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Integrated Studies

Main Aspects in Diagnostics and Treatment of Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorders: Clinical Cases

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1. Summary

Multiple Sclerosis is a chronic, heterogenous neurological disorder characterized by immune-mediated injury to the central nervous system and remains a condition without a definitive cure. [1]

Multiple sclerosis is the most common non-traumatic neurological condition causing long-term disability among individuals in early to mid-adulthood, with a global prevalence exceeding 2.3 million. [2]

It is a challenging disease not only for the patient but also for the treating physician. A combination of medical treatment as well as physical and psychological support is required with the goal of preventing progression and exacerbations of the condition, while also slowing the advancement of functional impairment. [1]

A timely diagnosis and adequate treatment are the first step in the long-term management and adaptation to achieve a life worth living despite the shattering diagnosis of multiple sclerosis.

It is yet to learn a lot about the pathogenesis of this disease, but it is expected to be a multifactorial highly complex genesis, with a lot of influential factors.

Neuromyelitis optica (NMO) previously termed Devic´s disease, is a chronic autoimmune inflammatory disorder of the central nervous system, primarily defined by episodic acute optic neuritis (ON) and transverse myelitis (TM). [3]

NMO was considered for a long time to be a particularly aggressive variant of multiple sclerosis, following the identification of Aquaporin-4 (AQP4) targeting IgG antibody, a differentiation of NMO from MS is possible and thus the classification of neuromyelitis optica spectrum disorder (NMOSD) has been established since 2007. [4]

Over the last years and decades, the treatment changed drastically especially for MS and a completely new path of treatment was established for NMOSD as it is finally possible to have a specific tailored treatment for NMOSD instead of treating it as a severe sub form of MS.

During this thesis we will figure out how to establish a diagnosis, what kind of lab work is essential as well as the imaging techniques needed to conclude a diagnosis and to follow up the patient.
We will discover the different medications which are best suited for the treatment of MS as well as NMOSD and which ones are no longer recommended.

2. Keywords

Multiple sclerosis, Neuromyelitis optica, disease activity, Disease-modyfying therapy (DMT), Magnetic resonance imaging (MRT)

3. Introduction

Multiple sclerosis (MS) is a highly complex and multifactorial driven condition which is yet to be fully explored and understood. A lot of crucial knowledge and questions related to pathophysiology, causation and susceptibility are still unanswered.

Most patients are in their 40s, on which the disease has a devastating impact on their functionality, mental health and their general quality of life. [5]

Also, it creates a huge burden for the health system as the costs are high and rise throughout the disease in relation to the disease intensity.

Due to the detrimental effect on the quality of life of the patients, an early diagnosis is critical and always newly evolving and adjusted diagnostic criteria are the cornerstone of the prevention of a disease progression.

Within the last decades a vastly life changing development happened in the exploration of the disease as well as the management. Mainly hope sparking and promising is the huge amount of newly developed disease-modifying treatments (DMTs). A significant amount of DMTs is available for the most prevalent course, the relapsing remitting variant of MS, however there are only a few therapeutic options available for the more aggressively progressing forms. [6]

Multiple sclerosis main mechanism is due T and B cell inflammation leading to demyelination and neurodegeneration. While it was once thought to be a variant of MS, neuromyelitis optica spectrum disorder (NMOSD) is now recognized as distinct disease entity. NMOSD mainly attacks the central nervous system by Aquaporin-4 antibodies, which has allowed for a seropositive definition. This advancement finally makes it possible to differentiate between MS and NMOSD and enabling more individual treatment for patients. [7]

The manifestation of MS relapses varies based on the area which is attacked or whether the spinal cord is involved and the exact localisation of the lesions. [8] Decisive for the nature of the attacks is not only the localization of the inflammation but also the course of the disease which can be categorized into clinically isolated syndrome (CIS), relapsing remitting MS (RRMS), secondary progressive MS (SPM) and primary progressive MS (PPMS) [9]

NMOSD could present on first sight similarly to MS, with optic neuritis and acute myelitis, however the onset and progression vary greatly. [10]

One of the main challenges for both disease is to early differentiate one from another and quickly determine the right treatment approach and follow up.

With the help of new Guidelines, which are under ongoing evolution, the aim is to create a clear pathway to guide physicians to a diagnosis with the limited resources available in the nowadays health system.

4. Multiple Sclerosis

4.1. Etiology and Epidemiology

Multiple sclerosis is a partially heritable autoimmune disease, with the highest prevalence occurring in individuals aged 40 to 60 years [5]. The further away from the equator, the higher is the incidence [11]. With over 100 cases per 100.000 inhabitants in the northern hemisphere compared to 2 cases per 100.000 in eastern Asia and African countries located closer to the equator. It can be summarized, that there is a north-south prevalence gradient.

Women have a risk of developing MS that is up to three times higher than that of men, with the relapsing-remitting variant being the most common course. [11]

Environmental factors play an important role in the etiology and pathogenesis of MS, though lot more research will be needed to clearly identify all factors contributing to disease onset and progression.

Symptomatic Epstein-Barr virus infection in childhood is considered a major contributing factor to the development of MS later in life. Lifestyle factors, such as smoking, obesity, as well as high salt consumption are identified to elevate the likelihood of MS development. [12] Controversial and often discussed are vaccines, stress, traumatic events and allergies, however recent studies indicate that these factors don't significantly increase the risk. [11]

Additional risk factors include night shift work and exposure to organic solvents. Furthermore, a deficiency of Vitamin D is important to be aware of, as it is thought to contribute to the initial stages of MS pathogenesis. [12]

An emerging focus of future research is the impact of alcohol and coffee consumption on the risk of developing MS. Currently, there is no clear evidence which proves an association between the consumption of these substances and an increased risk of MS. Some studies suggest that there is a reduced risk in individuals who consume large amounts of coffee daily, with amounts over 900ml caffeine, with its neuroprotective properties, could potentially suppress the production of proinflammatory cytokines thereby influencing the pathogenesis of MS [13]. For alcohol on the other hand, the risk is dose-dependent, and studies indicate that higher alcohol consumption is statistically significantly more likely to cause MS than refraining from alcohol. [14]

There is evidence that factors such as tobacco use, Epstein Barr virus exposure and excess body weight may synergize with genetic predispositions linked to HLA variants, potentially triggering disease through pathways related to adaptive immunity. [15] Over 200 genes have been connected to an elevated risk of MS. [16] Genetic predisposition plays an important aspect in the development of MS, with the incidence increasing to as high as one in four identical twins when one twin is affected. In addition, research indicates that approximately 3-4% of immediate family members may also develop the condition. The gene variant HLA-DRB1*15:01 has been identified as a major genetic factor, raising the likelihood of disease development by nearly three times. Additional class II alleles that contribute to susceptibility include HLA-DRB1*13:03, HLA-DRB1*03:01, HLA-DRB1*08:01 and HLA-DQB1*03:02. Beyond the HLA region, other associated genetic risk factors include CD25 and CD49d (also known as VCAM1). [16]

Genes regulating vitamin D synthesis and metabolism are additionally thought to play a significant role in the development of the disease. These include CYP27B1, which codes for an enzyme responsible for activating vitamin D, the receptor through which vitamin D exerts effects, and CYP24A1, which is involved in its degradation. [17] Additionally, certain alleles within the MHC class I region, such as HLA-A*02:01, HLA-B*44:02, HLA-B*38:01 and HLA-B*55:01, have been identified as offering a degree of genetic protection. [18]

Advancing research into these relevant genes will be crucial for developing optimal therapies for MS, as the newest drugs primarily target these genetic variants and offer a valuable new path for treatment.

4.2. History

The first description of Multiple sclerosis date back to around 700 years in the past. There are writings that already during the times of the Vikings, at the end of the 13th century, there was knowledge about a mysterious disease, causing blindness and aphasia. Remarkably, even the relapsing-remitting course was recognized, though it was believed to be cured through prayer and sacrifices. [19]

600 years later, in the 19th century, the disease finally gained recognition and received a name. For a very long time the disease was completely unknown and was even questioned to exist. Some speculated it might be a form of syphilis.

One of the earliest clinical observations resembling multiple sclerosis was documented in 1824 by Charles-Prosper Ollivier d´Angers. However, it was Jean-Martin Charcot who, in 1868, first identified the condition as a distinct neurological disorder, coning the term “Sclerose en plagues”. Charcot was also the first to link specific clinical symptoms to underlying pathological changes, and he introduced a diagnostic triad for the disease, which included scanning speech, intention tremor and nystagmus. [20] The therapy consisted of gold chloride, zinc sulphate, strychnine, belladonna and electrotherapy. [19]

In the last century, various hypotheses regarding the origin and development of MS evolved, alongside the emergence of the first evidence-based therapies. A key turning point in the therapeutic

management of MS was the commercialization of interferon-1b, the first proven effective medication, which was introduced to the market in 1993. [19]

From the history alone it is clear that MS is a disease with a thousand faces and is highly difficult to distinguish and even harder to treat. This underscores the ongoing need for continuous review and optimization of diagnostic guidelines and individual treatment plans for patients.

4.3. Pathophysiology

The pathophysiology of MS is highly complex and remains only partially understood. A lot of factors and genes contribute to the development of the disease. Understanding the pathophysiology is crucial for creating optimal, personalized treatment for MS patients.

A central element in the development of MS is the immune-driven inflammation involving both T and B lymphocytes, which are components of the adaptive immune response. [21] Under normal conditions, the central nervous system is protected by the blood brain barrier (BBB), which tightly controls the passage of immune cells. However, in MS, this protective barrier becomes compromised, allowing antigen-specific T and B lymphocytes to become activated. This disruption triggers a vicious cycle of CNS inflammation, demyelination and axonal damage as well as neurodegeneration, which are characteristic of the disease. Activated T helper cells recognize myelin as foreign and release pro inflammatory cytokines. B cells produce antibodies which in turn attack myelin, accelerating the demyelination process. [22]

T cells become autoreactive due to the presence of an unknown antigen and migrate into the lymphatic tissues where they undergo expansion. Stimulated by spingosine-1-phosphate, the T cells then enter systemic circulation. These activated T cells bind to upregulated adhesion molecules, which subsequently produce matrix metalloproteinases (MMP). Which in turn is the leading factor of the blood-brain barrier breakdown. [22]

When T cells infiltrate the CNS, they engage with antigen-presenting cells (APCs), initiating a cascade of immune responses that exacerbate myelin damage. This process results in the phagocytosis of myelin, its stripping, and breakdown of the myelin sheaths, ultimately leading to oligodendrogliopathy. T helper cells divide into two distinct subsets: pro-inflammatory Th1 cells and anti-inflammatory Th2 cells. Th1 cells secrete cytokines such as Interleukin-1 (IL-1) and interferon-gamma (IFN)-γ, which target and attack macrophages and microglial cells, promoting further immune responses. In contrast, Th17 cells release IL17, a cytokine that contributes to inflammation. [23]

Cytokine production triggers an increase in T cell stimulation, enhances the synthesis of metalloproteinases, and contributes to further impairment of the blood-brain barrier (BBB). [24] On the other hand, Th2 cells release anti-inflammatory cytokines such as IL-10 and IL-4, helping to mitigate the inflammatory response. [22]

Autoreactive T cells activate B cells to generate antibodies, which can transverse the BBB through the previously compromised areas, which in turn triggers the formation of myelin antibodies.

Furthermore, these antibodies activate the complement cascade leading to additional myelin damage. [2]

B cells are essential for the body's defence mechanisms as they differentiate into plasma cells to produce antibodies, which, in turn, regulate autoimmune activity, including the stimulation and regulation of T cells. Furthermore, B cells influence the inflammatory actions of other immune cells by controlling the release of various molecules. [25] in the CSF, clonally expanded B cells generate oligoclonal bands, and the accumulation of immunoglobulins in regions of CNS demyelination contributes significantly to the development of MS. Antibodies in the CSF lead to axonal damage and further promote complement-mediated demyelination. [25] These antibodies may specifically target antigens like myelin oligodendrocyte glycoprotein, myelin basic protein, neurofascin, and contactin-2.

In summary it can be said that antigen-activated B cells are instrumental in the advancement of MS by functioning as powerful antigen-presenting cells. Furthermore, B cells can transform into plasma blasts and plasma cells, that secrete autoreactive antibodies that exacerbate the course of the condition. [26]

At the beginning of the disease axons are typically not damaged. However, as the disease progresses, irreversible axonal destruction occurs. [27] Cytotoxic T cells can induce axonal damage within a couple of weeks after diagnosis. [2, 28] This is one of the major factors in disease progression.

Activated microglia and infiltrated macrophages generate reactive-oxygen species (ROS) and nitric oxide (NO), both of which play a crucial part in causing neuronal injury and exacerbating the progression of MS lesions. [29]

There is still a lot of research needed to fully understand the complexities of multiple sclerosis pathogenesis and progression, but identifying the missing links will be pivotal in developing optimal and personalized treatments in the future.

4.4 Classifications and Definitions:

Term	Definition	Characteristics
MS Exacerbation	New symptoms or aggravation of existing symptoms due to CNS damage. Symptoms persist for over 24 hours.	Must rule out infection or fever before diagnosis.
Remission	The period when a patient recovers after an exacerbation, and symptoms either completely vanish or are very mild.	
Pseudorelapse	A temporary exacerbation or aggravation of pre-existing symptoms triggered by	Symptoms worsen temporarily but are not due to new CNS damage.

	external factors like infection, heat, or metabolic changes.	
Radiologically Isolated Syndrome (RIS)	Early stage where MS-like demyelinating lesions appear on MRI, but no symptoms are present. Not yet classified as MS.	May progress to MS, often leading to primary progressive MS. [30]
Clinically Isolated Syndrome (CIS)	A first clinical attack suggesting CNS demyelination but not meeting full MS criteria. Symptoms may include optic neuritis, myelitis, or brainstem syndrome. [31]	Symptoms typically resolve over time, but a high likelihood of MS development.
Relapsing Remitting MS (RRMS)	85-90% of MS patients. Defined by acute flare-ups, succeeded by phases of remission with little or no disease progression.	Relapses occur at a rate of <1.5 per year; relapses lead to stepwise accumulation of impairment. Can be classified as: - Active: New relapses or gadolinium-enhancing lesions along with new or expanding T2 lesions on MRI, OR not active: No signs of disease progression - Deterioration: Progressive functional impairment OR stable: no progression of disability.
Secondary Progressive MS (SPMS)	Half of RRMS patients progress to SPMS, usually 19 years after onset of RRMS. Marked by gradual and persistent decline of cognitive and motor abilities, independent of relapses. [32]	Can be classified as: - Active: New relapses or gadolinium-enhancing lesions and/or new or progressing T2 lesions on MRI, OR not active: No signs of disease progression - With progression: reduction of neurological function, OR without progression
Primary progressive MS (PPMS)	10-20% of MS patients. Symptoms worsen continuously from the onset of disease, without relapses or remission. Some may have superimposed relapses.	Can be classified as: - Active: New relapses or gadolinium-enhancing lesions and/or new or progressing T2 lesions on MRI, OR not active: No signs of disease progression. - With progression: Increased

		disability OR without progression. [32]

Table 1. [30,31,32] - Table adapted from source 32, page 2-3.

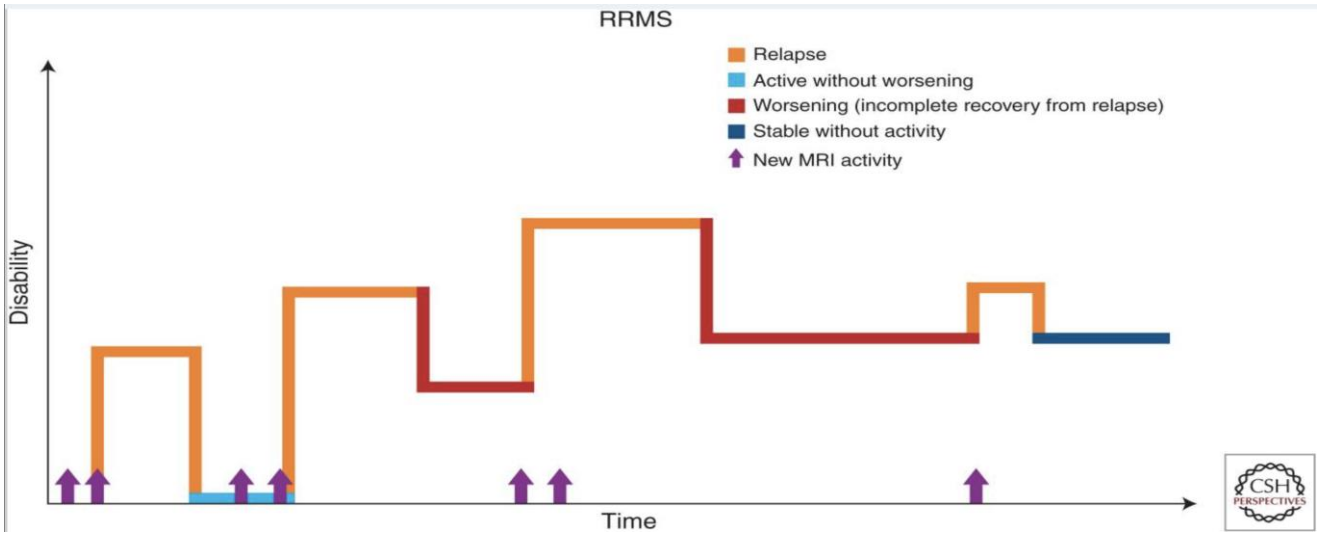


Figure 1, Relapsing remitting course of MS, PubMed Central (PMC) [Internet]. [cited 2025 Jan 21]. Clinical Course of Multiple Sclerosis. Figure 1. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC6120692/

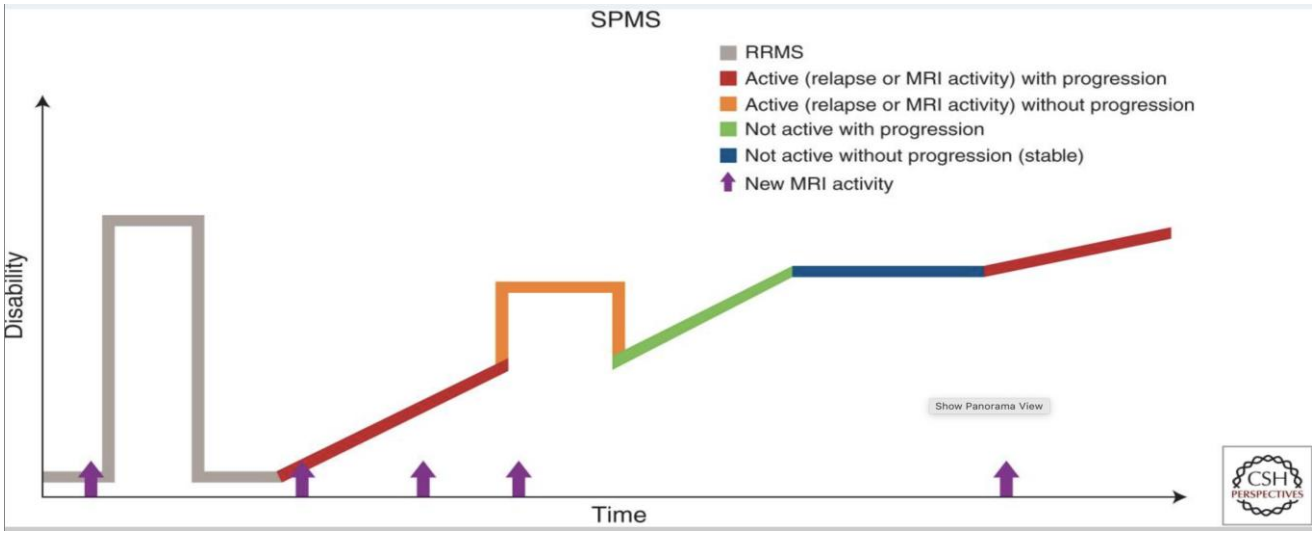


Figure 2, Secondary progressive course of MS, PubMed Central (PMC) [Internet]. [cited 2025 Jan 21]. Clinical Course of Multiple Sclerosis. Figure 2. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC6120692/

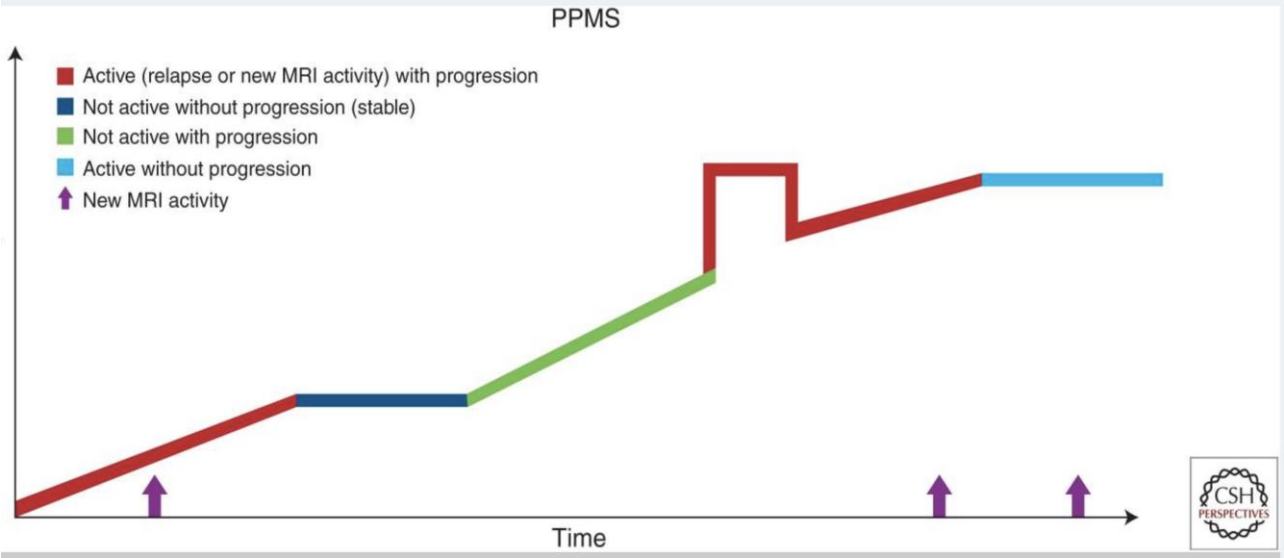


Figure 3, Primary progressive course of MS, PubMed Central (PMC) [Internet]. [cited 2025 Jan 21]. Clinical Course of Multiple Sclerosis. Figure 3. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC6120692/

4.5 Mc Donald Criteria

Introduced in 2001, the McDonald Criteria establish a framework to diagnose Multiple sclerosis. The criteria are based on two key principles: the dissemination in time (DIT) and dissemination in space (DIS), both of which rely on MRI findings to demonstrate the spread of demyelinating lesions across different areas of the CNS over time. Additionally, the diagnostic process involves ruling out other possible diagnosis through laboratory tests and clinical evaluation. [33]

The criteria have always been under constant revision and changes, the most current one is the 2017 McDonald criteria and with great expectations and interest the updated criteria is expected to be published at the beginning of 2025, with the goal of further simplifying MS diagnosis.

In general, the criteria are primarily determined by the identification of focal lesions in the white matter of CNS, which show increased intensity on T2-weighted and T2-weighted fluid-attenuated inversion recovery (FLAIR) by MRI. [34]

The Dissemination in space of the McDonald 2017 classification requires the presence of more than one T2 lesion in at least two of the following CNS regions: Periventricular, juxtacortical or cortical, infratentorial, and spinal cord. Both symptomatic and asymptomatic lesions are considered in the assessment.

The Dissemination in time can be proven through a newly found T2 and/or gadolinium-enhancing lesion on follow-up MRI. Another keypoint is the detections of gadolinium-enhancing and non-enhancing lesions existing at the same time, whether symptomatic or asymptomatic. The third and final point is the confirmation of MS-specific oligoclonal bands in the CSF in the absence of other CSF findings which are atypical of MS. [35]

The interpretation of the Mcdonald criteria is a straightforward process, if two or more attacks as well as two or more lesions have been detected the clinical evidence alone is sufficient to diagnose MS.

If two or more attacks are noted, though only one lesion is detected, additional evidence of dissemination in space is required for the diagnosis. This can be confirmed by detecting lesions in different anatomical regions on MRI. Alternatively, a subsequent episode affecting a separate region of the CNS can be awaited.

If only one attack but two lesions are detected, the dissemination in time must be demonstrated through MRI to conclude a diagnosis. This can be done by detecting a new lesion on a follow-up MRI or by confirming that lesions appeared at different times. Alternatively, another episode affecting an alternate CNS site may be anticipated. It is sufficient to make a diagnosis if oligoclonal bands can be detected in CSF.

If one attack and one lesion are detected, both dissemination in space and time needs to be established. It needs to be demonstrated during a follow-up MRI that new lesions are found or that existing lesions involve different anatomical regions. Alternatively, another episode affecting an alternative CNS site can be awaited. [33]

Evaluation of the Mcdonald Criteria

In 2022 a large cohort analysis was performed to evaluate the sensitivity and specificity of the 2017 Mcdonald criteria in comparison to the 2010 criteria. [36] In total 785 patients have been retrospectively analysed, and the conclusion was that a sensitivity of 83% vs 66% and a specificity of 39% vs 60% have been observed. The 2017 criteria allow for a up to 5 times faster diagnosis; 11.4 months compared to 58.5 months in patients without OCB. The average diagnostic time has been shortened by about 7.2 months. [37] However, the downside of the 2017 Mcdonald criteria is the relatively high false- positive rate, which causes a significant amount of risk of unwarranted medical intervention and thus increasing the likelihood of adverse effects from pharmacological treatment.

4.6 Symptoms

The symptoms of multiple sclerosis are very individual and can be very inspecific at initial presentation. Typically, they develop gradually over several days. MS primarily presents with neurological symptoms linked to demyelinating lesions in the brain and spinal cord, but systemic signs such as fever and headache, as well as psychological disorders, also contribute significantly to the disease burden. A comprehensive, patient-centred approach is essential to treat each person adequately, to ensure optimal management and improve quality of life.
For a clinical episode to be classified as an MS exacerbation, symptoms must persist for over 24 hours and are not associated with infection or elevated body temperature. [30]

Fatigue is one of the earliest and most common symptoms, impacting more than four out of five individuals. [39] Headache is another common but nonspecific early symptom. The specific

neurological symptoms depend on the location of demyelinating lesions within the central nervous system. [8]

Unilateral optic neuritis is a hallmark symptom of relapsing-remitting MS (RRMS). It is characterized by ophthalmalgia, gradual onset of one-sided vision loss, altered perception of colour vision and blurred vision. Some patients can recover completely within weeks, while others experience long lasting visual impairment. If the lesion affects the medial longitudinal fasciculus rather than the optic nerve, internuclear ophthalmoplegia occurs. This is characterized by ipsilateral medial rectus weakness and contralateral lateral gaze nystagmus commonly presenting bilaterally. [40]

Demyelination in the cerebrum can cause focal supratentorial syndrome, with symptoms varying based on the precise site of the lesion. Common manifestations include visual field impairments and hemisensory motor deficits. [41]

When the cerebellum is affected by the lesion, patients often complain of unsteadiness with limb or gait ataxia and gaze-evoked nystagmus, which can be either horizontal or torsional in presentation. The so-called Charcot neurological triad can be observed, consisting of dysarthria, nystagmus and intention tremors. [42]

Spinal cord lesions often present with multiple foci and are typically asymmetric. Partial myelitis can affect various pathways including the pyramidal tracts, spinothalamic tract or posterior columns. The onset of symptoms occurs over hours to days and varies from a mild sensory syndrome to a severe attack potentially leading to tetraparesis.

When the lesion is in the pyramidal tract, both upper and lower motor neurons are affected, leading to weakness that is more prominent in the distal muscles compared to the proximal muscles. In the arms, weakness is more pronounced in the extensors than the flexors and vice versa in the legs. Spasticity, weakness, a positive Babinsky sign as well as impaired gait are often observed. [40] When the spinothalamic tract or posterior columns are affected unilateral, or bilateral limb numbness or paraesthesia may occur. A common symptom is the Lhermitte's phenomenon which is described as a sharp, electric-like feeling that radiates along the spine when the neck is flexed. [38]

The generalized symptoms of any spinal cord lesion include increased urinary frequency, urge incontinence, constipation and erectile dysfunction as well as neuropathic pain and absent abdominal reflexes.

Lesions affecting the brainstem commonly result in signs such as internuclear opthalmoplegia, abducens nerve palsy, and gaze-evoked nystagmus. Individuals may also present with symptoms including double vision, oscillopsia, altered facial sensation, vertigo, and slurred speech. [40]

Transverse myelitis arises from inflammation that spans both sides of the spinal cord, leading to motor and sensory impairments on both sides of the body, as well as potential autonomic dysfunction. [43]

Cranial nerves can be affected and lead to cranial nerve palsies with symptoms including diplopia, facial palsy, trigeminal neuralgia. Trigeminal neuralgia can be a big challenge in up to 5% of MS patients. [44] Trigeminal neuralgia presents as sudden, recurrent episodes of sharp, electric shock

like pain on one side of the face, confined to areas served by the branches of the trigeminal nerve. The pain is typically set off by harmless stimuli. Usually, trigeminal neuralgia is observed unilaterally in patients, bilateral involvement should be a warning flag of concern in young patients with a high suspicion for MS. [45]

Clinicians should also recognize that psychological symptoms represent a significant aspect of the clinical representation in patients with MS. Throughout the disease a considerable amount of patients complain of significant depression and distress, sometimes even being more prominent and life-impairing than the mobility problems. Increased number of patients report of bipolar disorders, pseudobulbar affect as well as subsyndromal symptoms. Despite their prevalence, these conditions are often underdiagnosed and undertreated due to the lack of routine screening and clear clinical guidelines. [46]

Between 60 to 80% of MS patients exhibit the Uhthoff phenomenon, which is a temporary worsening of symptoms, triggered by an increase of core body temperature. Causes for this could be physical exertion, warm baths or fever. Patients report a significant worsening of visual acuity. It is expected to be the consequences of long-standing myelin damage in the presence of thermal stress. When thermal triggers are eliminated or cooling interventions are applied, the Uhthoff phenomenon typically resolves within minutes to an hour. [47]

4.7 Diagnosis

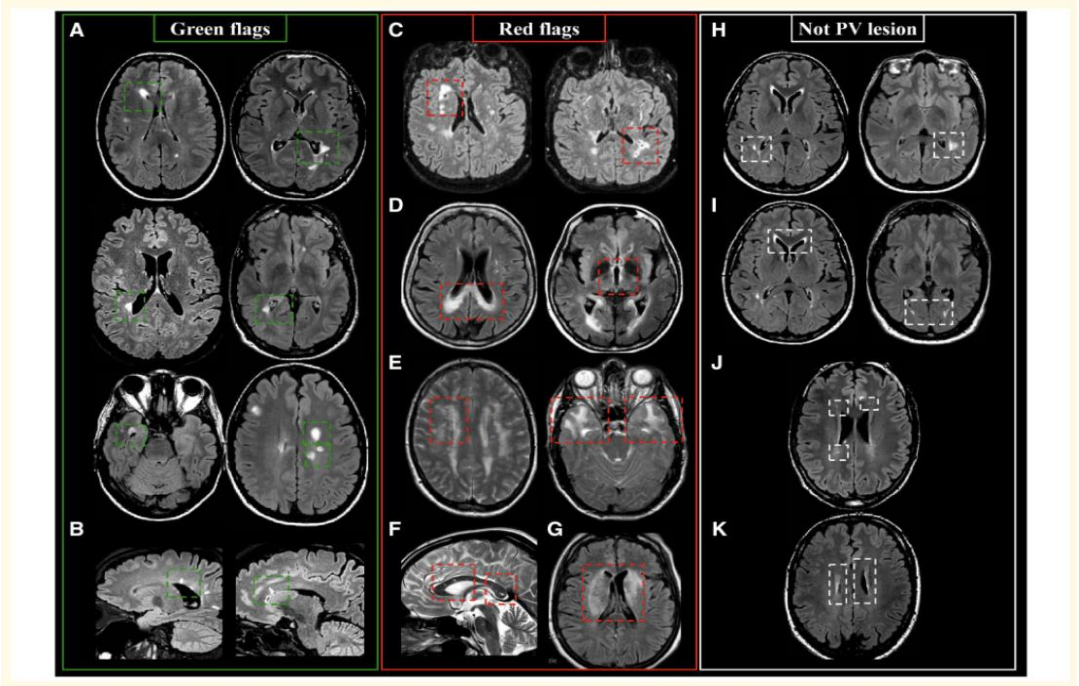
MS diagnosis requires an integration of clinical findings, imaging results and diagnostic assays. Key clinical indicators include optic neuritis, Lhermitte´s sign, sensory and motor neuron abnormalities and other characteristic symptoms. MRI is the gold standard for MS diagnosis and monitoring. The McDonald criteria, as discussed earlier, guide diagnosis by assessing DIT and DIS. Early and accurate diagnosis are the key elements for promptly tailoring the appropriate treatment at the onset of the disease. A few considerations need to be made when using MRI in a suspected multiple sclerosis patient, the Mcdonald criteria best suits patients between the age of 18 to 50, more consideration and more stringent criteria should be considered for patients out of this age group. The quality of the MRI machine should be assured with a minimum field strength of 1.5T. 3D acquisitions or 2 D with 3 mm thick slices with no gaps between slices will improve the accuracy significantly. As MS lesions can be present in various areas within the CNS it is needed to investigate cervical, thoracic as well as lumbar spine when the symptoms indicate spinal involvement. It is important to prove lesions in multiple planes as false positive findings happen frequently due to artefacts or insufficient quality of the images. For each lesion an optimal imaging sequence must be used. [48]

When suspicion for MS arises the initial step to conclude a diagnosis is brain and spinal cord magnetic resonance imaging. Dissemination in time and dissemination in space need to be demonstrated. As discussed above during the McDonald criteria the DIS can be proven by at least one T2-hyperintense lesion in at least two of the four regions of the CNS: The spinal cord, periventricular, cortical or juxtacortical and infratentorial. DIT can be detected by the presence of both non-enhancing and gadolinium enhancing lesions at any point, or by the emergence of new T2 lesions or gadolinium enhancing lesions during subsequent MRI assessments. [8]

Usually, lesions emerge in both hemispheres, though they are often asymmetric in the initial stages. While MS lesions can exist within the whole CNS, they are most commonly detected in distinct white matter regions, including the periventricular and juxtacortical areas, the corpus callosum, infratentorial areas, and the spinal cord.

Periventricular lesions are T2-hyperintense areas of white matter lesions in the brain, situated next to the lateral ventricles, with no direct connection to the surrounding white matter. These lesions also include those in the corpus callosum. Typically, they are found in proximity with the medullary veins. When viewed on the axial plane, they appear ovoid in shape forming the characteristic "Dawson's fingers" pattern. [49]

Characteristics of Periventricular MS Lesions: Typical (Green) and Atypical (Red) and Lesions which Should be Excluded in the Lesion Count:

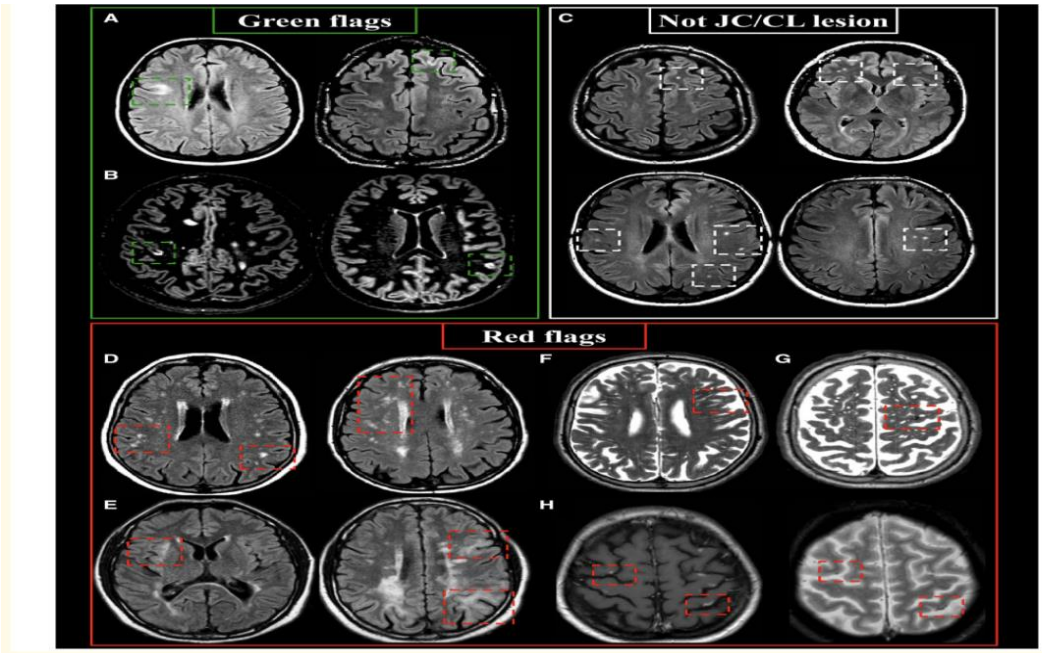


A: Periventricular lesions typical for MS. B: Periventricular lesions orthogonal to the corpus callosum "Dawsons fingers". C: Numerous WM lesions affecting paraventricular and deep GM regions – ischemic small-vessel condition. D: involvement of the posterior corpus callosum, bilateral diencephalic hyperintense lesions in NMOSD. E: numerous lesions in the deep WM, outer capsule, and temporal lobes. F: Intra-Callosal "snowball" lesions in Susac syndrome. G: widespread involvment of both WM and GM in SLE. H: lesion not in contact with the lateral ventricles. I: Symmetrically distributed periventricular "capping" in the ant. and post. regions. J: Lesion <3mm, K: bilateral, linear hyperintensities adjacent to the lateral ventricles.
Figure 4. adapted from: Periventricular lesions seen on MRI. Dawsons fingers in picture B, source 48. Filippi M, Preziosa P, Banwell BL, Barkhof F, Ciccarelli O, De Stefano N, et al. Assessment of lesions on magnetic resonance imaging in multiple sclerosis: practical guidelines. Brain. 2019 Jul;142(7):1858–75.

Juxtacortical lesions are T2-hyperintense abnormalities within the white matter that lie directly adjacent to the cerebral cortex. They are most effectively detected using 3D T2-FLAIR imaging. These lesions often affect the U-fibers and may appear in any central lobe, as well as within the cerebellum. [49]

Cortical lesions are localized disruptions found either entirely inside the cerebral cortex or extending into both the cortex and the neighbouring white matter. Like juxtacortical lesions, they are best detected using T2-FLAIR. It is challenging to detect them so specialized MRI sequences might be used to improve the quality. [49]

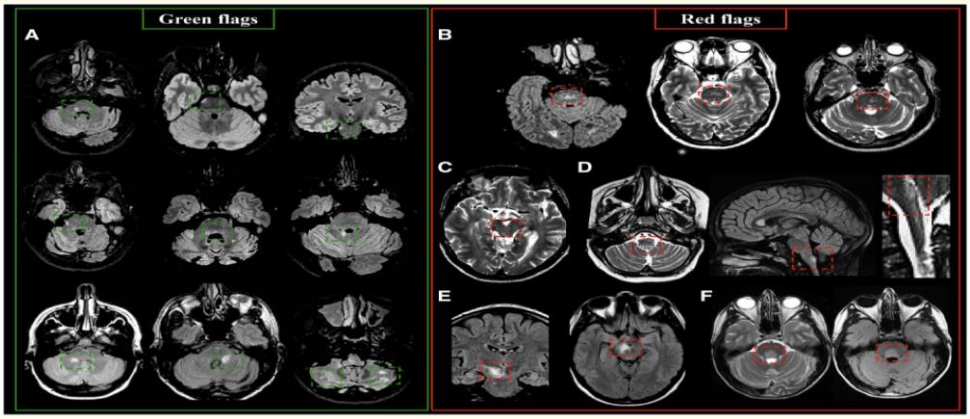
Characteristics of Cortical/Juxtacortical MS Lesions: Typical (Green) and Atypical (Red) and Lesions which Should be Excluded in the Lesion Count:



A. Juxtacortical lesions & B: Cortical lesions indicating MS. C: WM not reaching the cortex. D: Multiple WM lesions subcortical and deep WM – small-vessel condition. E: Lesions affecting GM-WM border of different lobes in progressive multifocal leukoencephalopathy. F: numerous CSF-like anomalies in distended Virchow-Robin region. G: Hypointensity on T2 suggestive of haemosiderin build-up due to microhemorrhage. H: Multiple meningeal/cortical hyperintensities on T1 associated with CNS vasculitis.
Figure 5. adapted from: Cortical/Juxtacortical lesions on MRI. Source 48. Filippi M, Preziosa P, Banwell BL, Barkhof F, Ciccarelli O, De Stefano N, et al. Assessment of lesions on magnetic resonance imaging in multiple sclerosis: practical guidelines. Brain. 2019 Jul;142(7):1858–75.

Infratentorial lesions are T2 hyperintense abnormalities, located in the brainstem, cerebellar peduncles or the cerebellum. They can be detected near the surface or along the trigeminal tract. [49]

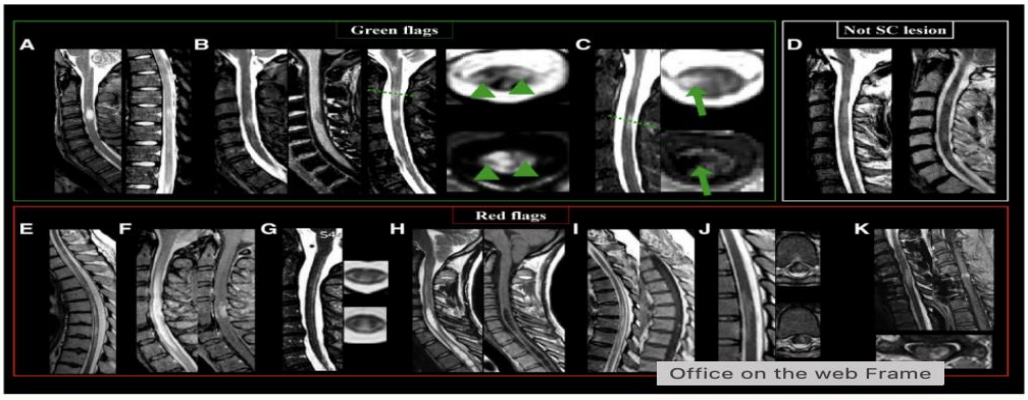
Characteristics of Infratentorial MS Lesions: Typical (Green) and Atypical (Red):



A: Infratentorial lesions indicating MS. B: bilateral central pontine defect in small-vessel disorder. C: Periaqueductal lesion in NMOSD. D: Area postrema lesions in NMOSD. E: mesencephalic-diencephalic lesion in anti-MOG syndrome. F: prominent oval lesion close to the base of 4th ventricle in neuro-behcet disease.
Figure 6. adapted from: Characteristics of Infratentorial lesions on MRI. Source 48. Filippi M, Preziosa P, Banwell BL, Barkhof F, Ciccarelli O, De Stefano N, et al. Assessment of lesions on magnetic resonance imaging in multiple sclerosis: practical guidelines. Brain. 2019 Jul;142(7):1858–75.

Spinal cord lesions are typically small, multifocal and T2-hyperintense. They can be present along the entire spinal cord, with predominant localisation in the cervical part. Lesions should be focal with clearly demarcated borders to support the diagnosis of MS. They predominantly affect the lateral and dorsal columns but may involve other parts of the spinal cord as well. [49]

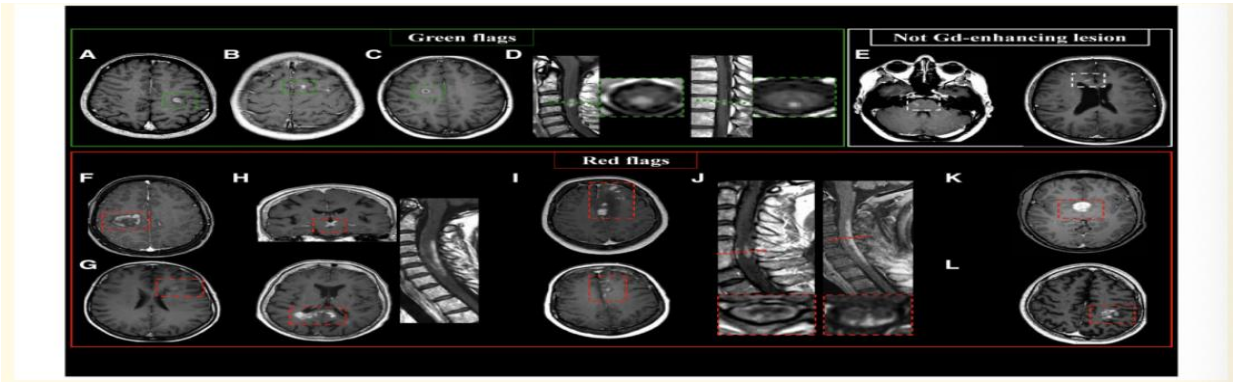
Characteristics of Spinal Cord MS Lesions: Typical (Green) and Atypical (Red) and Lesions which Have to be Excluded in the Lesion Count:



A: S.C. Plaques in cervical and thoracic cord. B: Cervical cord lesions reflecting hypointensity of T1 sequences at 3T. C: Cervical lesion revealing inclusion of the lateral column and central GM. D: Diffuse S.C. lesions with grossly-defined edges not used for definition! E: Long segmental transverse myelitis spanning over three vertebral levels in NMOSD. F: Long segmental spinal cord involvement over three vertebral segments, with leptomeningeal and peripheral spinal cord enhancement on contrast imaging in neuro-sarcoidosis. G: widespread and targeted damage of the lateral and posterior columns in subacute combined neurodegeneration. H: S.C. lesions in syringomyelia. I: widespread T2 hyperintense damage spanning from the conus with, with irregular and convoluted areas of contrast enhancement in AV fistula. J: Hyperintense plaque in anterior part of thoracic spinal cord spanning greater than two vertebral sections in acute ischemic myelopathy. K: T2 hyperintense plaque of the cervical cord demonstrating "pancake-like" gadolinium enhancement in the context of spondylotic myelopathy.
Figure 7. adapted from: Spinal cord lesions on MRI. Source 48. Filippi M, Preziosa P, Banwell BL, Barkhof F, Ciccarelli O, De Stefano N, et al. Assessment of lesions on magnetic resonance imaging in multiple sclerosis: practical guidelines. Brain. 2019 Jul;142(7):1858–75.

Gadolinium-enhancing lesions provide evidence of dissemination in time when some lesions enhance while other do not during a patient's initial presentation. To be classified as an enhancing lesion, it must be at least 3 mm in size and appear hyperintense on T1-weighted images 5-10 min after contrast administration. The enhancement must be correlated with an abnormality on T2 or T2-FLAIR images to confirm its significance. [48]

Characteristics of Gadolinium-enhancing MS Lesions: Typical (Green) and Atypical (Red) and Lesions which Should be Excluded in the Lesion Count:



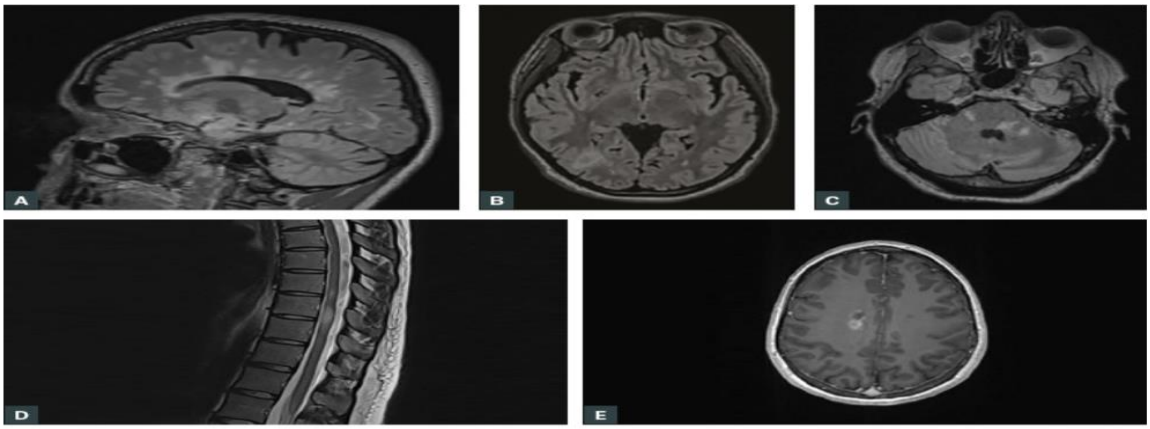
A: Nodular. B: Open-ring. C: Closed-ring. D: Spinal cord nodular enhancement. E: Capillary telangiectasis. F: Inhomogenous enhancement of large mass-like plaque indicative of atypical idiopathic inflammatory demyelinating condition. G: Band-like contrast accumulation in Balo disease. H: Enhancement of diencephalon, corpus callosum and longitudinally extensive S.C. lesion in NMOSD. I: heterogenous cortical and subcortical signal intensification with leptomeningeal involvement in CNS vasculitis. J: Leptomeningeal and pial signal intensification demonstrating the "trident sign" on cross-sectional view in neurosarcoidosis. K: Homogenous diencephalic

gadolinium uptake in anti-Ma2 encephalitis. L: pachy and inhomogenours signal intensification in glioblastoma.
Figure 8. adapted from: Gadolinium enhancing lesions on MRI. Source 48. Filippi M, Preziosa P, Banwell BL, Barkhof F, Ciccarelli O, De Stefano N, et al. Assessment of lesions on magnetic resonance imaging in multiple sclerosis: practical guidelines. Brain. 2019 Jul;142(7):1858–75.

Brain atrophy and neurodegeneration are key hallmarks of the MS course and up to 1% of brain volume is lost per year in untreated patients. This progressive atrophy is directly connected to the disability progression and cognitive decline. It can be assessed using various MRI techniques and CSF analysis, which reveal a reduction in tissue volume and a concomitant enlargement of intracranial CSF spaces. MRI-based evaluation includes measuring the ventricular width, corpus callosum thickness and / or the intercaudate distance. Additionally, newer automated high-resolution T1-weighted imaging techniques offer enhanced precision in detecting atrophic changes. [49]

Optic nerve lesions are key in differentiating MS and confirming involvement of the optic nerve. These lesions are best visualized using coronal fat-suppressed T2-weighted sequences with a slice thickness below 3mm. They typically exhibit T2-hyperintensity, enlargement of the optic nerve and enhancement with contrast agents. [48]

Typical MS MRI Findings:



A: White matter abnormalities adjacent to the lateral ventricles. B: Focal pathology near the cortical surface of the right parieto-occipital lobe. C: Infratentorial abnormalities involving the brainstem and cerebellum. D: Intramedullary changes within the thoracic segment of the spinal cord. E: Area of active contrast uptake following gadolinium administration.
Figure 9. adapted from: summarization of the most common lesions in MS. Source 67. Australian Journal of General Practice [Internet]. [cited 2024 Nov 10]. Multiple sclerosis diagnosis therapy and prognosis. Available from: https://www1.racgp.org.au/ajgp/2022/april/multiple-sclerosis-diagnosis-therapy-and-prognosis

On of the newest MRI markers for MS is the central vein sign, which is characterized by a central linear dark area within lesions on T2-weighted images. However, this sign has limitations, as it is highly dependent on the scanner filed strength. The effectiveness of this marker can be significantly improved with susceptibility weighted imaging (SWI) sequences, which increases its diagnostic value. Unfortunately, SWI sequences are not widely available or achievable in most hospitals, limiting the broader applicability of this marker. [33]

Paramagnetic rim lesions (PRL) are a type of chronic active lesions that may indicate a more aggressive disease progression and increased disability over time. On MRI, PRLs can be detected due to the magnetic properties of iron-laden macrophages and microglia along the lesion borders. These plaques can be observed in both relapsing and progressive MS using T2-weighted imaging or susceptibility-weighted imaging. Additionally, quantitative susceptibility mapping (QSM) can be employed to detect these lesions. [50] The term chronic active lesions, describes that ongoing demyelination takes place at the border of an inactive demyelinated centre. These lesions are confirmed in up to 40% of patients and are roughly 10% of all lesions detected in a patient. [51] How ever it is assumed that there is a significant underestimation of these lesions, due to MRIs relatively low sensitivity in detecting intracellular iron. [52]

The presence of more than four PRLs has been connected to a more severe physical and mental impairment at an earlier stage of the condition, compared to individuals with fewer or no PRLs. Further research and larger trials are needed to assess the significance of PRLs and potentially include them into future guidelines to predict MS disease progression. [51]

Optical coherence tomography (OCTs) is an investigation used to evaluate neurodegeneration by quantifying the reduction in retinal nerve fiber layer thickness and analysing the ganglion cell-inner plexiform layer (GCIPL) thickness, which serves as a marker for the loss of neuroaxonal tissue. This method allows for the analysation of structural abnormalities in the neuroretina. The functional aspects can be examined using the visual evoked potentials (VEPs). [53] By using these tests together, it is possible to examine how different factors contribute to the ongoing disease activity in MS, including inflammation, demyelination, axonal and neuronal loss, thereby offering insight into the current pathological state of the disease. These techniques could be used to monitor the disease activity and could be pivotal in clinical trials evaluating new neuroprotective or regenerative therapies. They may also help differentiate MS from other inflammatory diseases of the CNS. [54]

When clinical and MRI findings are inconclusive to provide a clear diagnosis of MS, cerebrospinal fluid (CSF) analysis should be considered. Oligoclonal bands (OCBs), proteins which are produced in the brain and spinal cord in response to inflammation, can serve as diagnostic marker for DIT and help confirm the diagnosis of RRMS in patients with clinically isolated syndrome and additional MRI evidence of DIS. OCBs are detected through electrophoresis or isoelectric focusing of the CSF. [8] They are regarded as the most reliable method for identifying immunoglobulins produced within the CNS. [55] CSF analysis is also valuable in diagnosing progressive MS or in cases with atypical clinical or imaging presentations. [8]

The activation of plasma cells leads to the production of free light chains (FLC), which can serve as markers of plasma cell activity. Specifically, Kappa free light chains (KFLC) are useful for diagnosing MS and detecting localized CNS inflammation in individuals with inflammatory CNS

diseases. KFLC have been studied for over 40 years, however no universal guidelines for their measurement have been established. They are more specific and sensitive than oligoclonal bands. KFLC are measured automatically and are stable against most influencing factors as well it is easy to perform and a labour and time saving procedure. Lambda FLC (LFLC) have a lower prognostic compared to OCB. Further research and broader studies are necessary to create appropriate threshold values for the KFLC levels and to assess the diagnostic accuracy including sensitivity and specificity. [55] KFLC are considered a medium-term prognostic marker for the disease course of MS, newer studies investigated their use as long-term prognostic markers but failed to conclude a significant result thus making it unlikely that it can be used for a long-term prognostication in MS. [56]

Neurofilament light chain (NFL) is an emerging biomarker that shows potential for evaluating disease progression and therapeutic effectiveness in MS patients. These neurofilaments, which are structural proteins found in neurons, are released when axons are damaged, making them a valuable indicator of neuronal injury. They can track the progression of RRMS to SPMS and reliably indicate disease activity. NFL are measured using single molecular array (SiMoA) technology, with the advantage of being detectable in serum, unlike OCBs which require CSF samples. [57] However, NFL is not highly specific for MS, as it can be elevated in over 30 different neurological disorders. Despite this, NFL shows strong promise as a short- and long-term prognostic marker as well as a clinical activity marker. Further studies are necessary to determine how it can be implemented into the clinical guidelines for MS. [58]

Regardless of their potential, biological biomarkers have not yet made it into clinical practice due to the lack of independent studies. However, some biomarkers have been validated and investigated in cohort studies for early identification of CIS transitioning to clinically defined MS (CDMS). These include CSF IgM OCBs, CXCL13, CHI3L1 and CSF neurofilament light chains. For differentiating MS subtypes, PPMS and RRMS, serum identification of microRNAs such as miR-22e and miR-15b could be useful. In patients with SPMS course a decreased level of CSF N-acetylaspartate has shown to differentiate it from RRMS and CIS. High relapse rate as well as early progression could be predicted by investigating CSF restricted IgM ICBs as well as increased CSF CHI3L1 levels, which could indicate quicker advancement to a more severe impairment in RRMS patients. The development of new biomarkers is a promising field and object for the future which could be a cost-effective tool for diagnosis and prediction of the disease course as well as treatment response. However, there is still a considerable way to go until enough studies evaluated the efficacy of these biomarkers and it could become a part in the everyday health-care setting. [32]

Laboratory studies play an important role in ruling out alternative diagnoses based on clinical suspicion. A standard work-up typically includes a complete blood count, vitamin B12 levels, thyroid function tests, as well as anti-nuclear antibodies. Syphilis and HIV serologies are also commonly recommended. Additional investigations may be chosen according to the patient's clinical physician's suspicion. [27]

The clinical history, family history, and any relevant genetic testing are also of great relevance when diagnosing MS. Key physical examination findings that might raise suspicion for Ms include a downward pronator drift on the pronator drift test, which can help localize the lesion. A downward drift suggests an upper motor neuron lesion, while an upwards drift could indicate a

cerebellar lesion, both type of lesions cause pronation. Gait instability and visual disturbances are common findings. The charcot triad, which commonly included intention tremor, abnormal eye movements, and dysarthria, is often observed. However, imaging studies are critical for confirming MS when the suspicion arises. [8]

The diagnosis of MS is a highly complex and technically demanding process. With advancements in diagnostic criteria, earlier diagnosis is possible, but there is still a risk of misdiagnosis. More research is needed to implement new techniques and biomarkers into the guidelines to ensure an accurate, timely diagnoses in everyday clinic.

4.8 Differential Diagnosis

Multiple Sclerosis is often referred to as “disease with a thousand faces” due to its complex and highly individualized nature. The broad differential diagnosis of MS is a significant challenge, especially considering the diseases ever-changing clinical features and its initial presentation. It's crucial to carefully rule out other conditions to prevent misdiagnosis, which could lead to inappropriate treatment and the potential harm associated with wrongly prescribed medications. [59]

A large group of disorders that can present with similar symptoms to MS are idiopathic inflammatory demyelinating disorders (IIDD).

One of the most challenging diseases in the differential diagnosis is neuromyelitis optica spectrum disorders, which can be differentiated by the onset of symptoms and serological tests that identify aquaporin-4 immunoglobulin G antibodies and myelin oligodendrocyte glycoprotein (MOG) antibodies. [27]

Acute disseminated encephalomyelitis (ADEM) often presents similarly to MS and mostly affects children and young adults following infections or vaccination. It can be distinguished through lumbar puncture and spinal and brain MRI, which reveal distinct features from MS. [8]

Schilder’s disease or Schildler’s myelinoclastic diffuse sclerosis presents as large supratentorial lesions predominantly found in children. This condition is characterized by impaired consciousness and rapid radiological progression. [60]

Balo’s concentric sclerosis involves headache, cognitive impairment, encephalopathy and epileptic seizures. Usually, the disease progresses rapidly and can be clearly identified on MRI by a helix-like structure with intertwined T2 hyper-and hypointense ribbons. [60]

The Marburg variant of MS is highly dangerous, marked by quickly progressing consciousness impairment leading to coma, decerebration and death within a few weeks. MRI scans often reveal rapidly advancing lesions in the infratentorial area, supratentorial region and spinal cord. When focal supratentorial lesion appear suddenly, it is critical to consider the risk of cerebral ischemia. [41]

Metabolic disorders that can mimic MS initially include B12-, folate-, and copper-deficiency, which can be distinguished with a serum work-up to differentiate symptoms. [59]

Adrenoleukodystrophy, particularly Addison-Schilder disease, caused by a defect in the ABCD1 gene on Xq28, is characterized by myelopathy and demyelination of the CNS. Usually, the onset is in children. The disease is diagnosed by typical MRI findings and the detection of abnormal lipid accumulation in specialized biochemical tests. [60]

Another significant group of diseases to consider are idiopathic inflammatory non-demyelinating diseases.

Neuro-Behcet's disease is diagnosed through clinical evaluation of symptoms and medical history, requiring recurrent oral ulcers occurring three or more times annually, along with at least two additional signs such as genital sores or scarring, skin abnormalities, or uveitis. MRI findings can show mesoencephalo-diencephalic lesions, sometimes extending to the basal ganglia, a distinctive MRI pattern known as the “bagel sign” may appear, indicating a spinal cord lesion characterized by a dark central area surrounded by a bright rim, with or without contrast enhancement. [60]

Sjörgen Syndrome is an autoimmune condition that mainly targets the bodys exocrine glands, resulting in keratoconjunctivitis sicca, xerostomia and a variety of systemic symptoms, including arthritis, Raynaud phenomenon, and other organ-specific involvements. Anti-SS-A and Anti-SS-B antibodies are typically present. Diagnosis can be supported through CSF analysis, where only one or two oligoclonal bands are present, along with the Schirmer test for exocrine dysfunction, the Rose Bengal test for ocular involvement, and antibody testing. [59]

Paraneoplastic neurological syndrome (PNS) are immune-mediated reactions associated with a malignant disease which could resemble MS optic involvement. However, it can be clearly differentiated with MRI, which reveals distinct features from MS. [60]

Sarcoidosis, characterized by granulomatous lesions that can affect various organs, including the CNS, can also present neurological symptoms. Lung X-ray, serum ACE levels, CRP and 24h urinary calcium levels and CSF investigation are needed. If the diagnosis remains unclear, tissue sampling from the lungs central region or from the skin may be considered. [59]

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disorder that can mimic MS both clinically and on imaging. Autoantibodies can help differentiate the disease as well as angiography which could show vasculitic involvement in the cerebral vessels. Wegener's Granulomatosis affects medium and small arteries and causes systemic symptoms. It can be diagnosed by elevated sedimentation rates and positive c-ANCA testing. [60]

Vasculitis, particularly primary central nervous system vasculitis (PCNSV), affects blood vessels throughout all parts of the CNS and has a broad set of symptoms. This condition lacks a specific diagnostic test and is often underdiagnosed. Brain MRI and CSF analysis are the investigations of choice to distinguish PCNSV from MS. ANCA-vasculitis, is a form of systemic vasculitis can be also differentiated with specific antibodies and MRI. [27]

Infections are another significant factor in the differential diagnosis of MS. Neuroborreliosis can mimic MS symptoms and can be diagnosed with CSF examination, which shows intrathecal borrelia-specific antibodies and lymphocytosis. Neurosyphilis, caused by untreated spirochaetal infection, may affect any region of the CNS or the peripheral nervous system. It presents with

supratentorial white matter lesions on MRI. CSF findings commonly show lymphocytic pleocytosis and increased protein levels. Diagnosis can be confirmed through the TPHA screening test. [59]

Progressive multifocal leukoencephalopathy (PML) and HIV-encephalopathy both present with white matter lesions on MRI, which can be challenging to differentiate from MS. However, a negative HIV test rules out these conditions. [60]

These are the most common diseases which should be differentiated from MS. Tough many other conditions can mimic the symptoms of MS, it is crucial to evaluate the patient´s specific symptoms, disease course, medical history, and imaging results to ensure an accurate diagnosis.

Overview of the Differential Diagnosis:

Clinical Presentation	Differential Diagnosis	Aspects and Investigations
Acute Optic Neuritis (ON)	1. Neuromyelitis Optica	1. Severe visual loss, bilateral rapidly progressing. AQP4 and MOG antibodies. MRI plaques in area postrema or diencephalon possible
	2. Leber hereditary ON	2. Genetic testing
	3. Toxic/Nutritional ON	3. Clinical history, alcohol and tobacco consumption. B12, methylmalonic acid, plasma homocysteine
	4. Non-arteritic ischaemic ON	4. Old age, history and examination, vascular risk factors
	5. Arteritic ischaemic ON	5. Old age, Autoimmune/ANA screen, ESR
Transverse Myelitis (TM) / Spinal cord syndrome	1. Neuromyelitis optica	1. Long transverse myelitis (>3 segments) affecting large areas of the central spinal cord with swelling and gadolinium intensification. MRI lesions in area postrema or diencephalon. AQP4 and MOG antibodies
	2. TM associated with systemic autoimmune disease	2. Systemic symptoms/ Autoimmune disease history, ANA screen, ESR
	3. Anterior spinal artery occlusion	3. immediate, severe start with anterior spinal cord syndrome. Old age. Vascular risk factors. MRI investigation

	4. Arteriovenous fistula / malformation	4. gradualonset, combination of upper and lower motor neurons. MRI / spinal angiography – Dilated or twisted dural veins
	5. Radiation myelopathy	5. Clinical history, vertebral changes on MRI
	6. B12/Folate deficiency	6. patients history includes nutritional deficiency or nitrous oxide exposure. CBC. MRI reveals extensive involvement of dorsal spinal columns. Blood B12 and plasma homocysteine/methylmalonic acid values
	7. Copper deficiency	7. patient history of gastrectomy or high zinc consumption. Longitudinal involvement of dorsal spinal columns on MRI. Blood copper concentration
Brainstem	1. Ischemic event (Polysymptomatic)	1. patient history, old age, MRI and CSF to discriminate
	2. Space occupying lesion	2. slow start, MRI to discriminate
	3. Migraine (Polysymptomatic)	3. Quicker recovery, intense headache. MRI to discriminate
	4. Brainstem encephalitis (Bickerstaff's)	4. encephalopathic or lethargic. MRI and CSF to discriminate
	5. Chronic lymphocytic inflammation with pontine perivascular enhancement response to steroids (CLIPPERS)	5. patient history, peripheral nerve inclusion in brainstem
Polysymptomatic	1. Cerebral autosomal dominant arteriopathy with cortical infarcts and leukoencephalopathy (CADASIL)	1. Family and patient history. Migraine, stroke-like episodes, significant mental impact. MRI and NOTCH-3 mutation testing
	2. Sarcoidosis	2. Multisystemic involvement, Chest CT, OCBs negative in CSF

	3. Systemic autoimmune disease	3. Systemic peculiarities, patient history of autoimmune condition, ANA test, ESR, Ro/La, SCL-70
	4. Primary CNS vasculitis	4. Encephalopathic. Minimal ischaemic plaque on MRI, MRI angiography
	5. Susac's syndrome	5. cerebral dysfunction, hearing loss and/or visual deficits. Retinal branch ischemia on fundus examination. Distinct lesions in the corpus callosum on MRI. Fluorescein angiography
	6. Neuro-Behcet's	6. Systemic and extra-CNS manifestations – cerebral venous thrombosis and inflammation of the meninges. linked with HLA-B5
	7. Acute disseminated encephalomyelitis (ADEM)	7. sudden multi-symptomatic presentation, typically following a viral infection. MRI reveals extensive areas of demyelination with contrast uptake, absent of T1-weighted hypointensities
Progressive disease	1. Spinal cord compression by disc, tumour etc	1. MRI
	2. Progressive metabolic myelopathy	2. Patient history, copper/B12 values, MRI
	3. genetic progressive spastic paraparesis / cerebellar ataxia (HSP, SCA)	3. Family and patient history, applicable genetic test
	4. Leukodystrophies	4. Family and patient history, applicable genetic tests
	5. infectious causes: HTLV and HIV	5. very long chain fatty acids, leukocyte enzymes, medical presentation, HLTV-1 and HIV antibody testing

Table 2. Differential diagnosis overview of MS. Cited from: Source 27. Dobson R, Giovannoni G. Multiple sclerosis – a review. European Journal of Neurology. 2019;26(1):27–40.

4.9 Treatment

Once the diagnosis of MS is confirmed the primary objective is to start the treatment promptly. The goal is to manage the initial flare-up, reduce the risk of future episodes and delay the progression of the disease.

A major part of the pharmacological treatment of MS are disease-modifying treatments (DMTs). For acute exacerbations, which affect physical functions, high doses of IV or PO glucocorticoids should be prescribed, an alternative would be plasmapheresis or Adrenocorticotropic hormone (ACTH) gel. [2]

Long term management should consist of a combination of medical treatment and lifestyle interventions to minimize exacerbation and optimize functional outcomes. A combination of DMTs and lifestyle modifications such as cessation of smoking, exercise, as well as the management of comorbidities are of high importance. Vitamin D supplements can help in diminishing the disease burden. [61] Another cornerstone of the treatment is the management of symptoms, namely spasticity, neuropathic pain as well as bowel and bladder dysfunction which can cause an immense impact on the quality of life of an individual. The treatment can be tailored according to the disease course and to the extend it affects each patient. [2]

In acute relapses the first line therapy consists of corticosteroids, either oral or IV which are both of equal efficacy. 500-1000mg/d Methylprednisolone IV or 1250mg/d oral for three to seven days is the standard approach with tapering afterwards. If Glucocorticoids are not sufficient or the patient doesn't respond to them, plasma exchange is a viable option. Five to seven exchanges of 40-60 ml/kg every second day for two weeks are the most common algorithm. The downsides are a high price and lack of studies proving the effectiveness of this approach. [2] Another option, if corticosteroids are not successful, is ACTH gel 80 U for five days reducing the symptoms and stabilization of the disease progression. [62]

Within the last decades an exciting development of new disease-modifying treatments have reached the market with more than 20 licensed medications, depending on the country. The goal of the DMTs is to stop or delay the clinical progression and reduce symptoms, as well as prevent the emergence of new disease progression detectable on MRI. This is achieved by suppression or modulation of the immune function. DMTs can be classified based of their mechanism of action into: Immunomodulators which include interferon beta and glatiramer acetate. Sphingosine-1-phosphate receptor modulators including fingolimod, Siponimod, ozanimod and ponesimod. Monoclonal antibodies including natalizumab, ocrelizumab, alemtuzumab and rituximab. Cytotoxic agents such as cladribine and mitoxantrone and anti-inflammatory agents as dimethyl fumarate and teriflunomide. [62]

Written below are the main DMTs for each course of MS and afterwards the mechanism of action as well as side effects will be discussed. The regimen for the use of DMTs follows two principals. Either high efficacy drugs are used as quickly as possible to prevent advancement and long-term impairments, while considering the notable side effects or a step-up approach to have a greater safety profile and the possibility to introduce more efficient medications if the initial medication is not sufficient. As the list of DMTS is increasing every year, the specific medication should be

chosen according to the patient. Mainly it should be focused on the age, comorbidities and if a pregnancy is planned, the site and number of lesions and the patients' preferences on the route of administration should all be considered. Only one medication is introduced at a time, combination therapy has not shown significant benefit. [63]

For the clinically isolated syndrome immunomodulators and anti-inflammatory drugs are used. interferon-ß, glatiramer acetate and teriflunomide are the medications of choice with the goal to delay or prevent the progression to definite MS. When the therapy is started as soon as possible a significant decrease in cognitive impairment is expected. [64]

The primary focus of MS treatment is on relapsing remitting MS course as most patients fall in this category. The selection of DMTs depends on many factors, including the physicians' preferences, MRI findings of lesions, as well as a risk reward assessment for each medication. The main objective of administering the DMT is to delay functional limitations and minimize the impairment of the patient. The group of medications which can be used are immunomodulators, anti-inflammatory, Sphingosine 1-phosphate receptor modulators, monoclonal antibodies and cytotoxic agents. Each group works through different mechanisms of action to target different aspects of the disease process. [62]

Autologous hematopoietic stem cell transplantation can improve and extend remission in RRMS and could be used in treatment refractory courses. The procedure is highly effective but carries the risks related to the induction chemotherapy required beforehand. [65, 27]

For secondary progressive MS, all the discussed DMTs can be used. Therapeutic decisions should be customized based on the specific needs of each patient, while considering a risk-benefit assessment.

Currently, treatment options for primary progressive MS are limited. Ocrelizumab is the only available DMT licenced for use. [62]

Since each medication has its own mechanism of action, it is important to be aware of the specific targets of involved in treatment. The knowledge of adverse effects associated with the use of medications is essential.

Interferon Beta acts as an immunomodulator and suppresses T cell activity with moderate efficacy. This leads to a decrease in proinflammatory cytokines and a decrease in lymphocytic invasion of the CNS. It is administered either intramuscular or subcutaneous. The most common adverse effects include reactions at the injection site, lymphopenia, leukopenia as well as flu-like symptoms. [27]

Glatiramer acetate, also an immunomodulator, has a similar mechanism of action and efficacy as interferon ß. The drug reduces proinflammatory Th1 lymphocytes, enhances the activity of anti-inflammatory Th2 lymphocytes, and inhibits the presentation of myelin antigens to T lymphocytes. It is injected subcutaneous. The side effects range from injection site reactions, lipoatrophy to postinjection reactions consisting of chest pain, palpitations and flushing. [62]

Dimethyl fumarate is administered orally as an immunomodulator with high efficacy with anti-inflammatory properties. The drug protects the nerve cells with its anti-inflammatory mechanism due to NRF2 activation and NFkB downregulation. The side effects are mainly gastrointestinal

symptoms such as nausea, diarrhea and abdominal pain. Lymphopenia and liver dysfunction could be observed and rarely a progressive multifocal leukoencephalopathy. [65]

Teriflunomide is a dihydro-orotate dehydrogenase inhibitor that reduces the pyrimidine synthesis and has an anti-proliferative anti-inflammatory effect. It has moderate efficacy and is administered orally. The adverse effects range from hair thinning to gastrointestinal symptoms and leukopenia. Teriflunomide has a significant risk of teratogenicity, making it contraindicated during pregnancy. [63]

Cladribine, a purine derivative with cytotoxic properties, disrupts DNA synthesis and repair, inducing cell death and resulting in the reduction of both T and B lymphocytes. It has a high efficacy. The main side effects are leukopenia, headache and nausea. As well as infections, most commonly herpes zoster. Mitoxantrone is another very potent nonselective cytotoxic agent that acts by inhibiting the topoisomerase. This leads to a reduced activity of T and B lymphocytes. The adverse are leukopenia, alopecia and gastrointestinal symptoms, as well as bone marrow suppression and secondary acute myeloid leukaemia. It has a significant cardiac toxicity. [27]

Sphingosine 1-phosphate receptor modulators namely Fingolimod, Siponimod, Ozanimod and Ponesimod are highly effective oral therapies that selectively modulate sphingosine 1-phosphate receptors. They work by sequestering lymphocytes in peripheral tissues, preventing their invasion into the CNS. There are several adverse effects which need to be considered. Many patients will experience bradycardia during the first dose. Liver dysfunction, hypertension, macular edema, headache, opportunistic infections and basal cell carcinoma have been observed. Fingolimod is linked to a slightly elevated risk of progressive multifocal leukoencephalopathy. [66]

Monoclonal Antibodies are a cornerstone of the MS treatment and are considered the most promising and most effective therapy. They are all administered intravenously.

Alemtuzumab is a targeted therapy that binds to CD52 protein, which is expressed on surface of lymphocytes and monocytes. It acts as an immune depleter, depleting B and T lymphocytes. The side effects include infusion reactions, infections, autoimmune phenomena also referred to as secondary autoimmunity, which can manifest as immune thrombocytopenia (ITP), glomerulonephritis and thyroid abnormalities.
Natalizumab is a monoclonal antibody that targets Anti-VLA4, inhibiting lymphocyte invasion into CNS. The side-effects are comparable to the other monoclonal antibodies and include headache, fatigue and infections. Specifically important to know for natalizumab is its potential to activate the John Cunningham virus, which can lead to progressive multifocal leukoencephalopathy. [63]
Ocrelizumab and Ofatumumab are monoclonal antibodies targeting CD20 on B-cells leading to their depletion. Adverse effects are reactions at the injection site, infections, resurgence of hepatitis B virus and development of progressive multifocal leukoencephalopathy. [27]

Close monitoring and follow up is indicated with majority of DMTs and should be strictly followed according to guidelines for each specific medication. [67]

Overview of the Most Used Disease-Modifying Therapies

DMTs	Reduction in relapses	Reduction in new MRI lesions	Reduction in disability progression	Reduction in whole brain atrophy
Alemtuzumab	75%	95%	42%	42%
Interferons beta	30%	50-70%	n.s.	n.s.
Cladribine	55-58%	73-77%	33%	16%
Daclizumab	45%	54%	n.s.	n.s.
Dimethyl fumarate	51%	60%	38%	30%
Fingolimod	52%	75%	18%	35%
Glatiramer Acetate	30%	30%	n.s.	n.s.
Natalizumab	68%	83%	42%	44%
Ocrelizumab	46%	77-83%	40%	23%
Teriflunomide	30%	50%	30%	25%

Table 3. DMT overview, Approximate efficacy of the approved DMTs on relapse rate, new MRI lesions, disability progression and brain atrophy when compared with placebo. [cited 2025 Feb 11]; Cited from: https://core.ac.uk/reader/1813321?utm_source=linkout

Supportive Care and Symptom Management

It is recommended to encourage every patient to be as physically active as possible and to adhere to the follow-ups with the neurologist It is recommended to refer every patient to a specialist if any signs of depression arise.

Urinary and bowel dysfunction can be improved by pelvic floor physical therapy that aids in decreasing the urinary frequency, as well as bladder training and anticholinergics or antimuscarinics could be used to relieve symptoms. In cases of urinary retention, intermittent catheterization and parasympathomimetic drugs could be prescribed. It is recommended to encourage dietary fibre and fluid intake in bowel dysfunction. Laxatives and stool softeners could be prescribed as well. [69]

Spasticity and chronic neuropathic pain are one of the main burdens of patients. The assistance for these symptoms can be pharmacological as well as physiological. For spasticity, stretching could be beneficial and in general an avoidance of triggers such as certain positions, pain or constipation could further ease the symptoms. Pharmacological options are baclofen, tizanidine, gabapentin, dantrolene or botulinum toxin. For the neuropathic pain antidepressants, especially TCAs are often prescribed as well as anticonvulsants. As recent studies have shown, cannabinoids could be a promising substance for patients, who complain of spasticity and neuropathic pain, to improve the quality of life immensely. [70] Tremors could be treated with deep brain stimulation techniques, beta blockers and gabapentin. [69]

If a patient experiences walking difficulties, mobility aids such as canes or walkers can be used. pharmacologically dalfampridine could be considered.

Common symptoms, as fatigue, could be counteracted by amantadine or modafinil. When sexual dysfunction is experienced sildenafil could be prescribed. Additionally, nonpharmacological measures such as vaginal lubricants or extracavernous injection therapy can be used. Rehabilitation, therapy, acupuncture and certain surgeries such as tenotomy, rhizotomy or neurectomy could be initiated depending on the patients needs and wishes. [71] It is important to see the patient as a whole and not only treat the obvious symptoms but also offer him guidance and assistance when it comes to mental health related problems.

In the future it is expected to have better medications for each MS subtype. The more knowledge about the pathophysiology and the aetiology of the disease development is gained the greater is the potential for treatment in all types of MS. Currently under investigations are remyelination therapies to repair damaged neurons, as well as neuroprotective therapies to prevent the progression and degeneration of demyelinated nerves. A lot more studies are needed to provide every patient the individual treatment approach he needs and deserves.

4.10 Prognosis:

Factors associated with a worse prognosis for disease progression include being male and having an onset age greater than 40 years. The presence of numerous symptoms, especially with early involvement of coordination and movement functions, also increase the risk for a worse prognosis. Failure to return to baseline level following an exacerbation, indicates a higher risk of a rapdily progressive form of MS. Another factor which contributes to a poor prognosis is a frequent relapse rate within two years after the first symptoms of the disease. [72]

4.11 Effect of Pregnancy on MS and Vice Versa:

The risk of exacerbations and relapses are reduced during pregnancy, but a significantly elevated risk of relapse is observed in the after-birth period. Breastfeeding is thought to reduce the rate of relapses postpartum. The long-term clinical progression of MS remains consistent. It is extremely important to closely monitor the DMTs prescribed, and a risk benefit assessment should be performed before prescribing any treatment during pregnancy. [67]
MS leads to an increased rate of elective caesarean sections and a decrease in birth weight. [68]

4.12 Future Diagnostic Techniques:

One promising field of ongoing research is not only the central vein sign discussed before, but also subpial demyelination. It is a type of cortical lesion, which is tightly linked to inflammation of the meninges and pro-inflammatory activity within the intrathecal space. It has shown high specificity for MS, however it is undetected in the majority of scans as ultra-high field imaging with T2 or MP2RAGE sequences are needed to reliably detect it. As of now it is not available in the clinical setting. Current guidelines do not provide sufficient recommendations for using this biomarker, but in the future, it could be a valuable tool for MS prediction and monitoring. [48]

Another potential biomarker for the future could be the leptomeningeal enhancement or cortical demyelination, which could provide insight into the accumulation of immune cells in specific brain regions, particularly B cells located along the meninges. However, this biomarker can only be reliably used for disease activity control in MRI machines with more than 7 Tesla, which makes the routine use impossible as of now. [33]

Smouldering or slowly evolving lesions, commonly found in chronic plaques of MS, are characteristic of long-standing disease and progressive forms. These lesions could play a crucial role in distinguishing MS from neuromyelitis optica spectrum disorders and cerebrovascular diseases, as they have so far been exclusively identified in MS. [48]

5. Neuromyelitis Optica Spectrum Disorders

Neuromyelitis optica (NMO), also called Devic´s disease is an Immune mediated, long-term inflammatory condition of the CNS, primarily impacting the optic nerve and spinal cord. It is characterized by astrocyte dysfunction and loss, with the result of demyelination and neurodegeneration. [3] A relapsing disease course is common. The disease is highly disabling and causes great impact on patients' functional outcomes and overall health status. Most patients are characterized by aquaporin-4-antibody positivity. [7] The understanding of the pathophysiology as well as clear diagnostic criteria are lacking and subject to ongoing studies.

5.1 Epidemiology and Aetiology

The prevalence of NMOSD varies based on regional factors and population groups. It is more prevalent in Africa and Asia. In low prevalence regions the incidence is around 0.05-0.40, while in high incidence regions the incidence ranges between 0.52-4.4 per 100.000 inhabitants. Like in MS women are much more susceptible, up to 9:1 compared to males. Most patients are at the beginning for their forties, thus the median age onset is later compared to MS. [10]

Risk factors are thought to be mainly genetic factors. HLA-DRB1*03 seems to be the most predisposing genetic risk factor with an odds ratio of 2.46. Many more genes are suspected to increase the likelihood of developing NMOSD but are still under investigation. [7].

Environmental risk factors range from infections, such as varicella and herpes zoster, to vaccinations, immune checkpoint inhibitor use, allergic reactions or surgical operations, previous malignant diseases and the presence of other autoimmune diseases. [7]

Vitamin D deficiency might play a role like in MS, but insufficient data is available as of now. [73] Smoking is linked to an elevated risk of developing NMOSD as well as a worse prognosis factor for the disease course. [7]

5.2 History

The first description of this disease was made in 1894 by Dr. Eugene Devic who reported of severe opticomyelitis in one of his autopsied cases.

In 1999 the first diagnostic criteria were proposed. It essentially consisted of two symptoms, optic neuritis and myelitis, without further CNS involvement. Patients who experienced only optic neuritis and myelitis were classified as “opticospinal MS”. When brain involvement was present, it was diagnosed as “conventional MS”. [74]

Groundbreaking for nowadays diagnostic criteria was the discovery of the Aquaporin4-IgG in 2004 which was quickly included in the 2006 diagnostic criteria. This was the first time were NMOSD was clearly differentiated and separatable from MS. Magnetic resonance imaging became an essential part of the diagnostic criteria, with the demonstration of longitudinally extensive transverse myelitis (LETM). [74]

In 2015, the most recent guidelines for the diagnostic criteria have been published. These guidelines helped a lot to identify seronegative forms, with negative AQP4-IgG. The focus lies on the myelin oligodendrocyte glycoprotein antibodies as well as two clinical criteria with either optic neuritis, acute myelitis or area postrema syndrome (APS) and one additional MRI feature. [7]

5.3 Pathophysiology

The pathophysiology of NMOSD remains incompletely understood and is exceptionally complex.

One major part of the disease development is the presence of selective aqua porin 4 antibodies (AQP4-ab), which target AQP4 proteins and trigger autoimmune astrocytopathy. AQP4 is predominantly located perivascularly and within peripheral astrocyte foot processes at the blood-brain barrier. [3] AQP4 plays an essential part in water homeostasis, glutamate reuptake, and neuroexcitation in the brain and spinal cord. [75]

AQP4 antibodies are primarily of the IgG1-isotype and are thought to stimulate interleukin-6(IL-6) production in astrocytes, which in turn activates endothelial cells and compromises the blood-brain barrier. Upon attaching to the extracellular portion of the AQP4 receptor, these antibodies activate the complement system, promote astrocyte-driven cell injury, and lead to sequestration of the glutamate transporter EAAT-2, contributing to excitotoxicity. [10] This cascade known as antibody-dependent-cellular cytotoxicity (ADCC) results in astrocyte destruction and inflammation depriving neurons and oligodendrocytes of essential support. [3] Consequently, granulocyte infiltration leads to oligodendrocyte injury, demyelination, axonal damage, and accelerated neurodegeneration. [7, 10] Evidence suggests, that AQP4-Ab are synthetized peripherally and enter the central nervous system through a disrupted BBB. [3]

B cells play a major role in the development of the condition. B cells produce AQP4-Ab after being stimulated by IL-6 and function as antigen presenting cells to follicular helper T cells, which support B cell maturation and isotope switching. This interaction establishes a self-reinforcing feedback loop between B and T lymphocytes, further amplifying the immune response. T cells, particularly Th17 cells, are crucial in NMOSD progression. IL-6 and IL-21 released by Th17 cells

contribute to BBB disruption by promoting endothelial activation and facilitating the migration of neutrophils across the endothelium, exacerbating inflammation and neurodegeneration. [3]

In summary for the seropositive NMOSD, both innate and adaptive immune cells play a role in the pathogenesis, leading to diminished AQP4 expression, activation of the complement cascade around blood vessels, accumulation of AQP4-IgG, structural damage to astrocytes, injury to axons and myelin sheaths, and invasion of immunecells including neutrophils and eosinophils. [7]

The pathophysiology of seronegative cases remains unclear; it appears to be heterogenous across individuals. It is characterized by an increased inflammatory response, mainly IL-6. Unlike seropositive NMOSD, it is uncertain whether astrocytopathy plays a central role in seronegative cases. Future research might identify autoantibodies or complement involvement which could provide further insights into seronegative NMOSD pathogenesis. [76]

5.4 Course and Subtypes of NMOSD

Approximately 80% of Neuromyelitis optica spectrum disorder cases are linked to the detection of pathogenic AQP4 antibodies. In some seronegative patients, autoantibodies directed at myelin oligondrocyte glycoprotein (MOG-IgG) have been detected, leading to a diagnosis of MOG-IgG-associated disease (MOGAD). A small subgroup of patients have neither AQP4 nor MOG-IgG antibodies, however, this form of the disease remains poorly understood. [77]

NMOSD typically follows a relapsing course, with superimposed exacerbations. A progressive course is unlikely, as disease burden is directly linked to relapses, which, if not promptly treated, can cause severe disability and blindness. Without appropriate intervention, around half of NMOSD patients become severly disabled and lose their vision, and about one-third of them pass away within five years of their initial episode. [10]

MOGAD patients are usually younger at disease onset and the prevalence of female patients is not as high as compared to NMOSD. [77]

The treatment regimens mainly focus on the AQP4-IgG-positive NMOSD subtype as still a lot of knowledge is missing to understand the double-negative subtypes, which makes finding an effective treatment for these cases a significant challenge.

5.5 Symptoms

The clinical symptoms of NMOSD are generally comparable to those of MS patients, however the clinical picture consists of more severe attacks, which, if left untreated can result in significant disability.

The hallmarks of the disease are episodic acute flare-ups that lead to rapid, stepwise decline, without any progression of symptoms during the periods between attacks.

The most suggestive and commonly observed symptoms include bilateral optic neuritis, often involving the optic chiasm, leading to severe visual field defects, significant vision loss and

retrobulbar pain. Additionally, NMOSD is characterized by the extensive spinal cord involvement, episodes of paroxysmal tonic spasms, and area postrema syndrome (APS), which typically manifests as persistent hiccups, nausea and vomiting. However, no single symptom is pathognomonic. [4] Optic neuritis is the first presenting symptom in up to 45% of patients. [7]

Transverse myelitis, is observed in as many 85% of patients, is characterized by symmetric paraplegia, sensory loss and bladder dysfunction, which is the initial symptom in roughly one-fourth of patients. [74]

Acute brainstem syndrome often overlaps with APS. Patients may present with oculomotor disturbances, such as double vision and abnormal eye movements, or other cranial nerve impairments, depending on the affected area. As AQP4 is found in periventricular regions, bilateral lesions can disrupt the function of hypothalamic hypocretin neurons, leading to narcolepsy associated with lesions in the diencephalon and decreased CSF hypocretin levels.

Although NMOSD primarily affects the spinal cord and optic nerve, brain involvement has been observed in up to 60% of individuals. While most of these changes are unspecific and asymptomatic, some patients may present with encephalopathy, seizures and hemiparesis. [10]

NMOSD symptoms can be broad, non-specific, and significantly impact quality of life. Systemic symptoms including neuropathic pain, tonic spasms, bladder and bowel dysfunction, sexual dysfunction, fatigue, sleep disorders, as well as psychiatric and cognitive impairments are a substantial burden on the patient's daily life. [78]

Due to the potential for rapid and severe disability, and the often-non-specific presentation, a prompt and thorough diagnosis is crucial to prevent permanent disability accumulation.

5.6 Diagnosis

The detection of AQP4-IgG is essential for diagnosing NMOSD, with testing commonly conducted through live cell-based assays on serum samples. These assays, utilizing flow cytometry, exhibit more than 80% sensitivity and over 99% specificity. [7] However, false-negative results may occur in patients receiving immunosuppressive therapy or those who have undergone plasma exchange. [79]

In CSF analysis, pleocytosis is expected, along with the absence of oligoclonal bands. However, CSF findings alone have only moderate specificity and sensitivity and are therefore insufficient to distinguish between NMOSD, MS and MOGAD. A helpful differentiating factor is the measles, rubella and zoster virus reaction. If out of the three viral antigens two yield a positive antibody index, it is regarded as a specific biomarker for MS and very rarely seen in NMOSD. [7]

To diagnose NMOSD with AQP4-IgG, at least one key clinical symptom, a confirmed positive AQP4 antibody test, and the exclusion of other potential conditions are required. [4]

If the AQP antibodies are negative or unknown the diagnosis requires two core symptoms related to at least one clinical attack which follows the underneath criteria: A: A mandatory symptom must be optic neuritis, acute myelitis with longitudinally extensive transverse myelitis lesions (LETM) or

area postrema syndrome. B: Dissemination in space must be proven. C: MRI criteria must be met. Additionally, an alternative diagnosis must be ruled out. [4]

The clinical core features used to diagnose NMOSD include optic neuritis, acute myelitis, area postrema syndrome, acute brainstem syndrome, narcolepsy, or acute diencephalic syndrome, along with characteristic MRI findings of brain lesions or cerebral syndromes. [7]

When AQP4-IgG is absent or it´s status remains uncertain, additional MRI criteria must be fullfilled. For acute optic neuritis, it is critical to observe either nonspecific or normal white matter lesions, or an MRI of the optic nerve showing T2 hyperintensities or T1 gadolinium-enhanced lesions spanning at least half of the length of the optic nerve or involving the optic chiasm. In acute myelitis, MRI should reveal longitudinally extensive transverse myelitis (LETM), defined as lesions covering more than three consecutive spinal segments, or evidence of focal spinal cord atrophy over three contiguous segments in patients with prior acute myelitis. When area postrema syndrome is suspected, MRI must demonstrate lesions in the dorsal medulla or area postrema. In cases of acute brainstem syndrome, MRI should detect periependymal lesions in the brainstem. [4]

The lesion location is crucial for the diagnosis and symptom development. In optic neuritis, the optic chiasm and the optic nerve are commonly involved. Brainstem lesions often occur periaqueductally or in the dorsal area, near the fourth ventricle, impacting structures like the area postrema and solitary tract. These lesions can result in narrowing of the aqueduct and lead to hydrocephalus due to obstruction. Pathognomonic lesions are in areas in which AQP4 are mainly expressed, such as the hypothalamic or periventricular regions. Helpful in the differentiation of NMOSD from MOGAD can be the fact that most lesions resolve in MOGAD, where in NMOSD the lesions typically persist. [7]

In general, T2-weighted brain changes are observed in over half of NMOSD patients, however, these are usually non-specific and asymptomatic. Unlike MS, there are no standardized guidelines for routine MRI follow-ups. [7]

Future diagnostic tools, such as optical coherence tomography (OCT) and visual evoked potential (VEPs) may aid in the diagnosis and differentiation. However, due to limited research and current diagnostic criteria, these methods are not yet widely used.

5.7 Treatment

The primary aim of treatment is to suppress relapses, specifically by decreasing their frequency and severity to prevent disease accumulation.

The pharmacological treatment includes both on-label use as well as some off-label medications, the latter of which have shown promising results in clinical trials. The older and current regiment consist of medications commonly used to treat NMOSD. Currently, numerous clinical trials are underway to investigate additional medications, which are briefly mentioned below.

Acute relapses should be treated aggressively to prevent residual disability with the goal of minimizing CNS injury and promote long-term neurological recovery. Management typically involves high-dose steroids and plasma exchange. [10] Standard treatment includes 1g

methylprednisolone IV therapy for 3-7 days, followed by a gradual oral taper over several weeks. [3] The treatment should be initiated as quickly as possible and even then, only approximately 35% of patients achieve complete recovery afterwards. [80] If the response of corticosteroids is insufficient or absent, plasma exchanges at every second day for two weeks with volumes of 1.5L per treatment or immunoadsorption may be considered, if the acute relapse is still within a five-day window. During immunoadsorption immunoglobulins get removed from the circulation via adsorption to tryptophan or protein A. The outcome of plasma exchange is usually better, and a full recovery is more likely compared to steroids. [81] Studies indicate that early treatment initiation significantly improves outcomes. [3]

Currently and previously used medications for long-term relapse prevention include azathioprine, rituximab, mycophenolate mofetil (MMF), tocilizumab, eculizumab, satralizumab and inebilizumab. [3]

Azathioprine inhibits purine synthesis, thereby suppressing DNA, RNA and protein synthesis. However, it does not cross the BBB and requires 4-6 months to achieve full efficacy. In the interim, corticosteroids should be administered. While results are generally promising, up to 62% of patients discontinue azathioprine due to severe adverse effects, including elevated liver enzymes and pancytopenia. [82] Additionally, rituximab and mycophenolate mofetil have demonstrated superior efficacy, leading to a decline in azathioprine use in many countries. [83] MMF is a prodrug of mycophenolic acid (MPA), which depletes guanosine nucleotides in T and B lymphocytes, inhibiting their activation and inhibiting both cell-mediated immune response and antibody production. It also prevents lymphocytes and monocytes recruitment to inflammatory sites. MMF side effects include gastrointestinal complications, hypercholesterolemia, elevated transaminases, myelotoxicity, infections, and, rarely, multifocal leukoencephalopathy. [84]

Several trials have proven that rituximab is more efficacious than MMF and AZA in reducing relapses. [3] Rituximab, a monoclonal antibody targeting the CD20 antigen, eliminates B cells and has been shown to markedly decrease relapse rates and enhance clinical outcomes in patients regardless of AQP4-IgG status. Side-effects are relatively rare, ranging from allergic reactions to infections and neutropenia. [84]

Tocilizumab inhibits IL-6 signalling by competitively blocking its binding site. It has been effective in patients who did not respond to rituximab, leading to significant reductions in clinical and radiological disease activity. Compared to AZA, tocilizumab is associated with lower relapse rates and fewer side effects [85].

Many of the aforementioned drugs are now outdated in some countries and are either not routinely or used or are prescribed off-label for NMOSD. More recently developed and currently in use in most countries is eculizumab, a humanized monoclonal antibody that blocks the terminal complement cascade by inhibiting the activation of C5, thereby prevention its conversion into C5a and C5b. Clinical trials have demonstrated significant relapse reduction with eculizumab, and it is generally considered safe and manageable. However, it carries an elevated risk of meningococcal infection, necessitating vaccination at least two weeks before the first dose. [3]

Inebilizumab is another recently developed humanized monoclonal antibody, that targets CD19, leading to a B cell depletion. Clinical trials have demonstrated a favourable safety profile, with side effects comparable to those in placebo groups, and a relapse risk reduction of up to 73%. [84]

Satralizumab, a humanized IL-6R monoclonal antibody, binds to membrane IL-6R and dissociates it in lysosomes. It is a next-gen antibody originating from tocilizumab. It has a longer half-life of around 30 days and a four times higher affinity for IL-6R compared to tocilizumab. Studies have shown an up to 80% relapse reduction compared to the placebo group, with side-effects similar to placebo.[86]

Cyclophosphamide, methotrexate and mitoxantrone have demonstrated disease stabilization, but are not the preferred medications for NMOSD. [3]

Several medications for acute treatment are currently being investigated in clinical trials. Bevacizumab binds to vascular endothelial growth factor, inhibiting angiogenesis and restoring the BBB. Ublituximab, a monoclonal antibody targeting CD20, may aid in acute B cell reduction and is administered, as Bevacizumab, alongside high-dose IV methylprednisolone to improves the disability outcomes. Early trials of HBM9161 and NPB-01have not shown improved patient response when combined with high-dose corticosteroids. NPB-01, an intravenous immunoglobulin, interrupts autoreactive T-cell interactions with antigen-presenting cells, while HBM9161, a human monoclonal antibody, targets FcRn to accelerate IgG degradation. Research continues to assess their therapeutic potential.

Ravulizumab, an anti-C5 monoclonal antibody, blocks C5 activation and prevents its cleavage into C5a and C5b, leading to lysosomal degradation of C5. Bortezomib binds to the active site of the 26S proteasome, eliminating plasmablasts and plasma cells, potentially protecting astrocytes from inflammatory damage in the early stages of the NMOSD. Interestingly, cetirizine a second-generation antihistamine, may serve as adjunct therapy by preventing eosinophil-mediated damage. Multiple additional drugs are currently under investigation, with the hope of improving acute relapse treatment and recovery outcomes. [3]

Future treatments for long-term relapse prevention include telitacipet, a recombinant fusion protein that targets the transmembrane activator and calcium modulator as well as cyclophilin ligand interactor pathways. It inhibits plasma and B cells maturation and has demonstrated both strong efficacy and a favourable safety profile. [87]

Mesenchymal stem cell therapy is not yet available in standard guidelines and is only used experimentally. However, it shows promise in modulating both innate and adaptive immune responses by suppressing T, B and natural killer cell function. Current studies suggest significant neurological improvement with minimal side effects. [78]

Pregnant women are at a significant elevated potential for flare-up, particularly in the period after birth. There is currently limited data on relapse risks during pregnancy, and optimal medication choices remain unclear. MMF, methotrexate or mitoxantrone should not be used, while AZA, rituximab, eculizumab and steroids are currently considered safe and may be used in cases of severe disease. In the future tocilizumab could play a valid option in the treatment of NMOSD in pregnant women. [3]

Symptomatic treatment should follow a similar approach to that of multiple sclerosis, incorporating lifestyle modification, rehabilitation, mobility aids, and pharmacological therapy. Treatment for tonic spasms and neuropathic pain should include anticonvulsants and muscle relaxants. Antidepressants may also be helpful for both neuropathic pain and mood disorders such as depression and anxiety. Fatigue, a hallmark symptom of NMOSD, may be managed with stimulants. Bladder dysfunction can be treated with oxybutynin, darifenacin, solifenacin and mirabegron. The specific medication and dosage should be prescribed by the treating specialist. The management of NMOSD should not be limited to neurologists but should involve a multidisciplinary team to optimize symptom control and improve quality of life despite the disease´s severe impact. [78]

In the future many new therapies will emerge as our understanding of NMOSD pathophysiology expands and the diagnostic criteria will be refined. The more we know about the disease mechanisms the more tailored medications will be developed targeting the different disease pathways. As of now there is a lack of therapies which can improve regeneration and restore functionality. Most medications are developed for the AQP-IgG positive subgroup of patients and a significant number of patients do not receive the optimal treatment due to their lack of representation in clinical trials. Still a lot of research must be conducted to understand more about the disease course of serum negative patients. A lot of questions remain unanswered: which is the optimal drug to initiate treatment? Does the severity of the disease impact the choice of medication use? Is monotherapy or combination therapy more desired? Can we even compare drugs in terms of efficacy – on what basis? Compared to MS a lot of questions are still not answered and are subject to studies and trials in the future.

5.9 Prevention

The cornerstone of managing patients with NMOSD should be relapse prevention, achieved by long-term immunosuppression tailored to the patient´s needs and individual disease mechanism.

A better understanding of the disease is essential, as many initial presentations NMOSD occur in emergency departments. It is crucial that not only neurologists but also physicians across all medical fields are aware of the disease, enabling them to suspect NMOSD and promptly refer patients to a neurologist. [10]

At present, we know too little about NMOSD to discuss preventing the disease before symptoms appear. However, future research should focus on fully understanding its pathogenesis and etiology to identify risk and protective factors. This knowledge would not only improve treatment options but also help prevent the disease from developing in the first place.

As I conclude my thesis, it is important to emphasize once again that MS and NMOSD are two distinct diseases with different treatment approaches. Their pathogenesis differs entirely, as does the type and location of lesions observed on MRI. While their symptoms may appear similar at first glance, NMOSD is characterized by rapid accumulation of disability and more pronounced symptoms, which should raise suspicion for NMOSD rather than MS. Additionally, the disease courses are fundamentally different: MS generally follows a progressively worsening trajectory,

while NMOSD is characterized by distinct relapses, often with superimposed exacerbations. The differentiation between MS and NMOSD is particularly important, as the long-term treatment options and prognosis of these two demyelinating conditions of the central nervous system differ significantly.

Differences Between Neuromyelitis Optica Spectrum Disorder and Multiple Sclerosis

	MS	NMOSD
Frequency of disease	Frequent	Low incidence
Latitude gradient	Identified	Not confirmed
Female sex, %	70%	90%
Ethnic variation	Common in whites	Higher in Africans and Asians
Age at onset	Around 30	Around 50
Progressive course	Typical	Uncommon
Coexistent autoimmune disease	Uncommon	Often: MG, SLE, Sjogren's. Thyroid, APL
Tissue involvement	White matter	White and grey matter
Necrosis/Cavitation	Uncommon	Often
Leukocyte infiltrate	T and B lymphocytes	Neutrophils and eosinophils
Attack severity	Typically minor	Usually intense
Spinal cord	Short-segment peripheral spinal cord abnormalities, may be asymptomatic	LETM, central cord infiltration, spread into medulla, symptomatic, acute T1 hypointense signal
Optic nerve	Short segment inflammation, anterior, one-sided, good outcome	Extended posterior inflammation, unilateral or bilateral, limited recovery
Brainstem	Any region, ventral or dorsal pontine plaque, clearly defined borders	Area postrema/dorsal medulla MRI plaque, could be in continuity with spinal lesion
Diencephalon	rare	Hypothalamic, thalamic, surrounding the ependymal 3rd ventricle area
Corpus callosum	Very often, small plaques, anterior/posterior CC	Uncommon, long lesions, Corpus callosum-septal junction in central and rear portions of CC
Cerebral hemispheres	round lesions adjacent to lateral ventricle (Dawson's fingers), lesions near corpus of lateral ventricle and inferior temporal lobe, juxtacortical U-fibre lesions	big, confluent subcortical or deep white matter plaques, long corticospinal tract plaques
CSF	minimal pleocytosis, mononucleic, OCBs 85%	sometimes markedly pleocytosis, lymphocytes, PMN and mononuclear cells, OCBs rare

Permanent disability	Commonly in later stage	Usually relapse-depending
Relapse treatment	Steroids for highly impairing exacerbation relapses	large dose of steroids, prompt treatment crucial. Plasma exchange as last resort
Long-term treatment	DMTs	AZA, MMF, RTX for AQP4-Ab positive NMOSD or relapsing seronegative NMOSD

Table 4. Comparison of MS and NMOSD, Cited from: Huda S, Whittam D, Bhojak M, Chamberlain J, Noonan C, Jacob A, et al. Neuromyelitis optica spectrum disorders. Clin Med (Lond). 2019 Mar;19(2):169–76.

6. Case Reports

In the following we will discuss about two case reports, dealing with an atypical first presentation of MS in the emergency department and an unusual case of NMOSD. We will examine the diagnostic challenges and assess whether the authors of the case reports followed guidelines correctly or if any mistakes hindered a quick diagnosis.

The first case report, published in 2022 from Colombia by MD Andrés Felipe Herrera Ortiz, discusses a 24-year-old patient who presented with cervicalgia, diplopia and vision problems to the emergency department. A head CT scan was performed, revealing a megacystic lesion, thus creating a diagnostic challenge.

The patient had a history of type 1 diabetes and came to the emergency department with symptoms lasting seven days. During the physical examination, limitations in abducting the right eye, left paresis and paraesthesia was observed. The head CT scan revealed a 3cm cystic lesion in the right frontal lobe without swelling or mass effect. Initially it was suspected to be a CNS infection. An MRI with spectroscopy was performed, demonstrating several regions of high-signal adjacent to the lateral ventricles on T2-weighted images, accompanied by a prominent cyst in the right frontal lobe. Spectral analysis revealed a small decrease in N-acetyl aspartate levels (NAA) and an elevation in lactate, lipids and choline. These findings strengthened the suspicion that the symptoms originated from a demyelinating disease with megacystic manifestations. A Lumbar puncture was done, revealing type 2 oligoclonal bands, which proved the diagnosis of MS. The patient was immediately started on 1g of methylprednisolone daily for 5 days. The symptoms improved, and he was discharged with a follow-up neurological appointment and natalizumab 300mg per month after a previously confirmed negative John Cunningham virus test.

MS with megacystic presentation is uncommon and the diagnostic workup can be difficult. The differential diagnosis includes infections, inflammatory disorders, demyelinating disorders and neoplasms. The most important tools for the diagnosis are MRI and CSF examination. MRI findings

helped rule out infections, as the detected pattern showed no signs of edema, mass effects or ring-enhancing lesions. The physician ruled out neoplasms based on the lesion's location and appearance.

Atypical inflammatory demyelinating conditions can be differentiated into four morphological subtypes, infiltrative, Balo-like, ring-like, and megacystic. [88] Usually, atypical lesions coexist with typical lesions, as seen in this case report, where the megacystic lesion was associated with a periventricular high signal focus, the so-called “Dawson fingers” in FLAIR sequences.

Imaging Characteristics of Atypical Demyelinating Disorders Subtypes:

Morphological subtypes	**Imaging appearance**	**T1**	**T2**
Infiltrative	Broad asymmetric poorly demarcated T2 signal alterations with variable contrast enhancement.	Hypointense	Hyperintense
Balo-like	Numerous concentric rings	Hypointense	Hyperintense
Ring-like	Spherical abnormalities exceeding 2cm, with partial ring-shaped contrast uptake and encircled by poorly outlines region of elevated T2 signal intensity, indicative of swelling.	Hypointense	Hyperintense
Megacystic	Expansive fluid-filled abnormality exceeding 3cm, exhibiting partial peripheral contrast uptake.	Hypointense	Hyperintense

Table 5. adapted from: Seewann A, Enzinger C, Filippi M, Barkhof F, Rovira A, Gass A, et al. MRI characteristics of atypical idiopathic inflammatory demyelinating lesions of the brain. J Neurol. 2008 Jan 1;255(1):1–10.

The levels of NAA depletion correlate with the subsequent development of physical disability. In the case of this 24-year-old patient, there was only a mild decrease in NAA, suggesting a good prognosis and recovery, which turned out to be accurate.

Discussion

In this case report, the physicians performed a remarkable workup to quickly diagnose of MS and initiate treatment immediately. The key takeaways from this case report include the unusual initial presentation in a young patient and the thorough differential diagnosis process to rule out infections or neoplasms. However, it was not mentioned if or what kind of blood work up was performed and neither were the exact values of N-acetyl aspartate, lactate, lipids and choline reported, which would have been useful given the correlation of NAA levels with prognosis and recovery expectations. Very well done and often overlooked was taking the JC virus into consideration before administering natalizumab. It is important to be aware, that MS lesions can present in various forms and locations and present often atypically.

However, some criticism can be raised. Although the differential diagnosis of infections and neoplasms was considered, it is unclear how thoroughly they were ruled out. While it was briefly discussed that a biopsy might be unnecessary, there was no mention of whether any serological tests were performed to exclude infections or autoimmune cause of the cystic brain lesion. Additionally,

the mechanism behind such an atypicial presentation was not explored in depth, maybe there are coexisting conditions contributing to this manifestation.

The case report states that the diagnosis was established quickly after arriving at the emergency department. Given the rarity of the cystic lesions in MS this raises concerns about the potential risk of misdiagnosis. It would be interesting to know if there was an initial misdiagnosis or hesitation before treatment was initiated. Discussing the diagnostic confidence of the physicians and any possible delays could provide deeper understanding of the challenges in diagnosing rare MS presentations and the potential for false-positive diagnoses. Despite mentioning a follow-up appointment with the neurologist, no details regarding the timeline and no information regarding the treatment response with natalizumab have been made. There was no follow-up on whether the lesion remained stable or progressed, nor was there an update on the patient's overall health status.

Conclusion

All in all, this case highlights the importance of maintaining a broad differential diagnosis when MRI findings are unclear in suspected MS cases. The authors emphasize the necessity for clinicians to be aware of such atypical MS presentations to avoid misdiagnosis and ensure appropriate management. This case underscores the pivotal role of MRI in accurate lesion identification and highlights the need for a thorough diagnostic approach, including biomarkers and CSF analysis to prevent misdiagnosis and optimize patient care.

Case 2

The following case report published by Oliver Cousins in the UK in 2019, discusses the delayed diagnosis of neuromyelitis optica spectrum disorder and the challenges posed by its nonspecific and rare symptoms in reaching a timely diagnosis.

The case report describes a 54-year-old women who arrived at the emergency department with recurring nausea for two weeks and a five-day history of severe, persistent vomiting. Her past clinical history included hypothyroidism, carpal tunnel syndrome, and ovarian cysts. She also had a significant 35 pack-year tobacco use background and drank alcohol in significant quantities, approximately 16 units per week.

On her initial presentation, she was quickly discharged with a diagnosis of gastroenteritis. However, she returned seven days later with persistent vomiting and dysphagia. She was again discharged, this time with a diagnosis of gastritis. A few weeks later, she presented once more with additional symptoms of dyspnoe and a productive cough and was discharged with a referral for an outpatient gastroscopy. That same night, she returned to the emergency department due to being unable to swallow and she was subsequently admitted to the gastroenterology department.

During the examination in the gastroenterology department, she reported of a three-day history of frontal headache, blurred vision and paraesthesia primarily affecting her arms and legs. A neurology

consultation revealed minimal bilateral palate elevation, absent bilateral gag reflexes, and upbeat nystagmus.

Laboratory investigation demonstrated an increased leukocyte cell count of 14.4x10^9/L (normal range 4.5-11.0x10^9/L) with a normal CRP level. Comprehensive tests, including liver function, urea, electrolytes, B12, folate, thyroid function, HIV serology, syphilis serology, lupus anticoagulant, antinuclear antibody, antineutrophil cytoplasmic antibody, creatine kinase, antineuronal antibodies and ganglioside antibodies, all yielded normal or inconclusive results.

A gastroscopy was performed, and a head CT scan showed no abnormalities. Afterwards MRI imaging demonstrated a T2-hyperintensitiy with diffusion limitation in the posterior brainstem and the upper cervical spinal segment. An MRI angiogram revealed a constricted right-sided vertebral vessel, leading to an initial diagnosis of acute ischemia secondary to vertebral dissection.

Cerebrospinal fluid analysis showed a leukocyte count of 4/mm^3 (normal range <5/mm^3) and a protein of 0.32g/L (normal range <0.45g/L), with negative oligoclonal bands. A follow up MRI one month later revealed persistent posterior cervical-medullary lesions with T2-hyperintensity. A reassessment of the initial MRI images showed increased signal on diffusion-weighted imaging (DWI) without a matching decreased signal on apparent diffusion coefficient (ADC) mapping. A spinal MRI was performed but showed no additional abnormalities. Repeated chest CT scans demonstrated ongoing bilateral consolidation.

A few weeks later, serum aquaporin-4 antibodies were confirmed, and a visual evoked potential proved a bilateral optic nerve conduction slowing.

Initially, the patient was diagnosed with achalasia cardia due to dysphagia and vomiting. However, the neurological symptoms raised concerns about alternative etiologies, including medullary lesions of vascular or inflammatory origin, Guillain-Barre syndrome, or myasthenia gravis. MRI findings suggested either stroke or demyelination and finally the AQP-4 antibodies concluded the diagnosis of neuromyleitis optica, manifesting with sudden brainstem involvement and area postrema syndrome.

The initial treatment was focused on a presumed brainstem infarction, with antiplatelet medication and an insertion of a percutaneous gastroscopy tube due to dysphagia and frequent aspiration-induced pneumonia. Once the diagnosis of NMOSD was confirmed, a five-day course of plasma exchange was initiated. However, treatment was paused for a few weeks due to severe lung infection. After recovery, therapy resumed with three days of 1g IV methylprednisolone, followed by tapering to 60mg oral prednisolone daily and initiation of mycophenolate mofetil.

Two weeks of plasma exchange resulted in a normalization of palate elevation, gag reflexes, and resolution of the nystagmus. However, the patient required an additional six weeks of antibiotics due to recurrent chest infections.

Discussion

This case highlights the diagnostic complexity and challenges associated with neuromyelitis optica spectrum disorders, particularly in atypical presentations such as dysphagia and intractable

vomiting. The patient initially presented multiple times with severe vomiting, which was attributed first to gastroenteritis and later to gastritis. These misdiagnoses delayed neurological evaluation, losing crucial time for appropriate intervention. Especially the absence of abnormalities on gastroscopy should have prompted consideration of alternative diagnoses earlier.

When dysphagia became the primary complaint, the diagnosis of achalasia cardia was made without considering a rare neurological cause. A neurology referral was only initiated once the patient developed absent gag reflexes and upbeat nystagmus, both of which strongly indicate a brainstem origin.

The case highlights the difficulty in differentiating brainstem demyelination from stroke based on imaging alone. The reliance on radiological findings without integrating the full clinical picture delayed the diagnosis immensely. The initial management focused on stroke treatment with antiplatelet therapy, further postponing immunosuppressive therapy.

Additionally, this case demonstrates the importance of early serological testing for aquaporin-4 antibodies when a demyelinating disorder is suspected. A positive result at an earlier stage would have led to more timely and appropriate management.

Once NMOSD was diagnosed treatment with plasma exchange and high dose IV corticosteroids was initiated appropriately. However, severe pneumonia interrupted therapy for several weeks. This highlights the crucial balance in NMOSD management between immunosuppression and infection risk, necessitating close monitoring and infection prevention strategies. Furthermore, the necessity of keeping the PEG tube in place longer than needed should be questioned, as it might have been a major source of infection.

Conclusion

This case reports highlights the diagnostic and management challenges of NMOSD and further strengthens my belief that every physician should be aware of NMOSD to facilitate a more timely referral to a neurologist. In this case, several aspects of care were suboptimal. Reaching the diagnosis took several months, during which the patient suffered without knowing the cause. It should also be questioned whether the patient´s complains were taken seriously from the beginning and how thorough the physical examination was performed during her first presentation in the emergency department. Even a quickly performed neurological examination, which should be standard in the emergency department, might have revealed the nystagmus and significantly accelerating the diagnosis.

The differential diagnosis was too narrow, and a neurological cause was never considered. Even though an MRI was conducted, it was misinterpreted and not correlated with the clinical picture. Once the diagnosis was established, treatment was administered according to protocol. However, questions remain regarding the patient's prognosis and whether the outcome could have been improved. It would also be interesting to know about the follow-up schedule agreed upon with the neurologist as well as the long-term outcome.

References

1. Giovannoni G, Butzkueven H, Dhib-Jalbut S, Hobart J, Kobelt G, Pepper G, et al. Brain health: time matters in multiple sclerosis. Multiple Sclerosis and Related Disorders. 2016 Sep 1;9:S5–48.
2. Haki M, AL-Biati HA, Al-Tameemi ZS, Ali IS, Al-hussaniy HA. Review of multiple sclerosis: Epidemiology, etiology, pathophysiology, and treatment. Medicine. 2024 Feb 23;103(8):e37297.
3. Contentti EC, Correale J. Neuromyelitis optica spectrum disorders: from pathophysiology to therapeutic strategies. Journal of Neuroinflammation. 2021 Sep 16;18:208.
4. Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015 Jul 14;85(2):177–89.
5. Kobelt G, Thompson A, Berg J, Gannedahl M, Eriksson J, MSCOI Study Group, et al. New insights into the burden and costs of multiple sclerosis in Europe. Mult Scler. 2017 Jul;23(8):1123–36.
6. Lorscheider J, Jokubaitis VG, Spelman T, et al. Anti-inflammatory disease-modifying treatment and short-term disability progression in SPMS. Neurology 2017; 89: 1050–9.
7. Siriratnam P, Huda S, Butzkueven H, van der Walt A, Jokubaitis V, Monif M. A comprehensive review of the advances in neuromyelitis optica spectrum disorder. Autoimmunity Reviews. 2023 Dec 1;22(12):103465.
8. Ford H. Clinical presentation and diagnosis of multiple sclerosis. Clinical Medicine. 2020 Jul 1;20(4):380–3.
9. Nowak-Kiczmer M, Niedziela N, Zalejska-Fiolka J, Adamczyk-Sowa M. 9. Evaluation of antioxidant parameters of multiple sclerosis patients' serum according to the disease course. Multiple Sclerosis and Related Disorders [Internet]. 2023 Sep 1 [cited 2025 Jan 18];77.
10. Huda S, Whittam D, Bhojak M, Chamberlain J, Noonan C, Jacob A. Neuromyelitis optica spectrum disorders. Clin Med (Lond). 2019 Mar;19(2):169–76.
11. Leray E, Moreau T, Fromont A, Edan G. Epidemiology of multiple sclerosis. Revue Neurologique. 2016 Jan 1;172(1):3–13.
12. Alfredsson L, Olsson T. Lifestyle and Environmental Factors in Multiple Sclerosis. Cold Spring Harb Perspect Med. 2019 Apr;9(4):a028944.
13. Hedström AK, Mowry EM, Gianfrancesco MA, Shao X, Schaefer CA, Shen L, et al. High consumption of coffee is associated with decreased multiple sclerosis risk; results from two independent studies. J Neurol Neurosurg Psychiatry. 2016 May 1;87(5):454–60.
14. Hedström AK, Hillert J, Olsson T, Alfredsson L. Alcohol as a Modifiable Lifestyle Factor Affecting Multiple Sclerosis Risk. JAMA Neurology. 2014 Mar 1;71(3):300–5.
15. Zeng R, Jiang R, Huang W, Wang J, Zhang L, Ma Y, et al. Dissecting shared genetic architecture between obesity and multiple sclerosis. eBioMedicine. 2023 Jun 8;93:104647.
16. Parnell GP, Booth DR. The Multiple Sclerosis (MS) Genetic Risk Factors Indicate both Acquired and Innate Immune Cell Subsets Contribute to MS Pathogenesis and Identify Novel Therapeutic Opportunities. Front Immunol. 2017 Apr 18;8:425.

17. Simpson S, Taylor BV, van der Mei I. The role of epidemiology in MS research: Past successes, current challenges and future potential. Mult Scler. 2015 Jul 1;21(8):969–77.
18. Moutsianas L, Jostins L, Beecham AH, Dilthey AT, Xifara DK, Ban M, et al. Class II HLA interactions modulate genetic risk for multiple sclerosis. Nature genetics. 2015 Sep 7;47(10):1107.
19. Christian. Geschichte der Multiplen Sklerose [Internet]. Multiple Sklerose Gesellschaft Wien. [cited 2025 Jan 21]. Available from: https://www.msges.at/multiple-sklerose/geschichte-der-multiplen-sklerose/
20. Nocentini U. Focus or Neglect on Cognitive Impairment Following the History of Multiple Sclerosis. NeuroSci. 2023 Feb 15;4(1):0.
21. Hemmer B, Kerschensteiner M, Korn T. Role of the innate and adaptive immune responses in the course of multiple sclerosis. The Lancet Neurology. 2015 Apr 1;14(4):406–19.
22. Mohammed EMA. Understanding Multiple Sclerosis Pathophysiology and Current Disease-Modifying Therapies: A Review of Unaddressed Aspects. FBL. 2024 Nov 19;29(11):386.
23. Clinical Course of Multiple Sclerosis - PMC [Internet]. [cited 2024 Nov 10]. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC6120692/
24. Sie C, Korn T, Mitsdoerffer M. Th17 cells in central nervous system autoimmunity. Experimental Neurology. 2014 Dec 1;262:18–27.
25. Arneth BM. Impact of B cells to the pathophysiology of multiple sclerosis. Journal of Neuroinflammation. 2019 Jun 25;16(1):128.
26. B Cells in the Multiple Sclerosis Central Nervous System: Trafficking and Contribution to CNS-Compartmentalized Inflammation - PMC [Internet]. [cited 2025 Jan 21]. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC4689808/
27. Dobson R, Giovannoni G. Multiple sclerosis – a review. European Journal of Neurology. 2019;26(1):27–40.
28. Martin R, Sospedra M, Eiermann T, Olsson T. Multiple sclerosis: doubling down on MHC. Trends in Genetics. 2021 Sep 1;37(9):784–97.
29. Ohl K, Tenbrock K, Kipp M. Oxidative stress in multiple sclerosis: Central and peripheral mode of action. Exp Neurol. 2016 Mar;277:58–67.
30. Kantarci OH. Phases and Phenotypes of Multiple Sclerosis. Continuum (Minneap Minn). 2019 Jun;25(3):636–54.
31. Garg N, Smith TW. An update on immunopathogenesis, diagnosis, and treatment of multiple sclerosis. Brain and Behavior. 2015 Aug 3;5(9):e00362.
32. Klineova S, Lublin FD. Clinical Course of Multiple Sclerosis. Cold Spring Harb Perspect Med. 2018 Sep;8(9):a028928.
33. Jankowska A, Chwojnicki K, Szurowska E. The diagnosis of multiple sclerosis: what has changed in diagnostic criteria? Pol J Radiol. 2023 Dec 12;88:e574–81.
34. Filippi M, Rocca MA, Ciccarelli O, De Stefano N, Evangelou N, Kappos L, et al. MRI CRITERIA FOR THE DIAGNOSIS OF MULTIPLE SCLEROSIS: MAGNIMS CONSENSUS GUIDELINES. Lancet Neurol. 2016 Mar;15(3):292–303.
35. Pozzilli C, Pugliatti M, Vermersch P, Grigoriadis N, Alkhawajah M, Airas L, et al. Diagnosis and treatment of progressive multiple sclerosis: A position paper. European Journal of Neurology. 2022 Oct 25;30(1):9.

36. Filippi M, Preziosa P, Meani A, Dalla Costa G, Mesaros S, Drulovic J, et al. Performance of the 2017 and 2010 Revised McDonald Criteria in Predicting MS Diagnosis After a Clinically Isolated Syndrome: A MAGNIMS Study. Neurology. 2022 Jan 4;98(1):e1–14.
37. New versus old: Implications of evolving diagnostic criteria for relapsing–remitting multiple sclerosis - Nuala McNicholas, Andrew Lockhart, Siew M Yap, Karen O'Connell, Niall Tubridy, Michael Hutchinson, Christopher McGuigan, 2019
38. McBenedict B, Goh KS, Yau RCC, Elamin S, Yusuf WH, Verly G, et al. Neuropathic Pain Secondary to Multiple Sclerosis: A Narrative Review. Cureus. 16(6):e61587.
39. Heine M, van de Port I, Rietberg MB, van Wegen EE, Kwakkel G. Exercise therapy for fatigue in multiple sclerosis. Cochrane Database Syst Rev. 2015 Sep 11;2015(9):CD009956.
40. Australian Journal of General Practice [Internet]. [cited 2025 Jan 22]. Multiple sclerosis diagnosis therapy and prognosis. Available from: https://www1.racgp.org.au/ajgp/2022/april/multiple-sclerosis-diagnosis-therapy-and-prognosis
41. Thakolwiboon MD, Natteru M. Unravel the Mysteries of Multiple Sclerosis Mimics. 2023 Nov 26 [cited 2025 Jan 22];6. Available from: https://www.neurologylive.com/view/unravel-mysteries-multiple-sclerosis-mimics
42. Makhoul K, Ahdab R, Riachi N, Chalah MA, Ayache SS. Tremor in Multiple Sclerosis-An Overview and Future Perspectives. Brain Sci. 2020 Oct 12;10(10):722.
43. Simone CG, Emmady PD. Transverse Myelitis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Jan 22]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK559302/
44. Solaro C, Cella M, Signori A, Martinelli V, Radaelli M, Centonze D, et al. Identifying neuropathic pain in patients with multiple sclerosis: a cross-sectional multicenter study using highly specific criteria. J Neurol. 2018 Apr 1;265(4):828–35.
45. Di Stefano G, Maarbjerg S, Truini A. Trigeminal neuralgia secondary to multiple sclerosis: from the clinical picture to the treatment options. J Headache Pain. 2019 Feb 19;20(1):20.
46. Filser M, Buchner A, Fink GR, Gold SM, Penner IK. The manifestation of affective symptoms in multiple sclerosis and discussion of the currently available diagnostic assessment tools. J Neurol. 2023;270(1):171–207.
47. Panginikkod S, Rayi A, Rocha Cabrero F, Rukmangadachar LA. Uhthoff Phenomenon. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Jan 22]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK470244/
48. Filippi M, Preziosa P, Banwell BL, Barkhof F, Ciccarelli O, De Stefano N, et al. Assessment of lesions on magnetic resonance imaging in multiple sclerosis: practical guidelines. Brain. 2019 Jul;142(7):1858–75.
49. Hemond CC, Bakshi R. Magnetic Resonance Imaging in Multiple Sclerosis. Cold Spring Harb Perspect Med. 2018 May;8(5):a028969.
50. Calvi A, Clarke MA, Prados F, Chard D, Ciccarelli O, Alberich M, et al. Relationship between paramagnetic rim lesions and slowly expanding lesions in multiple sclerosis. Mult Scler. 2023 Mar;29(3):352–62.
51. Ng Kee Kwong KC, Mollison D, Meijboom R, York EN, Kampaite A, Thrippleton MJ, et al. The prevalence of paramagnetic rim lesions in multiple sclerosis: A systematic review and meta-analysis. PLoS One. 2021 Sep 8;16(9):e0256845.

52. Dal-Bianco A, Grabner G, Kronnerwetter C, Weber M, Höftberger R, Berger T, et al. Slow expansion of multiple sclerosis iron rim lesions: pathology and 7 T magnetic resonance imaging. Acta Neuropathol. 2017;133(1):25–42.
53. Guerrieri S, Comi G, Leocani L. Optical Coherence Tomography and Visual Evoked Potentials as Prognostic and Monitoring Tools in Progressive Multiple Sclerosis. Front Neurosci. 2021 Aug 5;15:692599.
54. The visual pathway as a model to understand brain damage in multiple sclerosis - E H Martínez-Lapiscina, B Sanchez-Dalmau, E Fraga-Pumar, S Ortiz-Perez, A I Tercero-Uribe, R Torres-Torres, P Villoslada, 2014 [Internet]. [cited 2025 Jan 23]. Available from: https://journals.sagepub.com/doi/10.1177/1352458514542862?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed
55. Konen FF, Schwenkenbecher P, Jendretzky KF, Gingele S, Sühs KW, Tumani H, et al. The Increasing Role of Kappa Free Light Chains in the Diagnosis of Multiple Sclerosis. Cells. 2021 Nov 6;10(11):3056.
56. Arroyo-Pereiro P, García-Serrano L, Morandeira F, Urban B, Mas V, Framil M, et al. Kappa free light chains index in multiple sclerosis very long-term prognosis. Front Immunol. 2023 Oct 11;14:1223514.
57. Yang J, Hamade M, Wu Q, Wang Q, Axtell R, Giri S, et al. Current and Future Biomarkers in Multiple Sclerosis. Int J Mol Sci. 2022 May 24;23(11):5877.
58. Bittner S, Oh J, Havrdová EK, Tintoré M, Zipp F. The potential of serum neurofilament as biomarker for multiple sclerosis. Brain. 2021 Jun 28;144(10):2954–63.
59. Wildner P, Stasiołek M, Matysiak M. Differential diagnosis of multiple sclerosis and other inflammatory CNS diseases. Multiple Sclerosis and Related Disorders [Internet]. 2020 Jan 1 [cited 2025 Jan 23];37. Available from: https://www.msard-journal.com/article/S2211-0348(19)30440-7/fulltext
60. Ömerhoca S, Akkaş SY, İçen NK. Multiple Sclerosis: Diagnosis and Differential Diagnosis. Noro Psikiyatr Ars. 2018;55(Suppl 1):S1–9.
61. Sintzel MB, Rametta M, Reder AT. Vitamin D and Multiple Sclerosis: A Comprehensive Review. Neurol Ther. 2017 Dec 14;7(1):59–85.
62. Napoli S. ACTH gel in the treatment of multiple sclerosis exacerbation: a case study. Int Med Case Rep J. 2015 Jan 7;8:23–7.
63. Doshi A, Chataway J. Multiple sclerosis, a treatable disease. Clin Med (Lond). 2016 Dec;16(Suppl 6):s53–9.
64. Interferon beta-1b reduces black holes in a randomised trial of clinically isolated syndrome - Gijsbert JA Nagtegaal, Christoph Pohl, Mike P Wattjes, Hanneke E Hulst, Mark S Freedman, Hans-Peter Hartung, David Miller, Xavier Montalban, Ludwig Kappos, Gilles Edan, Dirk Pleimes, Karola Beckman, Brigitte Stemper, Christoph H Polman, Rupert Sandbrink, Frederik Barkhof, 2014
65. Hauser SL, Cree BA. Treatment of Multiple Sclerosis: A Review. The American journal of medicine. 2020 Jul 17;133(12):1380.
66. Berger JR, Cree BA, Greenberg B, Hemmer B, Ward BJ, Dong VM, et al. Progressive multifocal leukoencephalopathy after fingolimod treatment. Neurology. 2018 May 15;90(20):e1815–21.

67. Australian Journal of General Practice [Internet]. [cited 2024 Nov 10]. Multiple sclerosis diagnosis therapy and prognosis. Available from: https://www1.racgp.org.au/ajgp/2022/april/multiple-sclerosis-diagnosis-therapy-and-prognosis
68. Andersen JB, Kopp TI, Sellebjerg F, Magyari M. Pregnancy-Related and Perinatal Outcomes in Women With Multiple Sclerosis. Neurol Clin Pract. 2021 Aug;11(4):280–90.
69. Felecia M. Hart P, Jacquelyn Bainbridge Bsp. Current and Emerging Treatment of Multiple Sclerosis. 2016 Jun 1 [cited 2025 Feb 7];22. Available from: https://www.ajmc.com/view/cost-effectiveness-multiple-sclerosis-current-emerging-treatment
70. Filippini G, Minozzi S, Borrelli F, Cinquini M, Dwan K. Cannabis and cannabinoids for symptomatic treatment for people with multiple sclerosis. Cochrane Database Syst Rev. 2022 May 5;2022(5):CD013444.
71. Esfahani MZ, Ahmadi M, Adibi I. Ontology for Symptomatic Treatment of Multiple Sclerosis. Healthc Inform Res. 2022 Oct;28(4):332–42.
72. Iaffaldano P, Lucisano G, Patti F, Brescia Morra V, De Luca G, Lugaresi A, et al. Transition to secondary progression in relapsing-onset multiple sclerosis: Definitions and risk factors. Mult Scler. 2021 Mar;27(3):430–8.
73. Kusumadewi W, Imran D, Witjaksono F, Pakasi TA, Rusmana AI, Pangeran D, et al. Low vitamin D-25(OH) level in Indonesian multiple sclerosis and neuromyelitis optic patients. Multiple Sclerosis and Related Disorders. 2018 Oct 1;25:329–33.
74. Fujihara K. Neuromyelitis optica spectrum disorders: still evolving and broadening. Current Opinion in Neurology. 2019 Jun;32(3):385.
75. Chamberlain JL, Huda S, Whittam DH, Matiello M, Morgan BP, Jacob A. Role of complement and potential of complement inhibitors in myasthenia gravis and neuromyelitis optica spectrum disorders: a brief review. J Neurol. 2021 May 1;268(5):1643–64.
76. Wu Y, Geraldes R, Juryńczyk M, Palace J. Double-negative neuromyelitis optica spectrum disorder. Multiple Sclerosis (Houndmills, Basingstoke, England). 2023 Sep 23;29(11–12):1353.
77. Duchow A, Bellmann-Strobl J, Friede T, Aktas O, Angstwurm K, Ayzenberg I, et al. Time to Disability Milestones and Annualized Relapse Rates in NMOSD and MOGAD. Annals of Neurology. 2024;95(4):720–32.
78. Abboud H, Salazar-Camelo A, George N, Planchon SM, Matiello M, Mealy MA, et al. 80. Symptomatic and restorative therapies in neuromyelitis optica spectrum disorders. Journal of Neurology. 2021 Sep 5;269(4):1786.
79. False-Negative Platelet Factor 4 Antibodies and Serotonin Release Assay and the Utility of Repeat Testing in the Diagnosis of Heparin-Induced Thrombocytopenia and Thrombosis - Omer - 2019 - Case Reports in Hematology - Wiley Online Library [Internet]. [cited 2025 Feb 12]. Available from: https://onlinelibrary.wiley.com/doi/full/10.1155/2019/1585014
80. Kleiter I, Gahlen A, Borisow N, Fischer K, Wernecke KD, Wegner B, et al. Neuromyelitis optica: Evaluation of 871 attacks and 1,153 treatment courses. Annals of Neurology. 2016;79(2):206–16.

81. Kleiter I, Gahlen A, Borisow N, Fischer K, Wernecke KD, Hellwig K, et al. Apheresis therapies for NMOSD attacks. Neurol Neuroimmunol Neuroinflamm. 2018 Sep 26;5(6):e504.
82. Elsone L, Kitley J, Luppe S, Lythgoe D, Mutch K, Jacob S, et al. Long-term efficacy, tolerability and retention rate of azathioprine in 103 aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder patients: a multicentre retrospective observational study from the UK. Mult Scler. 2014 Oct;20(11):1533–40.
83. Immunotherapies in neuromyelitis optica spectrum disorder: efficacy and predictors of response - PMC [Internet]. [cited 2025 Feb 12]. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC5537514/
84. Kleiter I, Gold R. Present and Future Therapies in Neuromyelitis Optica Spectrum Disorders. Neurotherapeutics. 2016 Jan;13(1):70–83.
85. Zhang C, Zhang M, Qiu W, Ma H, Zhang X, Zhu Z, et al. Safety and efficacy of tocilizumab versus azathioprine in highly relapsing neuromyelitis optica spectrum disorder (TANGO): an open-label, multicentre, randomised, phase 2 trial. Lancet Neurol. 2020 May;19(5):391–401.
86. Chu YC, Huang TL. What's new in neuromyelitis optica spectrum disorder treatment? Taiwan J Ophthalmol. 2022 Sep 1;12(3):249–63.
87. Zeng L, Yang K, Wu Y, Yu G, Yan Y, Hao M, et al. Telitacicept: A novel horizon in targeting autoimmunity and rheumatic diseases. Journal of Autoimmunity. 2024 Sep 1;148:103291.
88. Seewann A, Enzinger C, Filippi M, Barkhof F, Rovira A, Gass A, et al. MRI characteristics of atypical idiopathic inflammatory demyelinating lesions of the brain. J Neurol. 2008 Jan 1;255(1):1–10.

1. Case report 1. Ortiz AFH, Aristizabal S, Arámbula JG, Castillo V del, Calderon J, Cuenca NTR, et al. Multiple sclerosis with megacystic presentation: A case report. Radiol Case Rep. 2022 Nov 24;18(2):515–8.
2. Case report 2. Cousins O, Girelli E, Harikrishnan S. Neuromyelitis optica: an elusive cause of dysphagia. BMJ Case Reports. 2019 Jan 14;12(1):bcr.

Graphics and Figures Sources

- Figure 1. RRMS Course picture: PubMed Central (PMC) [Internet]. [cited 2025 Jan 21]. Clinical Course of Multiple Sclerosis. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC6120692/
- Figure 2. SPMS Course Picture: PubMed Central (PMC) [Internet]. [cited 2025 Jan 21]. Clinical Course of Multiple Sclerosis. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC6120692/

- Figure 3. PPMS Course Picture: PubMed Central (PMC) [Internet]. [cited 2025 Jan 21]. PPMS Clinical Course of Multiple Sclerosis. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC6120692/
- Figure 4. Periventricular lesions seen on MRI. Filippi M, Preziosa P, Banwell BL, Barkhof F, Ciccarelli O, De Stefano N, et al. Assessment of lesions on magnetic resonance imaging in multiple sclerosis: practical guidelines. Brain. 2019 Jul;142(7):1858–75.
- Figure 5. Cortical/Juxtacortical lesions on MRI. Filippi M, Preziosa P, Banwell BL, Barkhof F, Ciccarelli O, De Stefano N, et al. Assessment of lesions on magnetic resonance imaging in multiple sclerosis: practical guidelines. Brain. 2019 Jul;142(7):1858–75.
- Figure 6. Characteristics of infratentorial lesions on MRI. Filippi M, Preziosa P, Banwell BL, Barkhof F, Ciccarelli O, De Stefano N, et al. Assessment of lesions on magnetic resonance imaging in multiple sclerosis: practical guidelines. Brain. 2019 Jul;142(7):1858–75.
- Figure 7. Spinal cord lesions on MRI. Filippi M, Preziosa P, Banwell BL, Barkhof F, Ciccarelli O, De Stefano N, et al. Assessment of lesions on magnetic resonance imaging in multiple sclerosis: practical guidelines. Brain. 2019 Jul;142(7):1858–75.
- Figure 8. Gadolinium enhancing lesions on MRI. Filippi M, Preziosa P, Banwell BL, Barkhof F, Ciccarelli O, De Stefano N, et al. Assessment of lesions on magnetic resonance imaging in multiple sclerosis: practical guidelines. Brain. 2019 Jul;142(7):1858–75.
- Figure 9. MS lesion location overview. Australian Journal of General Practice [Internet]. [cited 2025 Jan 22]. Multiple sclerosis diagnosis therapy and prognosis. Available from: https://www1.racgp.org.au/ajgp/2022/april/multiple-sclerosis-diagnosis-therapy-and-prognosis

Table Sources

- Table 1. Classifications and definitions. Kantarci OH. Phases and Phenotypes of Multiple Sclerosis. Continuum (Minneap Minn). 2019 Jun;25(3):636–54. [30]
  Garg N, Smith TW. An update on immunopathogenesis, diagnosis, and treatment of multiple sclerosis. Brain and Behavior. 2015 Aug 3;5(9):e00362. [31]
  Klineova S, Lublin FD. Clinical Course of Multiple Sclerosis. Cold Spring Harb Perspect Med. 2018 Sep;8(9):a028928. [32]
- Table 2. Differential diagnosis overview of MS. Dobson R, Giovannoni G. Multiple sclerosis – a review. European Journal of Neurology. 2019;26(1):27–40.
- Table 3. DMT overview, Approximate efficacy of the approved DMTs on relapse rate. Object Multiple sclerosis. DMT overview [cited 2025 Feb 11]; Available from: https://core.ac.uk/reader/1813321?utm_source=linkout
- Table 4. MS, NMOSD comparison: Huda S, Whittam D, Bhojak M, Chamberlain J, Noonan C, Jacob A, et al. Neuromyelitis optica spectrum disorders. Clin Med (Lond). 2019 Mar;19(2):169–76.
- Table 5. Imaging characteristics of atypical demyelination disorders subtypes. Seewann A, Enzinger C, Filippi M, Barkhof F, Rovira A, Gass A, et al. MRI characteristics of atypical

idiopathic inflammatory demyelinating lesions of the brain. J Neurol. 2008 Jan 1;255(1):1–10.