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The spread of EBV to ectopic lymphoid aggregates may be the final common pathway in the pathogenesis of ME/CFS

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ABSTRACT

According to the hypothesis presented here, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) develops over 3 steps: Step 1 is characterized by the aggregation of lymphoid cells in dorsal root ganglia or other nervous structures. The cause of this formation of ectopic lymphoid aggregates may be an acute infection, asymptomatic reactivations of a common neurotropic virus, exposure to a neurotoxin, or physical injury to peripheral nerves. In step 2, Epstein-Barr virus (EBV)-infected lymphocytes or monocytes bring EBV from the circulation to one or several of these lymphoid aggregates, whereupon cell-to-cell transmission of EBV and proliferation of latently EBV-infected lymphocytes lead to the presence of many EBV-infected cells in the lymphoid aggregates. The EBV-infected cells in the aggregates ignite an inflammation in the surrounding nervous tissue. This local inflammation elicits, in turn, a wave of glial cell activation that spreads from the EBV-infected area to parts of the nervous system that are not EBV-infected, disturbing the neuron-glial interaction in both the peripheral – and central nervous system. In step 3, immune cell exhaustion contributes to a consolidation of the pathological processes. There might be a cure: Infusions of autologous EBV-specific T-lymphocytes can perhaps remove the EBV-infected cells from the nervous system.

Background

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a disorder (or perhaps two or more disorders) that is characterized by severe fatigue and several other symptoms, such as pain, concentration problems, post-exertional malaise, and a persistent or recurrent 'flu-like' feeling [1–6]. It usually starts in adolescence or young adulthood [5]. The etiology is unclear, but many hypotheses have been set forth [7–19]. Several authors have suggested that ME/CFS might be the final common pathway of processes that may be precipitated by various triggering events [15,18,19].

During the 1980s and 1990s, there was a strong interest in the possible role of the Epstein-Barr virus (EBV) in the pathogenesis of ME/CFS [14,20–27]. Studies showed that unusual antibody titers against EBV-antigens were more frequent in ME/CFS patients than in healthy controls, suggesting increased EBV-activity [21–27]. One had also become aware that a significant proportion of patients with infectious mononucleosis developed a ME/CFS-like condition [28–30], although the link between infectious mononucleosis and ME/CFS was not thoroughly documented until several years later [31–34].

The interest for the EBV-connection faded [35,36], for several reasons: 1) Differences in EBV-serology between ME/CFS patients and healthy controls were not seen in all studies [4,36]. 2) Unusual EBV-serology was also seen in some healthy persons, and many ME/CFS patients had normal EBV-serology [36]. 3) A few studies suggested that EBV in pharynx and blood was not more often detected in ME/CFS patients than in healthy controls [36]. 4) Some studies suggested that ME/CFS patients may have increased antibody titers also against several other common viruses [36,37], raising the possibility that a "nonspecific polyclonal B-lymphocytic response" was present [37]. 5) A placebo-controlled study of 24 ME/CFS patients showed no effects of a 5-week course of acyclovir [14]. 6) It may have been difficult to believe that a mainly lymphotropic virus like EBV could cause all ME/CFS symptoms [7]. 7) It became increasingly clear that ME/CFS may start in connection with many types of events, including acute infections with several different microbes and non-infectious events like physical injuries and surgery [38–40].

In parts of the medical community, however, the interest for the EBV-connection remained, and several research findings from the last 15 years have kept the interest for the EBV-connection alive [9,16,31–33,41–55]. In addition, the potential role of ectopic lymphoid structures in chronic infections and autoimmune diseases

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has been explored [51,52,56], and research on glial cells has given new knowledge about the cellular mechanisms behind neuroinflammation and chronic pain [57–64].

Hypothesis

According to the hypothesis that is posited here, ME/CFS develops over 3 steps:

Step 1

Step 1 is characterized by the aggregation of lymphoid cells (B-lymphocytes, T-lymphocytes, and dendritic cells) in nervous structures. Dorsal root ganglia are the most common site for this aggregation of lymphoid cells, but autonomic ganglia, anterior roots, spinal nerves, and the CNS may also be affected. The factor that induces the aggregation of lymphoid cells varies from patient to patient. In many cases, asymptomatic reactivations of human herpesvirus-6 (HHV-6) in the glial cells lie behind. In other cases, acute or subacute infections with other microbes, exposure to environmental neurotoxins, or physical injuries that involve stretching, crushing, or tearing of peripheral nerves, lie behind.

Step 2

At some time during or after the formation of lymphoid aggregates, EBV-infected lymphocytes or monocytes bring EBV from the circulation to one or several of these ectopic lymphoid aggregates, whereupon cell-to-cell transmission of EBV and proliferation of latently EBV-infected lymphocytes lead to the presence of many EBV-infected cells in the aggregates. The EBV-infected lymphocytes avoid apoptosis and form long-lived clones because of survival signals from the virus.

The EBV-infected lymphocytes in the ectopic lymphoid aggregates ignite an inflammation in the surrounding nervous tissue. This local inflammation is ignited through several mechanisms: i) by substances secreted from latently EBV-infected lymphocytes, such as non-coding RNAs (EBERs); ii) by immune reactions to lytic replications of EBV (replications of the complete virus particle); iii) by EBV-encoded proteins that are produced and secreted in connection with abortive-lytic reactivations (incomplete lytic replications); and iv) by autoimmune processes with no or only weak elements of cytotoxicity. The relative importance of each of these mechanisms varies from patient to patient and over time.

This local inflammation elicits, in turn, a wave of glial cell activation that spreads from the EBV-infected area to parts of the nervous system that are not EBV-infected. Several types of glial cells may be activated. Among these are satellite cells in the peripheral ganglia, microglia and astrocytes in the CNS, and Schwann cells in the peripheral nerves, including the non-myelinating Schwann cells that ensheath the sensory nerve fibers and the postganglionic sympathetic nerve fibers. This glial activation influences the neurons chemically (disturbance of neuron-glial cross-talk, secretion of inflammatory cytokines) or mechanically (because of swelling within the nerve), and evokes the ME/CFS symptoms. The mechanical stress which the peripheral nerves are exposed to during physical activity increases the glial cell activation and gives post-exertional malaise.

Step 3

The local EBV-caused inflammation, the widespread glial activation, and, if present, reactivations of HHV-6 tend to induce new lymphoid aggregates. The new lymphoid aggregates receive EBV both from the circulation and the neighboring lymphoid aggregates. In this way, the area that is infiltrated by EBV-infected lymphoid aggregates becomes larger, and may include, for example, dorsal root ganglia at several spinal levels and parts of the spinal cord or brain stem. At the same time, some of the "old" lymphoid aggregates disappear. So, the situation is a dynamic one. The antigen-specificity of the lymphoid cells may vary between the aggregates, and may include specificity against viral antigens and a wide range of antigens uncovered or produced by the inflammation. For example, B-lymphocytes in one aggregate may be capable of producing antibodies against HHV-6, whereas B-lymphocytes in another aggregate can produce antibodies against an auto-antigen. If the patient's immune system is capable of removing the EBV-infected cells, a full resolution of the condition may occur. But if the EBV-infected cells are not removed from the nervous tissues within a few years, the pathological processes tend to be consolidated because of exhaustion of the immune cells that are involved in the immune response against the virus.

Comparison with some other hypotheses

In a hypothesis about the cause of autoimmune disorders, set forth by Michael Pender [65,66], EBV and ectopic lymphoid structures play important roles. Pender does not mention ME/CFS, but some of the pathophysiological mechanisms he describes might be relevant also for ME/CFS. However, there are important differences between his hypothesis and the one presented here. In Pender's hypothesis, autoimmunity (immune processes elicited and orchestrated by autoreactive lymphocytes) plays a central role. According to the hypothesis I have presented, autoimmunity plays a less prominent role, and the extent to which autoimmunity is involved in the pathological process varies from patient to patient and over time. In Pender's hypothesis, EBV is primarily seen as an agent that gives survival signals to the autoreactive cells, ensuring that these cells avoid apoptosis and can accumulate in the target organ. Pender mentions the possibility that immune response to lytic replication of EBV might be part of the picture [65], but it is the anti-apoptotic effects on autoreactive cells, and the reactions of these cells that represent the main consequences of the EBV-infection in his hypothesis. In the hypothesis I have presented, the effects of EBV and the consequences of the EBV-infection are assumed to be more differentiated and many-sided, with anti-apoptotic effects not only on autoreactive cells, and with several different types of immune reactions from both the innate and the adaptive immune system. In a recent paper, Pender and Burrows [50] discussed a series of possible mechanisms by which EBV might contribute to the development of multiple sclerosis (MS), but they did not address the relevance of these mechanisms in disorders other than MS.

Bansal et al. [16], in the concluding remarks of their review of ME/CFS literature, pointed out that infections or stress might lead to immune dysfunction, and that this immune dysfunction could elicit reactivation and "wide dissemination" of EBV or another latent virus. The reactivated virus could then "stimulate the release of pro-inflammatory cytokines" and, thereby, elicit fatigue and other ME/CFS symptoms. The authors suggested several possible treatment options, including transfer of ex-vivo expanded virus-specific T cells. Bansal et al. did not mention the possible roles of ectopic lymphoid structures and glial activation – two elements that, when combined, may explain how local EBV-activity may go on for years, disturbing all parts of the nervous system, without necessarily leaving signs of active infection in the blood. They also did not discuss the possible role of autoimmunity.

Jose Montoya, Andreas Kogelnik, and coworkers have published the results of two intervention studies of ME/CFS patients with elevated antibody titers against HHV-6 and EBV [9,48]. In the first