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Article Review

Evaluating The Association Between Epstein-Barr Virus And Multiple Sclerosis

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ABSTRACT

The highly contagious human herpes virus Epstein-Barr Virus (EBV) affects almost every person at some point in their lifetime. Seroconversion—the production of antibodies—occurs primarily in the early years of life, although it can also happen in adolescence or later in life as a result of EBV infection and the immunological response that goes along with it. Adolescents who contract infectious mononucleosis may experience extensive lymphocytosis, an acute, dangerous illness. Although semen or blood are rarely used in the transmission of EBV, saliva is the primary medium. Strong epidemiological and molecular evidence has been presented in recent research investigations supporting the causal role of EBV in multiple sclerosis (MS). MS is the most common chronic inflammatory and neurodegenerative illness of the central nervous system. It is believed that an infectious agent, primarily Epstein-Barr virus, causes the disease in genetically predisposed individuals. It is unclear how a common virus that usually causes benign latent infections might exacerbate autoimmune diseases and cancer in groups that are already at risk. Here, we summarise the data supporting EBV's role as a causative agent for MS and discuss how different risk variables could impact immunological regulation and EBV infection.

INTRODUCTION

Infectious mononucleosis (IM) is caused by the lymphotropic herpes virus known as Epstein- Barr virus (EBV) (1).After being identified in cells taken from African Burkitt's lymphoma, EBV was later found to be quite common around the world (2, 3). EBV belongs to the family of Human Herpes Viruses (HHVs), which is made up of eight viruses that are split into three subfamilies: Alpha, Beta, and Gamma. EBV, also known as HHV4, is a member of the Lymphocryptovirus genus within the Gammaherpesviridae family (4,5).

With about 100 genes that code for around 85 proteins and about 50 non-coding RNAs, the circular double-stranded genome of EBV is roughly 172 kilobases (6 – 9).There are different EBV strains. Type 1 (type A) and type 2 (type B) EBV variations were the first to be discovered. Although type 1 (B95-8, GD1, and Akata) is the most common EBV type globally, type 2 (AG876 and P3HR-1) is as

common in sub-Saharan Africa (10). Individuals may get superinfected with two or more strains of EBV due to the variations' differing replicative characteristics (11).

EBV's structure is similar to that of HHVs and other related viruses.Together with membrane proteins derived from the host cell, it also has an outer lipid envelope made of several viral proteins that are incorporated from the generating host cell. Glycoproteins (gPs) make up a large portion of the proteins found on the viral outer membrane. There are now 13 gPs known to exist; 12 of them express only during the productive, lytic replication cycle, and one of them—BARF1, a decoy viral colony-stimulating factor 1 receptor (vCSF1R)—may also express during latency. The viral tegument, in which the capsid with its encased DNA and related proteins is embedded, is found inside the envelope. (12,13)

Phases of primary infection, latency, and lytic reactivation comprise the life cycle of EBV, which is typical of a large enveloped DNA virus. Encoding nine distinct envelope entrance gPs is the EBV genome. Although the exact roles of the most significant gPs are unknown, their functions are all somewhat understood. The envelope glycoproteins (gPs), which differ slightly depending on the host cell, dictate the tropism of recently released EBV virions (14). B cells and epithelial cells are the two main cell types infected with EBV. The first cells to become infected with EBV are epithelial cells because the virus is spread by the saliva of recipients.After EBV is released from the oropharyngeal epithelium, it then infects B cells when it enters the underlying tissue (15,16). The composition of the envelope gPs in EBV virions released from epithelial cells favours B cells, while EBV virions released from B cells prefer epithelial cells (17, 18).

Viral envelope membrane fusion with target cell plasma membrane can directly result in epithelial cell infection. EBV gP350/220, which interact with complement receptor (CR)2 (CD21) and CR1 (CD35), also plays a role in epithelial cell attachment. The main mechanisms by which the virus attaches to the cell surface are through gH/gL interaction with Ephrin A2 (EphA2) and avb5/avb6/avb8 integrins as well as via BMRF1, which interacts with b1 integrins. The contact between gH/gL and integrins is mediated by a KGD motif on gH, while the interaction between gH/gL and EphA2 is mediated by the gP42 binding site on gH and the receptor's ligand binding as well as repeats of fibronectin type III.When integrins or EphA2 are attached to and interacting with gH/gL, a conformational shift in gH/gL permits interaction with the trimeric gB. This, in turn, causes a conformational change and acts as a fusogen to facilitate viral entry (19,20). The major histocompatibility complex (MHC)-II complex forms a complex with gP350/220, which binds CR2, CR1, and gP42 to facilitate B cell infection (21). Following attachment, the virion is endocytosed, allowing gH/gL to combine with gP42-MHC-II to produce a fusion complex that alters the shape of gH/Gl. Consequently, the virus is released into the cytoplasm when trimeric gB undergoes a conformational change that facilitates the fusing of the viral membrane with the endosome membrane (22, 23).

An orderly sequence of viral gene transcription, viral mRNA translation, viral DNA replication, and viral assembly of new virus results from the virus's successful invasion and takeover of cellular control (24). Though less well understood than the entry process, the virion assembly and egress from the host cell use the host cell exocytosis machinery and require other viral proteins in addition to the structural, tegument, and envelope proteins (25).EBV uses a variety of distinct major host cell membrane proteins for both entry and release. Because of the characteristics of gP42, it prefers to infect epithelial cells when produced by B cells and vice versa, ensuring that some virions will eventually revert to salivary gland cells and remain viable for spreading to new hosts (26).

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Natural killer (NK) and NK T cells (NKT) are activated, as well as the internal antiviral mechanisms and extracellular immune response against EBV antigens are triggered by infection (27). Specific helper T cells, antibodies, and cytotoxic T cells are produced. As a result, EBV has developed defence mechanisms against the host cell's innate antiviral systems, the extracellular innate immune system, and the adaptive immune system. The virus also dedicates a significant portion of its non-coding RNAs and proteins to these defence mechanisms (26, 28).EBV's innate and adaptive immune evasion mechanisms work together to guarantee the virus's survival in the host. EBV's capacity to adopt a latent state with little viral gene expression and little viral peptide presentation to the immune system is a key component of its immune evasion strategy (29). Although latency can also occur in epithelial cells, this primarily affects memory B cells. Occasionally, EBV can revive from the latent state, for example, in response to memory B cell antigen stimulation. This results in the lytic generation of virions upon the expression of an ordered sequence of viral genes (30, 31). Thus, an enhanced immune response against EBV is mounted, neutralising infected cells and driving the virus back into latent state. Reactivation can also happen when the virus's cellular immunity "wanes," and those who have been infected will always have an ongoing "battle" with EBV. Individuals may eventually develop EBV-related diseases, depending on their immune system and the environment. This can happen in certain cases due to EBV immune evasion or EBV infection of other cell types (such as T cells, NK cells, NKT cells, monocytes/macrophages, and others).(32). This review explores the association between EBV infection and MS, emphasizing the role of immunological responses, genetic factors, and viral reactivation in the pathogenesis of MS.

RESEARCH METHODS

This review analyzes recent literature focusing on the epidemiology, pathophysiology, and molecular mechanisms underlying the association between EBV and MS. The data was gathered from a range of studies, including epidemiological investigations, clinical trials, and molecular studies. Key findings related to the immunological responses to EBV infection, the role of viral antigens, and the genetic predisposition to MS are discussed. The review also highlights ongoing clinical research involving antiviral therapies, vaccines, and cell-based treatments targeting EBV in MS patients.

RESULTS AND DISCUSSION

Epstein-Barr Virus Epidemiology:

Most children contract EBV early in infancy, and seroconversion—the development of Abs to EBV—peaks between 1-2 years of age. Most infectious infections during this time are mild and may even go undetected. Puberty causes a second peak in seroconversion because it increases the frequency of close social contact with infected individuals. Adolescent infection is more dangerous and frequently leads to IM, sometimes known as "kissing disease" (13, 15). Latent infection does not appear to affect overall health in most infected individuals; nevertheless, dysregulation of latency or a failure to regulate the lytic infection can result in the development of lymphoproliferative disorders, including lymphoma (33).

The virus load and immune system condition of an individual define the course of an EBV infection. These factors are influenced to varying degrees by the individual's gene composition, prior infection history, and a number of environmental factors.

Due to the widespread prevalence of EBV, relatively little research has been done on the genetic components of disease. Therefore, genetic correlations will only be related to the age of infection, as almost everyone eventually contracts the disease. Studies looking at populations have shown a

correlation between EBV seropositivity and certain MHC-II and -I alleles. Furthermore, there is a connection between EBV seropositivity and inadequacy of mannan-binding lectin (34).
Additionally, there is a connection between EBV seropositivity and some polymorphisms in the (IL) 10 gene and other immune system genes (35).Nevertheless, the relative lack of seronegative individuals hinders all these investigations.One's EBV status is known to be influenced by environmental influences. The factors that have been found thus far are body mass index (BMI), smoking, and sunlight/Vitamin D (36).
These variables probably affect people's overall immunological health, which in turn affects how susceptible they are to contracting EBV. For example, it has been suggested that exposure to sunlight and VitD can prevent autoimmunity by boosting the quantity of CD8+ T cells that can manage EBV infection (37). Furthermore, it has been suggested that obesity affects the cellular immune response to infections and produces a persistent immune-mediated inflammatory state (38); however, additional research is needed to fully comprehend these connections.The more severe course of EBV infection in adolescence or later in life suggests that previous infections may influence an individual's immunological repertoire and consequent ability to fight off subsequent infections.

Association Between Ebr And Multiple Sclerosis :
It is well recognised that EBV infection is linked to a wide range of illnesses, and that prior IM raises the risk of many of these illnesses (40). The illness known as IM is characterised by a protracted fever, enlarged lymph nodes, lethargy, malaise, and other symptoms. Studies on genetic variables linked to IM are scarce. Certain MHC-I and -II alleles as well as polymorphisms in the IL10 gene have been linked to the development of IM, much like EBV infection itself (41).EBV is the cause of several cancers, including nasopharyngeal epithelial carcinomas and B cell lymphomas, which affect the two main cell types that the virus targets (42, 43).
It has been observed that MS CSF contains oligoclonal bands that are reactive to both human herpesvirus 6 and EBV, as well as antibody reactivity to EBNA1 and EBNA2 epitopes. Furthermore, it has been observed that the CSF of MS patients contains cytotoxic T lymphocytes (CTLs) that are reactive to EBV lytic proteins (44, 45). In individuals with early MS, the presence of serum antibodies to EBNA1 has been linked to higher intrathecal IgG levels, indicating a potential role for EBV at the start of MS symptoms.
With a distinctive elevation of various pro-inflammatory cytokines, such as IL-12, TNF, IFNγ, lymphotoxin-α, and osteopontin, cytokine production is severely disrupted in multiple sclerosis. TGFβ and IL-10 levels rise during illness remission, while IL-10 production is downregulated prior to disease return (46). In peripheral blood from MS patients, inflammatory B cells have also been found to secrete greater amounts of IL-10 and GM-CSF (47).
The significance of EBV as a driver of disease activity in MS patients is expected to be clarified by ongoing clinical research utilising antivirals, vaccines, and cell-based strategies that target EBV. EBV infection raises the chance of MS by around 32 times, and HLA-DR2b (HLA-DRB1*1501b and HLA-DRA1*0101a) and symptomatic to severe infectious mononucleosis enhance the risk even further. It is not entirely known how these environmental and genetic factors increase risk in multiple sclerosis, but there are still a lot of logical explanations (46, 48)
It is still difficult to identify which of these are the most common factors and how to intervene therapeutically in the most effective way. Autoantibodies that are cross-reactive with multiple EBV antigens are present in MS patients. Self-antigens and EBV antigens cross-react, involving humoral as well as cellular immune responses. MS patients' autoreactive antibodies also react with viral proteins,

particularly EBNA1 (49).Patients with MS1 usually have higher levels of EBNA1 antibodies in their serum and CSF (49, 50). It was discovered that there is more to elevated titres of EBNA1 antibodies than only HLA type123. High titres of EBNA1 antibodies are linked to a higher risk of MS (51). It's unclear which antigen triggers immunogenicity in many of these polyreactive EBNA1-specific antibodies.

CONCLUSION

It is yet unknown if EBV plays a major role in the onset of the illness (for example, through molecular mimicry) or if the infection is merely chronic and recurrent. The duration of infection probably has a role in the immune system's removal of viruses, autoreactive T cells, and antibodies that attack parts of the central nervous system. Several genetic risk alleles,particularly HLA-DRB1*1501, which may amplify the impact of EBV infection by aberrantly presenting autoreactive peptides, must further aggravate these occurrences.

REFERENCES

1. Rostgaard K, Balfour HHJr, Jarrett R, Erikstrup C, Pedersen O, Ullum H, et al. Primary Epstein-Barr virus infection with and without infectious mononucleosis. PLoS One (2019) 12:e0226436. doi: 10.1371/ journal.pone.0226436
2. Dunmire SK, Hogquist KA, Balfour HH. Infectious Mononucleosis. Curr Top Microbiol Immunol (2015) 390:211. doi: 10.1007/978-3-319-22822-8_9
3. Dunmire SK, Verghese PS, Balfour HHJr. Primary Epstein-Barr virus infection. J Clin Virol (2018) 102:84. doi: 10.1016/j.jcv.2018.03.001
4. Chan KH, Tam JS, Peiris JS, Seto WH, Ng MH. Epstein-Barr virus (EBV) infection in infancy. J Clin Virol (2001) 1:57. doi: 10.1016/s1386-6532(01) 00149-4
5. Epstein MA, Achong BG, Barr YM. Virus particles in cultured lymphoblasts from Burkitt's lymphoma. Lancet (1964) 7335:702. doi: 10.1016/s0140-6736 (64)91524-7
6. Majerciak V, Yang W, Zheng J, Zhu J, Zheng ZM. A Genome-Wide Epstein Barr Virus Polyadenylation Map and Its Antisense RNA to EBNA. J Virol (2019) 2:e01593. doi: 10.1128/JVI.01593-18
7. Sakamoto K, Sekizuka T, Uehara T, Hishima T, Mine S, Fukumoto H, et al. Next- generation sequencing of miRNAs in clinical samples of Epstein-Barr virus- associated B-cell lymphomas. Cancer Med (2017) 3:605. doi: 10.1002/cam4.1006
8. Tarbouriech N, Buisson M, Geoui T, Daenke S, Cusack S, Burmeister WP. Structural genomics of the Epstein-Barr virus. Acta Crystallogr D Biol Crystallogr (2006) 10:1276. doi: 10.1107/S0907444906030034
9. Longnecker R, Neipel F. Introduction to the human g-herpesviruses. In: Arvin A, Campadelli-Fiume G, Mocarski E, Moore PS, Roizman B, Whitley R, et al. editors. Human Herpesviruses. Cambridge, UK: Cambridge University Press (2007). p. 341– 59.
10. Delecluse S, Poirey R, Zeier M, Schnitzler P, Behrends U, Tsai MH, et al. Identification and Cloning of a New Western Epstein-Barr Virus Strain That Efficiently Replicates in Primary B Cells. J Virol (2020) 94:e01918. doi: 10.1128/JVI.01918-19
11. Smith NA, Baresel PC, Jackson CL, Ogolla S, Toko EN, Heit S, et al. Differences in the Epstein-Barr Virus gp350 IgA Antibody Response Are Associated With Increased Risk for Coinfection With a Second Strain of Epstein-Barr Virus. J Infect Dis (2019) 6:955. doi: 10.1093/infdis/jiy601

12. Liu F, Zhou ZH. Comparative virion structures of human herpesviruses. In: Arvin A, Campadelli-Fiume G, Mocarski E, Moore PS, Roizman B, Whitley R, et al., editors. Human Herpesviruses, Cambridge, UK: Cambridge University Press (2007). p. 27–43.
13. Buschle A, Hammerschmidt W. Epigenetic lifestyle of Epstein-Barr virus. Semin Immunopathol (2000) 42:131. doi: 10.1007/s00281-020-00792-2
14. Möhl BS, Chen J, Sathiyamoorthy K, Jardetzky TS, Longnecker R. Structural and Mechanistic Insights into the Tropism of Epstein-Barr Virus. Mol Cells (2016) 4:286. doi: 10.14348/molcells.2016.0066
15. Hammerschmidt W. The Epigenetic Life Cycle of Epstein-Barr Virus. Curr Top Microbiol Immunol (2015) 390:103. doi: 10.1007/978-3-319-22822-8_6
16. Hatton OL, Harris-Arnold A, Schaffert S, Krams SM, Martinez OM. The interplay between Epstein-Barr virus and B lymphocytes: implications for infection, immunity, and disease. Immunol Res (2014) 2-3:268. doi: 10.1007/s12026-014-8496-1
17. Odumade OA, Hogqu KA. Progress and Problems in Understanding and Managing Primary Epstein-Barr Virus Infections. Clin Microbiol Rev (2011) 1:193. doi: 10.1128/CMR.00044-10
18. Crawford DH. Biology and disease associations of Epstein-Barr virus. Philos Trans R Soc Lond B Biol Sci (2001) 1408:461. doi: 10.1098/rstb.2000.0783
19. Thorley-Lawson DA, Babcock GJ. A model for persistent infection with Epstein-Barr virus: the stealth virus of human B cells. Life Sci (1999) 65:1433. doi: 10.1016/s0024- 3205(99)00214-3
20. Möhl BS, Chen J, Park SJ, Jardetzky TS, Longnecker R. Epstein-Barr Virus Fusion with Epithelial Cells Triggered by gB Is Restricted by agL Glycosylation Site. J Virol (2017) 91:e01255. doi: 10.1128/JVI.01255-17
21. Shannon-Lowe C, Rowe M. Epstein Barr virus entry; kissing and conjugation. Curr Opin Virol (2014) 4:78. doi: 10.1016/j.coviro.2013.12.001
22. Heldwein EE. gH/gL supercomplexes at early stages of herpesvirus entry. Curr Opin Virol (2016) 18:1. doi: 10.1016/j.coviro.2016.01.010
23. Chesnokova LS, Hutt-Fletcher LM. Epstein-Barr virus infection mechanisms. Chin J Cancer (2014) 33:545. doi: 10.5732/cjc.014.10168
24. Zhang H, Li Y, Wang HB, Zhang A, Chen ML, Fang ZX, et al. Ephrin receptor A2 is an epithelial cell receptor for Epstein-Barr virus entry. Nat Microbiol (2018) 3:1. doi: 10.1038/s41564-017-0080-8
25. Latour S, Fischer A. Signaling pathways involved in the T-cell-mediated immunity against Epstein-Barr virus: Lessons from genetic diseases. Immunol Rev (2019) 1:174. doi: 10.1111/imr.12791
26. Münz C. Epstein-Barr Virus-Specific Immune Control by Innate Lymphocytes. Front Immunol (2017) 8:1658. doi: 10.3389/fimmu. 2017.01658
27. Chijioke O, Azzi T, Nadal D, Münz C. Innate immune responses against Epstein Barr virus infection. J Leukoc Biol (2013) 6:1185. doi: 10.1189/ jlb.0313173
28. Iizasa H, Kim H, Kartika AV, Kanehiro Y, Yoshiyama H. Role of Viral and Host microRNAs in Immune Regulation of Epstein-Barr Virus-Associated Diseases. Front Immunol (2020) 11:367. doi: 10.3389/fimmu.2020.00367
29. Münz C. Latency and lytic replication in Epstein-Barr virus-associated oncogenesis. Nat Rev Microbiol (2019) 17:691. doi: 10.1038/s41579-019-0249-7
30. Kempkes B, Robertson ES. Epstein-Barr virus latency: current and futureperspectives. Curr Opin Virol (2015) 14:138. doi: 10.1016/j.coviro.2015.09.007

EISSN 2963-6833
JURNAL VOKASI KESEHATAN

31. Liebermann PM, Hu J, Renne R. Maintenance and replication during latency. In: Arvin A, Campadelli-Fiume G, Mocarski E, Moore PS,Roizman B, Whitley R, et al.,editors. Human Herpesviruses. Cambridge, UK: Cambridge University Press (2007).p. 379–402.
32. Dugan JP, Coleman CB, Haverkos B. Opportunities to Target the Life Cycle of Epstein-Barr Virus (EBV) in EBV-Associated Lymphoproliferative Disorders. Front Oncol (2019) 9:127. doi: 10.3389/fonc.2019.00127
33. Houldcroft CJ, Kellam P. Host genetics of Epstein-Barr virus infection, latency and disease. Rev Med Virol (2015) 20152:71. doi: 10.1002/rmv.1816
34. Helminen M, Lahdenpohja N, Hurme M. Polymorphism of the interleukin-10 gene is associated with susceptibility to Epstein-Barr virus infection. J Infect Dis (1999) 180:496. doi: 10.1086/314883
35. Pender MP. The Essential Role of Epstein-Barr Virus in the Pathogenesis of Multiple Sclerosis. Neuroscientist (2011) 17:351. doi: 10.1177/1073858410381531
36. Hedström AK, Bonfim IL, Hillert J, Olsson T, Alfredsson L. Obesity interacts with infectious mononucleosis in risk of multiple sclerosis. Eur J Neurol (2015) 22:578. doi: 10.1111/ene.12620
37. Kasifoglu N, Oz S, Dinleyici EC, Us T, Bor O, Durmaz G, et al. Comparison of Methods Used for the Diagnosis of Epstein-Barr Virus Infections in Children. Pol J Microbiol (2018) 1:81. doi: 10.5604/01.3001.0010.6287
38. Lam WKJ, Jiang P, Chan KCA, Cheng SH, Zhang H, Peng W, et al. Sequencing- based counting and size profiling of plasma Epstein-Barr virus DNA enhance population screening of nasopharyngeal carcinoma. Proc Natl Acad Sci U S A (2018) 22:E5115. doi: 10.1073/pnas.1804184115
39. Cao P, Zhang M, Wang W, Dai Y, Sai B, Sun J, et al. Fluorescence in situ hybridization is superior for monitoring Epstein Barr viral load in infectious mononucleosis patients. BMC Infect Dis (2017) 1:323. doi: 10.1186/s12879-017- 2412-y
40. Joshi, N., Usuku, K. & Hauser, S. L. The T-cell response to myelin basic protein in familial multiple sclerosis:diversity of fine specificity, restricting elements, and T-cell receptor usage. Ann. Neurol. 34, 385–393 (1993).
41. Martin, C. et al. Absence of seven human herpesviruses, including HHV-6, by polymerase chain reaction in CSF and blood from patients with multiple sclerosis and optic neuritis. Acta Neurol. Scand. 95, 280–283 (1997).
42. Lisak, R. P. et al. B cells from patients with multiple sclerosis induce cell death via apoptosis in neurons in vitro. J. Neuroimmunol. 309, 88–99 (2017).
43. Li, R. et al. Proinflammatory GM-CSF-producing B cells in multiple sclerosis and B cell depletion therapy. Sci. Transl. Med. 7, 310ra166 (2015).
44. van Nierop, G. P., Mautner, J., Mitterreiter, J. G., Hintzen, R. Q. & Verjans, G. M. Intrathecal CD8 T-cells of multiple sclerosis patients recognize lytic Epstein-Barr virus proteins. Mult. Scler. 22, 279–291 (2016).
45. Virtanen, J. O., Wohler, J., Fenton, K., Reich, D. S. & Jacobson, S. Oligoclonal bands in multiple sclerosis reactive against two herpesviruses and association with magnetic resonance imaging findings. Mult. Scler. 20, 27–34 (2014).
46. Franciotta, D. et al. Cerebrospinal BAFF and Epstein-Barr virus-specific oligoclonal bands in multiple sclerosis and other inflammatory demyelinating neurological diseases. J. Neuroimmunol. 230, 160–163 (2011).

47. Cagol, A. et al. Association of brain atrophy with disease progression independent of relapse activity in patients with relapsing multiple sclerosis. JAMA Neurol. https://doi.org/10.1001/jamaneurol.2022. 1025 (2022).
48. Kim, W. & Patsopoulos, N. A. Genetics and functional genomics of multiple sclerosis.Semin. Immunopathol. 4, 63–79 (2022).
49. Hue SS, Oon ML, Wang S, Tan SY, Ng SB. Epstein-Barr virus-associated T and NK- cell lymphoproliferative diseases: an update and diagnostic approach. Pathology (2020) 1:111. doi: 10.1016/j.pathol.2019.09.011
50. Iwatsuki K, Miyake T, Hirai Y, Yamamoto T. Hydroa vacciniforme: a distinctive form of Epstein-Barr virus-associated T-cell lymphoproliferative disorders. Eur J Dermatol (2019) 1:21. doi: 10.1684/ejd.2018.3490
51. Robinson WH, Younis S, Love ZZ, Steinman L, Lanz TV. Epstein-Barr virus as a potentiator of autoimmune diseases. Nat Rev Rheumatol. 2024 Oct 10. doi: 10.1038/s41584-024-01167-9. Epub ahead of print. PMID: 393902