Epstein-Barr virus infections & micro-immunotherapy

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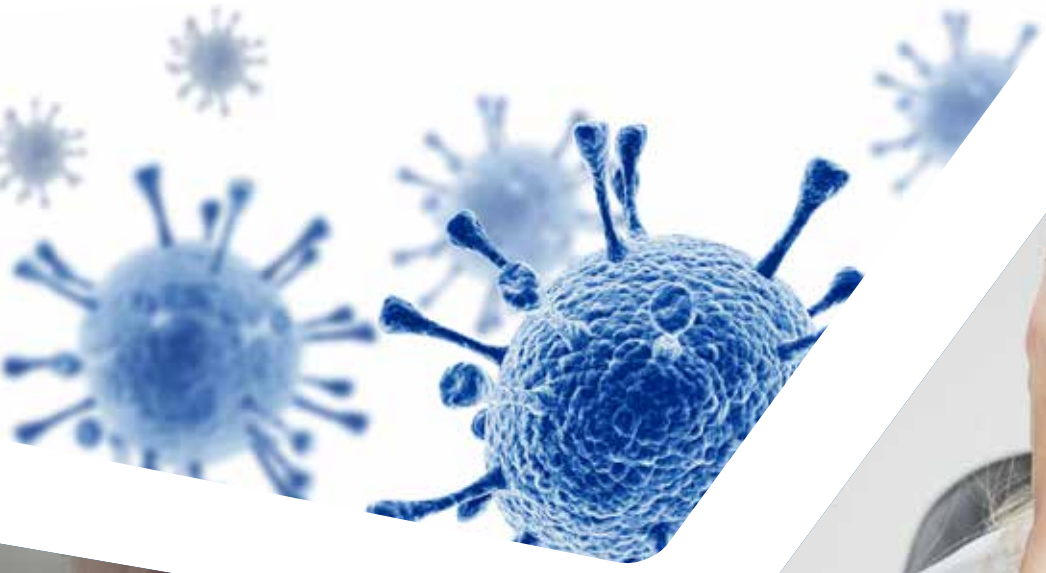

Restore the efficacy of the immune system with micro-immunotherapy

About the Epstein-Barr virus

The Epstein-Barr virus (EBV) or herpesvirus 4 is a DNA virus that is a member of the *Gammaherpesvirinae* subfamily[1].

In developing countries, primary infection usually occurs during the first years of life and is asymptomatic. In developed countries, there is a tendency for delayed primary infection in adolescents and young adults, manifesting clinically as infectious mononucleosis[2].

The virus enters the body through the upper respiratory tract, replicates in the epithelial cells of the oropharynx, and infects the B lymphocytes, from where it spreads to lymph nodes, blood, and mucous membranes. The virus penetrates differently depending on the cell type it infects: by endocytosis in B lymphocytes and by direct fusion with the cell membrane in epithelial cells[3].

EBV, like other herpes viruses, remains latent in the organism in B lymphocytes, kept under control mainly by CD8+ T cells. The carrier may undergo periodic reactivation of the virus from its latent state to the lytic phase, leading to the spread of the virions to other sites or to new hosts[4].

Diseases associated with EBV

Given the complexity of the EBV infection, this virus has been linked to a multitude of clinical conditions, reaching from mild disorders to serious diseases. These include:

- **B-cell malignancies**, such as Burkitt's lymphoma or other malignant neoplasms.
- **Autoimmune diseases**, such as multiple sclerosis, systemic lupus erythematosus, Sjögren's syndrome, autoimmune thyroiditis or rheumatoid arthritis[2].

The persistence and oncogenic potential of EBV can be attributed to its specific gene expression and relationship with lymphocytes. Patients with a weak immune system have a higher risk of developing B, T, and NK lymphomas, as well as epithelial neoplasms, such as breast, prostate, and stomach cancer, due to a decrease in T cell surveillance, which allows unlimited expression of the EBV genes[1].

Disorders like recurrent infections, fatigue, and unexplained exhaustion, as well as joint pain, may be signs of a reactivation of the Epstein-Barr virus. In fact, this virus is considered a trigger for Chronic Fatigue Syndrome.

Furthermore, the presence of the Epstein-Barr virus can also be suspected in certain dermatological conditions such as cutaneous lymphomas, Gianotti-Crosti syndrome or papular acrodermatitis during childhood, erythema multiforme, psoriasis, alopecia areata, lichen planus, and others.[1,5-7].

Stress & EBV reactivation

Stress, particularly if it is chronic, is one of the key factors implicated in the reactivation of the Epstein-Barr virus. This has been studied repeatedly in different contexts.

For example, EBV reactivation has been associated not only with psychological stress during exam periods[8], but also with social interactions[9] and even with perceived stress[10]. Furthermore, this correlation has been observed in groups that are more likely to experience stressful events, such as astronauts, during pre- and post-space travel periods[11], and young recruits who, in addition to having to deal with certain restrictions on freedom, go through hard and strict training, which contributes to developing stress. Indeed, this was argued in a paper by Coskun and colleagues, where they studied 100 male recruits for military service, and analysed samples of serological markers, stress hormones, and viral DNA during two periods: recruitment day and after one month[12].

These studies reveal that daily stressors can activate the autonomic nervous system and promote the increased release of pituitary and adrenal hormones, especially in susceptible people. This elevation in stress hormones can induce suppression of cellular immunity, favouring the reactivation of a latent infection, which is accompanied by a humoral response mediated by antibodies that target the virus antigens. This allows the quantification of specific serological markers.

In summary, reactivation of EBV should always be considered in patients in stressful conditions.

Serological diagnosis

Serology is based on the detection of antibodies that target virus antigens (IgM and IgG):

1. During primary infection, IgM antibodies against viral capsid antigen (VCA) appear first, followed by IgG which gradually increase and remain positive throughout life, while IgM antibodies disappear again after two or three months.

2. Immediately after, early antigen (EA) IgG antibodies appear.
3. IgG antibodies to Epstein-Barr nuclear antigen (EBNA) appear weeks or months later and remain positive throughout life: latent phase.

The interpretation of the results of the EBV serology is presented in Table 1.

TABLE 1: Interpretation of the EBV serology results[13-15]

	VCA (IgM)	EA (IgG)	VCA (IgG)	EBNA (IgG)
Negative	-	-	-	-
Primary acute infection	+	+	±	-
Past infection	-	-	+	+
Reactivation	±	±	+	+

In general lines, one can retain the following:

- A high level of anti-VCA IgG and negative anti-EBNA IgG suggests a recent primary infection. Nonetheless, it might also be a sign of a persistent primo-infection (chronic mononucleosis). In this case, it is recommended to test for IgM antibodies to EBV-associated antigens.
- Concurrent positive levels of anti-VCA, anti-EBNA and anti-EA IgG levels may be a sign of viral reactivation.
- In the presence of elevated levels of anti-VCA IgG and anti-EBNA IgG, a reactivation of the virus may be suspected, although it might also suggest an old infection since, in some cases, these antibodies remain elevated even in the absence of active infection.

Note: There is still a level of controversy about the existence of EBV reactivation. However, based on clinical observations of a large number of doctors and practitioners using micro-immunthereapy over the years, it seems accurate to interpret a 5-fold or more increase of antibody levels with respect to the reference range as a sign of viral reactivation. Nonetheless, in order to make a correct interpretation of the results of the serology, it is important to always take into account the patient's condition. Furthermore, additional biologic tests should be performed like a lymphocyte typing, which helps to determine the state of the immune system and its adaptability or non-adaptability to the clinical situation[16,17].

Micro-immunotherapy approach in EBV infections

By using a specific combination of immunomodulatory substances (e.g. cytokines) in low & ultra-low doses, micro-immunotherapy offers a multi-objective therapeutic approach to EBV infections:

- Hinder the virus' life cycle.
- Optimise immunosurveillance.
- Counteract the development of diseases associated with EBV infection.

The following micro-immunotherapy formulas are aimed to support the immune system in the defence against the Epstein-Barr virus:

- **EBV formula**: generally used in cases of normal or decreased immune activity (non-adaptability of the immune system to the clinical situation due to a deficiency). The recommended dosage in these cases is 1 capsule/day for 4 to 12 months (or even until disappearance of symptoms in a severe situation)[18].

- **XFS formula**: generally used in cases in which the immune system is in a hyperactivated state (non-adaptability of the immune system to the clinical situation due to an excess). The recommended dosage in these cases is 1 capsule/day for 4 months.

As an immunomodulatory treatment, micro-immunotherapy can also be useful in situations of stress that, as previously described, can favour viral reactivation:

- **MISEN formula**: acts on different physiopathological mechanisms associated with chronic stress and ageing. The recommended dosage is 1 capsule/day for 3-6 months.

Conclusion

The clinical importance of the Epstein-Barr virus infection lies in the fact that after the primary infection it remains latent in the body and may undergo periodic reactivation. This virus has been linked to a multitude of clinical conditions, from mild clinical symptoms to serious and/or chronic diseases. Reactivations occur in the context of immune suppression, which may be due to different factors like immunosuppressive drugs, stress, co-infections or severe illnesses like cancer.

Based on its immunoregulatory action, micro-immunotherapy can be a great ally in maintaining or restoring appropriate immune function in the context of viral infections with EBV or stress, and associated diseases.

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