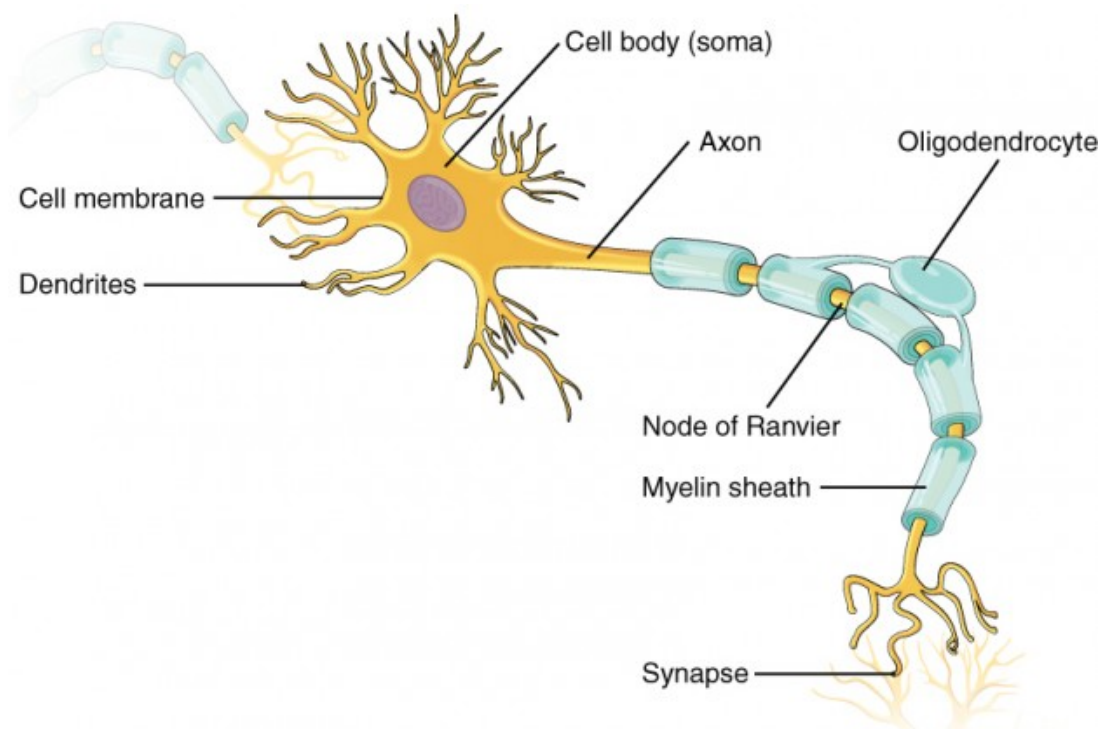


Multiple Sclerosis (MS) — Definition, Symptoms and Treatment

[See online here](#)

Multiple sclerosis (encephalitis disseminata) is a chronic inflammatory autoimmune disease of the central nervous system. Due to its wide range of symptoms, it is known as a disease with many manifestations and primarily affects younger female patients. It is not only one of the most common neurological diseases but is also frequently the topic of questions in exams due to its broad spectrum of symptoms and diagnostics.



Definition

The presence of **multiple indurations (sclerosis)** in the central nervous system (CNS) is defined as multiple sclerosis (MS). MS is a **chronic, immune-mediated progressive inflammatory CNS disease** that damages the **myelin sheath** and the nerve cells in variable degrees leading to physical disabilities.

Epidemiology

MS is the most common inflammatory disease of the brain and spinal cord. It has a frequency of approx. 1:1000 in the EU and the US.

MS is one of the **most common causes of long-term disability** in young patients, with

women being affected 2-3 times more frequently than men. It is a notable psychological burden for many previously healthy patients to be faced with an MS diagnosis. Thus, the conversation with the patient should be both empathetic and informative.

Etiological and histopathological features

The exact etiology of MS is unknown, but the disease is thought to be **multifactorial** with causative factors including:

- Genetic factors
- Environmental factors
- Auto-immunity

Genetic factors

No specific inherited gene has been identified as the cause of MS, but there are likely **polygenetic influences**. Particularly, changes in **MHC class II** can be associated with 2-4 times the risk of acquiring the disease. **Interleukin receptor polymorphism** also appears to increase the risk (Compston & Coles, 2002). For instance, the genetic component can be seen in the increased risk of the disease in children of afflicted parents. These children are 20 times more likely to be affected.

Environmental factors

The **prevalence of MS increases with distance from the Equator**. The US, Central Europe, and New Zealand have a prominently high prevalence. Given this information, the different levels of sun exposure, smoking, EBV infection, and humane herpesvirus 6 have been often discussed.

Studies of migratory patterns have revealed that migration from a low-risk area of MS to a high-risk area gave rise to an age-dependent risk adjustment; migrants under the age of 15 years exhibited a higher risk, whereas older migrants did not experience any change in their risk of acquiring MS.

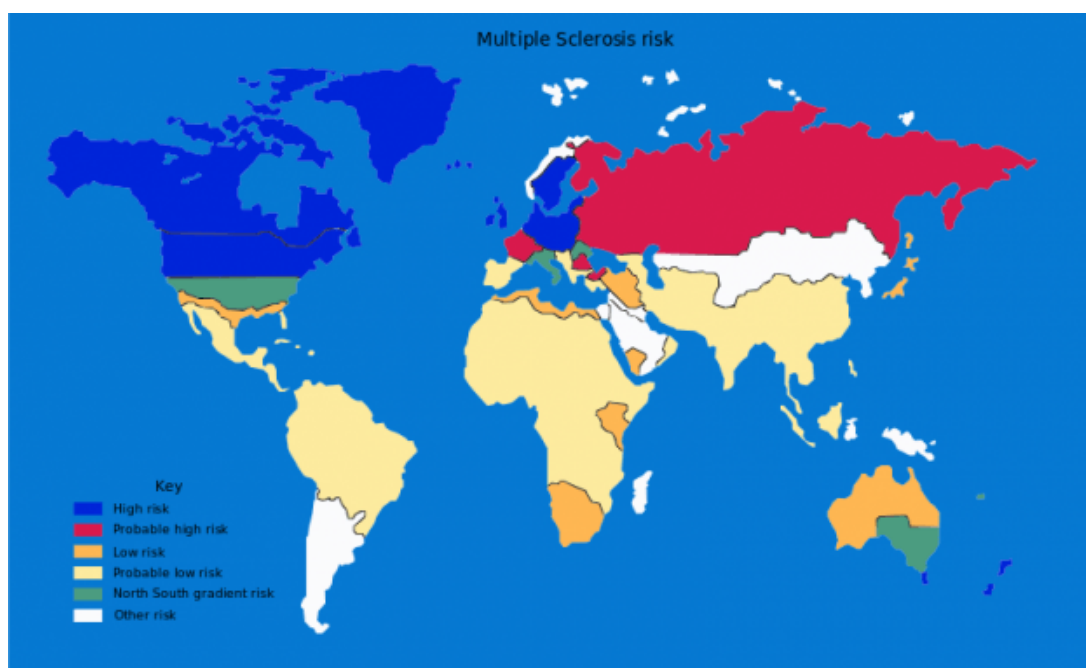


Image: Global prevalence of multiple sclerosis. By Dekoder, License: Public Domain

Auto-immune factors

With MS, the immune system attack of the body refers to a **reaction against CNS myelin antigens**. This results in a **reversible inflammatory reaction with demyelination**. If this reaction is notable, the neuronal system experiences **axonal damage** with the subsequent irreversible damage of nerve fibers.

At the functional level, the demyelinated nerves already begin losing the ability to effectively transmit action potentials, and the transmission of information is slowed. The periventricular white matter, **optic nerve**, **brain stem**, **cerebellar peduncles**, **corpus callosum**, and **myelon** are the most important predilection sites for these so-called demyelination lesions.

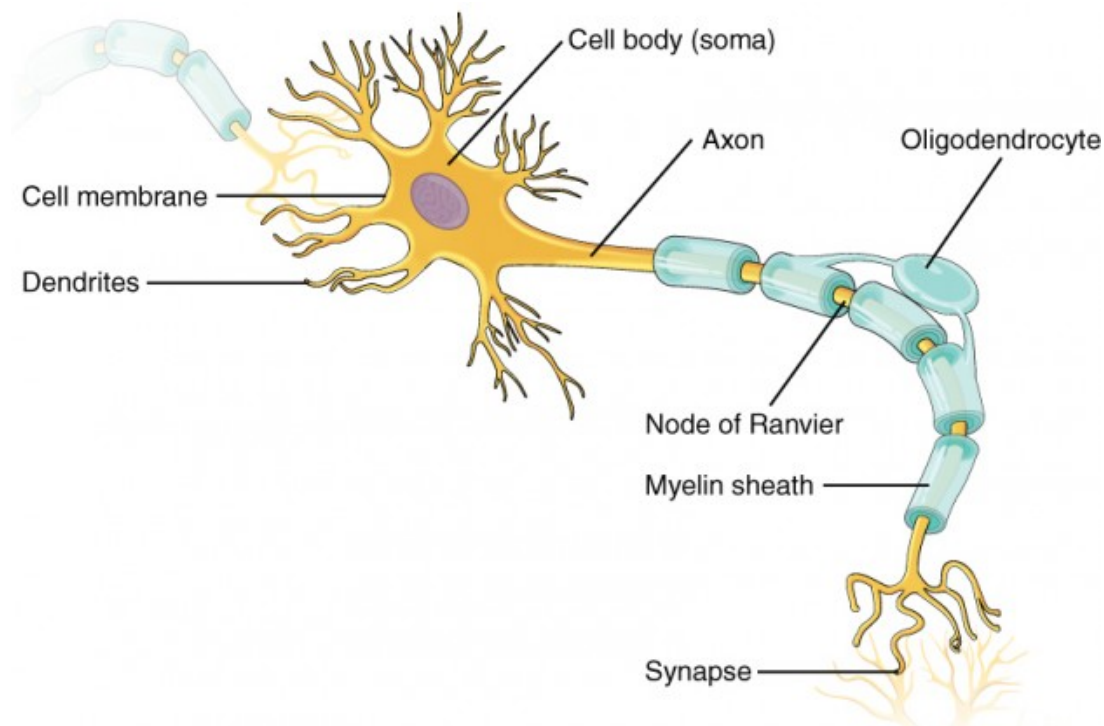


Image: Parts of a Neuron. By PhilSchatz, License: [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/)

Clinical Course and Symptoms

The clinical manifestations of MS can be distinguished into acute exacerbations as against the basic clinical course. These 2 components provide a full picture of the disease. The management of an acute exacerbation differs from the **prophylactic long-term treatment** oriented toward the overall clinical course.

Main symptoms of Multiple sclerosis

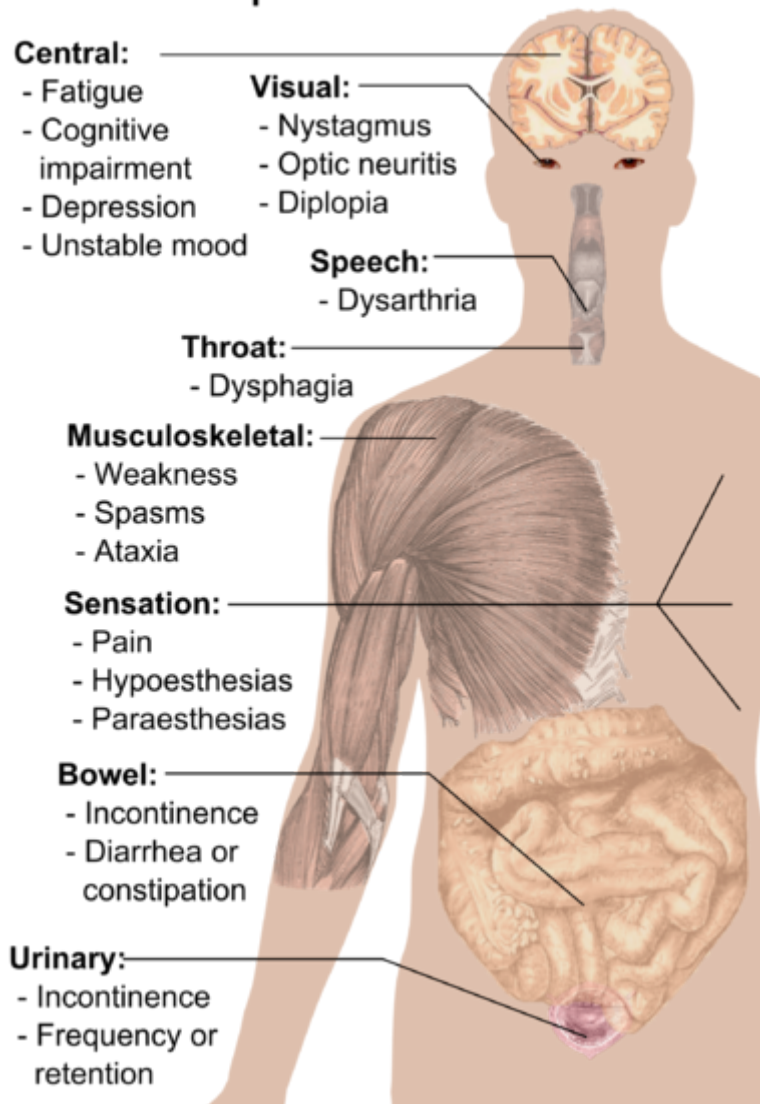


Image: Main symptoms of multiple sclerosis. By Mikael Häggström, License: Public Domain

Definition of an acute exacerbation of multiple sclerosis

Transient dysfunction lasting for at least 24 hours and which cannot be explained by fever or infections is considered an inflammatory exacerbation. Various neuronal qualities may be disrupted. This often results in:

- **Sensory disturbances** with dysesthesia, hypoesthesia, or neuralgiform pains. Along with tingling paresthesia. The Lhermitte sign (triggering of rapid downward paresthesia along the spine and/or extremities due to passive forward-leaning of the neck) is often positive.
- **Motor abnormalities** with (spastic) paresis and disrupted fine motor skills. This leads to positive pyramidal signs, a lack of abdominal skin reflexes with increased muscular reflexes, and clonuses.
- **Inflammation of the optic nerve** (retrobulbar neuritis, optic neuritis) with hazy vision, central scotoma, and painless loss of vision for hours or days, and pain when moving the bulb. **Double vision, internuclear ophthalmoplegia,**

or mononuclear vision impairment typically manifest.

- **Vegetative functional disorders** with urge incontinence, residual urine buildup, and sexual dysfunction.
- **Brain stem symptoms** like vertigo, impaired walking, loss of balance or coordination, and dysarthria.
- **Charcot's triad** with scanning speech, volitional tremor, and nystagmus as an expression of an inflammatory reaction around the cerebellum and cerebellar peduncles.

As the inflammatory reaction can fundamentally affect the entire CNS, the symptoms of MS are accordingly manifold. The so-called **pseudo-manifestations** must be separated from the true ones. These are neurological disorders stemming from infections, fever, physical strain, hot baths, or saunas, and are regarded as Uhthoff's phenomenon.

Clinical course

There are different clinical courses of MS. These courses vary greatly in terms of the **distribution and severity of the symptoms**, which makes MS a very heterogeneous disease. The level of impairment is determined by the **Expanded disability status scale** (EDSS).

The first, or non-recurring, inflammatory manifestation is called a **clinically isolated syndrome**.

Relapsing-remitting MS is initially present in 70–80% of all patients. This means that the neurological symptoms arise relatively suddenly and then recede.

In 50% of these patients, this is followed by conversion to a **secondary progressive course**, in which progressive deterioration of the symptoms occurs and manifestations are no longer clearly recognizable.

About 15% of all patients experience a **primary progressive course** from the onset. This group of patients is generally somewhat older without frequency by sex. It should be noted that this manifestation is notably difficult to treat.

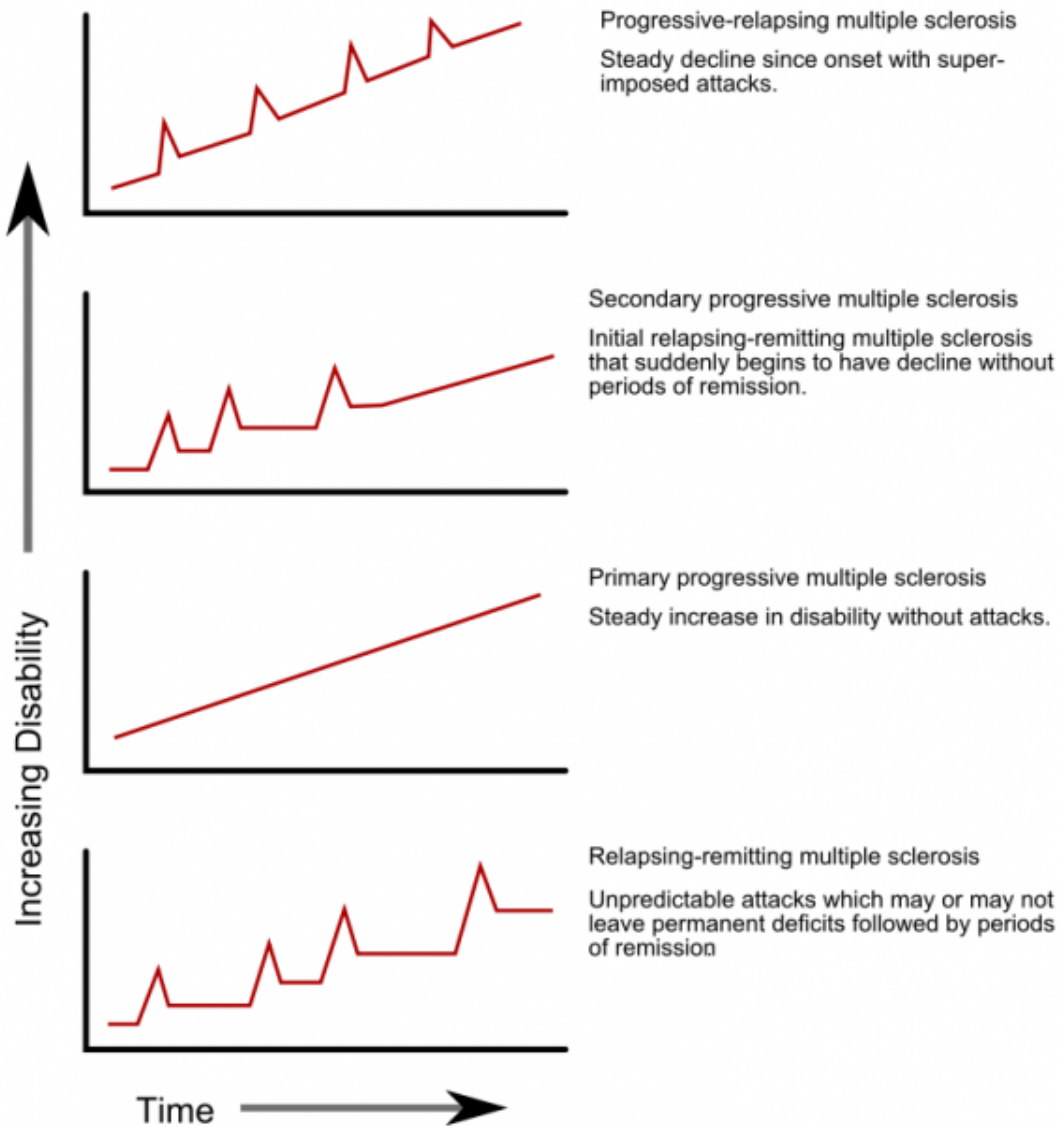


Image: Progression types of multiple sclerosis. By Faigl.ladislav, License: Public Domain

Diagnosis

Diagnosing MS is based on patient history and clinical examination, **imaging** of the entire CNS, **fluid diagnostics**, and **electrophysiological performance diagnostics**. History of past symptoms is crucial.

As MS can fundamentally affect every structure of the CNS, extensive diagnostics are necessary. The thorough physical and neurological evaluation should comprise all qualities, and especially enquire about and evaluate the aforementioned typical symptoms.

MS often manifests as visual and oculomotor symptoms, so **supplementary ophthalmological examinations** are useful. McDonald's diagnostic criteria have also proven useful in clinical practice. This stipulates the fulfillment of the following diagnostic requirements:

- Enquiring about and investigating the prior progression of the illness
- Verification of temporal and spatial dissemination of the disease via ...

- ... the clinical course with the presence of at least 2 manifestations (temporal dissemination)
- ... the presence of one manifestation and verification of activity via MRI
- Neurological symptoms cannot be better explained by anything other than MS; MS is thus a diagnosis of exclusion.

Imaging of multiple sclerosis

MRI plays a particularly significant role in MS diagnosis. The **typical predilection sites** (see above) should especially be examined. Should the clinical symptoms indicate a lesion in the region of the myelon, a spinal MRI should be conducted.

Exam tip: The imaging of the cervical spine and thoracic spine suffices for the spinal MRI as there is no myelin in the area of the lumbar spine!

Various sequences can be used to find various indications of MS:

- **T1 sequence:** hypointense lesions (black holes) and loss of brain volume as a sign of tissue loss
- **T1 sequence + contrast agent (gadolinium):** contrast agent enhancement of freshly active lesions as an indication of acute inflammation. Fading inflammatory foci (old lesions) do not absorb any contrast agent
- **T2 sequence, FLAIR sequence:** hyperintense lesions as signs of inflammation, cerebral edema, demyelination, and remyelination

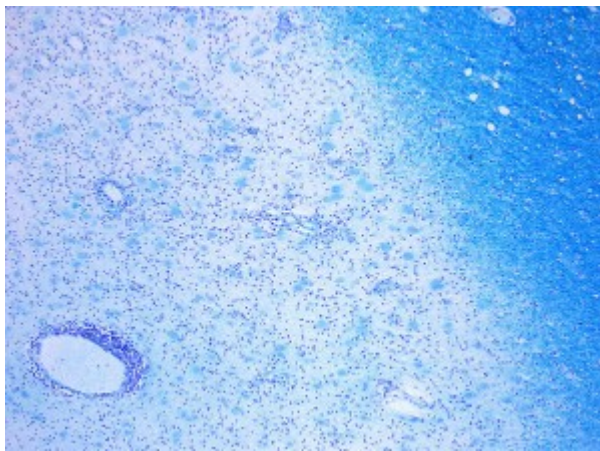


Image: Demyelination. By Marvin 101, License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/)

Fluid diagnostics for multiple sclerosis

Fluid diagnostics serve to determine the typical central inflammatory reaction of MS and are also an opportunity to rule out several differential diagnoses. For instance, a cell count increase in the cerebrospinal fluid of approx. 10–50/y/l suggests the presence of MS, whereby a **lymphocellular and monocytic image** forms. **However, it is not uncommon for the cell count in MS patients to remain normal.**

Furthermore, the diagnostics are intended to examine the presence of **fluid-specific, oligoclonal bands** as an indication of intrathecal IgG synthesis. If oligoclonal bands are present in the fluid, but not in the serum, it is an indication of MS. **Positive antibodies for various neurotropic viruses, such as measles, rubella, and shingles** in the

fluid are typical of MS. Should the findings in the fluid be non-indicative of MS, reexamination should occur after approx. 1 year. **The fluid results typical of MS are not specific.**

Electrophysiological diagnostics for multiple sclerosis

The various **evoked potentials** are examined via electrophysiological diagnostics. These potentials can be used to infer functional impairments in the CNS. If demyelination processes are occurring, latency delays in the cortical stimulus-response as a sign of retarded transmission of stimuli are noted.

Examinations for **visual, acoustic, sensory, or motor-evoked potentials** are common. Should the clinical evaluation reveal uncertainties as to whether the neuronal pathology is peripheral or central, the electrophysiological examination may, for instance, be supplemented with neurography or electromyography for differential diagnoses.

Differential diagnoses

As a diagnosis of MS often entails a life of disability, it is crucial to ensure an accurate diagnosis. The following differential diagnostic points should thus be considered:

Differential diagnoses	Helpful examination parameters
Collagenoses (systemic lupus erythematosus, Sjögren's syndrome, antiphospholipid syndrome, etc.)	ANA, rheumatoid factors, anti-DNS antibodies, X-ray, etc.
Neurosyphilis	<i>Treponema pallidum</i> hemagglutination test, FTA-Abs test to confirm
Neuroborreliosis	Borrelia AK in serum and cerebral fluid, ELISA, and immunoblot
HIV	HIV serology with AK evidence against HIV1 and HIV2, evidence of viral components, CD4 cell count
Cerebral abscesses	MRI diagnostics and possibly puncture
Neoplasia (CNS lymphoma)	MRI diagnostics and possibly puncture
Neurosarcoidosis	MRI diagnostics, fluid diagnostics (lymphocytosis, ACE, CD4/8 ratio)
Leukodystrophy	Disruption of a peroxisomal protein
Mitochondriopathy (e.g., Leber's hereditary optic neuropathy)	Molecular-genetic diagnostics, lactate in serum/cerebral fluid
Funicular myelosis, vitamin B12 deficiency	Holotranscobalamine, homocysteine, methylmalonate, vitamin B12 in cerebral fluid, erythrocyte indices
Vascular diseases (CADASIL, microangiopathy) with cerebral ischemia	Genetic testing, MRI diagnostics
MS-related disease: Neuromyelitis optica	Aquaporin 4 antibodies, usually no oligoclonal bands
MS-related disease: Acute disseminated encephalomyelitis (ADEM)	Usually no oligoclonal bands, monophasic course, childhood, infection in immediate history, fluid pleocytosis
Intoxications	

Treating Multiple Sclerosis

The treatment objectives of MS include the prevention or **reduction of new manifestations, hindering the progression of the disease, halting disease activity**, improvement of symptoms, and improvement of quality of life. Broad regime of treatments is available to achieve this, and it is divided into 3 pillars:

1. Treating the acute manifestation

The treatment of choice for the acute inflammatory manifestation includes the **intravenous administration of methylprednisolone over 3-5 days; 1000 mg each morning** with additional gastric protection (**proton pump inhibitor**) and thrombosis prevention. Clinically, blood sugar and blood pressure should be checked regularly. If the symptoms do not improve, the treatment may be increased to up to 2000 mg methylprednisolone IV over 5 days, or **plasma separation** may be discussed.

Note: For MS, there is no indication of oral steroids as a long-term treatment.

2. Immunomodulatory treatment

Preventative, long-term treatment should be adopted after careful considerations. A paradigm shift has occurred recently, and now the **recommendation of long-term early treatment** is common. The [BENEFIT study](#) revealed a delay in the progression of the disease by about 580 days when the treatment had already commenced by the time of diagnosis. The basic therapy is initially differentiated from the escalation of treatment. Interferon compounds and glatiramer acetate are primarily available as basic therapeutic agents.

- **Interferon-beta:** Endogenous cytokine, s.c. or i.m. administration—side effects: fever-like symptoms at the start of treatment, skin irritations, increased liver function readings. In some cases, neutralizing antibodies are produced that undermine effectiveness.
- **GLATiramer acetate:** Peptide mixture of **glutamate, lysine, alanine, and tyrosine** in identical molar ratios as a myelin protein—daily s.c. administration, well-tolerated

However, should greater disease activity with multiple (severe) manifestations result within a year despite basic treatment, treatment escalation is required. Natalizumab, mitoxantrone, and fingolimod are permitted. These pharmaceuticals are known for their strong efficacy, yet have a wider range of side effects than the basic therapeutics.

- **Natalizumab:** Recombinant humanized monoclonal antibody to inhibit lymphocyte transmigration via the blood-brain barrier, intravenous administration every 4 weeks, generally well-tolerated, but with a risk of **progressive multifocal leukoencephalopathy** of 1:1000 with high mortality and lethality
- **Mitoxantrone:** Cytostatic agent, cytotoxic for lymphocytes and macrophages, intravenous administration every 3 months. Relevant side effects: cumulative cardiotoxicity, increased risk of leukemia, and infections. Mitoxantrone is also permitted for secondary progressive MS.
- **Fingolimod:** Daily oral ingestion. Prevents the migration of lymphocytes into the inflamed target tissue. Side effects include infections, liver damage, macular edema, and cardiac arrhythmias.

Recent developments: Along with these known pharmaceuticals, there have been some recent developments in pharmaceutical treatment over the past few years.

Dimethyl fumarate is a new basic oral therapeutic agent. When treatment commences, gastrointestinal intolerance and flush phenomena often set in. Regular check-ups of the differential hemogram should be conducted even during long-term administration to avoid opportunistic infections.

Highly active, a monoclonal antibody for the treatment of MS has recently been introduced with **alemtuzumab**. Originally used for T cell lymphoma, alemtuzumab leads to the sustainable elimination of T and B cell sections of the immune system over months. The advantages are treatment cycles with 5 or 3 infusions in the first or second year, and possibly in the 3rd year, as well as a very positive effect on MS activity in many patients.

The disadvantages are a slight increase in vulnerability to infection during the months after infusion, and the development of secondary, B cell-transmitted auto-immunity phenomena or diseases (formation of autoantibodies, ITP (M. Werlhof), and glomerulonephritis). This requires a 48-month laboratory and urinary tests in a 4-week cycle after the last administration of alemtuzumab.

The DGN (German Neurological Society) also recommends the administration of **rituximab** as a basic therapy when treating neuromyelitis optica. Retrospective data showed that rituximab is highly effective and tolerable, even over a longer period. The administration of MS-specific therapeutics (especially interferons, fingolimod, natalizumab) should be avoided, as these have been shown to have deteriorating effects.

3. Symptomatic treatment for multiple sclerosis

Along with the therapeutic measures for treating or preventing an inflammatory manifestation, many other therapeutic approaches are taken for MS that are determined by the location of the neuronal damage (and corresponding symptoms).

Overall, many MS patients benefit from physical and physiotherapeutic measures, as well as sports, yoga, speech therapy, and ergotherapy. The following table provides a brief overview of the accompanying symptoms of MS and how they can be treated:

Symptom	Treatment
Spasticity	Tizanidine, baclofen, botox, cannabis
Gait disorder	Fampridine
Pain	Painkillers (carbamazepine, gabapentin, pregabalin, amitriptyline, duloxetine)
Bladder disorder	Detrusor overactivity: anticholinergics (oxybutynin, trospium chloride). Voiding disorder: alpha-blockers (phenoxybenzamine, prazosin), one-time catheterization
Depression	Selective serotonin reuptake inhibitors (citalopram, sertraline, paroxetine)
Fatigue	Amantadine, modafinil, serotonergic antidepressants

References

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