-onset counterparts, regardless of age or disease duration [280].

This study has several limitations, including its retrospective design, the small sample size compared to adult MS cohorts (which often include >1000 patients), and the lack of long-term safety data, particularly for newer DMTs. Additionally, clinicians were not blinded to the DMT received when reviewing patient records, which may have introduced measurement bias. Treatment switching, both horizontally (between older injectables) and vertically (escalating to newer DMTs), further complicates interpretation, as differences in drug mechanisms and time to efficacy may have influenced outcomes. Despite these limitations, the findings are broadly generalizable to paediatric MS patients across diverse regions of the UK.

Additionally, the lack of clinician blinding to the DMT received may have introduced measurement bias. The heterogeneity in treatment pathways, including horizontal switching between older injectables and vertical escalation to newer DMTs, complicates interpretation, as variations in drug mechanisms and time to efficacy could have influenced outcomes. Nonetheless, these findings remain broadly applicable to paediatric MS patients across diverse UK regions.

3.7.2 Prospective cohort

In the OPERA phase III randomised controlled trials, Ocrelizumab, a humanized monoclonal antibody targeting CD20-positive B cells was shown to be associated with lower rates of disease activity and disability accumulation vs. interferon beta-1a over in adult patients with relapsing remitting MS[261]. In addition, recent trials have shown that in adults with primary progressive multiple sclerosis, ocrelizumab was associated with lower rates of clinical and MRI progression than placebo[262].

To further assess the safety and efficacy of ocrelizumab in paediatric MS, the phase II OPERETTA I trial was conducted, focusing on pharmacokinetics and pharmacodynamics [281]. Over the two-year study period, no clinical relapses were observed in 23 patients recruited, and the safety profile was consistent with that reported in adult MS trials. Based on these findings, an ongoing phase 3 OPERETTA II trial is underway; actively recruiting double-blind, double-dummy study that evaluates the efficacy and safety of ocrelizumab compared with fingolimod (NCT05123703). In a recent small Turkish real-world study of 10 paediatric MS patients with median follow up of 28.3 months, Ocrelizumab significantly reduced the annualised relapse rate (ARR) from 2.01 to 0, with no patients demonstrating new MRI activity while on treatment[282]. Mean EDSS decreased from 1.75 to 1.20 (p=0.024) from ocrelizumab initiation to last follow up. One patient experienced anaphylaxis.

My preliminary results in this chapter show that ocrelizumab is highly effective with a reassuring short-term safety profile in paediatric MS. This is the largest Ocrelizumab paediatric cohort to date. A large reduction in ARR was observed in this cohort, with almost all children achieving NEDA-3 at 12 months with stable EDSS and BICAMS. This data adds weight for the early use of higher efficacy therapies in paediatric MS.

Supporting this, a recent multicentre observational study from the US Network of Pediatric MS Centers evaluated clinical and MRI outcomes in 52 children treated with ocrelizumab and 87 treated with fingolimod[283]. Ocrelizumab was associated with a marked reduction in ARR (from 0.64 to 0.09) and complete suppression of new T2 lesion formation on MRI, while fingolimod also significantly reduced relapse rates and MRI activity, though less completely. These findings align with broader evidence that paediatric MS is associated with more rapid CNS inflammatory activity than adult MS, increasing the risk of long-term neurodegeneration, and reinforcing the recommendation for early high-efficacy therapy. Longitudinal data have shown that early High-efficacy therapy can reduce the risk of persistent disability in paediatric MS by 50–70%, further supporting its early introduction as standard practice[284].

Due to systemic limitations of RCTs in paediatric MS, multicentre real-world observational cohort studies can provide a valuable alternative to analyse DMT efficacy and safety in paediatric MS[285]. Assessment for long-term efficacy and safety of Ocrelizumab in paediatric MS is ongoing with more comprehensive 5-year follow-up data planned for at least 120 recruited patients.

Rituximab, similar to Ocrelizumab, is also a monoclonal antibody targeting the CD20 antigen, effectively inhibiting B-cell activation and differentiation. Observational studies have demonstrated a favourable risk–benefit profile similar to Ocrelizumab for rituximab in the paediatric population[286-288]. A multicentre European cohort study evaluating rituximab in 61 paediatric patients with MS reported a significant reduction in the annualised relapse rate (ARR) from 0.6 to 0.03[289]. The most commonly reported adverse events included infusion-related reactions (48%), infections (20%), hypogammaglobulinemia (17%), and lymphopenia (7%).

The rapidly evolving landscape of MS therapeutics comes with significant challenges including: (i) recruiting a sufficiently high number of children to take part in randomized trials; (ii) the time and cost involved in conducting trials; and (iii) trials conducted based on old medications which become obsolete by the time trials have been completed. They key question is whether we can provide evidence of efficacy and safety in children for DMTs with a different approach. It would be attractive to rely on the efficacy of the DMTs from the adult cohorts (MS in adults and children MS is biologically the same disease), and provide safety data from large-scale multi-centre, real-world observational cohorts, which may provide larger sample sizes, which could be used to confirm the efficacy of the medication. In parallel to this effort, factors affecting treatment response and predicting prognosis in clinical practice should be investigated in the real world of Paediatric MS. Furthermore, a shift towards using MRI outcome measures as a valid surrogate endpoint for clinical relapses in paediatric trials may help reduce study times when evaluating DMT efficacy. A shift from a focusing on short-term DMT safety profiles to longer-term safety assessment (including in pre-pubescent patients) is recommended, so to ensure that treatment early in life does not expose patients to future risk.

3.8 Conclusions

In conclusion, this study adds weight to the argument for an imminent shift in practice towards the use of newer, more efficacious DMTs in the first instance. It also demonstrates a favourable safety profile for Ocrelizumab as one of the newest DMTs being used in children, similar to published adult data. As relapses are the highest and MRI activity continues whilst on DMTs, and this can impact on brain atrophy, which is most rapid in the first few years after onset of paediatric MS, this time period may present a critical therapeutic window for the use of highly effective therapies. Further

prospective research is clearly needed to establish evidence-based treatment strategies for paediatric MS.

In Chapters 2 and 3 I have demonstrated the long-term outcomes of acquired demyelinating syndromes in children and how real-world observational studies can provide useful data on the efficacy and safety of DMTs in paediatric MS. I have also looked at MRI outcomes in treated paediatric MS cohorts (both retrospective and prospective). In Chapter 4, I will investigate how MRI lesion dynamics can help differentiate between paediatric MS and its main mimic, Myelin-Oligodendrocyte Glycoprotein Antibody-Associated Disease (MOGAD), using real-world observational study data.

Chapter 4: Comparing MRI lesion dynamics between Paediatric Multiple Sclerosis and Myelin-Oligodendrocyte Glycoprotein Antibody-Associated Disease (MOGAD)

4.1 Summary

Children with Myelin-Oligodendrocyte Glycoprotein Antibody-Associated Disease (MOGAD) often exhibit lesion resolution on brain MRI, and asymptomatic lesions are less frequently observed in MOGAD compared to multiple sclerosis (MS). In this Chapter, I aimed to evaluate the evolution of brain MRI findings in paediatric MOGAD over time and assess the factors influencing lesion dynamics.

This retrospective study was conducted across eight UK paediatric neuroscience centres. Acute and follow-up brain MRIs of children diagnosed with MOGAD were reviewed. I analysed lesion changes over time, and potential predictors of lesion dynamics were assessed using multivariable regression models. I used Kaplan-Meier survival analyses to evaluate the association between lesion changes and the risk of relapse, disability progression, and MOG antibody (MOG-Ab) persistence.

A total of 200 children were included in the study, comprising 97 with MOGAD and 103 with MS. Following an initial attack, symptomatic and asymptomatic new lesions were more commonly observed in MS than in MOGAD (52/103 vs. 28/97, $p = 0.002$, and 37/103 vs. 11/97, $p < 0.001$, respectively). In contrast, lesion resolution was observed in 83% of MOGAD patients at their first follow-up MRI, with 23% achieving a completely normal scan. In comparison, only one MS patient showed resolution of a single lesion, and none had a normal MRI. Among MOGAD patients, lesion resolution was observed in 40% after the second attack, 21% after the third attack, and none beyond the fourth attack. The presence of new lesions at the first follow-up scan was

associated with an increased risk of relapse (p = 0.02) and persistent MOG-Ab positivity (p = 0.0016) compared to patients without new lesions. Additionally, plasma exchange (administered in 13 patients) was significantly linked to a higher likelihood of lesion resolution (p = 0.01). A delay in initiating steroid treatment was associated with an increased probability of new lesion formation, with a 50% higher risk observed at 20 days post-symptom onset (p = 0.01).

The observed differences in lesion dynamics between MOGAD and MS suggest that MOGAD has a greater capacity for lesion repair. Early administration of steroids and plasma exchange appears to reduce the likelihood of new lesion formation, emphasizing the importance of timely intervention in paediatric MOGAD management.

4.2 Introduction

Myelin-oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is a distinct CNS inflammatory demyelinating disorder, separate from Multiple Sclerosis (MS) and Aquaporin 4-antibody positive Neuromyelitis Optica Spectrum Disorder (AQP4-Ab NMOSD). It can present as either a monophasic or relapsing condition in both children and adults. Brain MRI abnormalities are found in over 50% of MOGAD patients, irrespective of their initial symptoms [290], with more widespread lesions in children compared to adults.

In January 2023, the International MOGAD Panel proposed new diagnostic criteria for MOGAD, aiming to standardise diagnosis and guide disease-specific research[186]. These criteria involve a three-step approach: identifying a core clinical demyelinating event, confirming MOG-IgG positivity, and excluding alternative diagnoses[291]. For patients with low-positive serum MOG-Ab titres, at least one supporting clinical or MRI feature is required for diagnosis. Recent validation studies, including a study by our

group, have demonstrated the high performance of these criteria, particularly in paediatric populations[292].

Radiological markers have been identified to help differentiate MOGAD from AQP4-Ab NMOSD and MS at first presentation in both adults and children. In a large cohort of 110 paediatric patients, our group found that MOG-Ab-positive children were less likely to present with area postrema syndrome or cerebellar peduncle lesions compared to AQP4-Ab NMOSD. They were also younger, had lower disability, and experienced longer intervals to relapse [11]. A retrospective study of 162 adult MOGAD patients, compared with 162 AQP4-Ab NMOSD and 189 MS patients, demonstrated that lesion location on interval non-attack imaging could aid in differentiation. Temporal lobe involvement, absence of Dawson's fingers, and longitudinally extensive cervical cord lesions were all characteristic of MOGAD [293].

Recent studies have expanded our understanding of MOGAD's clinical spectrum and relapse patterns. A study by Kim et al. on paediatric patients with relapsing MOGAD found that 34.9% of patients experienced their first relapse within 3 months of onset, with various relapse phenotypes observed[294]. This underscores the importance of early diagnosis and treatment initiation in MOGAD.

When evaluating serial MRIs over the disease course, asymptomatic or silent brain lesions have been previously reported in 10/74 (14%) paediatric MOGAD patients[295], commonly within the first months post-onset. In another study of 38 MOGAD patients (including adult and children), the brain T2-index lesion resolved completely in 13/18 (72%) of MOGAD patients at first follow-up MRI[296]. A more recent study from the same group demonstrated in paediatric patients that the MRI T2-index lesion resolved more

frequently and more completely in children with MOGAD (n=21) compared to MS (n=27) and AQP4-Ab NMOSD (n=8)[297].

4.3 Aims

The aims of the study were to (i) study the evolution of brain lesions after an acute attack and compare it between paediatric MOGAD and MS; (ii) correlate first follow-up MRI with patients' management at presentation, and (iii) evaluate if MRI lesion dynamics early in the disease can predict risk of relapse, disability accrual and MOG-Ab serostatus at follow-up.

4.4 Methodology

As per the retrospective cohort in Chapter 3, this project was a multi-institutional, retrospective study run within the UK Childhood Neuroinflammatory Disorders Network and included patients from Great Ormond Street Hospital (London), Evelina Children's Hospital (London), Birmingham Children's Hospital, Addenbrooke's Hospital (Cambridge), Alder Hey Children's Hospital (Liverpool), Royal Manchester Children's Hospital, Great North Children's Hospital (Newcastle) and John Radcliffe Hospital (Oxford). Two cohort of patients with MOGAD and MS (all relapsing remitting, RRMS), consecutively seen in the 8 UK paediatric neuroscience centres between January 2014 to January 2022, were included. The paediatric MS cohort was the same as the retrospective cohort reported in chapter 3. All patients (whether tested retrospectively for antibodies or at the time of disease onset) fulfilled their respective MOGAD[186] or MS diagnostic criteria[298]. All MOGAD patients were tested for MOG-IgG as part of the routine clinical care using cell-based assay.

From these cohorts, I used the following inclusion criteria: (1) first clinical attack occurring before 18 years old; (2) available acute brain MRI that revealed parenchymal T2-hyperintense lesion(s), obtained within 4 weeks of the attack nadir; and (3) available follow-up MRI at least 6 weeks after the acute MRI (off steroids).

When multiple acute MRIs were available, I chose the most representative of attack nadir (most extensive CNS radiological abnormality). I excluded patients with optic neuritis and/or transverse myelitis with normal brain MRI. I retrospectively reviewed clinical data including demographics, clinical findings, neuroimaging reports, and laboratory results, first and subsequent relapse characteristics, and treatment information from electronic medical records of patients and I entered these in a standardised database. Relapses were defined as "new neurological symptom" or "clear acute worsening of previous neurological deficits" with objective clinical signs, lasting for at least 24 hours and attributed to an inflammatory CNS event, and occurring after a period of clinical remission of >1 month, as defined by the International MOGAD Panel proposed criteria[186], confirmed by the treating physician. Asymptomatic lesions were used to only describe lesions occurring outside a clinical attack. I determined disability assessment from patient electronic medical record review, at all subsequent clinical follow-up timepoints using the Expanded Disability Status Scale (EDSS).

All available MRI were clinically reported by a paediatric neuroradiologist (Dr Kish Mankad). MRI scans were then independently re-evaluated by two neurologists (myself and Dr Yael Hacohen). For patients with a reported initial abnormal brain MRI, I grouped subsequent follow-up MRI scans into the following categories: i) Symptomatic lesions (associated with a clinical relapse), ii) New asymptomatic lesions, iii) Stable (no new lesions), iv) Lesion shrinking with at least one lesion resolution, and v) Normal MRI. I included patients with coexisting new lesions and shrinking lesions in

the ‘New lesions’ groups (either symptomatic or asymptomatic). A maximum of 10 MRIs per patient were evaluated.

For patients with MOGAD, I used clinical and paraclinical features at presentation to predict lesion dynamics at first follow-up MRI. I subsequently evaluated if new lesions on first follow-up MRI predict risk of relapse, disability accrual, and MOG-Ab serostatus at final follow-up.

4.5 Statistical Analysis

I performed descriptive statistics on the demographic and clinical variables. Mean, median, SD, and interquartile range (IQR) were reported as appropriate. To compare the demographic, clinical, and paraclinical characteristics between our MOGAD and MS cohorts, I used parametric or non-parametric statistical tests (Mann-Whitney-U and Kruskal-Wallis tests) for continuous distributions as appropriate given normality, and Pearson’s chi squared test with Yates’ continuity correction or Fisher exact tests for nominal data. Results associated with a value of $p < 0.05$ were considered significant.

For patients with MOGAD, I used multivariable logistic regression to calculate odds ratios (ORs) and 95% confidence intervals for potential confounders between the different MRI groups (including sex, age at presentation, cerebrospinal fluid analysis and acute immunotherapies). I also performed Kaplan-Meier survival analyses to estimate the cumulative risk of clinical relapses, risk of disability accrual (increase in EDSS score by 1 or more), and risk of seroconversion to MOG-Ab negative status, using the log-rank test to compare patients stratified to two groups: new lesions vs shrinking lesions. Data were analysed with GraphPad Prism 8 (GraphPad Software) and R (version 4.3.1; R Core Team 2020).

4.6 Results

Two hundred consecutive children were retrospectively studied (MOGAD 97; MS 103). Patients' demographics are summarised in Table 4.1. The median length of follow-up from first clinical presentation was 3.8 years (IQR 3-7 years) in the MS group and 3.8 years (IQR 2-6) the MOGAD group.

Comparison between children with MS and MOGAD

MS patients were older (median 14 yrs for MS vs 5 yrs in MOGAD, $p<0.0001$) with a greater female preponderance (73% vs 58%; $p=0.01$) and more likely to have positive oligoclonal bands (87/93, 94% vs 13/60, 22%; $p<0.0001$). I observed no difference in either EDSS at the time of first follow-up scan or EDSS at final follow-up between MOGAD and MS patients (Table 4.1).

During the period, a median of four repeated MRI scans were performed per patient (range 2–10, total MRI scans in MS patients 430 and in MOGAD 511). The median length of time between attack MRI and first post-attack/remission follow-up MRI was 0.4 years (IQR 0.2, 1.0). The median length of time between attack MRI and final follow-up MRI was 1.8 years (IQR 0.7, 4.8 yrs, range 0.1 to 12.6 yrs). When evaluating the first post-attack/remission follow-up MRI, I found that patients with paediatric MS, when compared to MOGAD, had more new symptomatic lesions (50% (52/103) vs 29% (28/97); $p=0.002$) and asymptomatic lesions (36% (37/103) vs 11% (11/97); $p<0.001$). Only one patient with MS had a single lesion resolve and none had normal MRI. In contrast, 60% (58/97) of MOGAD patients had at least one lesion resolution at first follow-up MRI and 23% (22/97) showed a normal MRI.

Table 4.1: Comparison between MOGAD vs MS paediatric cohorts

	MOGAD (N=97)	**MS (n=103)**	**p-value**
Age at presentation (yrs), median (IQR)	5 (4-9.5)	14 (12-14.8)	**<0.0001**
Sex (Male: Female)	41:56	28:75	**0.01**
Demyelinating phenotype at onset (%)			
ON	7 (7)	27 (26)	**0.0003**
TM	2 (2)	4 (4)	0.68
CIS -other	0 (0)	72 (70)	**<0.0001**
ADEM	66 (68)	0 (0)	**<0.0001**
Cortical encephalitis	22 (23)	0 (0)	**<0.0001**
Intensive care admission (%)	13 (13)	1 (1)	**0.0005**
Seizures at presentation (%)	21 (22)	0 (0)	**<0.0001**
CSF oligoclonal bands	12/57 (21)	87/93 (95)	**<0.0001**
EDSS at time of follow-up scan	1 (0,1.5)	1 (0,1.5)	0.51
MRI lesion location (initial MRI), n (%)			
Brain	97 (100)	102 (99)	0.33
Spinal Cord	35 (36)	60 (59)	**0.002**
Optic nerve	22 (23)	25 (24)	0.79
Contrast enhancement on initial MRI, n (%)	41/65 (63)	46/63 (73)	0.23
EDSS at last follow-up, median (IQR)	1 (0,2)	1 (1,1.5)	0.81
Brain lesion dynamics at first follow-up MRI, n (%)			
New symptomatic lesions	28 (29)	52 (50)	**0.0024**
New asymptomatic lesions	11 (11)	37 (36)	**<0.0001**
Stable (no new lesions)	0 (0)	10 (10)	**<0.0001**
Lesions shrinking with at least 1 lesion resolution	36 (37)	1 (1)	**<0.0001**
Normal MRI	22 (23)	0 (0)	**<0.0001**

Of the 39 patients with MOGAD with new lesions at the first follow-up scan, 23 (59%) had also at least one lesion disappearing (i.e., they showed a mix picture with both new lesions and disappearing lesions, Figure 4.1C). When examining the time taken for lesions to disappear by stratifying the results to when the first follow-up scan was performed, of the 81/97 (83%) patients who had at least one lesion resolved at the first follow-up scan, 25/30 (83%) patients showed lesion resolution when the interval was less than 3 months, 22/28 (79%) when the interval was between 3 and 6 months, 16/17 (94%) in 6 - 12 months interval, and 18/22 (82%) when the first follow-up scan was performed longer than 12 months from baseline.

Predictive factors for lesion changes at first follow-up MRI in MOGAD patients

I have illustrated examples of lesion changes in patients with MOGAD in Figure 4.1. When comparing patients whose first follow-up MRI demonstrated new lesions vs patients with shrinking lesions, I found no differences in demographic, clinical and paraclinical features at onset (Table 4.2). Similarly, I observed no differences between MOGAD patients who received intravenous immunoglobulin (IVIg) and steroids at presentation, and those who did not. All patients who received plasma exchange (PLEX) at onset (n=13) had shrinking lesions (with at least one lesion resolution) on follow-up MRI vs none of those who did not (p=0.01). Increased time from symptom onset to starting steroids was associated with increased likelihood of new lesions with 50% increase at 20 days (p=0.01, Table 4.2).

When evaluating brain MRI lesion outcomes after sequential relapses for MOGAD patients in 511 MRI scans, the proportion of normal brain MRI was reduced after each clinical relapse (Table 4.3, Figure 4.2). Disappearing lesions (lesion shrinking or normalisation of MRI) were seen in 40% after the 2nd attack, 21% after 3rd attack and none after the 4th attack. There was a trend to more lesions (symptomatic and

asymptomatic) with each subsequent attack. I have illustrated lesion dynamics throughout the disease course in a patient with MOGAD in Figure 4.3.

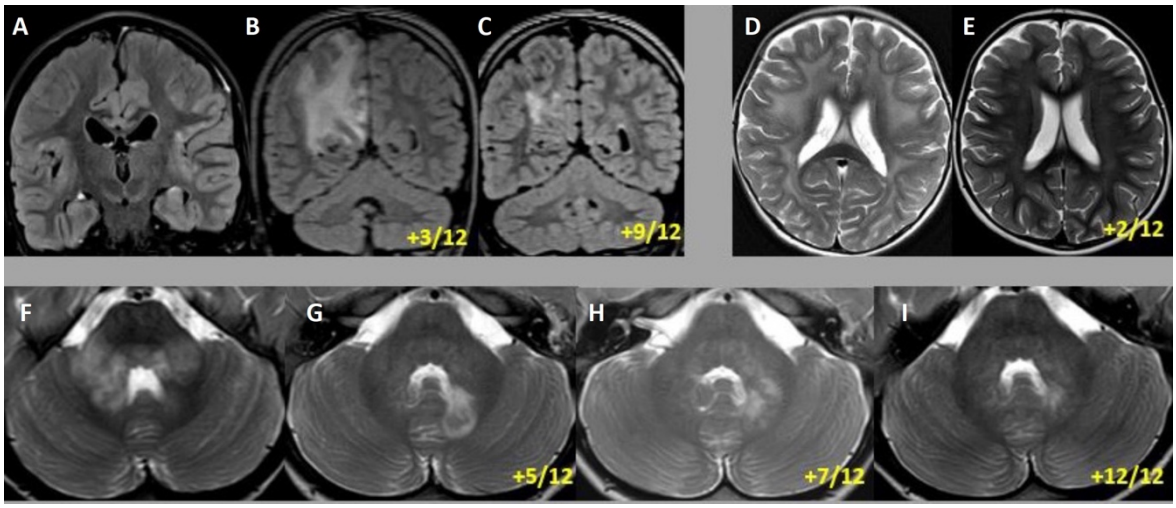
Table 4.2: MOGAD patients stratified by different brain lesion dynamics in first follow-up MRI.

	New symptomatic lesions (n=28)	**New asymptomatic lesions (n=11)**	**Lesions shrinking with at least 1 lesion resolution (n=36)**	**Normal MRI (n=22)**	**OR (CI) (New lesions vs no new lesions)**	**p-value***
Age at presentation (yrs), median (IQR)	5 (5.7)	5 (2.8)	5.1 (6.3)	7 (6)	1.03 (0.94-0.15)	0.34
Sex (Male: Female)	15:13	2:9	13:23	11:11	0.91 (0.4-2.0)	0.16
Positive oligoclonal bands (%)	4/14 (29)	2/6 (33)	3/23 (13)	3/14 (21)	0.635 (0.18-2.19)	0.45
Raised CSF protein (%)	7/14(50)	0/4 (0)	11/27 (41)	5/16 (31)	1.03 (0.33-3.31)	0.45
Time from first MRI to second MRI (month), median IQR	12 (2-36)	3.5 (2 - 8)	4 (2.5 – 7.5)	4 (2.5 – 7)	0.95 (0.9-0.97)	**0.03**
Acute management on 1st event						
Steroids (%)	16 (57)	5 (45.5)	27 (75)	17 (77)	2.69 (1.13- 6.54)	0.08
IVIg (%)	8 (29)	5(46)	6 (17)	5 (23)	0.16 (0.02- 0.72)	0.25
Time to steroids, days (mean)	4.7	38.9	10.8	6.9	**0.46, incr=20days (0.14- 0.98)**	**0.01**

Table 4.3: Normalisation of MRI lesions after sequential relapses for MOGAD patients with brain involvement on initial MRI (n=97)

Radiological findings in follow up MRI*s*	**1st attack, % (n)**	**2nd attack, % (n)**	**3rd attack, % (n)**	**4th attack, % (n)**	**5th attack, % (n)**
New symptomatic lesions	29% (28)	44% (17)	64% (9)	63% (5)	57% (4)
New asymptomatic lesions	11% (11)	15% (6)	14% (2)	20% (2)	29% (2)
Lesion shrinking including at least 1 lesion resolution	37% (36)	28% (11)	14% (2)	12% (1)	14% (1)
Normal MRI	23% (22)	12% (5)	7% (1)	0	0
Total patients	**97**	**39**	**14**	**8**	**7**

Figure 4.1: Brain imaging of three MOGAD patients demonstrating patterns of lesion dynamics.

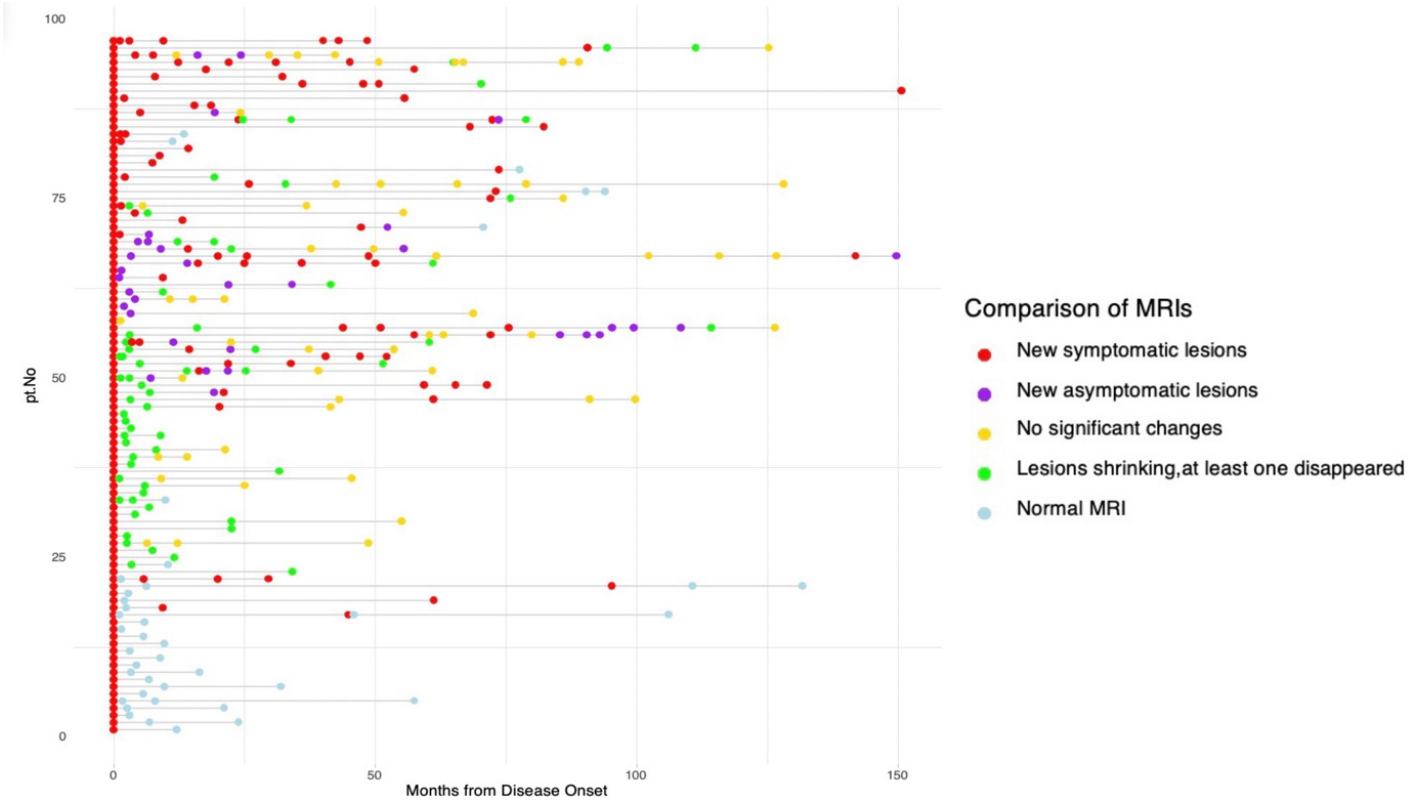


Coronal T2-weighted fluid-attenuated inversion recovery (FLAIR) images at onset (A), 3 months (B), 9 months (C) of patient 1 demonstrating appearance of new lesions at three months scan with significant resolution of lesions at 9 months. Axial T2-weighted images at onset (D) and 2 months (E) of patient 2 demonstrating confluent diffuse

white matter changes bilaterally at onset with complete lesion resolution at two months. Axial T2-weighted images of patient 3 focusing on the cerebellum at onset (F), 5 months (G), 7 months (H) and 12 months (I) demonstrating a mixed picture with some lesions appearing and some disappearing at the same timepoint.

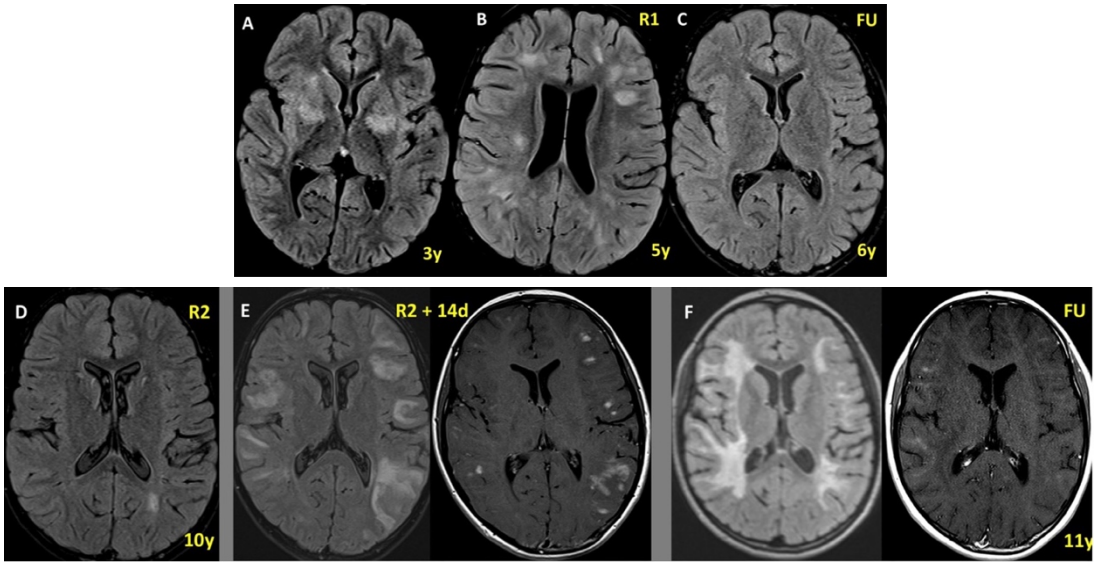
A total of 62 MRIs were performed on 23 MOGAD patients on maintenance immunotherapy (Table 4.4). Of these 19 MRIs were performed on patients on mycophenolate mofetil, MMF (4 new symptomatic lesions, 3 new asymptomatic lesions, 4 stable, 5 lesion shrinking, and 3 normal MRI), 3 on rituximab (all new symptomatic lesions), 12 on azathioprine (4 new symptomatic lesions, 7 stable and 1 lesion shrinking), 7 on IVIg (2 new asymptomatic lesions, one stable, 4 lesion shrinking), 13 on a combination of IVIg and MMF (1 new symptomatic lesion, 4 new asymptomatic, 6 stable and 2 lesion shrinking) and 8 on interferon beta 1a (2 new symptomatic lesions, 1 new asymptomatic and 5 stable). Asymptomatic lesions beyond the first follow-up MRI scan were more common in patients on maintenance immunotherapy than patients on no treatment (16% (10/62) vs 4% (9/255), p=0.009).

Figure 4.2: Lesion dynamics throughout the disease course in 97 patients with MOGAD.



Each horizontal line represents an individual patient time course. First follow-up MRI revealed new symptomatic lesions, i.e., associated with a relapse, (red) in 28 patients. New asymptomatic lesions (purple) were seen in 11 patients. Lesion shrinking with at least one lesion disappearing (green) was reported in 36 patients. Completely normal MRI (blue) was seen in 22 patients. Although not seen at first follow-up scan, many of the patients with initial partial lesion resolution remained stable in between attacks (yellow). In patients with multiple clinical relapses, new asymptomatic lesions appeared later in the disease course (purple). This was not seen in patients in whom MRI had previously normalised.

Figure 4.3: Brain imaging throughout disease course of a MOGAD patient with relapsing acute disseminated encephalomyelitis (ADEM)

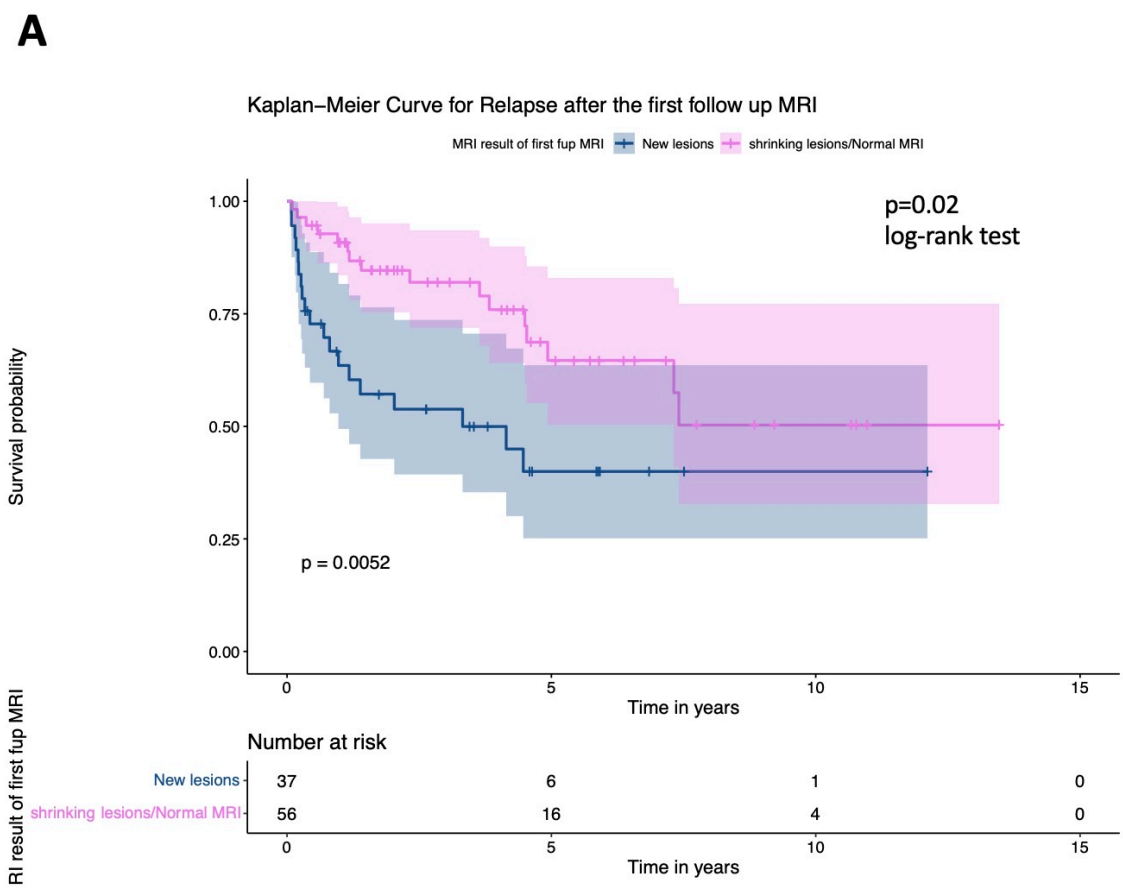


Acute presentation at age 3 years demonstrating bilateral globus pallidus signal change on T2-weighted imaging (A). Clinical relapse at age 5 with similar semiology, FLAIR-weighted images demonstrating multiple supratentorial T2 hyperintense lesions (B). Follow-up FLAIR-weighted imaging at age 6, demonstrating complete resolution of lesions (C). Third CNS attack aged 10 years, FLAIR-weighted imaging demonstrates a single lesion in the left parieto-occipital deep white matter (D); in view of worsening and lack of steroid responsiveness, repeat imaging was performed on day 14 (E) shows interval appearance of extensive multi-lobar bilateral subcortical white matter lesions with these foci showing intense nodular enhancement with a linear pattern of enhancement also apparent. There is no associated restricted diffusion (not shown). Follow up remission imaging at 11 years (F), EDSS 2.0, shows progression of signal abnormality in right frontal lobe subcortical white matter associated with new patchy enhancement. The subcortical signal abnormality elsewhere appears similar in extent.

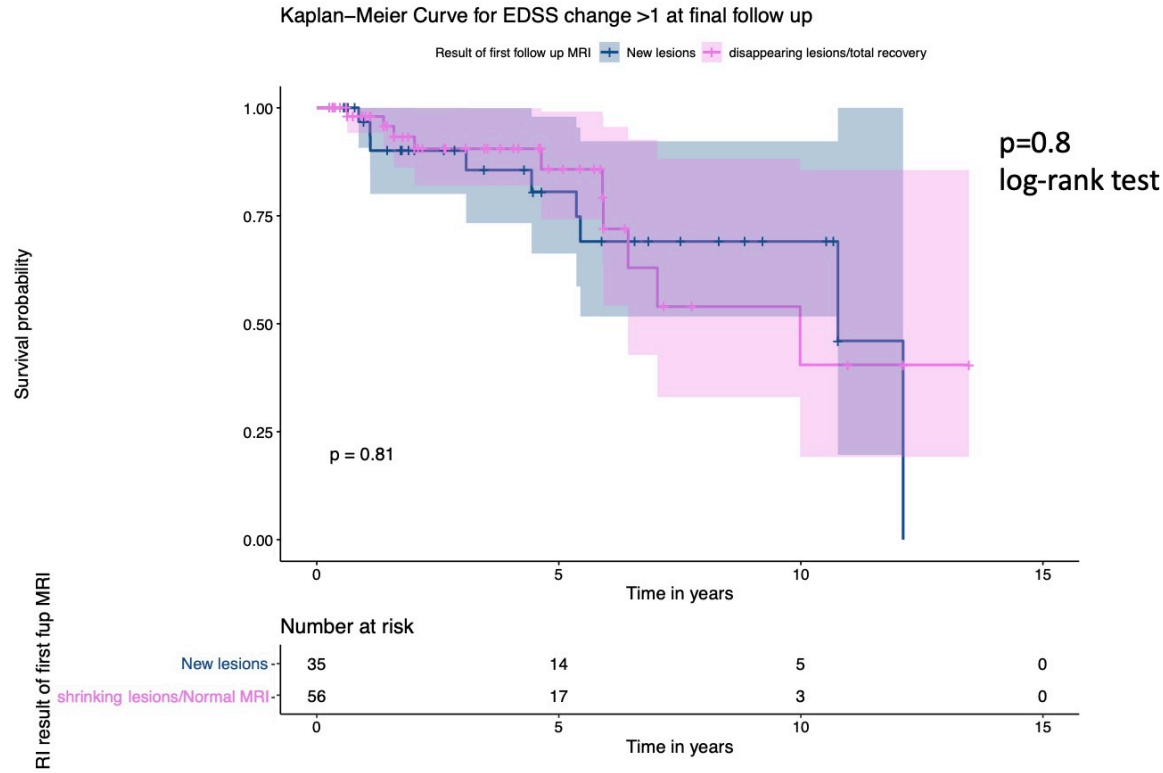
New lesions (symptomatic and asymptomatic) at first follow-up scan were associated with an increased likelihood of relapse (p=0.02, Figure 4.4A) and with persistent MOG-Ab seropositivity (p=0.0016, Figure 4.4B), but not with increased disability (EDSS increase >1, p=0.8, Figure 4.4C). Four patients in the group with new lesions and two patients in the group with no new lesions did not have a baseline EDSS and so were excluded from the Kaplan–Meier survival analysis. EDSS at final follow-up was also not different in the two groups, with a median of 1.5 (range 0–5) in the group with new lesions vs. median of 1 (range 0–6) in the group with shrinking lesions (p=0.28). EDSS >3 was seen in 10% (4/39) of patients in the group with new lesions on first follow-up MRI and 5% (3/58) in the group with no new lesions (p=0.44).

The survival curves highlight that the early MRI phenotype has prognostic relevance for relapse risk and antibody persistence but does not translate into sustained disability accrual. Patients with new lesions experienced earlier and more frequent relapses, whereas those with shrinking or normal MRI were more likely to achieve seronegative conversion over time. By contrast, disability progression was rare overall, and Kaplan–Meier curves for EDSS worsening showed near-complete overlap, with no significant difference between groups. These findings are consistent with the clinical observation that, unlike multiple sclerosis, long-term disability in MOGAD is less tightly coupled to early radiological activity, reflecting the generally good recovery between attacks.

Figure 4.4: Kaplan-Meier survival analyses for MOGAD cohort

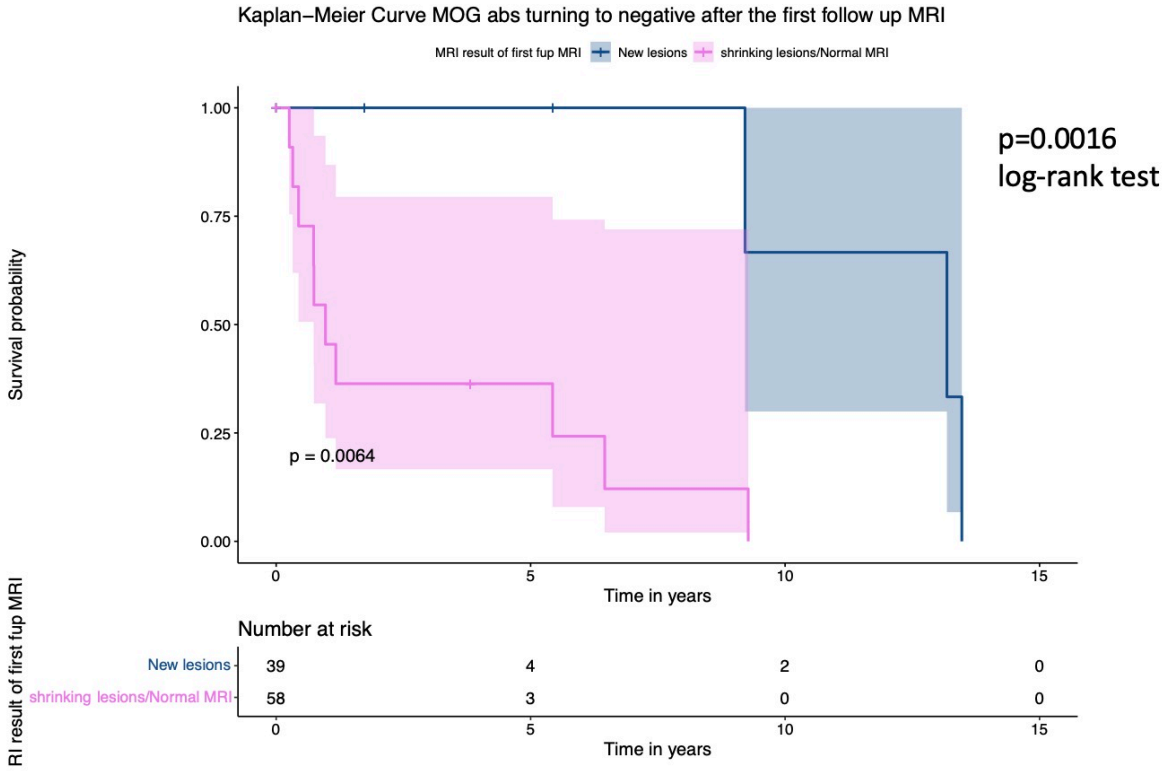


B



p=0.8
log-rank test

C



p=0.0016
log-rank test

Kaplan-Meier survival analyses were used to estimate the cumulative risk of clinical relapses (A), of disability accrual i.e. increase in EDSS score by 1 or more (B), and of seroconversion to MOG-Ab negative status (C), using the log-rank test to compare patients stratified to two groups of lesion dynamics on first follow-up MRI (new lesions vs shrinking lesions).

Table 4.4: Follow-up MRI lesion dynamics in 23 MOGAD patients on maintenance immunotherapy who had a total of 62 MRIs

Immunotherapy	**Follow-up MRI category**	**Number of MRIs**
MMF (n=19)	New symptomatic	4
	New asymptomatic	3
	Stable	4
	Lesion shrinking	5
	Normal MRI	3
Azathioprine (n=12)	New symptomatic	4
	New asymptomatic	0
	Stable	7
	Lesion shrinking	1
	Normal MRI	0
IVIg (n=7)	New symptomatic	0
	New asymptomatic	2
	Stable	1
	Lesion shrinking	4
	Normal MRI	0
IVIg + MMF (n=13)	New symptomatic	1
	New asymptomatic	4
	Stable	6
	Lesion shrinking	2
	Normal MRI	0

Interferon-beta 1a (n=8)	New symptomatic	2
	New asymptomatic	1
	Stable	5
	Lesion shrinking	0
	Normal MRI	0
Rituximab (n=3)	New symptomatic	3
	New asymptomatic	0
	Stable	0
	Lesion shrinking	0
	Normal MRI	0

4.7 Discussion

In this UK-wide observational study of paediatric MOGAD, we found that 83% of cases showed at least one resolved lesion on the first follow-up MRI. This contrasts sharply with the retrospective paediatric MS cohort (chapter 3), presenting in the same epoch to the same centres (n=103), where only one patient had a lesion resolve on follow-up imaging. The marked difference in lesion resolution between MOGAD and MS highlights distinct underlying pathobiological mechanisms and has practical diagnostic implications. In clinical practice, significant lesion resolution should raise suspicion against an MS diagnosis. Given the increasing trend toward early initiation of high-efficacy disease-modifying therapies (DMTs) in paediatric MS, ensuring an accurate diagnosis is critical before treatment initiation[299]. For patients with diagnostic uncertainty, my findings suggest that waiting for the first follow-up MRI could help clarify the diagnosis. In addition, it is important to consider a multimodal investigative approach, using paraclinical factors such as age at presentation, presence of intrathecal oligoclonal bands and EBV serology to help differentiate cases with diagnostic uncertainty[11].

The differential diagnosis between MOGAD and MS has been further enhanced by the publication of the 2023 International Diagnostic Criteria for MOGAD[186]. Recent validation studies have demonstrated the excellent performance of these criteria in real world clinical practice[292, 300-302]; in our group's study[292], we demonstrated sensitivity of 96.5% and specificity of 98.9% across all age groups[292]. Notably, the criteria showed even better performance in children compared to adults, with 100% sensitivity versus 91.9% in adults, while maintaining high specificity (98.9%) in both groups. This further supports the importance of accurate diagnosis in distinguishing these conditions.

This study found that most MOGAD patients showed lesion resolution on their first follow-up MRI. However, with sequential relapses, lesion resolution became less frequent, suggesting a declining capacity for brain repair over time. This was particularly evident in patients with the leukodystrophy-like phenotype[303], where new asymptomatic lesions and persistent enhancement were observed even outside of clinical attacks. These findings suggest that MOGAD disease mechanisms may evolve within individual patients, potentially altering their response to treatment. Environmental triggers, such as infection or vaccination, may influence lesion evolution, with some resolving naturally once the trigger is removed. Interestingly, asymptomatic lesions were more common in patients receiving maintenance immunosuppression, particularly IVIg. While these patients likely represent a more severe disease group, it raises the possibility that treatment may have prevented clinical relapses but not fully suppressed inflammatory activity. A key limitation is that MRI protocols in paediatric MOGAD are not standardised, unlike in paediatric MS. Many younger children require general anaesthesia for MRI, which may bias my findings toward a more severe disease cohort undergoing more frequent scans. Future studies are needed to determine the clinical significance of new asymptomatic lesions and whether they warrant treatment escalation.

Time to initiate steroids and the use of plasma exchange for the acute attack were the strongest predictors of MRI outcome following MOGAD attack. This aligns with a retrospective study of 75 children, where initiating immunotherapy within 7 days of symptom onset was linked to a lower relapse risk [224]. Additionally, steroids were shown to promote resolution of large T2 lesions (≥1 cm) but had no significant effect on smaller lesions (<1 cm) in a study analysing 585 lesions across 55 MOGAD patients [304]. Currently, PLEX is reserved for severe attacks [193], but my findings suggest that early antibody removal may influence long-term disease trajectory, similar to AQP4-Ab NMOSD [305, 306]. These results support considering PLEX earlier and in a broader range of MOGAD patients, rather than limiting its use to only the most severe cases.

This study found that the presence of new symptomatic and asymptomatic lesions on the first follow-up MRI was associated with a higher likelihood of future relapses. This aligns with a retrospective cohort study, where patients with new asymptomatic lesions had a shorter time to relapse [307]. However, two larger studies did not find a significant link between new asymptomatic lesions and relapse risk [295,308]. The conflicting findings may be due to variability in lesion dynamics in MOGAD. New lesions detected on the first follow-up MRI may reflect delayed evolution of lesions from the prior attack (radiologic lag) or new inflammatory activity occurring shortly after the acute MRI. These findings underscore the importance of re-baselining after an acute attack to accurately assess disease activity and guide treatment decisions.

Unlike MRI studies in MS, lesion dynamics in MOGAD are more variable, with lesions appearing and disappearing even within the same attack. Differences in timing and outcome measures between studies may impact comparisons. A prior study evaluating lesion evolution in MOGAD reported resolution of the index lesion (defined as symptomatic or largest lesion) in 60% (9/15) of paediatric MOGAD patients [309]. However, my study focused on children with abnormal brain MRI (ADEM and ADEM-

like phenotypes) presenting with cerebral polyfocal symptoms, making it difficult to identify a specific symptomatic or index lesion. The timing of follow-up neuroimaging likely explains discrepancies in lesion resolution rates across studies.

It is possible that the timing and interval between attack and first follow-up neuroimaging (remission MRI) in this cohort (with median 0.4 years) may explain the differences noted in this cohort's frequency of lesion resolution/normalisation of MRI compared to previous studies [217, 297] Longer intervals between attack and remission follow-up imaging are more likely to demonstrate T2-lesion resolution. Additionally, my study compared lesion evolution between initial and follow-up scans, regardless of whether the second MRI was performed for a new attack or routine follow-up (remission scan). This contrasts with other studies focusing strictly on attack-to-remission imaging, making lesion resolution in this cohort more complex to interpret, particularly when new lesions appeared in the same region as prior residual lesions. In a real-world clinical setting, obtaining remission MRIs outside of clinical attacks is often impractical, especially in young children who require general anaesthesia for imaging. This highlights the need for standardised follow-up protocols to better assess lesion dynamics in paediatric MOGAD.

This study has several limitations, primarily its retrospective design and lack of standardised MRI assessments at fixed intervals or on consistent scanners. However, this reflects real-world clinical practice, where MRIs are performed at variable time points on different machines. Despite analysing a large paediatric MOGAD cohort, the small sample size in each follow-up MRI category limited the statistical power of some findings. My analysis focused exclusively on patients with abnormal brain MRI at onset, regardless of clinical phenotype, and excluded those presenting only with optic neuritis or transverse myelitis. While this may limit the generalisability of some conclusions, it allowed for a more detailed assessment of lesion dynamics and their underlying pathobiological mechanisms. The rapid resolution of lesions seen on follow-

up imaging suggests that the changes may be driven more by transient myelin oedema rather than true demyelination and remyelination, which would typically take longer to occur. Understanding these dynamics is crucial for differentiating active pathology from reversible inflammatory changes in MOGAD.

Future studies should explore lesion dynamics in patients with non-brain involvement (ON and TM) compared to those with brain involvement (ADEM or cortical presentations) to better understand the heterogeneity of MOGAD. Given that EDSS is not a sufficiently sensitive clinical outcome measure for either MS or MOGAD (with a median score of 1.0 at final follow-up in both groups), alternative measures may provide greater clinical insight. Visual acuity and retinal nerve fibre layer (RNFL) thickness could serve as more meaningful outcome markers, particularly in patients with optic neuritis (ON) and brain involvement. However, the lack of systematic data for these parameters across this cohort limited their inclusion in this study.

My findings have clinical relevance when evaluating children with acquired demyelinating syndromes; for instance, in the cases when there is a diagnostic challenge with overlapping clinical features, lesion disappearance should point to a non-MS diagnosis. This is also of relevance for clinical trials in children with MOGAD; new or enlarging T2 lesions on brain MRI is often used as a primary outcome measure in MS, which relies on lesion persistence over time. In MOGAD this is not as straightforward given the dynamic nature of the lesions. Future studies evaluating temporal dynamics between white matter lesion evolution over time and long-term outcomes may help us to better understand the pathobiology of this condition, and act as a platform for further interventions.

4.8 Conclusions

Improving outcomes in MOGAD requires early and accurate diagnosis, based on reproducible MOG-Ab detection[310], alongside a better understanding of relapse mechanisms, treatment targets, and optimal timing for interventions. The disease course is highly heterogeneous, with clinical relapses alone not fully explaining disability accrual. Individual differences in myelin susceptibility, remyelination, and repair mechanisms likely contribute to this variability. Although younger children tend to present with more severe brain pathology and higher lesion loads, they often experience faster recovery from acute attacks than older children and adults. This pattern is also seen in MS, where every 10 years of age is associated with a 0.15-point reduction in EDSS recovery post-relapse[231]. This suggests a therapeutic window in paediatric patients, where early intervention may be particularly effective.

With no evidence-based guidelines for acute MOGAD treatment, my findings highlight the importance of timely steroid administration and plasma exchange in shaping early disease trajectory. These results reinforce the need for optimal management at disease onset, as it is a key predictor of long-term outcomes.

Chapter 5: Conclusions and Future Directions

5.1 Introduction

This thesis has provided significant insights into paediatric acquired demyelinating syndromes (ADS), with a focus on paediatric multiple sclerosis (MS) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). Through a combination of epidemiological, clinical, and imaging studies, this research has contributed to a deeper understanding of disease mechanisms, diagnosis, and management, with the overarching aim of improving patient outcomes. This concluding chapter summarises the key findings from my research, discusses their implications for clinical practice, and suggests directions for future research.

5.2 Summary of Novel Key Findings

The key findings and novel contributions to the field of this thesis are:

1) In Chapter 2, the long-term follow up of a UK-wide prospective surveillance study provides updated incidence rates of paediatric MS and MOGAD, highlighting their distinct disease trajectories. In MS, AQP4-NMOSD, and MOGAD, early identification and intervention are crucial for improving long-term neurological outcomes. Some children initially diagnosed with acquired demyelinating syndromes (ADS) were later reclassified with alternative diagnoses, reinforcing the need for thorough clinical evaluation and long-term follow-up. In cases with demyelinating symptoms, continuous monitoring ensures diagnostic accuracy and guides appropriate management.

2) The first UK multi-centre retrospective study in Chapter 3 evaluates the real-world effectiveness of disease-modifying therapies (DMTs) in paediatric MS.

The findings confirm the superior efficacy of newer DMTs over older injectables, supporting the early use of high-efficacy treatments. Patients on newer DMTs experience longer relapse-free periods, delayed treatment switching, and reduced new radiological activity. Multivariable analysis shows that older injectables increase the risk of clinical relapse twelvefold and double the risk of new radiological activity, reinforcing the need for early optimisation of treatment strategies in paediatric MS.

3) The largest prospective study of ocrelizumab in paediatric MS worldwide in Chapter 3 demonstrates its high efficacy and favourable safety profile. At 24 months, 93% of patients achieve no evidence of disease activity (NEDA-3), highlighting its potential as a highly effective treatment option. These findings support the use of Ocrelizumab in paediatric MS just as in adult MS patients, reinforcing its potential role in early disease control with a favourable side effect profile in children.

4) In Chapter 4, the evolution of brain MRI lesions in paediatric MOGAD reveals distinct lesion dynamics that differentiate it from MS. In MOGAD, lesions resolve at a high rate, whereas MS is characterised by persistent and accumulating lesions. Follow-up MRI findings establish lesion resolution as a key diagnostic biomarker, aiding in the differentiation of MOGAD from MS. These insights have important implications for treatment decisions and long-term disease management, reinforcing the role of MRI monitoring in clinical practice.

5.3 Clinical Implications

This thesis underscores the critical role of epidemiological analysis, MRI imaging techniques, and real-world observational studies in enhancing the understanding and management of paediatric demyelinating disorders. By addressing key gaps in the literature, it has contributed new perspectives on both disease progression and treatment response, with significant implications for future research and clinical practice.

A fundamental challenge in paediatric demyelinating diseases has been distinguishing between paediatric MS, MOGAD, and AQP4-NMOSD, given their overlapping clinical and radiological features. The epidemiological comprehensive longitudinal assessment of paediatric patients initially diagnosed with ADS over a decade, contributes valuable insights into the natural history of paediatric demyelinating disorders, including the incidence of MS, and MOGAD, and highlights the importance of thorough follow-up to refine diagnostic accuracy. The research presented here has demonstrated that imaging markers, particularly lesion dynamics on MRI, can provide valuable diagnostic clarity, supporting clinicians in differentiating between these disorders. This is particularly relevant in children, where early diagnosis is crucial for initiating appropriate treatment strategies and minimising long-term disability.

The findings also reinforce the evolving treatment paradigm in paediatric MS, where the shift towards early, high-efficacy therapy is increasingly supported by clinical and real-world data. The research presented in this thesis aligns with emerging evidence that children with highly active disease benefit from early aggressive treatment, reducing relapse rates and potentially altering the disease trajectory. Furthermore, the study on ocrelizumab in paediatric MS adds to the growing body of evidence from

adult literature supporting its efficacy, particularly in reducing disease activity and relapse rates.

From an imaging perspective, this thesis highlights the importance of MRI biomarkers in disease monitoring in the clinical setting, not only for initial diagnosis but also for monitoring disease progression and treatment response. The identification of distinctive lesion dynamics in MOGAD versus MS offers a practical clinical tool for differentiating between these conditions, particularly in cases where antibody testing results are equivocal or unavailable. This can guide appropriate treatment decisions, as the therapeutic approaches for MOGAD and MS differ substantially, with MS treatments potentially exacerbating MOGAD and vice versa.

Collectively, the studies presented in this thesis contribute to a more nuanced understanding of paediatric demyelinating diseases. They emphasise the importance of early diagnosis, personalised treatment approaches, and the integration of imaging biomarkers into routine clinical practice. By bridging the gap between clinical and radiological assessments, this research paves the way for more precise, evidence-based management strategies that can significantly improve outcomes for children affected by MS and MOGAD.

5.4 Future Directions

To build on new projects based on the work carried out as part of this thesis, I propose the following steps: to evaluate the long-term safety and effectiveness of newer high-efficacy therapies in paediatric MS through prospective, multicentre registries and real-world data studies; to integrate personalised medicine approaches in Paediatric MS; to identify sensitive, longitudinal biomarkers of neurodegeneration in paediatric MS and ADS; to assess the potential role of serum and cerebrospinal fluid biomarkers, such as

neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP) in disease monitoring and predicting treatment response in MS and MOGAD; and to apply advanced quantitative MRI techniques potentially providing deeper insights into the underlying pathophysiology of paediatric MS and MOGAD.

5.4.1 Evaluating newer DMTs with large real-world multicentre studies

Advancements in multiple sclerosis (MS) treatments over the past two decades have introduced a growing armamentarium of moderate and high-efficacy therapies such as dimethyl fumarate, teriflunomide, ocrelizumab, fingolimod, and natalizumab, which have demonstrated superior relapse prevention in paediatric MS and show promise in reducing long-term disability risk. However, more long-term clinical studies are required to establish the safety and efficacy of these DMTs in children. Two ongoing phase III trials—NEOS 3 [311], comparing ofatumumab and siponimod versus fingolimod, and OPERETTA 2 [312], evaluating ocrelizumab against fingolimod—aim to provide further evidence. Given the challenges of small sample sizes in paediatric MS, international collaboration and innovative trial designs are essential to ensure regulatory approval.

While high-efficacy DMTs have been shown to be both effective and well tolerated, data on their impact on subclinical and progressive disease activity remain limited. Key concerns include cortical lesion accumulation and brain atrophy over time, as well as the optimal duration of high-efficacy therapy in children. Identifying objective clinical and radiological markers is critical for guiding long-term management decisions. Advanced diagnostic tools, including high-resolution MRI and wearable sensors, may enhance disease monitoring and prognosis. Future clinical trials should focus on defining biomarkers of active disease, optimal treatment intervals, and long-term neurocognitive and physical outcomes in paediatric MS [313].

There is clear added value of high-quality international registries in providing real-world evidence to complement clinical trials. A recent study examined paediatric MS using data from the MSBase and Italian MS registries, covering 329 centres across 42 countries[115]. In this cohort of 5,224 paediatric MS patients, high-efficacy therapy significantly reduced disability accumulation over a five-year follow-up, with the greatest benefit observed when treatment began at mild disability stages, lowering the risk of severe disability by 60%. These findings reinforce the importance of early intensive therapy in preventing long-term disability, particularly in the highly inflammatory early stages of MS.

The rapid evolution of MS therapeutics presents challenges, including low paediatric trial recruitment numbers, high costs and length of time, and outdated study designs[314]. A new approach could involve extrapolating efficacy data from adult MS trials while using large real-world paediatric cohorts to assess safety and confirm effectiveness. Investigating treatment response predictors and shifting towards MRI-based outcomes as surrogate endpoints could further streamline trials. Although there is a need for high efficacy treatment in paediatric MS, the long-term cumulative risks of immunosuppression remain unclear, making safety a top priority in paediatric MS treatment. Both The International Pediatric Multiple Sclerosis Study Group (IPMSSG) and European experts stress the need for rigorous safety monitoring in this population[256, 315]. This is especially relevant in the younger and pre-pubertal MS patients that start DMTs at such a young age. Establishing structured long-term surveillance protocols is essential to mitigate potential risks from early-life DMT exposure.

Given the wealth of data available from our prospective paediatric MS cohort in Chapter 3, and the potential for long-term safety and efficacy monitoring, we plan

through the PITMS study to continue recruiting patients, including those starting newer DMTs such as ofatumumab, a subcutaneous anti-CD20 monoclonal antibody. This will allow us to monitor DMT safety in paediatric MS patients as they transition into adulthood for longer-term follow-up. There is also potential to collaborate with other centres to combine data on pre-pubescent MS patients, an under-researched and under-represented group in MS research.

5.4.2 Integrating Personalised medicine approaches in Paediatric MS

Following my PhD, data acquired as part of this thesis (reported in Chapters 2 and 3) will be combined with adult prospective (n=800) and retrospective (n=1500) MS cohorts (as part of the PITMS study), to predict the individual treatment response in MS by translating machine learning from the computer science field into clinical practice. In order, to do this, we will integrate all the demographic, clinical, radiological, serological and genetic variables that may shape the individual response to a treatment. Treatment response will be defined on clinical and MRI grounds. Machine learning techniques will be used to develop a high-dimensional model that predicts individual treatment response, using all the information collected. The model will be constructed from retrospective and prospective data and then validated on independent cohorts. We will test whether the predictive accuracy of the model varies with age. The ultimate aim, once our models are finalised and validated, is to develop as a decision aid system that generates prediction in clinic, to provide the best treatment for the individual patient.

With regards to outcome measure, cognition, fatigue, and quality of life are key factors in MS assessment, though such data are rarely collected in retrospective studies. Our current prospective study, as reported in Chapter 3, incorporates measures like BICAMS[316], which evaluates mental processing speed and memory. A key component,

the Symbol Digit Modalities Test (SDMT)[317], is widely used in MS research and trials, effectively distinguishing MS patients from controls and predicting real-world outcomes, such as employment status. The SDMT is inadequate for tracking cognitive decline over time due to practice effects[318]. Future paediatric studies will focus on more sensitive cognitive assessments. A recent study identified three distinct cognitive phenotypes in paediatric MS—preserved, mild verbal/semantic impairment, and multidomain impairment—each associated with specific structural and functional MRI changes[319]. These findings highlight the need for personalised cognitive monitoring approaches that reflect underlying brain network alterations. Additionally, patient-reported outcomes—including MS quality of life, fatigue scales, health economics, employment, and education data - will be explored to better evaluate DMT impact, areas often overlooked in clinical trials.

5.4.3 Investigating biomarkers of neurodegeneration

Brain and spinal cord atrophy in MS

Brain volume is reduced in children with MS when compared to healthy controls, which is evident at first clinical presentation[86, 87]. Brain atrophy accelerates over the first 2 years in children[86] and reflects neurodegeneration; the main correlate of disability progression in MS. The first paediatric MS RCT of fingolimod (a newer oral DMT) versus interferon beta-1a (an older injectable DMT) demonstrated the superiority of fingolimod vs interferon beta-1a in terms of reduction of annualised relapse rate, but brain atrophy continued to develop even in the patients who did not relapse[102, 257]. Despite the recognised importance of brain atrophy in correlating with, and predicting disease progression in MS, assessment of brain volume is currently not used when managing patients in the clinical setting. Given that brain atrophy measures have been correlated with neurological impairment and appear reproducible, they have been frequently included as endpoint outcomes when assessing therapies in the trial setting.

Early brain volume loss, detectable within a year, predicts disability in RRMS and PPMS[81, 82]. Cervical spinal cord atrophy is also linked to worsening disability, independent of other clinical and radiological markers[83]. In RRMS, the effect of disease-modifying therapies (DMTs) on brain atrophy correlates with reduced disability progression over two years[320]. Grey matter (GM) atrophy begins early, even in paediatric MS, and is a major contributor to whole-brain atrophy in adults[82]. A MAGNIMS study of 1,417 MS patients found a consistent pattern of GM atrophy progression, which spread over time and correlated with disability accumulation[85]. Early GM atrophy is linked to long-term physical and cognitive impairments. Studying asymptomatic brain and spinal cord atrophy in paediatric MS may reveal factors influencing long-term outcomes and help determine if halting relapses slows neurodegeneration.

Using MRI data (with up to 5 years follow-up) from our paediatric MS cohorts in Chapter 3, and a novel MRI image analysis pipeline developed by our group (MindGlide, a deep learning model that extracts volumes of brain regions and lesion from a single MRI modality) [321], I plan to run longitudinal, mixed-effect and multi-variable regression models to evaluate the added value of using brain volume and serum neurofilaments as novel biomarkers for disease progression in research and clinical practise. I will evaluate the association between different DMTs and age-expected brain growth in children.

In addition, given that most of our paediatric MS patients have had spinal cord imagine at baseline and follow-up post DMT initiation (often every 2 years), I will also measure cervical cord atrophy using spinal cord toolbox and correlate this with clinical, cognitive and radiological outcomes (including brain atrophy) using mixed-effects models.

Brain Atrophy in other Acquired Demyelinating Syndromes

Although brain atrophy is well described in MS as above, the impact of MOGAD on brain development during childhood remains unclear. Studies of brain volume in MOGAD are also scarce and limited by cross-sectional design. Only one recent study to date has investigated the trajectory of brain growth in 46 children with MOGAD, comparing this with the growth trajectories of age-matched and sex matched healthy children and 26 children with multiple sclerosis and 51 monophasic seronegative demyelination[322]. Children with MOGAD showed delayed growth of the thalamus, caudate, and globus pallidus ($p < 0.001$), with the greatest divergence in the first-year post-onset, even in monophasic cases. Thalamic volume abnormalities were present but less severe than in MS. In future, using our significantly larger paediatric MS and MOGAD cohorts described in Chapters 3 and 4, it would be useful to analyse our own imaging data to corroborate these results, and better determine the relative impact of monophasic vs relapsing MOGAD, and whether relapsing MOGAD with attacks isolated to the optic nerves or spinal cord affects brain volume over time.

Slowly expanding lesions (SELs)

A major challenge in paediatric MS is the lack of a sensitive, longitudinal biomarker for neurodegeneration across different ages. Slowly expanding lesions (SELs) could be a promising solution, offering a more objective and straightforward measure compared to brain volume assessments, which require statistical modelling and healthy control comparisons. SELs distinguish paediatric MS from MOGAD[323], as MS involves chronic neurodegeneration, while MOGAD causes relapse-related disability without ongoing axonal damage. Identified through longitudinal MRI[324], SELs show gradual expansion, reduced T1 intensity, and lower magnetisation transfer ratio (MTR)[325], indicating axonal loss and myelin damage. Pathologically, they feature microglial/macrophage accumulation at the edges[326]. SEL burden correlates with disability progression,

predicting conversion to SPMS and worsening EDSS[327], including in early-onset MS cases[325].

Using data from Chapter 3 for a future ongoing project, I aim to investigate prevalence of SELs in paediatric MS and their associations with clinical outcomes, serological biomarkers, and MRI measures. I will assess the number and localisation of SELs in a cohort of patients with paediatric MS. Additionally, I will seek to investigate potential clinical, serological (neurofilament levels), and brain volumetric predictors of SELs and evaluate whether SELs are associated with longitudinal changes in these variables over time.

Progression independent of relapse activity (PIRA)

Progression independent of relapse activity (PIRA) affects approximately 25% of patients with early relapsing MS (RMS) and is a major contributor to disability accumulation, especially when it emerges within the first five years of the disease[328-330]. The impact of progression independent of relapse activity (PIRA) versus relapse-associated worsening (RAW) on disability accrual in paediatric MS remains poorly understood, with current insights primarily derived from short-term clinical trial data. In a large Italian study (n=1,383), progression independent of relapse activity (PIRA) was found in 40% of paediatric MS cases, with minimal occurrence before 18 years and increasing between ages 21-30. This suggests that paediatric-onset MS offers early-stage resilience, with disability becoming more apparent in adulthood, particularly in patients treated with low-efficacy therapies. Paediatric patients may also exhibit greater plasticity, enhancing their capacity for repair and functional recovery compared to adults. These factors, combined with the overall clinical stability of paediatric MS cohort, highlight the challenges of detecting progression in well-treated paediatric MS populations.

Supporting these findings, a recent matched cohort study of natalizumab-treated paediatric MS and adult MS patients found no significant differences in relapse rates or MRI activity over 46 months, but PIRA events occurred only in adults (12.5%) and were absent in paediatric MS[331]. This further supports the notion that early high-efficacy treatment may prevent progression in paediatric MS and reinforces the case for natalizumab as a first-line option in this group. Whilst the cohorts I describe in Chapter 3 are relatively small compared to registry data, combining our data with adult MS prospective and retrospective cohorts in the future may allow further investigation on the pathologic substrates of PIRA.

5.4.4 Role of serum biomarkers in Paediatric MS and MOGAD

Serum Neurofilaments in Paediatric MS

Neurofilament light chain (NfL) is emerging as a key biomarker for neuroaxonal injury, with growing potential for paediatric applications. Elevated blood and cerebrospinal fluid (CSF) NfL levels correlate with CNS damage[332], making it a valuable tool for diagnosis, prognosis, and treatment monitoring in conditions such as multiple sclerosis (MS), MOGAD, stroke, and neurodegenerative diseases[333]. Notably, NfL levels decrease during remission and in response to disease-modifying treatments, reinforcing its role in tracking disease activity[332].

Recent research has established age-adjusted NfL reference ranges from 2667 healthy children and adolescents (aged 0–22 years) from the Coronavirus Antibodies in Kids from Bavaria study (Germany) and the US Network of Pediatric Multiple Sclerosis Centers[334]. This showed a natural decline until age 10, followed by stabilisation. A web-based tool has been developed to provide Z-score adjustments, enhancing the biomarker's clinical utility. However, challenges remain, as NfL levels overlap between healthy and diseased individuals, complicating interpretation. Further

research is needed to validate different assay platforms, establish CSF reference data, and integrate NfL testing into routine paediatric diagnostics. Despite these challenges, NfL holds significant promise as a non-invasive biomarker for early detection and monitoring of neurological diseases in children, especially paediatric MS.

In the prospective PITMS cohort described in Chapter 3, our team has collected blood samples to analyse serum NfL in paediatric MS patients at baseline and regular intervals for up to 5-year follow-up. I would hypothesise that higher serum NfL concentrations at baseline for children with MS are associated with greater brain volume loss and disability worsening at follow up, independent of disease-modifying therapies. Once these are analysed, I aim to use longitudinal, mixed-effect and multi-variable regression models to investigate longitudinal changes in NfL over time and its correlation with clinical disability. I will also evaluate relationships between the rates of change in imaging measures, NfL levels and clinical change, and the ability of NfL levels early in the disease course to predict clinical outcomes at five years. In fact, correlating the change in biomarkers to the patient's clinical status will help differentiate between relapse related and non-relapse related neurodegeneration.

Novel serum biomarkers in MOGAD

The 2015 NMOSD diagnostic criteria introduced a unifying concept, stratifying patients based on AQP4-IgG serostatus[152]. AQP4-IgG positivity, combined with one of six core clinical features, confirmed the diagnosis, while AQP4-IgG negative cases required stricter criteria, including clinical, imaging, and exclusionary assessments. The criteria increased diagnostic rates, including in seronegative cases, but challenges remain. Around 20-30% of AQP4-IgG-negative patients are later found to be MOG-IgG positive, reclassifying them as MOGAD[335]. Additionally, some limited-phenotype patients remain unclassified, and double-seronegative NMOSD appears to be a heterogeneous syndrome with severe presentations and poor treatment response[336].

No distinct imaging or CSF markers differentiate it from AQP4-NMOSD, MS, or MOGAD, necessitating comprehensive differential diagnosis.

The identification of fluid biomarkers presents a significant opportunity to better define a more homogenous seronegative NMOSD subgroup. Elevated levels of glial fibrillary acidic protein (GFAP) in CSF and serum have been reported in a subset of double seronegative NMOSD (DSN) patients[337], suggesting a potential marker of astrocytopathy. The advancement of single molecule array (SIMOA) technology has made GFAP testing more accessible, reinforcing its role as a promising biomarker. Additionally, some patients exhibit elevated CSF IL-6 levels, which may contribute to more targeted treatment strategies. These novel biomarkers present an opportunity for future paediatric MOGAD cohorts that are recruited by our research group.

5.4.5 Advanced imaging in paediatric MS and MOGAD

Recent years have witnessed significant progress in the development and application of advanced MRI techniques that go beyond conventional structural imaging to provide insights into the microstructural and functional aspects of brain pathology in paediatric MS. Diffusion tensor imaging (DTI) has emerged as a powerful tool for assessing white matter integrity by measuring the directional diffusion of water molecules within neural tissues. DTI studies in paediatric MS have revealed abnormalities in normal-appearing white matter, suggesting that pathological changes extend beyond visible lesions[338]. These findings highlight the diffuse nature of the disease process and may explain cognitive deficits observed in some paediatric MS patients despite relatively limited visible lesion load. The various DTI metrics, including fractional anisotropy, mean diffusivity, and radial diffusivity, provide complementary information about different aspects of white matter damage, from axonal injury to demyelination.

Magnetization transfer imaging (MTI) offers another window into the microstructural changes occurring in paediatric MS[339]. By quantifying the exchange of magnetization between protons bound to macromolecules (particularly myelin) and free water protons, MTI provides an indirect measure of myelin content. Studies employing this technique have demonstrated reduced magnetization transfer ratios in both lesional and normal-appearing brain tissue of paediatric MS patients, indicating widespread demyelination and microscopic tissue damage. These changes often precede the development of visible lesions on conventional MRI, suggesting that MTI might serve as an early biomarker of disease activity and progression in paediatric MS.

Magnetization transfer ratio (MTR) lacks pathological specificity as it is influenced by water content, inflammation, and scanner variability. New techniques like quantitative MTR (qMT)[340] and inhomogeneous MTR (ihMT)[341] offer more tissue-specific indices, with ihMT particularly sensitive to myelin lipids. Myelin water imaging (MWI), which measures T2 relaxation times, has shown strong correlation with myelin content, making it a promising biomarker for demyelination[342]. While MWI tracks myelin changes in MS, a 24-month study with alemtuzumab found no significant myelin alterations in lesions or normal-appearing white matter[343].

Recent evidence also suggests that MS-related neurodevelopmental changes may occur before clinical onset. A large population-based study of children without MS found that a higher MS polygenic risk score (PRS) was associated with smaller subcortical grey matter volumes, and that the combination of high PRS and exposure to household smoking predicted lower total brain and thalamic volumes[344]. These findings imply that genetic and environmental MS risk factors may influence brain structure during childhood, well before symptom onset.

Diffusion imaging studies have shown microstructural abnormalities in the subventricular zone (SVZ) of paediatric MS patients, with altered fractional anisotropy and mean diffusivity linked to greater white matter lesion burden and lower brain volumes, even in the absence of clinical disability[345]. These findings suggest that early SVZ disruption may play a role in disease propagation and offer a novel imaging biomarker for subclinical brain damage in paediatric MS.

Radiomics, which involves the extraction of quantitative features from MRI images, has shown promise in distinguishing MOGAD from other demyelinating disorders. A compound radiomics model combining T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), and FLAIR sequences achieved an area under the curve (AUC) of 0.989 in training sets, demonstrating high diagnostic accuracy[346]. Optical coherence tomography (OCT) has been used to assess optic nerve and retinal changes in paediatric MOGAD. Reduced macular vascular density and retinal nerve fibre layer thinning are observed in MOGAD-associated optic neuritis, correlating with visual acuity outcomes[347, 348].

Further research needs to be undertaken to check feasibility and utility of these advanced imaging techniques both in clinical and research settings; including standardisation of parameters related to image acquisition, the development of clinically available detection methods for nonconventional MRI techniques and a better definition of criteria for the validation of distinctive MS lesion characteristics. Our paediatric MS and MOGAD cohorts will be valuable for future research using advanced imaging modalities and techniques.

References

1. O'Mahony J, Marrie RA, Laporte A, et al. Recovery from central nervous system acute demyelination in children. Pediatrics 2015;136:e115-e123.
2. Waldman A, Ghezzi A, Bar-Or A, Mikaeloff Y, Tardieu M, Banwell B. Multiple sclerosis in children: an update on clinical diagnosis, therapeutic strategies, and research. The Lancet Neurology 2014;13:936-948.
3. Absoud M, Lim MJ, Chong WK, et al. Paediatric acquired demyelinating syndromes: incidence, clinical and magnetic resonance imaging features. Multiple Sclerosis Journal 2013;19:76-86.
4. Ketelslegers I, Catsman-Berrevoets C, Neuteboom R, et al. Incidence of acquired demyelinating syndromes of the CNS in Dutch children: a nationwide study. Journal of neurology 2012;259:1929-1935.
5. Langer-Gould A, Zhang J, Chung J, Yeung Y, Waubant E, Yao J. Incidence of acquired CNS demyelinating syndromes in a multiethnic cohort of children. Neurology 2011;77:1143-1148.
6. Reinhardt K, Weiss S, Rosenbauer J, Gärtner J, Von Kries R. Multiple sclerosis in children and adolescents: incidence and clinical picture–new insights from the nationwide G erman surveillance (2009–2011). European journal of neurology 2014;21:654-659.
7. Abdel-Mannan O, Absoud M, Benetou C, et al. Incidence of paediatric multiple sclerosis and other acquired demyelinating syndromes: 10-year follow-up surveillance study. Developmental Medicine & Child Neurology 2022;64:502-508.
8. Waubant E, Ponsonby A-L, Pugliatti M, Hanwell H, Mowry EM, Hintzen RQ. Environmental and genetic factors in pediatric inflammatory demyelinating diseases. Neurology 2016;87:S20-S27.
9. Waubant E, Lucas R, Mowry E, et al. Environmental and genetic risk factors for MS: an integrated review. Annals of clinical and translational neurology 2019;6:1905-1922.
10. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. The Lancet Neurology 2018;17:162-173.
11. Hacohen Y, Mankad K, Chong WK, et al. Diagnostic algorithm for relapsing acquired demyelinating syndromes in children. Neurology 2017;89:269-278.
12. Lennon VA, Wingerchuk DM, Kryzer TJ, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. The Lancet 2004;364:2106-2112.
13. Hacohen Y, Banwell B. Treatment approaches for MOG-Ab-associated demyelination in children. Current treatment options in neurology 2019;21:2.
14. Hacohen Y, Absoud M, Deiva K, et al. Myelin oligodendrocyte glycoprotein antibodies are associated with a non-MS course in children. Neurology-Neuroimmunology Neuroinflammation 2015;2.
15. Tackley G, O'Brien F, Rocha J, et al. Neuromyelitis optica relapses: race and rate, immunosuppression and impairment. Multiple sclerosis and related disorders 2016;7:21-25.
16. Koch-Henriksen N, Sørensen PS. The changing demographic pattern of multiple sclerosis epidemiology. The Lancet Neurology 2010;9:520-532.
17. Orton S-M, Herrera BM, Yee IM, et al. Sex ratio of multiple sclerosis in Canada: a longitudinal study. The Lancet Neurology 2006;5:932-936.
18. Krupp LB, Banwell B, Tenembaum S. Consensus definitions proposed for pediatric multiple sclerosis and related disorders. Neurology 2007;68:S7-S12.

19. Renoux C, Vukusic S, Mikaeloff Y, et al. Natural history of multiple sclerosis with childhood onset. New England Journal of Medicine 2007;356:2603-2613.
20. Ebers GC. Environmental factors and multiple sclerosis. The Lancet Neurology 2008;7:268-277.
21. Sawcer S, Hellenthal G, Pirinen M, et al. Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. Nature 2011;476:214.
22. Gay F, Drye T, Dick G, Esiri M. The application of multifactorial cluster analysis in the staging of plaques in early multiple sclerosis. Identification and characterization of the primary demyelinating lesion. Brain: a journal of neurology 1997;120:1461-1483.
23. Hohlfeld R, Dornmair K, Meinl E, Wekerle H. The search for the target antigens of multiple sclerosis, part 1: autoreactive CD4+ T lymphocytes as pathogenic effectors and therapeutic targets. The Lancet Neurology 2016;15:198-209.
24. Hemmer B, Kerschensteiner M, Korn T. Role of the innate and adaptive immune responses in the course of multiple sclerosis. The Lancet Neurology 2015;14:406-419.
25. Kutzelnigg A, Lucchinetti CF, Stadelmann C, et al. Cortical demyelination and diffuse white matter injury in multiple sclerosis. Brain 2005;128:2705-2712.
26. Eshaghi A, Prados F, Brownlee WJ, et al. Deep gray matter volume loss drives disability worsening in multiple sclerosis. Annals of neurology 2018;83:210-222.
27. Enzinger C, Barkhof F, Ciccarelli O, et al. Nonconventional MRI and microstructural cerebral changes in multiple sclerosis. Nature Reviews Neurology 2015;11:676-686.
28. Burton EV, Greenberg BM, Frohman EM. Optic neuritis: A mechanistic view. Pathophysiology 2011;18:81-92.
29. Harding KE, Liang K, Cossburn MD, et al. Long-term outcome of paediatric-onset multiple sclerosis: a population-based study. J Neurol Neurosurg Psychiatry 2013;84:141-147.
30. Gombolay G, Johnson L, King R, et al. Worldwide epidemiology of paediatric multiple sclerosis: data from the Multiple Sclerosis International Federation Atlas of MS. Journal of Neurology, Neurosurgery & Psychiatry 2025.
31. Belman AL, Krupp LB, Olsen CS, et al. Characteristics of children and adolescents with multiple sclerosis. Pediatrics 2016;138.
32. Akmatov MK, Graf J, Kohring C, et al. Symptoms Prior to Diagnosis of Multiple Sclerosis in Individuals Younger Than 18 Years. JAMA Network Open 2024;7:e2452652-e2452652.
33. Alroughani R, Boyko A. Pediatric multiple sclerosis: a review. BMC neurology 2018;18:1-8.
34. Milo R, Kahana E. Multiple sclerosis: geoepidemiology, genetics and the environment. Autoimmunity reviews 2010;9:A387-A394.
35. Neuteboom R, Boon M, Berrevoets CC, et al. Prognostic factors after a first attack of inflammatory CNS demyelination in children. Neurology 2008;71:967-973.
36. Dell'Avvento S, Sotgiu MA, Manca S, Sotgiu G, Sotgiu S. Epidemiology of multiple sclerosis in the pediatric population of Sardinia, Italy. European journal of pediatrics 2016;175:19-29.
37. Alroughani R, Boyko A. Pediatric multiple sclerosis: a review. BMC neurology 2018;18:1-8.
38. Izadi S, Nikseresht AR, Poursadeghfard M, Borhanihaghighi A, Heydari ST. Prevalence and incidence of multiple sclerosis in Fars province, Southern Iran. Iranian journal of medical sciences 2015;40:390.

39. De Mol C, Wong Y, Van Pelt E, et al. Incidence and outcome of acquired demyelinating syndromes in Dutch children: update of a nationwide and prospective study. Journal of neurology 2018;265:1310-1319.
40. Fang C-W, Wang H-P, Chen H-M, Lin J-W, Lin W-S. Epidemiology and comorbidities of adult multiple sclerosis and neuromyelitis optica in Taiwan, 2001–2015. Multiple Sclerosis and Related Disorders 2020;45:102425.
41. Disanto G, Magalhaes S, Handel A, et al. HLA-DRB1 confers increased risk of pediatric-onset MS in children with acquired demyelination. Neurology 2011;76:781-786.
42. Axisa P-P, Hafler DA. Multiple sclerosis: genetics, biomarkers, treatments. Current opinion in neurology 2016;29:345-353.
43. Gianfrancesco MA, Stridh P, Shao X, et al. Genetic risk factors for pediatric-onset multiple sclerosis. Multiple Sclerosis Journal 2018;24:1825-1834.
44. Bashinskaya V, Kulakova O, Boyko A, Favorov A, Favorova O. A review of genome-wide association studies for multiple sclerosis: classical and hypothesis-driven approaches. Human genetics 2015;134:1143-1162.
45. Banwell B, Bar-Or A, Arnold DL, et al. Clinical, environmental, and genetic determinants of multiple sclerosis in children with acute demyelination: a prospective national cohort study. The Lancet Neurology 2011;10:436-445.
46. Langer-Gould A, Brara SM, Beaber BE, Koebnick C. Childhood obesity and risk of pediatric multiple sclerosis and clinically isolated syndrome. Neurology 2013;80:548-552.
47. Huppke B, Ellenberger D, Rosewich H, Friede T, Gärtner J, Huppke P. Clinical presentation of pediatric multiple sclerosis before puberty. European journal of neurology 2014;21:441-446.
48. George IC, Makhani N. Genetic and Environmental Risk Factors for Pediatric Multiple Sclerosis. Journal of Pediatric Neurology 2018;16:141-147.
49. Banwell B, Krupp L, Kennedy J, et al. Clinical features and viral serologies in children with multiple sclerosis: a multinational observational study. The Lancet Neurology 2007;6:773-781.
50. Fadda G, Yea C, O'Mahony J, et al. Epstein–Barr Virus Strongly Associates With Pediatric Multiple Sclerosis, But Not Myelin Oligodendrocyte Glycoprotein-Antibody-Associated Disease. Annals of neurology 2024;95:700-705.
51. Mikaeloff Y, Caridade G, Rossier M, Suissa S, Tardieu M. Hepatitis B vaccination and the risk of childhood-onset multiple sclerosis. Archives of pediatrics & adolescent medicine 2007;161:1176-1182.
52. Mikaeloff Y, Caridade G, Suissa S, Tardieu M. Hepatitis B vaccine and the risk of CNS inflammatory demyelination in childhood. Neurology 2009;72:873-880.
53. Langer-Gould A, Qian L, Tartof SY, et al. Vaccines and the risk of multiple sclerosis and other central nervous system demyelinating diseases. JAMA neurology 2014;71:1506-1513.
54. Tremlett H, Fadrosh DW, Faruqi AA, et al. Gut microbiota in early pediatric multiple sclerosis: a case− control study. European journal of neurology 2016;23:1308-1321.
55. Amato MP, Derfuss T, Hemmer B, et al. Environmental modifiable risk factors for multiple sclerosis: Report from the 2016 ECTRIMS focused workshop. Multiple Sclerosis Journal 2018;24:590-603.
56. 75 MCHAJIBYLSMLSAVPSK. Locus for severity implicates CNS resilience in progression of multiple sclerosis. Nature 2023;619:323-331.

57. Jokubaitis VG, Campagna MP, Ibrahim O, et al. Not all roads lead to the immune system: the genetic basis of multiple sclerosis severity. Brain 2023;146:2316-2331.
58. Zhou Y, Graves JS, Simpson S, et al. Genetic variation in the gene LRP2 increases relapse risk in multiple sclerosis. Journal of Neurology, Neurosurgery & Psychiatry 2017;88:864-868.
59. McKay KA, Hillert J, Manouchehrinia A. Long-term disability progression of pediatric-onset multiple sclerosis. Neurology 2019;92:e2764-e2773.
60. Abdel-Mannan O, Cortese R, Wassmer E, et al. Primary progressive multiple sclerosis presenting under the age of 18 years: Fact or fiction? Multiple Sclerosis Journal 2021;27:309-314.
61. Waldman A, Ness J, Pohl D, et al. Pediatric multiple sclerosis: clinical features and outcome. Neurology 2016;87:S74-S81.
62. Gorman MP, Healy BC, Polgar-Turcsanyi M, Chitnis T. Increased relapse rate in pediatric-onset compared with adult-onset multiple sclerosis. Archives of neurology 2009;66:54-59.
63. Huppke P, Huppke B, Ellenberger D, et al. Therapy of highly active pediatric multiple sclerosis. Multiple Sclerosis Journal 2019;25:72-80.
64. Hor JY, Asgari N, Nakashima I, et al. Epidemiology of neuromyelitis optica spectrum disorder and its prevalence and incidence worldwide. Frontiers in neurology 2020;11:501.
65. Reindl M, Waters P. Myelin oligodendrocyte glycoprotein antibodies in neurological disease. Nature Reviews Neurology 2019;15:89-102.
66. Estrada K, Whelan CW, Zhao F, et al. A whole-genome sequence study identifies genetic risk factors for neuromyelitis optica. Nature communications 2018;9:1-10.
67. Chitnis T, Graves J, Weinstock-Guttman B, et al. Distinct effects of obesity and puberty on risk and age at onset of pediatric MS. Annals of clinical and translational neurology 2016;3:897-907.
68. Hedström AK, Bomfim IL, Barcellos L, et al. Interaction between adolescent obesity and HLA risk genes in the etiology of multiple sclerosis. Neurology 2014;82:865-872.
69. Mikaeloff Y, Caridade G, Tardieu M, Suissa S, Group KS. Parental smoking at home and the risk of childhood-onset multiple sclerosis in children. Brain 2007;130:2589-2595.
70. Mowry EM, Krupp LB, Milazzo M, et al. Vitamin D status is associated with relapse rate in pediatric-onset multiple sclerosis. Annals of neurology 2010;67:618-624.
71. Hacohen Y, Brownlee W, Mankad K, et al. Improved performance of the 2017 McDonald criteria for diagnosis of multiple sclerosis in children in a real-life cohort. Multiple Sclerosis Journal 2020;26:1372-1380.
72. Fadda G, Brown RA, Longoni G, et al. MRI and laboratory features and the performance of international criteria in the diagnosis of multiple sclerosis in children and adolescents: a prospective cohort study. The Lancet Child & Adolescent Health 2018;2:191-204.
73. Pohl D, Rostasy K, Reiber H, Hanefeld F. CSF characteristics in early-onset multiple sclerosis. Neurology 2004;63:1966-1967.
74. Chitnis T. Role of puberty in multiple sclerosis risk and course. Clinical Immunology 2013;149:192-200.
75. Chabas D, Ness J, Belman A, et al. Younger children with MS have a distinct CSF inflammatory profile at disease onset. Neurology 2010;74:399-405.
76. Mikaeloff Y, Adamsbaum C, Husson B, et al. MRI prognostic factors for relapse after acute CNS inflammatory demyelination in childhood. Brain 2004;127:1942-1947.

77. Callen D, Shroff M, Branson H, et al. Role of MRI in the differentiation of ADEM from MS in children. Neurology 2009;72:968-973.
78. Verhey LH, Branson HM, Shroff MM, et al. MRI parameters for prediction of multiple sclerosis diagnosis in children with acute CNS demyelination: a prospective national cohort study. The Lancet Neurology 2011;10:1065-1073.
79. Geurts J, Roosendaal S, Calabrese M, et al. Consensus recommendations for MS cortical lesion scoring using double inversion recovery MRI. Neurology 2011;76:418-424.
80. Sastre-Garriga J, Pareto D, Battaglini M, et al. MAGNIMS consensus recommendations on the use of brain and spinal cord atrophy measures in clinical practice. Nature Reviews Neurology 2020;16:171-182.
81. Di Filippo M, Anderson VM, Altmann DR, et al. Brain atrophy and lesion load measures over 1 year relate to clinical status after 6 years in patients with clinically isolated syndromes. Journal of Neurology, Neurosurgery & Psychiatry 2010;81:204-208.
82. Popescu V, Agosta F, Hulst HE, et al. Brain atrophy and lesion load predict long term disability in multiple sclerosis. Journal of Neurology, Neurosurgery & Psychiatry 2013;84:1082-1091.
83. Lukas C, Knol DL, Sombekke MH, et al. Cervical spinal cord volume loss is related to clinical disability progression in multiple sclerosis. Journal of Neurology, Neurosurgery & Psychiatry 2015;86:410-418.
84. Tsagkas C, Magon S, Gaetano L, et al. Spinal cord volume loss: A marker of disease progression in multiple sclerosis. Neurology 2018;91:e349-e358.
85. Eshaghi A, Marinescu RV, Young AL, et al. Progression of regional grey matter atrophy in multiple sclerosis. Brain 2018;141:1665-1677.
86. Aubert-Broche B, Fonov V, Narayanan S, et al. Onset of multiple sclerosis before adulthood leads to failure of age-expected brain growth. Neurology 2014;83:2140-2146.
87. De Meo E, Meani A, Moiola L, et al. Dynamic gray matter volume changes in pediatric multiple sclerosis: a 3.5 year MRI study. Neurology 2019;92:e1709-e1723.
88. Neumann B, Segel M, Chalut KJ, Franklin RJ. Remyelination and ageing: Reversing the ravages of time. Multiple Sclerosis Journal 2019;25:1835-1841.
89. De Santis S, Granberg T, Ouellette R, et al. Evidence of early microstructural white matter abnormalities in multiple sclerosis from multi-shell diffusion MRI. NeuroImage: Clinical 2019;22:101699.
90. Battiston M, Schneider T, Grussu F, et al. Fast bound pool fraction mapping via steady-state magnetization transfer saturation using single-shot EPI. Magnetic resonance in medicine 2019;82:1025-1040.
91. Kolind S, Matthews L, Johansen-Berg H, et al. Myelin water imaging reflects clinical variability in multiple sclerosis. Neuroimage 2012;60:263-270.
92. Filippi M, Rocca MA, Ciccarelli O, et al. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. The Lancet Neurology 2016;15:292-303.
93. Tintore M, Rovira À, Río J, et al. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. Brain 2015;138:1863-1874.
94. Verhey LH, Signori A, Arnold DL, et al. Clinical and MRI activity as determinants of sample size for pediatric multiple sclerosis trials. Neurology 2013;81:1215-1221.
95. Ghassemi R, Brown R, Banwell B, Narayanan S, Arnold DL, Group CPDDS. Quantitative Measurement of tissue damage and recovery within new T2w lesions in pediatric-and adult-onset multiple sclerosis. Multiple Sclerosis Journal 2015;21:718-725.

96. Verhey LH, Branson HM, Makhija M, Shroff M, Banwell B. Magnetic resonance imaging features of the spinal cord in pediatric multiple sclerosis: a preliminary study. Neuroradiology 2010;52:1153-1162.
97. Brownlee W, Altmann D, Alves Da Mota P, et al. Association of asymptomatic spinal cord lesions and atrophy with disability 5 years after a clinically isolated syndrome. Multiple Sclerosis Journal 2017;23:665-674.
98. Moraal B, van den Elskamp IJ, Knol DL, et al. Long-interval T2w subtraction MRI: A powerful new outcome measure in MS trials.
99. Tóth E, Szabó N, Csete G, et al. Gray matter atrophy is primarily related to demyelination of lesions in multiple sclerosis: a diffusion tensor imaging MRI study. Frontiers in neuroanatomy 2017;11:23.
100. Chitnis T, Tenembaum S, Banwell B, et al. Consensus statement: evaluation of new and existing therapeutics for pediatric multiple sclerosis. Multiple Sclerosis Journal 2012;18:116-127.
101. Duignan S, Brownlee W, Wassmer E, et al. Paediatric multiple sclerosis: a new era in diagnosis and treatment. Developmental Medicine & Child Neurology 2019;61:1039-1049.
102. Chitnis T, Arnold DL, Banwell B, et al. Trial of fingolimod versus interferon beta-1a in pediatric multiple sclerosis. New England Journal of Medicine 2018;379:1017-1027.
103. Chitnis T, Banwell B, Kappos L, et al. Safety and efficacy of teriflunomide in paediatric multiple sclerosis (TERIKIDS): a multicentre, double-blind, phase 3, randomised, placebo-controlled trial. The Lancet Neurology 2021;20:1001-1011.
104. Vermersch P, Scaramozza M, Levin S, et al. Effect of dimethyl fumarate vs interferon β-1a in patients with pediatric-onset multiple sclerosis: the CONNECT randomized clinical trial. JAMA Network Open 2022;5:e2230439-e2230439.
105. Baroncini D, Zaffaroni M, Moiola L, et al. Long-term follow-up of pediatric MS patients starting treatment with injectable first-line agents: a multicentre, Italian, retrospective, observational study. Multiple Sclerosis Journal 2019;25:399-407.
106. Abdel-Mannan OA, Manchoon C, Rossor T, et al. Use of disease-modifying therapies in pediatric relapsing-remitting multiple sclerosis in the United Kingdom. Neurology-Neuroimmunology Neuroinflammation 2021;8.
107. Krysko KM, Graves JS, Rensel M, et al. Real-world effectiveness of initial disease-modifying therapies in pediatric multiple sclerosis. Annals of neurology 2020;88:42-55.
108. Krämer J, Bar-Or A, Turner TJ, Wiendl H. Bruton tyrosine kinase inhibitors for multiple sclerosis. Nature Reviews Neurology 2023;19:289-304.
109. Montalban X, Vermersch P, Arnold DL, et al. Safety and efficacy of evobrutinib in relapsing multiple sclerosis (evolutionRMS1 and evolutionRMS2): two multicentre, randomised, double-blind, active-controlled, phase 3 trials. The Lancet Neurology 2024;23:1119-1132.
110. Fox RJ, Bar-Or A, Traboulsee A, et al. Tolebrutinib in Nonrelapsing Secondary Progressive Multiple Sclerosis. New England Journal of Medicine 2025.
111. Poon MM, Lorrain KI, Stebbins KJ, et al. Targeting the muscarinic M1 receptor with a selective, brain-penetrant antagonist to promote remyelination in multiple sclerosis. Proceedings of the National Academy of Sciences 2024;121:e2407974121.
112. Boiko A, Vorobeychik G, Paty D, Devonshire V, Sadovnick D. Early onset multiple sclerosis: a longitudinal study. Neurology 2002;59:1006-1010.

113. Harding KE, Liang K, Cossburn MD, et al. Long-term outcome of paediatric-onset multiple sclerosis: a population-based study. Journal of Neurology, Neurosurgery & Psychiatry 2013;84:141-147.
114. Renoux C, Vukusic S, Confavreux C. The natural history of multiple sclerosis with childhood onset. Clinical neurology and neurosurgery 2008;110:897-904.
115. Sharmin S, Roos I, Malpas CB, et al. Disease-modifying therapies in managing disability worsening in paediatric-onset multiple sclerosis: a longitudinal analysis of global and national registries. The Lancet Child & Adolescent Health 2024;8:348-357.
116. Bevan CJ, Cree BA. Disease activity free status: a new end point for a new era in multiple sclerosis clinical research? JAMA neurology 2014;71:269-270.
117. Ruano L, Branco M, Portaccio E, et al. Patients with paediatric-onset multiple sclerosis are at higher risk of cognitive impairment in adulthood: an Italian collaborative study. Multiple Sclerosis Journal 2018;24:1234-1242.
118. MacAllister W, Belman A, Milazzo M, et al. Cognitive functioning in children and adolescents with multiple sclerosis. Neurology 2005;64:1422-1425.
119. Amato M, Goretti B, Ghezzi A, et al. Cognitive and psychosocial features in childhood and juvenile MS: two-year follow-up. Neurology 2010;75:1134-1140.
120. Amato MP, Krupp LB, Charvet LE, Penner I, Till C. Pediatric multiple sclerosis: cognition and mood. Neurology 2016;87:S82-S87.
121. McKay KA, Manouchehrinia A, Berrigan L, Fisk JD, Olsson T, Hillert J. Long-term Cognitive Outcomes in Patients With Pediatric-Onset vs Adult-Onset Multiple Sclerosis. JAMA Neurol 2019.
122. McKay KA, Friberg E, Razaz N, Alexanderson K, Hillert J. Long-term Socioeconomic Outcomes Associated With Pediatric-Onset Multiple Sclerosis. JAMA neurology 2021;78:478-482.
123. Hacohen Y, Banwell B, Ciccarelli O. What does first-line therapy mean for paediatric multiple sclerosis in the current era? Mult Scler 2021;27:1970-1976.
124. Chitnis T, Banwell B, Kappos L, et al. Teriflunomide in pediatric patients with relapsing multiple sclerosis: Open-label extension of TERIKIDS. Multiple Sclerosis Journal 2024;30:833-842.
125. Sormani MP, Bruzzi P. MRI lesions as a surrogate for relapses in multiple sclerosis: a meta-analysis of randomised trials. The Lancet Neurology 2013;12:669-676.
126. Vermersch P, Oreja-Guevara C, Siva A, et al. Efficacy and safety of ocrelizumab in patients with relapsing-remitting multiple sclerosis with suboptimal response to prior disease-modifying therapies: A primary analysis from the phase 3b CASTING single-arm, open-label trial. European Journal of Neurology 2022;29:790-801.
127. Hacohen Y, Banwell B, Ciccarelli O. What does first-line therapy mean for paediatric multiple sclerosis in the current era? Multiple Sclerosis Journal 2020:1352458520937644.
128. Giovannoni G, Tomic D, Bright JR, Havrdova E. "No evident disease activity": The use of combined assessments in the management of patients with multiple sclerosis. Mult Scler 2017;23:1179-1187.
129. Kappos L, De Stefano N, Freedman MS, et al. Inclusion of brain volume loss in a revised measure of 'no evidence of disease activity' (NEDA-4) in relapsing-remitting multiple sclerosis. Mult Scler 2016;22:1297-1305.
130. Sormani MP, Arnold DL, De Stefano N. Treatment effect on brain atrophy correlates with treatment effect on disability in multiple sclerosis. Annals of neurology 2014;75:43-49.

131. Stangel M, Penner IK, Kallmann BA, Lukas C, Kieseier BC. Towards the implementation of 'no evidence of disease activity'in multiple sclerosis treatment: the multiple sclerosis decision model. Therapeutic advances in neurological disorders 2015;8:3-13.
132. Kalincik T, Brown JWL, Robertson N, et al. Treatment effectiveness of alemtuzumab compared with natalizumab, fingolimod, and interferon beta in relapsing-remitting multiple sclerosis: a cohort study. Lancet Neurol 2017;16:271-281.
133. Rotstein DL, Healy BC, Malik MT, Chitnis T, Weiner HL. Evaluation of no evidence of disease activity in a 7-year longitudinal multiple sclerosis cohort. JAMA neurology 2015;72:152-158.
134. Kutzelnigg A, Lucchinetti CF, Stadelmann C, et al. Cortical demyelination and diffuse white matter injury in multiple sclerosis. Brain 2005;128:2705-2712.
135. Anderson VM, Fox NC, Miller DH. Magnetic resonance imaging measures of brain atrophy in multiple sclerosis. J Magn Reson Imaging 2006;23:605-618.
136. Dalton CM, Chard DT, Davies GR, et al. Early development of multiple sclerosis is associated with progressive grey matter atrophy in patients presenting with clinically isolated syndromes. Brain 2004;127:1101-1107.
137. Rocca MA, Absinta M, Filippi M. The role of advanced magnetic resonance imaging techniques in primary progressive MS. Journal of neurology 2012;259:611-621.
138. Ingle GT, Stevenson VL, Miller DH, et al. Two-year follow-up study of primary and transitional progressive multiple sclerosis. Mult Scler 2002;8:108-114.
139. Gasperini C, Paolillo A, Giugni E, et al. MRI brain volume changes in relapsing-remitting multiple sclerosis patients treated with interferon beta-1a. Mult Scler 2002;8:119-123.
140. Fisher E, Rudick RA, Simon JH, et al. Eight-year follow-up study of brain atrophy in patients with MS. Neurology 2002;59:1412-1420.
141. Healy B, Valsasina P, Filippi M, Bakshi R. Sample size requirements for treatment effects using gray matter, white matter and whole brain volume in relapsing–remitting multiple sclerosis. Journal of Neurology, Neurosurgery & Psychiatry 2009;80:1218-1224.
142. Duignan S, Wright S, Rossor T, et al. Myelin oligodendrocyte glycoprotein and aquaporin-4 antibodies are highly specific in children with acquired demyelinating syndromes. Developmental Medicine & Child Neurology 2018;60:958-962.
143. Reindl M, Di Pauli F, Rostásy K, Berger T. The spectrum of MOG autoantibody-associated demyelinating diseases. Nature Reviews Neurology 2013;9:455-461.
144. Spadaro M, Winklmeier S, Beltrán E, et al. Pathogenicity of human antibodies against myelin oligodendrocyte glycoprotein. Annals of neurology 2018;84:315-328.
145. Kaneko K, Sato DK, Nakashima I, et al. CSF cytokine profile in MOG-IgG+ neurological disease is similar to AQP4-IgG+ NMOSD but distinct from MS: a cross-sectional study and potential therapeutic implications. Journal of Neurology, Neurosurgery & Psychiatry 2018;89:927-936.
146. Spadaro M, Gerdes LA, Krumbholz M, et al. Autoantibodies to MOG in a distinct subgroup of adult multiple sclerosis. Neurology-Neuroimmunology Neuroinflammation 2016;3.
147. Takai Y, Misu T, Kaneko K, et al. Myelin oligodendrocyte glycoprotein antibody-associated disease: an immunopathological study. Brain 2020;143:1431-1446.

148. Hyun J-W, Woodhall MR, Kim S-H, et al. Longitudinal analysis of myelin oligodendrocyte glycoprotein antibodies in CNS inflammatory diseases. J Neurol Neurosurg Psychiatry 2017;88:811-817.
149. Narayan R, Simpson A, Fritsche K, et al. MOG antibody disease: a review of MOG antibody seropositive neuromyelitis optica spectrum disorder. Multiple sclerosis and related disorders 2018;25:66-72.
150. Ramanathan S, Mohammad S, Tantsis E, et al. Clinical course, therapeutic responses and outcomes in relapsing MOG antibody-associated demyelination. J Neurol Neurosurg Psychiatry 2018;89:127-137.
151. Sun X, Qiu W, Wang J, et al. Myelin oligodendrocyte glycoprotein-associated disorders are associated with HLA subtypes in a Chinese paediatric-onset cohort. Journal of Neurology, Neurosurgery & Psychiatry 2020;91:733-739.
152. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 2015;85:177-189.
153. Bruijstens AL, Lechner C, Flet-Berliac L, et al. EU paediatric MOG consortium consensus: Part 1–Classification of clinical phenotypes of paediatric myelin oligodendrocyte glycoprotein antibody-associated disorders. European Journal of Paediatric Neurology 2020.
154. Ketelslegers I, Visser I, Neuteboom R, Boon M, Catsman-Berrevoets C, Hintzen R. Disease course and outcome of acute disseminated encephalomyelitis is more severe in adults than in children. Multiple Sclerosis Journal 2011;17:441-448.
155. Krupp LB, Tardieu M, Amato MP, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. Multiple Sclerosis Journal 2013;19:1261-1267.
156. Baumann M, Sahin K, Lechner C, et al. Clinical and neuroradiological differences of paediatric acute disseminating encephalomyelitis with and without antibodies to the myelin oligodendrocyte glycoprotein. Journal of Neurology, Neurosurgery & Psychiatry 2015;86:265-272.
157. Eyre M, Hameed A, Wright S, et al. Retinal nerve fibre layer thinning is associated with worse visual outcome after optic neuritis in children with a relapsing demyelinating syndrome. Developmental Medicine & Child Neurology 2018;60:1244-1250.
158. Chen Q, Zhao G, Huang Y, et al. Clinical characteristics of pediatric optic neuritis with myelin oligodendrocyte glycoprotein seropositive: a cohort study. Pediatric neurology 2018;83:42-49.
159. Dale RC, Tantsis EM, Merheb V, et al. Antibodies to MOG have a demyelination phenotype and affect oligodendrocyte cytoskeleton. Neurology-Neuroimmunology Neuroinflammation 2014;1.
160. Ramanathan S, Prelog K, Barnes EH, et al. Radiological differentiation of optic neuritis with myelin oligodendrocyte glycoprotein antibodies, aquaporin-4 antibodies, and multiple sclerosis. Multiple Sclerosis Journal 2016;22:470-482.
161. Ramanathan S, Mohammad S, Tantsis E, et al. Clinical course, therapeutic responses and outcomes in relapsing MOG antibody-associated demyelination. Journal of Neurology, Neurosurgery & Psychiatry 2018;89:127-137.
162. Salama S, Pardo S, Levy M. Clinical characteristics of myelin oligodendrocyte glycoprotein antibody neuromyelitis optica spectrum disorder. Multiple sclerosis and related disorders 2019;30:231-235.

163. Dubey D, Pittock SJ, Krecke KN, et al. Clinical, radiologic, and prognostic features of myelitis associated with myelin oligodendrocyte glycoprotein autoantibody. JAMA neurology 2019;76:301-309.
164. Hacohen Y, Wong YY, Lechner C, et al. Disease course and treatment responses in children with relapsing myelin oligodendrocyte glycoprotein antibody–associated disease. JAMA neurology 2018;75:478-487.
165. Huppke P, Rostasy K, Karenfort M, et al. Acute disseminated encephalomyelitis followed by recurrent or monophasic optic neuritis in pediatric patients. Multiple Sclerosis Journal 2013;19:941-946.
166. Narayan RN, McCreary M, Conger D, Wang C, Greenberg BM. Unique characteristics of optical coherence tomography (OCT) results and visual acuity testing in myelin oligodendrocyte glycoprotein (MOG) antibody positive pediatric patients. Multiple sclerosis and related disorders 2019;28:86-90.
167. Jurynczyk M, Messina S, Woodhall MR, et al. Clinical presentation and prognosis in MOG-antibody disease: a UK study. Brain 2017;140:3128-3138.
168. Wong Y, Hacohen Y, Armangue T, et al. Paediatric acute disseminated encephalomyelitis followed by optic neuritis: disease course, treatment response and outcome. European journal of neurology 2018;25:782-786.
169. Hintzen RQ, Dale RC, Neuteboom RF, Mar S, Banwell B. Pediatric acquired CNS demyelinating syndromes: features associated with multiple sclerosis. Neurology 2016;87:S67-S73.
170. Fujimori J, Takai Y, Nakashima I, et al. Bilateral frontal cortex encephalitis and paraparesis in a patient with anti-MOG antibodies. Journal of Neurology, Neurosurgery & Psychiatry 2017;88:534-536.
171. Ramanathan S, Reddel SW, Henderson A, et al. Antibodies to myelin oligodendrocyte glycoprotein in bilateral and recurrent optic neuritis. Neurology-Neuroimmunology Neuroinflammation 2014;1.
172. Armangue T, Olivé-Cirera G, Martínez-Hernandez E, et al. Associations of paediatric demyelinating and encephalitic syndromes with myelin oligodendrocyte glycoprotein antibodies: a multicentre observational study. The Lancet Neurology 2020;19:234-246.
173. Kim NN, Champsas D, Eyre M, et al. Pediatric MOG-Ab–associated encephalitis: supporting early recognition and treatment. Neurology: Neuroimmunology & Neuroinflammation 2024;11:e200323.
174. Ramanathan S, O'grady GL, Malone S, et al. Isolated seizures during the first episode of relapsing myelin oligodendrocyte glycoprotein antibody-associated demyelination in children. Developmental Medicine & Child Neurology 2019;61:610-614.
175. Foiadelli T, Gastaldi M, Scaranzin S, Franciotta D, Savasta S. Seizures and myelin oligodendrocyte glycoprotein (MOG) antibodies: two paradigmatic cases and a review of the literature. Multiple sclerosis and related disorders 2020;41:102011.
176. Zhou J, Lu X, Zhang Y, et al. Follow-up study on Chinese children with relapsing MOG-IgG-associated central nervous system demyelination. Multiple sclerosis and related disorders 2019;28:4-10.
177. Cobo-Calvo A, Ayrignac X, Kerschen P, et al. Cranial nerve involvement in patients with MOG antibody–associated disease. Neurology-Neuroimmunology Neuroinflammation 2019;6.

178. Reindl M, Linington C, Brehm U, et al. Antibodies against the myelin oligodendrocyte glycoprotein and the myelin basic protein in multiple sclerosis and other neurological diseases: a comparative study. Brain 1999;122 (Pt 11):2047-2056.
179. Egg R, Reindl M, Deisenhammer F, Linington C, Berger T. Anti-MOG and anti-MBP antibody subclasses in multiple sclerosis. Mult Scler 2001;7:285-289.
180. O'Connor KC, Appel H, Bregoli L, et al. Antibodies from inflamed central nervous system tissue recognize myelin oligodendrocyte glycoprotein. J Immunol 2005;175:1974-1982.
181. Di Pauli F, Mader S, Rostasy K, et al. Temporal dynamics of anti-MOG antibodies in CNS demyelinating diseases. Clin Immunol 2011;138:247-254.
182. Lalive PH, Hausler MG, Maurey H, et al. Highly reactive anti-myelin oligodendrocyte glycoprotein antibodies differentiate demyelinating diseases from viral encephalitis in children. Mult Scler 2011;17:297-302.
183. Berger T, Rubner P, Schautzer F, et al. Antimyelin antibodies as a predictor of clinically definite multiple sclerosis after a first demyelinating event. N Engl J Med 2003;349:139-145.
184. Akaishi T, Takahashi T, Misu T, et al. Difference in the Source of Anti-AQP4-IgG and Anti-MOG-IgG Antibodies in CSF in Patients With Neuromyelitis Optica Spectrum Disorder. Neurology 2021.
185. Mariotto S, Gajofatto A, Batzu L, et al. Relevance of antibodies to myelin oligodendrocyte glycoprotein in CSF of seronegative cases. Neurology 2019;93:e1867-e1872.
186. Banwell B, Bennett JL, Marignier R, et al. Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: International MOGAD Panel proposed criteria. The Lancet Neurology 2023;22:268-282.
187. Carta S, Cobo Calvo Á, Armangué T, et al. Significance of myelin oligodendrocyte glycoprotein antibodies in CSF: a retrospective multicenter study. Neurology 2023;100:e1095-e1108.
188. Matsumoto Y, Kaneko K, Takahashi T, et al. Diagnostic implications of MOG-IgG detection in sera and cerebrospinal fluids. Brain 2023;146:3938-3948.
189. Olivé-Cirera G, Bruijstens AL, Fonseca EG, et al. MOG antibodies restricted to CSF in children with inflammatory CNS disorders. Neurology 2024;102:e209199.
190. Hamid SH, Whittam D, Saviour M, et al. Seizures and encephalitis in myelin oligodendrocyte glycoprotein IgG disease vs aquaporin 4 IgG disease. JAMA neurology 2018;75:65-71.
191. Hacohen Y, Wong YY, Lechner C, et al. Disease Course and Treatment Responses in Children With Relapsing Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease. JAMA Neurol 2018;75:478-487.
192. Cobo-Calvo A, Ruiz A, Maillart E, et al. Clinical spectrum and prognostic value of CNS MOG autoimmunity in adults: The MOGADOR study. Neurology 2018;90:e1858-e1869.
193. Hacohen Y, Banwell B. Treatment Approaches for MOG-Ab-Associated Demyelination in Children. Curr Treat Options Neurol 2019;21:2.
194. Cobo-Calvo A, Ruiz A, D'Indy H, et al. MOG antibody-related disorders: common features and uncommon presentations. J Neurol 2017;264:1945-1955.
195. Jarius S, Pellkofer H, Siebert N, et al. Cerebrospinal fluid findings in patients with myelin oligodendrocyte glycoprotein (MOG) antibodies. Part 1: Results from 163 lumbar punctures in 100 adult patients. J Neuroinflammation 2020;17:261.

196. Jarius S, Lechner C, Wendel EM, et al. Cerebrospinal fluid findings in patients with myelin oligodendrocyte glycoprotein (MOG) antibodies. Part 2: Results from 108 lumbar punctures in 80 pediatric patients. J Neuroinflammation 2020;17:262.
197. Jurynczyk M, Geraldes R, Probert F, et al. Distinct brain imaging characteristics of autoantibody-mediated CNS conditions and multiple sclerosis. Brain 2017;140:617-627.
198. Baumann M, Grams A, Djurdjevic T, et al. MRI of the first event in pediatric acquired demyelinating syndromes with antibodies to myelin oligodendrocyte glycoprotein. J Neurol 2018;265:845-855.
199. Jurynczyk M, Tackley G, Kong Y, et al. Brain lesion distribution criteria distinguish MS from AQP4-antibody NMOSD and MOG-antibody disease. J Neurol Neurosurg Psychiatry 2017;88:132-136.
200. Hacohen Y, Rossor T, Mankad K, et al. 'Leukodystrophy-like' phenotype in children with myelin oligodendrocyte glycoprotein antibody-associated disease. Dev Med Child Neurol 2017.
201. Ramanathan S, O'Grady G L, Malone S, et al. Isolated seizures during the first episode of relapsing myelin oligodendrocyte glycoprotein antibody-associated demyelination in children. Dev Med Child Neurol 2018.
202. Rossor T, Benetou C, Wright S, et al. Early predictors of epilepsy and subsequent relapse in children with acute disseminated encephalomyelitis. Mult Scler 2019:1352458518823486.
203. Armangue T, Olive-Cirera G, Martinez-Hernandez E, et al. Associations of paediatric demyelinating and encephalitic syndromes with myelin oligodendrocyte glycoprotein antibodies: a multicentre observational study. Lancet Neurol 2020;19:234-246.
204. Narayan RN, Wang C, Sguigna P, Husari K, Greenberg B. Atypical Anti-MOG syndrome with aseptic meningoencephalitis and pseudotumor cerebri-like presentations. Mult Scler Relat Disord 2019;27:30-33.
205. Tzanetakos D, Tzartos JS, Vakrakou AG, et al. Cortical involvement and leptomeningeal inflammation in myelin oligodendrocyte glycoprotein antibody disease: a three-dimensional fluid-attenuated inversion recovery MRI study. Multiple Sclerosis Journal 2022;28:718-729.
206. Chen JJ, Flanagan EP, Jitprapaikulsan J, et al. Myelin oligodendrocyte glycoprotein antibody–positive optic neuritis: clinical characteristics, radiologic clues, and outcome. American journal of ophthalmology 2018;195:8-15.
207. Hassan MB, Stern C, Flanagan EP, et al. Population-based incidence of optic neuritis in the era of aquaporin-4 and myelin oligodendrocyte glycoprotein antibodies. American journal of ophthalmology 2020;220:110-114.
208. Jarius S, Ruprecht K, Kleiter I, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 2: epidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome. Journal of neuroinflammation 2016;13:1-45.
209. Mariano R, Messina S, Kumar K, Kuker W, Leite MI, Palace J. Comparison of clinical outcomes of transverse myelitis among adults with myelin oligodendrocyte glycoprotein antibody vs aquaporin-4 antibody disease. JAMA Network Open 2019;2:e1912732-e1912732.
210. Mariano R, Messina S, Roca-Fernandez A, Leite MI, Kong Y, Palace JA. Quantitative spinal cord MRI in MOG-antibody disease, neuromyelitis optica and multiple sclerosis. Brain 2021;144:198-212.

211. Deneve M, Biotti D, Patsoura S, et al. MRI features of demyelinating disease associated with anti-MOG antibodies in adults. Journal of Neuroradiology 2019;46:312-318.
212. Fadda G, Alves CA, O'Mahony J, et al. Comparison of spinal cord magnetic resonance imaging features among children with acquired demyelinating syndromes. JAMA network open 2021;4:e2128871-e2128871.
213. Dubey D, Pittock SJ, Krecke KN, et al. Clinical, Radiologic, and Prognostic Features of Myelitis Associated With Myelin Oligodendrocyte Glycoprotein Autoantibody. JAMA Neurol 2018.
214. Liu H, Zhou H, Wang J, et al. The prevalence and prognostic value of myelin oligodendrocyte glycoprotein antibody in adult optic neuritis. J Neurol Sci 2019;396:225-231.
215. Chen JJ, Flanagan EP, Jitprapaikulsan J, et al. Myelin Oligodendrocyte Glycoprotein Antibody-Positive Optic Neuritis: Clinical Characteristics, Radiologic Clues, and Outcome. Am J Ophthalmol 2018;195:8-15.
216. Ramanathan S, Prelog K, Barnes EH, et al. Radiological differentiation of optic neuritis with myelin oligodendrocyte glycoprotein antibodies, aquaporin-4 antibodies, and multiple sclerosis. Mult Scler 2016;22:470-482.
217. Sechi E, Krecke KN, Messina SA, et al. Comparison of MRI lesion evolution in different central nervous system demyelinating disorders. Neurology 2021;97:e1097-e1109.
218. Cacciaguerra L, Redenbaugh V, Chen JJ, et al. Timing and Predictors of T2-Lesion Resolution in Patients With Myelin Oligodendrocyte Glycoprotein Antibody–Associated Disease. Neurology 2023;101:e1376-e1381.
219. Cacciaguerra L, Abdel-Mannan O, Champsas D, et al. Radiologic lag and brain MRI lesion dynamics during attacks in MOG antibody–associated disease. Neurology 2024;102:e209303.
220. Ramanathan S, Mohammad S, Tantsis E, et al. Clinical course, therapeutic responses and outcomes in relapsing MOG antibody-associated demyelination. J Neurol Neurosurg Psychiatry 2018;89:127-137.
221. Jurynczyk M, Messina S, Woodhall MR, et al. Clinical presentation and prognosis in MOG-antibody disease: a UK study. Brain 2017;140:3128-3138.
222. Wong YYM, Hacohen Y, Armangue T, et al. Paediatric acute disseminated encephalomyelitis followed by optic neuritis: disease course, treatment response and outcome. Eur J Neurol 2018;25:782-786.
223. Jarius S, Ruprecht K, Kleiter I, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 2: Epidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome. J Neuroinflammation 2016;13:280.
224. Nosadini M, Eyre M, Giacomini T, et al. Early immunotherapy and longer corticosteroid treatment are associated with lower risk of relapsing disease course in pediatric MOGAD. Neurology-Neuroimmunology Neuroinflammation 2023;10.
225. Chatterton S, Parratt JDE, Ng K. Eculizumab for acute relapse of neuromyelitis optica spectrum disorder: Case report. Frontiers in Neurology 2022;13:951423.
226. McLendon LA, Gambrah-Lyles C, Viaene A, et al. Dramatic response to anti-IL-6 receptor therapy in children with life-threatening myelin oligodendrocyte glycoprotein-associated disease. Neurology: Neuroimmunology & Neuroinflammation 2023;10:e200150.
227. Zhou J, Lu X, Zhang Y, et al. Follow-up study on Chinese children with relapsing MOG-IgG-associated central nervous system demyelination. Mult Scler Relat Disord 2019;28:4-10.

228. Chen JJ, Flanagan EP, Bhatti MT, et al. Steroid-sparing maintenance immunotherapy for MOG-IgG associated disorder. Neurology 2020.
229. Cobo-Calvo A, Sepulveda M, Rollot F, et al. Evaluation of treatment response in adults with relapsing MOG-Ab-associated disease. J Neuroinflammation 2019;16:134.
230. Durozard P, Rico A, Boutiere C, et al. Comparison of the Response to Rituximab between Myelin Oligodendrocyte Glycoprotein and Aquaporin-4 Antibody Diseases. Ann Neurol 2020;87:256-266.
231. Chitnis T, Aaen G, Belman A, et al. Improved relapse recovery in paediatric compared to adult multiple sclerosis. Brain 2020;143:2733-2741.
232. Waters P, Fadda G, Woodhall M, et al. Serial anti–myelin oligodendrocyte glycoprotein antibody analyses and outcomes in children with demyelinating syndromes. JAMA neurology 2020;77:82-93.
233. Amato MP, Goretti B, Ghezzi A, et al. Neuropsychological features in childhood and juvenile multiple sclerosis: five-year follow-up. Neurology 2014;83:1432-1438.
234. De Meo E, Portaccio E, Giorgio A, et al. Identifying the distinct cognitive phenotypes in multiple sclerosis. JAMA neurology 2021;78:414-425.
235. Eyre M, Absoud M, Abdel-Mannan O, et al. Academic outcomes before and after clinical onset of acquired demyelinating syndromes in children: a matched cohort data linkage study. Annals of Clinical and Translational Neurology 2024;11:3025-3030.
236. O'Mahony J, Bar-Or A, Arnold DL, et al. Masquerades of acquired demyelination in children: experiences of a national demyelinating disease program. Journal of child neurology 2013;28:184-197.
237. Chhabda S, Malik P, Reddy N, et al. Relapsing Demyelinating Syndromes in Children: A Practical Review of Neuroradiological Mimics. Frontiers in Neurology 2020;11:627.
238. Scolding N. The differential diagnosis of multiple sclerosis. Journal of Neurology, Neurosurgery & Psychiatry 2001;71:ii9-ii15.
239. Schiffmann R, van der Knaap MS. Invited article: an MRI-based approach to the diagnosis of white matter disorders. Neurology 2009;72:750-759.
240. Wolf NI, Toro C, Kister I, et al. DARS-associated leukoencephalopathy can mimic a steroid-responsive neuroinflammatory disorder. Neurology 2015;84:226-230.
241. Bindu PS, Sonam K, Chiplunkar S, et al. Mitochondrial leukoencephalopathies: a border zone between acquired and inherited white matter disorders in children? Multiple sclerosis and related disorders 2018;20:84-92.
242. Bittner F, Falardeau J, Spain RI. Myelin Oligodendrocyte Glycoprotein Antibody–Associated Demyelination Comorbid With Leber Hereditary Optic Neuropathy. JAMA neurology 2019;76:227-228.
243. Hacohen Y, Zuberi S, Vincent A, Crow YJ, Cordeiro N. Neuromyelitis optica in a child with Aicardi-Goutières syndrome. Neurology 2015;85:381-383.
244. Rahman S, Copeland WC. POLG-related disorders and their neurological manifestations. Nature Reviews Neurology 2019;15:40-52.
245. Girard B, Bonnemains C, Schmitt E, Raffo E, Bilbault C. Biotinidase deficiency mimicking neuromyelitis optica beginning at the age of 4: a treatable disease. Multiple Sclerosis Journal 2017;23:119-122.
246. Benson LA, Li H, Henderson LA, et al. Pediatric CNS-isolated hemophagocytic lymphohistiocytosis. Neurology-Neuroimmunology Neuroinflammation 2019;6.

247. Taieb G, Kaphan E, Duflos C, et al. Hemophagocytic Lymphohistiocytosis Gene Mutations in Adult Patients Presenting With CLIPPERS-Like Syndrome. Neurology-Neuroimmunology Neuroinflammation 2021;8.
248. Schmid JP, Côte M, Ménager MM, et al. Inherited defects in lymphocyte cytotoxic activity. Immunological reviews 2010;235:10-23.
249. Whitworth A. Population Estimates for UK, England and Wales Scotland, and Northern Ireland Mid-2010 Population Estimates. Office for National Statistics. 2011.
250. Eusebi A, Zara P, Zarbo IR, et al. Long-term trajectory of acquired demyelinating syndrome and multiple sclerosis in children. Developmental Medicine & Child Neurology 2021.
251. De Mol C, Wong Y, van Pelt E, et al. The clinical spectrum and incidence of anti-MOG-associated acquired demyelinating syndromes in children and adults. Multiple Sclerosis Journal 2020;26:806-814.
252. Fadda G, Armangue T, Hacohen Y, Chitnis T, Banwell B. Paediatric multiple sclerosis and antibody-associated demyelination: clinical, imaging, and biological considerations for diagnosis and care. The Lancet Neurology 2021;20:136-149.
253. Papp V, Magyari M, Aktas O, et al. Worldwide Incidence and Prevalence of Neuromyelitis Optica: A Systematic Review. Neurology 2021;96:59-77.
254. Cossburn M, Tackley G, Baker K, et al. The prevalence of neuromyelitis optica in South East Wales. European journal of neurology 2012;19:655-659.
255. Jacob A, Panicker J, Lythgoe D, et al. The epidemiology of neuromyelitis optica amongst adults in the Merseyside county of United Kingdom. Journal of neurology 2013;260:2134-2137.
256. Waubant E, Banwell B, Wassmer E, et al. Clinical trials of disease-modifying agents in pediatric MS: opportunities, challenges, and recommendations from the IPMSSG. Neurology 2019;92:e2538-e2549.
257. Arnold DL, Banwell B, Bar-Or A, et al. Effect of fingolimod on MRI outcomes in patients with paediatric-onset multiple sclerosis: results from the phase 3 PARADIGMS study. Journal of Neurology, Neurosurgery & Psychiatry 2020;91:483-492.
258. Krysko KM, Graves JS, Rensel M, et al. Real-World Effectiveness of Initial Disease-Modifying Therapies in Pediatric Multiple Sclerosis. Annals of Neurology 2020.
259. Saponaro A-C, Tully T, Maillart E, Maurey H, Deiva K. Treatments of paediatric multiple sclerosis: efficacy and tolerance in a longitudinal follow-up study. European Journal of Paediatric Neurology 2023;45:22-28.
260. Spelman T, Simoneau G, Hyde R, et al. Comparative effectiveness of natalizumab, fingolimod, and injectable therapies in pediatric-onset multiple sclerosis: a registry-based study. Neurology 2024;102:e208114.
261. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. New England Journal of Medicine 2017;376:221-234.
262. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. New england journal of medicine 2017;376:209-220.
263. Blueteq Ltd. High Cost Drugs Management System [online]. Available at: http://www.blueteq.com/. Accessed 25 Jan.
264. Health UDo, Services H. Common Terminology Criteria for Adverse Events (CTCAE) v5. 0. Published Nov. 27, 2017. 2018.
265. Rocca MA, Amato MP, De Stefano N, et al. Clinical and imaging assessment of cognitive dysfunction in multiple sclerosis. The Lancet Neurology 2015;14:302-317.

266. Deiva K, Huppke P, Banwell B, et al. Consistent control of disease activity with fingolimod versus IFN β-1a in paediatric-onset multiple sclerosis: further insights from PARADIGMS. Journal of Neurology, Neurosurgery & Psychiatry 2020;91:58-66.
267. Ghezzi A, Amato MP, Makhani N, Shreiner T, Gärtner J, Tenembaum S. Pediatric multiple sclerosis: conventional first-line treatment and general management. Neurology 2016;87:S97-S102.
268. Krysko KM, Waltz M, Chitnis T, et al. Study of the association between menarche and disease course in pediatric multiple sclerosis. Neurology 2025;104:e210213.
269. Benallegue N, Rollot F, Wiertlewski S, et al. Highly effective therapies as first-line treatment for pediatric-onset multiple sclerosis. JAMA neurology 2024;81:273-282.
270. Graves JS, Thomas M, Li J, et al. Improving pediatric multiple sclerosis interventional phase III study design: a meta-analysis. Therapeutic Advances in Neurological Disorders 2022;15:17562864211070449.
271. Chitnis T, Aaen G, Belman A, et al. Improved relapse recovery in paediatric compared to adult multiple sclerosis. Brain 2020.
272. Simone I, Carrara D, Tortorella C, et al. Course and prognosis in early-onset MS: comparison with adult-onset forms. Neurology 2002;59:1922-1928.
273. Brown JWL, Coles A, Horakova D, et al. Association of initial disease-modifying therapy with later conversion to secondary progressive multiple sclerosis. Jama 2019;321:175-187.
274. Bartels F, Nobis K, Cooper G, et al. Childhood multiple sclerosis is associated with reduced brain volumes at first clinical presentation and brain growth failure. Multiple Sclerosis Journal 2019;25:927-936.
275. Giovannoni G. Disease-modifying treatments for early and advanced multiple sclerosis: a new treatment paradigm. Current opinion in neurology 2018;31:233-243.
276. Lulu S, Julian L, Shapiro E, Hudson K, Waubant E. Treatment adherence and transitioning youth in pediatric multiple sclerosis. Multiple sclerosis and related disorders 2014;3:689-695.
277. Schwartz CE, Grover SA, Powell VE, et al. Risk factors for non-adherence to disease-modifying therapy in pediatric multiple sclerosis. Multiple Sclerosis Journal 2018;24:175-185.
278. MacAllister WS, Christodoulou C, Milazzo M, Krupp LB. Longitudinal neuropsychological assessment in pediatric multiple sclerosis. Developmental neuropsychology 2007;32:625-644.
279. Amato M, Goretti B, Ghezzi A, et al. Cognitive and psychosocial features of childhood and juvenile MS. Neurology 2008;70:1891-1897.
280. McKay KA, Manouchehrinia A, Berrigan L, Fisk JD, Olsson T, Hillert J. Long-term cognitive outcomes in patients with pediatric-onset vs adult-onset multiple sclerosis. Jama Neurology 2019;76:1028-1034.
281. Mar S, Valeriani M, Steinborn B, et al. Ocrelizumab dose selection for treatment of pediatric relapsing–remitting multiple sclerosis: results of the OPERETTA I study. Journal of neurology 2025;272:137.
282. Amirov CB, Saltık S, Yalçınkaya C, et al. Ocrelizumab in pediatric multiple sclerosis. European Journal of Paediatric Neurology 2023;43:1-5.
283. Nasr Z, Casper TC, Waltz M, et al. Clinical and magnetic resonance imaging outcomes in pediatric-onset MS patients on fingolimod and ocrelizumab. Multiple Sclerosis and Related Disorders 2024;87:105647.

284. Baroncini D, Simone M, Iaffaldano P, et al. Risk of persistent disability in patients with pediatric-onset multiple sclerosis. JAMA neurology 2021;78:726-735.
285. Sormani MP, Waubant E. Paediatric multiple sclerosis: A lesson from TERIKIDS. The Lancet Neurology 2021;20:971-973.
286. Beres SJ, Graves J, Waubant E. Rituximab use in pediatric central demyelinating disease. Pediatric neurology 2014;51:114-118.
287. Dale RC, Brilot F, Duffy LV, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. Neurology 2014;83:142-150.
288. Salzer J, Lycke J, Wickström R, Naver H, Piehl F, Svenningsson A. Rituximab in paediatric onset multiple sclerosis: a case series. Journal of neurology 2016;263:322-326.
289. Breu M, Sandesjö F, Milos RI, et al. Rituximab treatment in pediatric-onset multiple sclerosis. European Journal of Neurology 2024;31:e16228.
290. Marignier R, Hacohen Y, Cobo-Calvo A, et al. Myelin-oligodendrocyte glycoprotein antibody-associated disease. Lancet Neurol 2021;20:762-772.
291. Banwell B, Bennett JL, Marignier R, et al. Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: International MOGAD Panel proposed criteria. The Lancet Neurology 2023.
292. Varley JA, Champsas D, Prossor T, et al. Validation of the 2023 international diagnostic criteria for MOGAD in a selected cohort of adults and children. Neurology 2024;103:e209321.
293. Cortese R, Battaglini M, Prados F, et al. Clinical and MRI measures to identify non-acute MOG-antibody disease in adults. Brain 2023;146:2489-2501.
294. Han JY, Kim SY, Kim W, et al. Phenotype of Relapsing Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease in Children. Journal of Clinical Neurology (Seoul, Korea) 2025;21:65.
295. Fadda G, Banwell B, Waters P, et al. Silent New Brain MRI Lesions in Children with MOG-Antibody Associated Disease. Annals of Neurology 2021;89:408-413.
296. Sechi E, Krecke KN, Messina SA, et al. Comparison of MRI Lesion Evolution in Different Central Nervous System Demyelinating Disorders. Neurology 2021;97:e1097-e1109.
297. Redenbaugh V, Chia NH, Cacciaguerra L, et al. Comparison of MRI T2-lesion evolution in pediatric MOGAD, NMOSD, and MS. Multiple Sclerosis Journal 2023:13524585231166834.
298. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17:162-173.
299. Hacohen Y, Banwell B, Ciccarelli O. What does first-line therapy mean for paediatric multiple sclerosis in the current era? Multiple Sclerosis Journal 2021;27:1970-1976.
300. Kurd M, Pratt L-t, Gilboa T, et al. Validation of the 2023 international diagnostic criteria for MOGAD in a pediatric cohort. European Journal of Paediatric Neurology 2024;49:13-16.
301. Filippatou AG, Said Y, Chen H, Vasileiou ES, Ahmadi G, Sotirchos ES. Validation of the international MOGAD panel proposed criteria: a single-centre US study. Journal of Neurology, Neurosurgery & Psychiatry 2024;95:870-873.
302. Kim KH, Kim S-H, Park NY, Hyun J-W, Kim HJ. Validation of the international MOGAD panel proposed criteria. Multiple Sclerosis Journal 2023;29:1680-1683.

303. Hacohen Y, Rossor T, Mankad K, et al. 'Leukodystrophy-like'phenotype in children with myelin oligodendrocyte glycoprotein antibody-associated disease. Developmental Medicine & Child Neurology 2018;60:417-423.
304. Cacciaguerra L, Redenbaugh V, Chen JJ, et al. Timing and Predictors of T2-Lesion Resolution in Patients With Myelin-Oligodendrocyte-Glycoprotein-Antibody-Associated Disease. Neurology 2023.
305. Kleiter I, Gahlen A, Borisow N, et al. Apheresis therapies for NMOSD attacks: A retrospective study of 207 therapeutic interventions. Neurol Neuroimmunol Neuroinflamm 2018;5:e504.
306. Bonnan M, Valentino R, Debeugny S, et al. Short delay to initiate plasma exchange is the strongest predictor of outcome in severe attacks of NMO spectrum disorders. Journal of Neurology Neurosurgery and Psychiatry 2018;89:346-351.
307. Camera V, Holm-Mercer L, Ali AAH, et al. Frequency of new silent MRI lesions in myelin oligodendrocyte glycoprotein antibody disease and aquaporin-4 antibody neuromyelitis optica spectrum disorder. JAMA Network Open 2021;4:e2137833-e2137833.
308. Syc-Mazurek SB, Chen JJ, Morris P, et al. Frequency of New or Enlarging Lesions on MRI Outside of Clinical Attacks in Patients With MOG-Antibody-Associated Disease. Neurology 2022;99:795-799.
309. Redenbaugh V, Chia NH, Cacciaguerra L, et al. Comparison of MRI T2-lesion evolution in pediatric MOGAD, NMOSD, and MS. Mult Scler 2023;29:799-808.
310. Reindl M, Schanda K, Woodhall M, et al. International multicenter examination of MOG antibody assays. Neurology-Neuroimmunology Neuroinflammation 2020;7.
311. Pharmaceuticals N. A 2-year Randomized, 3-arm, Double-blind, Non-inferiority Study Comparing the Efficacy and Safety of Ofatumumab and Siponimod Versus Fingolimod in Pediatric Patients with Multiple Sclerosis Followed by an Open-label Extension (Clinical Trial Registration NCT04926818; Issue NCT04926818). [online]. Available at: https://clinicaltrials.gov/study/NCT04926818 Accessed 1 December.
312. Roche H-L. A Phase III Multicenter, Randomized, Double-Blind, Double-Dummy Study to Evaluate Safety and Efficacy of Ocrelizumab in Comparison with Fingolimod in Children and Adolescents with Relapsing-Remitting Multiple Sclerosis (Clinical Trial Registration NCT05123703; Issue NCT05123703). [online]. Available at: https://clinicaltrials.gov/study/NCT05123703. Accessed 1 December.
313. Walsh R, Chitnis T. Therapeutic Advances in Pediatric Multiple Sclerosis. Children 2025;12:259.
314. Abdel-Mannan O, Ciccarelli O, Hacohen Y. Considering the future of pediatric multiple sclerosis trials after the CONNECT open-label randomized trial. JAMA Network Open 2022;5:e2230451-e2230451.
315. Ghezzi A, Amato MP, Edan G, et al. The introduction of new medications in pediatric multiple sclerosis: open issues and challenges. Multiple Sclerosis Journal 2021;27:479-482.
316. Benedict RH, Amato MP, Boringa J, et al. Brief International Cognitive Assessment for MS (BICAMS): international standards for validation. BMC neurology 2012;12:1-7.
317. Van Schependom J, D'hooghe M, Cleynhens K, et al. The S ymbol D igit M odalities T est as sentinel test for cognitive impairment in multiple sclerosis. European journal of neurology 2014;21:1219-e1272.
318. Skorve E, Lundervold AJ, Torkildsen Ø, Myhr K-M. A two-year longitudinal follow-up of cognitive performance assessed by BICAMS in newly diagnosed patients with MS. Multiple Sclerosis and Related Disorders 2020;46:102577.

319. Mistri D, Margoni M, Pagani E, et al. Structural and functional imaging features of cognitive phenotypes in pediatric multiple sclerosis. Annals of Clinical and Translational Neurology 2024;11:1840-1851.
320. Tur C, Moccia M, Barkhof F, et al. Assessing treatment outcomes in multiple sclerosis trials and in the clinical setting. Nature Reviews Neurology 2018;14:75-93.
321. Goebl P, Wingrove J, Abdelmannan O, et al. Repurposing Clinical MRI Archives for Multiple Sclerosis Research with a Flexible, Single-Modality Approach: New Insights from Old Scans. medRxiv 2024:2024.2003. 2029.24305083.
322. Fadda G, Cardenas de la Parra A, O'Mahony J, et al. Deviation from normative whole brain and deep gray matter growth in children with MOGAD, MS, and monophasic seronegative demyelination. Neurology 2023;101:e425-e437.
323. Fadda G, Banwell B, Elliott C, et al. Slowly Expanding Lesions Differentiate Pediatric Multiple Sclerosis from Myelin Oligodendrocyte Glycoprotein Antibody Disease. Annals of Neurology 2024;96:1086-1091.
324. Elliott C, Wolinsky JS, Hauser SL, et al. Slowly expanding/evolving lesions as a magnetic resonance imaging marker of chronic active multiple sclerosis lesions. Multiple Sclerosis Journal 2019;25:1915-1925.
325. Calvi A, Tur C, Chard D, et al. Slowly expanding lesions relate to persisting black-holes and clinical outcomes in relapse-onset multiple sclerosis. NeuroImage: Clinical 2022;35:103048.
326. Jäckle K, Zeis T, Schaeren-Wiemers N, et al. Molecular signature of slowly expanding lesions in progressive multiple sclerosis. Brain 2020;143:2073-2088.
327. Preziosa P, Pagani E, Meani A, et al. Slowly expanding lesions predict 9-year multiple sclerosis disease progression. Neurology: Neuroimmunology & Neuroinflammation 2022;9:e1139.
328. Kappos L, Wolinsky JS, Giovannoni G, et al. Contribution of relapse-independent progression vs relapse-associated worsening to overall confirmed disability accumulation in typical relapsing multiple sclerosis in a pooled analysis of 2 randomized clinical trials. JAMA neurology 2020;77:1132-1140.
329. Portaccio E, Bellinvia A, Fonderico M, et al. Progression is independent of relapse activity in early multiple sclerosis: a real-life cohort study. Brain 2022;145:2796-2805.
330. Tur C, Carbonell-Mirabent P, Cobo-Calvo Á, et al. Association of early progression independent of relapse activity with long-term disability after a first demyelinating event in multiple sclerosis. JAMA neurology 2023;80:151-160.
331. Puthenparampil M, Gaggiola M, Ponzano M, et al. High NEDA and no PIRA in natalizumab-treated patients with pediatric-onset multiple sclerosis. Neurology: Neuroimmunology & Neuroinflammation 2024;11:e200303.
332. Yuan A, Nixon RA. Neurofilament proteins as biomarkers to monitor neurological diseases and the efficacy of therapies. Frontiers in neuroscience 2021;15:689938.
333. Thebault S, Booth RA, Freedman MS. Blood neurofilament light chain: the neurologist's troponin? Biomedicines 2020;8:523.
334. Abdelhak A, Petermeier F, Benkert P, et al. Serum neurofilament light chain reference database for individual application in paediatric care: a retrospective modelling and validation study. The Lancet Neurology 2023;22:826-833.
335. Marignier R, Hacohen Y, Cobo-Calvo A, et al. Myelin-oligodendrocyte glycoprotein antibody-associated disease. The Lancet Neurology 2021;20:762-772.

336. Wu Y, Geraldes R, Juryńczyk M, Palace J. Double-negative neuromyelitis optica spectrum disorder. Multiple Sclerosis Journal 2023;29:1353-1362.
337. Carta S, Dinoto A, Capobianco M, et al. Serum biomarker profiles discriminate AQP4 seropositive and double seronegative neuromyelitis optica spectrum disorder. Neurology: Neuroimmunology & Neuroinflammation 2023;11:e200188.
338. Longoni G, Brown RA, MomayyezSiahkal P, et al. White matter changes in paediatric multiple sclerosis and monophasic demyelinating disorders. Brain 2017;140:1300-1315.
339. Moll NM, Rietsch AM, Thomas S, et al. Multiple sclerosis normal-appearing white matter: Pathology–imaging correlations. Annals of neurology 2011;70:764-773.
340. Bagnato F, Hametner S, Franco G, et al. Selective inversion recovery quantitative magnetization transfer brain MRI at 7T: clinical and postmortem validation in multiple sclerosis. Journal of Neuroimaging 2018;28:380-388.
341. Zhang L, Chen T, Tian H, et al. Reproducibility of inhomogeneous magnetization transfer (ihMT): A test-retest, multi-site study. Magnetic Resonance Imaging 2019;57:243-249.
342. Laule C, Moore GW. Myelin water imaging to detect demyelination and remyelination and its validation in pathology. Brain Pathology 2018;28:750-764.
343. Vavasour IM, Tam R, Li DK, et al. A 24-month advanced magnetic resonance imaging study of multiple sclerosis patients treated with alemtuzumab. Multiple Sclerosis Journal 2019;25:811-818.
344. de Mol CL, Lamballais S, Muetzel R, et al. Environmental multiple sclerosis (MS) risk factors, genetic MS risk, and brain development in a general paediatric population. Journal of Neurology, Neurosurgery & Psychiatry 2024.
345. Margoni M, Storelli L, Pagani E, et al. Subventricular Zone Microstructure in Pediatric-Onset Multiple Sclerosis. Annals of Neurology 2025.
346. Li T, Chen X, Jing Y, et al. Diagnostic Value of Multiparameter MRI-Based Radiomics in Pediatric Myelin Oligodendrocyte Glycoprotein Antibody–Associated Disorders. American Journal of Neuroradiology 2023;44:1425-1431.
347. Guniganti R, Rho S, Morales-León JF, et al. A single-center retrospective series of OCT and MRI findings in pediatric MOGAD optic neuritis patients. Canadian Journal of Ophthalmology 2024.
348. Peng C, Li S, Zuo H, et al. Macular vascular density alteration patterns in paediatric optic neuritis patients with serum MOG antibody positivity detected by optic coherence tomography angiography. Multiple Sclerosis and Related Disorders 2024;91:105857.