Available online at
ScienceDirect
www.sciencedirect.com
Elsevier Masson France
EM|consulte
www.em-consulte.com

Multiple sclerosis on behalf SFSEP

Environmental factors in the development of multiple sclerosis

L. Michel

Department of Neurology, Hôpital Pontchaillou, 2, rue Henri-Le-Guilloux, 35000 Rennes, France

INFO ARTICLE

Article history:
Received 6 December 2017
Received in revised form
6 March 2018
Accepted 8 March 2018
Available online xxx

Keywords:
Environmental factors
Multiple sclerosis
EBV infection
Vitamin D
Smoking
Obesity
Salt
Gut microbiota

ABSTRACT

Epidemiology of Multiple Sclerosis (MS) has been intensively studied and we know now that its occurrence result from the combined action of genetic and environmental factors. There are significant geographic and temporal variations in MS incidence and the risk associated with the development of MS may be affected by many potential factors (including infections, climate, diet, etc.). But none of these factors has been identified as ''causal''. The accumulation of these different agents as well as their interactions probably contribute to the development of the disease.

1. Introduction

As the epidemiology of multiple sclerosis (MS) has been intensively studied, the disease is now known to be the result of the combined action of genetic and environmental factors. However, there are significant geographical and temporal variations in MS incidence, and the risk associated with the development of MS may be affected by numerous potential factors (including, for example, infections, climate and diet); however, none of these factors has yet been identified as ''causal''. Accumulation of these different factors as well as their interactions most likely also contributes to development of the disease.

2. Role of environmental factors

The distribution of MS is widely heterogeneous not only between countries, but also from one region to another within the same country. This heterogeneity appears to correlate with a gradient increasing from south to north in the Northern Hemisphere [1] that also appears to be linked in part to genetic

E-mail address: laure.michel@chu-nantes.fr.
https://doi.org/10.1016/j.neurol.2018.03.010
0035-3787/

factors. Thus, the scarcity of MS among Chinese, Japanese and Amerindians, together with its high incidence in Sardinians and Palestinians, clearly indicate different susceptibilities from one ethnic group to another [2]. Contrary to the belief that MS is rare in blacks [3], a recent American study supports a higher incidence of MS in blacks, and a lower incidence in Hispanics and Asians [4]. A French study also showed that there was more aggressive disease in African people in France compared with Caucasians [5].

In addition, monozygotic twins have a significantly greater risk of developing the disease compared with dizygotic twins [6,7]. This risk was estimated, according to studies, to be between 25% and 76%, compared with 5% in dizygotic twins and 2% among first-degree relatives [7–14]. Thus, this lack of concordance (< 100%) for monozygotic twins proves that the development of MS cannot be attributed solely to genetic factors.

Indeed, interactions with the environment are likely to have a significant impact on the susceptibility of developing MS. This environmental role has been reinforced by migration studies. In the French West Indies, the emergence of MS seems to be related to emigration to metropolitan France, especially before the age of 15 years [6]. In Australia, immigrant Anglo-Saxon communities see their risk of developing MS cut by half [15]. Moreover, risk transfer appears to depend on the age of departure. For example, those migrating after age 15 retain the risk of their region of origin whereas those migrating before age 15 acquire the risk of the region of arrival, suggesting that a decisive event arises during the onset of adolescence (several years before onset of the disease) [16–18].

While the identification of environmental factors is still ongoing, new agents have recently been identified. However, the ones best known and best characterized are still Epstein–Barr virus (EBV) infection, low levels of vitamin D and smoking.

3. What are these environmental factors?

3.1. *EBV infection*

Infectious agents, especially viral ones, are often blamed for their role in MS development in part because migration studies have suggested the presence of an early environmental agent. Measles, rubella, mumps and chickenpox viruses are common infections of childhood and have therefore been extensively studied. Yet, despite controversial results, no study has actually demonstrated the possible involvement of these different viruses in MS disease, and EBV remains of particular interest. Prolonged latent infection with this virus involves B lymphocytes and affects 90% of the adult population. Infection is often mild in children, but the symptoms may be more severe in cases of primary infection in adults with the development of infectious mononucleosis.

The nearly ubiquitous presence (> 99%) of anti-EBV antibodies and signs of reactivation of the virus in patients with MS are indirect evidence of the likely role of this infectious vector in the pathogenesis of MS [19]. In addition, people with high titers of anti-EBV antibodies have a higher risk of developing MS than those with low titers [20], while increases in these antibody levels precede the development of the disease by several years [20]. In contrast, the risk of MS in EBV-negative (EBV–) people is extremely low or even zero, with an odds ratio (OR) of 0.06 compared with EBV-positive (EBV+) people [21,22]. In a longitudinal study of US army personnel, all of those found to be seronegative for EBV seroconverted prior to MS onset compared with only 35.7% of the controls who were initially seronegative [23]. Thus, EBV infection appears to be a prerequisite for the development of MS.

In pediatric cases of MS, an association between disease development and EBV infection is also found, but less frequently than in adults. In one North American study, 86% of children with MS had a history of EBV infection compared with 64% of controls [24] while, in a European study, 99% of children with MS were seropositive for EBV vs 72% of controls [25]. More recently, this increase in EBV seropositivity in MS children was confirmed (77.3% vs 45% in controls) and oral excretion of EBV DNA was significantly increased in MS children vs EBV+ controls, suggesting a lack of regulation of the lytic phase of EBV in these children [26].

More recently, B lymphocytes infected with EBV have been found in the brains of MS patients with signs of viral reactivation within acute lesions [27]. It should also be noted that these results have been questioned [28], but were then found in another study [29]. Nevertheless, it raises the question of whether this virus plays a genuine role in the initiation and development of MS, or is just an epiphenomenon, a reflection of the immune ''disorder''.

One hypothetical mechanism is based on the theory of molecular mimicry [30]. Just as the T-cells that recognize EBV antigens react to CNS antigens [31], 3–4% of the anti-EBV-encoded nuclear antigen 1 (EBNA1) CD4+ T-cells in patients and controls are able to recognize myelin peptides [32]. It is, however, probable that this mechanism has a minor part in the pathophysiology of MS. Another hypothesis is that EBV infection induces expression of αβ-crystallin (a ''heat-shock protein'') by B lymphocytes [33]. As this protein is not expressed in either tissues or thymus, no immune tolerance can develop and, instead, expression of this protein generates a CD4+ response with oligodendrocyte lesions to express it [34]. Infection with EBV also leads to viral interleukin (IL)-10 secretion, a homolog of human IL-10 that competes for IL-10 receptors, but without the same anti-inflammatory effects [35]. Finally, an hypothesis concerning the development of autoimmune diseases in general [36] proposes that, following a decrease in CD8+ response, EBV infects self-reactive B cells in the periphery. These B cells then proliferate and migrate within their target organs, where they produce autoantibodies and present antigens to self-reactive T-cells [37,38]. This hypothesis has been reinforced by the recent (but controversial) description of EBV-infected B cells within the central nervous system (CNS) of MS patients [27], and also by the description in two studies of deregulation of the CD8+ response against EBV peptides [39,40].

Thus, there are strong arguments favoring the involvement of EBV in the pathophysiology of MS. As EBV infection appears to be relatively ubiquitous in MS patients, preventing its development may be a feasible option for preventing the disease. However, the implications of a preventative population-wide vaccination strategy are as yet unknown and needs to be explored first.

Please cite this article in press as: Michel L. Environmental factors in the development of multiple sclerosis. Revue neurologique (2018), https://doi.org/10.1016/j.neurol.2018.03.010