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Antibody producing B lineage cells invade the central nervous system predominantly at the time of and triggered by acute Epstein–Barr virus infection: A hypothesis on the origin of intrathecal immunoglobulin synthesis in multiple sclerosis

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ABSTRACT

Patients with multiple sclerosis (MS), a chronic inflammatory disease of the central nervous system (CNS), typically have an intrathecal synthesis of immunoglobulin (Ig)G. Intrathecal IgG is produced by B lineage cells that entered the CNS, but why and when these cells invade the CNS of patients with MS is unknown. The intrathecal IgG response in patients with MS is polyspecific and part of it is directed against different common viruses (e.g. measles virus, rubella virus, varicella zoster virus). Strong and consistent evidence suggests an association of MS and Epstein–Barr virus (EBV) infection and EBV seroprevalence in patients with MS is practically 100%. However, intriguingly, despite of the universal EBV seroprevalence, the frequency of intrathecally produced IgG to EBV in patients with MS is much lower than that of intrathecally produced IgG to other common viruses. The acute phase of primary EBV infection is characterized by a strong polyclonal B cell activation. As typical for humoral immune responses against viruses, EBV specific IgG is produced only with a temporal delay after acute EBV infection. Aiming to put the above facts into a logical structure, we here propose the hypothesis that in individuals going on to develop MS antibody producing B lineage cells invade the CNS predominantly at the time of and triggered by acute primary EBV infection. Because at the time of acute EBV infection EBV IgG producing B lineage cells have not yet occurred, the hypothesis could explain the universal EBV seroprevalence and the low frequency of intrathecally produced IgG to EBV in patients with MS. Evidence supporting the hypothesis could be provided by large prospective follow-up studies of individuals with symptomatic primary EBV infection (infectious mononucleosis). Furthermore, the clarification of the molecular mechanism underlying an EBV induced invasion of B lineage cells into the CNS of individuals going on to develop MS could corroborate it, too. If true, our hypothesis would link EBV infection, the most important environmental risk factor for MS, with intrathecal IgG synthesis, the most characteristic laboratory feature of MS. Besides explaining the origin of intrathecal IgG synthesis in patients with MS, the hypothesis could thus also provide a conceptual framework for clarifying the mechanism through which EBV contributes to the development of MS.

Background

Multiple sclerosis and intrathecal IgG synthesis

Multiple sclerosis (MS) is chronic inflammatory disease of the central nervous system (CNS) typically affecting young adults [1]. The most characteristic laboratory feature of MS is an intrathecal synthesis of immunoglobulin (Ig)G, found in more than 90% of

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patients with MS [2]. Intrathecal IgG is produced by B lineage cells that entered the CNS [3,4], but *why and when these cells invade the CNS of patients with MS is currently unknown*. The intrathecally produced IgG in patients with MS is polyspecific and part of it is directed against common viruses, including measles virus, rubella virus, and varicella zoster virus (VZV) [2]. Intrathecally synthesized antibodies against those viruses can be detected by elevated antiviral antibody indices (AIs, for methodological details see [5]), which are present in more than 80% of patients with MS [2].

Multiple sclerosis and Epstein–Barr virus

Strong and consistent evidence suggests an association of Epstein–Barr virus (EBV) infection and MS [6,7]. Numerous studies unisonously showed a practically 100% EBV seroprevalence in patients with MS, indicating that MS risk among EBV seronegatives is extremely low [6,8–13]. Furthermore, a large longitudinal study demonstrated that EBV infection precedes the onset of MS, as initially seronegative persons, who later go on to develop MS, became EBV seropositive before the onset of MS [14]. Primary EBV infection occurring in early childhood is usually asymptomatic. In approximately half of the population in developed countries primary EBV infection is delayed until adolescence, where it manifests in up to 75% as infectious mononucleosis (IM) [15,16]. Individuals with a history of IM, which can be regarded as a marker of late EBV infection, have a 2.17-fold increased risk of MS when compared to those without symptomatic EBV infection [17]. Altogether, there is substantial evidence supporting a causal role for EBV in the initiation of MS, however, the underlying mechanisms are unclear [7,8,18,19].

Intrathecal IgG synthesis to Epstein–Barr virus in multiple sclerosis

Remarkably, all studies on the intrathecal synthesis of EBV IgG in patients with MS conducted to date consistently observed an unexpectedly low frequency of intrathecally produced IgG to EBV as compared to IgG to other common viruses [20–26]. For instance, an analysis of antiviral AIs in 50 adult patients with MS found elevated AIs to the Epstein–Barr nuclear antigen-1 (EBNA-1) in only 8% and to the EBV viral capsid antigen (VCA) in only 2%, while elevated AIs to measles virus were detected in 60%, to rubella virus in 42%, and to VZV in 32% of patients [22]. To further illustrate and confirm this very important point, Fig. 1 shows the results of an own pilot study on the intrathecal IgG production to EBV and EBV VCA as well as to measles virus, rubella virus, and VZV in 34 patients with a clinically isolated syndrome (CIS, i.e. the first clinical manifestation of MS) or MS. As can be clearly seen, the frequency as well as the extent of the intrathecal IgG production to EBV and EBV VCA is much lower than that to measles virus, rubella virus or VZV. Given the universal EBV seroprevalence in patients with MS, the low frequency of an intrathecal EBV specific antibody synthesis is rather surprising and we refer to this very intriguing finding as the "EBV serum/CSF paradox".

Natural course of EBV infection

When trying to understand the EBV serum/CSF paradox it seems reasonable to consider the natural course of EBV infection, which has in particular been studied in individuals with IM [16,27,28]. Following transmission of EBV via oral secretions, EBV enters through the epithelium that lines the nasopharynx (Waldeyer's ring), where it infects naïve B cells. These are activated by EBV to become proliferating lymphoblasts, differentiate through a germinal center reaction into memory B cells, circulate in the periphery, return to the tonsil, and release infectious virus, renewing the cycle [27]. Before EBV infection is controlled by the immune system this process can repeat endlessly, resulting in a massive perturbance of the B cell system [27,29]. Once the immune system is triggered the release of infectious virus is reduced and the numbers of latently EBV infected memory B cells decline. As typical for humoral immune responses to viruses, there is a temporal delay between primary infection and the generation of EBV-specific IgG [28]. A prospective study of patients with IM demonstrated that VCA IgG may be first detectable as late as 91 days after onset of clinical symptoms. Likewise, EBNA-1 IgG first appeared 25 days after symptom onset [16].

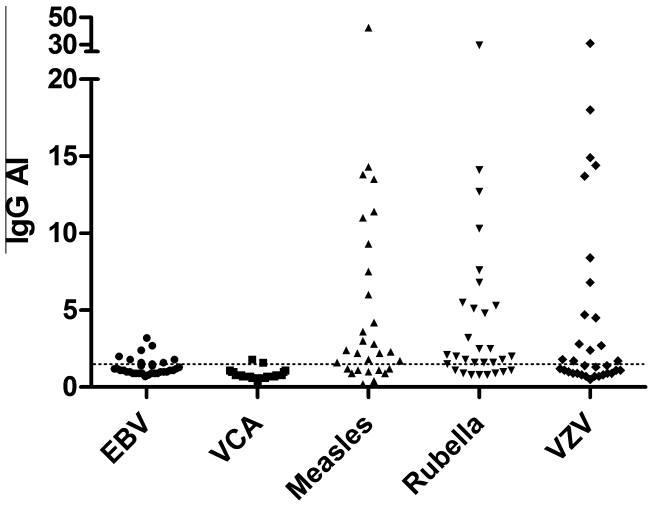

Fig. 1. Levels of antiviral antibody indices (AIs) in patients with a clinically isolated syndrome (CIS) or MS. AIs for IgG antibodies to EBV, measles virus, rubella virus, and VZV were determined by enzyme linked immunosorbent assays (ELISA, Enzygnost [OWIS15, OWLN15, OWBF15, OWLT15], Siemens Healthcare Diagnostics, Eschborn, Germany) in paired serum and CSF samples of 34 patients with CIS ($n = 16$) or MS ($n = 18$) exactly as previously described [20]. The Enzygnost anti-EBV ELISA plate is coated with antigens from EBV infected lymphoblastoid cell lines comprising EBV VCA, Epstein–Barr nuclear antigens and early antigen. AIs for IgG antibodies specific to EBV VCA were determined by VCA ELISA (EBVG0150DB, Novagnost, Siemens Healthcare Diagnostics, Eschborn, Germany). While all 34 patients investigated were EBV seropositive, serum IgG to measles virus was detectable in 31/34, to rubella virus in 30/34, and to VZV in 33/34 of patients. The figure shows absolute values of EBV, VCA, measles virus, rubella virus, and VZV AIs for patients seropositive to the respective virus. The dotted line indicates the threshold of 1.5, AI values above which are considered elevated. Based on this cut-off, the frequencies of elevated AIs were: 24% (EBV), 6% (EBV VCA), 65% (measles virus), 73% (rubella virus), and 46% (VZV). Note that in addition to the lower frequencies of elevated AIs, the absolute EBV and EBV VCA AI levels are between 3-fold to 7-fold lower than measles virus, rubella virus, and VZV AI levels. CIS = clinically isolated syndrome, MS = multiple sclerosis, Ig = immunoglobulin; AI = antibody index; VZV = varicella zoster virus; EBV = Epstein–Barr virus, VCA = Epstein–Barr viral capsid antigen.

Aiming to put the above outlined facts into a logical structure, we here propose a hypothesis of why and when intrathecal antibody producing B lineage cells invade the CNS of patients with MS, which could explain the EBV serum/CSF paradox.

Hypothesis

We propose that in individuals going on to develop MS antibody producing B lineage cells invade the CNS predominantly at the time of and triggered by acute primary EBV infection.

Derivation of the hypothesis

Under physiological conditions there are no antibody producing B lineage cells in the CNS. The B cell lineage cells responsible for intrathecal production of antibodies, including intrathecal production of antiviral antibodies, must therefore migrate into the CNS of