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Risk factors increasing the incidence of multiple sclerosis (MS)

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ABSTRACT

Multiple sclerosis is a chronic demyelinating disease. It is characterized by multifocal and disseminated over time damage to the CNS, with a variety of symptomatology and clinical course, ultimately leading to significant motor disability. The etiology of MS is complex and can be associated with many different factors acting simultaneously or in a cascade. The immune system is widely recognized as one of the key components of the pathological process, especially its components, such as autoreactive T lymphocytes, regulatory cells, and pro-inflammatory cytokines and chemokines. There is ample evidence that latitude, light and vitamin D exposure, and migration have a major influence on the incidence of MS. This shows the uneven distribution of the sick population across the globe. The participation of environmental factors such as bacteria and viruses as well as smoking is not excluded. However, it was not possible to identify the pathogen that would be clearly associated with this disease or unambiguously caused by this disease.

KEY WORDS: multiple sclerosis, risk factors

INTRODUCTION

Multiple sclerosis (SM) is the most common demyelinating disease. It usually starts in young adults, mostly between the ages of 20 and 40, and predominates in women [1]. The pathogenesis of the disease is a complex process, including: damage to the blood-brain barrier, multifocal inflammation within the central nervous system, astroglial hyperplasia, axonal damage within myelinated neuronal pathways. A complex genetic background is of great importance. It is now assumed that MS is the result of the genetic susceptibility of an organism to specific immune responses against host CNS antigens in response to environmental factors. The involvement of environmental factors including viruses and bacteria, and geography, vitamin D deficiency and smoking are also taken into account. The pathomechanism of MS consists in the formation of disseminated primary demyelination foci and the neurodegenerative process in the gray and white matter of the CNS [2]. Considering the course of the disease, five different clinical forms can be distinguished: relapsing-relapsing (RRMS), secondary progressive (SPMS), primary progressive (PPMS), relapsing-progressive (PRMS) and mild (BSMS). The most common symptoms of the disease include, among others, sensory disturbances, impaired motor coordination, weakened muscle strength, chronic fatigue, speech deficits and memory disorders [4]. The diagnosis of MS is based on McDonald's diagnostic criteria, which link the clinical picture with characteristic changes in tests including imaging diagnostics, such as magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) assessment and electrophysiological tests [5]. This article presents the risk factors influencing the incidence of multiple sclerosis.

GENETIC SUBSTRATE

Multiple sclerosis is a result of the coexistence of genetic susceptibility to a specific reaction of the immune system against its own antigens, in response to environmental factors. There is a presumption that there is a specific genetic system responsible for the onset of MS susceptibility. It cannot be concluded that there is a gene responsible for the occurrence of MS that activates the disease under the influence of environmental factors. Studies of the population with MS have shown a higher risk of the disease among descendants [6]. Genetic research has identified one gene locus actually associated with MS. It is the coding region for the major class II histocompatibility complex (HLA class II system). The primary allele of MS susceptibility is considered to be HLA DR1501[3]. In contrast, expression of the HLA class I A2 allele reduces the risk of disease [2]. It is estimated that the HLA system accounts for 15–60% of the genetic basis of multiple sclerosis, which also suggests the involvement of other factors in the development of the disease [8]. Currently, it is assumed that 10-15% of MS cases have family history, and the concordance rate in monozygotic twins is 35%, while in fraternal twins of the same sex it is only 2-5%. The occurrence of multiple sclerosis in close relatives of a person with MS is therefore much more frequent than the value derived from the calculus of probability. There are assumptions that the increase in the number detected in relatives of MS patients may be due to the fact that they may undergo a more detailed examination compared

to that used in the general population [8].

LATITUDE

MS is a disease that occurs irregularly around the globe. The incidence increases with increasing latitude. The incidence rate in Mediterranean countries is lower than in northern European countries. It is a rare disease in Japan, China or South America. Multiple sclerosis occurs mainly in white people [1,7]. When migration takes place between zones with different risk of disease, the most important factor is the age of migration. If the change of risk zone occurs before the age of 15, the person assumes the risk of the zone to which he has migrated. Subsequent change of the climatic zone has no impact on the risk of developing MS. This shows that genetic factors are essential for the acquisition of the disease, but that its occurrence still requires the presence of a factor or associated factors before adolescence [1]. So far, it has not been possible to clarify what components of the environment may contribute to the occurrence of MS. It is assumed that the differences in the risk of developing MS may be influenced by: climatic factors, duration of sunlight or air pollution, respectively [3].

VITAMIN D AND SUNLIGHT EXPOSURE

Vitamin D is an important compound in the functioning of the immune system and nervous system. Populations at risk of vitamin D deficiency have the highest incidence of MS. All patients were diagnosed with a reduced level of 25(OH)2D3 [1]. The exceptions are the northern countries (Alaska, Greenland), where the number of cases is low, which can be explained by the increased consumption of fish [1,6]. A similar relationship has been observed with several other autoimmune diseases. The action of vitamin D may take place through the functioning of the vitamin D receptor (VDR), which mediates the biological activity of vitamin D, but also mediates the regulation of the metabolism of the vitamin itself. It is possible that polymorphisms of the vitamin D receptor gene may be related to disease susceptibility, and that HLA alleles together with the VDR gene may correlate with the risk of developing MS [8]. The length of exposure to sunlight also applies to pregnant women. It was shown that women who were pregnant in the summer had offspring that were less likely to suffer from multiple sclerosis. Pregnant women exposed to a low dose of UVB light, especially in the first trimester, showed a higher incidence of MS among the offspring [10]. Moreover, pregnancy during the winter period is associated with lower air temperature, greater air pollution due to smog, less consumption of fresh vegetables and fruit, which implies a lower intake of vitamins, and a greater probability of seasonal viral infections. These factors increase the risk of developing MS early in life and adolescence.

INFECTIONS

The autoimmune response in MS to bacterial and viral infections may be the phenomenon of molecular mimicry. In this phenomenon, the host antigen is recognized as foreign due to its identity with the foreign antigen (environmental factor), which consequently leads to the development of the disease [8]. Another possible mechanism is the activation of autoreactive

T cells by a non-specific process in their vicinity. This activation may result from the action of cytokines, superantigens and ligands of receptors that recognize the products of pathogens produced in response to infection, including receptors from the Toll family [3]. Many bacteria have been described that may be involved in the development of this disease, including: *Chlamydia pneumoniae*, *Porphyromonas gingivalis*, *Bacteroides fragilis* and *Staphylococcus aureus*. The most common viruses associated with the development of MS are human herpes virus 6 (HHV-6), Epstein-Barr virus (EBV), varicella-zoster virus (VZV) and human endogenous retroviruses (HERV) [8]. However, their causal relationship with MS has yet to be proved indisputably. The lack of undisputed evidence for the presence of latent infection in MS patients does not exclude the participation of an infectious agent in the early stages of the development of an immune response against CNS-expressed antigens [3]. An important element of the immune system is the intestinal microbiota. Changes in the gut microbiome can deregulate the immune response not only in the gut, but also in distant parts of the body. It has been observed that altering some of the bacterial populations present in the gut can lead to a pro-inflammatory disease that can trigger the development of autoimmune diseases, especially multiple sclerosis. However, populations of naturally occurring bacteria and their products, can protect against inflammation in the central nervous system [8]. There is a hypothesis that the immature immune system is deprived of the possibility of modulating the immune response as a result of increased hygiene standards or the use of antibiotics [6].

SMOKING

Nicotinism increases the risk of developing MS, but also of optic neuritis or amyotrophic lateral sclerosis. In women who smoke, the disease occurs twice as often as in non-smoking women [9]. Moreover, passive smoking may also increase the risk of developing MS [6]. The effects of smoking significantly accelerated the disability of the patients and increased the volume of lesions and brain atrophy on resonance images. In addition, smoking increased the risk of many other diseases and could have increased mortality [9]. The harmful effects of smoking disappear 10 years after stopping smoking. It is assumed that the adverse effect of smoking is due to the increase in pro-inflammatory factors (CRP, fibrinogen, IL6), decreased cellular and humoral immunity, and the direct effect of toxic compounds contained in smoke. Cigarette smoking also causes chronic cyanide intoxication, which causes demyelination. Poisoning also contributes to the increase in the amount of free radicals, including NO and its metabolites, which lead to axonal damage [11].

IMMUNOLOGY

CD4 + lymphocytes are an important component of the inflammatory infiltrates present in the CNS in patients with multiple sclerosis. They are also present in the cerebrospinal fluid of patients. The genetic basis of susceptibility to the onset of MS associated with MHC class II antigens points to antigen-recognizing CD4 + lymphocytes as potentially involved in the pathological process. However, CD4 + lymphocytes specific for a variety of myelin and oligodendrocyte antigens are present in the peripheral blood of both MS patients and healthy individuals. This phenomenon is explained by functional differences of autoreactive CD4 +

lymphocytes and disorders of peripheral tolerance mechanisms [3]. CD4 + Th1 T cells secrete pro-inflammatory cytokines such as TNF-alpha during the ongoing autoimmune process. Autoreactive T cells mediate the early stages of the onset of new MS-related lesions by acting against myelin antigens. It is believed that in MS there is an imbalance between two types of immune response: the Th1 type - mediated by Th1 lymphocytes and the cytokines they secrete: IL-2, IFN- γ , and Th2 type - mediated by Th2 lymphocytes and cytokines secreted by them: IL-4, IL-5, IL-13 [3]. T helper cells with the Th17 phenotype are also involved in the development of MS, they mainly produce IL-17 and induce the autoimmunity process. Regulatory CD8 + T cells also play a role in the development of the disease. Pathogenic function has been assigned to CD8 + cells due to their abundant presence in MS lesions. They can influence autoimmune activity in the central nervous system [8]. In addition to the cellular immune response, the humoral response is also involved in the pathogenesis of MS. B lymphocytes, plasma cells and immunoglobulins are typical components of demyelinating foci in MS patients [3]. Cytokines and chemokines are important components of any type of immune response. They are characterized by a very high diversity, broad function and a complex pattern of receptor expression, often of different specificity and affinity [2].

SUMMARY

Multiple sclerosis is the most common disease of the nervous system. The exact cause of the disease is still unambiguous. Epidemiological research shows that the development of the disease is affected by environmental and genetic factors. The development of the disease is likely due to the simultaneous or cascading action of all these factors. Despite the wide range of activities and studies, it was not possible to establish the exact etiology and pathological process. Geographic distribution is of great importance, with incidence increasing with distance from the equator. It may also correlate with a vitamin D deficiency. Smoking cigarettes significantly increases the risk of developing MS. But all factors co-exist with the immune response. Regardless of the accepted theory of MS pathogenesis, there is a coexistence of demyelination and remyelination of neurons with a neurodegenerative process that leads to axonal damage, oligodendrocyte apoptosis and gliosis.

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