

FONDATION CHARCOT STICHTING

60

Fighting multiple sclerosis

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VIRUS, ENVIRONMENTAL FACTORS AND LIFESTYLE: GAINING A BETTER UNDERSTANDING OF MS

There is no single cause of multiple sclerosis (MS). The disease develops in cases involving a combination of genetic susceptibility, certain environmental factors and an abnormal immune response. Gaining a better understanding of these interactions is essential if we are to identify the disease mechanisms and, ultimately, break new ground in terms of prevention and treatment.

In the first article in this newsletter, Dr Dries De Wit reflects on the role played by the Epstein-Barr virus. Following decades of suspicions, we now know that an infection by this virus is a vital prerequisite to developing MS in the vast majority of cases, but it is not a cause in and of itself. In fact, while most of us will become infected with this virus at some point in our lives, only a fraction will develop MS. Researchers are now focusing on what makes these people different.

Professor Souraya El Sankari is also examining three other environmental factors being studied within the context of MS: vitamin D, smoking and obesity. Knowledge and the level of evidence vary for each. Whereas the negative effects of smoking are well documented nowadays, studies on obesity and vitamin D continue to shed light on their respective roles with regard to the risk of developing the disease or in disease progression.

These two articles therefore offer complementary perspectives on the factors that may contribute to the development of MS and influence disease progression. While some factors are modifiable, it is essential to remind ourselves that MS is complex and multifactored: an MS diagnosis is never the patient's fault.

Poised to celebrate its 40th anniversary, the Belgian Charcot Foundation continues to pursue its original mission set in 1987: to support multiple sclerosis research in Belgium and make breakthroughs available to all. These breakthroughs are the result of the tireless work of researchers and the ongoing generosity of our donors.

We hope you enjoy reading this newsletter and thank you for your trust and support.



Prof. Dr. **Bénédicte Dubois**
CHAIR OF THE BELGIAN CHARCOT FOUNDATION

The references for all studies mentioned in this newsletter are available upon request from the Charcot Foundation.

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SLOWLY TRACING THE PATHWAY FROM EPPSTEIN-BARR VIRUS TO MULTIPLE SCLEROSIS.

The idea that MS is caused by a microbe is almost as old as the very first description of the disease by Jean-Martin Charcot in the nineteenth century.

It was first proposed by Pierre Marie, his successor. While there was no concrete evidence to support it at the time, given that the concept of microorganisms was extremely new, the role of one virus – the Epstein-Barr virus (EBV) – has become increasingly clear over the last few years.

Discovered in the 1960s by Michael Epstein and Yvonne Barr, EBV was the first virus to be associated with non-communicable medical diseases, playing a major role in the development of various lymphomas. Like all herpes viruses, such as cold sores, EBV persists in a latent form in the body following infection. EBV's primary 'hiding place' are memory B cells. These cells work within our adaptive immune system to fight off infection, such as by triggering the production of antibodies.

> The link between EBV and MS was made as early as the 1980s. For instance, we know that an EBV infection that causes symptoms of glandular fever more or less triples the risk of MS

However, it was only in 2022 that a large epidemiological study yielded compelling evidence that EBV is a vital prerequisite to developing MS. It is estimated that 90% of all people in our region will become infected with EBV, but only 0.1% will go on to develop MS. Just like lymphoma, we can consider MS to be a rare complication of an EBV infection that develops in cases in which genetic predisposition and other external factors are also unfavourable.

It is not known how EBV contributes to the development of MS, nor why it affects some people and not others. Over the past four years, scientists have worked tirelessly to trace this mechanism.

Results of immunological and virological research appear to indicate that people with MS have mildly weaker 'control' mechanisms of EBV. As a result, the virus is slightly more active in the B cells and more likely to reactivate. Our immune system must therefore work harder to contain the virus, leading to higher anti-EBV antibodies in the blood. This leads us seamlessly into the two major hypotheses that seek to explain the underlying mechanism.

Alongside their role as a primary site of EBV, B cells also play a pivotal role in the central nervous system's autoimmune response in MS. Various modern MS drugs target B cells. If EBV resides in a B cell, it changes the cell. For instance, the virus will produce membrane proteins that interact with other immune cells, or transcription factors that bind with endogenous DNA. In this way, EBV influences a B cell's normal immune functions. It may be that EBV uses this mechanism to throw off the delicate balance between our body's defences against infection and autoimmunity. In fact, recent animal testing suggests that EBV could influence B cells to migrate into and damage the central nervous system.

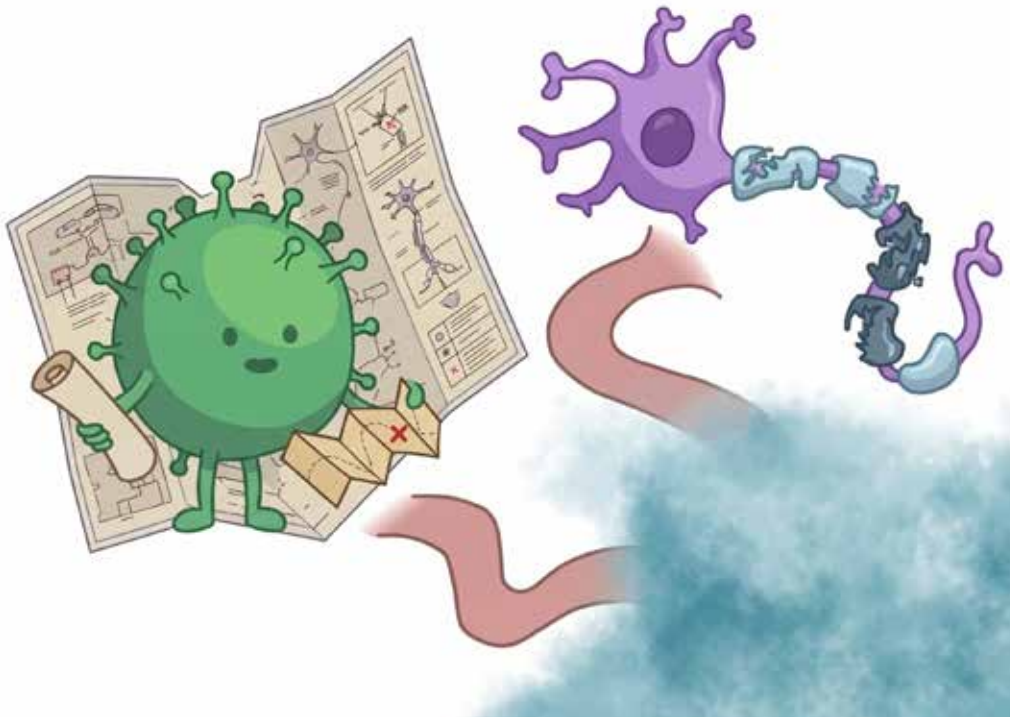
Another hypothesis proposes that the problem isn't caused by EBV in and of itself, but by our immune system's furious attempts to contain EBV. Various researchers have demonstrated an intriguing similarity between the viral protein EBNA-1 and different endogenous proteins in the central nervous system. It is therefore possible that an immune response misfire against EBNA-1 may also target our own tissues, leading to MS.

Both hypotheses are undergoing extensive further research, but aren't completely mutually exclusive. At the same time, another important question remains as yet unanswered: whether EBV merely triggers the illness, or also plays an active role during disease progression.

> What is certain is that scientists around the world are working hard to trace the pathway leading from initial EBV infection to MS.

Time will tell whether this will help us to better predict disease activity, provide more targeted MS therapy or perhaps even prevent the disease.

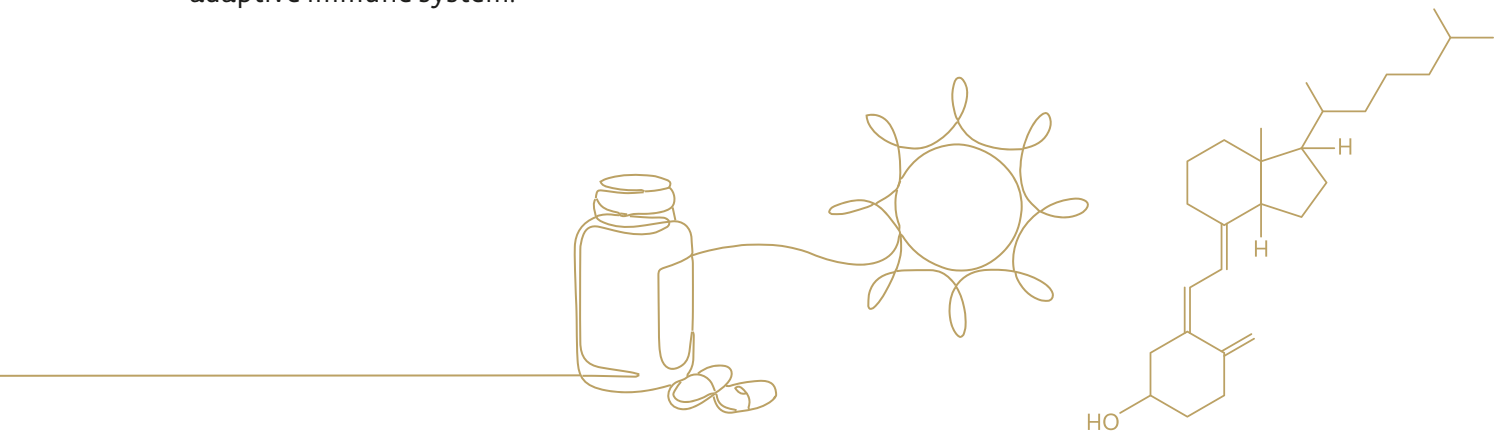
Dr **Dries De Wit**
UZ LEUVEN – KU LEUVEN



VITAMIN D, SMOKING AND OBESITY: WHAT DO WE KNOW ABOUT THEIR ROLE IN CAUSING MS?

Although the etiological mechanisms of multiple sclerosis (MS) are not fully understood, we know that it is a multifactorial disease linked to the interaction between genetic susceptibility and environmental or lifestyle factors.

In addition, interaction with HLA genes has been proven for certain factors such as smoking or obesity, suggesting pathogenic mechanisms that involve the adaptive immune system.



ROLE OF VITAMIN D

Scientists have looked at the role played by vitamin D (vitD) deficiency in MS etiopathogenesis in the 1970s, focusing on two elements: epidemiological on the one hand, with a higher MS prevalence in regions with weaker UV exposure, and immunological on the other, with the active form of vitD playing a role in lymphocyte activation and proliferation, the production of specific antibodies and immune response regulation.

Thanks to records from Scandinavia, it has been possible to establish an inverse correlation between the risk of developing MS as an adult and the level of vitD at birth, if not *in utero*. Although these records (as well as others) suggested that vitD supplements could be beneficial for relapse rates and MRI radiological activity, these results were invalidated in other studies.

The contradictory nature of this data underscores the need for additional studies with standardised methodologies, appropriate timing for intervention and recommendations for target vitD levels.



Nevertheless, if oral supplementation has no harmful effect, it appears reasonable torecommend treating patients for vitD deficiency.

ROLE OF SMOKING

Active smoking that irritates the airways triggers a pro-inflammatory immune profile that favours the development of MS in those with risk genes. Accordingly, a Swedish study on patients with genetic risk factors (HLA-DRB1*15 positive and HLA-A*02 negative) found that the risk of developing MS was 4.9 in non-smokers compared with 13.5 in smokers.

> Active smoking therefore increases the risk of developing MS, and this risk is dose-dependent (duration of smoking and number of cigarettes smoked/daily intake).

The Swedish records also showed, amongst other things, that passive smoking increased the risk of developing MS by a factor of 1.3 in proportion to the duration of exposure.

Once MS manifests, smoking continues to negatively influence disease prognosis: shorter period of time before a second relapse, higher number of relapses, higher number of brain lesions on MRI and earlier progression (around 10 years earlier) to secondary progressive MS.

Lastly, smoking increases the risk of developing neutralising antibodies to certain immunomodulating drugs (such as interferon and natalizumab), which may affect their effectiveness.

The effect of smoking cessation is less well documented; however, a few studies suggest a beneficial effect on gait dysfunction, independently of the effects on anxiety and depression.

ROLE OF OBESITY

Many studies have shown that a high body mass index in adolescents or young adults is associated with an increase, and as much as a doubling, of the risk of developing MS. This association was stronger among adolescents. The causes of this interaction are still poorly understood, but a role may be played by genetics (modulated by adipokines) or gut microbiota. More recently, it has been suggested that obesity is an aggravating factor in terms of disability in MS progression, independent of other risk factors.

As a result, MS therapy nowadays must involve appropriate immunomodulators or immunosuppressants as well as lifestyle modifications.

Smoking cessation and obesity reduction are part of the arsenal of immunomodulatory interventions, which may also be termed 'immunoprotective', that should be implemented at the time of diagnosis.

More generally, smoking prevention (including passive smoking) and obesity prevention as early as possible could play a role in disease prevention, in particular in patients who present genetic risk factors or have a family history of MS.

Prof. **Souraya El Sankari** MD, PhD
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3 REASONS

- MS remains incurable and very often develops into a disability, shattering the lives of thousands.
- All our current endeavours are bringing us closer to solutions: slowing down the disease, repairing its damage and hopefully, one day, curing it completely.
- We undertake to invest the full amount of your legacy in multiple-sclerosis research.

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