

# **Pediatric MS and other demyelinating disorders in childhood**

Current understanding,  
diagnosis and management



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## Contributors

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## Pediatric MS and other demyelinating disorders in childhood:

### Current understanding, diagnosis and management

The understanding of multiple sclerosis (MS) and other demyelinating disorders in childhood has advanced considerably in the last ten years.

This publication accompanies a series of articles written by subject experts that highlight the advances, unanswered questions and new challenges in understanding, diagnosis and management.

It provides a short summary of the key points from each article, and a list of resources and further reading where you can find links to the full articles, all of which are available open access (free).



#### Childhood MS

A guide for parents



You may also be interested in a publication called *Childhood MS: A guide for parents*. This free resource aims to help you to understand more about the care a child should receive, and the kind of support parents and families are entitled to in order to manage the changes MS can bring. [www.msif.org/about-ms/childhood-ms/](http://www.msif.org/about-ms/childhood-ms/)

## Pediatric MS from the perspective of both the child and the family

Multiple sclerosis (MS) in children presents many complications and considerations from both the child and the family perspective. Like other chronic illnesses, MS can affect young people's growth and development, their appearance, identity, cognition, emotional well-being, engagement with education and employment, as well as their relationships with peers and family.

Given the potential for isolation, a priority should be facilitating connections with other children and their families to share experiences. Support at the time of diagnosis and throughout management can facilitate a successful transition to adult care.

Care through an interdisciplinary specialised centre and ongoing clinician support can help both the child and parent as they navigate the diagnosis.

Further involvement of children with MS and their families in scientific efforts with the clinical and research community will help pave the way to a brighter future.

**Netherlands: Pieter was diagnosed with MS when he was 13.**



## Biological reasons why children develop MS

Children who develop multiple sclerosis (MS) seem to share the same genetic and environmental risk factors that have been found to contribute to the risk of adults developing MS. This suggests that MS in children is, in general, the same condition as MS in adults.

The normal immune system has several main jobs, including fighting infections, preventing development of tumours, and providing help during tissue repair. To accomplish its multiple jobs, the immune system is made up of different types of white blood cells (such as T cells, B cells and others) that communicate with each other and release various substances (such as cytokines, antibodies etc.) that influence neighbouring cells.

In order for the normal immune system to do its jobs properly, it must be able to recognise anything that is strange or foreign, as opposed to part of one's own body ('self'). In some people, this ability is impaired. For reasons that are not entirely clear, the immune system in these individuals mistakenly attacks self, resulting in an 'autoimmune' condition. For example, when the autoimmune condition attacks the joints, the person can get arthritis, if the cells that make insulin are attacked, the person can get type 1 diabetes, and if the attack is against the central nervous system (CNS), the person can get MS or a related condition.

While many questions remain, our simple understanding of how MS attacks occur in adults is that immune cells (such as particular types of white blood cells called T cells) get inappropriately activated outside of the CNS, then make their way into the CNS. This results in local inflammation (activated immune cells releasing various substances) that

can injure the cells of the CNS (the oligodendrocytes which make myelin, and the fibres (axons) that the myelin covers). The current thinking is that a similar sequence of immune events occurs in children with MS.

There are, however, some very important differences to consider when it comes to children developing MS or related disorders. One difference is that the immune system and CNS in children are still developing. With this in mind, the strength and pattern of immune attacks in young people, the recovery potential of the injured CNS, and the benefits and risks of emerging treatments are all among the important questions that need to be answered.

## Genetic and environmental risk factors for pediatric MS

The onset of multiple sclerosis (MS) occurs in childhood in up to 10% of all people with MS. The disease in adults appears to result from a complex interaction of genetic and environmental factors. One of the main genetic risk factors, also confirmed in pediatric MS, is HLA DRB1\*1501. This is one common gene variation among a group of genes that play an important role in immune responses, called HLA – human leukocyte antigen. HLA genes in essence place flags on a person's individual cells, and those flags help the immune system distinguish between the body's own cells and those of a foreign invader, such as bacteria or viruses.

In addition to genetic factors, environmental factors such as low vitamin D levels, exposure to cigarette smoke and remote Epstein-Barr virus (EBV) infection significantly contribute to a person's risk of MS.

In children, both exposure to cigarette smoke and prior EBV infection have consistently been reported as risk factors for MS. To date, the role of vitamin D has not been confirmed in this age category.

Some of the risk factors for MS have also been shown to affect the disease course, such as low 25(OH) vitamin D serum levels in pediatric and adult MS. Age also modifies the ways MS appears clinically, in the cerebrospinal fluid (CSF) and on magnetic resonance imaging (MRI) in children.

Future studies will have to clarify whether interventions such as vitamin D supplementation can modify pediatric and adult MS susceptibility and disease course.

Netherlands: Mireille was 12 years old when she was diagnosed with MS.

## Clinical features and outcome

Multiple sclerosis (MS) in children follows a relapsing remitting MS (RRMS) disease course. Acute relapses consist of new neurological deficits (problems with nerve, spinal cord, or brain function, e.g. loss of balance, weakness of the arms or legs etc.) that last longer than 24 hours, when no other illness or fever is present.

Early relapses are more frequent in pediatric MS than in adults with MS. Most children with MS recover well from these early relapses, and cumulative physical disability is rare in the first 10 years of disease.

Attacks accompanied by lesions in the brain-stem, poor recovery from an attack, and a higher frequency of attacks point to a greater likelihood of future disability.

Although there are groups of children with MS who are being studied over time, very limited data are available to demonstrate the clinical outcome of pediatric-onset MS in adulthood. Whether the availability of MS therapies, and the largely off-label (unapproved) use of these therapies in pediatric MS have improved prognosis is unknown.

The need for standardised, validated and robust outcome measures is highlighted by the increasing recognition of pediatric MS worldwide, the recent launch of Phase III trials for new treatments for pediatric MS, and the urgency to achieve a better understanding of the impact of pediatric MS on health-related quality of life into adulthood.



## Cognition and mood

Cognitive functioning and mood related difficulties are common in pediatric multiple sclerosis (MS). Defects in memory, complex attention and processing speed and, sometimes, language, are found in nearly 30% of children with MS. Mood disturbance, in particular depressive symptoms and behavioural problems, can be associated with cognitive difficulties and are also increasingly recognised in children with MS.

As in adults with MS, cognitive problems can be detected from the early stages of the disease – unrelated to the level of physical disability – and can have a negative impact on lifestyle, current and future school achievements, and quality of life.

The search for effective treatment approaches, particularly through cognitive rehabilitation that could enhance brain plasticity in these young children, should be a key focus in this area of research.

## MRI features

The ability to obtain high quality images of the brain using magnetic resonance imaging (MRI) has dramatically improved the ability to diagnose multiple sclerosis (MS) in both children and adults.

MRI studies have shown that children with MS have as many, if not more, MS lesions compared with adults. MS also has an impact on normal brain growth during childhood and disrupts normal brain pathways – which explains why some children and teens with MS have difficulty with learning and other cognitive tasks.

The ability of MRI to guide treatment is an active area of research, and MRI studies are a key component of clinical trials of new MS therapies.

**Netherlands: Mikki was four years old when she was diagnosed with MS.**



## Conventional first-line treatment and general management

No medication currently approved for adults with relapsing-remitting multiple sclerosis (MS) has completed testing for pediatric MS, although several pediatric MS trials have recently been launched. Therefore, the use of disease modifying treatments (DMTs) in pediatric MS remains off-label (unapproved) in the large majority of countries, especially for children under 12 years of age.

However, clinicians need to treat children with MS in order to prevent relapses, protect the brain from new demyelinating lesions and irreversible damage, and delay the accumulation of disability – particularly since children have a higher relapse rate than adults and more significant inflammation on MRI. Also, experience in adult-onset MS suggests that DMTs are more effective if administered early in the relapsing disease course.

The current view is to classify DMTs as first- or second-line treatment, according to regulatory rules in each country. Several phase 4 observational studies have evaluated the safety and effectiveness of interferon beta (IFNB) and Glatiramer acetate (GA) in pediatric MS, whereas comparable information is not currently available for teriflunomide, dimethyl fumarate or fingolimod, which should be used in children only within controlled clinical trials or with extreme caution in selected cases.

**Interferon beta (IFNB):** From the observational studies that have been done in children, the general conclusion is that IFNB is effective in reducing relapse rates in the majority, though about 30% of children with MS do not respond as expected and require more aggressive treatments.

Brazil: Beatriz experienced her first symptoms of MS while at school, when she was 13 years old.



The most common side effects include flu-like symptoms, muscle aches, headache, injection-site reactions, elevation of liver enzymes and blood cell abnormalities. With the limited information that is available, there is no indication that IFNB negatively affects body development in children.

**Glatiramer acetate (GA):** The clinical outcomes in two small pediatric studies were positive and no major adverse events were recorded. Some studies have included children under the age of 10 - 12 years, for whom the results and side effects were similar to those seen in older people.

The consensus among pediatric MS experts is that IFNB and GA should be considered standard of care for all children with MS and that treatment should be started early to prevent relapses, accumulation of disability and accumulation of brain damage. Regular follow-up is also recommended to:

- Assess clinical response with regular clinical evaluations and brain MRI
- Check the tolerability/safety
- Assess blood cell count, liver function, thyroid and kidney function

Although these treatments are administered by intramuscular (directly into a muscle) or subcutaneous (under the skin) injections, they are well-tolerated by most people, and continue to have a generally favourable safety profile. The use of acetaminophen or ibuprofen before an IFNB injection or when flu-like symptoms occur can reduce their frequency and severity.

Some rare but significant side effects have recently been reported after long term use of IFNB by adults. Careful monitoring helps to ensure that these kinds of rare adverse events are discovered promptly, which is particularly important in children who are being exposed to medications during key periods of growth and body development.

Education for children and their parents at the beginning of treatment is important for setting realistic expectations for the treatment and for providing training on injection technique and strategies to manage side effects. Switching treatment if there is an inadequate or suboptimal response should be considered.



## Escalation and emerging treatments

Over the past 20 years, there has been significant progress in treatments for multiple sclerosis (MS). Regulatory bodies in many countries have approved approximately 13 treatments for use in adults. For children there is only limited approval for use of beta-interferons and glatiramer acetate in children 12 years of age and older by the European regulatory agency (EMA).

Availability of disease-modifying therapies (DMTs) for children and adolescents with MS varies by region, and in some regions of the world is extremely limited. Up to 30% of children taking a beta-interferon medication or glatiramer acetate experience new disease activity (breakthrough disease) and require therapies beyond the traditional first-line treatments.

Recent legislation in both the U.S. and Europe means that new treatments that might be used in children must be evaluated in clinical studies that include children. Therefore, several clinical trials in children are underway that will provide important information regarding the effectiveness and safety of newer drugs.

The current thinking about the management of breakthrough disease involves two approaches; the escalation approach (starting with beta-interferon or glatiramer acetate and switching to different and/or more powerful medications as needed); and the induction approach (using a very aggressive approach at the outset in an effort to control very active disease) in children with MS.

## Defining MS in childhood and differentiating it from mimics

In 2012, the International Pediatric Multiple Sclerosis Group Study Group (IPMSSG) published definitions for pediatric multiple sclerosis (MS) and related disorders. These definitions have been used and evaluated in large groups of children around the world, and have led to earlier diagnoses and more rapid initiation of treatment.

However, the existence of a number of diseases that can mimic an acute inflammatory demyelinating event - including other inflammatory disorders of the white matter, primary tumours in the CNS and neurometabolic diseases (disorders resulting from a lack or dysfunction of an enzyme that affects the development or functioning of the nervous system) - can make the diagnosis of pediatric inflammatory demyelinating disorders very challenging. Physicians need to be aware of these mimics in order to arrive at the correct diagnosis and treatment recommendations.

**Argentina: Serena (centre) was 13 years old when she was diagnosed with MS.**



## Acute disseminated encephalomyelitis (ADEM)

Acute disseminated encephalomyelitis (ADEM) and multiple sclerosis (MS) are currently viewed as different conditions that are distinguishable from one another, most often at the onset of initial symptoms.

Most children with ADEM will only have a single episode, followed by a good recovery. Less frequently, children with ADEM may experience relapses and subsequently be diagnosed with other immune-mediated disorders of the central nervous system (CNS). One such disorder, which has been described recently, is ADEM followed by an episode of optic neuritis. This disorder is referred to as ADEM-ON.

New biomarkers (measurable indicators), including production of antibodies that bind to myelin proteins, are currently being explored in an effort to improve the accuracy of diagnosis and prediction of likely outcomes.

## Acute transverse myelitis (ATM)

Childhood acute transverse myelitis (ATM) occurs when the immune system targets the spinal cord. ATM is a rare but potentially devastating condition with varying possible outcomes. Weakness or paralysis of the legs and/or arms, incontinence and constipation, and loss of sensation usually develop over several hours, and can progress to a severely disabling state.

ATM needs to be distinguished from other, rarer spinal cord disorders. ATM may also be an early sign of chronic diseases such as neuromyelitis optica (NMO) or multiple sclerosis (MS). The criteria for diagnosing ATM are generally relevant for children, but some modifications may be necessary in young children.

In ATM, MRI lesions tend to affect a large segment of the spinal cord. MRI lesions of the brain that do not cause symptoms are seen in more than one-third of children with ATM and predict MS or NMO. Children generally have a better outcome than adults, with 50% making a complete recovery within two years.

There are no robust controlled trials in children or adults to inform optimal treatment of ATM, with one study to date currently open to recruitment.



France: An information day for children with MS and their families.

## Optic neuritis

Optic neuritis is a condition in which swelling and inflammation of the optic nerve leads to decreased vision, including worsening of visual acuity (clarity of vision), colour vision, and field of vision.

Approximately one-third of children with demyelinating disorders of the central nervous system (CNS) may experience optic neuritis as a first symptom. In most cases, vision will return to almost normal, but subtle changes, including changes in colour vision, and contrast vision may occur. These changes may accumulate over time.

As no clinical trials have been performed in pediatric optic neuritis, clinical practice currently follows this protocol in children: 30 mg/kg per day intravenous methylprednisolone, maximum 1g daily, for 3-5 days. The need for a prolonged course of oral steroids is unknown.

## Neuromyelitis optica (NMO)

Neuromyelitis optica (NMO) is a disease of the central nervous system (CNS). In NMO, immune system cells and antibodies attack and destroy myelin in the optic nerves and the spinal cord, causing optic neuritis (resulting in pain in the eye and vision loss) and transverse myelitis (causing weakness, numbness and sometimes paralysis of the arms and legs, as well as bladder and bowel problems).

Because NMO causes symptoms that are similar to those seen in multiple sclerosis (MS), it was considered until recently to be a form of MS. However, the discovery of an antibody (NMO-IgG) in the blood of individuals with NMO now makes it possible to distinguish NMO from MS.

NMO attacks are more severe than those seen in MS and in early disease are generally confined to optic nerves and the spinal cord. Other symptoms are rare, although uncontrollable vomiting and hiccups are now recognised as symptoms of NMO caused by damage in the brain-stem.

NMO is treated initially with a combination of a corticosteroid and an immunosuppressant medication. Some patients may need corticosteroid treatment for a longer period of time and may also require plasmapheresis (a technique that separates antibodies out of the blood stream). The disease-modifying treatments (DMTs) used to treat MS are not effective for NMO.

## Acquired demyelinating syndrome (ADS)

The first attack of multiple sclerosis (MS) in childhood can appear very different from one child to another. An acute (abrupt) onset of inflammatory demyelination of the central nervous system (CNS) is called acquired demyelinating syndrome (ADS). The demyelination can occur in a single location (unifocal) or in more than one location (polyfocal) in the CNS.

Approximately one third of children with ADS will be diagnosed with MS, typically within 2-4 years after ADS. The diagnosis can sometimes be made immediately based on the 2010 McDonald MS criteria (the criteria used by medical professionals to diagnose MS), or later on the basis of additional clinical or MRI evidence of relapsing disease.

The children with ADS who have the highest likelihood of MS are adolescent girls with demyelination in more than one area of the CNS.



USA: Heather was diagnosed with MS when she was 14.

## References and further reading

The articles summarised in this publication are taken from a supplement in the *Neurology* journal, published in August 2016. *Neurology* provides peer-reviewed articles aimed at physicians working with diseases and conditions of the nervous system. The supplement was written by the International Pediatric MS Study Group - a global network of adult and pediatric neurologists, scientists, and other healthcare professionals.

The references below are presented in the same order as the summaries.

### **Pediatric MS from the perspective of both the child and the family**

**Article title:** Pediatric multiple sclerosis: Perspectives from adolescents and their families

L.B. Krupp, D. Rintell, L.E. Charvet, M. Milazzo, E. Wassmer

<http://neurology.org/lookup/doi/10.1212/WNL.0000000000002879>

### **Biological reasons why children develop MS**

**Article title:** Immunopathophysiology of pediatric CNS inflammatory demyelinating disease

A. Bar-Or, R.Q. Hintzen, R.C. Dale, K. Rostasy, W. Brück, T. Chitnis

<http://neurology.org/lookup/doi/10.1212/WNL.0000000000002821>

### **Genetic and environmental risk factors for pediatric MS**

**Article title:** Environmental and genetic factors in pediatric inflammatory demyelinating diseases

E. Waubant, A.-L. Ponsonby, M. Pugliatti, H. Hanwell, E.M. Mowry, R.Q. Hintzen

<http://neurology.org/lookup/doi/10.1212/WNL.0000000000003029>

### **Clinical features and outcome**

**Article title:** Pediatric multiple sclerosis: Clinical features and outcome

A. Waldman, J. Ness, D. Pohl, I.L. Simone, B. Anlar, M.P. Amato, A. Ghezzi

<http://neurology.org/lookup/doi/10.1212/WNL.0000000000003028>

### **Cognition and mood**

**Article title:** Pediatric multiple sclerosis: Cognition and mood

M.P. Amato, L.B. Krupp, L.E. Charvet, I. Penner, C. Till

<http://neurology.org/lookup/doi/10.1212/WNL.0000000000002883>

### **MRI features**

**Article title:** MRI in the evaluation of pediatric multiple sclerosis

B. Banwell, D.L. Arnold, J.-M. Tillema, M.A. Rocca, M. Filippi, B. Weinstock-Guttman, R. Zivadinov, M.P. Sormani

<http://neurology.org/lookup/doi/10.1212/WNL.0000000000002787>

### **Conventional first-line treatment and general management**

**Article title:** Pediatric multiple sclerosis: Conventional first-line treatment and general management

A. Ghezzi, M.P. Amato, N. Makhani, T. Shreiner, J. Gärtner, S. Tenenbaum

<http://neurology.org/lookup/doi/10.1212/WNL.0000000000002823>

### **Escalation and emerging treatments**

**Article title:** Pediatric multiple sclerosis: Escalation and emerging treatments

T. Chitnis, A. Ghezzi, B. Bajer-Kornek, A. Boyko, G. Giovannoni, D. Pohl

<http://neurology.org/lookup/doi/10.1212/WNL.0000000000002884>

### **Defining MS in childhood and differentiating it from diseases that mimic MS**

**Article title:** Consensus definitions for pediatric MS and other demyelinating disorders in childhood

M. Tardieu, B. Banwell, J.S. Wolinsky, D. Pohl, L.B. Krupp

<http://neurology.org/lookup/doi/10.1212/WNL.0000000000002877>

**Article title:** Differential diagnosis and evaluation in pediatric inflammatory demyelinating disorders

K. Rostasy, B. Bajer-Kornek, S. Venkateswaran, C. Hemingway, M. Tardieu

<http://neurology.org/lookup/doi/10.1212/WNL.0000000000002878>

### **Acute disseminated encephalomyelitis (ADEM)**

**Article title:** Acute disseminated encephalomyelitis: Updates on an inflammatory CNS syndrome

D. Pohl, G. Alper, K. Van Haren, A.J. Kornberg, C.F. Lucchinetti, S. Tenembaum, A.L. Belman

<http://neurology.org/lookup/doi/10.1212/WNL.0000000000002825>

### **Acute transverse myelitis (ATM)**

**Original title:** Pediatric transverse myelitis

M. Absoud, B.M. Greenberg, M. Lim, T. Lotze, T. Thomas, K. Deiva

<http://neurology.org/lookup/doi/10.1212/WNL.0000000000002820>

### **Optic neuritis**

**Article title:** Pediatric optic neuritis

E.A. Yeh, J.S. Graves, L.A. Benson, E. Wassmer, A. Waldman

<http://neurology.org/lookup/doi/10.1212/WNL.0000000000002822>

### **Neuromyelitis optica (NMO)**

**Article title:** Neuromyelitis optica spectrum disorders in children and adolescents

S. Tenembaum, T. Chitnis, I. Nakashima, N. Collongues, A. McKeon, M. Levy, K. Rostasy

<http://neurology.org/lookup/doi/10.1212/WNL.0000000000002824>

### **Acquired demyelinating syndrome (ADS)**

**Article title:** Pediatric acquired CNS demyelinating syndromes: Features associated with multiple sclerosis

R.Q. Hintzen, R.C. Dale, R.F. Neuteboom, S. Mar, B. Banwell

<http://neurology.org/lookup/doi/10.1212/WNL.0000000000002881>



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