

**José Gutiérrez,
Barbara Koppel,
Anne Kleiman,
Gokhan Akfirat**

Department of
Neurology, Metropolitan
Hospital Center,
New York Medical
College

Multiple Sclerosis and Epstein-Barr Virus: A Growing Association

RESUMEN

La etiología en la esclerosis múltiple es un campo elusivo debido a la carencia del modelo etiológico directo para explicar la enfermedad. De hecho, con toda la evidencia que ahora se tiene, la esclerosis múltiple se comienza a ver como una enfermedad multifactorial donde un agente infeccioso en un ambiente permisivo y en un huésped susceptible, puede crear una reacción inflamatoria, desmielinización y daño neurológico irreversible con consecuencias devastadoras para los pacientes. Esta revisión se enfocará en el papel de los virus en la etiología de esclerosis múltiple, especialmente del virus Epstein-Barr.

SUMMARY

The etiology of multiple sclerosis is an elusive field due to the lack of the usual cause-effect relationship model to explain a disease. In fact, with all the current evidence we start thinking in multiple sclerosis as a multi-factorial disease, where an infective agent on a genetically permissive host can lead to inflammation, demyelination and ultimately to neurological damage with dire consequences for the patients. This review will focus on the role of viruses in multiple sclerosis etiology and give some insight regarding this complicated issue.

Comunicación con:
José Gutiérrez.
Correo electrónico:
drjosegc@hotmail.com

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The triad used for an epidemiologist to determine the etiology of a disease is an interesting approach to a complex disease like multiple sclerosis. In the nineteenth century, Charcot suggested that multiple sclerosis could be related to an infectious agent; since then, a myriad of publications has discussed this still debated topic. The "prevalence" hypothesis states that the disease is more common where the agent is more widespread, which would account for the geographical pattern seen in multiple sclerosis.¹ On the other hand, the fact that, only 5 % of dizygotic twins have multiple sclerosis compare to the 30 % in monozygotic twins has been seen as proof of the interaction of genetics and environment in the expression of multiple sclerosis.²

Traditionally, the medical and scientific communities have used Koch's postulate to establish the etiologic relationship between microorganisms and diseases. Until now, no single etiological agent has fulfilled the postulates for multiple sclerosis, although more advanced accurate laboratory techniques used have allowed considerable evidence strengthening the role of infectious agents in multiple sclerosis.

The high prevalence of elevated IgG antibodies in cerebrospinal fluid of multiple sclerosis patients is related to an immunological response against an antigen. Whether this antigen is infectious in nature is still debated since there is cross reactivity of this antibodies with the myelin basic protein (MBP) that forms part of the myelin sheath and the microorganism (mainly viruses, although some bacteria have also been proposed).³⁻⁸ The bacteria implicated is *Chlamydia pneumoniae*, but the evidence collected until now has been weak to establish a stronger role for causing multiple sclerosis.^{9,10}

A candidate microorganism must have biological plausibility to be related to the natural history of multiple sclerosis, i.e. neurotropism, latency and reactivation; this would explain the exclusive involvement of nervous tissue, the prolonged course and the relapses characteristic of multiple sclerosis.^{1,11,12} The herpes virus family has been widely studied in the context of neurological pathology; Epstein-Barr virus (EBV) and human herpes virus 6 (HHV-6) have been related to multiple sclerosis, although their exact role is still to be determined. How these viruses can trigger a disease is summarized in table I.^{3,12-17}

Palabras clave

- ✓ esclerosis múltiple
- ✓ virus de Epstein-Barr
- ✓ enfermedades desmielinizantes

Key words

- ✓ multiple sclerosis
- ✓ human herpesvirus 4
- ✓ demyelinating diseases

EBV and multiple sclerosis

The most studied virus in the etiology of multiple sclerosis has been the EBV, which causes infectious mononucleosis. There is evidence of a serological relationship between previous EBV infection and increased risk for multiple sclerosis. Aschecio *et al.* showed an increased risk of developing multiple sclerosis in subjects with a serologic profile of chronic EBV infection as compared to an acute attack of the same virus;¹⁸ Levis *et al.* found the same correlation with a stronger trend when one is exposed to the virus before 20 years of age.¹⁹ Interestingly, Ponsoby *et al.* demonstrated a protective effect against developing multiple sclerosis in adult life by more frequent exposure to siblings before 6 years of age, suggesting an improvement of the immune system maturity with earlier exposures to an antigen; the same study also demonstrated an inverse relationship between the previous episodes of infectious mononucleosis and the sibling exposure, i.e. Infectious mononucleosis occurs frequently when less contact is documented. The infectious mononucleosis is a sub

acute/chronic response to EBV that is suggested caused by an immune mishandling of the antigen.²⁰ Alotaibi *et al.* and Goldacre *et al.*, showed protective effects of early antigen exposures for developing effect, and on the other hand the history of previous infectious mononucleosis was linked to increased incidence of multiple sclerosis in adult life. These finding suggest that the immune system has a critical period of time when, by exposure to antigens, i.e. getting infected, it can help to better distinguish self from foreign epitopes; the age is still to be defined but as per Ponsoby, it is before 6 years.²¹⁻²³ The higher the antibody activity, the stronger the evidence for future a multiple sclerosis diagnosis according to Sundström *et al.* We could say that the more intense the immune reaction is against an antigen, the higher the chance of confounding the original objective and directing it against the wrong one, in this context, a self one.²⁴ This finding suggests that an abnormal relationship between the EBV and the host takes place triggering chronic infection with an increased risk for developing multiple sclerosis. The fact that the early years exposure to more infectious agents protects against multiple sclerosis, supports the “hygiene theory”, which states that the exposure to infectious agents in a period of immunological immaturity can increase the tolerance to the antigens presented and better handling of later exposures to the agent. By handling the adequate distinction between self and foreign as well as the adequate termination of the inflammatory process when the antigen is cleared and later disease is prevented.²⁵ This model had also been use to explain the more classic autoimmune disease like rheumatoid arthritis, SLE or ankylosing spondylitis.

Additionally, Wandinger *et al.* found increased viral activity in patients with clinically active multiple sclerosis and Buljerac *et al.* demonstrated a correlation between reactivation of EBV infection and the number of enhancing lesions seen on MRI.^{26,27} Bech *et al.* in a randomized, double blind, placebo controlled trial treated multiple sclerosis patients with valacyclovir prospectively and found that in patient with very active multiple sclerosis, the valacyclovir reduced the number of enhancing lesions seen on a single MRI and the number of MRI with no new lesion taken during the 2 years that the study lasted. Put-

Table I. Proposed mechanism in virus-mediated multiple sclerosis

Mechanism	Facts
Molecular mimicry	■ An immunological epitope is shared between the microbe and the host ■ 4% of all viral induced antibodies react with self proteins ■ Viral peptides can activate autoreactive T cell lymphocytes against MBP ■ Oligoclonal bands are polyspecific but react with viral particles as well as with self proteins
Bystander activation	■ The antigen presenting cells activated by a viral infection can activate preprimed autoreactive T cells ■ The killing of an infected cell presenting viral peptides can produce damage to surrounding cells for the cytokines released
Epitope spreading	■ Widening of the immune response from an initiating antigenic epitope to different epitopes on the same molecule (intramolecular spread) or to a epitopes on a different antigenic molecule (intermolecular spread)
Viral persistence	■ The constant presence of viral antigen triggers a repetitive challenge to inflammatory cells leading to chronic inflammation and demyelination

References 3,12-17

ting this together, there's no doubt that there a link between EBV and multiple sclerosis, but the fact that there are multiple sclerosis patients with negative EBV profiles leaves room for other explanations about the etiology of multiple sclerosis and also the need for more studies with larger populations.

Other virus

The multiple sclerosis related virus has been found virtually in all the nervous tissue samples that have been analyzed, thus its name, and although this virus is normally inactive, when co infecting with Herpes Virus family occur, it can be expressed. Further studies are needed to obtain more information of the potential role for occult virus in multiple sclerosis.²⁸

The HHV-6 has been identified in higher percentages in normal appearing white matter and multiple sclerosis plaques samples of multiple sclerosis patient when compared with healthy controls.²⁹ Viral DNA has been obtained from multiple sclerosis patient peripheral blood and cerebrospinal fluid during acute exacerbation, although latter studies couldn't reproduce the finding.³⁰⁻³² The increase in prevalence when compared to healthy controls are not considered the ultimate link to establish causality, although helps to guide future studies to explain this fact. More information is needed to establish the role of HHV-6 in multiple sclerosis.

There are conflicting data with other viruses studied in multiple sclerosis and currently there is not evidence to support a causative role between multiple sclerosis and measles, rubella, mumps, parainfluenza and coronavirus.²⁹

Conclusions

Multiple sclerosis is a very complex disease with an even more complex etiology. The interaction between the immune system, viral agents and environmental exposure must be better understood, although significant advances have been obtained in the field thanks to the active research, either in basic science as in the clinical field. There is enough evidence to support a role for EBV in multiple sclerosis, although it does not explain the whole

picture. A proposed model would be that EBV can trigger chronic inflammation in a genetically susceptible host that can cause demyelination either through a direct infection and damage for the immune system or by abnormal response to self antigens induced by its infection. A "second virus" hypothesis is also plausible although still further evidence is required to support it.

The findings above give rise to many theoretical trials that could help to clarify our understanding of multiple sclerosis and of course to offer more alternatives to patients with the multiple sclerosis regarding treatment and prevention of those who are at risk for developing this still incapacitating disease.

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