

Editorial

What Causes Multiple Sclerosis? Criteria for New Hypotheses

Konstantin E Balashov*

Department of Neurology, Rutgers-Robert Wood Johnson Medical School, USA

***Corresponding author:** Konstantin E Balashov,
Department of Neurology, Rutgers-Robert Wood Johnson Medical School, 125 Paterson Street, 6th Floor, New Brunswick, NJ 08901, USA, Tel: 732-235-7727; E-mail: konstantin.balashov@rutgers.edu

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Multiple Sclerosis (MS) was recognized as a distinct disease involving both the brain and spinal cord and associated with disseminated demyelinating plaques and axonal damage more than 145 years ago [1]. Since that time, the world has witnessed many remarkable discoveries in biomedical sciences and MRI has become a powerful tool in MS diagnosis. Based on progress made in the field of immunology, a number of immunomodulatory disease-modifying treatments have been discovered and have become standards of care for the treatment of patients with relapsing-remitting form of MS. Medications used in MS are called Disease-Modifying Treatments (DMTs) since they do not stop the disease but only delay its activity and progression. Due to the lack of specificity, these DMTs have limited clinical efficacy and may have significant adverse effects. At present, we do not know what causes MS and, therefore, we cannot design the MS cure.

It has been proven by numerous studies that MS pathogenesis involves both inflammation and neurodegeneration. Inflammation is more common in relapsing-remitting form of MS compared to primary-progressive form of MS and in the past, was considered a primary feature of demyelination in MS. However, myelin destruction has recently been reported to occur before inflammation [2]. It is believed that MS occurs as a result of a combination of genetic background and environmental factors. Studies show MS prevalence approximately 1 per 100,000 in certain areas of China, Japan and India whereas numbers in Europe, Canada, and the United States are much higher. For example, MS prevalence is 248 per 100,000 in Saskatoon, a city in central Saskatchewan, Canada [3]. In contrast to African American, Asian Americans continue to have low MS prevalence [4].

The human leukocyte antigen DRB1*1501 haplotype is associated with both relapsing-remitting and primary-progressive forms of MS [5]. However, the DRB1*1501 allele is highly expressed in both Caucasian and Asian populations [6]. The prevalence of MS is significantly increased among Epstein-Barr virus (EBV) seropositive subjects [7]. However, EBV seropositivity in Asia is not decreased compared to Western countries [8].

There are at least three hypotheses addressing the cause of MS which try to combine the generated data into likely explanations, but none has proved definitive. The most well-known hypothesis suggests that MS is an autoimmune process which leads to neuroinflammation and demyelination. The autoimmune hypothesis has existed for many years and is based on the model of experimental autoimmune encephalomyelitis (EAE) which is one of several animal models of demyelinating disease in the central nervous system (CNS). The main mechanism of EAE is an autoimmune T-cell-specific reaction to one of several myelin antigens present in the CNS. Several DMTs for MS (e.g., Glatiramer acetate and Natalizumab), were developed from studies in EAE. However, the EAE model has a number of pitfalls in failing to predict the outcome of certain approaches in MS [9]. After many years of intensive studies and clinical trials, no myelin protein has been identified inducing autoimmune reaction in only MS patients. In addition, the autoimmune theory cannot explain neurodegenerative processes documented in the CNS of MS patients at the very early stage of the disease.

The second hypothesis suggests that MS is an infectious disease. For example, it was hypothesized that a certain virus might reactivate after years of latency and lyse oligodendrocytes in the CNS of patients with MS, as in progressive multifocal leukoencephalopathy, or initiate immunopathological demyelination, as in animals infected with Theiler's murine encephalomyelitis virus or corona viruses [10]. However, no MS-specific virus has yet been isolated from the brains of patients.

The third hypothesis suggests that patients with MS have chronic cerebrospinal venous insufficiency (CCSVI) causing delayed venous outflow from the brain and spinal cord [11]. However, the initial promising results of Dr. Zamboni and coauthors could not be reproduced by other researchers. It was later reported that CCSVI occurs rarely in both patients with MS and in healthy people [12].

All three hypotheses mentioned above provide a reasonable explanation why the disease selectively involves the brain and spinal cord and does not affect other organs. However, they do not explain the key epidemiological finding of decreased MS prevalence in Asian countries. It is very likely that new hypotheses addressing the cause of MS are going to emerge in the near future. Therefore, two mandatory criteria are proposed for a new biological factor/mechanism hypothesized to be a MS cause:

Criterion 1. The new hypothesis has to explain why the disease is restricted to the CNS and causes both inflammation and neurodegeneration.

Criterion 2. The new hypothesis has to explain why the disease has low prevalence in Asia.

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