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An Overview of the History, Pathophysiology, and Genetic Polymorphisms of Multiple Sclerosis

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Multiple sclerosis (MS) is a chronic disorder of the central nervous system (CNS) characterized by an autoimmune response directed against myelin proteins and other unidentified antigens, resulting in demyelination and dense astrogliosis in the white substance of the CNS (Mohamed ., et al., 2024) (Aharoni et al ., 2021). The oldest and best recorded of the early reports of MS concerns St Lidwina of Schiedam in Holland. Knowledge of her symptoms comes from a biography written shortly after her death in 1433. In 1396, following a fall whilst skating, Lidwina developed walking difficulties, headaches and violent pains in her teeth. Within a few years, she was walking with difficulty and a weakness in her face caused her lip to droop on one side.

1. Introduction

Multiple sclerosis definition and history

Multiple sclerosis (MS) is a chronic disorder of the central nervous system (CNS) characterized by an autoimmune response directed against myelin proteins and other unidentified antigens, resulting in demyelination and dense astrogliosis in the white substance of the CNS (Mohamed ., et al., 2024) (Aharoni et al ., 2021).

The oldest and best recorded of the early reports of MS concerns St Lidwina of Schiedam in Holland. Knowledge of her symptoms comes from a biography written shortly after her death in 1433. In 1396, following a fall whilst skating, Lidwina developed walking difficulties, headaches and violent pains in her teeth. Within a few years, she was walking with difficulty and a weakness in her face caused her lip to droop on one side. Throughout the remainder of her life, Lidwina's condition slowly deteriorated, although with apparent periods of remission (Murray et al ., 2009).

. However, the first systematic description of this new disease is from 1868 when Professor Charcot reported about “sclerose en plaques”. He described MS lesions in detail and reported on inflammation and the scarring of the nerves at these sites. He attributed symptoms to impaired conduction in the central nervous system, though with periods of remission, and identified the 'triad' of symptoms - nystagmus (unsteadiness of the eyes), scanning speech and intention tremor - as indicators of multiple sclerosis (Murray et al ., 2009).

Disease sub-types

The Four Types of Multiple Sclerosis and Their Symptoms

1. Relapsing-Remitting MS (RRMS): The most common type of MS is called relapsing-remitting MS (RRMS) accounting for up to 85% of patients. It is defined by temporary periods called relapses, flare-ups, or exacerbations when symptoms appear. These attacks are followed by periods of remission when the symptoms may disappear or subside. Remissions can last anywhere from weeks to months or years. Approximately 85% of people with MS are initially diagnosed with RRMS (Brownlee WJ et al., 2014).

2. Secondary-Progressive MS (SPMS): Over time, RRMS may advance to the secondary progressive phase: secondary progressive MS (SPMS). This type of MS does not have the distinctive remissions, flare-ups, or plateaus that RRMS does, but instead is characterized by slowly worsening symptoms and neurologic function. Without treatment, approximately half of the individuals with RRMS convert to SPMS within 10 to 20 years (Pasquali L,et al., 2015).

3- Primary-Progressive MS (PPMS): People diagnosed with primary- progressive MS (PPMS) have symptoms that steadily worsen with no periods of remission and flare-ups. Approximately 10% of people with MS are diagnosed with this form of the condition. (Pasquali L,et al., 2015).

4- Progression-Relapsing MS (PRMS): A small percentage of individuals may be diagnosed with a relatively rare type of MS known as progression-relapsing MS (PRMS). This type of MS steadily worsens from the onset of the first symptoms, regardless of relapses or periods of remission. Approximately 5% of people with MS are diagnosed with PRMS (Nelson et al ., 2016).

Epidemiology

MS is one of the most prevalent neurologic illnesses in the world and, in many countries, the leading cause of non-traumatic neurologic impairment in young people. MS affects around 400,000 people in the United States and 2.5 million worldwide (Dilokthornsakul et al., 2016).

MS is now more prevalent among women; however, this was not always the case. In the early 1900s, the sex ratio was about equal. Since then, the sex ratio in most industrialized nations has progressively increased and is close to 3:1 (F: M) ((Dilokthornsakul et al., 2016).

. Smoking raises MS risk by about 50% (Palacios et al., 2011). Although the average age of onset is between 20 and 40 years, the disease can manifest at any age. Almost 10% of cases are diagnosed before the age of 18. In some cases, MS diagnosed after the age of 50 is known as "late-onset multiple sclerosis" (LOMS), which is a rare case. Populations of European ancestry are estimated to have a prevalence of one in 1000. Less is known about prevalence among non-European groups, and most research points to a lower frequency among

individuals of East Asian and African heritage. Recent research has shown that African-American communities have a prevalence rate comparable to European communities (Wallin, et al., 2012).

MS has a prevalence gradient dependent on latitude, with a higher incidence in the northern latitudes of Europe and North America. Observations indicating varied genetic susceptibility factors have also been observed in distinct human subpopulations, independent of latitude, indicating the interaction of poorly understood genetic and environmental components. Multiple studies have shown that populations that relocate to regions with a higher incidence of MS during infancy have a higher chance of developing the disease (Huang et al., 2017).

Pathophysiology of MS

MS refers to the formation of plaques in CNS along with inflammation, demyelination, axonal damage, and axonal loss. These plaques are located in the brain and spinal cord, mainly in the white matter surrounding the ventricles, optic nerves and tracts, corpus callosum, cerebellar peduncles, long tracts, and subpial area of the spinal cord and brainstem, as well as gray matter. MS is considered an autoimmune disease caused by autoreactive immune cells that traverse BBB and attack the CNS. Regular deletion of autoreactive immune cells during development occurs in the thymus or bone marrow through central tolerance B cells. Although some may escape this process and be released into circulation, peripheral tolerance mechanisms prevent them from causing disease in most cases. The impaired function of regulatory T cells and the resistance of autoreactive T cells to suppression are two mechanisms through which peripheral tolerance might fail. A complicated interaction between genetic and environmental risk factors may affect the activity and activation of these autoreactive cells, therefore contributing to the development of disease (Zéphir et al ., 2018).

The primary T cell subsets implicated in MS include CD8+ T cells, CD4+ Th1 cells, and Th17 cells. Interferon-gamma, IL-17, and granulocyte-macrophage colony-stimulating factors are cytokines produced by autoreactive T cells that may contribute to the pathophysiology of MS. The increased immunoglobulin in cerebral fluid suggests a role for B cells in MS. Intrathecal production of oligoclonal immunoglobulins, also known as oligoclonal bands (OCBs), is a diagnostic feature of MS. In MS, the majority of B cells in cerebrospinal fluid (CSF) and brain parenchyma are CD27+ memory B cells. Memory B cells are clonally enlarged in the CSF and brain parenchyma and exhibit somatic hypermutation and class-switched immunoglobulin transcripts. Furthermore, the overlap of the CSF immunoglobulin proteomes and the B cell immunoglobulin transcriptomes provides evidence that antibody-secreting cells derived from clonally expanded B cells within the CNS are a significant source of excessive intrathecal clonal immunoglobulin production, as demonstrated by the presence of OCBs in CSF(Ochi, H. 2021) .

Meninges in MS patients include inflammatory B cell infiltrates, and a greater load of these injects to the severity of cortical lesions, neurodegeneration, and clinical impairment. B cells may serve as Epstein-Barr Virus (EBV) reservoirs . After EBV infection, B cells transform into antigen-processing cells, resulting in a more precise presentation of antigens. Recombinant human myelin oligodendrocyte glycoprotein was shown to be internalized and cross-presented by EBV-infected B-cells, which were efficiently identified by cytotoxic CD8+ T-cells. Furthermore, B cells obtained from MS patients had more CD40 on their surface,

indicating that B cells deliver antigens more effectively. Increased expression of B cell activation markers in individuals with relapsing-remitting multiple sclerosis (RRMS) was related to a high degree of neurodegeneration, as indicated by a rise in the number of T1 hyperintense lesions and a decrease in brain volume. In addition to B-cell-related diseases, loss of normal functioning in the effector T-cell population can contribute to the course of MS. In healthy people, CD8+ cytotoxic T cells that eliminate EBV-infected lymphoblastoid cell lines keep EBV infection under control. Since particular cytotoxic CD8+ cells are prepared to identify and kill infected cells that express EBV latent proteins, they will be referred to as "latency-specific T cells" from now on. During MS exacerbation, the EBV-specific T-cell population expands, and the latency-specific CD8+ T-cell activity increases. However, as MS progresses, latency-specific CD8+ T-cells exhibit a fatigued phenotype and cannot inhibit the proliferation of latently infected cells. This results in a vicious loop in which an increased number of infected cells inhibits the autoregulatory system and further depletes T cells. Recurrent relapses can be linked to poor management of EBV reactivation, leading to increased infection of naive B cells and viral generation (Guan et al ., 2019).

Antigen presentation to T cells and releasing chemicals that may harm oligodendrocytes are additional pathogenic pathways involving B cells in MS . Microglia and macrophages release many cytokines, including tumor necrosis factor (TNF)-α, and interleukin (IL)-1β, which can contribute to neurodegeneration through cytokine-induced cell death, inhibition of astrocytic glutamate reuptake, and induction of dysfunctional ribonucleic acid-binding proteins. Microglia and macrophages can also release glutamate, which might contribute to glutamate excitotoxicity and neurodegeneration. Microglia and macrophages produce reactive oxygen/nitrogen species, which can contribute to dementia by generating oxidative stress and mitochondrial damage. Microglia can also express anti-inflammatory phenotypes, promoting remyelination (Ward et al., 2022).

Genetic polymorphisms and MS

The cause of MS is unknown; however, susceptibility to MS is thought to be conferred by a combination of genetic and environmental factors (Olsson et al., 2017) (Ismail et al ., 2023)

The risk of MS is increased in first-degree relatives (siblings, 5%; parents and children, 2%) and 1% in second-degree and third-degree relatives. These data strongly support a genetic impact on MS susceptibility. So far, several genes have been identified to be involved in disease susceptibility that have mostly functions in the immune system encouraging the hypothesis of an underlying autoimmune process (Sawcer et al., 2014).

HLA genes

The human leukocyte antigen (HLA) exerts the largest genetic contribution to MS susceptibility but exactly how it alters the risk of developing MS is not yet fully understood. Association studies based first on serological typing and more recently on genome-wide association studies (GWAS) have been conducted for MS and other autoimmune diseases and have identified specific HLA-DR/DQ genes. However, the remarkably strong linkage disequilibrium (LD) across the HLA region has hampered the unequivocal ascertainment of the primary disease-risk HLA gene. This Class II association has been mapped to the DRB5*0101- DRB1*1501-DQA1*0102- DQB1*0602 haplotype in the North European

population. These alleles are almost always present together in this population, making it impossible to distinguish the primary association. The mechanism for the strong LD in these HLA haplotypes has been shown to be consistent with a functional epistatic interaction between DRB1*1501 and DRB5*0101 alleles(Goodin et al., 2021).

On the other hand, association studies in African-American populations have suggested that the DRB1*1501 allele itself determines MS-associated susceptibility (Goodin et al., 2021).

However, in other populations, the risk allele or haplotype is different or does not contain DRB1*1501 as in Sardinians where MS is associated with the DRB1*0301–DQA1*0501–DQB1*0201 and DRB1*0405– DQA1*0501–DQB1*0301 haplotypes, or in African–Brazilian MS patients where the strongest association was observed with DQB1*0602 rather than DRB1*1501 (Delfan et al., 2021)

In Caucasians, heterogeneity at the DRB1 locus has also been found with respect to MS risk. In Canadian MS families it has been observed that some DRB1*1501 haplotypes determine susceptibility while others do not and that DRB1, DQA1 and DQB1 alleles contribute to MS susceptibility through epistatic interactions suggesting haplotypic rather than allelic HLA association (Alcina et al .,2012).

Variation in gene transcription is important in mediating disease susceptibility. Gene transcript abundance might be modified by polymorphisms in regulatory elements. In particular, much of the variation in gene expression levels and alternative splicing can be inherited . Polymorphisms that affect the expression levels of a gene are most often found near the gene itself, especially near the transcription start site (Alonge et al., 2020).

NON-HLA GENES AND MS

These genes were the major non-HLA gene that showed potential correlation with MS, along with their contribution to normal physiological conditions. obtained after a vigorous search conducted, using PubMed, from the published articles dated from January 2005 till January 2023 (Borjac et al .,2023).

Cluster of Differentiation 58 (CD58)

CD58 encodes for a glycosylated cell adhesion molecule known as lymphocyte-associated antigen 3(LFA3) that is found on human chromosome 1p13. It is present on the surface of antigen-presenting cells (APCs), especially macrophages, and is able to promote their specific adherence to the CD2 ligand on the T-cell surface. A whole-genome association scan has proposed that genetic variations in CD58 are associated with MS risk. The most studied genetic variant is rs2300747, where supported by the fact that MS patients carrying the G protective allele presented higher CD58 mRNA expression level during clinical remission . However, this genetic variant association with MS was not consistent among other studies (Ghavimi et al., 2020).

Cluster of Differentiation 6 (CD6)

CD6 encodes a cell surface scavenger implicated in thymocyte differentiation as well as in T-cell activation and differentiation. It has been suggested that CD6 may play a crucial role in MS pathogenesis as it was shown to be involved in the transmigration of leukocytes across the blood-brain barrier (BBB). However, its definite role in regulating T-cell responses remains

controversial. Genome-wide association studies have identified a large number of genetic variants associated with autoimmune diseases, including MS. Previous reports showed an association between CD6 genetic variant rs17824933 and MS (Li et al., al 2017).

. C-type Lectin Domain Containing 16A (CLEC16A)

C-type lectins are key players in immune regulation as they drive different functions of antigen presenting cells (APCs) . Located on chromosome 16p13, a susceptible locus for various autoimmune diseases, this gene is considered among the first non-HLA genes associated with MS . Moreover, upregulation of CLEC16A was observed in T cells of MS patients homozygous for the risk allele rs12927355 CLEC16A. Additionally, higher expression of CLEC16A was detected in the white matter of MS patients, especially in the peripheral blood mononuclear cells (PBMCs) (Leikfoss et al., 2015).

Cytochrome P450 Family 27 Superfamily B Peptide 1

(CYP27B1)

CYP27B1, located on chromosome 12q13-14, encodes for vitamin D metabolizing enzyme, the hydroxyvitamin D3-1- alpha-hydroxylase. Pre-vitamin D3 is produced in the skin and converted to 25(OH)D3 in the liver. In skin, kidney and immune cells, CYP27B1 enzyme converts 25(OH)D3 into 1,25 (OH)2D3 that binds to the vitamin D receptor present at the surface of T-cells and antigen presenting cells (APCs). Consequently, it suppresses the adaptive immune response, decreases dendritic cell and T-cell proliferation, differentiation, and maturation as well as Th1/Th2 ratio, and enhances the suppressive function of regulatory T-cells. Several studies have highlighted the role of rs703842 in MS with inconsistent results reported. Most studies showed an association between this risk variant and MS in Caucasian, Slovakian, and Han Chinese populations but not in others (Smagina et al., 2020).

Forkhead box P3 (FoxP3)

FoxP3 encodes a transcription factor that is predominantly expressed in CD4(+) CD25(+) regulatory T cells, playing a key role in maintaining immune homeostasis. It is considered the master transcription factor of these cells, responsible for the polarization of naïve T cells into Treg cells. Recently, T regulatory (Treg) cells have been known to present an impaired suppressive function in MS disease . Accumulating evidence showed that functional alterations in FoxP3 gene expression have been observed in several autoimmune diseases , linking thereby the defect in functional peripheral immunomodulation to an established genetic variant implicated in immune regulation and autoimmunity. A positive correlation was found between the genetic variant rs3761548 and M. Additional single nucleotide polymorphisms were also investigated with conflicting results. FoxP3 gene expression level was validated to be decreased in experimental autoimmune encephalomyelitis (EAE) models or in MS patients (Zhang et al., 2019).

Interleukin 2- receptor Alpha (IL2-Rα)

IL2-Rα, also known as CD25, is located on chromosome 10 and encodes the specific component of the high affinity IL2- R system that is implicated in autoimmunity and immune regulation, where IL2/IL2-R signaling pathway allows the proliferation and survival of affected T cells and regulatory T cells production. Genome wide-association studies and fine

mapping have revealed a tight link between SNPs in IL2- Rα and increased risk of immune mediated diseases including MS. Different studies were conducted on IL2-Rα polymorphisms and MS, mostly studying SNP rs2104286 that showed a risk susceptibility for the disease according to several publications. Additionally, one report has found that this SNP was accompanied by a reduced frequency of CD25(+) follicular helper T1 (TFH1) cells in patients carrying the risk genotype (Stefanović et al., 2020) .

Interleukin 7- receptor Alpha (IL7-Rα)

IL7-Rα, located on 5p13 human chromosome, encodes a subunit of IL7 receptor that plays a role in immune homeostasis by assisting in the maturation of B and T cells. Various genome wide association studies revealed that IL7-Rα is correlated with various immunological disorders , such as MS , and thus is considered among the top listed candidate genes implicated in MS. Evidence illustrates the tight association between MS and SNPs in the promoter and exon region of IL7-Rα. Genotyping of 123 SNPs in 66 genes chosen according to their chromosomal location or biological roles has identified that IL7-R includes at least 3 significantly associated SNPs with MS risk . Additionally, alteration in the expression of genes encoding IL7-Rα and its IL7 ligand has been shown in the cerebrospinal fluid (CSF) compartment of MS patients. Most studies tackled the association between genetic variant located in exon 6 of IL7-Rα and MS with a well-established association or association reaching significance after stratification analysis in progressive MS subjects only or more specifically in secondary progressive MS (SPMS). It has been suggested that rs6897932 risk variant is linked to altered alternative splicing of exon 6 that contributes to its skipping, affecting therefore, the ratios of soluble (sIL7- Rα) to membrane-bound IL7-Rα. However, a reduced expression of sIL7-Rα was detected in progressive MS subjects regardless of their genotypes and showed no effect of genotype or protein isoforms expression on MS phenotype (Vinoy et al., 2021) .

The role of epigenetic modifications in the heritability of multiple sclerosis

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system. Human leukocyte antigen (HLA) alleles, located within the major histocompatibility complex (MHC) region, have been identified as major genetic determinants for the disease. In addition, more than 100 non-MHC MS susceptibility variants have been described. Many of the genes carrying known susceptibility variants are involved in the regulation of either immune cell differentiation or signaling. However, because the heritability of MS is limited, environmental contributions to disease etiology are also important. Environmental influences can alter gene expression via epigenetic mechanisms. Epigenetic alterations, such as DNA methylation or histone modifications, have been observed in tissues and cells of MS patients (Olsson et al.,2017).

The McDonald criteria for diagnosis of multiple sclerosis

The McDonald criteria are a set of guidelines that incorporate clinical and laboratory evaluations, as well as magnetic resonance imaging (MRI) data, to establish an MS diagnosis. The first version of the criteria was published in 2001 by an international team led by neurologist Ian McDonald. The criteria have since been extensively updated several times, most recently in 2017 revisions (McNicholas et al., 2018).

The McDonald criteria for diagnosis of multiple sclerosis Table1.

Clinical presentation	Additional data needed
2 or more attacks (relapses) 2 or more objective clinical lesions	None; clinical evidence will suffice (additional evidence desirable but must be consistent with MS)
2 or more attacks 1 objective clinical lesion	Dissemination in space, demonstrated by MRI Or a positive (cerebrospinal fluid) CSF and 2 or more MRI lesions consistent with MS Or further clinical attack involving different sites
1 attack 2 or more objective clinical lesions	Dissemination in time, demonstrated by MRI Or second clinical attack
1 attack 1 objective clinical lesion (monosymptomatic presentation)	Dissemination in space demonstrated by MRI Or positive CSF and 2 or more MRI lesions consistent with MS And Dissemination in time demonstrated by MRI Or second clinical attack
Insidious neurological progression suggestive of MS (primary progressive MS)	One year of disease progression (retrospectively or prospectively determined) and two of the following Positive brain MRI (nine T2 lesions or four or more T2 lesions with positive VEP) Positive spinal cord MRI (two focal T2 lesions) Positive CSF

Treatment of multiple sclerosis

Although no medication reverses or completely prevents the progressive neurological deficits caused by MS, several drugs have been approved by the US Food and Drug Administration in the last two decades for the treatment of the disease (Hauser et al., 2020).

IFN-β blocks MMPs; in turn, this blockage stabilizes the BBB, reduces proinflammatory cytokine levels, and enhances Th2 cytokine production. IFN-β is also reported to induce IL-27 expression, boosting the differentiation of IL-10-producing Tregs while interfering with the generation of effector T cell (Dobson et al., 2019).

Glatiramer acetate is a copolymer composed of four amino acids. Its mechanism of action is not fully understood but is thought to involve the expansion of Tregs and Th2 cells, the enhancement of regulatory CD8+ T cells, and the generation of anti-inflammatory monocytes; it may also interfere with antigen presentation (Torkildsen et al.,2016).

Mitoxantrone is a chemotherapeutic agent that provides immunosuppression by depletion of activated lymphocytes. Adverse events include cardiotoxicity and hematologic malignancies (Kappos et al., 2018).

Monoclonal antibodies including natalizumab, alemtuzumab, daclizumab, rituximab, ocrelizumab, and ofatumumab provide strong immunomodulatory approaches for MS therapy. Natalizumab is a humanized monoclonal antibody that binds the adhesion molecule α4-integrin, preventing immune cell infiltration into the CNS (Chisari et al., 2018).

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