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The Final thesis

Multiple Sclerosis and Other Autoimmune Disorders. Clinical Case

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1 Introduction

Autoimmune diseases have been a mystery for a long time since pioneering studies of Macfarlane Burnett in 1950s with his book “The Clonal Selection Theory of Acquired Immunity” and his Nobel Prize-winning hypothesis of the “forbidden clone” supplied us with new explanations. These works helped physicians tremendously in understanding the mechanism of autoimmunity. Not only this but also the understanding of apoptosis, thymic education, lymphoid cell development or the interaction between certain immune cells. Modern theories tell us that autoimmune diseases require genetic triggers and environmental factors that activate the immune system to act in such a self-destructive way and lead ultimately to tissue destruction and pathological dynamics that in the end can cause death in young age.

Although there is extensive research, nobody has found a genetic pool which could predict incidence of autoimmune disease yet. Twin studies and research found 12-67% concordance in identical twins, which not only shows the importance of environmental triggers but also the consideration it is possibly related to epigenetics.(1) Also, new research highlighted the importance of chemokines and cytokines on receptors triggering immune responses, which improved the treatment strategies by involving novel therapies. Such as monoclonal antibody treatment regimens, which suppress certain signalling pathways to limit the self-immune response. All in all, diagnostics and therapy improved highly since the last decades, and it is expected to have a breakthrough in understanding and predicting autoimmune disease courses within the next decade.(2)

This case report outlines a special case of a patient who suffers not only from one nervous autoimmune disease, but two. Only the above-mentioned achievements in therapeutic measures allow her to live a largely normal life. In terms of time, these two immune disorders were diagnosed by a wide margin, but the task of this case report is to remind any physician reading this that sudden changes in symptoms or conspicuous limitations in everyday life can be associated with a second autoimmune disease. This may happen either independent or dependent on the first autoimmune disease. Recognizing this, is a challenge but autoimmune diseases often occur at a young age, so that every physician should be even more motivated to rule out these avoidable coincidences.

At the beginning, this thesis will start with a focus on the interesting complex disease “Multiple Sclerosis”. A lot of research is still going on about the disease, especially about

pathophysiology and immunological relationships and will be full of expectation from each multiple sclerosis patient.

2 Multiple Sclerosis

2.1 General

Multiple Sclerosis (MS), also called "Encephalomyelitis disseminata" is a chronic degenerative disease, characterized by a picture of heterogenicity. It is a chronic disease of the central nervous system (CNS) which causes demyelination and axonal degeneration of the brain and spinal cord. Early neurologic symptoms can range from visual disturbances, motoric dysfunctions to sensibility losses.

Traditionally it is seen as a two-stage disease. In the early phase the disease expresses focal inflammatory und regenerative processes with demyelination and evident axonal damage.

In the late phase it presents with diffuse activation of microglia and consecutive degeneration, demyelination, and already more advanced axonal damage. (3)

It predominantly affects people in the early adult life with a fundamental impact on financial and functional quality of life. Also, the costs expand with increasing disability and lead to a financial burden for the public. Therefore, it is crucial to identify patients with symptoms, which are included in the differential diagnosis of MS as early as possible. Understanding the aetiology, dynamics, genetics (e.g. HLA DRB*15:01), environmental triggers (e.g. vitamin D, lifestyle, viral infections etc.) and immunity (innate and adaptive) will help to discover new treatment modalities, which are specified and individualised to treat the patient with the right medicine at the optimal time. A well prescribed treatment plan can regain a better quality of life and a close to normal life expectancy for the patient.(4) Modern strategies already succeed with B-Cell targeted therapies expelling the dogma of T-cell mediated autoimmunity.

A small group of people with MS were treated with an aggressive approach with biologicals and hematopoietic stem cell transplantation to target a state of no evident disease activity (NEDA) what potentially can offer a cure for a small group of patients already. (5)

Additionally, other research is focusing on the dynamics of MS by investigating monozygotic twins to understand what triggers a change in disease progress. This helps to precisely switch the treatment modality to attack this point of autoimmune cascade. (6)

The general therapy is discussed and whether there is a possibility in the future, as already described above, to treat relapses or to recognize them earlier and treat them adequately at this

stage of disease. A lot is in change and new methods challenges the traditional point of view on this disease.

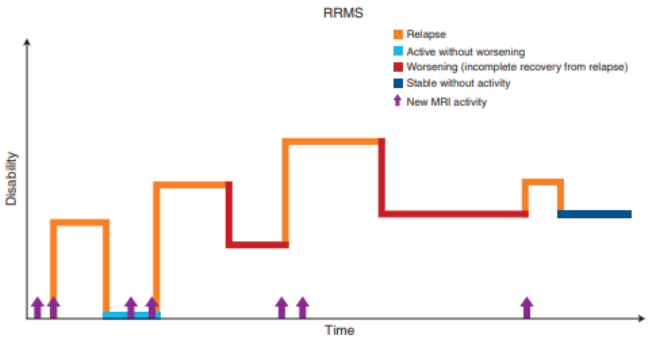
2.2 Epidemiology

The epidemiology of MS depends on the geographical region, the ethnicity and the environmental factors individuals are confronted with in different socioeconomic levels.
Worldwide, approximately 2,5 million people are affected. People of European inheritance are predominantly affected (e.g., Europe, USA, Australia, New-Zealand). As an example, 2 out of 100.000 Japanese people are affected whereas 100 per 100.000 Europeans are affected by MS. Theories include that this significant difference in incidences must be linked to Vitamin D metabolism, obesity, endemic infections, and smoking.
Females are affected twice as often as men. The mean age of the first symptoms is around 30 years of age, roughly between 20 and 40 years of age. (7)

2.3 Definitions and Clinical forms

Descriptions of the clinical course of a certain patient with MS should be very accurate, because they are important for the interaction between doctors, prognosis, treatment decisions and the design of clinical trials.
Traditional definitions provide four MS courses: Relapsing-remitting (RRMS), secondary progressive (SPMS), primary progressive (PPMS) and Progressive relapsing (PRMS) but nowadays it is classified in three different types (RRMS, SPMS, PPMS) because of misunderstanding and vague definitions by relapsing progressive MS.(8)

Figure 2 1 RRMS possible disease course Klineova S, Lublin FD. et al 2018

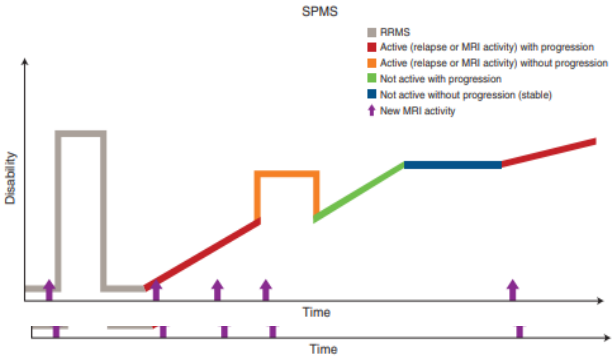


RRMS:
It is the most common MS form (up to 85%) of MS patients. The beginning of the disease is usually between 15-29 years of age. It's characterized by episodes of clearly definable relapses with complete or partial residuals, whereby no progression is noticeable in the relapse intervals. This may be related to recovery of the myelin sheets due to young age and early phases of disease. (3)

However, this can be further classified by 2013 disease course definitions in active which shows new evidence of new gadolinium enhancing lesions and/or new enlarging T2 lesions on MRI or non-active which is defined as no evidence of pathologic activity. Furthermore, this type of MS can worsen over time by increased disability or stability, which is defined as no evidence of disability over a certain period of time. (Illustrated in Figure 2.1) (8)

Figure 2 2 SPMS disease course Klineova S, Lublin FD. et al 2018

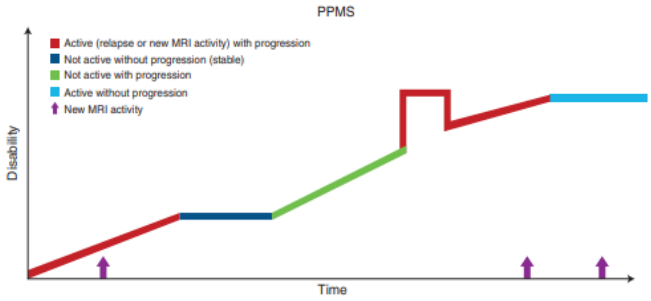
SPMS:



The onset is most often around 40-49 years of age and is characterized by initial relapsing-remitting MS that progresses with or without relapses. Another characteristic is the low remission rate of the relapses. It is assumed that 50-60% of SPMS patients who initially had RRMS show remissions of relapses. (3) (Visualized in Figure 2.2)

Figure 2 3 PPMS disease dynamics Klineova S, Lublin FD. et al 2018

PPMS:



According to literature, it begins at around 40 years of age. From early onset on a slow progression can be observed, but without relapsing deterioration. There are temporary plateau phases and in 10-15% of cases symptoms may regress.

PPMS is special because it is associated with increased age and is more common in men. Furthermore, spinal lesions predominate over cerebral ones. (3) (Figure 2.3)

Additional, SPMS and PPMS you can be further classified as in RRMS by 2013 disease course definitions, which highlight, that in both cases it is differentiated from active and non-active, as it is mentioned earlier in RRMS, as well as if the disease is on progression or without progression. This depends on evidence of disease worsening, objectively measured by clinical scoring systems over a defined time, which will be mentioned in a later section of this paper.

Other definitions include the clinically isolated syndrome (CIS) which is described as a first clinical manifestation of possible multiple sclerosis (typical early symptoms: sensory or gait

disturbance, unilateral optic neuritis), but in which diagnostic criteria for clinical definitive MS (CDMS) are not met. (9)

Radiologically isolated syndrome (RIS) describes incidental findings on MRI with inflammatory demyelination signs in absence of clinical signs. Those patients may be at high risk and should be followed prospectively.

At the end of this subitem it should be clarified what a relapse defines.
A relapse is a new onset or marked worsening of multiple sclerosis symptoms that persisted for at least 24 hours and occurred at least 30 days after the onset of a previous relapse without a setting of infection or elevated body temperature. “Uhthoff phenomenon” is a term used to describe a pseudo relapse, which may be caused by elevated temperature.(3)

2.4 Aetiology

The aetiology of MS is not well understood yet. Modifiable risk factors such as obesity, lifestyle and smoking do have an impact on disease onset. Genetics may play a role since the risk of MS increases in family members by 2-3-fold and more than 100-times in monozygotic twins than in general population.(10)
Also, it seems that certain traits in Europeans in terms of sunlight exposure and vitamin D metabolism may play a role. Vitamin D has been found to be strongly associated with MS because a MS-associated human leukocyte antigen DRB21*15:01 (HLA-DRB1*15:01) allele was found, which is located in the promoter region of a regulatory vitamin D response element (VDRE). Any by that, it would explain why abnormal vitamin D serum concentrations affect MS-risk. (11)
Another factor is the Cytochrome P450 family 27 subfamily B member 1 gene (CYP27B1 gene), which encodes an enzyme that converts vitamin D into its active form. High vitamin D levels are associated with reduced MS risk.(3)
An increased level of Vitamin D (20-50nmol/L) was a positive prognosis factor for a decreased relapse-rate, decreased T2-MRT lesions and less brain atrophy in a study. (11)
One of the most researched etiological correlating factors nowadays are infections in particular Epstein-Barr virus (EBV). (11). One research from the LMU München figured out that: “MS not only does precede EBV infection, but it is also associated with a broader EBV-specific T-

cell Receptor (TCR) repertoire, consistent with an ongoing anti-EBV immune response in MS."(12)

Another research focused on the B-cell repertoires in the Cerebrospinal fluid (CSF) of MS patients. They concluded that the risk of MS increased 32-fold after infection with EBV but no other virus infection (e.g., Cytomegalovirus (CMV)) should be included as aetiologic factor. Furthermore, it was found that Epstein–Barr nuclear antigen 1 (EBNA1) is mimicking GlialCAM, a glycoprotein which facilitates cell adhesions in CNS. This causes a cross reaction and facilitates autoimmune interactions. „This ultimately proofs a pathomechanic link between EBV and MS." (13)

Smoking increases the relative risk for MS, especially in women by factor 1,8 to 1,4 in men. It also has an accelerating effect on the conversion from RRMS to SPMS. (3)

Further considerations in the aetiology, is the possible activation of the autoreactive lymphocytes in MS, and their influence of the intestinal microbiota or their metabolic products on immune cells in intestinal tissue. "Here we summarize the current state of research and highlight on the one hand at the start but it is highlighted that studies that use human material to investigate and characterize the microbiome of MS patients is expecting new theories and approaches in order to develop therapies.(14) Lastly, it is discussed, if increased salt intake, especially in the western world lead to an increase in numbers of MS patients. In general, it is assumed that the western lifestyle, which includes higher salt intake led to an overall increase in autoimmune diseases. (3) Results from a study of 2015 found that the exacerbation rate of MS relapses is 2.75 higher in individuals with medium or high sodium intake. (15) But on the other hand, another study from 2017 propagates, that it has no effect on MS disease course. (16)

2.5 Pathology

2.5.1 Pathophysiology

As the name already describes, the disease is characterized by inflammatory lesions which Jean Martin Charcot described as "sclerose en plaques".(11) Essential feature is the CNS invasion of autoreactive peripheral T lymphocytes, although the exact cause of autoreactivity is still unknown. Role of B lymphocytes is also partly still unclear but since there is evidence of efficacy of anti-B cell therapeutics, the importance of B lymphocytes in the disease process of MS can be assumed. A MS-lesion is defined as a site in the CNS where focal inflammatory

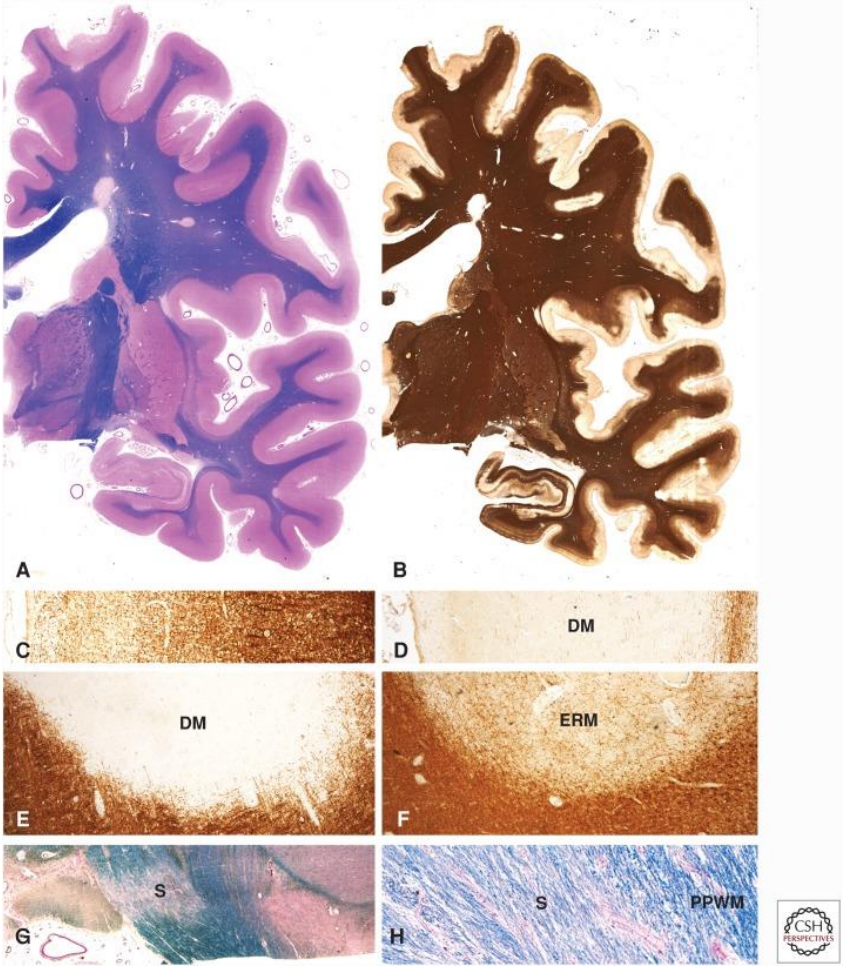
damage (inflammation), loss of neuronal myelin sheaths (demyelination), and axonal and neuronal damage (neurodegeneration) occurs.
Active plaques have a soft, oedematous, blurred and pinkish character, whereas chronic plaques have a coarse, hard and greyish substance.
Furthermore, active plaques are typical seen in RRMS and less commonly in PPMS. There in which you will find inactive lesions surrounded by a ring of activated macrophages and microglia. (3)
A study assumed that "peripheral immune cells can enter the CNS through an impaired Blood-brain-barrier (BBB) by defective neurovascular unit (NVU) and mitochondrial dysfunction of endothelial cells."(17) Another mechanism which is responsible for autoimmunity, is the peripheral activation of Lymphocytes by microorganism antigens mimicking CNS molecules.
However, after infiltrating the CNS, many CD8+ T-cells, Macrophages, a lesser number of CD4+ T-cells, B-cells and plasma cells are found after an inflammation cascade with involvement of proinflammatory cytokines, such as tumour necrosis factor (TNF) or Interferon-ß. (18)
White matter is usually more affected by lesions, but with time also grey matter becomes more and more affected. This is related to the time dependent diffuse infiltration of T-and B-cells. Axonal damage becomes also more widespread after which proliferative astrocytes and oligodendrocytes are present. Related to that, CNS atrophy and disability increase is also part of the later signs.(19)
Predilection sites in MS include optic nerve, periventricular area, brainstem, cerebellum, frontal lobe, posterior cord especially cervical medulla.

The clinic and the most common symptoms between PPMS and RRMS in inflammatory infiltrate are similar although plasma cells, and B-cells are more aberrant in PPMS than RRMS. The reason is still unclear. There is no significant histologically differences in between any MS form, which underlines the transient switch from RRMS to SPMS. (11)

2.5.2 Pathologic details:

Figure 2 4 „Pathologic changes in the brain of a patient with secondary progressive multiple sclerosis" Lassmann H. Multiple Sclerosis Pathology 2018

"Pathological changes in the brain of a patient with secondary progressive multiple sclerosis (MS). Large confluent focal demyelinated lesions are present in the white matter (A). In addition, there is extensive subpial cortical demyelination that can only be detected by sensitive immunocytochemistry for myelin proteins (e.g., proteolipid protein) (B). In contrast to the normal myelin pattern in the cerebral cortex, as shown in C, complete loss of myelin is observed in subpial lesions (D). Demyelinated plaques in the white matter may appear as inactive demyelinated lesions ([DMs] in E), as early remyelinated lesions with a low density of thin myelin sheaths visible only by immunocytochemistry for myelin proteins (ERM in F), or as remyelinated shadow plaques (G and H)." (20)



2.6 Clinic and Symptoms

As it is already described in the section of definitions, MS usually starts as a relapse remitting course. Mostly symptoms occur between the 15th and 45th year of life. Only 7% before the 20th year of age and 12% after the 50th year of life.

Early signs include sensibility disturbances (30-40%), retrobulbar neuritis (20-30%) and chronic fatigue syndrome, which is according to different literatures more than 50% of cases. Recovery of these symptoms is usually within days to weeks. In case of PPMS, it is also possible to see disability progress already in the early stage.(11) The most common symptoms of MS course are listed in Figure 2.5.

Figure 2 5 Table of common symptoms in MS Hufschmidt A. et al 2017 (3)

Domain:	Symptoms:
motor disturbances	Spastic paresis (mono, hemi or paraparesis).
Sensory disturbances:	Lhermitte sign: "electric shock" along the spine during head movements. Paraesthesia such as furriness, tingling, girdling and corset feeling, altered sensation of heat and/or cold with asymmetric distal accentuated distribution. Sign of "useless hand" → decreasing spatial sensation
Cerebellum:	Stance-gait and pointing ataxia Charcot Trias: 1) Nystagmus 2) intention tremor 3) dysarthria.
Eyes	Temporal optic disc fading, agent muscle paresis with cranial nerve involvement (III>VI>IV). Double vision Internuclear ophthalmoplegia (INO)
Bladder and sexual organs	Disturbed urination with retention or incontinence. Erectile dysfunction Decreased libido
Fatigue syndrome **Initially > 50%** **60-95% of all MS patients**	Causes the most severe impairment in everyday life
Cognitive disorders: **(40-65% of MS patients)**	Decreased performance in daily life and work. affects attention, concentration, information processing speed, executive functions. Depression Memory loss
Other cranial nerves	Nervus Trigeminus (V) involvement → sensible deficit Facial paresis
Pain	Neuropathic pain Head pain Musculoskeletal pain

Rare symptoms include epileptic seizures (2-3%), polyneuropathy, both-sided trigeminus seizures.(3)

2.6.1 Clinical scoring system EDSS

The expanded disability status scale (EDSS) systematically captures the severity of disability in MS in terms of walking distance and into eight functional systems graded from 1-5. (Figure 2.6)

In addition to the overall assessment, therapists can use other measurement tools that document the effects of the disease at the activity level of the disease. For example, the Functional Independence Measure (FIM) is suitable when it comes to the recording of independence in everyday life.(3,21)

Figure 2 6 Functional systems and EDSS scale (21)

Functional systems:

1) Pyramidal tract
2) Cerebellum
3) Brain stem
4) Sensibility
5) Bladder and rectum functions
6) visual function
7) cerebral functions
8) other functions (findings not previously mentioned that are related to related to MS, for example pain or cardiovascular limitations of the CVS

Grade 0 = normal
Grade 1 = abnormal signs without disability
Grade 2 = mild disability
Grade 3 = moderate impairment
Grade 4 = marked impairment
Grade 5 = complete loss of function

Scale	***Finding***
0	normal neurological examination in all functional systems (=FS) grade 0
1.0	no disability, minimal symptoms (grade 1) in one FS
1.5	no disability, minimal symptoms (grade 1) in more than one FS
2.0	minimal disability (grade 2) in one FS
2.5	minimal disability in two FS
3	moderate disability (grade 3) in one FS or mild disability in three to four FS, fully ambulatory
3.5	fully ambulatory, but moderate disability in one FS and grade 2 in one to two FS or grade 3 in two FS or grade 2 in five FS
4	able to walk without assistance and rest for 500m, active for approx. 12 hours per day despite relatively severe disability
4.5	able to walk without assistance and rest for 300m, able to work all day, some limitation of activity, requires minimal assistance, relatively severe disability. Grade 4 in one FS (remaining 0 or 1) or combinations or lesser degrees, which exceed the limits of the previous grades
5	able to walk without assistance and rest for 200m, disability severe enough to interfere with daily activity Grade 5 in one FS (remaining 0 or 1) or combinations of of lesser grades exceeding 4.0
5.5	able to walk without assistance and rest for 100m, disability severe enough to make normal daily activity impossible. Grade 5 in one FS (either 0 or 1) or combinations of lesser degrees exceeding 4.0
6.0	Temporary or permanent support (braces, splint) on one side required to walk approximately 100m with with or without rest Combination of grade 3+ in more than two FS
6.5	Permanent support on both sides required to walk approx.20m without pause. Combination of grade 3+ in more than two FS
7.0	Unable to walk more than 5 m despite assistance. wheelchair, moves wheelchair himself/herself and can get in and out of wheelchair independently, is mobile in wheelchair about 12 hours a day. wheelchair mobile combination of grade 4+ in more than two FS; very rare Grade 5 in pyramidal tract function alone
7.5	unable, even with assistance, to walk more than a few steps, reliant on wheelchair, needs help to transfer, Moves wheelchair by self, but cannot spend a full day in it spend a full day in it, may need power wheelchair. Combination of grade 4+ in more than two FS.
8.0	Largely confined to bed or chair or is moved around in a wheelchair around - but is out of bed for large parts of the day out of bed, able to perform many activities independently and use arms effectively. Combinations of grade 4+ in several FS
8.5	Largely confined to bed for most of the day, can still perform some tasks independently and can use

	use arms effectively to some extent. Combinations of grade 4+ in several FS
9.0	helpless and bedridden, can eat and communicate Combinations of grade 4+ in most FS
9.5	completely helpless and bedridden, unable to eat, swallow and communicate. Combinations grade 4+ in almost all FS
10.0	Death due to multiple sclerosis

2.7 Diagnostics

Multiple sclerosis is thought to have a long pre-symptomatic period that can last up to several decades. That´s why among other things, a strikingly large number of conspicuous MRI findings with multiple lesions that do not lead to symptomatic manifestation are recorded at the time of initial diagnosis.

The same applies to patients with CIS, who often have old inactive lesions on MRI. CIS is usually an incidental finding in people who have headaches or have experienced trauma. It is also known that young people with CIS are found to have a loss of brain mass, and they have also performed remarkably poorly in school.(11) The aforementioned applies for patients with RIS as well, where a quarter of patients show significantly reduced cognitive function.(22)

All of this suggests that MS pre-symptomatically causes damage in the CNS, not only through inflammatory responses but also neurodegenerative. An important question is whether a screening program should be introduced, but that belongs to another discussion. (11)

Three principles should be followed by an experienced physician. It is important to establish a suspected clinical diagnosis of chronic inflammatory CNS disease with clues from the history and/or matching neurologic examination findings.

Second, evidence of inflammatory CNS lesions with temporal and local dissemination ("scattering") must be proven by accurate history, MRI, and cerebrospinal fluid (CSF) diagnosis using the McDonald criteria.

And lastly, differential diagnosis of other diseases should be excluded, done by means of MRI images and laboratory diagnostics. (10)

The medical history of the patient is very crucial in the diagnosis of multiple sclerosis, as it is still an initial step of the clinical diagnosis.

Dynamics are important to ask about including onset, duration and progression of symptoms. Indications of relapses that have already occurred can be obtained by asking about episodes of coordination, bladder, visual, sensory and paresis symptoms.

In addition, the family history is a crucial question, for example, whether there is a chronic inflammatory CNS or rheumatologic disease in the family.

As the physical examination would be the next step, knowledge of a thorough neurological examination procedure is considered a prerequisite. Objectification of the findings should be aimed at.(23)

Lab chemistry and blood tests are obligate but should be seen in this disease as differential diagnosis considerations.(3)

Lumbar punction in case of suspicion is also obligate. It can substitute for MRI detection of temporal dissemination when oligoclonal bands are detected. Positive findings have also scientifically substantiated the chronic inflammatory aetiology and is essential component to rule out possible other CNS pathologies. Moreover, it can give information about the functionality of the BBB by using the albumin quotient.
The findings can be very different, but usually a normal cell count or a latent lymphocytic pleocytosis is found.
Intrathecal immunoglobulin synthesis can provide qualitative and quantitative evidence.
Qualitative means that oligoclonal bands representing intrathecal proliferation of Immunoglobulin G (IgG) subfractions can be found. (95-97% of MS patients)
Quantitatively, the so-called “Reiber diagram” is used to compare the CSF content of IgG to the total IgG content. An intrathecal IgG synthesis without barrier disturbance means that IgG in CSF alone is elevated as in MS. Specific intrathecal synthesis of IgG against measles, rubella and/or varicella-zoster viruses is called MRZ-reaction. This antibody formation is not an expression of a persistent viral infection and probably also not of an involvement of the mentioned viruses in the development of MS. The MRZ reaction is positive in about 90% of MS patients and increases the specificity of CSF diagnostics.(23)

Gold-standard of investigations is the MRI.
Cranial and spinal MRI is done when multifocal lesions are expected. Localization of these lesions is white and/or grey matter. Typical locations in the CNS are supra- and infratentorial, spinal and preferably in the periventricular medullary bed and juxtacortical. Morphology of these lesions is mostly oval or roundish. In T1-weighted MRIs, the lesions are iso- or slightly hypointense, but in progression they are markedly hypointense, which may be an expression of already advanced tissue reduction. With contrast (gadolinium), acute lesions are hyperintense, and the uptake is also a reflection of BBB damage.

T2 and flair MRI's show hyperintense lesions, which is mainly beneficial due to high sensitivity, but at the expense of specificity.

The findings must be classified objectively by the McDonald criteria (2017). Figure 2.7 illustrated these criteria by applicating in a more practical way.

They define MRI lesions into dissemination in time and space.

Dissemination in space means that at least one T2-hyperintense lesion must be seen in at least two of four MS-typical regions (periventricular, cortical or juxtacortical, infratentorial, spinal).

Dissemination in time means that the MRI must show evidence of gadolinium-enhancing and nongadolinium-enhancing lesions or a progressive MRI finding with a new T2 and/or gadolinium-enhancing lesion.(24)

Figure 2 7 practical application of McDonald score for RRMS and PPMS Thompson Ajet al 2018 (3,25)

≥2 relapses	Objective evidence of ≥2 relapses		
	Objective evidence of 1 Lesion	Dissemination in space (MRI) Or Waiting for another relapse which concerns another localisation	
1 relapse	Objective evidence of ≥2 lesions	Dissemination in time (MRI) Or Second clinic relapse	Diagnosis of RRMS
	Objective evidence of 1 lesion (mono-symptomatic event; clinically isolated syndrome)	Dissemination in space (MRI) And Dissemination in time (MRI) Or 2nd clinical relapse	
Neurologic progression with suspicion of MS	Mc Donald criteria	1 year of disease progression (retro or prospective) 2 of 3 criteria: 1) Positive brain MRI (≥ 1 T2 lesion in MS typical region, no contrast needed) 2) Positive spinal cord MRI (≥ 2 T2 lesions, no contrast needed) 3) Positive liquor diagnostics	Diagnosis of PPMS

2.8 Differential Diagnosis

Important differential diagnosis you will find in the Figure 2.8.

Figure 2 8 Table of Differential Diagnosis of MS Fadil H et al 2007 (26)

Differential Diagnosis	**Investigation examples (not all mentioned)**
Neuromyelitis Optica	cMRI: Usually no/few lesions. Spinal MRI: Long-stretch spinal cord lesion (≥3 vertebral body segments), if any. Serology: aquaporin-4 antibodies in serum (70% positive).

Chronic Neuroborreliosis	Serology and Liquor diagnostics, important to differentiate from RRMS
AIDS	Positive HIV serology
Sarcoidosis	Chest x-ray (Hilus enlargement)
Cerebral vasculitis	CRP, ANA, complement serology, Skin morphology, brain biopsy
Cerebral Lupus erythematosus	dsDNA-antibodies, skin morphology, visceral organ involvement
Morbus Wegener	Necrotising Vasculitis, polyneuropathy
Morbus Whipple	Dementia with psychomotor symptoms, visual loss, macrophages in liquor
Vitamin B12 deficiency	Vitamin B9 and B12 in serum
others	Spinocerebellar ataxia, Morbus Behcet, Sjögren Syndrome

2.9 Therapy

General Principles:

MS is having three substantial trees of treatment.

The first involves relapse therapy of MS. Secondly, the course-modified therapy and lastly, the symptomatic therapy.

Relapse therapy has the goal to eliminate the symptoms as soon as possible.

As a rule, the patient is admitted as an inpatient. Exclusion of infection is done by routine laboratory and urine diagnostics. The EDSS is collected each time.

Golden standard in case of relapse is the glucocorticoid therapy in high doses for 2-5 days with Methylprednisolone 500-1.000 mg/day intravenously in the morning.

Secondly, plasmapheresis if glucocorticoid therapy is without beneficial effect or as escalation therapy can be assessed. Proton pump inhibitors for gastric ulcer prophylaxis, such as omeprazole is indicated during steroid therapy. Also, drug thrombosis prophylaxis with low-molecular-weight heparin during hospital visit is recommended.(27)

Typical used disease-modifying drugs used according to clinical diagnosis are listed in Figure 2.7.(28)

Figure 2 9 Table of most common disease modyfying therapeutics in MS Dobson R et al 2019 (11)

	Name	Trade name	Mechanism	Efficacy	Route	Main adverse	Monitoring
CIS	IFN ß	Rebif Extavia	Immunmodulatory pleinotropc immune effects	Moderate	Variable	Injection site reations, flu,lymphopenia,leukopenia	Baseline: FBC, U&E, LFTs, JCV,serology Follow-up: LFTs 3 monthly for a year. NABs at 12 months. JCV serology 6month
	Glatiramer acetate	Copaxane	Pleiotropic immune effects	Moderate	Syringe SC twice weekly	Flushing reaction, injection site reactions	Baseline: FBC, U&E, LFTs, TFTs, SPE, urine protein Follow-up: 1-month, 3-month, 6-month and 6-monthly FBC, U&E and LFTs. TFTs 12 monthly. NABs 12 and 24 months
	Teriflunomide	Aubagio	Reduced de novo pyrimidine synthesis →	Moderate	PO 7-14 daily	Alopecia, GI Symptoms	Baseline: BP, FBC, U&E, LFTs, urine protein Follow-up: fortnightly LFTs for 6 months then every 8 weeks. Weekly

			antiproliferative			Abnormal LFTs, leukopenia	LFT if ALT 2–3 9 ULN. 3-monthly FBC for 1 year then 6 monthly
RRMS	IFN ß	see above					
	Glatiramer acetate	See above					
	Fumarates: Dimethyl fumarate	Tecfidore	Pleotropic, NRF2 activation, downregulation of NFκB	Moderate/high	240mg twice daily	Flushing, GI symptoms, lymphonpenia, abnormal LFTs, Proteinuria, PML	Baseline: FBC, U&E, LFTs, urine protein Follow-up: FBC and urine protein 3 monthly for a year, then 6 monthly
	Teriflunomide	See above					
	Fingolimod, Siponimod	Gilenya	Selective sphingosine 1-phosphate modulator, prevents egress of lymphocytes from lymph nodes	High	0,5mg daily PO	bradycardia (first dose), hypertension, bronchospasm, lymphopaenia, abnormal LFTs, infections, basal cell carcinoma, macular oedema,opportunistic infections (PML, cryptococcosis etc.	Baseline: BP, FBC, U&E, LFTs, TFTs, serum immunoglobulin levels, serology (VZV, HIV 1 and 2, hepatitis B and C, syphilis), interferon gamma assay for tuberculosis (or similar), electrocardiogram Follow-up: 3-monthly FBC, U&E and LFTs. TFTs 12 monthly. Optical coherence tomography at 3 months for macular oedema
	Ocrelizumab	Ocrevus	Anti CD20, B-cell deplete	Very high		Infusion reactions, infections, possible hypogammaglobulinemia with prolonged use	Baseline: FBC, U&E, LFTs, TFTs, serum immunoglobulin levels, serology (VZV, HIV 1 and 2, hepatitis B and C, syphilis), TB elispot, cervical smear Follow-up: annual serum immunoglobulin levels
	Natalizumab	Tysabri	Anti-VLA4, selective adhesion molecule inhibitor	Very high	300mg IV 4 weekly	Infusion reactions PML	Baseline: FBC, U&E, LFTs, JCV serology Follow-up: LFTs 3 monthly for a year. NABs at 12 months. JCV serology 6 Monthly
	Alemtuzumab	Lemtrada	Anti CD52, non-selective	Very high	12mg IV x 5days year 1, 12 mg IV x 3days 2year	Infusion reactions, infections, opportunistic infections, leukopaenia, secondary autoimmunity (thyroid, immune thrombocytopenic purpura, renal etc.)	Baseline: FBC, U&E, LFTs, TFTs, serum immunoglobulin levels, serology (VZV, HIV 1 and 2, hepatitis B and C, syphilis), TB elispot, cervical smear Follow-up (for 48 months after last course): monthly FBC, U&E and urine analysis and 3-monthly TFTs
SPMS	All disease-modifying therapies could be used for treating SPMS						
PPMS	Ocrelizumab						

"ALT, alanine aminotransferase; BP, blood pressure; FBC, full blood count; HIV, human immunodeficiency virus; IV, intravenous; IVI, intravenous infusion; JCV, John Cunningham virus; LFT,

liver function test; MS, multiple sclerosis; NABs, neutralizing antibodies; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; PML, progressive multifocal leukoencephalopathy;
PO, oral; SC, subcutaneous; SPE, serum protein electrophoresis; TFT, thyroid function test; U&E, urea and electrolytes; ULN, upper limit of normal; VZV, varicella zoster virus." (11)

Symptomatic therapies in multiple sclerosis (MS) encompass pharmaceutical and physical treatments that target symptoms resulting from central nervous system (CNS) damage. While not MS-specific, these therapies address various symptoms such as bladder dysfunction and neuropathic pain. Cognitive impairment management in MS is complex and focuses on identifying contributing factors. Specific therapies licensed for MS include Sativex for spasticity and Fampridine for walking difficulties. Sleep difficulties are prevalent in MS, increasing with disease duration and often associated with anxiety, depression, and fatigue. A comprehensive review of symptomatic therapies is beyond the scope of this paper.(11)

2.10 Prognosis

The overall prognosis for patients with multiple sclerosis (MS) has significantly improved in recent decades, thanks to the advancements in disease-modifying therapies (DMTs). However, accurately predicting outcomes for patients on DMTs remains challenging as the long-term effects of these treatments on disease progression are still being observed. A recent study conducted over a 16-year period found that 18% of patients with relapsing-remitting MS (RRMS) progressed to secondary progressive MS (SPMS), and 11% experienced sufficient disability to require assistance for walking. The study also revealed an increased burden of morbidity, with an estimated loss of 13.1 quality-adjusted life years per patient. Modifiable risk factors associated with disease progression include low levels of vitamin D and current smoking. On the other hand, non-modifiable factors such as older age at MS onset, male sex, high relapse frequency in the early stages, longer disease duration, higher initial disability score, increased lesion burden on imaging, involvement of the spinal cord, and lower brain volume are linked to a higher risk of progression from RRMS to SPMS. Despite advancements in the treatment of RRMS, options for progressive forms of the disease remain limited. Ongoing efforts, such as the international registry MS Base led by Australian clinicians, are aimed at monitoring MS prognosis.(29)

3 Case Report

3.1 Medical history

2005/01/15. A 27-year-old female arrives at the hospital. She complains of delayed reactions and muscle weakness in her arms. In addition, the eyelids would fall unintentionally. These symptoms would increase in the second half of the day.

In general, she mentions complaints since December 20, 2004, that would mimic a severe cold. She also reports pain in the upper arms and lack of strength in both arms and legs.

In outpatient care, a rheumatologic examination revealed no findings. However, after further examination, she was referred to the Department of Nervous Diseases at Vilnius University Hospital (VUH) due to stance and gait unsteadiness. An inpatient admission with treatment and examination by a neurologist was planned.

On 25 January, a brain magnetic resonance imaging (MRI) scan was performed, which found diffuse demyelinating foci.

Preliminary diagnosis of post-infectious demyelinating encephalitis was taken. She was treated with pulse therapy with solu-medrol (methylprednisolone) 1 gram intravenously for two consecutive days.

The pain in the upper arms has almost completely regressed, but the other symptoms mentioned earlier remain. A dynamic monitoring for multiple sclerosis was recommended. The patient was admitted to the neurology department of Vilnius university hospital for clarification of the diagnosis and treatment.

04/04/2005. At the neurologic unit at VUH, a neurologic examination was made.

„The general condition of the patient is satisfactory but appears asthenic. Heart is rhythmic, blood pressure and pulse are within the normal range", the neurologists says,

And describes the patient as tense and performs a test on the cerebrobulbar nerves (CBN).

Consequently, the Simpson-test is positive, showing irregular partial ptosis of both eyelids - and marked ptosis of the upper eyelids. The holding test of arms and legs shows instability.

In the following biochemistry tests were performed, they did not show any abnormalities except of mild lymphocytopenia (20,5% of 6,7 10e^9/l Leukocytes)

Additional laboratory tests on glucose and antibodies have been made, which revealed a normal oral glucose tolerance test, but significantly elevated antibodies against striated muscle (Anti-MuSK-AK) (2.8 - normal: up to 0.4).

Due to this positive result an electro neuroradiography (ENM) was undertaken that highlighted a normal M-response amplitude, with a constant decrement recorded before the

load, which decreases slightly immediately after the load and then deepens afterwards.
As conclusion, the findings are typical of a post-synaptic type of conduction disturbance, with a positive myasthenic reaction.

Because of positive myasthenic reaction some other investigations have been done, as imaging of the thorax and an ECG.
ECG was normal, except for a partial right bundle branch block.
Besides that, for excluding of a thymoma a CT-scan pointed out that the lungs are free, no pathological signs within thorax and the thymus gland is without lesions.

In summary, the diagnosis of a generalized form of **myasthenia gravis (classified as stage II by Osserman)** was made.
The treatment included:

- Inpatient treatment with calimine 60 mg × 3 daily (initially × 2 daily, then increased to 3 tablets daily).
- Plasmapheresis treatment every 2 days of 6 treatment courses.

Course:
The patient's well-being improved during the inpatient treatment. She did not have recurrent attacks of weakness and episodes of eyelid drooping, but still had periodic wavering of the eyes.
The patient was discharged from the ward on 15 April 2005. Referral to the thoracic surgery department for further surgical treatment of thymoma was given.
Recommendation: Continued treatment with calimine (mestinon) 60 mg 2-3 times a day (until thymectomy) and a repeated neurological consultation is recommended after surgery for further medical treatment.
Since the patient was diagnosed with myasthenia gravis at an early age, the following is a brief overview of the disease.

Myasthenia gravis

Abstract:

It is an autoimmune disease, associated with a disturbance of signal transmission at the synapses between neuron and muscle. At the motor endplate, the acetylcholine receptors are inhibited and impaired in the long term, so that after repeated stimuli, the response becomes steadily smaller, so-called decrement.
In the patient, it leads to a pathological fatigability of the muscles. Natural muscle work is restored only after physical rest.
The diagnosis is made clinically, by laboratory diagnostics and electrophysiological. Clinically, this is made with a Simpson test (looking upward for one minute provokes ptosis) and holding tests of the arms, legs and head.
Labor diagnostically, for example the detection of antibodies to acetylcholine receptors or muscle-specific antibodies, supports the diagnosis.
Electrophysiological, decrement is established after provoked muscle activity.
Computer tomography indicates a suspicious thymus.
Frequently, an alteration of the thymus is associated with myasthenia gravis, making thymectomy indicated.
Symptomatically, patients are treated with cholinesterase inhibitors (e.g. pyridostigmine bromide Mestinon® or Kalymin® 30 mg p.o up to. 4×/day) and plasmapheresis to end acute relapses.

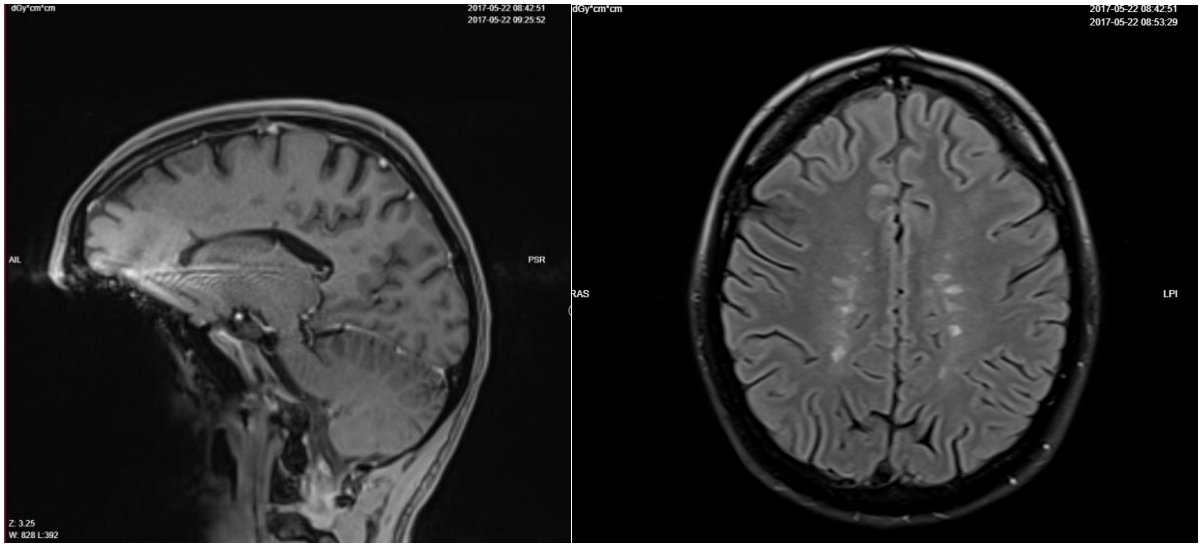
Remission is often achieved and this therapy should prevent in any case a myasthenic crisis, which is the abrupt worsening of symptoms.
If symptoms worsen or intensify, therapy can be escalated toward DMRDs and biologics.

19/05/2017. 12 years later the now 39 years old female complaints about general fatigue, pain in the lumbar region and over the whole leg during right leg flexion. The patient experienced an increasing feeling of weakness in the right leg one year earlier, which was initially not very pronounced. 6 months ago, the symptom worsened, especially during extension of the right leg, until it became particularly badly 2-3 weeks ago. She was not able to walk normally, climbing stairs became increasingly difficult. Her current medication regimen includes pyridostigmine 60 mg 2-3 times per day and periodic plasmapheresis. She denies other chronic diseases and drug allergies. Operations only include a 2005 performed thymectomy.

After neurologic inspection: „Conscious, oriented. Eye movements are free, no nystagmus. Other CBN without abnormalities. Vivid reflexes in arms (right>left), patellar reflex (right > left), pathological Babinski reflex right sided. Pyramidal hypertonus and clonus right leg.
No sensory deficit. Finger-nose test right and left accurately, Romberg test left and right accurately although with ataxia right-sided“, it is suspected a diagnosis of a CNS disease.

	Strength right	**Strength left**
Hand	5	5
Leg proximal	4	5
Leg distal	4	4++
Foot	4	4++

The general examination of heart, lungs and abdomen were normal. Biochemistry analysis registered mildly elevated neutrophils (73,3%, 10e^9/l: 6,92), Haemoglobin and MCV at the lower border (129 and 91,8).
By excluding pathologic processes in inner organs and the highly suggestive finding of central nervous system involvement by neurological examination, it was decided to perform more lab tests and investigations including electrophoresis and lumbar punction. Protein and electrophoresis highlighted a normal value for albumin (44 g/l) and IgG (12,99 g/L).
CSF examination revealed a clear, pure coloured, normal cell count liquor with lymphocytosis. Glucose, electrolytes, and proteins were also in normal range.
Consequently, electrophoresis of CSF was performed, in which intrathecal IgG synthesis (oligoclonal bands in liquor) was positive.
Further blood analysis for EBV virus is negative.
For detection of inflammatory CNS lesions with temporal and local dissemination ("scattering") by means of accurate history, MRI diagnosis is obligatory. (Figure 2.10)



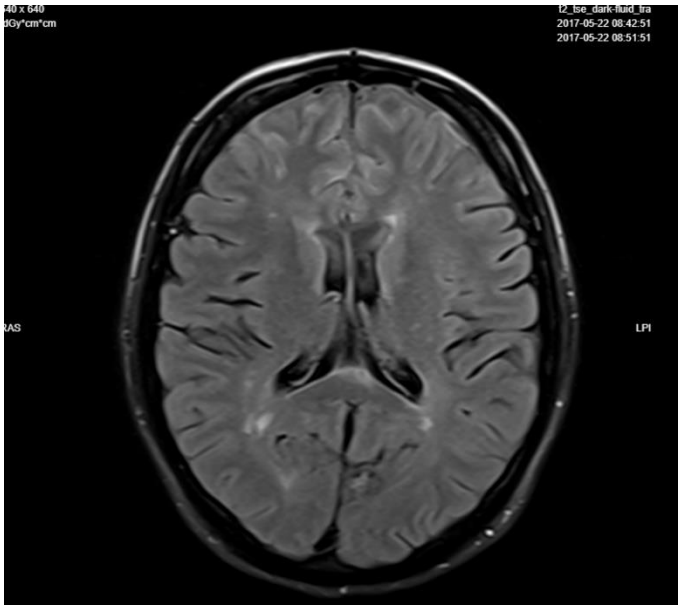


Figure 2 10 MRI in sagittal and axial plane, kindly permitted by Vilnius university hospital radiologic unit 2017

22/05/2017 Findings of the MRI shows multiple foci up to 11/8 mm in size supra- and infratentorially in the brain, characteristic of demyelinating foci. Diffusion sequences are not evaluated for artefacts; no evidence of c/m accumulation.
Left occipital lobe parasagittal dorsal to sulcus parietooccipitalis shows heterogeneous signal, with haemosiderin inclusions, no surrounding reaction, limited 14/12 mm mass typical of cavernoma. (Figure2.10)

The patient's complaints, medical and life history, objective examination data and results of investigations led to the following clinical diagnosis:

- **Multiple sclerosis first documented attack: inferior paraparesis, right hemisyndrome, ataxic syndrome, EDSS score of 3 during exacerbation.**
- Myasthenia gravis, generalized form, Stage IIA according to Osserman.
- Condition after thymectomy in 2005.

An immediate exacerbation therapy was initiated with methylprednisolone (1000mg sol. NaCL 0.9%, 500 ml i/v) for three consecutive days. The symptomatology under therapy improved immediately. The EDSS score declined from 3 to 1.

In the following, the patient was consulted by physio-and communicative therapy with designing a rehabilitation programme. Physiotherapy council: „In case of stable clinical neurological condition, but with continued difficulty in mobility and ambulation, the patient is recommended for a further phase of rehabilitation - outpatient rehabilitation with the recommendation: Conservative physiotherapy 1x/d on weekdays on the ward, patient education. “

Initial treatment after hospitalization was successful and remission was achieved. The medication was as follows:

	Morning	**Daytime**	**Evening**	**Note**
Pyridostigmine 60mg tabl.	1x		1x	
Methylprednisolone 1g sol. NaCL 0.9% 500ml i.v	1x			Every day: blood sugar, electrolytes
Diazepam 5mg tabl.				As needed
Paracetamol 500mg tabl.	1x		1x	
Bromazepam 1,5mg tabl.	1x		1x	
Omeprazol 20mg tabl.	1x			
Kaliumchlorid (KCL) 750mg tabl.		1x		
Clonazepam 0,5mg tabl.				Nightly 2days

At discharge the neurologic condition improved, normal muscle strength was regained. Pathological reflexes predominant on right side persist. It was recommended to consult a specialist at the MS clinic of VUH, supplementation of Vitamin D and B12/9, continued Pyridostigmine intake, KCL 750 mg once per day and regular blood control by family physician.

11 Month later, the patient's medical history reveals that in May 2017, there was negative progression in the neurological status, with an increase in the EDSS score from 3.0 to 5.5 during remission. In January 2018, plasmapheresis was administered during an exacerbation, and the patient had to discontinue interferon beta 1a (Rebif) injections due to intolerance and side effects.

In April 2018, the patient developed claudication and hesitation, leading to the discontinuation of dimethyl fumarate (Tecfidera) treatment. Following these challenges, a re-diagnosis was made in 2018, classifying the patient's condition as multiple sclerosis with an extremely active

relapsing-remitting course. The patient presented with exacerbation of inferior paraparesis primarily affecting the right leg, along with a pronounced ataxic syndrome.

To address the recurrent exacerbations and neurological disability caused by the previous first-line immunomodulatory therapies, the patient's request and the recommendation of the neurologic council led to the decision to prescribe Rituximab. The decision to prescribe Rituximab was based on the combined manifestation of multiple sclerosis and myasthenia gravis, recurrent exacerbations, significant neurological signs affecting multiple systems, and the patient's intolerance to previous medications.
The patient received a 1000 mg dose of Rituximab on June 7, 2018, followed by a second dose in July 2018.
Positive effects were observed as early as one month after the first Rituximab infusion, although the patient experienced fever, flu symptoms, and worsening hesitation and weakness, which necessitated outpatient plasmapheresis as a treatment. Since then, no abnormalities have been noticed in the last 6 months since the last Rituximab injection.

As of March 26, 2019, the patient has been admitted for hospitalization to receive the third dose of Rituximab infusion.
By considering the patient's medical history and test results, Rituximab was deemed an appropriate course of action to manage the condition and provide potential therapeutic benefits. Since the last administration of Rituximab (11/07/2018) no exacerbation was observed. A control MRI is planned in 6 months during the next Rituximab infusion comparing it to the last MRI from April 2018 (Figure 2.11,12)
Comparing these images, it indicates that the focal lesions in the brain supra- and infratentorially are characteristic of demyelinating lesions, but with no clear dynamics, diffusion restriction or signs of contrast agent accumulation. (Figure 2.11,12)

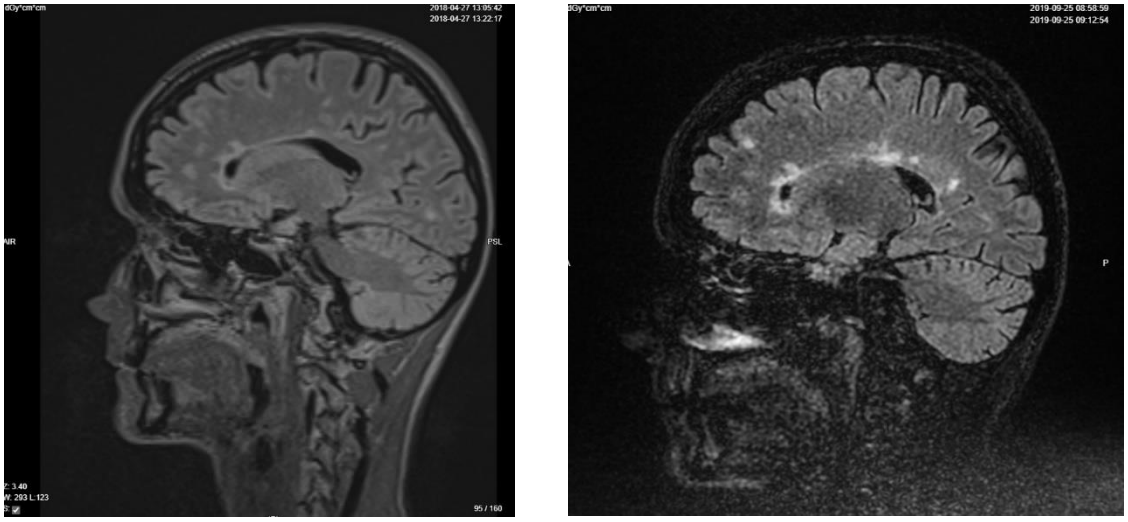


Figure 2 11 left image: saggittal MRI from April 2018; right image: sagittal view from September 2019

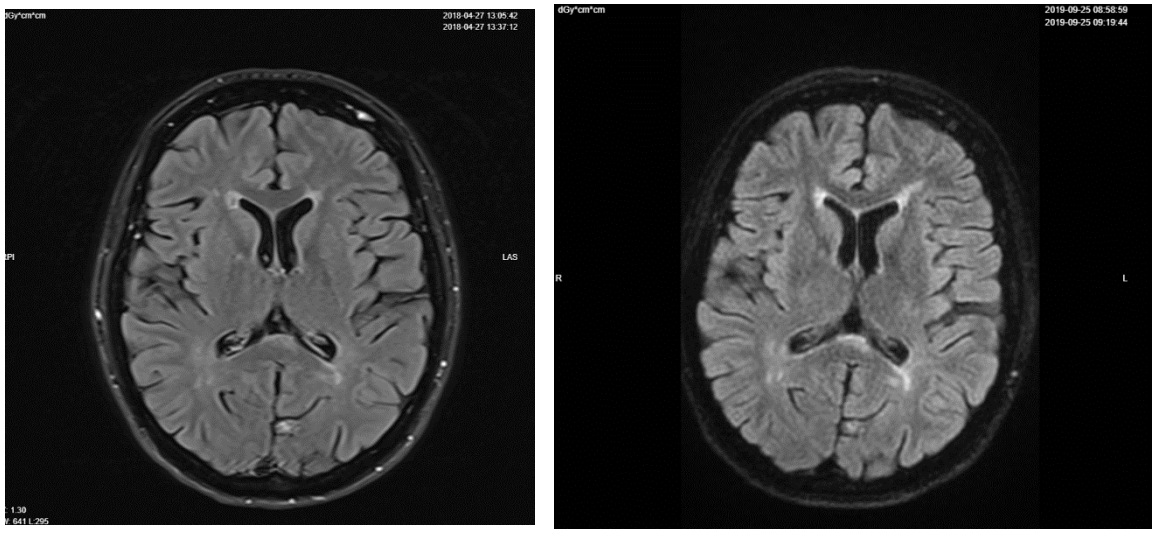


Figure 2 12 left image: axial MRI from April 2018, right image: axial MRI from September 2019

Prior to the last infusion of the monoclonal antibody, the patient's condition was stable, and no relapse had occurred.

06/10/2019 Neurological Consultation:

Due to recurrent exacerbations, a persistent highly active relapsing-remitting course and high John-Cunningham virus (JCV) titers (1.53), it was recommended to initiate treatment with Ocrelizumab instead of Rituximab. The patient requested and consented to this treatment, and the first two doses of Ocrelizumab (300 mg each) were infused on 02.10.2019 and 17.10.2019, respectively. Infusions continued at a dose of 600 mg every six months.

The patient is in a satisfactory condition, conscious, alert, and oriented. There are delayed eye movements in saccades without nystagmus. No cranial nerve deficits or sensory disturbances

are detected. Hand strength is normal, while leg strength is slightly reduced, particularly in the right leg. Tendon reflexes are more active on the right side, and a pathological Babinski reflex is observed on the right. The patient exhibits pyramidal tone and clonus in the right leg. Performance on specific tests indicates ataxia and a complex gait pattern characterized by paraparesis, spasticity, and ataxia. The patient can walk 100 meters unassisted without resting. The EDSS score is 5.5.
Additionally, a herpetic rash is present on the lower lip.

Laboratory and instrumental tests were conducted, revealing normal blood results and normal urine results.
Inpatient treatment plan:

	Morning	**Daytime**	**Evening**	**Note**
Metyhlprednisolone 1g sol. 500ml i.v.	1x			Every day: Electrolytes and glucose
Paracetamol 500mg	1x		1x	
Clemastine 1mg	1x			
Mestinon 60mg	1x	1x	1x	
Sol Ocrelizumab 600mg + sol NaCL 0.9% 500ml i.v.	1x			
Aciclovir 400mg	1x		1x	Herpetic rash

The patient tolerated the administration of ocrelizumab well, with no adverse effects reported. The herpetic rash is improving and no longer spreading, so that the patient could be discharged from the hospital.

The recommended ongoing treatment includes on top of the ocrelizumab to continue with Mestinon, completing the Aciclovir course, and adding Fampridine and vitamin supplements. A follow-up consultation with a neurologist at the Multiple Sclerosis Clinic is advised after three months, or earlier if there is a deterioration in the patient's condition. No sick note is required.

October 2023
The patient is in a stable condition, treated two times a year with Ocrelizumab. During the last three years no MS exacerbation was recognized.
Neurologic examination did not change a lot compared to last examination.

Decreased nervus abducens induced abduction of right eye. Strength in left hand and arms 5/5, left leg proximal 5/5, distal 4/5, right hands and arms 4/5, right leg proximal 4/5, distal 3/5. Ataxic gait. Shinbone test with ataxia. Finger to nose test accurately but ataxic on right side. Positive Romberg test with closed eyes. Normal sensibility in face, trunk and legs. No decrement of muscles observed. Vivid reflexes (right > left). Babinski positive on the right. Patient is mobile and can walk without assistance. The EDSS score is 5.5.

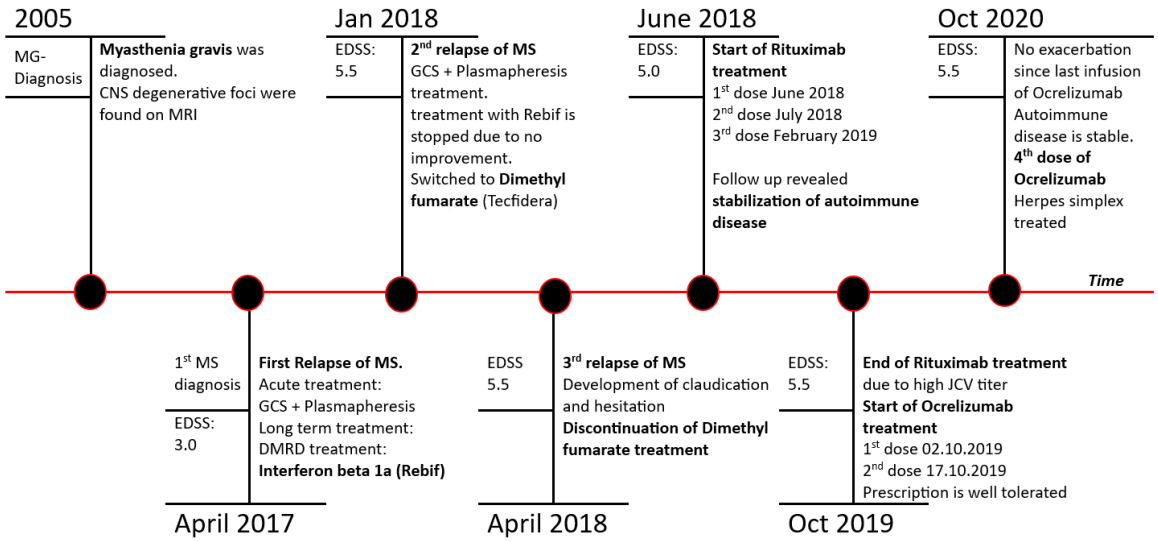


Figure 2 13 Timeline of diagnosis and exacerbations of Myasthenia gravis and MS

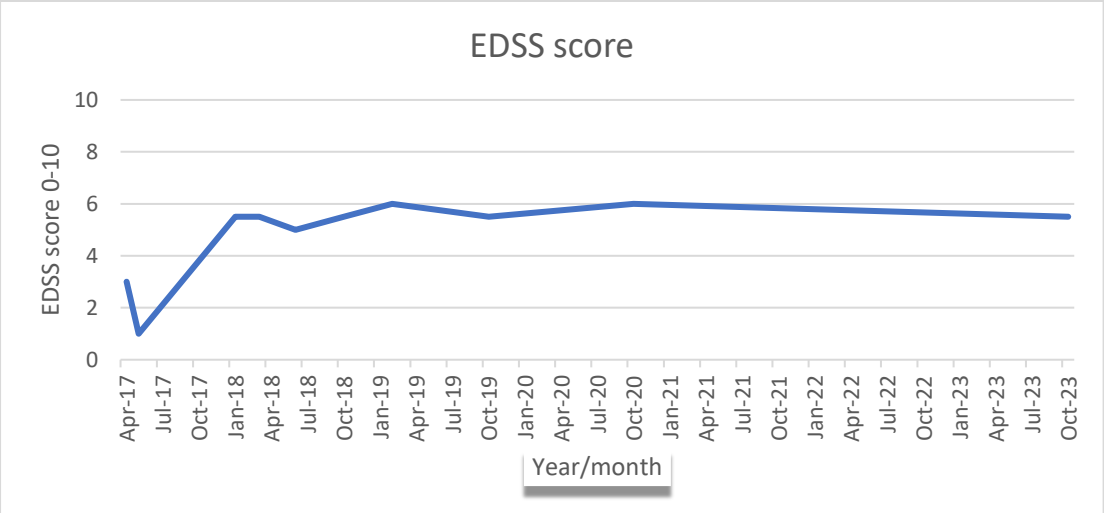


Figure 2 14 EDSS score evaluated during consultations and hospital visits between 2017(1st exacerbation and 2023)

4 Discussion

This case report documents a rare case of the co-occurrence of Myasthenia gravis and Multiple sclerosis. The literature is describing similar cases about this coincidence; therefore, it is assumed that "the co-occurrence of MS and MG may be more common than reported."(30)

Both diseases share a familiar pathogenesis, as they are autoimmune diseases and is thought of sharing similar immunological mechanism. It is also well known, that MS immunomodulators such as glatiramer acetate or interferon beta can cause MG exacerbations. Suggesting a close link in mechanisms. (30)

Our patient initially presented with diffuse demyelination foci, which may have been already a radiologically isolated syndrome back in 2005. In consequence, it can be criticized that the patient should have been more closely monitored. However, the timeline (figure 2.13) leads to the suggestion that there is a big gap between the onset of both diseases; but in fact, it is as already described in clinic-and diagnostic section, that MS is a disease which may have a long course without any clinical symptoms. The onset of MS in this patient may have been even earlier than the one of myasthenia gravis, and thus creates the question, which disease may have kept the other out of sight or if the exacerbation interacted with each another.
Answers to these questions we probably never will ascertain. It is also possible that both diseases exist coincidentally next to each other.

The co-occurrence can be described as autoimmune syndrome. In MG the antibody mediated immunity plays a major role, but what if it supposed of a similar mechanism in this MS case. The patient is negative for EBV virus, which is very uncharacteristic for MS. „Prior analyses demonstrated increased serum antibodies to EBV in ~99.5% of MS patients compared with ~94% of healthy individuals" (31) Besides, the current therapy with Ocrelizumab which acts on plasma cells and cause depletion of antibody secretion, shows a very beneficial effect on creating a state of NEDA in a patient with a highly active form of RRMS (compare timeline and EDSS score in figure 2.13;14). Consequently, the pathogenesis might be antibody mediated in this patient, with no predominant autoreactive T-cell causality as it is propagated in literature. Natalizumab is one of the 1st line monoclonal antibody treatments for MS, but it was not prescribed due to elevated JCV titer. As it also seems to be the right decision to use Ocrelizumab as treatment in this case, since „Anti–VLA-4 treatment amplified this

observation, while interferon β– or anti-CD20 treatment did not modulate EBV-specific T cell occurrence“ (12). Moreover, underlining the hypothesis of a dominantly autoantibody mediated immune response.

According to the literature, another case of MG and MS co-occurrence, suggests that both diseases are initially caused by humoral and cell-mediated autoimmunity. Autoreactive T-cells and B-cells would have an equal impact in disease onset. (32)

Diagnosing MS after MG or vice versa is an ongoing challenge, as the symptoms clearly overlap with each other, both incorporating especially bulbar, ocular and gait symptoms.
Nevertheless, poly-autoimmune disorder is a complex disease which is not as rare as many physicians may think. It should always be considered, especially in patients who present uncharacteristically as in the here prescribed case.

5 Glossary

MS	Multiple Sclerosis
CIS	Clinically isolated syndrome
EDSS	Expanded Disability Status Scale
NMSS	National Multiple Sclerosis Society
PR	Progressive relapsing
RIS	Radiologically isolated syndrome
RR	Relapsing-remitting
SP	Secondary progressive
PP	Primary progressive
CDMS	Clinically definitive MS
NEVA	No evident disease activity
EBV	Epstein Barr virus
MRZ	Mumps, measles, zoster
HLA-DRB1*15:01 Mutation	Human Leukocyte antigen MHC Class II Region DRB1 15:01
EBNA1	Epstein–Barr nuclear antigen 1
CYP27B1 gene	Cytochrome P450 family 27 subfamily B member 1 gene
TCR	T-cell receptor
BBB	Blood-brain barrier
INO	Internuclear Ophthalmoplegia
CVS	Cardiovascular system
EDSS	Expanded disability status scale
CNS	Central nervous system
CSF	Cerebrospinal fluid
CRP	C-reactive Protein
ANA	Anti-nuclear antibody
Anti-MuSK-AK	Antimuscarinic antibodies
ENM	Electrical neuroradiography
TNF	Tumor necrosis factor
FS	Functional systems
MRI	Magnetic resonance imaging
JCV	John Cunningham virus

6 List of figures

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