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Multiple Sclerosis: I. Symptomatology and Etiology

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Abstract

Multiple sclerosis (MS) is the most common autoimmune disorder of the central nervous system. It is a chronic, debilitating, demyelinating disease caused by an autoimmune attack that results in the progressive loss of the myelin sheath surrounding neuronal axons. The condition can be thought of as a stripped electrical wire and, as with damaged electrical wires, signals sent along damaged nerves between the brain and the body can be slowed or blocked. Depending on which nerves are involved, the resultant decrease in the speed of signal transduction leads to a loss of functionality that includes both cognitive and motor impairment, sensations, and other functions. The inflammatory response contributes to the loss of the grey matter and, as a result, current literature devotes itself to combatting the auto-inflammatory aspect of the disease. There are several proposed causal links between the Epstein-Barr virus (EBV) and the HLA-DRB1*15:01 allele to the onset of MS. While contributing to the degree of autoimmune attack and the resultant inflammation, unfortunately, such links do not determine the onset of MS. In this article, I analyze demyelinating autoimmune diseases, defining as accurately as could be the disease, its types and variants, its signs, symptoms, and stages, and its pathophysiology and causes.

Abbreviations

α-Syn: Alpha-synuclein protein; AD: Alzheimer's disease; ANS: Autonomic nervous system; ASON: Anti-sense oligonucleotide; ATMP: Advanced therapy medicinal products; BDNF: Brain-derived neurotrophic factor; BP: Blood pressure; CBD: Corticobasal degeneration; CNS: Central nervous system; CT: Computerized tomography; CUP: Compassionate use program; DMD/T: Disease-modifying drugs/therapies; FTLD: Frontotemporal lobar degeneration; GCI: Glial cytoplasmic inclusions; GDNF: Glial-derived neurotropic factor; GHT: GHT: Growth hormone therapy; GT: Gene therapy; GWAS: Genome-wide association study; IGF: Insulin/insulin-like growth factor; IT: Immunotherapy; LB: Lewy bodies; LBD:

Lewy body dementia; MOD: Multiple organ dysfunction; MOS: Multiple organ system; MRI: Magnetic resonance imaging; MS: Motor system; MSA: Multiple system atrophy; MSCT: Mesenchymal stem cell therapy; MSP: Multiple system proteinopathy; NDD: Neurodegenerative disease/disorder; NSAID: Non-steroidal anti-inflammatory drug; OPCA: Olivopontocerebellar atrophy; PD: Parkinson's disease; PET: Positron emission tomography; PSP: Progressive supranuclear palsy; REM/SBD: Rapid eye movement/sleep behavior disorder; ROS: Reactive oxygen species; SBOD: Steele-Richardson-Olszewski disease; SDS: Shy–Drager syndrome; SND: Striatonigral degeneration; SPECT: Single photon emission computerized tomography; TLR: Toll-like receptor; VD: Vascular dementia.

Keywords

Multiple sclerosis; demyelinating disease; autoimmune attack; inflammatory response; types and variants; signs, symptoms and stages; pathophysiology and causes.

Introduction

Multiple sclerosis (MS) presents itself as a spectrum of disorders based on the degree of inflammation subsequent to autoimmune attack. A majority of patients experience early relapsing and remitting episodes of neuronal deterioration following a period of recovery. Some of these individuals may transition to a more linear progression of the disease, while about 15% of others begin with a progressive course on the onset of MS. It is estimated that 50 million people worldwide have neurodegenerative diseases and that, by 2050, this figure will increase to 115 million people.

The progression of MS occurs due to episodes of increasing inflammation, which is proposed to be due to the release of certain antigens (myelin oligodendrocyte glycoprotein; myelin basic protein; proteolipid protein, and others), causing an autoimmune response. This sets off a cascade of signaling molecules that result in T-cells, B-cells, and macrophages that cross the blood-brain barrier (BBB) and attack the myelin on neuronal axons, leading to inflammation. Further release of antigens drives subsequent degeneration, causing increased inflammation.

Now, a demyelinating disease can be caused by genetics, environmental factors, autoimmune reactions, and other unknown factors. Environmental factors can be triggered by a viral infection, chemical exposure factors (including organophosphate poisoning by commercial insecticides such as sheep dip, weed killers, and flea treatment preparations for pets). Chronic neuroleptic exposure may also cause demyelination as (controversially) may Vitamin B12 deficiency.

In this article, I analyze demyelinating autoimmune diseases (the parent of MS), define MS, its phenotypes, variants and stages, and its etiology and causes. In companion articles, I will consider the different approaches to managing the symptoms of the disease, the available treatment portfolio and the prognosis of the disease.

On Demyelinating Autoimmune Diseases

A demyelinating disease is any condition that causes damage to the protective covering (myelin sheath) that surrounds nerve fibers in the brain, the optic nerves that lead to the eyes, and the spinal cord. This attack causes inflammation and injury to the nerve sheath and ultimately to the nerve fibers that it surrounds. When the myelin sheath is damaged, nerve impulses slow or even stop, causing neurological problems. The damage impairs the conduction of signals in the affected nerves. The process can result in multiple areas of scarring (sclerosis). In turn, the reduction in conduction ability causes deficiencies in sensation, movement, cognition, or other functions, depending on which nerves are involved. The most well known example of demyelinating diseases is multiple

sclerosis (MS).

The term MS refers to the distinctive areas of scar tissue (sclerosis—also called 'plaques' or 'lesions') that result from the attack on myelin by the immune system. These plaques are visible using magnetic resonance imaging (MRI) in the white and/or gray matter of people who have MS. Plaques can be as small as a pinhead or as large as a golf ball. In the brain, MS damages the nerve cell bodies found in the gray matter as well as the axons themselves commonly called white matter. Elsewhere in the central nervous system (CNS), it attacks the spinal cord and the optic nerves that transmit visual information from the eyes to the brain. As the disease progresses, the outermost layer of the brain, called the cerebral cortex, shrinks (this is what is known as 'cortical atrophy').

During an MS exacerbation, most of the myelin (and to a lesser extent the axons within the affected area) is damaged or destroyed by different types of immune cells (also known as 'inflammation'). The symptoms of MS depend on the severity of the inflammatory reaction as well as the location and extent of the plaques, which primarily appear in the brain stem, cerebellum (involved with balance and coordination of movement, among other functions), spinal cord, optic nerves, and the white matter around the brain ventricles (fluid-filled spaces).

Now, demyelinating diseases are traditionally classified in two kinds: Demyelinating myelinoclastic diseases and demyelinating leukodystrophic diseases. In the first group, a normal and healthy myelin is destroyed by a toxicant, a chemical, or an autoimmune substance. In the second group, myelin is abnormal and degenerates.

In MS, evidence has shown that the body's own immune system is at least partially responsible. Acquired immune system cells called T-cells are known to be present at the site of lesions. Other immune-system cells called macrophages (and possibly mast cells) also contribute to the damage.

Demyelinating diseases can be caused by genetics, autoimmune reactions, environmental factors (such as being triggered by a viral infection, a chemical exposure, chronic neuroleptic exposure, and vitamin B12 deficiency), and other unknown factors. Regarding chemical exposure, organophosphate poisoning by commercial insecticides such as sheep dip, weed killers, and flea treatment preparations for pets can also result in nerve demyelination. Other types of demyelinating diseases and their causes include: Optic neuritis (ON), neuromyelitis optica spectrum disorder (NMOSD), myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), transverse myelitis (TM), and acute disseminated encephalomyelitis (ADEM). I will not dwell here on these various diseases (for more details, see Fymat 2023.)

What is MS?

MS is a primary example of an autoimmune illness of the central nervous system (CNS). It is the most common immune-mediated disorder affecting the CNS. This autoimmune attack results in the progressive loss of the myelin sheath covering neuronal axons. The resultant decrease in (or loss of) the speed of signal transduction leads to a loss of functionality that includes both cognitive and motor impairments depending on the location of the lesion.

Also known as encephalomyelitis disseminata, MS is a myelinating disease in which the immune system, which normally protects the body, attacks the protective sheath (myelin) that covers nerve fibers. The name multiple sclerosis refers to the numerous glial scars (or sclerae – essentially plaques or lesions) that develop on the white matter of the brain and spinal cord. It is an unpredictable, often disabling disease of the CNS. It is not contagious.

The nerves send information from the brain and spinal cord to other nerves in the body, the myelin helping make this transmission efficient. Damage to the myelin causes communication problems between the brain and the rest of the body, affecting the brain and the spinal cord that make up the CNS. The condition can be thought of as a stripped electrical wire and, as with damaged electrical wires, signals sent along damaged nerves between the brain and the body can be slowed or blocked.

MS is the most common potentially disabling and debilitating neurologic illness of North American and European young and middle-aged adults. The average person in the U.S. has about a 1 in 750 (0.13%) chance of developing it. At least 2.3 million people worldwide have MS of whom roughly 1.3 million have relapsing MS. An estimated 1 million people live with MS in the U.S. In the U.K., there are about 130,000 people living with MS. When they were first told they had MS, 85% of them were diagnosed with the relapsing-remitting (RRMS) type (to be later discussed). In that country, they are most likely to find out they have MS in their 30s, 40s, and 50s but the first signs of MS often start years earlier.

People from many different ethnic backgrounds can get MS. Many of them notice their first symptoms years before they get their diagnosis. Symptom onset generally occurs between the ages of 20 to 50 years, affecting women three times more often than men. A small number of those with MS will have a mild course with little to no disability, whereas others will have a steadily worsening disease that leads to increased disability over time. Most people with MS, however, will have short periods of symptoms followed by long stretches of relative quiescence (inactivity or dormancy), with partial or full recovery. For unknown reasons, women are affected more frequently (about three times) compared to men. In the long-term, pregnancy does not affect how someone's MS develops. Most medications are not recommended during pregnancy so if you are planning to become pregnant, or think you might already be, you should discuss this with your MS nurse or doctor.

The disease is rarely fatal and most people with MS have a normal life expectancy. It is a chronic disease that affects people differently. It is further unpredictable and everyone's MS is different. It may have a prodromal phase in the years leading up to MS manifestation, and is characterized by psychiatric issues, cognitive impairment, and increased utilization of healthcare. Once diagnosed, it stays with the individual for life but treatments and specialists can help manage the condition and its symptoms. Eventually, the disease can cause permanent damage or deterioration of the nerves. Currently, there are still no cures and no clear ways to prevent the disease from developing. Fortunately, new treatments can reduce long-term disability for many people with MS.

Symptoms range from numbness and tingling to blindness and paralysis, and there is currently no cure for MS. The progress, severity and specific symptoms of MS in any one person cannot yet be predicted, but advances in research and treatment are leading to better understanding and moving us closer to a world free of MS.

Course of the disease - A preliminary look

Losses of function during MS may be temporary or long lasting, and everyone's experience with MS is different. The disease takes several forms, with new symptoms either occurring in isolated attacks (relapsing forms) or building up over time (progressive forms). The course of MS can be classified into the four basic patterns below:

- **Relapsing-remitting MS (RRMS):** In RRMS, most people will have a relapsing-remitting disease course. They experience periods of new symptoms or relapses that develop over days or weeks and usually

improve partially or completely. These relapses are followed by quiet periods of disease remission that can last months or even years. Small increases in body temperature can temporarily worsen signs and symptoms of MS but these are not considered true disease relapses. Symptoms may disappear completely, although some permanent neurological problems often remain, especially as the disease advances. Most people will have a relapsing-remitting course, which often develops in secondary progressive MS (SPMS). The term 'benign' is sometimes used to refer to RRMS cases in which the disease is mild and the patient remains fully functional in all systems for 10-15 years. Because of this long time period, it is difficult to reliably predict and formulate early treatment decisions. (Note: This disease type does not figure in the accepted MacDonald's classification discussed below).

- **Secondary progressive MS (SPMS):** In SPMS, at least 50% of those affected eventually develop a steady progression of symptoms, with or without periods of remission, within 10 to 20 years from disease onset.

- **Primary progressive MS (PPMS):** In PPMS, the worsening of symptoms usually includes problems with mobility and gait. The rate of disease progression varies greatly and some people will experience a gradual onset and steady progression of signs and symptoms without experiencing any relapses.

- **Peculiar developments:** Such developments may be particular characteristics of MS. They include: Uhthoff's phenomenon (UP) - a worsening of symptoms due to exposure to higher than usual temperatures and Lhermitte's sign (LS) - an electrical sensation that runs down the back when bending the neck.

How fast will MS get worse and what are the associated complications?

It is impossible to answer the question of how fast MS will get worse as everyone's MS is different. Research is hoping to find ways to better predict this for each individual. Until then, we do know that MS tends to get worse faster if one: Has never been on a disease-modifying drug/therapy (DMD/T); still had relapses while on DMD/Ts; has lesions on the spinal cord; has more or bigger lesions (or other unusual signs) on brain scans; has more disability early on; is older; is male; has a faster rate of brain atrophy. On average, there is no difference between people with SPMS and PPMS when it comes to how fast their MS gets worse.

MS can cause many complications, some of which are a direct result of the disease and others are a consequence of MS treatments. The main complication that occurs as MS progresses is vision problems such as blurry vision, diplopia, nystagmus and, in more severe cases, vision loss. Other common complications include bladder and bowel problems, such as constipation, diarrhea, and urinary and fecal incontinence.

MS can also cause cognitive impairment and mental health complications. Cognitive issues may include memory loss, slower intellectual processing, reduced ability to problem-solve, and impairment of verbal and visual-spatial abilities. Anxiety, depression, and bipolar disorder are also more common in patients with MS than in the general population. These complications could be the result of neuronal damage caused by the disease, the burden of having to live with a chronic condition, or a side effect of certain medications such as corticosteroids used to treat MS relapses.

Other complications related to the use of corticosteroids include weight gain, mood disorders, infections, hypertension, ocular hypertension, hyperglycemia, thrombocytopenia, fractures, cataracts, bruises, adrenal insufficiency, and venous thromboembolism (which can also be the result of MS complications such as disability, spasticity, and reduced mobility, although the risk is low).

Types of MS

Phenotypes (commonly termed types) of MS, or patterns of progression, have been described according to the progression of symptoms over time. Phenotypes use the past course of the disease in an attempt to predict the future course. They are important not only for prognosis but also for treatment decisions.

The International Advisory Committee on Clinical Trials (IACCT) of MS describes five types of MS (revised in 2013). Independently of the types published by the MS associations, regulatory agencies like the (U.S.) Food & Drug Administration (FDA) often consider special courses, trying to reflect results of me clinical trials on their approval documents. Some examples could be "Highly Active MS" (HAMS), "Active Secondary MS" (ASMS), which is similar to the old “Progressive-Relapsing MS” (PRMS), and "Rapidly progressing” (RPMS).

Also, when deficits always resolve between attacks, this is sometimes referred to as “Benign MS” (BMS), although people will still build up some degree of disability in the long term. On the other hand, the term “Malignant MS” (MMS) is used to describe people with MS who have reached a significant level of disability in a short period of time. In addition, an international panel has published a standardized definition for the course of MS. These several phenotypes will now be revisited.

Active multiple sclerosis (AMS)

In AMS, the immune system attacks myelin, the fatty protective covering around nerves. When this happens, inflammation showing as new lesions (areas of damage to nerves) are seen on MRI scans of the brain or spinal cord.

Another sign that the immune system is attacking myelin is when having a relapse. The symptoms suddenly get worse or new ones appear. A relapse is usually followed by some sort of recovery as the body does its best to repair the myelin.

If the MS does not cause relapses or inflammation, it is ‘not active’. Note that people with all types of MS might describe it as ‘active’ during a flare-up of their symptoms, or if their MS is generally getting worse. This is not to be confused with the clinical definition wherein “active” means the presence of inflammation or relapses. If the symptoms and disability keep getting worse, the disease will instead be called 'progressive” (see below).

Relapsing-remitting multiple sclerosis (RRMS)

RRMS is the most common type of MS - around 85% of people with MS are diagnosed with this type. It usually begins with a clinically-isolated syndrome (CIS) in which a person has an attack suggestive of demyelination but does not fulfill the criteria for MS. About 30% to 70% of persons who experience a CIS later develop MS.

RRMS in first-diagnosed patients is characterized by an unpredictable pattern of relapses (symptoms getting worse) followed by periods of months to years of relative quiet (remissions) with no new signs of disease activity. People often recover well from a relapse with complete remission. But around half of all relapses may leave some lingering problems. Relapses often last a number of weeks and possibly even months. Taking a disease modifying drug/therapy (DMD/T) can mean fewer and less serious relapses and it could slow down the disease. The disability does not necessarily get worse between relapses but, after each relapse, it can end up worse than before. As time goes on, the body finds it harder to repair the damage each relapse brings. The disability is likely to get worse, especially if one does not start treatment.

Deficits that occur during attacks may either resolve or

leave problems, the latter in about 40% of attacks and being more common the longer a person has had the disease. A relapse may be called by other names, such as an attack, exacerbation, flare-up, acute episode or clinical event. The periods of disease inactivity or quiescence between MS attacks is referred to as remission. Weeks, months, or even years may pass before another attack occurs, followed again by a period of inactivity. Most people with MS are initially diagnosed with this form of the disease.

To be classed as a relapse, the symptoms need to last for 24 hours or more, and not be caused by an infection. They would also need to happen at least 30 days after any previous relapse. For days, weeks or months, the symptoms may get worse or new ones may appear. Then, while the body does its best to repair the damaged myelin, the symptoms can get better or go completely. This recovery is called remission during which MS can still be damaging the nerves and one might nonetheless be left with some disability. As time goes on, it gets harder for the body to repair the damage after each relapse.

Primary progressive multiple sclerosis (PPMS)

PPMS is less common and is characterized by progressively worsening symptoms from the beginning with no noticeable relapses or exacerbations of the disease, although there may be temporary or minor relief from symptoms. Some unknown cause is damaging the nerves. The build-up of disability or symptoms is usually quite slow with some exceptions. In the past, this situation was called “progressive relapsing MS” (PRMS); now it is called “active primary progressive MS” (APPMS).

PPMS occurs in approximately 10%–20% of individuals with the disease, with no remission after the initial symptoms. They tend to be diagnosed with it in their 40s or older. Men are just as likely as women to get it, unlike relapsing MS which affects women more.

PPMS is characterized by progression of disability from onset, with no, or only occasional and minor, remissions and improvements. The disease gets steadily worse with occasional relapses. MRI scans show inflammation is still happening. The usual age of onset for the PPMS subtype is later than that of the RRMS subtype. It usually begins around 40 years of age. A few DMD/Ts can help with the inflammation and relapses that come with PPMS if it has an active part to it.

There are two main kinds of PPMS diagnosis; the line between them and relapsing MS is not very clear, even to specialists.

Evolving to secondary progressive multiple sclerosis (SPMS)

Most people with RRMS will eventually develop SPMS. It varies widely from person to person, but on average, around 65% of people with RRMS will develop SPMS 15 years after being diagnosed. Usually, with SPMS, disability or other symptoms gradually get worse. The old pattern of getting relapses followed by getting better usually comes to an end. However, some people may still get relapses but with no full recovery afterwards. Having relapses means there still is active SPMS - 'active' meaning the immune system is still attacking the myelin around the nerves, causing inflammation. A relapse is a sign of this inflammation. Another sign of it is when new lesions can be seen in the MRI scans.

SPMS patients might notice more difficulties getting around than before, or other symptoms might get worse, changes happening very slowly. Everyone's MS is different - even if someone else has SPMS, they are likely to be affected in an individual way.

Secondary progressive multiple sclerosis (SPMS)

SPMS is a stage of MS which comes after RRMS for many people. With this type of MS, disability gets

steadily worse and there likely are no longer relapses. In the past, before DMD/Ts came along, it usually took many years for relapsing MS to change into SPMS. The most common length of time between disease onset and conversion from RRMS to SPMS is 19 years. But, thanks to today's MS drugs, this is changing: fewer people are likely to go on to SPMS and, for those that do, it could take longer to happen. In a small number of cases, some people are not diagnosed with MS until their condition has reached the secondary progressive stage.

SPMS occurs in around 65% of those with initial RRMS who eventually have progressive neurologic decline between acute attacks without any definite periods of remission. Occasional relapses and minor remissions may appear.

People with SPMS usually have had a previous history of MS attacks, but then start to develop gradual and steady symptoms and deterioration in their function over time. Most individuals with severe RRMS may go on to develop SPMS if they are left untreated.

SPMS is thus called because the progressive stage comes second, after an earlier stage that had inflammation and relapses. A lot of people who start off with relapsing MS see it turn into SPMS many years later.

The body can repair myelin on its own, but after each attack on it, it finds it harder to repair. As demyelination occurs, the nerve underneath becomes exposed. Over time, it suffers damage, stops working, and does not grow back. When nerves break down like this, it leads to a build-up of symptoms and disability. Eventually, the pattern of relapses followed by recovery comes to an end. Inflammation and relapses usually stop, or they happen much less often. What is left thereafter is damaging the nerves in a way we do not yet fully understand.

Disability or symptoms used to be stable between relapses, but now things gradually get worse making it difficult to discern when relapsing MS has changed into SPMS. The change to SPMS is likely if the disability or symptoms get slowly worse over at least six months without a relapse happening. Some people with SPMS can still sometimes have a relapse or get inflammation on their MRI scans.

In the past, it usually took up to 20 years on average for relapsing MS to change into SPMS. Now that people with relapsing MS take DMD/Ts, this is changing for the better in that fewer people go on to SPMS and, for those that do, it should take longer to happen.

Progressive multiple sclerosis (PMS)

For some people with PMS from the very start, their symptoms and disability gradually keep getting worse over the years ('progression' here means 'things are getting worse'). There are no periods of remission and the condition gradually gets worse over time. But, the speed at which this happens varies greatly and it is not yet possible to predict exactly how it will affect one person. Obvious signs of inflammation can be seen on their MRI scans. The pattern of relapses followed by recovery, like with relapsing MS, is not seen. Inflammation has stopped, or there was not much to begin with. Instead, something else is now damaging the nerves directly. We do not yet know what is causing the nerves to break down and stop working. For another, and much bigger, group of people with active (relapsing) MS, after many years, their body cannot repair or replace damaged myelin any longer. Relapses and inflammation stop, their MS has now become progressive. Compared to active MS, progressive MS does not have as many disease-modifying drugs/therapies (DMD/Ts) to treat it. The above several phenotypes have been summarized in Table 1 below:

Phenotype	Etiology	Manifestations
Active (AMS)	Immune system attacks myelin	o Inflammation shows as new lesions o Relapse (worse or new symptoms o MS generally getting worse
Relapsing-remitting (RRMS)	After a relapse, the immune system re-attacks myelin	o Most common type o Begins with a CIS o Unpredictable pattern of relapses followed by remissions o Disease gets worse if untreated o As time goes on, more difficult to repair damage after relapses
Secondary progressive (SPMS)	Disability gets steadily worse and there likely no longer are relapses	o Progressive neurologic decline o Possible occasional relapses o More difficulties with getting around than before o Other symptoms get worse o Changes happen very slowly
Primary progressive (PPMS)	Progressive worsening of symptoms from the beginning with no noticeable relapses or exacerbations	o Varies wildly from person to person
Progressive (PMS)	Symptoms and disability gradually getting worse over time	o Symptoms and disability keep getting worse o Inflammation

CIS= Clinically-isolated syndrome

Reference: A, L, Fymat (2023)

Table 1: Multiple sclerosis phenotypes

What are relapses?

A relapse is an exacerbation of MS, that is the occurrence of new symptoms or the worsening of old symptoms. Medical staff might call relapses things like an attack, flare-up, exacerbation, acute episode or clinical event. It occurs when, after a period when MS was stable, the immune system attacks the nerves again, causing inflammation to the myelin coating around them. This damage stops signals traveling along the nerves like they should and causes symptoms of MS. An example of a relapse could be blurred or no vision or not being able to lift a leg.

Relapses can vary from mild to severe or severe enough to interfere with a person's ability to function. At their worst, acute relapses may need hospital treatment, but many relapses are managed at home, with professional support (general physician, MS specialist nurse, and other care professionals). Keep in mind, though, that no two exacerbations are alike.

To be a true exacerbation, the attack must last at least 24 hours and be separated from the previous attack by at least 30 days. It must also occur in the absence of infection, or other cause. Most exacerbations last from a few days to several weeks or even months.

Symptoms of a relapse

Symptoms which come and go can sometimes be considered a relapse – they do not always have to be

continuous. Symptoms experienced before, or perhaps accustomed to dealing with, might appear in a different part of the body.They usually come on over a short period of time – over hours or days. They often stay for a number of weeks and, for most people, are usually over within a month. But, this can vary from very short periods of only a few days to many months. For example, some people experience a shock-like sensation when they bend their neck. This can be considered a relapse if, for 24 hours or more, it happens every time one bends one's neck.

Symptoms vary from person to person and from one exacerbation to another. For example, the exacerbation might be an episode of optic neuritis (caused by inflammation of the optic nerve that impairs vision), or problems with balance or severe fatigue. Some relapses produce only one symptom (related to inflammation in a single area of the CNS). Other relapses cause two or more symptoms at the same time (related to inflammation in more than one area of the CNS).

What can trigger or prevent MS relapses?

Many people with MS feel they can identify things that might trigger a relapse for them. Unfortunately, what appears to affect one person does not always apply to someone else, and research has not yet found what triggers every relapse that people have. This makes it hard to give definite strategies for avoiding relapses altogether. But there is one thing we know that can reduce the number of relapses people get... that is treatment with a disease-modifying drug/therapy (DMD/T).

What causes exacerbations?

MS relapses are caused by inflammation in the CNS that damages the myelin coating around nerve fibers. This damage slows or disrupts the transmission of nerve impulses and causes the symptoms of MS. In the most common disease course in MS, that is RRMS, clearly defined acute exacerbations are followed by remissions as the inflammatory process gradually comes to an end. Going into remission does not necessarily mean that the symptoms disappear totally. Some people will return to feeling exactly as they did before the exacerbation begun, while others may find themselves left with some ongoing symptoms.

Managing relapses

It is not possible to predict when relapses will happen or how often. Every person’s MS is different and so is every relapse. Some people experience several in a year but others will go for many years between relapses. As the number and timing of relapses is beyond one's control, the best strategy is to manage them well when they happen.

Rehabilitation

The goal of a rehabilitation program is to restore or maintain functions essential to daily living. Rehabilitation can be especially useful soon after an exacerbation to help one get back on track. The members of the rehab team — including physical therapists, occupational therapists, speech/language pathologists, and cognitive remediation specialists — address problems with mobility, dressing and personal care, role performance at home and work, and overall fitness. They also provide evaluation and treatment of speech, swallowing difficulties, and problems with thinking and memory that may have appeared or worsened during the exacerbation.

Pseudo-relapses

A pseudo-relapse is a worsening of symptoms for a short time without an increase in MS activity. Pseudo-relapses are often caused by a rise in body temperature because of an illness or infection, exercise, or simply being in a hot environment. When the body temperature rises, it can slow down the speed of messages

transmitted along nerve fibers. If the coating myelin has been damaged, this slowing down can make the symptoms worse, or make old symptoms reappear. These pseudo-relapses are not thought to cause long-term harm. Once whatever is causing the body temperature to rise has gone away, the symptoms go away too.

Variants of MS

Atypical variants of MS have been described. There is a debate on whether they are MS variants or different diseases. Some diseases previously considered MS variants, like Devic's disease (DD), are now considered outside the MS spectrum. Rare and unusual variants of MS include Balo's concentric sclerosis, Marburg's acute MS, Schilder's diffuse sclerosis, and tumefactive MS, as briefly discussed below.

Balo's concentric sclerosis (BCS)

BCS is a demyelinating disease similar to standard MS, but with the particularity that the demyelinated tissues form concentric layers (Figure 1). The disease was described by József Mátyás Baló who initially named it "leuko-encephalitis periaxialis concentrica".

Historically, however, it was first described by Otto Marburg in 1906. It was only later, in 1928, that Baló studied it in a Hungarian patient, showing also demyelination of the peripheral nervous system (PNS). It appears to be more common in Chinese and Filipino populations (both Asiatic) than in caucasians. In BCS, the white matter of the brain appears damaged in concentric layers that can be seen on MRI, leaving the axis cylinder intact.

It is currently considered one of the borderline forms of MS. Note that the concentric ring appearance is not specific to BCS as it has also been reported in patients with neuromyelitis optica (NO), standard MS, progressive multifocal leukoencephalopathy (PMLE), cerebral autosomal dominant arteriopathy (CADA) with subcortical infarcts, leukoencephalopathy (LE), concomitant active hepatitis C, and human herpes virus 6 (HHV-6). BCS patients can survive, or even have spontaneous remission and asymptomatic cases.

Figure 1 (a) is the original case of Baló (1928), showing several anastomoses located in the lower half of the lesion. Figures 1(b) and (c) depict the lesion centered by a veinule showing ring fragmentation in a constrained area, respectively from Hallervorden et al. (1933) and Castaigne et al. (1984). progress of the pathologic process from a center located in a constrained area. The bands are shown in Figure 1(d) (from Behr, 1950) and Deutsch Z. Nervenheilk. Here, Loyez staining shows myelin in black and destroyed areas in white (scale bars:1 cm).

Marburg's acute multiple sclerosis (MAMS)

Marburg's acute multiple sclerosis (MAMS) (aka 'Marburg's MS', 'fulminant MS', or 'malignant MS') took its name from Otto Marburg. It is considered one of the MS borderline diseases, which is a collection of diseases classified by some as MS variants and by others as different diseases. It causes swift and relentless symptoms and decline in function, and can result in significant disability or even death shortly after disease onset.

Other diseases in this group are neuromyelitis optica (NMO), Balo's concentric sclerosis (BCS), and Schilder's diffuse sclerosis (SDS) or Schilder's disease. The graver course is one form of malignant MS, with patients reaching a significant level of disability in less than five years from their first symptoms, often in a matter of months. Sometimes, MAMS is considered a synonym for tumefactive MS, but not for all authors.

Schilder's diffuse myelinoclastic sclerosis (SDMS)

SDMS was first described by Paul Ferdinand Schilder in 1912. The name comes from the traditional

classification of demyelinating diseases in two groups: 'Demyelinating myelinoclastic diseases' and 'demyelinating leukodystrophic diseases'. In the first group, a normal and healthy myelin is destroyed .

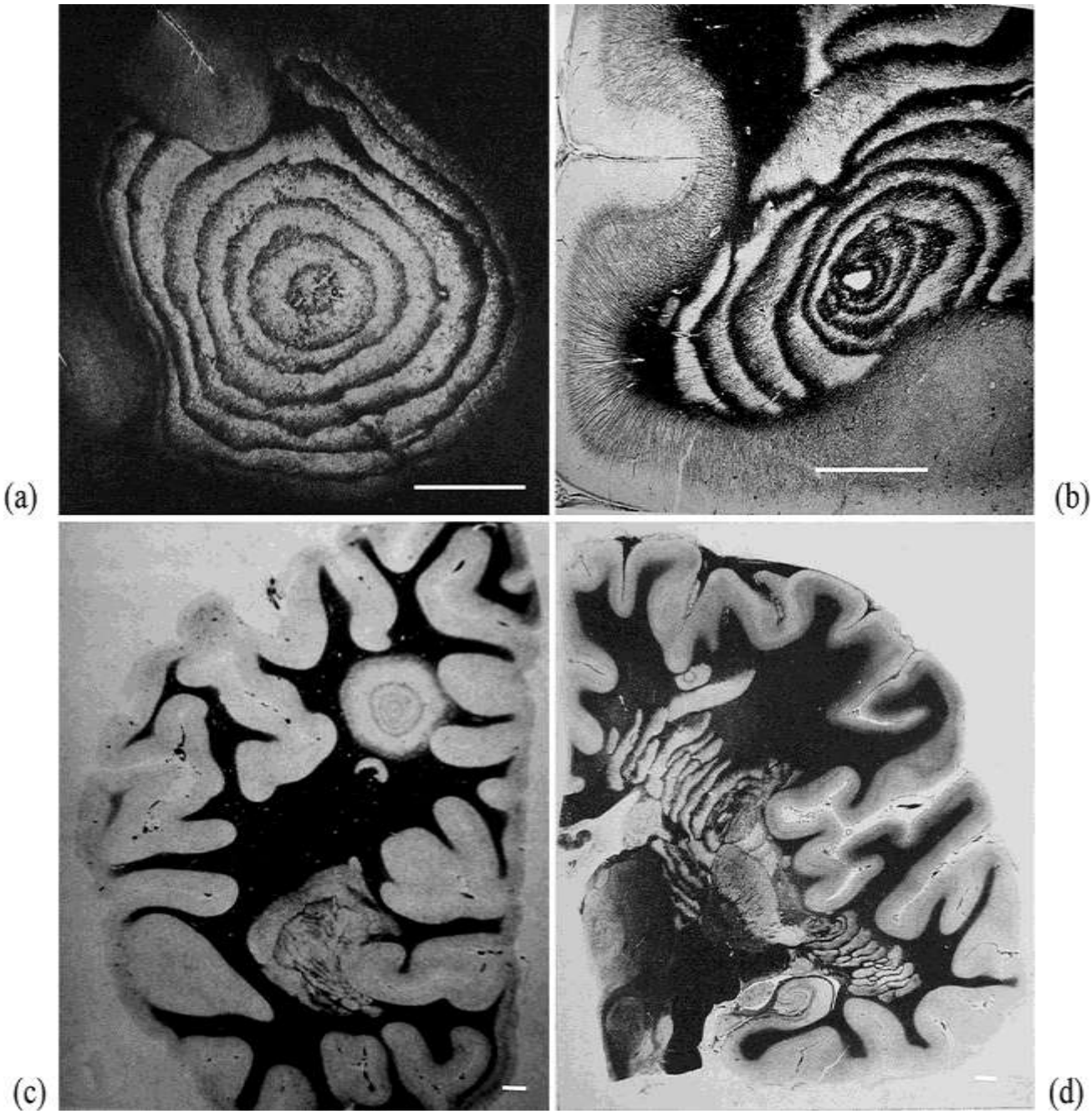

Figure 1: Typical aspects of Baló's concentric sclerosis

Source: Khonsari RH and Calvez V, 2007 (reproduced in Wikipedia) doi:10.1371/journal.pone.0000150.g001

By a toxic, chemical, or autoimmune substance. In the second group, myelin is abnormal and degenerates. SDMS is a very infrequent neurodegenerative disease that presents clinically as pseudo-tumoral demyelinating lesions, making its diagnosis difficult. It usually begins in childhood, affecting children between 5 and 14 years old, but cases in adults are also possible. SDMS is considered to be one of the borderline forms of MS.

Tumefactive multiple sclerosis (TMS)

In TMS, the central nervous system of a person has multiple demyelinating lesions with different characteristics from the typical standard MS. It is called tumefactive because the lesions are "tumor-like" and mimic tumors clinically, radiologically, and even sometimes pathologically. These atypical lesion characteristics include a large intracranial lesion of size greater than 2.0 cm with a mass effect, an edema, and an open ring enhancement. The 'mass effect' is the effect of a mass on its surroundings, for example, exerting pressure on the surrounding brain matter; the 'edema' is the build-up of fluid within the brain tissue; and the ring enhancement is directed toward the cortical surface.

Normally a tumefactive demyelinating lesion appears together with smaller disseminated lesions separated in time and space, yielding a diagnosis of MS. Hence, the name "tumefactive MS". When the demyelinating lesion appears alone, it has been termed “solitary sclerosis”. These cases belong to a borderline MS and there is currently no universal agreement on how they should be considered. An initial tumefactive lesion can evolve to various pathological entities: MS (the most common), BCS, SDMS, and acute disseminated encephalomyelitis.

TMS cases make up 1 to 2 of every 1000 MS cases. As in general MS, there are differences for gender, (higher percentage of females affected than males), ethnicity (most common among Caucasians), and geographic location (greater incidence at latitudes above 40° as compared to at the equator). The median age of onset is 37 years. While these associations have been made, it is still unclear how they result in an increased risk of MS onset.

Signs and symptoms of MS

Signs and symptoms of MS may differ greatly from person to person and also over the course of the disease depending on the location of the affected nerve fibers and the amount of nerve damage. Further, some people with severe MS may lose the ability to walk independently or at all, while others may experience long periods of remission without any new symptoms.

In MS, damage to the myelin coating around the nerve fibers in the CNS and to the nerve fibers themselves interferes with the transmission of nerve signals between the brain, spinal cord, and the rest of the body. Disrupted nerve signals cause the symptoms of MS, which vary from one person to another and over time for any given individual, depending on where and when the damage occurs. A person with MS can have almost any neurological symptom or sign, with autonomic, visual, motor, and sensory problems being the most common. Symptoms may include some or many of the following: Tiredness and weakness, pain and body spasms, vision difficulties, speech difficulties, sensation difficulties, motor difficulties, cognitive difficulties, psychological difficulties, posture difficulties, metabolic difficulties, and seizures.

Measure of disability and severity of the disease

The two main measure of disability and severity of MS

are the expanded disability status scale (EDSS) and the minimal record of disability (MRD). MRD is a standardized method for quantifying the clinical status of a person with MS. It assists in assessing the impact of MS and in planning and coordinating the care of people with MS. It includes six parts: Demographic information, functional systems, disability status scale (DSS), expanded disability status scale (EDSS) [see Figure 2 and Table 2], incapacity status scale (ISS), and environmental status scale (ESS). The multiple sclerosis functional composite (MSFC) is increasingly being used in research.

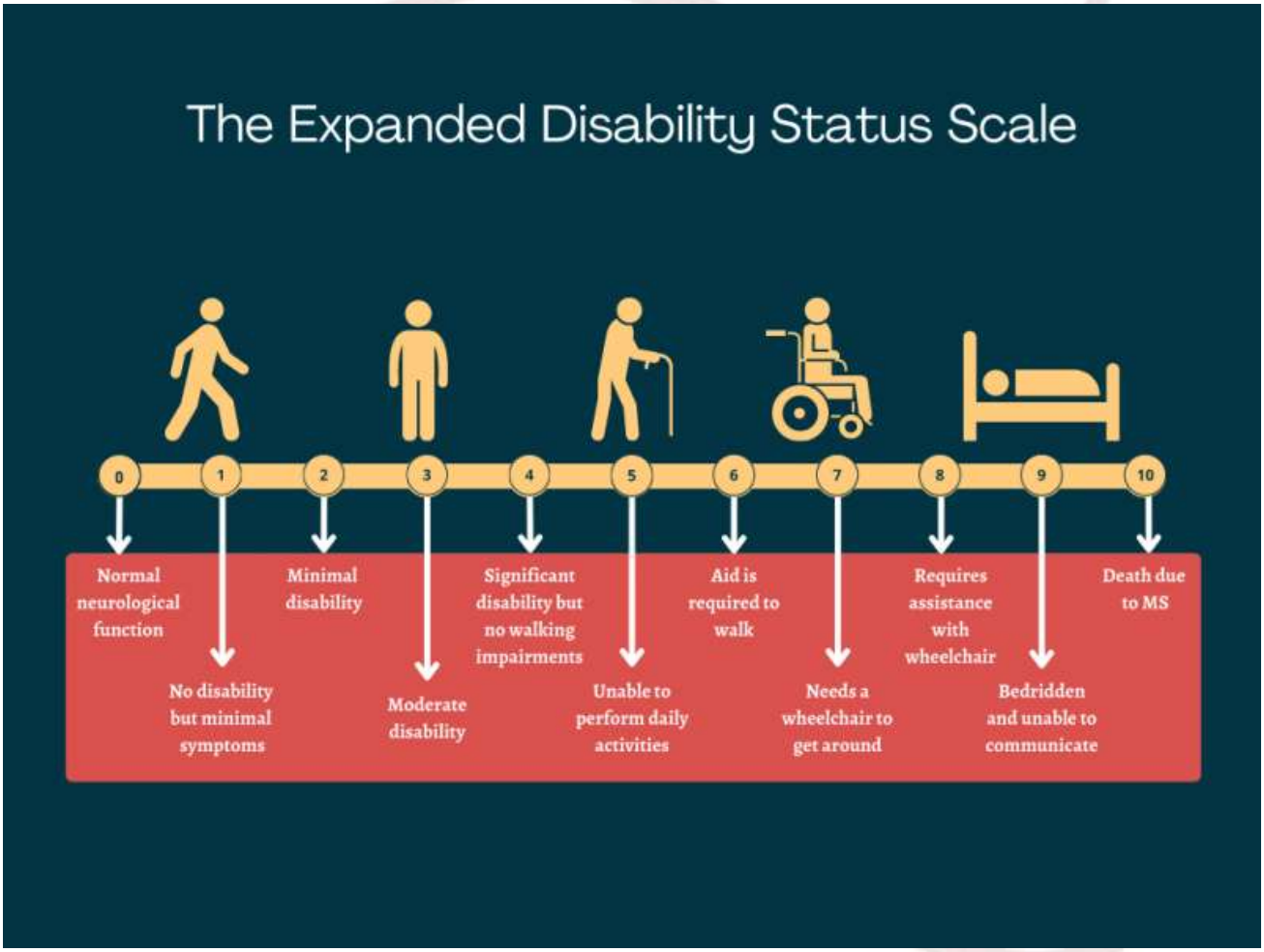

Figure 2: The Expended Disability Status scale

Scale #	Meaning
0	No sign of neurological abnormality.
1	No disability but minimal signs in one functional system.
1.5	No disability but minimal signs in two or more functional systems.
2	Minimal disability in one functional system.
2.5	Minimal disability in two functional systems or mild disability affecting one system.
3	Moderate disability in one functional system or mild disability in three or four systems without any walking difficulties.
3.5	Moderate disability in one functional system with more than minimal impairments in multiple others but no walking difficulties.
4	Significant disability but able to function mostly independently in daily life. Ability to walk about **500** meters (about one-third of a mile) without aid or rest.
4.5	Significant disability that may necessitate some minor help in day-to-day life. Ability to walk **300** meters (about one-fifth of a mile) without aid or rest.
5	Severe disability that causes substantial impairment in daily life, necessitating accommodations. Ability to walk **200** meters (about one-tenth of a mile) without aid or rest.
5.5	Severe disability to the point that some activities that had been a part of normal day-to-day life can no longer be done independently. Ability to walk **100** meters (about 330 feet) without aid or rest.
6	Requires a walking aid such as a cane or a crutch to walk **100** meters (about 330 feet) with or without stopping to rest.
6.5	Requires two walking aids such as a pair of canes or crutches to walk **100** meters (about 330 feet) without stopping to rest.
7	Inability to walk more than a few feet even with aid. Requires a wheelchair to get around but is still up and about for most of the day and is able to maneuver the chair and get in and out of it independently.
7.5	Inability to take more than a couple of steps and needs help to get in and out of a wheelchair and wheeling around.
8	Inability to stand and usually reliant on a wheelchair that is motorized or pushed to get around but still up and about for much of the day. Generally, still has function in the arms and can still take care of most self-care activities.
8.5	Stays in bed for most of the day with some impairment in arm function and ability to handle self-care functions.
9	Inability to get out of bed but still able to communicate clearly and eat voluntarily.
9.5	Confined to bed without the ability to communicate effectively or swallow properly.
10	Death due to MS.

Table 2: Meaning of the Expanded Disability Status Scale numbers

Course of symptoms

The condition begins in 85% of cases as a clinically-isolated syndrome (CIS) over a number of days with 45% having motor or sensory problems, 20% having optic neuritis, and 10% having symptoms related to brainstem dysfunction, while the remaining 25% have more than one of the difficulties listed above. This is followed by some improvement or as a gradual worsening over time without periods of recovery (10–15% of cases). A combination of these two patterns may also occur or people may start in a relapsing and remitting course that, then, becomes progressive later on.

Relapses are usually not predictable, occurring without warning. Exacerbations rarely occur more frequently than twice per year. Some relapses, however, are preceded by common triggers and they occur more frequently during spring and summer. Similarly, viral infections such as the common cold, influenza, or gastroenteritis increase their risk. Stress may also trigger an attack.

Women with MS who become pregnant experience fewer relapses; however, during the first months after delivery, the risk increases. Overall, pregnancy does not seem to influence long-term disability. Many events have been found not to affect relapse rates including vaccination, breast feeding, physical trauma, and Uhthoff's phenomenon.

Course of the disease

The natural course of MS is different for each person, which makes it difficult to predict. The onset and duration of MS symptoms usually depends on the specific type. They may begin over a few days and go away quickly or develop more slowly and gradually over many years.

Early MS symptoms: They often include:

- **Vision problems:** Such as blurred or double vision, or optic neuritis, which causes pain with eye movement and a rapid loss of vision.
- **Muscle weakness:** Often in the hands and legs.
- **Muscle stiffness:** Accompanied by painful muscle spasms.
- **Tingling, numbness, or pain:** In the arms, legs, trunk, or face.
- **Clumsiness:** Particularly difficulty staying balanced when walking.
- **Bladder Issues:** Control problems.
- **Dizziness:** Intermittent or more constant.

Later symptoms: These include:

Fatigue: Mental or physical, accompanies the early symptoms during an attack.
Mood changes: Such as depression or difficulty with emotional expression or control.
Cognitive dysfunction: Problems concentrating, multitasking, thinking, learning, or difficulties with memory or judgment.

Muscle weakness, stiffness, and spasms may be severe enough to affect walking or standing. In some cases, MS leads to partial or complete paralysis and the use of a wheelchair is not uncommon, particularly in individuals who are untreated or have advanced disease. Many people with MS find that weakness and fatigue are worse when they have a fever or when they are exposed to heat. MS exacerbations may occur following common infections.

Pain is rarely the first sign of MS, but pain often occurs with optic neuritis and trigeminal neuralgia (a disorder that affects one of the nerves that provides sensation to different parts of the face). Painful limb spasms and sharp pain shooting down the legs or around the abdomen can also be symptoms of MS. Many individuals with MS may experience difficulties with coordination and balance. Some may have a continuous

trembling of the head, limbs, and body, especially during movement.

MS exacerbation

An exacerbation is a sudden worsening of MS symptoms, or the appearance of new symptoms that last for at least 24 hours. MS relapses are thought to be associated with the development of new areas of damage in the brain. Exacerbations are characteristic of relapsing-remitting MS (RRMS). An exacerbation may be mild, or severe enough to significantly interfere with life's daily activities. Most exacerbations last from several days to several weeks, although some have lasted for as long as a few months.

Prodromal Phase

MS may have a prodromal phase in the years leading up to disease manifestation. It is characterized by psychiatric issues, cognitive impairment, and increased utilization of healthcare.

Stages and Clinical Progression

Much effort has been expended in an attempt to accurately classify the various stages of MS. Clinical relapses at a younger age, coupled with radiological evidence of CNS inflammation, provide good support for the earlier RRMS. This may be important from a practical point of view to guide clinical therapeutic decisions given the many options for effective anti-inflammatory agents that are currently available. But, with time, identifying the transition from relapsing to secondary progressive disease often becomes problematic.

The absence of clinical relapses does not imply absence of inflammatory activity on MRI, and absence of inflammatory radiological lesions does not imply lack of inflammation at the tissue level. Indeed, it has been proposed that MS is a condition in which disability progression is driven in two stages, and early relapsing inflammatory activity has little influence on the second, later stage of progressive deterioration.

Therefore, identifying the transition to secondary progression has important practical implications because it appears that current anti-inflammatory drugs offer little benefit in the absence of ongoing inflammatory activity. Also, continuing treatment entails expenses and potential risks from potent immunosuppressants with potentially little benefit in return. This is not to say that inflammation disappears at later stages. Indeed, recent studies show that substantial inflammatory lesion activity persists well into the progressive phase and, perhaps counterintuitively, that SPMS and PPMS samples exhibit a higher lesion load compared with relapsing subjects.

Moreover, there are few differences in lesion morphology or immunopathology in SPMS versus PPMS brain, even though decades of recurrent inflammatory attack preceded the former. Instead, the quality of ongoing inflammation seems to shift in favor of activated macrophages/microglia.

The MS brain in progressive stages shows ongoing cortical demyelination and slowly expanding demyelinating lesions in the white matter. Such lesions were recently shown to be important predictors of future disability. Interestingly, there is scant lymphocytic activity (B-cells are a peculiar exception). Instead, microglial activation is seen at the borders of expanding lesions. This suggests that adaptive autoimmunity plays a lesser role at this stage and that innate responses predominate.

A key question is whether innate immune cells are somehow dysregulated and become primary drivers of degeneration, or simply react, as they are expected to, against an unidentified primary injury that itself is the underlying cause of tissue destruction. Taken together,

recent data seem to support the idea that all types of MS might be variations of a similar underlying pathophysiological theme and that degeneration and concomitant inflammation begin early and proceed inexorably, regardless of whether relapse activity is a prominent feature. If so, why some patients assume a more relapsing inflammatory pattern at first whereas others begin later with a progressive course is unclear. Here, the genetic background and the environment likely play major roles in programming the various clinical phenotypes without the need to invoke fundamentally different disease mechanisms.

Pathophysiology and causes of MS

MS is one of the most common causes of neurological disability in young adults. Its etiology has been intensively investigated for over a century and, although much has been discovered about the immunobiology, genetics, and epidemiology of this disease, the fundamental cause remains a mystery. MS is distinguishable from most other chronic neurological disorders by its unique fluctuating course. The majority of patients with MS present with early relapsing and remitting episodes of neurological and radiological worsening followed by varying degrees of recovery (relapsing-remitting MS, or RRMS). In most patients, this initial relapsing remitting phase is followed years later by a more chronic progressive phase (secondary progressive MS, or SPMS), whereas a minority (≈15%) of patients begin with a progressive course from onset (primary progressive MS, or PPMS) for unknown reasons.

On the etiology of MS

MS involves the CNS (brain and spinal cord) or the optic nerves. The peripheral nervous system (PNS) and the long nerves to the body and limbs are unaffected. There is evidence of an immune reaction manifesting as patches or plaques of inflammation showing swelling of tissue, breakdown and loss of myelin surrounding the nerve fibers, and some damage to the nerve fibers or axons themselves. As healing occurs, some scar of tissue can form in the area. There may be many such scars or lesions widely distributed in the CNS (from which the name of the disease derives). In addition, immune cells (T, B, and macrophages) are present in the lesions. The major questions are:

What initiates the immune reaction to myelin? This is the more so as the CNS is normally “immune privileged” and immune cells usually remain in the bloodstream outside of the CNS. In MS, however, such cells become activated against myelin and are able to penetrate the blood-brain barrier (BBB), triggering a further complex process of immune mediated damage of myelin and underlying nerve fibers.

What is it in the myelin that the immune reaction is directed toward? Studies have not shown that there is anything distinctly different about the basic structure of myelin in a person with MS.

Are the plaques of inflammation in the white matter the only affected areas? Sophisticated MRI and pathological studies have shown that brain areas that appear normal are actually not entirely normal and show subtle inflammation changes as well. There are also changes in the grey matter area. In other words, MS is more widespread than normally seen from the patches viewed on MRI.

Traditional “outside-in” autoimmune model

Traditionally, the etiology of MS was based on an “outside-in” autoimmune hypothesis whereby dysregulated auto-reactive T-cells in the periphery cross into the CNS parenchyma and, together with macrophages and B-cells, proceed to attack various CNS elements, where myelin is a prominent target. These inflammatory events, resulting in a relapsing-remitting clinical course, likely contribute

independently to accumulating CNS injury.

The extent of inflammatory activity, which varies by patient and over time within the same individual, determines the spectrum of MS phenotypes. Importantly, the "inside-out" hypothesis maintains that primary degeneration is present from the start (probably years before the first overt clinical symptoms) and continues throughout the entire course of the disease. Given that CNS inflammation in MS can be well controlled with modern therapies, the current challenge is progressive disease, during which most irreversible disability occurs. At present, we neither understand the mechanisms driving this phase of MS nor have very effective treatment options for patients in whom degeneration predominates in the absence of overt inflammation.

Most work in the field has been directed at the autoimmune inflammatory nature of the disease, resulting in over a dozen (U.S.) Food & Drug Administration/European Medicines Agency (EMA) approved treatments to date.

The challenging "inside-out" autoimmune model

The above traditional "outside-in" model has been challenged by a competing theory proposing an "inside-out" autoimmune hypothesis. Initial malfunction occurs within the CNS, as suspected for other neurodegenerative disorders (NDDs) such as Alzheimer's (AD) and Parkinson's diseases (PD). This alternative "inside-out" hypothesis argues that MS is a primary degenerative disease accompanied by varying degrees of inflammation, leading to the release of antigenic cell components such as myelin oligodendrocyte glycoprotein, myelin basic protein, and proteolipid protein. This chronic shedding of auto-antigens secondarily promotes an autoimmune inflammatory response in the predisposed host, in turn driving additional degeneration in a vicious cycle.

MS typical progression

Usually a chronic recurring illness, MS typically begins with 1-mm to 3-cm patches of inflammation developing in the oligodendrocyte-generated myelin sheaths of CNS axons. T-cell-mediated inflammation strips myelin from (demyelinates) axons and eventually leaves sclerotic (Greek, sklerosis, hard) plaques scattered throughout the CNS. Plaques disseminated throughout the myelin or "white matter" of the cerebrum, cerebellum, spinal cord, ocular motility system, and optic nerves constitute the signature of MS.

When deprived of their myelin insulation, axons transmit nerve impulses slowly or not at all. Some deficits resolve as myelin inflammation spontaneously subsides or anti-inflammatory medications, such as steroids, suppress it. As plaques recur, develop in new areas, and accumulate, MS evolves from an acute inflammatory to a chronic degenerative condition. Sooner or later the plaques leave permanent neurologic deficits.

Although MS acts primarily as a CNS demyelinating disorder, its pathology includes prominent axon degeneration. In contrast to demyelination associated with plaques, axon degeneration regularly produces permanent mental and physical disabilities.

The illness' mean age of onset is 33 years, with 70% of cases developing between ages 21 and 40 years. Some studies have reported that many patients suffered their first or a subsequent MS attack after a medical insult, such as infection, childbirth, head or spine trauma, intervertebral disk surgery, or electrical injury. Other studies have reported that psychologic stress preceded the first MS or subsequent attacks. However, most carefully controlled prospective studies have shown that these insults do not play a major role in either causing or exacerbating MS. Thus, the cause of MS remains unknown. It is considered an autoimmune disease in which the body's immune system attacks its own tissues. Here, this immune system malfunction destroys the fatty substance (myelin) that coats and protects nerve

fibers in the brain and spinal cord. Myelin can be compared to the insulation-coating on electrical wires. When the protective myelin is damaged and the nerve fiber is exposed, the messages that travel along that nerve fiber may be slowed or blocked. It is not clear why MS develops in some people and not others. A combination of genetics, environmental, and lifestyle factors appears to be responsible. Remember, however, that "risk is not causation".

The Three Hallmarks Of MS

The three main characteristics of MS are the formation of lesions (also called "plaques") in the CNS, inflammation, and the destruction of myelin sheaths of neurons (acronym LIM). These features interact in a complex and not yet fully understood manner to produce the breakdown of nerve tissue and, in turn, the signs and symptoms of the disease. Cholesterol crystals are also believed both to impair myelin repair and to aggravate inflammation.

Lesions

The name multiple sclerosis refers to the scars (sclerae – better known as 'plaques' or 'lesions') that form in the nervous system. These lesions most commonly affect the white matter in the optic nerve, the brain stem, the basal ganglia, and the spinal cord, or the white matter tracts close to the lateral ventricles. The function of white matter cells is to carry signals between grey matter areas, where the processing is done, and the rest of the body. The peripheral nervous system (PNS) is rarely involved.

Specifically, MS involves the loss of oligodendrocytes, the cells responsible for creating and maintaining a fatty layer (the myelin sheath), which helps the neurons carry electrical signals (called "action potentials"). This results in a thinning or complete loss of myelin and, as the disease advances, the breakdown of the axons of neurons. When the myelin is lost, a neuron can no longer effectively conduct electrical signals. A repair process, called "remyelination", takes place in the early phases of the disease, but the oligodendrocytes are unable to completely rebuild the cell's myelin sheath. Repeated attacks lead to successively less effective remyelinations, until a scar-like plaque is built up around the damaged axons. These scars are the origin of the symptoms. During an attack, MRI often shows more than ten new plaques. This could indicate that there are a number of lesions below which the brain is capable of repairing itself without producing noticeable consequences. Another process involved in the creation of lesions is an abnormal increase in the number of astrocytes due to the destruction of nearby neurons. A number of lesion patterns have been described in the scientific literature.

Inflammation

Apart from demyelination, the other sign of the disease is inflammation that develops along the following process. T-cells (kind of lymphocytes that play an important role in the body's defenses) gain entry into the brain via disruptions in the blood–brain barrier (BBB), recognize myelin as foreign, and attack it. These cells are also called "autoreactive lymphocytes".

Destruction of neuronal myelin sheaths

The attack on myelin starts inflammatory processes, which trigger other immune cells and the release of soluble factors like cytokines and antibodies. In turn, a further breakdown of the BBB causes a number of other damaging effects such as swelling, activation of macrophages, and more activation of cytokines and other destructive proteins. Inflammation can potentially reduce transmission of information between neurons in at least three ways. The soluble factors released might stop neurotransmission by intact neurons. These factors could lead to or enhance the loss of myelin or, else, may cause the axon to break down completely.

Disease Biomarkers

Since disease progression is the result of degeneration of neurons, the roles of proteins showing loss of nerve tissue such as neurofilaments, tau, and N-acetylaspartate are under investigation. Improvement in neuroimaging techniques such as positron emission tomography (PET) or MRI carry a promise for better diagnosis and prognosis predictions. Regarding MRI, there are several techniques that have already shown some usefulness in research settings and could be introduced into clinical practice, such as 'double-inversion recovery sequences' (DIRS), 'magnetization transfer diffusion tensor' (MTDT), and 'functional magnetic resonance imaging' (fMRI).

These techniques are more specific for the disease than existing ones, but still lack some standardization of acquisition protocols and the creation of normative values. This is particularly the case for proton magnetic resonance spectroscopy (pMRS), for which a number of methodological variations observed in the literature may underlie continued inconsistencies in CNS metabolic abnormalities, particularly in N-acetyl aspartate, myonositol, choline, glutamate, GABA, and GSH, observed for MS and its subtypes. There are other techniques under development that include contrast agents capable of measuring levels of peripheral macrophages, inflammation, or neuronal dysfunction, and techniques to measure iron deposition that could serve to determine the role of this feature in MS, or that of cerebral perfusion.

On the pathogenesis and pathophysiology of MS

MS is a clinically defined entity with several atypical presentations.

Pathogenesis of MS

Some auto-antibodies have been found in atypical MS cases, giving birth to separate disease families and restricting the previously wider concept of MS.

Anti-AQP4 autoantibodies were found in neuromyelitis optica (NMO), which was previously considered a MS variant. A spectrum of diseases named NMOSD (NMO spectrum diseases) or anti-AQP4 diseases has been accepted. Some cases of MS were presenting anti-MOG autoantibodies, mainly overlapping with the Marburg's variant. Anti-MOG autoantibodies were found to be also present in ADEM, and a second spectrum of separated diseases is being considered. This spectrum is named inconsistently across different authors, but it is normally something similar to anti-MOG demyelinating diseases.

A third kind of auto-antibodies is accepted. They are several anti-neurofascin auto-antibodies which damage the Ranvier nodes of the neurons. These antibodies are more related to the peripheral nervous demyelination, but they were also found in chronic progressive PPMS and combined central and peripheral demyelination (CCPD), which is considered another atypical MS presentation.

In addition to the significance of auto-antibodies in MS, four different patterns of demyelination have been reported, opening the door to consider MS as a heterogeneous disease.

Pathophyslology of MS

Although inflammation-mediated demyelination of white matter tracts with partial preservation of axons is a hallmark of MS, recent advances in histopathological imaging techniques have emphasized the prevalence of cortical demyelination, where lymphocyte or macrophage infiltrates are limited. Cortical demyelination, grey matter demyelination in cerebellar cortex and the hippocampus, and deep grey matter nuclei are major histological features of progressive MS.

Evidence is growing to suggest that grey matter involvement is related to disease activity and more aggressive forms. Recent studies have shown that cortical and deep grey matter lesions in the thalamus, caudate, putamen, and cerebellar cortex during the early stage of disease are independent of white matter pathology. These recent findings strongly support the hypothesis proposed a decade ago that neurodegeneration becomes independent of inflammation during progressive MS and MS could be a primary degenerative disease.

In support of the finding that neurodegeneration during MS is independent of inflammation, it was recently reported that inflammatory relapses are associated with transient short-term disability, but long-term worsening was largely independent of relapses. The concept of "silent progression" was proposed, consistent with an underlying degenerative process proceeding largely independently of autoimmune inflammation. The age and gender differences between relapse-onset MS (ROMS) (younger age at onset and greater prevalence in women) and primary progressive MS (PPMS) (later age at onset and equal prevalence among the sexes) do not necessarily imply a fundamentally different etiology. Such differences can be readily explained by the known difference in autoimmune predilection which is greater in women. A person afflicted with the same underlying cytodegeneration, but more prone to react with an inflammatory lesion, would naturally present earlier inflammatory lesions in more obvious clinical disability. As age and accompanying immune senescence progress, MS at later ages would be expected to exhibit less inflammation.

In contrast to relapsing-remitting MS (RRMS), which has major involvement of peripheral immune cell infiltration in actively demyelinating plaques, progressive MS may involve the development of compartmentalized pathological processes within the resident CNS cells. Microglia are the most abundant resident macrophage-like cells in the CNS and constitute one of the key cell types that could trigger neurotoxic pathways leading to progressive neurodegeneration or, in contrast, could exert important roles in promoting neuroprotection, downregulation of inflammation, and stimulation of repair. Activated microglia exhibit cytoplasmic hypertrophy, retraction of processes, and upregulation of MHC class II molecules and pro-inflammatory cytokines.

Not only is microglial activation observed in early active lesions, it also accompanies diffuse axonal injury in normal-appearing white and grey matter of progressive MS lesions. In addition, microglial nodules (a clustering of activated microglia) are abundant in the areas adjacent to plaques, particularly in patients with progressive MS. In an attempt to understand the neuropathological processes occurring in progressive MS, a positron emission tomography (PET) imaging method with radioligands binding to the 18-kDa translocator protein (TSPO) molecule on activated microglia was developed for monitoring these cells in living patients with MS. It revealed that TSPO binding was significantly increased in the normal-appearing white matter (NAWM) of patients with secondary progressive MS (SPMS) but only modestly in the NAWM of RRMS brain. In PPMS, such studies are still limited. Most recently, TSPO-PET studies showed significantly increased signals in subcortical grey matter regions, especially in the thalamus in SPMS, and this was associated with accelerated brain atrophy. Thus, activated microglia are observed in progressive MS; however, what is not yet known is whether they contribute to ongoing degeneration or reflect a normal reaction to injury and serve a protective role.

Mitochondrial dysfunction in MS

Mitochondria play a central role in the supply of energy to electrically active axons and neurons. Dysfunction of this organelle likely contributes to "virtual hypoxia" and may be especially relevant for chronically demyelinated axons where an action potential may exact a higher toll

on energy supply. This imbalance of supply versus demand could further exacerbate degeneration of vital tracts through energy failure, induction of apoptosis, and enhanced production of reactive oxygen species (ROS). Therefore, this topic has been gaining interest as an important mechanism of neuronal death.

Oxidative burst in activated microglia produces reactive oxygen and nitrogen species which contribute to mitochondrial dysfunction. Therefore, the activated microgliosis described above could exacerbate axo-glial injury in white matter that does not exhibit overt pathological changes. A marker of mitochondrial dysfunction, cerebrospinal fluid (CSF) lactate showed a positive correlation with disease onset, severity, and progression, suggesting that this organelle might be under stress from the earliest stages of the disease. A recent study reported that ceramides in CSF from patients with progressive MS induced mitochondrial elongation and reduced respiratory chain complex activity in cultured neurons, providing evidence of a specific factor contributing to mitochondrial injury. This supports previous findings that decreased functional activity of mitochondrial respiratory chain complexes in progressive MS motor cortex neurons may contribute to accumulating neurological disability in patients with MS. In addition, respiratory chain complex IV–deficient neurons and choroid plexus (CP) epithelial cells are more abundant in MS brain and this respiratory enzyme deficiency is caused by a high level of mitochondrial DNA (mtDNA) deletions. Interestingly, no significant change in the extent of respiratory-deficient skeletal muscle fibers was found in patients with progressive MS compared with age-matched controls, indicating that such mitochondrial changes are induced within the CNS. The cause of this mitochondrial damage, which likely plays an important role in further compromising the health and function of brain neurons and axons, is not completely understood.

MS progression occurs in episodes of increasing inflammation

The progression of MS occurs due to episodes of increasing inflammation, which is due to the release of antigens (such as myelin oligodendrocyte glycoprotein, myelin basic protein, and proteolipid protein), causing an autoimmune response. This sets off a cascade of signaling molecules that result in T-cells, B-cells, and macrophages to cross the BBB and attack myelin on neuronal axons leading to inflammation. Further release of antigens drives subsequent degeneration causing increased inflammation.

MS presents itself as a spectrum based on the degree of inflammation, a majority of patients experiencing early relapsing and remitting episodes of neuronal deterioration following a period of recovery. Some of these individuals may transition to a more linear progression of the disease, while about 15% of others begin with a progressive course on the onset of MS. The inflammatory response contributes to the loss of the grey matter and, as a result, current literature devotes itself to combatting the auto-inflammatory aspect of the disease. While there are several proposed causal links between the Epstein-Barr virus (EBV) and the HLA-DRB1*15:01 allele to the onset of MS – they may contribute to the degree of autoimmune attack and the resultant inflammation – they do not determine the onset of MS.

Why does the immune system attack the central nervous system's myelin?

Researchers are looking at several possible explanations for why the immune system attacks the CNS myelin, including:

- **Molecular mimicry:** Fighting an infectious agent (for example, a virus) that has components that mimic components of the brain.

- **Destruction of unhealthy brain cells.**

- **Misidentification of normal brain cells as foreign.**

- **Disruption of the blood-brain barrier:** The barrier separates the brain and spinal cord from the body's immune system. A disruption in the barrier exposes the brain to the immune system. When this happens, the immune system may misinterpret structures in the brain (such as myelin) as "foreign".

While the cause of MS is unclear, the underlying mechanism is thought to be either destruction by the immune system or failure of the myelin-producing cells.

Like for other neurodegenerative diseases (and indeed other illnesses), MS is believed to be an immune-mediated disorder that develops from a complex interaction of the individual's genetic's susceptibility and as yet unidentified environmental and lifestyle causes. (acronym GEL). Damage is believed to be caused, at least in part, by attack on the nervous system by a person's own immune system.

Etiology of MS

On genetic susceptibility and MS vulnerability

MS itself is not inherited, but susceptibility to MS may be inherited. Studies show that some individuals with MS have one or more family members or relatives who also have MS. Current research suggests that dozens of genes and possibly hundreds of variations in the genetic code (called "gene variants") combine to create vulnerability to MS.

Some of these genes have been identified, and most are associated with functions of the immune system. Many of the known genes are similar to those that have been identified in people with other autoimmune diseases (e.g., type 1 diabetes, rheumatoid arthritis, lupus).

Although genetic factors clearly confer susceptibility, they do not constitute the entire explanation. The concordance rates in twins, while striking, are far smaller than if the illness resulted from conventional genetic inheritance. Moreover, affected twins tend to display different symptomatology and follow a different disease course.

Family and ethnic influences

Approximately 20% of all individuals with MS have at least one family member either in the same or a different generation who has or had MS. While small, this concordance rate among family members does not support a direct disease inheritance; it may suggest however a genetic influence. The above low rate may be due to a shared environmental cause or trigger for MS.

Results of studies of genetic influence across world countries and ethnicities are summarized in Table 3. Their current statuses are provided for families having more than one case of MS, ethnic/religious populations, and for racial differences:

Genetics of MS

MS is not considered a hereditary disease. Having a relative with MS does mean the chance of getting MS is a bit higher than otherwise, but it is still low. A parent with MS can pass on the genes that make the risk of getting MS higher (a 1.5% risk), but the child does not automatically get MS. Genes play some part but they do not decide who gets MS. Most people with MS have no history of it in their family (Table 3).

World region/ethnicity	Concordance rate	Notes
Families (more than one case) in: o Australia o Canada o Europe o United Kingdom o U.S.A.	Quite low and lower with distant relationship High o ~ 1/1000 when family member (parent, sibling) has the disease o 2-5% depending on degree of relationship: - Fraternal twin: 30% - Non-identical twin: 5%	Genetic risk greater through the maternal line Strong proof of genetic factor. Some other trigger is involved o Studies under way o Truly genetic; not due to environment or lifestyle factors o Studies under way o Studies under way
Ethnic/religious populations genetically isolated: o Canada: Hutterites o Eastern Europe: Gypsies o Western Finland o Tasmania o Iceland	MS never or rarely occurs o Protected from MS o Protected from MS o Studies under way o Studies under way o Studies under way	
Racial differences o North America (genetically-mixed African-Americans) o Pure African Bantus o Asians		Show genetic influence: o Disease more common among whites than African-Americans o Virtually never develop MS o Much less than in whites

Reference: A. L. Fymat (2023)

Table 3: MS genetic influences across world countries and ethnicities

There is not one gene that causes MS. Over 200 genes could affect the chances of getting it; however, a number of genetic variations have been shown to increase the risk. Some of these genes appear to have higher levels of expression in microglial cells than expected by chance. The probability of developing the disease is higher in relatives of an affected person, with a greater risk among those more closely related. An identical (fraternal) twin of an affected individual has a 30% chance of developing MS, 5% for a non-identical twin, 2.5% for a sibling, and an even lower chance for a half-sibling. If both parents are affected, the risk in their children is 10 times that of the general population. MS is also more common in some ethnic groups than others.

Although some studies link several different chromosome mutations to the development of MS, none were either necessary or sufficient but not both. As in most other neurodegenerative diseases (NDDs), genetic influences play a role in MS. However, unlike in a number of other NDDs where specific mutations have been identified as causes for at least a subset of these, such mutations have yet to be identified in MS. Instead, a large number of susceptibility loci, the vast majority of which are related to immune function, have been found through genome-wide association studies (GWAS). Together, these studies unequivocally confirm the importance of immune-related genes, and genetic maps from a very recent GWAS further implicate both the adaptive and innate immune systems. Specific genes that have been linked with MS include differences in the human leukocyte antigen (HLA) system—a group

of genes on chromosome 6 that serves as the major histocompatibility complex (MHC). That differences in the HLA region are related to susceptibility has been known since the 1980s, and this same region has also been implicated in the development of other autoimmune diseases such as diabetes type I and systemic lupus erythematosus. Other examples which demonstrate an association with MS include HLA class II (DP, DQ, and DR) haplotypes, although contradictory results were shown in various studies among different races. The most consistent finding is the association between MS and alleles of the MHC defined as DR15 and DQ6. Other loci have shown a protective effect, such as HLA-C554 and HLA-DRB1*11.

The HLA-DRB1*15:01 allele is one of the most intensively studied, exhibiting a consistent association with a lower age of onset, greater white matter lesion volume, and faster brain atrophy in RRMS. In addition, a recent report suggested that the high-risk HLA genotype (two predisposing haplotypes) associates with significant reduction in whole brain and grey matter volumes compared with medium- or low-risk genotypes (one or no predisposing haplotypes). Many loci outside the MHC have also been correlated with MS risk and involve other immune pathways, including B-cell activation, cytokine release, and activation of immune cells both in the periphery and within the CNS. This study identified additional novel candidates associating with regulators of CD4 + Th1 and Th17 induction and apoptosis. Genes involved in neurodegeneration, such as mitochondrial genes CRYAB, CB1 and Prnp, have been studied, but associations with PPMS risk seem to involve mainly variants of immune-related genes, similar to what was found with ROMS.

Overall, it has been estimated that HLA differences account for between 20% and 60% of the genetic predisposition. Modern genetic methods (GWAs) have revealed at least 200 variants outside the HLA locus that modestly increase the probability of MS (Table 4).

Genotype	Haplotype	Allele	GWAS results
HLA class II	DP, DQ, DR	MHC alleles: DR15, DQ6	o Contradictory results among different races o Protective effect from: HLA-C554
		HLA-DRB1*15.01	o Protective effect from HLA- DRB1*15.01 o Consistent association with lower onset age o Greater white matter lesion volume o Faster brain atrophy in RRMS
High-risk genotype	2 predisposing haplotypes		o Significant reduction in whole brain and grey matter volumes
Medium- or low-risk genotypes	1 or no predisposing haplotypes		o Lesser reduction in whole brain and grey matter volumes
Outside MHC loci			o Correlation with MS risk o B-cell activation o Cytokine release o Activation of immune cells (both in the periphery and within the CNS)

Reference: A. L. Fymat (2023)

Table 4: Genetics of multiple sclerosis

However, none of these has a strong association with progressive MS, suggesting that these immune-related factors are unlikely to be causative but instead might determine the intensity of autoimmune reactivity to a degenerating brain. Genetic studies on patients with PPMS are less comprehensive because of the much lower incidence of this MS phenotype. However, despite the striking difference in clinical phenotypes between ROMS and PPMS, clear genetic differences have not emerged. Interestingly, however, MS patients exhibiting a higher degree of neurodegeneration had variants in genes related to glutamate signaling, supporting the concept of a neurodegenerative underlay driven at least in part by “chronic excitotoxicity”.

Moreover, such chronic excitotoxicity is likely further exacerbated by glutamate released by immune cells. Finally, it was recently shown that primary myelin damage is a strong trigger for a secondary immune reaction driven in large part by biochemically altered myelin proteins; it is quite likely that chronic excitotoxicity, originating from both the as-yet-unknown underlying degenerative process(es) and glutamate release from infiltrating immune cells, promotes a persistent source of pathological myelin products resulting in a vicious cycle of degeneration–inflammation–more degeneration.

Taken together, data so far unequivocally support the contribution of multiple immune-related genetic loci to RRMS, but a direct causal relationship remains elusive. One could also argue that studies of MS genetics provide information on host susceptibility and response to some causative factor that nonetheless remains unknown. By extension, elucidating multiple immune-related genetic loci associated with MS may not bring us any closer to identifying the root cause.

In addition to immunogenetics, MS risk is strongly associated with environmental factors, in particular infection with Epstein–Barr virus (EBV), sun exposure/vitamin D deficiency, and smoking.

Environmental factors

Environmental factors, in particular during childhood, may perhaps play a role such as, for example, an environmental toxin or even a dietary imbalance. However, there is no related convincing evidence. On the other hand, several studies found that people who move to a different region of the world before the age of 15 acquire the new region's risk of MS. Whatever factor is involved, it would have to have taken place before the approximate age of 15 for the disease process to be triggered later in life. If migration takes place after age 15, however, the person retains the risk of their home country. However, there is some evidence that the effect of moving may still apply to people older than 15.

Geographical factors

MS is more common in people who live farther from the equator, although exceptions exist. These exceptions include ethnic groups that are at low risk and that live far from the equator such as the Sami, Amerindians, Canada's Hutterites and Inuit, New Zealand's Māori, as well as groups that have a relatively high risk and that live closer to the equator such as Sardinians, inland Sicilians, and Parsi.

The cause of this geographical pattern is not clear. While the north–south gradient of incidence is decreasing, as of 2010 it is still present. MS is more common in regions with northern European populations and the geographic variation may simply reflect the global distribution of these high-risk populations. A relationship between season of birth and MS lends support to this idea, with fewer people born in the northern hemisphere in November compared to May being affected later in life.

Climate

MS is more common in people who live farther from the equator, although exceptions exist, including Canada, the northern United States, New Zealand, southeastern Australia, and Europe.

Infectious agents

One hypothesis is that infection by a widespread microbe contributes to disease development, and the geographic distribution of this organism significantly influences the epidemiology of MS. Two opposing versions of this hypothesis include the "hygiene hypothesis" and the "prevalence hypothesis", the former being more favored. The hygiene hypothesis proposes that exposure to certain infectious agents early in life is protective, the disease being a response to a late encounter with such agents. The prevalence hypothesis proposes that an early, persistent, and silent infection increases the risk of disease, and thus the disease is more common where the infectious agent is more common. Only in a few cases and after many years does it cause demyelination.

Some infections, for example a bladder infection, may also make a relapse more likely. For this reason, people with MS are encouraged to treat infections early and to avoid things that can cause them. That is why they are advised to have an annual flu jab, for example. While supporting evidence has not been found, the bacterium Chlamydiae pneumoniae, responsible for walking pneumonia has not been substantiated.

Viruses

A variety of viruses have been invoked as the cause of MS. Searches for such viruses are going on, especially as technology has advanced for their detection. For example, polymerase chain reaction (PCR) analysis can detect the presence of protein footprints in blood, CSF, and even tissue even if whole viruses cannot be seen. Unfortunately, supporting evidence for viral etiology has not yet been found.

A few suspect viruses remain and are under investigation. Evidence for a virus as a cause of MS includes the presence of oligoclonal bands in the brain and the CSF of most people with MS, the association of several viruses with human demyelinating encephalomyelitis, and the occurrence of demyelination in animals caused by some viral infections.

Human herpes viruses (HHVs) are a candidate group of viruses. (HHV-6 is a common virus that causes roseola in infants.) Individuals having never been infected by the Epstein–Barr virus (EBV) are at a reduced risk of getting MS, whereas those infected as young adults are at a greater risk than those having had it at a younger age. Although some consider that this goes against the hygiene hypothesis, since the non-infected have probably experienced a more hygienic upbringing, others believe that there is no contradiction, since it is a first encounter with the causative virus relatively late in life that is the trigger for the disease. Other diseases that may be related include measles, mumps, and rubella.

Several viruses have been found in people with MS, but the virus most consistently linked to the development of MS is EBV (the virus which causes infectious mononucleosis). It infects approximately 95% of adults and has been increasingly suspected to be the primary cause of MS, even though only a small proportion of those infected with EBV will later develop MS. Past EBV exposure as evidenced by seropositivity to the virus is virtually a prerequisite for developing MS. However, given the very high global prevalence of EBV exposure, clearly the converse is not true, i.e., only a small minority of exposed individuals will develop MS, indicating that EBV may be necessary but not sufficient to trigger the disease.

Epidemiological evidence supporting the important role of this virus includes observations that patients with a history of symptomatic EBV infection carry a higher risk of developing MS, and the risk of MS dramatically

increases in seronegative individuals after seroconversion. These strong associations lead to the hypothesis that B-lymphotropic EBV infection of CNS-infiltrating B-cells may somehow drive MS pathology, although such a direct causative role of EBV remains controversial as some groups report absence of EBV infection in MS brains. A possible explanation for this discrepancy is that EBV is one of many possible triggers of secondary autoimmune response or that EBV alone is not sufficient. Although there is no consensus regarding a direct role of EBV-infected B-cells as a primary cause of MS, increasing evidence, including therapeutic strategies, indicates a potentially important role in MS pathogenesis.

For instance, recently, a preliminary clinical trial of autologous EBV-specific T-cell therapy showed clinical improvement in patients with progressive MS. Although only 10 subjects underwent treatment, this small study provides some of the most direct evidence to date of a potentially central role of EBV-infected B cells in MS. Moreover, the fact that patients in the progressive phase (a phase largely resistant to current therapies) experienced improvement is equally noteworthy. Whether the beneficial effects of T-cell mediated killing of EBV-infected B-cells were due to a reduction of disease-causing immunoglobulin production, or of other toxic soluble factors produced by B-cells, remains to be seen. A hypothesized mechanism of EBV causing MS is molecular mimicry between EBV proteins and nervous system molecules, causing autoimmunity

Only about 5% of the population has not been infected by EBV. These individuals are at a lower risk for developing MS than those who have been infected. People who were infected with EBV in adolescence or adulthood and who therefore develop an exaggerated immune response to EBV are at a significantly higher risk for developing MS than those who were infected in early childhood. This suggests that it may be the type of immune response to EBV that may lead to MS, rather than EBV infection itself. However, there is still no proof that EBV causes MS and the mechanisms that underlie this process are poorly understood.

Rather than focusing on a single infectious agent, many scientists believe that people with MS have a heightened immune antibody response against a host of common and uncommon viruses and other infectious agents and that past claims based on antibody responses against a specific agent are likely misleading.

Lifestyle factors

Vitamin D supplementation

Having low levels of vitamin D and low exposure to sunlight is associated with a greater risk of certain autoimmune diseases. Some (not all) studies show that being low in vitamin D is linked to having more relapses. They also showed that getting extra vitamin D reduced the number of relapses. Several studies indicate that people who spend more time in the sun and those with relatively higher levels of vitamin D are less likely to develop MS or have a less severe course of disease and fewer relapses. Bright sunlight helps human skin produce vitamin D. Researchers believe that vitamin D may help regulate the immune system in ways that reduce the risk of MS or autoimmunity in general. People from regions near the equator, where there is a great deal of bright sunlight, generally have a much lower risk of MS than people from temperate areas such as the United States and Canada.

Vitamin D supplementation in people with MS appears to be safe but at high doses can lead to changes in calcium levels. More research is needed to determine whether it is truly beneficial. A connection between vitamin D and MS could be tied to the positive effects vitamin D has on the immune system. The connection is strengthened by the association between sunlight and the risk of MS. The recommendations of the (U.S.) Institute of Medicine (IoM) are provided in Table 5.

Research studies have indicated that taking 400 IUs or

more of vitamin D per day significantly decreases the risk of MS in women.

Age (years)	Recommended daily dose
Up to 70	600
> 71	800
Women pregnant or breast feeding	600
Dose recommended for women	> 400
Maintenance dose after deficient status	2,000 – 5,000 Weekly: Up to 50,000 for up to 3 months until normal; then switch to maintenance dose

Reference: A. L. Fymat (2023)

Table 5: (U.S.) Institute of Medicine's guidelines for vitamin D supplementation

(Daily doses are in IUs)

In case of vitamin D deficiency, it is recommended to use a dose up to 50,000 IUs weekly for up to three months until vitamin D levels become normal, and then to switch to a maintenance dose. The maintenance dose varies, but is usually between 2,000 and 5,000 IUs daily. Very large doses of vitamin D over an extended period can result in toxicity. Signs and symptoms include nausea, vomiting, constipation, poor appetite, weakness, and weight loss. In addition, vitamin D toxicity can lead to elevated levels of calcium in the blood, which can result in kidney stones.

Smoking

Our brains get a bit smaller as we get older, whether we have MS or not, but brain atrophy is linked to having more disability, poorer memory and thinking, and being less able to recover from the damage MS does to the brain. Studies suggest that smoking could increase risk, possibly by affecting the immune system. People who smoke are more likely to develop MS, have a more aggressive disease course, and tend to have more brain lesions and brain shrinkage than non-smokers (the reasons for this are currently unclear).

Giving up smoking (or never starting) also means one is likely to have fewer relapses in the long run. That is because smoking makes one more prone to infections (of the chest or lungs, but also colds and flu), and these can trigger a relapse. Smoking also stops some DMD/Ts from working as they should. Smoking while on some DMD/Ts increases the chance of a relapse compared to people on the same drug who do not smoke. Smokers who experience an initial event of symptoms that may signal MS are more likely than nonsmokers to develop a second event that confirms RRMS. Smoking is also linked to going from relapsing MS to progressive MS at a faster rate.

Diet and hormone intake

Several other possible risk factors, such as diet and hormone intake, have been looked at, however, evidence on their relation with the disease is "sparse and unpersuasive".

Gout

Gout occurs less than would be expected and lower levels of uric acid have been found in people with MS. This has led to the theory that uric acid is protective, although its exact importance remains unknown.

Obesity

Studies have found that being very overweight (obese), especially during adolescence and young adulthood is a risk factor for MS. This could be because being very overweight can make one low in vitamin D or/and make one's immune system overactive and cause inflammation inside the body. There may be other currently not understood conditions.

Stress

Over the years, many studies have looked at whether

there is a link between psychological stress and MS getting worse. The evidence is not absolutely clear, but many experts believe that stress might be one of many factors which could increase the risk of a relapse. Anecdotally, many people affected by MS cite stress as a major factor in bringing on a relapse.

Occupational exposures

Association with occupational exposures and toxins (mainly organic solvents) has been evaluated, but no clear conclusions have been reached.

Vaccinations

Vaccinations were studied as causal factors; however, most studies show no association. There is no proven link between vaccinations (for example, for flu, hepatitis B, or nearly all travel vaccines) and a relapse. If going to an area where a serious infectious disease is prevalent, it is generally far better to have a vaccination than to risk serious illness, which could have far worse consequences.

Pregnancy

Many women with MS find that they have fewer relapses during pregnancy. But, in the months after the baby is born, the risk of a relapse often goes up. So, soon after the birth, it is recommended that the mother starts a DMD/T (or goes back to taking the one she was on before the pregnancy).

Other risk factors

The following factors may increase the risk of developing MS:

Age: MS can occur at any age, but onset usually occurs around 20 and 40 years of age. However, younger and older people can be affected.

Sex: Women are more than two to three times as likely as men are to have relapsing-remitting MS.

Family history: If one of parent or a sibling has had MS, the risk of developing the disease is higher.

Race: White people, particularly those of Northern European descent, are at highest risk of developing MS. People of Asian, African or Native American descent have the lowest risk.

Complications

People with MS may develop several complications such as:

Muscle stiffness or spasms.

- Paralysis, typically in the legs.
- Problems with bladder, bowel or sexual function.
- Mental changes, such as forgetfulness or mood swings.
- Depression.
- Epilepsy [for a complete treatment of this topic, see Fymat (2022)].

The Case for the Underlying Immune SystemIn MS

The evidence for the involvement of the immune system in MS is as follows:

- **Presence of specific white blood cells in the CNS:** T- and B- lymphocytes in the CNS are primed to recognize and launch attacks against tissues of the nervous system such as myelin and nerve fibers.

- **Clear and specific reactions of T- and B-cells against CNS myelin protein:** In individuals with MS, such reactions are observed. Recent successful therapies have been directed to the B-cells.

- **In individuals without MS, circulation of T-cells in the bloodstream is separated from the CNS by the BBB:** By contrast, in people with MS, the BBB is breached allowing the immune cells to move into the CNS tissue and initiate damage.

- **Pro-inflammatory cells are overrepresented and mediator cells are under-represented:** In individuals with MS, there is an over-representaion of cells and other immune cell components that enhance immune reponses and an under-representation of immune mediators (anti-inflammatory cells).

Use of laboratory animal models

The actual proof of autoimmunity requires that immune system cells that cause damage in one MS patient be injected into a different healthy patient and cause damage and disease there as well. Unfortunately, such an experiment would be unthical and unacceptable because it would cause an autoimmune disease in an otherwise healthy individual. However, such an experiment can be, and has been conducted in animal models with a disease called experimental allergic (or autoimmune) encephalomyelitis (EAE). The model mimics the changes in MS. It has shown that an autoimmune disease can produce similar changes seen in MS lesions. Such an esperiment has also provided a "proof of concept" for new immune modulatory drugs/therapies that might be used in humans with MS.

In Summary

MS is a complex disease for which there is no known single initiating cause. It is likely the result of several contributing factors. While the symptoms come from the nervous system, the cause appears to be a disease of immune system function, most likely an autoimmune disease that attacks the central nervous system ... another illustration of the adage "symptoms, correlations., associations, and the likes ...are not causation". The disease is not genetically inherited although there is genetic susceptibility without necessarily contracting the disease. While one, several or a combination of triggering factors are suspected, such as bacteria, viruses (including the Epstein-Barr virus), or other environmental or lifestyle factors, so far, none have been found or identified.

References

General

1. Alonso A and Hernán MA (2008). "Temporal trends in the incidence of multiple sclerosis: A systematic review". Neurology 71(2):129–35. doi:10.1212/01.wnl.0000316802.35974.34.
2. Amato MP and Ponziani G (1999). "Quantification of impairment in MS: Discussion of the scales in use". Multiple Sclerosis5(4):216–9. doi:10.1191/135245899678846113.
3. Andravizou A, Dardiotis E, Artemiadis A, Sokratous M, Siokas V, Tsouris Z, et al. (2019). "Brain atrophy in multiple sclerosis: Mechanisms, clinical relevance and treatment options". Auto- Immunity Highlights 10(1):7. doi:10.1186/s13317-019-0117-5.
4. Ascherio A and Munger KL (2007). "Environmental risk factors for multiple sclerosis. Part I: The role of infection". Annals of Neurology 61(4):288-99. doi:10.1002/ana.21117.
5. Ascherio A and Munger KL (2007).

"Environmental risk factors for multiple sclerosis. Part II: Noninfectious factors". Annals of Neurology 61(6):504–13. doi:10.1002/ana.21141.

6. Balak DM, Hengstman GJ, Çakmak A, and Thio HB (2012). "Cutaneous adverse events associated with disease-modifying treatment in multiple sclerosis: A systematic review". Multiple Sclerosis 18(12):1705–17. doi:10.1177/1352458512438239. hdl:1765/73097.
7. Baranzini SE (2011). "Revealing the genetic basis of multiple sclerosis: Are we there yet?". Current Opinion in Genetics & Development 21(3):317–24. doi:10.1016/j.gde.2010.12.006.
8. Berer K and Krishnamoorthy G (2014). "Microbial view of central nervous system autoimmunity". FEBS Letters 588(22):4207–13. doi:10.1016/j.febslet.2014.04.007.
9. Bernitsas E (2020). "The Central Vein Sign". Practical Neurology.
10. Biogen (2013). “Biogen Idec's TECFIDERA™ (Dimethyl Fumarate) Approved in the U,S, as a first- line oral treatment for multiple cclerosis" (Press release). 27 March 2013.
11. Bjornevik K, Cortese M, Healy BC, et al. (2022). "Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis". Science 375(6578): 296-301.Bibcode:2022Sci...375.296B. doi:10.1126/science.abj8222.
12. Bonduelle M, Gelfand T, and Goetz CG (1996). “Charcot, un grand médecin dans son siècle”. Éditions Michalon (In French: Charcot: A great physician of his century.)
13. Bordon Y (2022). "Linking Epstein-Barr virus infection to multiple sclerosis". Nature Reviews Immunology 22(3):143. doi:10.1038/s41577-022-00686-4.
14. Burton JM, O'Connor PW, Hohol M, and Beyene J (2012). "Oral versus intravenous steroids for treatment of relapses in multiple sclerosis". The Cochrane Database of Systematic Reviews 12: CD006921. doi:10.1002/14651858.CD006921.pub3.
15. Cameron MH and Nilsagard Y (2018). "Balance, gait, and falls in multiple sclerosis". Handbook of Clinical Neurology 159: 237–250. doi:10.1016/b978-0-444-63916-5.00015-x.
16. Cantuti-Castelvetri L, Fitzner D, Bosch-Queralt M, Weil MT, Su M, Sen P, Ruhwedel T, Mitkovski M, Trendelenburg G, Lütjohann D, Möbius W, and Simons M (2018). "Defective cholesterol clearance limits remyelination in the aged central nervous system". Science 359(6376):684–8.
17. Charcot J-M (1868). "Histologie de la sclerose en plaques". Gazette des Hopitaux, Paris 41:554–5. (In French: Histology of multiple sclerosis.)
18. Charcot J-M (1885-1887). “Leçons sur les maladies du système nerveux”. Paris: Delahaye et Lecrosnier. (In French: Lectures on the illnesses of the nervous system.)
19. Charcot J-M, “De l'hérédité dans les maladies du système nerveux”.(In French: On the heredity of the the illnesses of the nervous system.)
20. Chari DM (2007). "Remyelination in multiple sclerosis". International Review of Neurobiology 79: 589–620. doi:10.1016/S0074-7742(07)79026-8.
21. Chen Y and Popko B (2018). "Cholesterol crystals impede nerve repair". Science 359(6376):635-6. doi:10.1126/science.aar7369.
22. Christensen S, Farkas DK, Pedersen L, Miret M, Christiansen CF, and Sørensen HT (2012). “Multiple sclerosis and risk of venous thromboembolism: A population-based cohort study”, Neuroepidemiology 38(2):76-83. doi:10.1159/000335496.

23. Chwastiak LA and Ehde DM (2007). "Psychiatric issues in multiple sclerosis", Psychiatr Clin North Am. 30(4):803-17. doi:10.1016/j.psc.2007.07.003.
24. Clerico M, Faggiano F, Palace J, et al. (2008). "Recombinant interferon beta or glatiramer acetate for delaying conversion of the first demyelinating event to multiple sclerosis". Cochrane Database Syst Rev (2):CD005278. doi:10.1002/14651858.CD005278.pub3.
25. Coetzee T, Cohen JA, Marrie RA, and Thompson AJ (2020). "The 2013 clinical course descriptors for multiple sclerosis: A clarification". Neurology 94(24):1088-92. doi:10.1212/WNL.0000000000009636.
26. Compston A (1988). "The 150th anniversary of the first depiction of the lesions of multiple sclerosis".Journal of Neurology, Neurosurgery, and Psychiatry 51(10):1249–52. doi:10.1136/jnnp.51.10.1249.
27. Compston A and Coles A (2002). "Multiple sclerosis". Lancet 359(9313):122-31. doi:10.1016/S0140- 6736(02)08220-X.
28. Compston A and Coles A (2008). "Multiple sclerosis". Lancet 372(9648):150-7. doi:10.1016/S0140-6736(08)61620-7.
29. Cooper, Law and Sarnoff. "ADA and People with MS". (Available as a download from the National MS Society)
30. Cree BA, Gourraud PA, et al. (2016). "Long-term evolution of multiple sclerosis disability in the treatment era". Ann Neurol. 80(4):499–510. doi:10.1002/ana.24747.
31. Dyment DA, Ebers GC, and Sadovnick AD (2004). "Genetics of multiple sclerosis". The Lancet Neurology 3(2):104–10. CiteSeerX 10.1.1.334.1312. doi:10.1016/S1474-4422(03)00663-X.
32. Feinstein A (2005). "The clinical neuropsychiatry of multiple sclerosis". CNS Spectrums10(5):362. doi:10.1017/s1092852900022720.
33. Feinstein A and Pavisian B (2017). "Multiple sclerosis and suicide", Mult Scler. 23(7):923-7. doi:10.1177/1352458517702553.
34. Fymat AL (2023). "Multiple Sclerosis: The progressive demyelinating autoimmune disease", Tellwell Talent Publishers pp 504, 30 March 2023. ISBN: 978-0-2288-9292-2 (Hardcover); 978-0-2288-3 (Paperback). https://portal.tellwell.ca/Tellwell/Design/212669.
35. Grimaldi LM, Salemi G, Grimaldi G, Rizzo A, Marziolo R, Lo Presti C, Maimone D, and Savettieri G (2001). "High incidence and increasing prevalence of MS in Enna (Sicily), southern Italy. Neurology 57(10):1891–3. doi:10.1212/wnl.57.10.1891.
36. Guisset F, Lolli V, Bugli C, Perrotta G, Absil J, Dachy B, et al. (2021). "The central vein sign in multiple sclerosis patients with vascular co-morbidities". Multiple Sclerosis 27(7):1057-65. doi:10.1177/1352458520943785.
37. Harding K, Zhu F, Alotaibi M, Duggan T, Tremlett H, and Kingwell E (2020). "Multiple cause of death analysis in multiple sclerosis: A population-based study", Neurology 94(8):e820 doi:10.1212/WNL.0000000000008907.
38. Hassan-Smith G and Douglas MR (2011). "Epidemiology and diagnosis of multiple sclerosis". British Journal of Hospital Medicine 72(10):M146-51. doi:10.12968/hmed.2011.72. Sup10 .M146.
39. Hassan-Smith G and Douglas MR (2011). "Management and prognosis of multiple sclerosis". British Journal of Hospital Medicine 72(11):M174-6. doi:10.12968/hmed.2011.72.Sup11.M174.
40. Hayes S, Galvin R, Kennedy C, Finlayson M, McGuigan C, Walsh CD, and Coote (2019). "Interventions for preventing falls in people with multiple sclerosis". The Cochrane Database of Systematic Reviews 2019

(11):CD012475. doi:10.1002/14651858.CD012475.pub2.

41. Hedström A, Hössjer O, and Katsoulis M (2018). "Organic solvents and MS susceptibility: Interaction with MS risk HLA genes". Neurology 91(5):455–62. doi:10.1212/WNL.0000000000005906.
42. Holmøy T (2006). "A Norse contribution to the history of neurological diseases". European Neurology 55(1):57–8. doi:10.1159/000091431.
43. International Multiple Sclerosis Genetics Consortium (2019). "Multiple sclerosis genomic map implicates peripheral immune cells and microglia in susceptibility". Science 365(6460). doi:10.1126/science.aav7188.
44. Irvine KA, Blakemore WF, and Teunisse C (2008). “Faculty opinions recommendation of remyelination protects axons from demyelination-associated axon degeneration", Brain: A Journal of Neurology 131(6):1464-77. doi:10.3410/f.1115522.571562. https://doi.org/10.1093/brain/awn080.
45. Jacobsen C, Hagemeier J, Myhr KM, Nyland H, Lode K, Bergsland N, et al. (2014). "Brain atrophy and disability progression in multiple sclerosis patients: a 10-year follow-up study". Journal of Neurology, Neurosurgery, and Psychiatry 85(10):1109–15. doi:10.1136/jnnp-2013-306906.
46. Jakimovski D, Guan Y, Ramanathan M, Weinstock-Guttman B, and Zivadinov R (2019). “Lifestyle-based modifiable risk factors in multiple sclerosis: Review of experimental and clinical findings”, Neurodegener Dis Manag. 9(3):149-72. doi:10.2217/nmt-2018-0046.
47. Kalb R, Beier M, Benedict RH, Charvet L, Costello K, Feinstein A, et al. (2018). "Recommendations for cognitive screening and management in multiple sclerosis care". Multiple Sclerosis 24(13):1665-80. doi:10.1177/1352458518803785.
48. Kaufman DM (2013). "Multiple Sclerosis", Chapter 15 in Kaufman's Clinical Neurology for Psychiatrists, Eds: Kaufman DM and Milstein MJ.
49. Kingwell E, Leray E, Zhu F, et al. (2019). “Multiple sclerosis: Effect of beta interferon treatment on survival”, Brain 142(5):1324-33. doi:10.1093/brain/awz055.
50. Kurtzke JF (1983). "Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS)". Neurology 33(11):1444–52. doi:10.1212/WNL.33.11.1444.
51. Kurtzke JF (1993). "Epidemiologic evidence for multiple sclerosis as an infection". Clinical Microbiology Reviews 6(4):382–427. doi:10.1128/CMR.6.4.382.
52. Lane J, Ng HS, Poyser C, Lucas RM, and Tremlett H (2022). "Multiple sclerosis incidence: A systematic review of change over time by geographical region". Mult Scler Relat Disord.63:103932. doi:10.1016/j.msard.2022.103932.
53. Lanz TV, Brewer RC, Ho PP, et al. (2022). "Clonally-expanded B-cells in multiple sclerosis bind EBV EBNA1 and glialCAM". Nature 603(7900):321–7. doi:10.1038/s41586-022-04432-7.
54. Lassmann H (1999). "The pathology of multiple sclerosis and its evolution". Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences 354(1390):1635–40. doi:10.1098/rstb.1999.0508.
55. Lassmann H (2005). "Multiple sclerosis pathology: Evolution of pathogenetic concepts". Brain Pathology 15(3):217–22. doi:10.1111/j.1750-3639.2005.tb00523.x.
56. Leray E, Moreau T, Fromont A, and Edan G (2016). "Epidemiology of multiple sclerosis".

Revue Neurologique 172(1):3–13. doi:10.1016/j.neurol.2015.10.006.

57. Lublin FD and Reingold SC (1996). "Defining the clinical course of multiple sclerosis: Results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis". Neurology 46(4):907–911. doi:10.1212/WNL.46.4.907.
58. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sørensen PS, Thompson AJ, Wolinsky JS, Balcer LJ, Banwell B, Barkhof F, Bebo B, Calabresi PA, Clanet M, Comi G, Fox RJ, Freedman MS, Goodman AD, Inglese M, Kappos L, Kieseier BC, Lincoln JA, Lubetzki C, Miller AE, Montalban X, O'Connor PW, Petkau J, Pozzilli C, Rudick RA, Sormani MP, Stüve O, Waubant E, and Polman CH (2014). "Defining the clinical course of multiple sclerosis: the 2013 revisions". Neurology 83(3):278–86. doi:10.1212/WNL.0000000000000560.
59. Makhani N and Tremlett H (2021). "The multiple sclerosis prodrome". Nature Reviews. Neurology 17(8):515–521 doi:10.1038/s41582-021-00519-3.
60. Marrie RA (2004). "Environmental risk factors in multiple sclerosis etiology". The Lancet Neurology 3(12):70-8. doi:10.1016/S1474-4422(04)00933-0.
61. Marrie RA (2019). "Mounting evidence for a multiple sclerosis prodrome". Nature Reviews. Neurology 15(12):689-90. doi:10.1038/s41582-019-0283-0.
62. Martinelli V (2000). "Trauma, stress, and multiple sclerosis". Neurological Sciences 21(4 Suppl 2): S849-52. doi:10.1007/s100720070024.
63. Mazumder R, Murchison C, Bourdette D, and Cameron M (2014). "Falls in people with multiple sclerosis compared with falls in healthy controls". PLOS ONE 9(9): 2014PLoSO...9j7620M. doi:10.1371/journal.pone.0107620.
64. Medaer R (1979). "Does the history of multiple sclerosis go back as far as the 14th century?". Acta Neurologica Scandinavica 60(3):189–92. doi:10.1111/j.1600-0447.1979.tb08970.x.
65. Miller D, Barkhof F, Montalban X, Thompson A, and Filippi M (2005). "Clinically isolated syndromes suggestive of multiple sclerosis. Part I: Natural history, pathogenesis, diagnosis, and prognosis". The Lancet Neurology 4(5):281–8. doi:10.1016/S1474-4422(05)70071-5.
66. Miller DH and Leary SM (2007). "Primary-progressive multiple sclerosis". The Lancet Neurology 6(10):903–12. doi:10.1016/S1474-4422(07)70243-0. hdl:1871/24666.
67. Milo R, Kahana E (2010). "Multiple sclerosis: Geoepidemiology, genetics and the environment".Autoimmunity Reviews 9(5):A387-4. doi:10.1016/j.autrev.2009.11.010.
68. Multiple Sclerosis International Foundation(MSIF). "Principles to promote the quality of life of people with multiple sclerosis".
69. Murray TJ. "Multiple sclerosis: The history of a disease", 580pp, ISBN 1-888799-80-3 (p/b) New York: Demos Medical Publishing.
70. Nakahara J, Maeda M, Aiso S, and Suzuki N (2012). "Current concepts in multiple sclerosis: Autoimmunity versus oligodendrogliopathy". Clinical Reviews in Allergy & Immunology 42(1):26-34. doi:10.1007/s12016-011-8287-6.
71. National Collaborating Centre for Chronic Conditions (2004). "Treatment of acute episodes". Multiple sclerosis: National clinical guideline for diagnosis and management in primary and secondary care. London: Royal College of Physicians pp. 54–8.
72. (U.S.) National Institute of Neurological Disorders and Stroke (NINDS) (2015).

"NINDS Multiple Sclerosis Information Page". 19 November 2015.

73. (U.S.) National Institute of Neurological Disorders and Stroke (NINDS) (2020). “Multiple Sclerosis: Hope Through Research", NIHPublication No. 20-NS-75. www.ninds.nih.gov.
74. (U.S.) National Multiple Sclerosis Society. "Epidemiology of MS"
75. Nourbakhsh B and Mowry EM (2019). "Multiple sclerosis risk factors and pathogenesis". Continuum 25(3):596–610. doi:10.1212/CON.0000000000000725.
76. Oreja-Guevara C, Ayuso Blanco T, Brieva Ruiz L, Hernández Pérez MÁ, Meca-Lallana V, and Ramió- Torrentà L (2019). "Cognitive dysfunctions and assessments in multiple sclerosis". Frontiers in Neurology 10:581. doi:10.3389/fneur.2019.00581.
77. Pearce JM (2005). "Historical descriptions of multiple sclerosis". European Neurology 54(1):49–53. doi:10.1159/000087387.
78. Peter KS and Shigeki T (2019). “Recent advances in understanding multiple sclerosis”. F1000 Research.8:2100. doi:10.12688/f1000research.20906.1.ISSN 2046-1402.
79. Piryonesi SM, Rostampour S, and Piryonesi SA (2021). "Predicting falls and injuries in people with multiple sclerosis using machine learning algorithms". Multiple Sclerosis and Related Disorders 49:102740. doi:10.1016/j.msard.2021.102740.
80. Pittock SJ and Lucchinetti CF (2007). "The pathology of MS: New insights and potential clinical applications". The Neurologist 13(2):45–56. doi:10.1097/01.nrl.0000253065.31662.37.
81. Pittock SJ and Rodriguez M (2008). "Benign multiple sclerosis: A distinct clinical entity with therapeutic implications". Current Topics in Microbiology and Immunology 1-17. doi:10.1007/978-3-540-73677-6_1.
82. Popescu BF, Pirko I, and Lucchinetti CF (2013). "Pathology of multiple sclerosis: Where do we stand?". Continuum (Minneapolis, Minn.) 19(4 Multiple Sclerosis):901 doi:10.1212/01.CON.0000433291.23091.65.
83. Pugliatti M, Sotgiu S, and Rosati G (2002). "The worldwide prevalence of multiple sclerosis". Clinical Neurology and Neurosurgery 104(3):182–91. doi:10.1016/S0303-8467(02)00036-7.
84. Rae-Grant A, Day GS, Marrie RA, Rabinstein A, Cree BA, Gronseth GS, et al. (2018). "Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology". Neurology 90(17):777-88. doi:10.1212/WNL.0000000000005347.
85. Rashid W and Miller DH (2008). "Recent advances in neuroimaging of multiple sclerosis". Seminars in Neurology 28(1):46– doi:10.1055/s-2007-1019127.
86. Rice GP, Incorvaia B, Munari L, et al. (2001). "Interferon in relapsing-remitting multiple sclerosis”. Cochrane Database Syst Rev (4):CD002002. doi:10.1002/14651858.CD002002.
87. Rietberg MB, Brooks D, Uitdehaag BM, and Kwakkel G (2005). in Kwakkel G (ed.). "Exercise therapy for multiple sclerosis". The Cochrane Database of Systematic Reviews 2005(1): CD003980. doi:10.1002/14651858.CD003980.pub2.
88. Robinson WH, Steinman L (2022). "Epstein-Barr virus and multiple sclerosis". Science 375(6578):264–5. ibcode:2022Sci...375.264R. doi:10.1126/science.abm7930.
89. Rosati G (2001). "The prevalence of multiple

sclerosis in the world: An update". Neurological Sciences 22 (2):117–39. doi:10.1007/s100720170011.

90. Rosti-Otajärvi EM and Hämäläinen PI (2014). "Neuropsychological rehabilitation for multiple sclerosis". The Cochrane Database of Systematic Reviews 2014(2): CD009131. doi:10.1002/14651858.CD009131.pub3.
91. Rovaris M, Confavreux C, Furlan R, Kappos L, Comi G, and Filippi M (2006). "Secondary progressive multiple sclerosis: Current knowledge and future challenges". The Lancet Neurology 5(4): 343-54. doi:10.1016/S1474-4422(06)70410-0.
92. Rovira À (2017). "Diagnosis of multiple sclerosis". Journal of the Belgian Society of Radiology 101 (S1):12. doi:10.5334/jbr-btr.1426.
93. Rudick RA, Cutter G, and Reingold S (2002). "The multiple sclerosis functional composite: A new clinical outcome measure for multiple sclerosis trials". Multiple Sclerosis 8(5):359-65.
94. Saida T (2004). "Multiple sclerosis: Treatment and prevention of relapses and progression in multiple sclerosis". Rinsho Shinkeigaku (Review) (in Japanese) 44(11):796–8. doi:10.1191/1352458502ms845oa.
95. Scalfari A, Knappertz V, Cutter G, Goodin DS, Ashton R, and Ebers GC (2013). "Mortality in patients with multiple sclerosis, Neurology 81(2):184-92. doi:10.1212/WNL.0b013e31829a3388.
96. Sedel F, Bernard D, Mock DM, and Tourbah A (2016). "Targeting demyelination and virtual hypoxia with high-dose biotin as a treatment for progressive multiple sclerosis". Neuropharmacology 110 (Pt B):644–653. doi:10.1016/j.neuropharm.2015.08.028. .
97. Stadelmann C and Brück W (2004). "Lessons from the neuropathology of atypical forms of multiple sclerosis". Neurological Sciences 25(Suppl 4):S319–S322. doi:10.1007/s10072-004-0333-1.
98. Stowe J, Andrews N, and Miller E (2020). "Do vaccines trigger neurological diseases? Epidemiological evaluation of vaccination and neurological diseases using examples of multiple sclerosis, Guillain-Barré syndrome and narcolepsy". CNS Drugs 34(1):1–8. doi:10.1007/s40263-019- 00670-y.
99. Stys PK and Tsutsui S (2019). "Recent advances in understanding multiple sclerosis". F1000Research 8: 2100. doi:10.12688/f1000research.20906.1.
100. Swanberg KM, Landheer K, Pitt D, and Juchem C (2019). "Quantifying the metabolic signature of multiple sclerosis by in vivo proton magnetic resonance spectroscopy: Current challenges and future outlook in the translation from proton signal to diagnostic biomarker". Frontiers in Neurology 10: 1173. doi:10.3389/fneur.2019.01173.
101. Thompson AJ, Baranzini SE, Geurts J, Hemmer B, and Ciccarelli O (2018). "Multiple sclerosis".Lancet391(10130):1622–36. doi:10.1016/S0140-6736(18)30481-1.
102. University of Rochester Medical Center (2021). "Multiple sclerosis (MS)".
103. van Munster CE, Uitdehaag BM (March 2017). "Outcome measures in clinical trials for multiple sclerosis". CNS Drugs 31(3): 217–236. doi:10.1007/s40263-017-0412-5.
104. Weinshenker BG (1994). "Natural history of multiple sclerosis". Annals of Neurology 36 (Suppl): S6-11. doi:10.1002/ana.410360704.
105. World Health Organization (2004). "Atlas: CountryResources for Neurological Disorders".
106. World Health Organization (with Multiple Sclerosis International Federation) (2008): "Atlas: Multiple sclerosis resources in the Wwrld 2008." Geneva: World Health Organization. pp. 15–6. hdl:10665/43968:
107. Xu Z, Zhang F, Sun F, et al. (2015). "Dimethyl fumarate for multiple sclerosis". Cochrane

Database Syst Rev (4):CD011076. doi:10.1002/14651858.CD011076.pub2.

108. Yang C, Hao Z, Zhang L, Zeng L, and Wen J (2015). "Sodium channel blockers for neuroprotection in multiple sclerosis". The Cochrane Database of Systematic Reviews 2015(10): CD010422. doi:10.1002/14651858.CD010422.pub2.

Types and variants

109. Fontaine, B. (2001). "Les formes frontières de sclérose en plaques" [Borderline forms of multiple sclerosis]. Revue Neurologique (in French) 157(8–9 Pt 2):929–34.

110. Fujihara K (2019). "Neuromyelitis optica spectrum disorders: Still evolving and broadening". Current Opinion in Neurology (Review)32(3):385–94. doi:10.1097/WCO.0000000000000694.

111. Hallervorden, Castaigne et al. (1934). Rev Neurol 140:479–87.

112. Hardy TA, Reddel, Barnett, Palace, Lucchinetti, and Weinshenker (2016). “Atypical CNS inflammatory demyelinating disease”. The lancet Neurology. 4422(16)30043-6, doi:https://doi.org/10.1016/S1474

113. Inojosa H, Proschmann U, Akgün K, and Ziemssen T (2021). "A focus on secondary progressive multiple sclerosis (SPMS): Challenges in diagnosis and definition". J Neurol. 268(4):1210–21. doi:10.1007/s00415-019-09489-5.

114. Khonsari RH and Calvez V (2007). “The origins of concentric demyelination: Self-organization in the human brain”. PLoS ONE. 2007; 2(1): e150.

115. Leussink VI, Lehmann HC, Zu M, Hörste G, Hartung HP, Stüve O, Kieseier BC (2008). "Rituximab induces clinical stabilization in a patient with fulminant multiple sclerosis not responding to Natalizumab". Journal of Neurology 255(9):1436–8. doi:10.1007/s00415-008-0956-x.

116. Loyez doi:10.1371/journal.pone.0000150.g001

117. Ontaneda D (2019). "Progressive multiple sclerosis". Continuum (Minneap Minn). 25(3):736–52. doi:10.1212/CON.0000000000000727.

118. Turatti M, Gajofatto A, Rossi F, Vedovello M, Benedetti MD (2010). "Long survival and clinical stability in Marburg's variant multiple sclerosis". Neurological Sciences 31(6):807-11. doi:10.1007/s10072-010-0287-4.

Balo's concentric sclerosis

119. Bahador D, Litofsky, and Ahsan M (2013). "Baló's concentric sclerosis: Imaging findings and pathological correlation". J of Radiology Case Reports 7(6):1–8. doi:10.3941/jrcr.v7i6.1251.

120. Baló J (1928). "Encephalitis periaxialis concentrica". Archives of Neurology and Psychiatry 19(2): 242–4. doi:10.1001/archneurpsyc.1928.02210080044002.

121. Behrens J et al. (2018). “7-Tesla MRI of Balo's concentric sclerosis versus multiple sclerosis lesions”, Annals of clinical and translational neurology 5(8):900-12. https://doi.org/10.1002/acn3.572

122. Br ü ck W, Popescu B, Lucchinetti CF, Markovic ‐ Plese S, Gold R, Dietmar RT, and Metz I (2012). ″Neuromyelitis optica lesions may inform multiple sclerosis heterogeneity debate. https://doi.org/10.1002/ana.23621

123. Capello E and Mancardi GL (2004). "Marburg type and Balò's concentric sclerosis: Rare and acute variants of multiple sclerosis". Neurol. Sci. 25(Suppl):S361–3. doi:10.1007/s10072-

004-0341-1

124. Charles et al. (2015). "Multiple sclerosis lesion formation and early evolution revisited: A weekly high-resolution magnetic resonance imaging study". Multiple Sclerosis 22(6):761–9.doi:10.1177/1352458515600247.

125. Ertuğrul Ö, Çiçekçi E, Cudi Tuncer M, and Ufuk Aluçlu M (2018). "Balo's concentric sclerosis in a patient with spontaneous remission based on magnetic resonance imaging: A case report and review of literature". World J Clin Cases 6(11):447–54. doi:10.12998/wjcc.v6.i11.447.

126. Garbern J, Spence AM, and Alvord EC (1986). "Balo's concentric demyelination diagnosed pre- mortem". Neurology 36(12):1610–4. doi:10.1212/WNL.36.12.1610.

127. Grüter T, Metz I, Gahlen A, Kneiphof J, Stork L, Brück W, Gold R, and Kleiter I (2018). "Mitoxantrone treatment in a patient with multiple sclerosis and pattern III lesions". Clinical and Experimental Neuroimmunology 9(3):169–72. doi:10.1111/cen3.12466.

128. Hardy tA, Oliver TW, and Lucchinetti CF (2016). "Exploring the overlap between multiple sclerosis, tumefactive demyelination, and Baló's concentric sclerosis". Multiple Sclerosis Journal 22(8):986–92. doi:10.1177/1352458516641776.

129. Hardy TA, (2019). "Atypical inflammatory demyelinating syndromes of the central nervous system", Neuroimmune Diseases pp 543-6.

130. Hauser S. "Genetic susceptibility in MS" in Rare Neuroimmunologic Disorders Symposium.

131. Iannucci et al. (2000). "Vanishing Balò-like lesions in multiple sclerosis". J of Neurology, Neurosurgery & Psychiatry 69(3):399–400. doi:10.1136/jnnp.69.3.399.

132. Jarius S, König FB, Metz I, Ruprecht K, Paul F, Brück W, and Wildemann B (2017). "Pattern II and pattern III MS are entities distinct from pattern I MS: Evidence from cerebrospinal fluid analysis". J of Neuroinflammation 14(1):171. doi:10.1186/s12974-017-0929-z.

133. Jarius S, Würthwein C, Behrens JR, Wanner J, Haas J, Paul F, and Wildemann B (2018). "Baló's concentric sclerosis is immunologically distinct from multiple sclerosis: Results from retrospective analysis of almost 150 lumbar punctures". J. of Neuroinflammation 15(1):22. doi:10.1186/s12974-017-1043-y.

134. Karaarslan E, Altintas A, Senol U et al. (2001). "Baló's concentric sclerosis: Clinical and radiologic features of five cases". American Journal of Neuroradiology 22(7):1362–7.

135. Khonsari RH and Calvez V (2007). in Monk N (ed.). "The origins of concentric demyelination: Self- organization in the human brain". PLOS ONE.2 (1): e150. Bibcode:2007PLoSO...2..150K. doi:10.1371/journal.pone.0000150.

136. Kira J (2011). "Astrocytopathy in Balo's disease".Multiple Sclerosis 17(7):771–9. doi:10.1177/1352458511400475.

137. Laule C et al. (2008). "Myelin water imaging of multiple sclerosis at 7 T: Correlations with histopathology". NeuroImage 40(4):1575–80. doi:10.1016/j.neuroimage.2007.12.008.

138. Lindquist S (2007). "Histopathology and serial, multimodal magnetic resonance imaging in a multiple sclerosis variant". Multiple Sclerosis 13(4):471–82. doi:10.1177/1352458506071329.

139. Linnoila J and Chitnis T (2014). "Balo's concentric sclerosis in children: A case series". J of Child Neurology 29(5):603–7. doi:10.1177/0883073813517294.

140. Mahad DJ, Ziabreva I, Campbell G, Lax N, White K, Hanson PS, Lassmann H, and Turnbull DM (2009). "Mitochondrial changes

within axons in multiple sclerosis". Brain 132(5):1161–74. doi:10.1093/brain/awp046.

141. Moore GR, Berry K, Oger JJ, Prout AJ, Graeb DA, and Nugent RA (2001). "Baló's concentric sclerosis: surviving normal myelin in a patient with a relapsing-remitting clinical course". Multiple Sclerosis 7(6):375–82. doi:10.1177/135245850100700606.

142. Novoselova OM, Il'Ves AG, Savintseva ZI, Prakhova LN, Zaplakhova OV, and Bakhtiyarova KZ (2018). "A case-report of Balo's concentric sclerosis transformed into definite multiple sclerosis]".Zh Nevrol Psikhiatr Im S S Korsakova 118(8):103–6. doi:10.17116/jnevro2018118082103.

143. Popescu BF, Istvan P, and Lucchinetti CF (2013). "Pathology of multiple sclerosis: Where do we stand?".Continuum (MinneapMinn)19 (4Multiple Sclerosis):90121. doi:10.1212/01.CON.0000433291.23091.65.

144. Purohit et al. (2015). "Balo's concentric sclerosis with acute presentation and co-existing multiple sclerosis-Typical lesions on MRI". Case Reports in Neurology 7(1):44–50. doi:10.1159/000380813.

145. Qiao LC, Rone M, Khan D, Bedard M, Almazan G, Ludwin S, Kennedy T, and Antel J (2016). "Oligodendrogliopathy in multiple sclerosis: Relation to low glycolytic metabolic rate of oligodendrocytes(I10.004)", neurology 86(16) Supplement I10.004.

146. Roman-Filip C, Ungureanu A, and Pra*f*variu I (2018). "Baló-like lesion with psoriasis and autoimmune thyroiditis", Essays, UK.

147. Stork L, Ellenberger D, Beißbarth T, Friede T, Lucchinetti CF, Brück W, and Metz Imke (2018). "Differences in the responses to apheresis therapy of patients with 3 histopathologically classified immunopathological patterns of multiple sclerosis". JAMA Neurology 75(4):428–35. doi:10.1001/jamaneurol.2017.4842.

148. Stork et al. (2020). "Antibody signatures in patients with histopathologically-defined multiple sclerosis patterns". Acta Neuropathol. 139(3):547–64.doi:10.1007/s00401-019-02120-x.

149. Takeshi M et al. (2010). "Aquaporin-4 astrocytopathy in Baló's disease". Acta Neuropathologica 120(5):651–660. doi:10.1007/S00401-010-0733-7.

150. Woerner A(2014). "Bacterial toxin may trigger multiple sclerosis, research finds". Fox News. Marburg's acute multiple sclerosis

151. Capello E and Mancardi GL (2004). "Marburg type and Balò's concentric sclerosis: Rare and acute variants of multiple sclerosis". Neurol. Sci. 25(Suppl):S361–3. doi:10.1007/s10072-004-0341-1

152. Jeffery, Douglas R; Lefkowitz DS, Crittenden, and Jeffrey P (2004). "Treatment of Marburg's variant multiple sclerosis with Mitoxantrone". Journal of Neuroimaging 14(1):58– 62. doi:10.1111/j.1552-6569.2004.tb00217.x.

153. Labat E et al. (2019). "An extremely aggressive case of Marburg's disease treated with high dose Cyclophosphamide: A case report". Multiple Sclerosis and Related Disorders 31:51-3. https://doi.org/10.1016/j.msard.2019.03.014.

Schilder's diffuse myelinoclastic sclerosis

154. Afifi AK, Bell WE, Menezes AH, and Moore SA (1994). "Myelinoclastic diffuse sclerosis (Schilder's disease): Report of a case and review of the literature". J. Child Neurol. 9(4):398–403. doi:10.1177/088307389400900412.

155. Bacigaluppi S, Polonara G, Zavanone ML, Campanella R, Branca V, Gaini SM;,Tredici G, and Costa A (2009). "Schilder's disease: non-invasive diagnosis? :A case report and review". Neurological Sciences 30(5):421–30.

doi:10.1007/s10072-009-0113-z.

156. Fernández O, Fernández VE, and Guerrero M. (2015). "Demyelinating diseases of the central nervous system". Medicine 11(77):4601–9. doi:10.1016/j.med.2015.04.001.
157. Fontaine B (2001). "Borderline forms of multiple sclerosis". Rev. Neurol. (Paris) (in French) 157(8–9 Pt 2):929–34.
158. Garell PC, Menezes AH, Baumbach G, Moore SA, Nelson G, Mathews K, and Afifi AK (1998). "Presentation, management and follow-up of Schilder's disease". Pediatric Neurosurgery 29(2):86–91. doi:10.1159/000028695.
159. Garrido C, Levy-Gomes A, Teixeira J, and Temudo T (2004). "Schilder's disease: Two new cases and a review of the literature". Revista de Neurología (in Spanish) 39(8):734–8. doi:10.33588/rn.3908.2003023.
160. Jarius S et al. (2019). "Myelinoclastic diffuse sclerosis (Schilder's disease) is immunologically distinct from multiple sclerosis: Results from retrospective analysis of 92 lumbar punctures", J of Neuroinflammation. https://doi.org/10.1186/s12974-019-1425-4
161. Lacour de A, Guisado F, Zambrano A, Argente J, Acosta J, and Ramos C (1998). "Pseudotumor forms of demyelinating diseases: Report of three cases and review of the literature". Revista de Neurología (in Spanish) 27(160):966–70.
162. Leuzzi V, Lyon G, Cilio MR, Pedespan JM, Fontan D, Chateil JF, and Vital A (1999). "Childhood demyelinating diseases with a prolonged remitting course and their relation to Schilder's disease: Report of two cases". J. Neurol. Neurosurg. Psychiatry 66(3):407–8. doi:10.1136/jnnp.66.3.407.
163. Martin JJ and Guazzi GC (1991). "Schilder's diffuse sclerosis". Dev. Neurosci. 13(4–5):267–73. doi:10.1159/000112172.
164. (U.S.) National Institute of Neurological Diseases and Stroke (NINDS): Schilder's Disease Information Page (2009).
165. Poser CM (1961). "Leukodystrophy and the concept of dysmyelination". Arch Neurol. 4(3):323–32. doi:10.1001/archneur.1961.00450090089013.
166. Poser CM, Goutières F, Carpentier MA, and Aicardi J (1986). "Schilder's myelinoclastic diffuse sclerosis". Pediatrics 77(1):107–12.
167. Pretorius ML, Loock DB, Ravenscroft A, and Schoeman JF (1998). "Demyelinating disease of Schilder type in three young South African children: Dramatic response to corticosteroids". J. Child Neurol.13 (5):197–201. doi:10.1177/088307389801300501.
168. Schilder PF (1912). "Zur Kenntnis der sogenannten diffusen Sklerose (über Encephalitis periaxialis diffusa). Zeitschrift für die gesamte Neurologie und Psychiatrie" 10 Orig.: 1-60.

Tumefactive multiple sclerosis

169. Antonella et al. (2014). "Neuronavigation-guided biopsy for differential diagnosis of pseudotumoral demyelinating brain lesions". Interdisciplinary Neurosurgery 1(3):44–6. doi:10.1016/j.inat.2014.04.002
170. Arango JA, Uribe Uribe CS, and Toro González G (2013). "Lesser-known myelin-related disorders: Focal tumor-like demyelinating lesions". Neurologia 30(2):97–105.doi:10.1016/j.nrl.2013.06.004.
171. Balloy G et al. (2018). "Inaugural tumor-like multiple sclerosis: Clinical presentation and medium-term outcome in 87 patients". J Neurol. doi: 10.1007/s00415-018-8984-7
172. Bomprezzi R and Powers JM (2011). "IFNβ-1b may severely exacerbate Japanese optic-spinal MS in neuromyelitis optica spectrum: Japanese optic-spinal MS: Is it MS or

neuromyelitis optica and does the answer dictate treatment?". Neurology 77(2):195–6. doi:10.1212/WNL.0b013e318219dde5.

173. Broadfoot JR (2015). "Paraneoplastic tumefactive demyelination with underlying combined germ cell cancer". Pract Neurol. 15(6):451–5. doi:10.1136/practneurol-2015-001146.
174. Harirchian MH et al. (2015). "Emerging tumefactive MS after switching therapy from Interferon-beta to Fingolimod: A case report". Multiple Sclerosis and Related Disorders4(5):4002. doi:10.1016/j.msard.2015.05.007.
175. Harmel J, Ringelstein M, Ingwersen J, Mathys C, Goebels N, Hartung HP, Jarius S, and Aktas O (2014). "Interferon-β-related tumefactive brain lesion in a Caucasian patient with neuromyelitis optica and clinical stabilization with tocilizumab". BMC Neurol. 14(1):247. doi:10.1186/s12883-014-0247-3.
176. HellmannMA (2014). "Tumefactive demyelination and a malignant course in an MS patient during and following Fingolimod therapy". J Neurological Sciences 344(1–2):193–7. doi:10.1016/j.jns.2014.06.013.
177. Hussam YA, Al-Qudahl ZA, Huey-Jen L, Baisre A, and Nizar S (2011). "Tumefactive multiple sclerosis presenting as acute ischemic Stroke". J of Vascular and Interventional Neurology 4(2):21–3.
178. Ikeda K et al. (2011). "Repeated non-enhancing tumefactive lesions in a patient with a neuromyelitis optica spectrum disorder". Internal Medicine 50(9):1061–4. doi:10.2169/internalmedicine.50.4295.
179. Ikeguchi R et al. (2018). "Proton magnetic resonance spectroscopy differentiates tumefactive demyelinating lesions from gliomas, multiple sclerosis, and related disorders". doi:https://doi.org/10.1016/j.msard.2018.08.025
180. Kaeser MA, Scali F, Lanzisera FP, Bub GA, and Kettner NW (2011)."Tumefactive multiple sclerosis: An uncommon diagnostic challenge". J of Chiropractic Medicine 10:29-35.
181. Kaeser MA, Scali F, Lanzisera FP, Glenn BA, and Kettner NW (2011). "Tumefactive multiple sclerosis: An uncommon diagnostic challenge". Journal of Chiropractic Medicine 10(1):29–35. doi:10.1016/j.jcm.2010.08.002.
182. Kalavakunta JK, Tokala H, and Loehrke M (2011). "Solitary lesion in magnetic resonance imaging: tumor versus multiple sclerosis". The American Journal of the Medical Sciences 342(2):168. doi:10.1097/MAJ.0b013e318200d247.
183. Kantorová E, Marcinek J, Zeleňák K, Kantor K, Michalik J, Sivák Š, Kurča E, and Plank L (2015). "Tumefactive demyelination of the spinal cord: A case report". Spinal Cord. 53(12):877–80. doi:10.1038/sc.2015.52.
184. Kazuo F and Misu T (2015). "AQP4 in biopsied demyelinating lesions as a diagnostic clue to NMOSD and MS". Neurology 84(2):110–1. doi:10.1212/WNL.0000000000001135.
185. Kilic AK, Kurne AT, Oguz KK, Soylemezoglu F, and Karabudak R (2013). "Mass lesions in the brain: Tumor or multiple sclerosis? Clinical and imaging characteristics and course from a single reference center". Turk Neurosurg. 23(6):728–35. doi:10.5137/1019-5149.
186. Krysko K et al. (2015). "Clinical course, radiologic features and treatment response in patients with tumefactive demyelinating lesions in Toronto". Neurology 84(14): Supplement P4.018.
187. Lee Y et al. (2014). "Tumefactive multiple sclerosis in a patient on Fingolimod". Neurology 82(10): 226.
188. Lew K et al. (2016). "Role of therapeutic

plasma exchange in treatment of tumefactive multiple sclerosis-Associated low CD4 and CD8 levels". Case Rep Neurol. 8(2):179–84. doi:10.1159/000448704.

189. Lucchinetti CF, Gavrilova RH, Metz I, Parisi JE, Scheithauer BW, Weigand S, et al. (2008). "Clinical and radiographic spectrum of pathologically confirmed tumefactive multiple sclerosis". Brain 131(7): 1759–175. doi:10.1093/brain/awn098.
190. Mamilly A, Aslan A, Adeeb N, Al Asfari A, and Cuellar H (2020). "Tumefactive multiple sclerosis of the cervical spinal cord: A rare case report".Cureus 12(1):e6754. doi:10.7759/cureus.6754.
191. Masaki et al. (2014). "Gadolinium enhancement patterns oftumefactive demyelinating lesions: Correlations with brain biopsy findings and pathophysiology". J of Neurology261(10):1902-10. doi:10.1007/s00415-014-7437-1.
192. Moore GRW and Esiri MM (2011). "The pathology of multiple sclerosis and related disorders". Diagnostic Histopathology 17(5):225–31. doi:10.1016/j.mpdhp.2011.02.001.
193. Peterson JW and Trapp BD (2005). "Neuropathobiology of multiple sclerosis". Neurol Clin. 23(1): 107–29. doi:10.1016/j.ncl.2004.09.008.
194. Rissardo JP and Caprara ALF (2018). “Management of recurrent tumefactive multiple sclerosis: Case report and literature review, Asian J Neurosurg. 13(3):893–6. doi: 10.4103/ajns.AJNS_94_18
195. Rudick RA (2004). “Contemporary diagnosis and management of multiple sclerosis”. Pennsylvania: Handbooks in Health Care Co.
196. Sajja BR, Wolinsky JS, and Narayana PA (2009). "Proton magnetic resonance spectroscopy in multiple sclerosis". Neuroimaging Clin N Am. 19(1):45–58. doi:10.1016/j.nic.2008.08.002.
197. Steinhoff TB and Scott TF (2015). "Tumefactive demyelination with white matter necrosis following cessation of Natalizumab treatment". Neurological Cases 2(1).
198. Takeuchi T, Ogura M, Sato M, Kawai N, Tanihata H, Takasaka I, Minamiguchi H, Nakai M, and Itakura T (2008). "Late-onset tumefactive multiple sclerosis". Radiat Med. 26(9):549–52. doi:10.1007/s11604-008-0273-4.
199. Tintore M, Rovira A, Martinex MJ, Rio J, Diaz-Villoslada P, Brieva L et al. (2000). "Isolated demyelinating syndromes: Comparison of different MR imaging criteria to predict conversion to clinically definite multiple sclerosis". Am J Neuroradiol. 21(4):702–6.
200. Ujjawal R et al. (2016). "Neuromyelitis optica spectrum disorder with tumefactive demyelination mimicking multiple sclerosis: A rare case". Front. Neurol. 7:73. doi:10.3389/fneur.2016.00073.
201. Vaknin-Dembinsky et al. (2015). "Tumefactive demyelination following in vitro fertilization (IVF)". J Neurol Sci. 348(1–2):256–8. doi:10.1016/j.jns.2014.11.016.
202. Yiu EM, Laughlin S, Verhey LH, Banwell BL (2013). "Clinical and magnetic resonance imaging (MRI) distinctions between tumefactive demyelination and brain tumors in children". J Child Neurol. 29(5):654–65. doi:10.1177/0883073813500713.

Solitary demyelinating lesions

203. Ayrignac X, Carra-Dalliere C, Homeyer P, and Labauge P (2013). "Solitary sclerosis: Progressive myelopathy from solitary demyelinating lesion. A new entity?". Acta Neurol Belg. 113(4):533– 4.

doi:10.1007/s13760-013-0182-x.

204. Brunot E and Marcus JC (1999). "Multiple sclerosis presenting as a single mass lesion". Pediatr. Neurol.20(5):383–6. doi:10.1016/S0887-8994(98)00164-7.
205. Crayton HJ, Rossman HS (2006). "Managing the symptoms of multiple sclerosis: A multimodal approach". Clinical Therapeutics 28(4):445–60. doi:10.1016/j.clinthera.2006.04.005.
206. Fymat AL (2017a). "Management and treatment of glioblastoma", https://juniperpublishers.com/reprints.php?rs=surgery and https://juniperpublishers.com/view-reprints.php?rid-36.
207. Fymat AL (2017b). "Glioblastoma treatments: Where do we stand? (2017). MedPlus J of Cancer & Oncology Research 1(1)1-12.
208. Fymat AL (2017c). "Antiangiogenic targeting of early developing glioblastoma behind a weakened blood-brain barrier". J of Anti-Tumor Medicine & Prevention 2(3):1-6.
209. Fymat AL (2017d). "Nanomedicine as a precursor to precision Medicine for Glioblastoma Treatment", J of Current Opinions in Neurological Science 1(4):200-. 6.
210. Fymat AL (2017e). "Surgical and non-surgical management and treatment of glioblastoma: II. Recurring tumors", Open Access J of Surgery 7(1):1-7, doi: 10.19080/OAJS.2017.07.555703,
211. Fymat AL (2017f). "Surgical and non-surgical management and treatment of glioblastoma: I. Primary tumors", Open Access J of Surgery 7(2):1-8. doi: 10.19080/OAJS 2017 07 555706.
212. Lattanzi S (2012). "Progressive myelopathy from solitary demyelinating lesion". Neurology 79(4): 393. doi:10.1212/01.wnl.0000418061.10382.f7.
213. Lattanzi S (2012). "Solitary sclerosis: Progressive myelopathy from solitary demyelinating lesion". Neurology 79(4):393, author reply 393. doi:10.1212/01.wnl.0000418061.10382.f7.
214. Lebrun C, Cohen M, Mondot L, Ayrignac X, and Labauge P (2017). "A case report of solitary sclerosis: This is really multiple sclerosis". Neurology and Therapy pp 1–5.
215. Rathnasabapathi DR, Liene E, Krishnan A, Young C, Larner A, and Jacob A (2015). "Solitary sclerosis:Progressive neurological deficit from a spatially isolated demyelinating lesion: A further report". The Journal of Spinal Cord Medicine 38(4):551–5. doi:10.1179/2045772314Y.0000000283.
216. Schmalstieg WF, Mark KB, and Weinshenker BG (2012). "Progressive myelopathy from solitary demyelinating lesion". Neurology 78(8):540–4. doi:10.1212/WNL.0b013e318247cc8c.
217. Tohyama S et al. (2019). "Trigeminal neuralgia associated with solitary pontine lesion", PAIN: doi: 0.1097/j.pain.0000000000001777.
218. White LJ and Dressendorfer RH (2004). "Exercise and multiple sclerosis". Sports Med. 34(15):1077– 100. doi:10.2165/00007256-200434150-00005.