Multiple Sclerosis (MS) — Definition, Symptoms and Treatment

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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 name of this disease describes the multiple presence of indurations (scleroses) in the central nervous system. This is a chronic, immune mediated progressive inflammatory CNS disease that harms 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 approximately 1:1000 in the EU and the U.S. For example, about 2,500 patients in Germany are diagnosed with this disease every year. Most of these patients
are very young (20 to 30 years old) and are in a phase of their lives in which chronic diseases are far removed from daily life.

MS is one of the **most common causes of long-term disability** in young patients, with women being affected 2 to 3 times more frequently. It is an extreme burden for many previously healthy patients to be faced with a MS diagnosis. The conversation with the patient should therefore be both empathetic and informative.

**Etiological and Histopathological Traits of MS**

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

- Genetic factors
- Environmental influences
- Auto-immunity

**Genetic Factors of Multiple Sclerosis**

There is not yet any specific inherited gene that can be deemed the cause of MS, but there are likely **polygenetic influences**. Especially changes of the **MHC class II** can be associated with 2 to 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 appearing in children of afflicted parents. These children are 20 times more likely to be affected.

**Environmental Factors of Multiple Sclerosis**

When observing an epidemiological map of the world, the distribution of the disease makes it apparent that **prevalence of MS increases with the distance from the Equator**. The U.S., Central Europe, and New Zealand have a prominently high prevalence. Given this information, the different level of sun exposure, smoking, EBV infection, and humane herpes virus 6 have been often discussed.

Interestingly, 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 exhibited a higher risk, whereas older migrants did not experience any change in their risk of acquiring MS.
Auto-immune Factors of Multiple Sclerosis

With MS, the immune system attacking the body’s own components refers to a reaction against CNS myelin antigens. This results in a reversible inflammatory reaction with demyelination. If this reaction is strong, the neuronal system experiences axonal damage with subsequent irreversible decay of nerve fibres.

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, the optic nerve, the brain stem, the cerebellar peduncles, the corpus callosum and the myelon are the most important predilection sites for these so-called demyelination lesions.
Clinical Course and Symptoms of Multiple Sclerosis

The clinical manifestations of multiple sclerosis can be distinguished into acute exacerbations versus the basic clinical course. These two components can be compiled to form a full picture of the disease. This is significant insofar as the management of an acute exacerbation differs from the prophylactic long-term treatment oriented toward the overall clinical course.
Definition of an Acute MS Exacerbation

A **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 cloni.

- **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**, **Dysarthria**, **Dysphagia**, **Diplopia**, **Fatigue**, **Cognitive impairment**, **Depression**, **Unstable mood**, **Weakness**, **Spasms**, **Ataxia**, **Pain**, **Hypoesthesias**, **Paraesthesias**, **Incontinence**, **Diarrhea or constipation**, **Incontinence**, **Frequency or retention**, **Nyagmos**, **Optic neuritis**.
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 expression of an inflammatory reaction around the cerebellum and the cerebellar peduncles.

As the inflammatory reaction can fundamentally affect the entire central nervous system, 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, compiled together under Uhthoff’s phenomenon.

### Clinical Course of Multiple Sclerosis

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 heterogenous 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 once more.

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

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

Diagnosing MS is based on the patient’s history and clinical examination, imaging of the entire CNS, liquor diagnostics, and electrophysiological performance diagnostics. Past symptoms must especially be enquired and examined.

As multiple sclerosis can fundamentally affect every structure of the central nervous system, extensive diagnostics are absolutely necessary. The thorough physical, neurological evaluation should comprise all qualities, and especially enquire about and evaluate the aforementioned typical symptoms.

As MS can often be made apparent in the form of visual and oculomotoric symptoms, supplementary ophthalmological examinations are useful. McDonald’s diagnostic criteria have proven useful in clinical practice as well. This stipulates the fulfilment 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 two manifestations (temporal dissemination)
...the presence of one manifestation and verification of activity via MRT imaging
- Neurological symptoms cannot be better explained by anything other than MS; MS is thus a diagnosis of exclusion

Imaging of Multiple Sclerosis

MRT plays a particularly significant role here. 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 MRT should be conducted.

Exam tip: Do not be led up the garden path! The imaging of the cervical spine and thoracic spine suffices for the spinal MRT 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**: hypointensive 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**: hyperintensive lesions as signs of inflammation, cerebral edema, demyelination, and remyelination

Fluid Diagnostics of 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/μl speaks to 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 indication of intrathecal IgG synthesis. If oligoclonal bands are present in the fluid, but not in the serum, this is an indication of MS. Also typical of MS is
if the fluid contains **positive antibodies for various neurotropic viruses, such as measles, rubella and shingles**. Should the findings in the fluid be insignificant with suspected MS, this should be reexamined after approximately one year. The fluid results typical of MS are not specific.

**Electrophysiological Diagnostics of Multiple Sclerosis**

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

The visual (**VEP**), acoustic (**AEP**), sensory (**SEP**), or motor evoked potentials (**MEP**) are common examinations. 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 in a few differential diagnostic areas.

**Differential Diagnostic Considerations for Multiple Sclerosis**

Diagnosing MS is equivalent to a heavy stroke of fate. The term MS is widespread nowadays and the idea that many people have of this disease often entails a life of disability. It is thus all the more crucial to ensure an accurate diagnosis. The following differential diagnostic points should thus be considered:

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

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

### 1. Treating the Acute Manifestation of MS

The treatment of choice for the acute inflammatory manifestation includes **intravenous administration of methylprednisolone over 3 - 5 days. 1000 mg** are applied each morning with additional gastric protection (**proton pump inhibitor**) and thrombosis prevention. Clinically, blood sugar and blood pressure should be checked regularly. Should the symptoms not nominally improve, the treatment may be extended 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 long-term treatment.

### 2. Immunomodulatory Treatment of MS

One must choose carefully when to commence preventative, long-term treatment. A paradigm shift occurred a few years ago, and now the **recommendation of long-term early treatment** is ubiquitous. The BENEFIT study revealed a delay in 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 start of treatment, skin irritations, increased liver function readings; in some cases, neutralizing antibodies are produced that undermine effectiveness accordingly.
- **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 this result in greater disease activity with multiple (severe) manifestations within a year despite basic treatment, a treatment escalation should be done to expand the treatment. Natalizumab, mitoxantrone and fingolimod are permitted. These pharmaceuticals are all 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: risk of PML (= **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 effect: cumulative
cardiotoxicity, increased risk of leukemia, infections; mitoxantrone is also permitted for secondary progredient MS

- **Fingolimode**: Daily oral ingestion, prevents the migration of lymphocytes into inflamed target tissue, side effects: infections, liver damage, macular edema, 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 in order to avoid opportunistic infections.

A highly active, monoclonal antibody for the treatment of MS has recently been introduced with **alemtuzumab**. Originally used for T-cell lymphoma, alemtuzumab leads to sustainable elimination of T- and B-cell sections of the immune system over a span of months. The advantages are treatment cycles with 5 or 3 infusions in the 1st or 2nd 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 48-month lab 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 (NMO). Retrospective data showed that rituximab is highly effective and tolerable, even over a longer period of time. The administration of MS-specific therapeutics (especially interferons, fingolimode, natalizumab) should be avoided, as these have been shown to have deteriorating effects.

### 3. Symptomatic Treatment Options of MS

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 the ways in which they can be treated:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Spasticity</td>
<td>Tizanidine, baclofen, botox, cannabis</td>
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<tr>
<td>Gait disorder</td>
<td>Fampridine</td>
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<tr>
<td>Pain</td>
<td>Painkillers (carbamazepine, gabapentin, pregabalin, amitriptyline, duloxetine)</td>
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<tr>
<td>Bladder disorder</td>
<td>Detrusor overactivity: anticholinergics (oxybutynin, trospium chloride); voiding disorder: alpha blockers (phenoxybenzamine, prazosin), one-time catheterization</td>
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<tr>
<td>Depression</td>
<td>Selective serotonin reuptake inhibitors (citalopram, sertraline, paroxetine)</td>
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<tr>
<td>Fatigue</td>
<td>Amantadine, modafinil, serotonergic antidepressants</td>
</tr>
</tbody>
</table>
Review Questions

The answers are found below the references.

1. **Lhermitte’s sign, which can be ascertained in an MS patient during a clinical neurological examination, is most likely found in...**

   A. ...the triggering of rapid downward paresthesia along the back and/or extremities by passive forward leaning of the neck.
   B. ...the triggering of severe lumbar pain by lifting an outstretched leg with a forward leaning neck.
   C. ...a plantar flexion of both feet during passive forward leaning of the head with pains in the lumbar area.
   D. ...the triggering of a reflexive bending of the legs in the hip and knee joints by passive forward leaning of the neck.
   E. ...the triggering of a rapid recline of the head with overflexion of the trunk as a delayed reaction to passive forward leaning of the neck.

2. **When diagnosing MS, differential diagnoses should always be eliminated. Which of the following blood tests should be indicated first when commencing stationary hospitalization?**

   A. Immunoblot on borrelia AK
   B. FTA-Abs test with IgM fractioning
   C. Antibody examination for parvovirus B19
   D. TRH test
   E. HIV test

3. **Which of the following lab results is most typical of multiple sclerosis, and would thereby most support this diagnosis?**

   A. Greater concentration of beta-amyloid fragments in the patient’s cerebral fluid
   B. Serological evidence of oligoclonal IgG bands in the patient’s serum
   C. Lower concentration of α-synuclein in the patient’s cerebral fluid
   D. MRZ reaction (greater measles/rubella/zoster [shingles] antibody index)
   E. Lower concentration of cobalamin in the patient’s plasma

4. **The treatment concept of the acute inflammatory manifestation of MS is based on glucocorticoid treatment. Which of the following forms of treatment is most suitable here?**

   A. Peroral long-term treatment with hydrocortisone in a weight-based dose of 20 – 45 mg/d
   B. Intravenous administration of methylprednisolone and in a high dosage (1 g/d) as pulse therapy over 3 – 5 days, perhaps with subsequent peroral gradual reduction
   C. Peroral treatment with prednisolone in a dosage of 100 mg/d for 6 months
   D. Inhalative administration of budesonide in a dosage of 9 mg/d as pulse therapy over 3 – 5 days
   E. Intravenous, symptom-dependent administration of methylprednisolone in dosages of 100 mg/d - 1.5 g/d with daily dosage adjustment until symptoms are halted

References


Correct answers: 1A, 2E, 3D, 4B

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