Multiple sclerosis: an overview

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ABSTRACT

Multiple sclerosis (MS) is an autoimmune disease in which body’s immune system eats away the protective sheath that covers nerves which interferes with the communication between brain and the rest of body. Ultimately this may result in deterioration of the nerves themselves a process that’s irreversible. Symptoms vary widely, depending on the amount of damage and the type of nerves affected. Patients with severe cases of multiple sclerosis may lose the ability to walk or speak. Multiple sclerosis can be difficult to diagnose early in the course of the disease because symptoms often come and go sometimes disappearing for months. There’s no cure for multiple sclerosis. However treatments can help treat attacks, modify the course of the disease and treat symptoms.

1. Introduction

Multiple sclerosis (shortened to MS, known as disseminated sclerosis or encephalomyelitis disseminata) is an inflammatory disease in which the fatty myelin sheaths approximately the axons of the brain and spinal cord are damaged, leading to demyelination and scarring in addition to a broad spectrum of signs and symptoms[1]. Disease onset is more in young adults and more common in women than man[1]. It has a prevalence rate ranges between 2 and 150 per 100,000[2]. An alternative hypothesis has been proposed implicating chronic cerebrospinal venous insufficiency (CCSVI) as a potential cause of multiple sclerosis (MS)[3]. MS affects the ability of nerve cells in the brain and spinal cord to communicate with each other efficiently. Nerve cells communicated by transfer electrical signals called action potentials which are contained within an insulating substance called myelin (Figure 1).

Multiple sclerosis is a chronic disease of the central nervous system that often has a disabling effect, resulting in reduced quality of life for patients. Bladder dysfunction is a common and distressing symptom. A number of inflammatory, infectious, neoplastic and idiopathic disorders affect the eye and the central nervous system (CNS) concurrently or at different time frames.

Figure 1.

These conditions pose a diagnostic challenge to the
 Several subtypes or patterns of progression, have been classified. Subtypes 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 therapeutic decisions. In 1996 the United States National Multiple Sclerosis Society standardized four subtype definitions[6] (Figure 2).

![Subtypes of Multiple Sclerosis](image)

2. Medical discovery

First person to recognize multiple sclerosis as a distinct disease was French neurologist Jean–Martin Charcot (1825–1893)[60]. He summarized previous reports and added his own clinical and pathological observations, the compilation of old and new knowledge had helped Charcot to elaborate these diseases and Charcot called MS as sclerose en plaques. The three signs of MS known as Charcot’s triad are

1) Nystagmus,
2) Intention tremor,
3) Telegraphic speech, though these are not unique to MS.

Charcot also observed cognition changes, describing his patients as having “marked enfeeblement of the memory” and “conceptions that formed slowly”.

Prior to Charcot, Robert Carswell (1793–1857) a British professor of pathology, and Jean Cruveilhier (1791–1873) a French professor of pathologic anatomy had worked on clinical details of MS but did not identify it as a separate disease[66]. Specifically Carswell described the injuries he found as a remarkable lesion of the spinal cord accompanied with atrophy[1]. Multiple sclerosis may have a non-progressive symptomatology for decades; however, it is not clear whether the disease activity may abate completely. Relapses are a common feature of relapsing–remitting multiple sclerosis (RRMS) and increasing severity has been shown to be associated with higher healthcare costs, and to result in transient increases in disability. Increasing disability likely impacts work and leisure productivity, and lowers quality of life[67,68].

2.1. Classification

a) The relapsing remitting subtype is characterized by unpredictable relapses followed by periods of months to years of relative quiet (remission) with no new signs of disease activity. Deficits suffered during attacks may either resolve or leave sequelae, the latter being more common as a function of time[1]. This describes the initial course of 80% of individuals with MS[1]. Exercise therapy is an important part of symptomatic and supportive treatment in patients with multiple sclerosis (PwMS). According to the literature, equine–assisted therapies—such as therapeutic horseback riding (THR) and hippotherapy (HT) are exercise therapies that can have positive physical effects on coordination, muscle tone, postural alignment, stiffness/flexibility, endurance and strength, correcting abnormal movement patterns and improving gait and balance[8] although patients will still accrue some degree of disability in the long term[1]. The relapsing–remitting subtype usually begins with a clinically isolated syndrome (CIS). In CIS a patient has an attack suggestive of demyelination but does not fulfill the criteria for multiple sclerosis[1,9]. However only 30 to 70% of persons experiencing CIS later develop MS[8]. Secondary progressive MS (sometimes called galloping MS) describes around 65% of those with an initial relapsing–remitting MS who then begin to have progressive neurologic decline between acute attacks without any definite periods of
Removal and minor remissions may appear. Experimental Autoimmune Encephalomyelitis (EAE) is the most commonly used animal model for Multiple Sclerosis (MScl). CSF metabolomics in an acute EAE rat model was investigated using targeted LC–MS and GC–MS.

Research into multiple sclerosis (MS) has shown that cells purportedly important to myelin repair within the CNS, namely neural stem cells (NSC) and oligodendrocyte progenitor cells (OPC), are recruited to active lesion sites during the course of the disease. It is characterized by progression of disability from onset with no, or only occasional and minor remissions and improvements. The age of onset for the primary progressive subtype is later than for the relapsing remitting, but similar to mean age of progression between the relapsing remitting and the secondary progressive. In both cases it is around 40 years of age. Progressive relapsing MS describes those individuals who from onset have a steady neurologic decline but also suffer clear superimposed attacks. This is the least common of all subtypes. Peripheral facial palsy is a clinical entity, which may be presented as the first symptom of multiple sclerosis (MS). Although MS is mostly a multifocal chronic inflammation of the central nervous system, peripheral nervous system can also be involved. Multiple sclerosis also behaves differently in children, taking more time to reach the progressive stage. Nevertheless they still reach it at a lower mean age than adults.

Multiple sclerosis is a complex neurodegenerative disease, thought to arise through autoimmunity against antigens of the central nervous system. The autoimmunity hypothesis fails to explain why genetic and environmental risk factors linked to the disease in one population tend to be unimportant in other populations. Multiple sclerosis (MS) is a chronic inflammatory autoimmune demyelinating disease of the central nervous system. It affects approximately 400,000 people in the United States and onset is usually during young adulthood. There are four clinical forms of MS, of which relapsing remitting type is the most common. As the etiology of MS is unknown, finding a cure will remain challenging.

Ankylosing spondylitis is reported to involve not only the joints but also neurologic systems as well. The association between multiple sclerosis and alleles of the major histocompatibility complex (MHC) in humans increase the probability of suffering MS. The risk of acquiring MS is higher in relatives of a person with the disease than in the general population, especially in the case of siblings, parents, and children. The disease has an overall familial recurrence rate of 20%. In the case of monozygotic twins, concordance occurs only in about 35% of cases while it goes down to around 5% in the case of siblings and even lower in half-siblings. This indicates susceptibility is partly polygenically driven. It seems to be more common in some ethnic groups than others. Apart from familial studies specific genes have been linked with MS. Differences in the human leukocyte antigen (HLA) system a group of genes in chromosome 6 that serves as the major histocompatibility complex (MHC) in humans increase the probability of suffering MS. The most consistent finding is the association between multiple sclerosis 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.
sun[22,24]. Severe stress may also be a risk factor although evidence is weak[22]. Smoking has also been shown to be an independent risk factor for developing MS. Association with occupational exposures and toxins mainly solvents has been evaluated, but no clear conclusions has been reached.[22] Vaccinations were also considered as causal factors for the disease however most studies show no association between MS and vaccines.[22] Depression and anxiety have been reported in patients with multiple sclerosis (MS) and in patients with clinically isolated syndrome (CIS). However, the precise mechanisms that lead to depressive and anxiety symptoms in these patients are still unclear.[23].

**Figure 3.** HLA region of Chromosome 6. Changes in this area increase the probability of suffering MS.

Complex association analysis of copaxone (glatiramer acetate) immunotherapy efficacy with allelic polymorphism in the number of immune response genes, which encode interferon beta (IFNB1), transforming growth factor beta1 (TGFB1), interferon gamma (IFNG), tumor necrosis factor (TNF), interferon alpha/beta receptor 1 (IFNAR1), CC chemokine receptor 5 (CCR5), interleukin 7 receptor alpha subunit (IL7RA), cytotoxic T-lymphocyte antigen 4 (CTLA4) and HLA class II histocompatibility antigen beta chain (DRB1) was performed with APSampler algorithm for 285 multiple sclerosis patients of Russian ethnicity. [25] Gout occurs less than would statistically be expected in people with MS and low levels of uric acid have been found in MS patients as compared to normal individuals. This led to the theory that uric acid protects against MS although its exact importance remains unknown[26].

### 2.4. Infections

Many microbes have been founded to be potential infectious triggers of MS. Genetic susceptibility can explain some of the geographic and epidemiological variations in MS incidence like the high incidence of the disease among some families or the risk decline with genetic distance but does not account for other phenomena such as the changes in risk that occur with migration at an early age. Different hypotheses have elaborated on the mechanism by which this may occur. According to hygiene hypothesis which proposes that exposure to several infectious agents early in life is protective against MS the disease being a response to a later encounter with such agents[1]. According to prevalence hypothesis which proposes that the disease is due to a pathogen which was more common in regions of high MS prevalence. This pathogen is very common causing in most individuals an asymptomatic/persistent infection. Only in a few cases and after many years since the original infection does it cause demyelination[27]. The hygiene hypothesis has received more support than the prevalence hypothesis.

Evidence for viruses as a cause includes the presence of oligoclonal bands in the brain and cerebrospinal fluid of most patients the association of several viruses with human demyelination encephalomyelitis and induction of demyelination in animals through viral infection[28]. Human herpes viruses are a candidate group of viruses linked to MS. Individuals who have never been infected by the Epstein Barr virus have a reduced risk of having the disease and those infected as young adults have a greater risk than those who had it at a younger age[1]. 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 at a later moment with the causative virus that is the trigger for the disease.[1] Other diseases that have also been related with MS are measles mumps and rubella[1].

### 2.5. Pathophysiology

#### 2.5.1. Blood–brain barrier breakdown

The blood brain barrier is a capillary system that should prevent entrance of T cells into the nervous system. The blood brain barrier is normally not permeable to these types of cells, unless triggered by infection or a virus which decreases the integrity of the tight junctions forming the barrier. When the blood brain barrier regains its integrity typically after infection or virus has cleared the T cells are trapped inside the brain.

#### 2.5.2. Auto immunology

MS is currently believed to be an immune-mediated disorder mediated by a complex interaction of the individual’s genetics and as yet unidentified environmental insults. Damage is believed to be caused by the patient’s own immune system. The immune system attacks the nervous system, possibly as a result of exposure to a
molecule with a similar structure to one of its own (Figure 4).

Figure 4. Demyelination in MS. On Klüver Barrera myelin staining, decoloration in the area of the lesion can be appreciated.

2.5.3. Lesions

The name multiple sclerosis refers to the scars (scleroses better known as plaques or lesions) that form in the nervous system. MS lesions most commonly involve white matter areas close to the ventricles of the cerebellum brain stem basal ganglia and spinal cord and the optic nerve. 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 is rarely involved.

More specifically, MS destroys oligodendrocytes, the cells responsible for creating and maintaining a fatty layer known as the myelin sheath which helps the neurons carry electrical signals. MS results in a thinning or complete loss of myelin and as the disease advances, the cutting (transsection) of the neuron’s extensions or axons. When the myelin is lost a neuron can no longer effectively conduct electrical signals. A repair process called remyelination takes place in early phases of the disease, but the oligodendrocytes cannot completely rebuild the cell’s myelin sheath. The pathways leading to autoimmunity remain enigmatic despite numerous lines of experimental inquiry and epidemiological evidence. The mechanisms leading to the initiation and perpetuation of specific diseases such as primary biliary cirrhosis (PBC) or multiple sclerosis (MS) remain largely enigmatic. Repeated attacks lead to successively fewer effective remyelinations until a scar like plaque is built up around the damaged axons[20]. Amyloid precursor protein (APP) accumulation in axonal ovoids is a sensitive marker for acute axonal injury in multiple sclerosis (MS) lesions[30].

2.5.4. Inflammation

Apart from demyelination, the other pathologic hallmark of the disease is inflammation. According to a strictly immunological explanation of MS the inflammatory process is caused by T cells, a kind of lymphocyte. Lymphocytes are cells that play an important role in the body’s defenses. In MS T cells gain entry into the brain via the previously described blood brain barrier. Evidence from animal models also point to a role of B cells in addition to T cells in development of the disease. The T cells recognize myelin as foreign and attack it as if it were an invading virus. This triggers inflammatory processes stimulating other immune cells and soluble factors like cytokines and antibodies. Leaks form in the blood brain barrier which in turn causes a number of other damaging effects such as swelling activation of macrophages and more activation of cytokines and other destructive proteins. Following the recent approval of the first oral therapy for multiple sclerosis (MS), fingolimod, multiple other oral compounds, and also a number of monoclonal antibodies (mab) are currently in phase III clinical testing[31].

3. Diagnosis

Multiple sclerosis can be difficult to diagnose since its signs and symptoms may be similar to other medical problems. Electromagnetic-field therapy has beneficial short-term effects in multiple sclerosis (MS) patients with major fatigue, but long-term data are lacking.[1][2][3] Medical organizations have created diagnostic criteria to ease and standardize the diagnostic process especially in the first stages of the disease.[1] Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS) while neuromyelitis optica (NMO) is an inflammatory disease of the CNS that selectively affects the optic nerves and spinal cord.[33] Currently the McDonald criteria focus on a demonstration with clinical laboratory and radiologic data of the dissemination of MS lesions in time and space for non invasive MS diagnosis, though some have stated that the only proved diagnosis of MS is autopsy or occasionally biopsy where lesions typical of MS can be detected through histopathological techniques[1,34,35].

Clinical data alone may be sufficient for a diagnosis of MS if an individual has suffered separate episodes of neurologic symptoms characteristic of MS[34]. Since some people seek medical attention after only one attack other testing may hasten and ease the diagnosis. The most commonly used diagnostic tools are neuroimaging, analysis of cerebrospinal fluid and evoked potentials. Magnetic resonance imaging of the brain and spine shows areas of demyelination (lesions or plaques). Multiple sclerosis (MS) is a complex autoimmune disease of the central nervous system characterized by chronic inflammation, demyelination, and axonal damage. As microRNA (miRNA)–dependent alterations in gene expression in hematopoietic cells are critical for mounting an appropriate immune response, miRNA deregulation may result in defects in immune tolerance[34,36]. Testing of cerebrospinal fluid obtained from a lumbar puncture can provide evidence of chronic inflammation of the central nervous system. Treatment of multiple sclerosis (MS)
with disease—modifying drugs (DMDs) can reduce relapse frequency and delay disability progression. Although adherence to DMDs is difficult to measure accurately, evidence suggests that poor adherence is common and can compromise treatment success. [34][37] The nervous system of a person with MS responds less actively to stimulation of the optic nerve and sensory nerves due to demyelination of such pathways. These brain responses can be examined using visual and sensory evoked potentials.[38]

3.1. Management

Although there is no known cure for multiple sclerosis, several therapies have proven helpful. The primary aims of therapy are returning function after an attack, preventing new attacks and preventing disability. As with any medical treatment, medications used in the management of MS have several adverse effects. Alternative treatments are pursued by some patients despite the shortage of supporting comparable replicated scientific study.

3.2. Acute attacks

During symptomatic attacks, administration of high doses of intravenous corticosteroids, such as methylprednisolone, is the routine therapy for acute relapses.[1] Although generally effective in the short term for relieving symptoms corticosteroid treatments do not appear to have a significant impact on long term recovery.[39] Oral and intravenous administration seems to have similar efficacy. [40] Consequences of severe attacks which do not respond to corticosteroids might be treated by plasmapheresis.[1]

3.3. Disease-modifying treatments:

Five drugs where used in diseases modifying treatments:
*Fingolimod
*Interferon beta–1a and interferon beta–1b
*Glatiramer acetate
*Mitoxantrone
*Natalizumab[1]

The interferons and glatiramer acetate are delivered by frequent injections varying from once–per–day for glatiramer acetate to once per week (but intra muscular). Natalizumab and mitoxantrone are given by IV infusion at monthly intervals. The incidence of seizures is generally accepted to be greater in patients with multiple sclerosis (MS) than in the general population, and rarely, MS can initially present as seizure. To present a case report of seizure as the initial symptom of MS, to quantify the occurrence of seizures among MS patients, and to classify patients according to when seizures occur relative to onset of MS. [1][41] Several trials have demonstrated improved outcomes following inpatient rehabilitation for Multiple Sclerosis patients. Two populations were studied: patients in relapse and patients with no active medical problems recruited from the community. In every day practice, most admissions for MS inpatient rehabilitation aim to improve function following sudden deterioration.[42] Mitoxantrone may be the most effective of them all; however, it is generally not considered as a long–term therapy as its use is limited by severe secondary effects.[1] The earliest clinical presentation of RRMS is the clinically isolated syndrome (CIS). Treatment with interferons during an initial attack can decrease the chance that a patient will develop clinical MS.[1]

Treatment of progressive MS is more difficult than relapsing remitting MS. Mitoxantrone has shown positive effects in patients with secondary progressive and progressive relapsing courses. It is moderately effective in reducing the progression of the disease and the frequency of relapses in patients in short term follow up.[43] Achieving good adherence to self–injected treatments for multiple sclerosis can be difficult. Injection devices may help to overcome some of the injection–related barriers to adherence that can be experienced by patients.[44] Immune system related factors are important in the pathogenesis of multiple sclerosis (MS). [45] Some patients taking glatiramer experience a post injection reaction manifested by flushing chest tightness heart palpitations breathlessness and anxiety which usually lasts less than thirty minutes.[46] More dangerous but much less common are liver damage from interferons[47] severe cardiotoxicity infertility and acute myeloid leukemia of mitoxantrone[1] and the putative link between natalizumab and some cases of progressive multifocal leukoencephalopathy.[1]

3.4. Research directions

Research directions on MS treatments include investigations of MS pathogenesis and heterogeneity research of more effective convenient or tolerable new treatments for RRMS creation of therapies for the progressive subtype’s neuroprotection strategies and the search for effective symptomatic treatments.[74] A number of treatments that may curtail attacks or improve function are under investigation. Emerging agents for RRMS that have shown promise in phase 2 trials include alemtuzumab daclizumab rituximabdirucotide BHT 300 cladribine, dimethyl fumarate, estriol, fingolimod, laquinimod, minocycline,statins, temsirolimus and teriflunomide.[74] In 2010, an FDA committee recommended approving fingolimod for the treatment of MS attacks[75] and on September 22, 2010, fingolimod (trade name Gilenya) became the first oral drug approved by the Food and Drug Administration to reduce relapses and delay disability progression in patients with relapsing forms of multiple sclerosis.[76] Clinical trials of fingolimod have demonstrated side effects in treated patients including cardiovascular conditions, macular edema, infections, liver toxicity and malignancies.[77][78] Much interest has been focused on the prospect of utilizing vitamin D analogs in the prevention and management of CIS and MS, especially given its possible role in the pathogenesis of the disease. While there is anecdotal evidence of benefit
for low dose naltrexone,[79] only results from a pilot study in primary progressive MS have been published.[80]

3.5. Disease biomarkers

The variable clinical presentation of MS and the lack of diagnostic laboratory tests lead to delays in diagnosis and the impossibility of predicting diagnosis. New diagnostic methods are being investigated. These include work with anti myelin antibodies, analysis of microarray expression and studies with serum and cerebrospinal fluid but none of them has yielded reliable positive results.[81] Currently there are no clinically established laboratory investigations available that can predict prognosis. However, several promising approaches have been proposed. Investigations on the prediction of evolution have centered on monitoring disease activity. Disease activation biomarkers include interleukin 6 nitric oxide and nitric oxide synthase, osteopontin and fetuin-A.[81] On the other hand since disease progression is the result of neurodegeneration the roles of proteins indicative of neuronal axonal and glial loss such as neurofilaments, tauand N acetylaspartate are under investigation.[81] A final investigative field is work with biomarkers that distinguish between medication responders and nonresponders.[81]

3.6. Chronic cerebrospinal venous insufficiency

During 2008, Italian vascular surgeon Paolo Zamboni reported research suggesting that MS involves a vascular disease process he referred to as chronic cerebrospinal venous insufficiency (CCSVI, CCVI), in which veins from the brain are constricted. He found CCSVI in the majority of MS patients, performed a surgical procedure to correct it and claimed that 73% of patients improved.[82] Concern has been raised with Zamboni’s research as it was neither blinded nor controlled[83] and further studies have had variable results. This has raised serious objections to the hypothesis of CCSVI originating multiple sclerosis. The neurology community currently recommends not using the proposed treatment unless its effectiveness is confirmed by controlled studies, the need for which has been recognized by the scientific bodies engaged in MS research.

4. Conclusion

Multiple sclerosis (MS) is an incurable neurological illness that frequently causes chronic disability. There is a great deal of ongoing research in multiple sclerosis, and there continues to be a focus on the immune system in investigational therapies. In addition, scientists are trying to develop techniques that allow brain cells to generate new myelin or that prevent the death of nerves. Other promising approaches include the use of precursor (neuronal stem or progenitor) cells that could be implanted into the brain or spinal cord to repopulate areas of missing cells. Future therapy may involve methods designed to improve impulses traveling over the damaged nerves. Scientists also are exploring the effects of diet and other environmental factors on multiple sclerosis. The selection of drug treatment/therapy should be made after the patient with multiple sclerosis has been properly informed of drug efficacy, particular FDA approved uses administration routes risks of adverse events and methods to enhance tolerability and compliance. The presented review would be beneficial for the researchers working in the field of multiple sclerosis treatment to look forward for more effective strategies so as to eradicate this disease completely.

Conflict of interest statement

We declare that we have no conflict of interest.

References


[73] FDA press release on approval of Gilenya


