Environmental and genetic factors in pediatric inflammatory demyelinating diseases

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ABSTRACT

The onset of multiple sclerosis (MS) occurs in childhood in about 5% of all patients with MS. The disease in adults has a complex genetic and environmental inheritability. One of the main risk factors, also confirmed in pediatric MS, is *HLA DRB1*1501*. In addition to genetic factors, a large part of disease susceptibility in adults is conferred by environmental risk factors such as low vitamin D status, exposure to cigarette smoking, and remote Epstein-Barr virus (EBV) infection. In children, both exposure to cigarette smoking and prior EBV infection have been reported consistently as risk factors for MS. The role of vitamin D remains to be confirmed in this age category. Finally, although very likely critical in disease processes, few gene–environment interactions and epigenetic changes have been reported for adult and pediatric MS susceptibility. Of interest, some of the risk factors for MS have also been associated with disease course modification, such as low 25(OH) vitamin D serum levels in pediatric and adult MS. Age is also a clear disease modifier of clinical, CSF, and MRI phenotype in children with the disease. Finally, although much has yet to be unraveled regarding molecular processes at play in MS, there is a larger gap in our knowledge of genetic and environmental risk factors for pediatric neuromyelitis optica spectrum disorders and acute disseminated encephalomyelitis and only collaborative studies will answer those questions. ***Neurology*® 2016;87 (Suppl 2):S20–S27**

GLOSSARY

25(OH)D = 25-hydroxyvitamin D; **ADS** = acquired demyelinating syndromes; **BMI** = body mass index; **CIS** = clinically isolated syndromes; **CMV** = cytomegalovirus; **EBV** = Epstein-Barr virus; **GWAS** = genome-wide association studies; **HLA** = human leukocyte antigen; **HSV** = herpes simplex virus; **MS** = multiple sclerosis; **NMO** = neuromyelitis optica.

Among pediatric acquired demyelinating disorders of the CNS, multiple sclerosis (MS), including clinically isolated syndromes (CIS), acute disseminated encephalomyelitis, and neuromyelitis optica (NMO) spectrum disorders are the most common. Due to its chronicity and proportionally higher incidence, substantial efforts have focused on understanding factors contributing to MS, although the study of risk factors for NMO is also accelerating.[1]

Despite the fact that several genetic and environmental risk factors have been consistently reported for adult MS,[2] underlying molecular processes at play remain largely unknown. The onset of MS in children, although representing only approximately 5% of all MS onsets, leads us to question whether the load of genetic factors and environmental exposures contributing to disease onset may in fact be higher than in adults who develop the disease. As such environmental risk factors should be easier to identify in younger patients and if disease processes at play overlap in all age groups, this information might be extended to adult-onset MS. It is unknown why disease onset is relatively rare in children vs adults. This could be in part due to developmental changes in the CNS or immune systems.

Exposures to environmental risk factors for adult MS are believed to occur for the most part before age 15.[2] As such, studying risk factors in pediatric MS during the putative window of disease susceptibility may considerably shorten the time between exposure action and time of

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exposure capture, thus improving accuracy and reliability of these observations. This work reviews the state of our knowledge regarding risk factors and disease modifiers for pediatric MS and NMO. Most of the publications on this topic have used age 18 as a cutoff for pediatric or childhood onset, but some have used age 16.

ENVIRONMENTAL RISK FACTORS FOR PEDIATRIC MS SUSCEPTIBILITY OTHER THAN VITAMIN D

Place of residence. The place of residence during childhood, rather than ancestry, has been hypothesized to be a remarkable demographic determinant of MS risk in both age populations.[3] In a study of 44 pediatric patients and 573 patients with adult-onset MS residing in the same region, the former were more likely to report Caribbean, Asian, or Middle Eastern ancestry, and less likely to report European heritage, compared with patients with adult-onset MS (table).[3]

Infections. The role of viral infections acquired during childhood has been a focus but the interpretation of findings is complex and interactions with genetics may drive associations. In a case-control study conducted on 189 patients with early pediatric MS and 66 pediatric controls, Epstein-Barr virus (EBV) nuclear antigen-1 seropositivity was significantly associated with an increased risk for MS after adjusting for age, sex, race, ethnicity, and *HLA-DRB1*1501/1503* status, whereas a remote infection with cytomegalovirus (CMV) was associated with a lower risk of developing MS irrespective of EBV seropositivity (table).[4] A remote infection with herpes simplex virus (HSV)–1 was not associated with an increased disease risk per se, but interaction with *HLA-DRB1*15* negative status led to increased odds of MS and with *HLA-DRB1*15* positive was found to protect from MS.[5]

Perinatal exposures were investigated in 36 pediatric patients with NMO, 491 with MS, and 224 healthy controls by means of a case-control study.[1] Daycare (exposure to other young children) and breastfeeding were found in reverse association with pediatric NMO (table). No significant association with NMO was found for cesarean delivery or with EBV, CMV, or HSV-1 antibody responses, or positivity to *HLA-DRB1*15* status.

Smoking exposure. Parental smoking was found to be significantly associated with pediatric MS onset (table) in a population-based case-control study conducted on 129 MS cases from the French KIDSEP neuropediatric cohort and 1,038 controls.[6] The dose-response effect by duration of exposure favors a possible causal association between parental smoking and the risk to develop MS in childhood or adolescence.

Risk periods. The known difference in sex ratio between prepubertal and postpubertal onset of MS[7–10] has led to investigations on the role of puberty and menarche in determining the risk of pediatric MS. In the Canadian Pediatric Demyelinating Disease Study,[11] a later age at menarche was associated with a decreased risk of conversion to MS, independently from patient age at acquired demyelinating syndromes (ADS) onset and from MRI burden.[11] While the age at first menarche has progressively declined by about 4 years over the past 150 years, the frequency of both pediatric and adult MS has increased. Whether this evidence is causally related (i.e., hormones acting as immune modulators and driving MS sexual dimorphism in childhood) or whether it is confounded or modified by other factors (e.g., lifestyle) remains to be investigated.

Low vitamin D status. Two separate population-based nested case-control studies in Sweden assessed the relationship between vitamin D status (defined by circulating 25-hydroxyvitamin D concentrations [25(OH)D]) in very early life and risk of MS.[12,13] Risk of MS in the offspring was not associated with circulating 25(OH)D levels measured in either the mothers during early pregnancy[12] or in the offspring at birth.[13] Further research to determine whether prenatal or perinatal vitamin D status relates specifically to risk of pediatric MS may be warranted.

Circulating 25(OH)D levels are commonly lower than expected among both children and adults with MS.[14] However, studies of vitamin D status in prevalent cases are of dubious value for assessing vitamin D as an MS risk determinant as post-MS onset vitamin D status may be a poor proxy for prediagnostic status. Thus, measurement of 25(OH)D levels at the time of a first clinical presentation is preferable. Circulating 25(OH)D levels at onset of ADS were inversely associated with the likelihood of MS among Canadian children,[15] suggesting a protective role of vitamin D. This has not yet been confirmed using healthy controls.

Obesity. In a California case-control study of pediatric MS cases and demographically matched controls (table), overweight and obesity were associated with a subsequent increased risk of MS/CIS in girls but not in boys.[16] In another pediatric case-control study, obesity was associated with increased risk of pediatric MS onset in both girls and boys.[17] Obesity in childhood and adolescence is associated with lower 25(OH)D levels, and both prepubescent obesity and vitamin D deficiency may contribute to younger age at menarche. Among girls presenting with ADS, younger age at menarche predicted a higher likelihood of subsequent MS diagnosis, a finding that persisted even after accounting for the higher body mass and lower 25(OH)D levels observed in those with MS at first attack.[11] A number of factors that typically precipitate,

Table Significant associations between exposure to environmental factors and development of pediatric multiple sclerosis (MS) or neuromyelitis optica (NMO)

Environmental factor	Source population	Study design	Study population	Effect measure (95% CI, where applicable)		*p*
Place of birth (Kennedy et al., 2006)[3]	Canada	Cross-sectional	44 Pediatric MS	Born in Asia	6/44 (13.6%) Pediatric vs 7/573 (1.2%) adult MS	0.0001[a]
			573 Adult-onset MS	Born in Europe	95/573 (16.6%) Adult vs 1/44 (2.3%) pediatric MS	0.0082[a]
Ancestry (Kennedy et al., 2006)[3]	Canada	Cross-sectional	43 Pediatric MS	Caribbean maternal	4/43 (9.3%) Pediatric vs 11/555 (2.0%) adult MS	0.0177[a]
			555 Adult	Caribbean paternal	6/43 (13.9%) Pediatric vs 11/555 (2.0%) adult MS	0.0007[a]
			MS (known maternal ancestry)	Asian maternal	11/43 (25.6%) Pediatric vs 10/555 (1.8%) adult MS	<0.0001[a]
			546 Adult MS (known paternal ancestry)	Asian paternal	11/43 (25.6%) Pediatric vs 7/555 (1.3%) adult MS	<0.0001[a]
				European maternal	24/43 (55.8%) Pediatric vs 510/555 (91.9%) adult MS	<0.0001[a]
				European paternal	507/555 (91.3%) Adult vs 22/43 (51.2%) pediatric MS	<0.0001[a]
Common viral infections (Waubant et al., 2011)[4]	USA	Case-control study	189 Early pediatric MS	EBNA-1 seropositivity	OR 3.78 (1.52–9.38)	0.004[b]
			66 Pediatric controls	Remote CMV infection	OR 0.27 (0.11–0.67)	0.004[c]
				HSV-1 and HLA-DRB1*15 allele negative	OR 4.11 (1.17–14.37)	0.03
				HSV-1 and HLA-DRB1*15 allele positive	OR 0.07 (0.02–0.32)	0.001
Parental smoking (Mikaeloff et al., 2007)[6]	France	Case-control study	129 Pediatric MS and 1,038 pediatric controls		RR 2.12 (1.43–3.15)[d]	—
Age at menarche (Ahn et al., 2015)[11]	Canada	Cohort study	40 Pediatric MS and 54 pediatric monophasic ADS		HR 0.67 (0.52–0.87)	—[e]
Low vitamin D (Banwell et al., 2011)[15]	Canada	Cohort study	63 Pediatric MS and monophasic ADS	25(OH)D (per 10 nmol/L decrease)	HR 1.11 (1.00–1·25)	—[f]
Overweight/obesity (Langer-Gould et al., 2013)[16]	USA	Nested case-control study	75 Pediatric cases of MS/CIS	Overweight vs normal weight	OR 1.58 (0.71–3.50)	0.005 (for trend)[g]
			913,097 Healthy children	Moderately obese vs normal weight	OR 1.78 (0.70–4.49)	
				Extreme obese vs normal weight	OR 3.76 (1.54–9.16)	
Daycare (exposure to other young children) (Graves et al., 2014)[1]	USA	Case-control study	36 Pediatric NMO vs 224 pediatric healthy controls	Yes vs no	OR 0.33 (0.14–0.78)[h]	<0.01[h]
Age at start of daycare (Graves et al., 2014)[1]	USA	Case-control study	36 Pediatric NMO vs 224 pediatric healthy controls	Older than 12 months	OR 0.30 (0.10–0.95)	—

Continued

Table Continued

Environmental factor	Source population	Study design	Study population	Effect measure (95% CI, where applicable)		*p*
Breastfeeding (Graves et al., 2014)[1]	USA	Case-control study	36 Pediatric NMO vs 224 pediatric healthy controls	Yes vs no	OR 0.42 (0.18–0.99)	0.05[h]
Gut microbiome (Tremlett et al., in press 2016)[20]	USA	Case-control study	18 Pediatric MS vs 17 pediatric controls	Higher abundance for members of the *Desulfovibrionaceae* (*Bilophila*, *Desulfovibrio*, and *Christensenellaceae*) and depletion in *Lachnospiraceae* and *Ruminococcaceae*		All p and $q < 0.000005$
Dietary salt (McDonald et al., 2016)[18]	USA	Case-control study	170 MS cases vs 331 controls	Dietary sodium intake (for each 100 mg/day increase in sodium)	OR 1.00 (0.98–1.02)	0.93
Dietary iron (Pakpoor et al., 2016)[19]	USA	Case-control study	260 Cases vs 393 controls	Dietary iron intake (low vs normal)	OR 1.58 (1.00–2.50)	0.05
C-section (Graves et al., 2016)[21]	USA	Case-control study	275 Pediatric MS vs 437 pediatric controls	Yes vs no	OR 0.6 (0.20–0.82)	0.01[i]
Maternal illness during pregnancy (Graves et al., 2016)[21]	USA	Case-control study	275 Pediatric MS vs 437 pediatric controls	Yes vs no	OR 2.3 (1.20–4.21)	0.01[i]
Paternal garden-related occupation (Graves et al., 2016)[21]	USA	Case-control study	275 Pediatric MS vs 437 pediatric controls	Yes vs no	OR 2.03 (1.07–3.84)	0.03[i]

Abbreviations: 25(OH)D = 25-hydroxyvitamin D; ADS = acquired demyelinating syndrome; CI = confidence interval; CIS = clinically isolated syndrome; CMV = cytomegalovirus; EBNA-1 = Epstein Barr virus nuclear antigen-1; HLA = human leukocyte antigen; HR = hazard ratio; HSV-1 = herpes simplex virus 1; OR = odds ratio; RR = rate ratio.

[a] Fisher exact test.

[b] Adjusted for age, sex, race, ethnicity, and HLA-DRB1*1501/1503 status.

[c] Adjusted for age, sex, race, ethnicity, HLA-DRB1*1501/1503, and EBV status.

[d] Adjusted for a family history of MS, another autoimmune disease, and socioprofessional status of the head of the family.

[e] Adjusted for age at onset and the presence of at least 1 T2-bright lesion on initial brain MRI.

[f] Not adjusted.

[g] Adjusted for age at onset and race/ethnicity.

[h] Adjusted for sex, race, and ethnicity.

[i] Adjusted for sex, race, ethnicity, and socioeconomic status.

accompany, or arise from both obesity and menarche are presently under investigation for their pathobiological association with risk of MS. However, the interrelatedness of obesity, vitamin D status, and menarche—all of which are influenced by both environmental and genetic factors—complicates elucidation of pathobiological processes underlying the etiology of MS.

Diet. Salt intake measured with a nonspecific food frequency questionnaire was not reported to be strongly associated with pediatric MS cases.[18] Multivariate analyses in the same pediatric study suggested an association between low dietary iron intake and pediatric MS while other nutrients such as fat, fibers, and proteins were not associated with the disease.[19]

Sex. Several reports have highlighted that sex ratio was different in cases with onset before age 11 with a ratio close to 1:1, while the ratio in teenagers was closer to that reported in adults.[7–10]

Gut microbiota. A total of 160 operational taxonomic units have been reported to be increased in pediatric MS compared to controls, while 163 are decreased in cases.[20] These findings have to be replicated and established prospectively and may thus provide new clues to molecular processes involved in MS course.

Pregnancy exposures and birth method. Maternal illness during pregnancy was recently reported to be associated with 2.3-fold increase in odds to have pediatric MS and C-section with 60% reduction.[21] In a model adjusted for these variables, maternal age and body mass index (BMI), tobacco smoke exposure during pregnancy, and breastfeeding were not associated with risk of pediatric MS. Exposure to pesticides through father's occupation or use in household during pregnancy was also associated with increased risk of pediatric MS.[21]

ENVIRONMENTAL FACTORS AS DISEASE MODIFIERS OF PEDIATRIC MS

While some scientists believe that risk factors for MS must necessarily be considered prognostic factors as well, it is important to note that factors that influence the risk of the disease may no longer be important once the pathogenic processes are set in motion. Of the several environmental factors that have been identified as important to MS risk in adults or children, only vitamin D insufficiency has been shown to be associated with features of MS course in both age groups. In 110 children with pediatric-onset MS, each 10 ng/mL (25 nmol/L) increase in 25(OH) D level was associated with a 34% reduction in the risk of subsequent relapses (incidence rate ratio 0.66, 95% confidence interval 0.46–0.95), even after accounting for potential confounders.[22]

Another potential factor that may modify the course of pediatric MS relates to age at onset. One study demonstrated that among those with MS onset ≤18 years of age, those whose onset was at a very young age (<11 years) were more likely to demonstrate fewer, but more confluent, T2-weighted hyperintense brain lesions than those whose onset was at age 11 or greater.[23] Further, those in the early-onset group were more likely to demonstrate resolution of the brain lesions than the older-onset children. Similarly, distinct CSF features have been reported in children younger than 11 years (see other related chapters). More recently, the perimenarche epoch was reported to be associated with increased risk of relapse in girls with MS.[24]

More recently, 2 pediatric MS studies have highlighted risk factors associated with relapse risk. One looked at the effect of *DRB1* status on the association of 25(OH) vitamin D levels with relapse rate and has confirmed an interaction of *DRB1* and vitamin D.[25] The second report highlighted the potential role of the gut microbiota composition with high *Firmicutes phylum* abundance and absent *Fusobacteria phylum* associated with higher risk of relapse.[26] These findings have to be replicated and may provide new clues to molecular processes involved in MS course. Finally, salt intake measured with a nonspecific food frequency questionnaire was not associated with relapse risk in pediatric MS.[27]

GENETIC RISK FACTORS FOR PEDIATRIC MS SUSCEPTIBILITY AND DISEASE MODIFICATION

Most of our knowledge about genetics as a risk factor for MS comes from studies in adults.[28] Given the rarity of the disease in children, specific studies in childhood-onset MS are scarce. For many diseases, a childhood onset is related to a higher genetic risk burden. This may not be the case for pediatric MS because it occurs rarely in first-degree relatives.[29] Alternative mechanisms that could account for childhood onset are environmental or epigenetic factors, and most likely gene–gene and gene–environment interactions. Most of the newly identified non–human leukocyte antigen (HLA) risk genes are related to immune function and many of their gene products are likely to interact with endogenous or exogenous infectious agents, and some of them with vitamin D.[30]

The frequency of these novel risk alleles in pediatric-onset MS needs to be investigated in depth. A first study on the overall genetic risk score of a set of 57 of these novel MS risk genes revealed comparable risk scores in adults and children. Both childhood- and adult-onset MS groups had significantly higher scores than population-based controls. Genetic risk scores clearly differed from those in children with

monophasic acquired demyelinating syndromes.[31] Several studies have shown a significant skew to *HLA DRB1*1501* in pediatric patients with MS vs healthy controls or individuals with monophasic ADS.[4,32,33] A recent study in white pediatric patients with MS has confirmed that, in addition to the strong effect of *DRB1*1501*, 36 of the 110 genetic variants associated with adult MS are also associated with the disease in children.[34] In fact, a larger effect size was reported for several of these variants compared with adult MS, suggesting that genes may have a stronger effect on pediatric MS susceptibility. Finally, in the same cohort, results from a Mendelian randomization analysis demonstrated a causal association between higher BMI and pediatric MS onset as represented by the risk score of >20 BMI gene variants after adjusting for sex, ancestry, *HLA-DRB1*15:01*, and 110 non-HLA MS risk variants.[35] This is important given studies have generally found a larger risk effect for BMI with regard to adolescent vs adult BMI.

Several observations suggest higher risks for children of non-European ancestry from lower incidence areas residing in regions of relatively high incidence such as Europe and North America.[5,29,36]

Non-HLA MS risk genes may not differ much between different ethnicities[37] and the *HLA-DRB1* risk allele is less frequent in non-Europeans. Therefore an increased risk for pediatric MS in populations from lower incidence areas now living in higher risk North American and European areas strongly supports an important role for environmental etiologic factors.

Finally, recent work in pediatric MS has reported a lack of association between genetic ancestry and relapse risk.[25]

GENE–GENE AND GENE–ENVIRONMENT INTERACTIONS IN PEDIATRIC MS SUSCEPTIBILITY The evaluation of gene–gene and gene–environment interactions may help account for the missing heritability for pediatric MS. However, most of the pediatric MS studies have not been large enough to be adequately powered to examine interactions.

In a pediatric MS case-control study, the adverse effect of *HLA-DRB1*15* on MS risk was found to be attenuated by HSV immunoglobulin G positivity,[4] a finding replicated in an adult case-control study.[38] HSV-1 infection was not associated with an increased disease risk per se, but interaction between HSV and HLA-DRB1*15 positive status was found to be associated with reduced MS risk.[5] Thus, early life viral infection may assist the development of the immune response in high-risk HLA children. Based on the knowledge that both *HLA-DRB1*15* and EBV exposure are associated with MS risk, the interaction of these 2 factors has been interrogated.[39,40] A novel bioinformatic approach importantly looked indirectly at gene–viral interactions in MS.[41] Candidates were defined as viral factors contributing to MS risk, particularly EBV. Statistical gene enrichment was tested within these interactomes among loci associated with MS in genome-wide association studies (GWAS). EBV interactome genes were enriched within GWAS-identified loci, suggesting that gene–EBV interaction was a likely contributor to MS risk.[41] Low infant sibling exposure by age 6 (a marker of decreased early life microbial exposure) and *HLA-DRB1*15* are associated with higher risk for disease. The effect of these 2 factors combined was 3.9 times greater ($p = 0.02$) than expected. This suggests that those at high genetic risk may particularly benefit from early life immune priming. This interaction was replicated.[42] However, a subsequent Canadian study[43] reported no difference in the distribution of *DRB1*15* alleles between the exposure groups, and hence suggested the interaction may vary by populations. Additional gene–environment interactions have been studied in adult MS, as previously reviewed, but have not yet been studied in children with the disease.

For many autoimmune diseases, there is now a molecular method of evidence of gene–environment interaction. Modifications of DNA, including DNA methylation, may be the result of epigenetics. Specifically, these modifications can alter gene transcription and cell function. The influence of gene expression through the epigenetics pathway may mechanistically underlie some gene–environment interaction in MS. Epigenetic work has commenced in MS.[44] Pediatric MS is likely to be a useful MS subtype for examining early-life epigenetic programming.

DISCUSSION Because of its unique setting closer to environmental exposures, and the possibility of a higher susceptibility burden, the study of risk factors in children with MS may identify more readily factors that otherwise may be more challenging to study in adults many years after exposures. That some risks associated with MS are identical in children and adults supports the contention that MS shares many characteristics in both age groups. As such, future risk factors identified in children may well be generalizable to adults with MS and vice versa. The consistent reports of new risk factors associated with MS will hopefully increase the number of investigations of gene–environment interactions in the future. Given the relatively low numbers of pediatric MS cases, identification of those interactions will almost certainly require international collaborative efforts to not only adequately power such studies but also to provide the diverse environmental and genetic backgrounds needed

to elucidate the etiologic factors and the pathobiological molecular processes underlying the major MS risk factors.

AUTHOR CONTRIBUTIONS

Emmanuelle Waubant: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval. Anne-Louise Ponsonby: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval. Maura Pugliatti: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, topic review. Heather Hanwell: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval. Ellen M. Mowry: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval. Rogier Q. Hintzen: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval.

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