Risk Elements for the Progression of Multiple Sclerosis from Pregnancy to Adulthood

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Abstract

A strong inflammatory response to myelin sheath antigens characterises the autoimmune disease known as Multiple Sclerosis (MS), which results in the activation of astrocytes and microglia and demyelination of the Central Nervous System (CNS). In autoimmune disorders like MS and the Experimental Autoimmune Encephalomyelitis (EAE) model, the immune response is known to be influenced by a variety of genetic predispositions and environmental factors. Although the risk of developing MS appears to be multifaceted, pregnancy is a particularly vulnerable time due to variables that affect the CNS and immune system's development and differentiation, increasing the risk of MS in the foetus. In this context, there is evidence that a lack of thyroid hormone during pregnancy, such as hypothyroidism or hypothyroxinemia, may raise a person's risk of developing autoimmune illnesses like Multiple Sclerosis (MS). The importance of the gestational era for the emergence of MS in adulthood is covered in this paper.

Keywords: Thyroid hormones • Gestational period • Hypothyroxinemia • Immune response • Risk factors • Multiple sclerosis • Experimental autoimmune encephalomyelitis

Introduction

One of the most common autoimmune diseases in the world, Multiple Sclerosis (MS) affects the Central Nervous System (CNS) and causes severe physical, mental, and neurological impairments in those who are affected. MS is thought to afflict about 2.8 million persons globally, the majority of whom being young adult women. Self-antigens from the myelin sheath and neuronal cells are the primary targets of the autoimmune response in MS [1]. Th1 and Th17 CD4+ T cells, in particular, infiltrate the CNS and induce local inflammation and impair immunological tolerance, leading to the death of oligodendrocytes and neurons. Multiple Sclerosis (MS) can have a variety of different underlying causes, some of which may start during pregnancy. This review will talk about the prenatal factors, like maternal thyroid hormone insufficiency, that may make the offspring more likely to have more severe MS as adults. This idea is based on the idea of foetal programming, according to which epigenetic and long-lasting changes are acquired during pregnancy and may make offspring more susceptible to autoimmune diseases like MS [1].

Multiple sclerosis

The autoimmune disorder known as Multiple Sclerosis (MS) is primarily directed against CNS antigens and causes neurodegeneration. Myelin sheath and neuronal protein selfantigens are targeted by autoimmune reactions, leading to tissue damage that impairs synaptic transmission and harms nerves. Numbness or weakness in the limbs, electric shock-like feelings that cause uncontrollable movements and tremors, decreased coordination, unsteady gait, partial or whole vision loss, dizziness, weariness, and tingling in various body areas are all clinical indications of MS. Variability in symptoms is related to how the CNS damage locations look spatiotemporally. In the white and grey matter of the brain and spinal cord, MS is characterised by confluent demyelinated regions, or plaques, with a loss of oligodendrocytes and myelin sheaths. As the disease progresses, neuroaxonal function gradually declines due to patient impairments, brain shrinkage, and ventricular enlargement. Although the progression of MS varies greatly from person to person, there are three main stages: (I) a pre-clinical stage detected only by MRI imaging in which the first brain lesions are observed; (II) the onset of recurrent symptoms followed by partial or complete recovery known as relapsing-remitting multiple sclerosis (RRMS); and (III) a progressive stage in which significant neuronal damage affects the patient's motor ability. In 50% of untreated patients, the disease's symptoms become chronic after roughly 15 years, leading to a noticeable and steady decline. Secondary Progressive Multiple Sclerosis (SPMS) is the medical term for this disease kind. On the other hand, Primary Progressive MS (PPMS), which is more common in males than in women, affects 10 to 15% of MS cases and steadily worsens neurological function. Less white matter lesions, greater microglia activation, and axonal loss caused by PPMS result in spinal cord atrophy. The last kind of MS is Progressive-relapsing MS (PRMS), which is less prevalent and is defined by a continuous deterioration of the disease since the onset of the illness brought on by severe nerve loss and destruction. Because of inflammation in the nerves and spinal cord, there are sporadic relapse episodes with comparable symptoms that worsen RRMS. According to the Atlas of MS (third edition, 2020), the prevalence of MS is thought to be 35.9 per 100,000 persons worldwide; 2.8 million people now have MS, and young adult women are more likely than males to have it. Since 2013, when 2.3 million persons were diagnosed with MS [2]. However, the average age of disease onset has remained at 30, and about 25 years following diagnosis, 50% of patients need to use a wheelchair permanently. Distance from the equator increases the prevalence of MS globally; it is more prevalent among northern Europeans. The three nations in Europe and the globe with the greatest MS prevalence are San Marino (337 per 100,000), Germany (303 per 100,000), and Denmark (282 per 100,000). The United States has the greatest informed prevalence in North America (288 per 100,000), but just 112 per 100,000 on the entire American continent. Afro-Americans and Hispanic Americans, for example, in North America, exhibit a quicker rate of disease progression than White Americans. The stated MS prevalence declines in the remaining WHO regions. This holds true for the eastern Mediterranean (30 per 100,000), southeast Asia (9 per 100,000), Africa (5 per 100,000), and the western Pacific (both with 5 per 100,000). A medical issue is treating comorbidities in MS patients without exacerbating any secondary conditions [3]. Although MS comorbidities are common in North America and Europe, there is little information available about these conditions in South and Central America, Africa, and Asia. Asthma, anxiety, depression, diabetes, hypertension, hyperlipidemia, vascular disease, cardiac arrhythmias, ischemic heart disease, chronic pulmonary disease, and psychosis are the most common comorbidities seen in these patients [3].

Interaction of MS's adaptive and innate immune response

Inflammation, demyelination, oligodendrocyte loss, gliosis, and neuroaxonal degeneration are the hallmark symptoms of MS and are aided by immune cell infiltration across the Blood-brain Barrier (BBB). The innate immune response also plays a crucial role in MS, however imaging and pathology studies point to

adaptative immune cells as key participants in MS pathogenesis. The innate immune system has been linked to autoimmune diseases, but it also serves as the body's initial line of defence against infections and foreign substances. Through the Toll-like Receptors (TLR) expressed in Dendritic Cells (DCs), macrophages, neutrophils, mast cells, lymphocytes, endothelial cells, and epithelial cells, the system is able to recognise conserved Pathogen-associated Molecular Patterns (PAMPs) originating from pathogens. When PAMPs are recognised, inflammatory responses such the production of cytokines and effector mechanisms likes the generation of lysozymes, phagocytosis, and ROS are activated. Innate immune cells play a role in the development and progression of MS. As one of the initial processes underlying MS lesions, activated macrophages cause pro-inflammatory responses from T and B cells as well as early microglial activation. Mast cells, which are common in allergic reactions, make up a small fraction of the CNS population. However, a RANTES production, a mast cell chemoattractant that is elevated in MS lesions, has been shown to have a crucial role in MS progression. Histamine and tryptase, two other mediators secreted by mast cells, have also been discovered in increased concentrations in the CSF of MS patients. These mediators improve leukocyte adherence, rolling, and extravasation into the CNS compartment during the BBB opening. Due to their impact on Th1 responses in the context of MS, mast cells have also been postulated to function as APCs; however, this theory has not yet been fully supported. Mast cell degranulation in response to MBP stimulation causes demyelination and the death of oligodendrocytes and neurons, according to in vitro studies. However, phagocytic cells have been shown to produce significant amounts of ROS and RNS species, which have antimicrobial properties. Large quantities of Nitric Oxide (NO), produced by the Inducible Nitric Oxide Synthase (iNOS) enzyme in MS lesions, cause the death of microglia and neurons. In mice with EAE, NO mediates the cytotoxicity of microglial cells and the necrosis of oligodendrocytes. Last but not least, MS patients have lower levels of NK cells and NKT cells. Invariant TCR -chains, hypothesised to connect innate and adaptive responses, are expressed by NKT cells. The disease progresses because of the decrease in NK and NKT cells. Collectively, these findings point to an important role for innate immune responses in the aetiology of MS. In this situation, Myelin Basic Protein (MBP) autoantigens in the CNS are likely responsible for the release of effector T cells and B cells into the circulation [3]. Antigen-specific lymphocytes are expanded from precursor cells in the lymph nodes that were originally activated by Antigen-presenting Cells (APCs), such as skilled Dendritic Cells (DCs), in immune responses produced by these cells. The "outside-in" theory has been used to describe T cell arrangement within the lesions. T CD4+ cells exhibit a centric localization within the lesions, whereas T CD8+ lymphocytes exhibit a peripheral localization. APCs at the CNS parenchyma reactivate autoreactive T lymphocytes once they have entered the CNS, attracting additional T lymphocytes and innate immune cells, and producing inflammatory lesions. This immune-related interaction. IFN- and TNF-producing Th1 lymphocytes and IL-17-producing CD4+ T lymphocytes (Th17) cells, which play a crucial role in the development of the disease, are among the subtypes of T CD4+ lymphocytes associated with MS. Also released by Th17 cells are IL-21, IL-22, and TNF-. These cytokines cause Th1 lymphocyte polarisation and B cell activation, both of which support inflammation.

The presence of IL-17, IFN-, and cytolytic granules produced by cytotoxic CD8+ T cells in cortical lesions, perivascular CNS, and Cerebrospinal Fluid (CSF) suggested a role for these cells in MS aetiology. Major Histocompatibility Complex Class I (MHC-I), which is intriguingly expressed in oligodendrocytes, astrocytes, and neurons of MS patients, is a protein that CD8+ T cells universally express. This finding suggests that these antigen-presenting glial cells may increase the frequency of pathogenic CD8+ T cells by presenting antigen to reactive T cells in the brain parenchyma [4]. These reactive cytotoxic cells also release IFN- and cause myelin-expressing cells to die, which promotes the development of the illness. After death, postmortem brains were subjected to immunohistochemical examinations, which revealed the presence of cytotoxic cytokines and lytic granules, which are primarily found in projection neurons in the outermost layers of the cortex and are crucial for connecting dispersed cortical regions into a networked whole. Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) are produced in greater quantities when pathogenic CD8+ T cells are present, activating immunological resident cells such microglia, astrocytes, and innate immune cells. When all of these things happen simultaneously, myelin loss, oligodendrocyte death, and axonal injury result, which impairs neuronal function.

Postnatal life risk factors associated with MS pathogenesis

Growing data indicates that nutritional factors, obesity, hormones, and antioxidant capacity have an impact on MS severity. Other environmental and physiological factors, including as vitamin D levels, smoking, and the makeup of the microbiota, are also linked to MS intensity. So, in this section, we talk about how these elements relate to the immune system's instability, which is closely linked to the emergence of MS [5].

Birthing circumstances and feeding of newborns

For instance, an observational study discovered that maternal sickness during pregnancy increased the risk of MS in the foetus by 2.3 times, whereas caesarean birth served as a protective factor by lowering the risk of MS by 60%. The likelihood of juvenile MS development is simultaneously influenced by maternal disease, caesarean delivery, birth weight, and socioeconomic position [6]. Additionally, it was found that male patients who were breastfed for four months or longer and who had the HLA-DRB1*15:01 polymorphism had a lower risk of developing MS. In fact, breastfeeding benefits both the mother and the infant by reducing their risk of developing multiple sclerosis. Additionally, it aids in the development of the intestinal barrier. Additionally, breastfeeding has immunomodulatory effects that promote the growth of Treg cells and inhibit the generation of pro-inflammatory cytokines, which aid in the maturation of the neonatal immune system. In this setting, it's critical to emphasise the inherent protection that breastfeeding offers. Breastfeeding helps the immune system develop properly and significantly reduces a child's risk of developing inflammatory disorders like MS.

Reduced antioxidant capacity

When oxidative stress is linked to an imbalance between free radical production and the antioxidant defensive system, activated microglia and infiltrated macrophages produce molecules like superoxide, hydroxyl radicals, hydrogen peroxide, and nitric oxide that greatly increase the risk of the progression of MS lesions. There is a chance that the decline in total antioxidant capacity is connected to the onset of the disease, especially in MS's early stages and an increased proinflammatory condition [7]. To reduce aberrant immune responses in autoimmune disease, reactive oxygen species are required for T CD4+ cell activation through metabolic reprogramming. These findings are believed to be connected to the variations in mitochondrial activity found in the lymphocytes of MS patients. Periphery T cells from MS patients produce more superoxide anion, have much less antioxidant capability, and exhibit altered expression of mitochondrial proteins. This may be due to impaired mitochondrial activity in these cells, which promotes chronic oxidative stress and the generation of reactive oxygen species by the redox scavenger enzyme NADPH oxidase 2 (Nox2), aggravating EAE pathogenesis and contributing to MS pathogenesis. As a result, MS severity in these patients has been linked to reduced lymphocyte mitochondrial activity. According to Bhargava et al., who discovered altered -glutamyl amino acid metabolism, impaired redox homeostasis, and branched-chain amino acid (i.e., alanine, arginine) as well as phenylalanine and lysine metabolites, among other amino acid changes, oxidative stress can cause an imbalance in the metabolic state of MS patients. Additionally, they discovered a number of xenobiotic metabolites and substances that show altered gut microbial metabolism. After vitamin D administration, metabolic changes in the redox homeostasis have also been observed, and the levels were linked to one of the risk factors for developing MS [8].

Risk factors during pregnancy for MS in offspring as adults

Evidence from the literature suggests that maternal health during pregnancy will affect immune system development, which may have an impact on the onset and severity of MS in adults. As a result, key immune system development components that relate to the gestational risk factors for MS will be discussed in this section.

Development of the adaptive immune system during gestation

The first three stages of immune development start during gestation and include the onset of hematopoiesis, stem cell migration, and cell expansion and colonisation of bone marrow and the thymus. The initial blood cells are extraembryonic and form in close contact with yolk sac-

-endothelial cells; shortly after, progenitors from the yolk sac and Hematopoietic Stem Cells (HSC) from the embryo's mesoderm layer populate the liver and foetal Bone Marrow (BM). Around the sixth week of gestation, foetal liver hematopoiesis can be seen. Up until a short time after birth, the liver and spleen bear a smaller portion of the hematopoiesis burden [9]. The organ that supplies the conditions for T cell development is the thymus. During the first trimester of foetal development, lymphoid progenitors from the foetal liver go to the thymus, where they give rise to naive T lymphocytes. The interaction between thymic stromal cells and immunological compartments, such as thymic epithelial cells, mesenchymal cells, and early-developing thymic progenitors that support the formation and maturation of T and other immune cells, mediates the growth and maturation of the thymus. During the first trimester of pregnancy, HSC-like progenitors, macrophages, Mast Cells (MC), Natural Killer (NK) cell progenitors, and Innate Lymphoid Cell progenitors (ILC), together with megakaryocytes and erythroid cells, have all been identified. At the conclusion of the first trimester, mature neutrophils are present. Within the second trimester of pregnancy, lymphocyte maturation and the thymus' formation of central tolerance take place. Between the first and second trimesters of pregnancy, regulatory T cells (Tregs) that take part in the active tolerance process multiply, creating a reservoir of foetal Tregs [10]. In the early stages of pregnancy, the foetal liver contains B cell precursors; during the first trimester, these cells will develop into mature B cells. During the second trimester, BM becomes the main source of B lymphocytes. Mature B cells then colonise the spleen and create a broad repertoire of B lymphocytes in order to prepare for antigen exposure after delivery. Importantly, immune cell proliferation and the development of prenatal and neonatal immunological responses depend on appropriate maternal nutrition. The immune system has been linked to maternal deficiencies in a few micronutrients, including zinc for lymphocyte activity, iodine for thyroid hormone production, folate for maintaining the Tregs, and vitamins A and D for cell-mediated and humoral immunological responses. Therefore, maternal T4 insufficiency during the first trimester of pregnancy may have an impact on how the embryonic immune system develops. If this happens early in pregnancy, the progeny's immune system may not function properly, increasing their risk of developing autoimmune illnesses.

Discussion

The evidence from MS in humans and animals supports the idea that a number of factors contribute to the development and progression of this inflammatory illness. There is undoubtedly a crucial balance between tolerance and immunity, as well as Treg and Th17 lymphocytes, for the course of MS. However, other factors, such as hypothyroidism and HTX, may help or worsen the condition because they have an impact on the immune system's development as well as the CNS's development, oligodendrocyte differentiation, and astrocytes and microglia's inflammatory response. Additionally, both gestational HTX and gestational hypothyroidism heighten the immune system's pro-inflammatory response in infections and EAE. Unfortunately, studies linking TH insufficiency during pregnancy to a higher risk of MS in the children were generated from animal models due to the difficulty of collecting retrospective data from people who were gestating while suffering from TH deficiency. Given that HTX is not identified and, as a result, is not treated in pregnant women, gestation in HTX is particularly delicate. In conclusion, there are a number of risk factors that humans are exposed to throughout pregnancy and the postnatal period that raise their risk of developing MS. The data supporting the link between maternal thyroid hormone deficit and the progeny's susceptibility to more severe autoimmune illnesses, such as MS, are highlighted in particular. Strong clinical and epidemiological research are therefore strongly advised since they help to clarify the effects of gestational factors like maternal TH on foetal development and their impact on the propensity of the children to acquire autoimmune illnesses as adults.

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