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REVIEW ARTICLE

Paediatric Acquired Demyelinating Syndromes: A review of the epidemiology and risk factors

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Abstract

Paediatric acquired demyelinating syndromes (ADS) are characterised by neurological deficits persisting for at least 24 hours, involving the optic nerve, spinal cord or brain with a clinical spectrum of diagnoses including multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein (MOG) antibodies (Ab) associated disease (MOGAD). In this review, we examine the current literature regarding the epidemiology and demographics of these different ADS entities with a particular focus on the genetic and environmental risk factors for MS in children. Both genetic (e.g., human leucocyte antigen, HLA-DRB1*1501 allele) and environmental risk factors (e.g. low serum vitamin D levels and prior exposure to Epstein–Barr virus) may contribute to the risk of MS in children. Some of these risk factors not only confer increased susceptibility to MS but may also affect the disease course. Paediatric AQP4-Ab NMOSD is a rare disease worldwide but variations in incidence/prevalence have been described among different geographic regions and ethnicities. One-third of children who present with an ADS have MOG-Ab, and approximately half of patients with MOG-Ab have a relapsing disease course. It seems there is no racial or gender predominance in MOGAD, which contrasts with the female and ethnic minority predominance seen in both MS and NMOSD. While insights into disease pathophysiology in paediatric ADS have led to recent therapeutic advances, well designed and collaborative large scale epidemiological studies are likely to provide the critical next step to a personalised approach to these conditions.

Keywords: paediatric multiple sclerosis (MS), acquired demyelinating syndromes (ADS), MOG-antibody associated disease (MOGAD), neuromyelitis optica spectrum disorders (NMOSD), aquaporin-4 antibodies.

Introduction

Acquired demyelinating syndromes (ADS) represent acute neurological illnesses characterised by deficits persisting for at least 24 hours and involving the optic nerve, brain, or spinal cord, associated with regional areas of increased signal on T2-weighted images (Figure 1). ADS may occur as a monophasic illness, such as optic neuritis (ON), transverse myelitis (TM), acute disseminated encephalomyelitis (ADEM), or as a chronic relapsing condition, such as multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) [1]. These diseases are known 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 [2, 3].

Studies have shown that 15% to 46% of children presenting with ADS will be diagnosed with multiple sclerosis (MS) at a five-year follow-up [4]. MS diagnosis requires evidence of dissemination of CNS inflammation, both in more than one location (dissemination in space [DIS]) and over time (dissemination in time [DIT]) [5]. Almost all young people presenting with MS have a relapsing-remitting course with clinical relapses presenting as either ON, TM or polysymptomatic presentations [6].

MOG-Ab associated disease (MOGAD) and aquaporin 4-Ab (AQP4-Ab)-positive NMOSD were once considered variants of MS; however, recent studies established that these are distinct entities [7, 8, 9]. 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). The fact that the disease is antibody-mediated means immunomodulatory therapy is useful to reduce relapses, which are the primary cause of disability, morbidity and mortality [10]. One-third of paediatric patients with ADS have MOG-antibodies (MOG-Ab), with the frequency of relapsing paediatric MOG-Ab-positive patients ranging widely between studies. Younger patients are more likely to present with ADEM whereas older children and adults typically present with ON and TM [8].

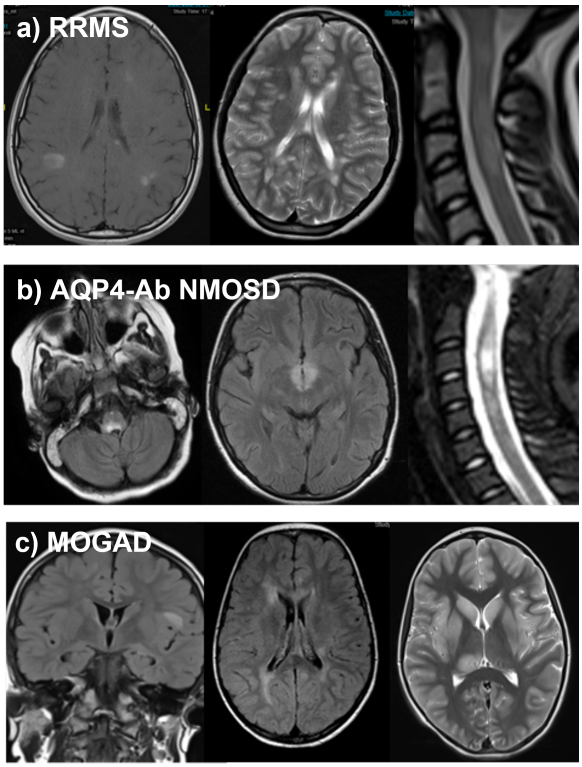

Figure 1. MRI brain and spine scans showing typical neuroimaging features of three patients with a) periventricular and juxtacortical lesions or plaques (arrows) on the left and short segment transverse myelitis on the right, typical of relapsing remitting multiple sclerosis (RRMS); b) hypothalamic lesion (arrow) on the left, and a longitudinally extensive transverse myelitis indicated by hyperintensity in the spinal cord on the right, in a child with AQP4-Ab NMOSD; c) confluent, enhancing and poorly marginated lesions of the cortical grey matter in a patient with MOG-Ab associated disease (MOGAD).

Identification and distinction of the different subtypes of ADS, especially at first presentation, has important implications for treatment and prognosis [1], with accurate diagnosis and management of inflammation being key to improving patient outcomes [5].

The aim of this review is to focus primarily on the most up to date literature regarding the epidemiology, demographics and risk factors associated with paediatric ADS, comparing MS to MOGAD and NMOSD. We will also specifically look at the growing list of genetic and environmental risk factors identified for paediatric MS.

Methods

Studies were identified by conducting thorough systematic online searches of MEDLINE, Embase, Web of Science, and hand-searching reference lists of included studies. Search terms were tailored to each database, and included the words 'paediatric', 'child', 'adolescent', 'juvenile', 'early-onset', 'young person', or 'young people' combined with 'multiple sclerosis', 'MS', 'demyelinating disease', 'acquired demyelinating syndromes', 'neuromyelitis optica spectrum disorders', 'NMOSD', 'aquaporin-4 antibodies', 'AQP4', 'myelin oligodendrocyte glycoprotein', 'MOG-antibodies', 'MOGAD' and 'epidemiology', 'risk factors', 'environmental', 'genetic'. No publication date limits were applied, but limits were applied to include only papers published in English. References from each database search were collated in Endnote. Duplicates were removed and titles and abstracts were screened. Studies not meeting these criteria were removed and the full texts of all remaining studies were retrieved and screened. Identified studies were few and diverse, and thus precluded meta-analysis. A narrative synthesis was conducted.

Paediatric MS – epidemiology and risk factors

Demographics and epidemiology

A recent meta-analysis suggested that the global incidence of paediatric MS is approximately 0.87 (ranging from 0.05 to 2.85) per 100,000 children annually, and the global prevalence is 8.11 (ranging from 0.7 to 26.9) per 100,000, which vary between countries and regions (Table 1) [4].

Table 1. Paediatric vs. adult MS incidence across different countries.

Country	Incidence of paediatric (per 100,000/year)	Incidence of adults (per 100,000/year)
Germany	0.64	0.33
Netherlands	0.8	5.9
UK	0.98	4.7
Italy (Sardinia)	2.85	2.7
USA	1.66	5.1
Iran (Shiraz)	0.19	3.6
Kuwait	2.1	2.6
Taiwan	0.52	6.69

In a study of paediatric MS conducted in the United States [11], the mean age at time of first event was 13.2 years; 66% of the patients were females, 67% were Caucasian and 20.6% were of African American ethnicity (ethnic breakdown of general population under 18 years old was 73% Caucasian and 15% African American). In younger patients, there was an almost equal sex ratio, however female predominance increased with age, especially in adolescence. In addition, the results showed that the children's parents were less likely to be Caucasian and more likely to be of Asian, Middle Eastern or Caribbean ancestry, relative to adult-onset MS. This is supported by a retrospective study of children in southern California, which found a higher incidence of ADS in children with African American and Asian ethnicities compared to Caucasian and Hispanic children [12].

The incidence of first onset ADS in children aged 1–15 years old was calculated at 0.98 per 100,000 annually in a UK-wide study [13], with 51% of the cases being female. Mean age at presentation was 9.7 years, similar to other studies from France [14] and Canada [15], but older than a Dutch study [16] of a paediatric

MS cohort. Other ethnic minority groups were over-represented, in contrast to adult MS patients, however this did not reach statistical significance. In addition, there was overrepresentation of cases from areas with lower socio-economic groups. In this study, more female cases were also seen in the older age groups.

A Dutch study showed ADS incidence of 0.8 cases per 100,000 per year [17]. In patients more than 11 years old, the female-to-male ratio was higher (1.8:1) than in patients less than 11 years old (1.02:1), with 32% of children being of other ethnic minorities (17% of the general population in the Netherlands). This study also showed a higher incidence of ADS and MS in the period of 2011–2016 than in the period of 2007–2010.

In a Taiwanese study [18], the incidence of paediatric MS was 0.52 cases per 100,000 annually, with prevalence ranging from 0.05 to 0.34 per 100,000 children. The mean age at diagnosis was 14.4 years and 67.7% were female.

All these studies demonstrate the demographic and epidemiological factors associated with paediatric MS, with a higher prevalence in other ethnic minorities, in addition to females in the older MS paediatric group, which may be attributed to the age of puberty-onset. Nevertheless, a recent UK study showed that the revised 2017 McDonald diagnostic criteria for MS can be applied to children at any age [19].

Paediatric MS genetic and environmental risk factors (Table 2) The most established genetic risk factor for MS in adults and children is the human leucocyte antigen (HLA)-DRB1*1501 allele of the major histocompatibility complex (MHC), located on chromosome 6. There is an increased likelihood of MS in children presenting with ADS who have at least one copy of the HLA-DRB1*1501, particularly Caucasian children [20]. Genome-wide association studies (GWAS) have also shown several single nucleotide polymorphisms (SNPs) associated with increased risk of MS in adults [21]. Initial studies suggest that children and adults with MS share a similar genetic burden, while children with monophasic ADS have a genetic profile that is closer to healthy individuals [22]. Preliminary results from an ongoing GWAS study in paediatric MS suggest that there is a significant association between the presence of HLA-DRB1*1501 and 36 non-MHC SNPs previously identified as susceptibility genes for MS in adults [23]. Three SNPs in particular—rs2744148, rs3007421 and rs1800693—demonstrated a strong association with paediatric MS. In adults, the non-HLA risk SNPs are generally located near protein-coding genes that regulate T-cell function, and it is hypothesised that these SNPs may modify gene expression, resulting in increased proinflammatory immune responses [24].

Lower serum levels of 25-hydroxyvitamin D have also been associated with increased risk for paediatric MS [25]. Furthermore, there is evidence that low circulating vitamin D might have an interaction with obesity (also an MS risk factor), thereby modulating MS risk. This is explained by the fact that vitamin D, being a fat-soluble vitamin, will be stored in adipose tissue of obese patients, reducing its concentration in the circulation [26].

Obesity may also be associated with increased risk of paediatric MS, with an increased risk of MS relative to the degree of obesity. This risk association was shown in female but not male paediatric patients [27]. There are several mechanisms to explain the increased risk due to obesity, among them proinflammatory adipokines released by adipose tissue, and the link between obesity and earlier puberty-onset, which is another MS risk factor in children. Prior to puberty, the ratio of male-to-female children diagnosed with MS is roughly 1:1, while after puberty, there is a female predominance of 2.7:1 [28]. The female predominance seen in older children may be related to a contribution of female sex hormones to MS risk, or to a protective effect of male sex hormones [26].

Epstein Barr Virus (EBV) exposure has also been shown to have significant association with both adult and paediatric MS risk; higher EBV nuclear antigen-1 (EBNA-1) antibody titres have been found in children with MS, compared to healthy children [29]. In a study of 110 children with relapsing demyelinating syndromes, evidence of remote EBV infection was reported in 100% of MS patients compared to 42.9% in non-MS relapsing demyelination [6]. No significant interactions have been found between EBV seropositivity and the presence of an HLA-DRB*1501 allele [25].

Other possible MS risk factors include exposure to parental smoking and gut microbiome differences, namely increased Desulfovibrionaceae bacteria and reduced Lachnospiraceae and Ruminococcaceae in MS patients [30].

Interactions between genetic and environmental risk factors

HLA-DRB1*1501, the most established genetic risk factor for MS, has been found to interact with several environmental risk factors. In fact, a Vitamin D Response Element (VRDE) is present in the HLA-DRB1 promotor region, and specifically in the HLA-DRB1*15 haplotype [31]. The presence of VRDE influences gene expression and imparts 1,25-dihydroxyvitamin D3 (the active form of Vitamin D) sensitivity to the haplotype. Furthermore, it was shown that other VDRE variants, present on other HLA-DRB1 haplotypes that are not MS-associated, were not responsive to 1,25-dihydroxyvitamin D3. A significant interaction has also been observed between HLA-DRB*15 and obesity in adolescents, suggesting these factors may interact to increase MS risk [32].

In contrast, EBV-positivity, the main viral risk factor, has not been shown to interact with the HLA-DRB1*1501 genetic risk factor. However, prior HSV-1 infection was associated with greater MS risk in HLA-DRB1*1501-negative children. Nevertheless, prior HSV-1 infection was associated with reduced risk of MS in HLA-DRB1*1501-positive children [33].

Risk factors altering MS disease course

A small study in Detroit, Michigan, showed significantly higher MS annualised relapse rates in children of African American origin compared with those of Caucasian ethnicity [34]. This suggests that African American children are not only at higher risk of paediatric MS, but also have a more aggressive disease course.

Table 2. Paediatric vs. adult MS risk factors.

Risk factor	Paediatric (95% CI)	Adults (95% CI)
Tobacco exposure	RR 2.12 (1.43–3.15)	OR 2.7 (2.0–3.8)
Decreased Vitamin D levels	HR 1.11 (1.00–1.25) per 10 nmol/l decrease in concentration	OR 0.59 (0.19–0.75) for a 50 nmol/l increase in concentration
HLA-DRB1*15 allele	OR 2.95 (2.33–3.32)	OR 3.5 (2.7–4.4)
EBV antibodies	OR 3.78 (1.52–9.38)	RR 2.9 (1.4–6.1) (EBNA-2 Abs)
Obesity	Females premenarcheal OR 1.48	
	Females postmenarcheal OR 1.68	
	Males OR 1.42	OR 2.1 (1.5–3.0)

Abbreviations: HR, Hazard ratio; OR, Odds ratio; RR, Relative risk; CI, Confidence interval

Lower serum 25-hydroxyvitamin D3 level are also associated with a substantially increased relapse rate in paediatric-onset MS [35]. Furthermore, HLA-DRB1*15 has been shown to modify the association of vitamin D levels with relapse rates, suggesting it also has a role in the disease course and prognosis [36].

Obesity in paediatric MS patients has been linked to higher relapse rates on first-line disease-modifying therapies (DMTs) with interferon beta and glatiramer acetate, in comparison to non-obese controls. However, no direct association has been shown between obesity and a worse disease course [37].

Sex hormones may also affect disease activity in female paediatric MS; relapse rates are higher in the peri-menarche period (six months before and after menarche), as compared to pre-menarche and post-menarche periods [38].

In a case-controlled study from the US Network of Pediatric MS Centres, higher BMI in early adolescence was found to be a risk for MS [39]. Age of disease onset is influenced by sexual maturity, particularly in association with obesity.

Paediatric MOGAD and AQP4-Ab NMOSD—epidemiology and risk factors

AQP4-Ab NMOSD and MOGAD demographics and epidemiology

Worldwide prevalence of NMOSD ranges between 0.039 and 0.73 per 100,000 person-years for adults and between 0.01 and 0.06 per 100,000 person-years for children (age more than 18 years) [40]. Several population-based studies over the past two decades have also shown inter-racial variation that remained consistent across geographical regions [41]. For instance, studies showed higher prevalence (around 3.5 per 100,000) in East Asians (Japanese, Chinese, Taiwanese, and Koreans) compared to Caucasian patients and other Asian ethnic groups. Other studies suggest that the estimated prevalence among African American ethnic groups varies from 1.8 to 13 (in specific populations) per 100,000 and is higher compared to Caucasian patients. NMOSD incidence among Caucasian patients is generally around 0.5–0.8 per million per year. Ethnicity may also influence the severity of the disease, with higher relapse rates associated with Afro-Caribbean patients in addition to paediatric-onset disease [10]. In contrast, in a study of 106 AQP4-Ab-positive Japanese and UK patients, better outcomes were reported in the Japanese cohort, specifically for visual disability, motor disability, wheelchair dependency and mortality [42]. A recent systematic review demonstrated female predominance in NMOSD adult patients (and in AQP4-Ab seropositive patients) and confirmed that African ethnicity is associated with the highest incidence and prevalence, and Caucasian ethnicity is associated with the lowest incidence and prevalence [40].

In a recent retrospective, a multicentre study of 67 patients with AQP4-Ab NMOSD aged more than 18 years from Europe and Brazil, 29 (43.3%) were Caucasian, 14 (20.9%) Black, 13 (19.4%) Brazilian mixed ethnicity, and 11 (16.4%) other ethnicities [43]. Patients of other ethnic minorities were more common in both European (25/47) and Brazilian (13/20) populations. Patients of other ethnic minorities had both a more severe disease course as well as a shorter time to first relapse. Furthermore, in a study looking at the risk of endocrinopathies in patients with paediatric-onset AQP4-Ab NMOSD, morbid obesity was seen in 88% of children of Caribbean origin [44].

In a large multicentre dataset of 441 patients from the UK, USA, Japan and Martinique, advanced mathematical modelling found that Japanese patients had a lower risk of subsequent relapse, with a relative relapse risk of 0.68 compared to Caucasian patients [45]. Similarly, African patients had a higher relative relapse risk of 3.31 compared to Caucasian patients. In addition, female patients were more likely to relapse than male patients, and those with a younger age of disease onset were more likely to have ON relapses.

Children with MOG-Ab are typically younger, with lower Kurtzke Expanded Disability Status Scale (EDSS) at two years and have a longer time to relapse when compared to AQP4-Ab-positive NMOSD [19]. In contrast to AQP4-Ab-positive NMOSD, which is extremely rare in children, MOGAD has a higher incidence in paediatric patients compared to adult patients, with around 34% of paediatric patients with ADS being MOG-Ab-positive [46]. It seems there is no racial or gender predominance in MOGAD, which contrasts with the female and other ethnic minority predominance seen in both MS and NMOSD.

NMOSD and MOGAD genetic and environmental risk factors

There is limited literature about paediatric NMOSD risk factors. However, studies have shown that attending day care (exposure to other young children) as well as breastfeeding were associated with lower odds of having NMOSD [36]. However, caesarean section delivery is associated with a twofold increase in the odds of having NMOSD compared to having MS and healthy controls. Other possible MS risk factors, including HSV-1, EBV, CMV past infections and HLA-DRB1*15-positivity have not been shown to be associated with NMOSD. A GWAS of 215 NMOSD patients and 1244 healthy controls showed no significant results in Korean patients. However, in Caucasian patients, SNPs and copy number variation (CNV) analysis found two independent significant genetic signals in the MHC-region associated with IgG-seropositive NMOSD. One signal, HLA-DRB1*03:01, is more abundant in European than Asian populations. An additional genetic marker, rs28383224 (encoding to HLA-DQA1), was found to be associated with NMOSD (both AQP4-Ab-positive and -negative). It was also found that increased copy numbers of the rs1150757 marker (of the C4A gene, encoding to the C4a subunit of the C4 complement system protein) was associated with reduced risk of NMOSD [47].

HLA class II alleles DQB*05:02 and DRB1*16:02 haplotypes were higher in paediatric-onset MOGAD in Chinese patients [48]. These alleles were not associated with adult-onset MOGAD, MS or NMOSD [49]. Although a HLA association similar to other autoantibody-associated diseases is likely, in a recent study of 43 Dutch patients with MOGAD no significant HLA association was found [50].

Future directions

The paradigm shift seen with the role of newly discovered autoantibodies in paediatric ADS over the past decade (namely MOG and AQP4 Abs) has significant implications when calculating the incidence, prevalence, and demographics of each disease. Epidemiological data for AQP4-Ab NMOSD and MOGAD will likely undergo further revisions as existing antibody assays are improved, new autoantibodies are discovered, and disease registries continue to be developed. Importantly, defining diseases by disease-specific biomarkers and not by the clinical phenotypes has significant implications on prognostic factors, therapeutic algorithms, and approaches to repair.

Understanding the actual 'real-world' burden of individual demyelinating conditions by geographic location, age, sex and ethnicity will help facilitate more accurate diagnostics, resource allocation and precision medicine. Further exploring how demographics and risk factors relate to disease course and prognostic prediction will no doubt help guide therapy.

Although most of the 'traditional' MS risk factors are not associated with paediatric AQP4-Ab NMOSD and MOGAD, other risk factors have been shown to be associated with these ADS entities (Table 3). However, since these rare disease groups were only recently distinguished from MS, there is still limited data on other potential risk factors, which warrant further studies for exploration.

For instance, the varying prevalence rates of NMOSD, most striking amongst different ethnicities, suggests that certain genetic and environmental factors associated with ethnic groups may be involved in NMOSD pathobiology. Likewise, both epidemiological and risk factor data on MOGAD paediatric patients remains insufficient and needs further exploration.

When selecting therapies for acquired demyelinating conditions, individual patient characteristics and demographics need to be considered and there remains an unmet need with selecting the most appropriate therapies for some conditions such as MOGAD and seronegative NMOSD. Future regenerative approaches under investigation for MS and other conditions may stall or even reverse disability, and it will be interesting to see whether this can also be used in paediatrics. The success of these experimental therapies will depend on individual patient characteristics and demographics, with greater plasticity of the developing brain and consequently a greater capacity for repair. This age-related decline in remyelination has a major impact on the natural history of MS and it may suggest a therapeutic window in which appropriate early treatment may prevent later disability. While insights into disease pathophysiology in paediatric ADS have led recent therapeutic advances, well designed and collaborative large scale epidemiological studies are likely to provide the critical next step to a personalised approach to these conditions.

It is important to note that since children with MS represent a unique group closer to the early pathobiological processes that lead to MS, continuing to study genetic and environmental risk factors in MS may provide us with unique insights into better understanding the pathobiological processes that lead to the disease in both children and adults. Given the rarity of MS, NMOSD and MOGAD in paediatrics, future studies will be aided by ongoing international collaborative research efforts.

Table 3. Risk factors in MS vs. NMO vs. MOGAD.

	Risk factor	MS risk (95% CI)	AQP4-Ab NMOSD risk (95% CI)	MOGAD risk (95% CI)
Demographic	Ethnicity - Black	+	+	-
	Ethnicity - East Asian	-	+	-
	Gender (Female) >11 years old	+	-	-
Genetic	HLA-DRB1*15:01	OR 2.95 (2.33–3.32)	OR 1.67 conditioned on HLA-DRB1*03:01 (1.13–2.47)	-
	HLA-DRB1*03:01	-	OR 4.09 (2.98–5.99)	-
	HLA-DQB1*05:02	-	-	OR 1.95 (1.25–3.00)
	HLA-DRB1*16:02	-	-	OR 2.21 (1.15–4.08)
Environmental	Low serum 25-hydroxyvitamin D	HR 1.11 (1.00–1.25) per 10 nmol/l decrease in 25-OH-vit D	-	-
	Obesity	Females premenarcheal OR 1.48 (0.88–2.51). Females postmenarcheal OR 1.68 (1.21–2.34). Males OR 1.42 (1.09–1.86).	-	-
	EBV exposure	OR 3.78 (1.52–9.38)	-	-
	HSV-1 exposure, HLA-DRB1*15 neg	OR 4.11 (1.17–14.37)	-	-
	HSV-1 exposure, HLA-DRB1*15 pos	OR 0.07 (0.02–0.32)	-	-
	Low serum 25-OH-vit D 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)	-	-
	Caesarean delivery	-	OR 1.95 (0.81–4.71)	-

+ association between risk factor and disease

- no association between risk factor and disease

Competing interests

None of the authors had conflicts of interest or disclosures.

Author contributions

O.H.: Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. Y.H.: Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; Analysis or interpretation of data. O.A-M.: Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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References

[1] 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(2):136-49. **PubMed**.

[2] Waubant E, Ponsonby AL, Pugliatti M, Hanwell H, Mowry EM, Hintzen RQ. Environmental and genetic factors in pediatric inflammatory demyelinating diseases. Neurology. 2016;87(9 Supplement 2):S20-7. **PubMed**.

[3] Waubant E, Lucas R, Mowry E, Graves J, Olsson T, Alfredsson L, et al. Environmental and genetic risk factors for MS: an integrated review. Annals of Clinical and Translational Neurology. 2019;6(9):1905-22. **PubMed**.

[4] 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(9):936-48. PubMed.

[5] Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. The Lancet Neurology. 2018;17(2):162-73. PubMed.

[6] Hacohen Y, Mankad K, Chong WK, Barkhof F, Vincent A, Lim M, et al. Diagnostic algorithm for relapsing acquired demyelinating syndromes in children. Neurology. 2017;89(3):269-78. PubMed.

[7] Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock SJ, Lucchinetti CF, Fujihara K, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. The Lancet. 2004;364(9451):2106-12. PubMed.

[8] Hacohen Y, Banwell B. Treatment Approaches for MOG-Ab-Associated Demyelination in Children. Current Treatment Options in Neurology. 2019;21(1). PubMed.

[9] Hacohen Y, Absoud M, Deiva K, Hemingway C, Nytrova P, Woodhall M, et al. Myelin oligodendrocyte glycoprotein antibodies are associated with a non-MS course in children. Neurology - Neuroimmunology Neuroinflammation. 2015;2(2):e81. PubMed.

[10] Tackley G, O'Brien F, Rocha J, Woodhall M, Waters P, Chandratre S, et al. Neuromyelitis optica relapses: Race and rate, immunosuppression and impairment. Multiple Sclerosis and Related Disorders. 2016;7:21-5. PubMed.

[11] Belman AL, Krupp LB, Olsen CS, Rose JW, Aaen G, Benson L, et al. Characteristics of Children and Adolescents With Multiple Sclerosis. Pediatrics. 2016;138(1). PubMed.

[12] Langer-Gould A, Zhang JL, Chung J, Yeung Y, Waubant E, Yao J. Incidence of acquired CNS demyelinating syndromes in a multiethnic cohort of children. Neurology. 2011;77(12):1143-8. PubMed.

[13] Absoud M, Lim MJ, Chong WK, Goede CGD, Foster K, Gunny R, et al. Paediatric acquired demyelinating syndromes: incidence, clinical and magnetic resonance imaging features. Multiple Sclerosis Journal. 2012;19(1):76-86. PubMed.

[14] Mikaeloff Y, Suissa S, Vallée L, Lubetzki C, Ponsot G, Confavreux C, et al. First episode of acute CNS inflammatory demyelination in childhood: prognostic factors for multiple sclerosis and disability. The Journal of Pediatrics. 2004;144(2):246-52. PubMed.

[15] Banwell B, Kennedy J, Sadovnick D, Arnold DL, Magalhaes S, Wambera K, et al. Incidence of acquired demyelination of the CNS in Canadian children. Neurology. 2009;72(3):232-9. PubMed.

[16] Neuteboom RF, Boon M, Berrevoets CEC, Vles JS, Gooskens RH, Stroink H, et al. Prognostic factors after a first attack of inflammatory CNS demyelination in children. Neurology. 2008;71(13):967-73. PubMed.

[17] de Mol CL, Wong YYM, van Pelt ED, Ketelslegers IA, Bakker DP, Boon M, et al. Incidence and outcome of acquired demyelinating syndromes in Dutch children: update of a nationwide and prospective study. Journal of Neurology. 2018;265(6):1310-9. PubMed.

[18] Lin WS, Wang HP, Chen HM, Lin JW, Lee WT. Epidemiology of pediatric multiple sclerosis, neuromyelitis optica, and optic neuritis in Taiwan. Journal of Neurology. 2019;267(4):925-32. PubMed.

[19] Hacohen Y, Brownlee W, Mankad K, Chong WKK, Thompson A, Lim M, et al. Improved performance of the 2017 McDonald criteria for diagnosis of multiple sclerosis in children in a real-life cohort. Multiple Sclerosis Journal. 2019;26(11):1372-80. PubMed.

[20] Disanto G, Magalhaes S, Handel AE, Morrison KM, Sadovnick AD, Ebers GC, et al. HLA-DRB1 confers increased risk of pediatric-onset MS in children with acquired demyelination. Neurology. 2011;76(9):781-6. PubMed.

[21] Axisa PP, Hafler DA. Multiple sclerosis. Current Opinion in Neurology. 2016;29(3):345-53. PubMed.

[22] Gianfrancesco MA, Stridh P, Shao X, Rhead B, Graves JS, Chitnis T, et al. Genetic risk factors for pediatric-onset multiple sclerosis. Multiple Sclerosis Journal. 2017;24(14):1825-34. PubMed.

[23] Barcellos L, Shao X, Rhead B, Gianfrancesco M, Graves J, Waldman A, et al. First Genome-Wide Analysis in Pediatric Multiple Sclerosis (MS) Confirms a Role for Adult MS Risk Variants and Reveals New Candidates (S29.001). Neurology. 2016;86(16 Supplement).

[24] Bashinskaya VV, Kulakova OG, Boyko AN, Favorov AV, Favorova OO. A review of genome-wide association studies for multiple sclerosis: classical and hypothesis-driven approaches. Human Genetics. 2015;134(11-12):1143-62. PubMed.

[25] Banwell B, Bar-Or A, Arnold DL, Sadovnick D, Narayanan S, McGowan M, 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(5):436-45. PubMed.

[26] Makhani N, George I. Genetic and Environmental Risk Factors for Pediatric Multiple Sclerosis. Journal of Pediatric Neurology. 2017;16(03):141-7.

[27] Langer-Gould A, Brara SM, Beaber BE, Koebnick C. Childhood obesity and risk of pediatric multiple sclerosis and clinically isolated syndrome. Neurology. 2013;80(6):548-52. PubMed.

[28] Huppke B, Ellenberger D, Rosewich H, Friede T, Gärtner J, Huppke P. Clinical presentation of pediatric multiple sclerosis before puberty. European Journal of Neurology. 2013;21(3):441-6. PubMed.

[29] Banwell B, Krupp L, Kennedy J, Tellier R, Tenembaum S, Ness J, et al. Clinical features and viral serologies in children with multiple sclerosis: a multinational observational study. The Lancet Neurology. 2007;6(9):773-81. PubMed.

[30] Tremlett H, Fadrosh DW, Faruqi AA, Zhu F, Hart J, Roalstad S, et al. Gut microbiota in early pediatric multiple sclerosis: a case-control study. European Journal of Neurology. 2016;23(8):1308-21. PubMed.

[31] Ramagopalan SV, Maugeri NJ, Handunnetthi L, Lincoln MR, Orton SM, Dyment DA, et al. Expression of the Multiple Sclerosis-Associated MHC Class II Allele HLA-DRB1∗1501 Is Regulated by Vitamin D. PLoS Genetics. 2009;5(2):e1000369. PubMed.

[32] Hedstrom AK, Bomfim IL, Barcellos L, Gianfrancesco M, Schaefer C, Kockum I, et al. Interaction between adolescent obesity and HLA risk genes in the etiology of multiple sclerosis. Neurology. 2014;82(10):865-72. PubMed.

[33] Waubant E, Mowry EM, Krupp L, Chitnis T, Yeh EA, Kuntz N, et al. Common viruses associated with lower pediatric multiple sclerosis risk. Neurology. 2011;76(23):1989-95. PubMed.

[34] Boster AL, Endress CF, Hreha SA, Caon C, Perumal JS, Khan OA. Pediatric-Onset Multiple Sclerosis in African-American Black and European-Origin White Patients. Pediatric Neurology. 2009;40(1):31-3. PubMed.

[35] Mowry EM, Krupp LB, Milazzo M, Chabas D, Strober JB, Belman AL, et al. Vitamin D status is associated with relapse rate in pediatric-onset MS. Annals of Neurology. 2010:NA-NA. PubMed.

[36] Graves J, Grandhe S, Weinfurtner K, Krupp L, Belman A, Chitnis T, et al. Protective environmental factors for neuromyelitis optica. Neurology. 2014;83(21):1923-9. PubMed.

[37] Huppke B, Ellenberger D, Hummel H, Stark W, Röbl M, Gärtner J, et al. Association of Obesity With Multiple Sclerosis Risk and Response to First-line Disease Modifying Drugs in Children. JAMA Neurology. 2019;76(10):1157. PubMed.

[38] Lulu S, Graves J, Waubant E. Menarche increases relapse risk in pediatric multiple sclerosis. Multiple Sclerosis Journal. 2015;22(2):193-200. PubMed.

[39] Chitnis T, Graves J, Weinstock-Guttman B, Belman A, Olsen C, Misra M, 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(12):897-907. PubMed.

[40] Papp V, Magyari M, Aktas O, Berger T, Broadley SA, Cabre P, et al. Worldwide incidence and prevalence of NMO: A systematic review. Neurology. 2020:10.1212/WNL.0000000000011153. PubMed.

[41] Flanagan EP, Cabre P, Weinshenker BG, Sauver JS, Jacobson DJ, Majed M, et al. Epidemiology of aquaporin-4 autoimmunity and neuromyelitis optica spectrum. Annals of Neurology. 2016;79(5):775-83. PubMed.

[42] Kitley J, Leite MI, Nakashima I, Waters P, McNeillis B, Brown R, et al. Prognostic factors and disease course in aquaporin-4 antibody-positive patients with neuromyelitis optica spectrum disorder from the United Kingdom and Japan. Brain. 2012;135(6):1834-49. PubMed.

[43] Paolilo RB, Hacohen Y, Yazbeck E, Armangue T, Bruijstens A, Lechner C, et al. Treatment and outcome of aquaporin-4 antibody–positive NMOSD. Neurology - Neuroimmunology Neuroinflammation. 2020;7(5):e837. PubMed.

[44] Hacohen Y, Messina S, Gan HW, Wright S, Chandratre S, Leite MI, et al. Endocrinopathies in paediatric-onset neuromyelitis optica spectrum disorder with aquaporin 4 (AQP4) antibody. Multiple Sclerosis Journal. 2017;24(5):679-84. PubMed.

[45] Palace J, Lin DY, Zeng D, Majed M, Elsone L, Hamid S, et al. Outcome prediction models in AQP4-IgG positive neuromyelitis optica spectrum disorders. Brain. 2019;142(5):1310-23. PubMed.

[46] Reindl M, Waters P. Myelin oligodendrocyte glycoprotein antibodies in neurological disease. Nature Reviews Neurology. 2018;15(2):89-102. PubMed.

[47] Estrada K, Whelan CW, Zhao F, Bronson P, Handsaker RE, Sun C, et al. A whole-genome sequence study identifies genetic risk factors for neuromyelitis optica. Nature Communications. 2018;9(1). PubMed.

[48] Sun X, Qiu W, Wang J, Wang S, Wang Y, Zhong X, 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(7):733-9. PubMed.

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

[50] Bruijstens AL, Lechner C, Flet-Berliac L, Deiva K, Neuteboom RF, Hemingway C, et al. E.U. paediatric MOG consortium consensus: Part 1 – Classification of clinical phenotypes of paediatric myelin oligodendrocyte glycoprotein antibody-associated disorders. European Journal of Paediatric Neurology. 2020;29:2-13. PubMed.