Teaching Course 10

Paediatric MS

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Acquired Demyelinating Syndromes and Multiple Sclerosis

It is estimated that up to 10% of people with Multiple Sclerosis (MS) have their first clinical event before the age of 18 years\(^1\). In a national MS registry from Wales, 5.4% of patients had developed clinical symptoms before the age of 18 years, and only 0.3% presented before the age of 10 years\(^2\). Diagnosis may though be delayed for many years. This results from lack of awareness on account of the relative rareness of the condition in the paediatric age group and the diversity of presenting symptoms. Even in those with recurrent demyelination, the diagnosis is sometimes missed, resulting in prolonged distress to patient and family and lost treatment opportunities. It is though often not an easy diagnosis, and one which needs to be carefully considered as, in contrast to adults, the majority of acquired demyelinating syndromes (ADS) in childhood are not MS. Furthermore, in young people, the characteristic presentations seen in adult onset MS are not always present, and the differential diagnoses are significantly wider. With the advent of multiple new treatments and the evidence that early treatment is of significant long term benefit, it is becoming vitally important to make an early, accurate diagnosis of relapsing remitting MS. Furthermore, as many of the mimics of demyelination may require alternative treatments for best long-term outcome, an in-depth understanding of the pathophysiology and range of possible conditions which can mimic MS is important. The talk will cover the new diagnostic criteria for acquired demyelinating syndromes and some of the important mimics.

Acquired demyelinating syndromes represent acute neurological illnesses characterised by:

- deficits persisting for at least 24 hours which
- involve the optic nerve, brain or spinal cord, and are
- associated with regional areas of increased T2 signal on conventional MRI.

The overall incidence of ADS in children and adolescents ranges from 0.6 to 1.66 per 100,000 children/year\(^1\). It is estimated that around 20%\(^4\) of these
individuals with an ADS will go on to have further episodes of demyelination with important determinants of recurrence being amongst others (reviewed in Waldman et al. Lancet Neurology 2014)

- the absence or presence of encephalopathy,
- the age of the child and
- the presence of silent brain lesions.

Manifestations of the events may be localised to a single CNS site (clinically known as monofocal) such as the eyes (optic neuritis) or the spine (acute transverse myelitis), or may be polyfocal; the events can also occur without impairment in level of alertness or can be associated with encephalopathy (then the presentation is termed Acute Disseminated Encephalomyelitis - ADEM). Recurrent cases of demyelination with encephalopathy do exist, but are rare, and account for less than 15% of all patients presenting with ADEM. The MRI in these cases can show new or re-emergent findings. Patients must present more than 3 months following the first episode. These cases are termed multiphasic ADEM and are not classified as MS.

The diagnosis of MS in children, as in adults, requires evidence of dissemination of CNS inflammatory activity distributed in more than one CNS location (i.e. dissemination in space-DIS) and recurrent disease over time (i.e. dissemination in time-DIT). The 2010 McDonald diagnostic criteria permit the diagnosis of MS at first presentation in a child over 12 years provided that

- the MRI features demonstrate lesions in areas typical for MS (periventricular white matter, juxtacortical, brainstem, and spinal cord) and
- there are at least two clinically silent lesions, one of which enhances with gadolinium.

Evidence of clinical or MRI new disease over time also confirms the diagnosis of MS in patients not meeting the criteria at onset. These 2010 McDonald MS diagnostic criteria have been incorporated into the International Pediatric Multiple Sclerosis Study Group (IPMSSG) consensus criteria for MS that also provide criteria for ADS presentations including optic neuritis, transverse
myelitis, and for pediatric NMO\textsuperscript{7}. Consensus criteria for NMO spectrum disorders (NMOSD) also have specific considerations for pediatric patients. These new criteria will be discussed further in the presentation.

The benefit of strict diagnostic criteria and accurate phenotyping was implemented in paediatric MS and ADS with the publication of IPMSSG definitions initially in 2007\textsuperscript{8} and revised in 2013\textsuperscript{7}. The inclusion of encephalopathy for a diagnosis of ADEM, in addition to polyfocal neurologic symptoms, has highlighted that ADEM is a monophasic disease in most children. In contrast, children with polyfocal neurologic symptoms without encephalopathy are more likely to be a first clinical presentation of MS. The 2010 McDonald criteria have further enabled the earlier identification of paediatric MS in children presenting with a first clinical event in conjunction with MRI\textsuperscript{9}. Radiological phenotyping has enabled the differentiation between various diseases with similar clinical presentations as was demonstrated in the comparison of paediatric MS from patients with CNS vasculitis\textsuperscript{10} or tumefactive demyelination from a CNS tumor\textsuperscript{11}.

There is growing interest in clinical phenotyping of patients with relapsing demyelination who do not fulfill criteria for MS diagnosis. Some of these clinical syndromes have been highlighted by the IPMSSG such as ADEM followed by optic neuritis (ADEMON) and chronic relapsing inflammatory optic neuropathy (CRION)\textsuperscript{12}. The pathobiology of these syndromes is not completely understood. However, the identification of aquaporin-4 antibodies in neuromyelitis optica (previously called optico-spinal MS prior to the identification of the antibody) suggests that relapsing demyelination is not necessarily MS and may require different management. In the presentation some cases of non-MS demyelination will be discussed.

**Antibodies in Acquired Demyelinating Syndromes**

Antibodies against the astrocyte water channel protein, aquaporin-4 (AQP4) were first described in 2004 in patients with Neuromyelitis optica (NMO). NMO preferentially affects the optic nerves and spinal cord. The discovery of the AQP4 antibodies (which are not found in patients with MS\textsuperscript{13}), has directly
influenced the diagnosis and management of these patients. Initial treatment with B-cell targeting treatments (such as azathioprine, mycophenolate mofetil, and rituximab) following the first clinical attack, has been shown to significantly reduce relapse rates in NMO and NMO spectrum disorder patients. Additionally, several conventional MS therapies such as interferon beta have been associated with disease worsening in patients with NMO. As AQP4 antibodies have now been identified in patients who do not fulfill the current clinical criteria for NMO, presenting with a single or recurrent attacks of optic neuritis, myelitis, or brain/brainstem disease, they have been proposed as specific disease biomarker for NMO spectrum disorders (NMOSD). The clinical features, MRI abnormalities and AQP4-Ab seropositivity reported in children with NMO is similar to the adult phenotype. As observed in children with MS, children with NMO have longer time to disability than adults with NMO. Importantly AQP4 seropositivity is more prevalent in children with relapsing NMO than in children with monophasic NMO suggesting this antibody may be used as a positive predictor for relapse in this childhood entity. Two studies looking at the prevalence of AQP4 antibodies in paediatric patients presenting with a first episode of demyelination have only identified these in 0.7% (2/279) to 4.5% (3/64) of children. Thus it is unclear how much AQP4 antibodies contribute to non-NMO presentations in children.

MOG-Ab have been reported in about 40% of children at first presentation of ADS. These antibodies have been reported in predominantly monophasic disease. In a large Austrian cohort of children with ADEM, 19/33 (58%) had MOG-Ab, with antibody positive patients more likely to have large, bilateral and widespread lesions on brain MRI, an increased frequency of longitudinal extensive transverse myelitis and a favorable clinical outcome despite 4/19 (21%) having a multiphasic clinical course. Two recent studies from the UK/France and the Netherlands suggested that the presence of MOG-Ab may be associated with non-MS disease course with additional absence of MRI and CSF features typically seen in both adults and children with multiple sclerosis. Nevertheless, in a selected cohort of relapsing demyelination, these antibodies were identified in 12/15 children with recurrent optic neuritis, in
7/7 children with ADEM followed by recurrent or monophasic optic neuritis (ADEM-ON), and in both adults and children with AQP4-Ab negative neuromyelitis spectrum disorder (NMOSD).

**Conclusion**

In the past decade, increasing attention has been paid to paediatric multiple sclerosis (MS), with prospective population based study aiming to identify patients at the onset in order to study the incidence of ADS and MS in children and collaborative research projects to investigate the complex environmental and genetic factors contributing to the early onset of the disease in comparison to adults. Although these disorders are relatively rare in children, the phenotypic similarities of paediatric demyelination with other both inflammatory and non-inflammatory conditions remains a significant challenge when trying to identify children for the specific prospective studies. With new therapeutic trials strict application of the 2012 IPMSSG definition is crucial while awareness of clinical scenarios that do not conform to the current definition.

**Reference**

Neuroimaging in Pediatric Multiple Sclerosis

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Overview:

The diagnosis of multiple sclerosis (MS) in both children and adults rests on confirmation of dissemination of inflammatory disease involving multiple areas of the CNS and recurring or progressing over time. Pediatric-onset MS follows a relapsing-remitting MS (RRMS) course at onset in over 97% of such patients, and thus the present lecture will focus entirely on pediatric RRMS. Primary progressive MS is exceptionally rare in children and adolescents - progressive neurological dysfunction in a pediatric patient should prompt consideration of a metabolic, structural, malignant or other process.

Confirming a diagnosis of MS requires a sentinel clinical attack consistent with CNS demyelination, followed by clinical and/or MRI evidence indicative of dissemination in time. MRI features play a key role in the current diagnostic criteria for MS. The diagnosis of MS can be conferred at the time of a first attack, provided that specific MRI features are present, and predicated on exclusion of other disorders. MRI findings suggestive of non-demyelinating diseases will also be illustrated.

MRI also provides a window into MS pathobiology. Focal MS plaques appear as regional areas of T2 hyperintensity, while more chronic lesions evolve into T1 hypointense “black holes”. The volume of T2 and T1 lesions can be quantified and provide a metric of disease severity-
although such volumes are not powerfully associated with clinical outcomes. Perhaps more informative in terms of imaging-clinical correlations are whole brain and regional brain volumes. Considerations of volumetric analyses in pediatric patients will be discussed in detail, given the importance of considering age-expected brain growth when evaluating MS impact in childhood.

More advanced MR techniques are now also being applied in pediatric MS cohorts. Diffusion tensor imaging (DTI) evaluates the integrity of white matter trajectories, with marked abnormalities noted in pediatric MS patients relative to healthy youth. Functional MRI interrogates both resting-state and task-based neural networks. While research in this areas is very limited in pediatric MS to date, early findings demonstrate an impact of MS on developing networks- a major concern for future cognitive function.

While the majority of neuroimaging studies in pediatric MS have utilized MRI, it is important to note the contribution of optical coherence tomography (OCT) as a tool to evaluate anterior visual pathway integrity. Whether OCT findings also provide insight into the more global degenerative processes occurring in MS remains to be determined.

**MRI Features of Pediatric MS**

The distribution of lesions in the brain and spinal cord of pediatric MS patients is very similar to that reported in adult-onset disease. This fundamental similarity led to inclusion of pediatric patients in the recent 2010 McDonald diagnostic criteria. Specifically, dissemination in space (DIS) requires evidence of 1 or more clinically-silent lesions involving at least 2 out of 4 typical
white matter (WM) locations: juxtacortical, periventricular, infra-tentorial and spinal cord. In patients presenting with a spinal cord or brainstem syndrome, these symptomatic lesions do not count towards the lesion count. Dissemination in time (DIT) requires that at least one of the clinically-silent lesions enhances followed administration of gadolinium, and that at least one other lesion does not enhance. When these features are present on an MRI obtained at the time of a first demyelinating attack, the diagnosis of MS can be made immediately.

Special considerations for pediatric patients include the following: (1) if the clinical presentation meets criteria for a diagnosis of acute disseminated encephalomyelitis (ADEM: a polyfocal clinical attack with encephalopathy), then an MS diagnosis requires at least one non-ADEM attacks with further MRI evidence of accrual of new MRI lesions over time, or two clinical non-ADEM attacks; and (2) application of the 2010 criteria should be considered cautiously in children less than 11 years of age given that the positive predictive value of the 2010 criteria in these young patients is only about 60%. In other words, approximately 40% of young patients may be “2010 positive” at onset, yet fail to experience further attacks of new MRI lesions over time (at least for the next 5 years, as evaluated in prospective studies). It is advised that the diagnosis of MS in very young children be based on two or more attacks, or at least by one attack and MRI evidence of accrual of clinically silent lesions on serial imaging. It is also noteworthy, that younger pediatric MS patients tend to have larger, poorly-demarcated T2 bright lesions that may disappear on serial imaging. Serial imaging in these patients ultimately reveals the discrete focal lesion patterns more consistent with adult-onset MS.

**MRI as a tool to identify disorders in the differential of pediatric MS**
The imaging features of demyelinating diseases to consider in the differential of pediatric MS will be illustrated during the presentation. ADEM is characterized by large, poorly defined areas of T2 hyperintensity in the brain and in the spinal cord, that often resolve rapidly following administration of corticosteroids. The imaging features of neuromyelitis optica spectrum disorders (NMOSD) classically involve longitudinally extensive spinal cord lesions (spanning more than 3 spinal segments), bilateral optic nerve involvement (initially optic nerve T2 bright lesions, followed by optic atrophy), and brain lesions involving the diencephalon. An ADEM-like picture can also occur in young patients with NMOSD.

MRI is also invaluable in identifying children with inherited white matter disorders, malignancies, infection, and metabolic disease. Several reviews have been written on this subject and are included in the Suggested Reading section. Summary tables will be provided in the slides presented.

**MRI as a window into MS pathobiology**

Quantitative analyses, which require research-quality images, can compute the total T2 and T1 lesion volumes, as well as evaluate changes in these volumes over time. Pediatric MS patients have been shown to have comparable lesion volumes to those measured in adults with MS, when matched for disease duration. Thus, the young age of pediatric MS patients does not appear to protect them from accrual of focal MS pathology. Examples of such studies will be illustrated during the talk.
Quantitative MRI can also determine whole brain as well as regional brain volumes. In order to determine the impact of MS on brain volume, as well as on brain changes over time, it is necessary to have well-established research quality normative serial MRI datasets. The National Institutes of Health normative healthy cohort has provided valuable normative data on 1.5T MRI, and new normative datasets on 3T MRI are becoming available.

Pediatric MS patients have reduced brain volumes, and particularly reduced thalamic volumes, as compared to age- and sex-matched youth. When measured serially, pediatric MS patients fail to demonstrate age-expected brain growth, and by mid-adolescence, demonstrate brain atrophy. These worrisome features will be illustrated during the presentation.

**Advanced MRI Techniques in Pediatric MS**

DTI studies provide interrogation of the structural integrity of white matter pathways, as determined by water diffusion. Intact, stringently oriented pathways limit water diffusion, measures as a high fractional anisotropy (FA, maximum 1). Pure water has an FA value of 0. Mean diffusivity (MD) is more sensitive to myelin integrity. Regional white matter, and the corpus callosum in particular, in pediatric MS patients have reduced FA and increased MD, as compared to healthy white matter.

Functional MRI, in which the brain oxygenation signal is utilized to determine connectivity between cerebral regions. FMRI can be used to evaluate “resting-state”, evaluating the connections activated when individuals are instructed to relax and not think about specific tasks. While the physiological relevance of these resting state networks, such as the default
mode and salience networks, are still be defined, disruption of these normative patterns of connectivity have been recently demonstrated in pediatric MS patients. Task-based FMRI analyses also show differences in the extent of activation required to perform such tasks in pediatric MS patients. While still very preliminary, these findings raise the possibility that compensatory “over-activation” may be required in order to maintain expected task performance early in pediatric-onset disease.

**Optical Coherence Tomography (OCT)**

OCT is an ultrasound method that quantifies the retinal nerve fiber layer (RNFL), ganglion cell layer (GCL) and can thus inform on non-myelinated MS-related insult. OCT studies in both pediatric and adult MS have clearly illustrated a robust relationship between clinical optic neuritis and OCT measures of reduced RNFL and GCL thickness. Maximal reductions appear to occur by 6 months post an acute optic neuritis episode. OCT has also been informative of optic nerve involvement in patients with MS who did not have clinical optic neuritis. It has also been suggested that OCT may correlate with more global measures of tissue loss, and as such might serve as tool to interrogate the degenerative aspects of MS. To date, OCT studies in pediatric MS patients have most robustly demonstrated the relationship between loss of RNFL and GCL thickness of clinical optic neuritis. The relationship between OCT and volumetric MRI is an area of active investigation.

**Summary:**
The role of MRI and OCT in pediatric MS diagnosis, monitoring, and as measures of
pathobiology will be discussed and illustrated. The quality of images acquired is essential for
maximal interpretation, and the importance of consistent imaging protocols will be
emphasized. The potential for MRI to serve as a key measure of response to disease-modifying
therapies will be briefly presented- a very active point of discussion given the emerging clinical
trials in pediatric MS.

Suggested Readings:

Polman CH, Reingold SC, Banwell B et al. Diagnostic criteria for multiple sclerosis: 2010 revisions

Waubant E, Chabas D, Okuda DT et al. Difference in disease burden and activity in pediatric

Yeh EA, Weinstock-Guttman B, Ramanathan M et al. Magnetic resonance imaging

Banwell B, Shroff M, Ness J et al. MRI features of pediatric multiple sclerosis. *Neurology*

Chabas D, Castillo-Trivino T, Mowry EM, Strober JB, Glenn OA, Waubant E. Vanishing MS T2-

Verhey LH, Signori A, Arnold DL et al. Clinical and MRI activity as determinants of sample size

Hummel HM, Bruck W, Dreha-Kulaczewski S, Gartner J, Wuerfel J. Pediatric onset multiple
sclerosis: McDonald criteria 2010 and the contribution of spinal cord MRI. *Mult Scler*

Sadaka Y, Verhey LH, Shroff MM et al. 2010 McDonald criteria for diagnosing pediatric multiple


Genes and environment in pediatric MS

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Introduction

Research performed in the last two decades indicates that it is highly unlikely that there is a single cause for multiple sclerosis. It is a complex disease. Its origin lies in the complex interplay between genes, genes and environment, epigenetics and probably stochastic events at the level of epigenetic modifications. We have now only begun to unravel what are the players in the process that leads to this inflammatory and neurodegenerative ailment of brain and spinal cord. The factors that have been identified have in common that they link to the immune system. Most appear not specific to MS, because they are involved in several other inflammatory-autoimmune diseases.

A few percent of the MS population worldwide starts with the disease at childhood age (below age 18). This may be seen as a mere extreme part of a Gaussian curve, but the alternative is more interesting. Perhaps factors that play a causal role in the disease per se, are more prominent in individuals that develop the disease when still young. The identification of important environmental factors has practical relevance as this may yield novel strategies for prevention of the disease. Up to now no specific factors have been identified that specifically influence the risk of pediatric onset MS (and not of adult onset). Most of the knowledge here stems from studies on adult onset MS. Another important field for the future will be the identification of environmental and genetic factors that influence the course of the disease. Very little on that can be covered in this teaching course, because of current lack of knowledge.

Epidemiological risk factors

Residential area

The direct environment appears relevant, as 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. These
observations cannot be seen as prove, as most of these studies have not corrected for the fact that in many areas childbirth numbers are relatively higher amongst non-Europeans. Possible environmental factors involved here are unknown, but there are of course numerous candidates, not only at the level of the children themselves but also at the level of the mothers during childbearing periods.

**Genes**

As stated above, our knowledge about genetic risk factors for MS is derived from studies in adults. Genetic studies in MS have been stimulated by the observed increased familial occurrence in adult MS. MS in children is relatively rare. Therefore specific studies in childhood onset MS are scarce. In many diseases an onset at childhood age appears related to a higher genetic risk burden. This may not be the case for a complex disease as MS because MS occurs rarely in another person in a family with a childhood-onset case and this may be even rarer than observed for adult MS. But there may be alternative mechanisms involved. Other possibilities that could account for childhood onset of the disease are environmental and/or epigenetic factors, and most likely gene-gene and gene-environment interactions.

Classically, known since the seventies, MS is firmly associated with HLA alleles. Most of the newly identified non-HLA risk genes are related to immune function and many of their gene products are likely to interact with endogenous or exogenous infections, and some of them with vitamin D.

The frequency of these novel risk alleles (that have been identified in adult MS) in the specific subgroup of patients with pediatric onset MS needs to be investigated in depth. However, a first study on the overall genetic risk score of a set of 57 of these novel MS risk genes revealed comparable compound risk scores in between adults and children. Both childhood- and adult-onset MS groups had significantly higher scores than population based controls and the overall genetic risk scores clearly differed from children with monophasic acquired demyelinating syndromes. Also several studies have shown a significant skew to HLA DRB1*1501 in pediatric MS patients versus healthy controls or individuals with monophasic acquired demyelinating syndrome.
These studies were conducted in children with Western European ancestry. Of course these results remain to be replicated in other ethnicities, and novel studies can include now a set of about a total of 200 newly identified MS risk genes.

**Environmental risk factors**

**Vitamin D**

Virtually all studies in adults have shown lower vit D levels in MS compared with control groups. However, having the disease may negatively influence per se, for example because of less sunlight exposure or differences in metabolism.

Therefore it seems more relevant to measure vit D levels in patients at the time of a first attack. This may better approach the true pre-onset level within the individual.

Such studies have been performed. Circulating 25(OH)D levels at onset of acquired demyelinating syndromes (ADS) were inversely associated with the likelihood of MS among Canadian children with a first demyelinating CNS event. This suggests a protective role of vitamin D against risk of pediatric MS.

**Sunlight**

Sun exposure and vitamin D status may have independent roles in the risk of CNS demyelination. Sunlight seems to lower the risk for MS, but this has not been investigated in children sufficiently.

**EBV**

Findings that link EBV to MS pathogenesis come from epidemiological studies. It has been known for long that in adults the risk for MS is higher in individuals that had clinically manifest mononucleosis and serological studies demonstrated that virtually all MS patients are EBV seropositive, this against 90% in controls. Moreover, cohort studies showed higher levels of IgG’s against EBV proteins in patients that developed MS over the years compared with individuals that remained healthy.
In a case-control study conducted on 189 early pediatric MS subjects and 66 pediatric controls, EBV nuclear antigen-1 seropositivity was significantly associated with an increased risk for MS (odds ratio 3.8).

**Cigarette Smoking**

Parental smoking was found to be significantly associated to pediatric MS onset (RR=2.12; 95% CI: 1.43-3.15) in a population-based case-control study conducted on 129 MS cases from the French KIDSEP pediatric cohort, and 1038 controls. 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.

**Salt**

It has been suggested that high dietary salt intake might represent an environmental risk factor for the development of MS through the induction of pathogenic TH17 cells. This suggestion is receiving considerable attention in both adults and pediatric studies.

**Risk periods**

There is a clear difference in gender ratio between pre-pubertal and post-pubertal onset of MS. This has given an impulse to further studies on the role of puberty and menarche in the risk of pediatric MS. The National Canadian Pediatric Demyelinating Disease Study investigated the relationship between age of menarche on MS outcome in 116 female children with acquired demyelinating syndromes (ADS) and younger than 16 years. Later age of menarche was significantly associated with a decreased risk of conversion to MS [Hazard Ratio (HR)=0.67]. Whether this is a direct effect of puberty on MS or whether there are confounders remains unknown at this stage. In any case, this phenomenon may be related to the same lifestyle factors that led to the female increase in MS worldwide.
**Obesity**

A case-control study in pediatric MS cases and demographically matched controls, indicated that obesity is associated with increased risk of later MS/CIS. This was found in girls but not in boys.

This may not be a direct effect of obesity as in childhood and adolescence overweight is associated with lower 25(OH)D levels. In addition vitamin D deficiency appears related to younger age at menarche.

The interrelation of factors such as menarche, vitamin D levels and obesity illustrates how difficult it is to unravel real causal factors in a complex disease such as MS.

Another, novel observation has been on physical activity. Children with MS are less physically active than children with mono-ADS. This may be related to ongoing disease activity, perceived limitations, or symptoms such as depression or fatigue. Children with higher physical activity had lower MRI T2 lesion volumes and lower relapse rates. Whether this association is causal remains to be determined.

**Gene-gene and gene-environment interactions in pediatric MS susceptibility**

The phenomenon of gene-gene or gene-environment interactions could prove an enormous contribution to MS risk. Most currently identified factors have relatively small effects, but in a synergistic way OR's of these genetic and environmental factors may jump. Statistical analyses on this are quite difficult to perform as large numbers are needed and most of the (pediatric) MS studies have not been large enough to be adequately powered to examine interaction. Still, a few types of interactions have been demonstrated, for example between the major MS risk allel HLA-DRB1*15 and serum antibodies against EBV, against HSV, and between this risk allele and exposure to another infant (sibling).

**Epigenetics**

For MS as well as for several other autoimmune conditions, the evidence of gene-environment interaction is indirect. Epigenetic modifications are the most likely route
via which environment affects disease susceptibility. Epigenetic studies focus on the chemical modification of DNA, for example DNA methylation, that has the capacity to alter gene transcription and thus cell function. Epigenetic studies in MS have only recently taken off, but much has to be expected in the future.

**Conclusions**

A revolution in genetics led to the identification of around 200 genetic loci that are associated with the risk for MS in adults. Most of them relate to cellular immunological functions, such as viral eradication. Some relate to vitamin D metabolism. It remains to be determined whether these are also involved in the risk for pediatric onset MS.

The environmental risk factors identified in pediatric MS have all overlapping effects in adult MS. The most prominent currently know are EBV infection, low vitamin D, low sunlight, smoking. Perhaps not independent of these are the higher risks constituted by early menarche and/or obesity. The study of risk factors in children may yield important information about the causes of MS in general, because of the child’s proximity in time to environmental exposures and the possibility of a higher susceptibility burden. Studies on gene-gene and gene-environment interaction, as well on epigenetic modifications are still in its infancy.

**References**


