Lyme borreliosis and multiple sclerosis are associated with primary effusion lymphoma

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Summary Multiple sclerosis (MS) is a chronic disease of the central nervous system characterized by chronic inflammation and demyelination. Studies suggested that the viral, especially Epstein-Barr virus infection, and bacterial infections, especially Borrelia burgdorferi infection, play a role in etiology of MS. MS prevalence parallels the distribution of the Lyme disease pathogen B. burgdorferi.

Criteria used for diagnosis of MS can also be fulfilled in other conditions such as Lyme disease, a multisystem disorder resulting from infection by the tick-borne spirochete, B. burgdorferi. In the late period of Lyme disease demyelinating involvement of central nervous system can develop and MS can be erroneously diagnosed. A Lyme borreliosis can mimic central nervous system lymphoma. Also, B. burgdorferi has been implicated not only in etiology of MS, but also in etiology of lymphoma.

Studies suggested that there is an increased risk of non-Hodgkin lymphoma in patients, who had a history of autoimmune diseases such as MS and that both non-Hodgkin’s lymphomas and Hodgkin’s disease were associated with Epstein-Barr virus infection.

A small group of lymphomas called primary effusion lymphomas (PEL) is a recently individualized form of non-Hodgkin’s lymphoma (WHO classification) that exhibit exclusive or dominant involvement of serous cavities, without a detectable solid tumor mass. These lymphomas have also been linked to Epstein-Barr virus and human herpes virus type 8 infections but virus negative cases have been described.

Therefore, we propose that MS and neuroborreliosis are linked to central nervous system primary effusion lymphomas.

As a first step in confirming or refuting our hypotheses, we suggest a thorough study of CSF in the patients suspected for the diagnosis of MS and Lyme borreliosis.

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Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system responsible for a large portion of neurological disabilities in young adults. It is characterized by chronic inflammation and demyelination in the central nervous system [1]. Similar to other complex diseases, both unknown environmental factors and genetic predisposition are required to generate MS. Geographic distribution and epidemics of MS and data from migration studies provide evidence for some, thus far unidentified, environmental effects [1].

Studies suggested that the viral infections play a role in MS etiopathogenesis especially Epstein-Barr virus infection [2]. Also, bacterial infections were suggested as a cause of MS [3], especially B. burgdorferi infection, since a statistically significant relationship between the clinically confirmed diagnosis of MS and the positive serologic reaction with Borrelia antigen has been found [4]. The concept of molecular mimicry provides an elegant framework as to how cross-reactivity between antigens from a foreign agent with self-proteins may trigger autoimmune diseases [5]. These basic principles of cross-recognition and their pathogenic significance have been shown to be relevant in MS [5].

Criteria used for diagnosis of MS can also be fulfilled in other conditions such as Lyme disease. Lyme disease is a multi-system disorder resulting from infection by the tick-borne spirochete, B. burgdorferi. In the late period of Lyme disease demyelinating involvement of central nervous system can develop and MS can be erroneously diagnosed [6]. A Lyme borreliosis mimicking central nervous system lymphoma have been described [7].

An increased risk of non-Hodgkin lymphoma in patients, who had a history of autoimmune diseases such as MS has been suggested [8]. Also, studies have shown that both non-Hodgkin’s lymphomas and Hodgkin’s disease were associated with a history of previous infectious mononucleosis [9] suggesting a role of Epstein-Barr virus in triggering lymphoma. This study also detected an association between non-Hodgkin’s lymphomas and a history of MS in the subjects themselves or in their first-degree relatives. It is important to note that none of the patients reporting MS in their family group also reported infectious mononucleosis [9]. Another link between lymphomas and MS is therapeutic efficacy of Rituximab, a human–mouse chimeric monoclonal antibody that targets the B-cell CD20 antigen and causes a rapid and specific B-cell depletion [10] suggesting a similar etiopathogenic factor.

It is possible that persistent antigen stimulation, viral or bacterial (EBV; Borrelia), could result in triggering the different diseases like MS, neuroborreliosis and central nervous system lymphoma as a type of primary effusion lymphoma developing in CSF.

Hypotheses

We hypothesize, in the light of the similarities detected in clinical, CSF and morphological findings as well as etiological factors, that MS and neuroborreliosis are linked to central nervous system primary effusion lymphomas and could represent the different stage of the same disease. The differences in clinical and other findings could be due to different triggering factors (viral or bacterial), individual genetic predisposition or immune disposition in an affected patient.

Discussion

Worldwide, MS prevalence parallels the distribution of the Lyme disease pathogen B. burgdorferi. In America and Europe, the birth excesses of those individuals, who later in life develop MS exactly mirror the seasonal distributions of Borrelia transmitting Ixodes ticks. With exception of acute infections, no other disease exhibits equally marked epidemiological clusters by season and locality. These findings suggest the role of B. burgdorferi in MS [4] that has also been implicated in etiology of lymphoma [11].

Nervous system borreliosis can result in an elevated number of large atypical cells, resembling lymphoma cells in CSF [7,12]. Atypical cells in CSF could be also detected in multiple sclerosis and malignant non-Hodgkin lymphoma. So, Lyme borreliosis can mimick central nervous system malignancy in the form of abnormal lymphocytic pleocytosis with malignancy criteria fulfilling lymphoid cells [7,12]. This malignancy mimicking cytology was linked to a blastoid transformation of B- and T-lymphocytes due to the antigenic stimulus of B. burgdorferi infection.

Also, it has been suggested that there is a clustering of positive serology for Lyme disease Borrelia in primary cutaneous B-cell lymphoma possibly related to an etiopathogenic relationship. This study suggested that mechanisms of Borrelia escape from immunosurveillance mechanisms, persistence of both their mitogenic and antigenic stimuli for B-cells may be involved in the pathogen-
esis of a subset of primary cutaneous B-cell lymphoma [13].

Although, lymphomas rarely present as serous effusion without the involvement of other thoracic and extrathoracic sites, a small group of lymphomas called primary effusion lymphomas (PEL) exhibit exclusive or dominant involvement of serous cavities, without a detectable solid tumor mass [14,15]. PEL is a recently individualized form of non-Hodgkin’s lymphoma (WHO classification) that mainly develops in immuno-suppressed patients but it can also occur in immunocompetent individuals [14]. Most of non-Hodgkin’s lymphomas and Hodgkin’s disease are associated with a history of previous infectious mononucleosis [9]. PEL has been linked to Epstein-Barr virus and human herpes virus type 8 but virus negative cases have been described [14,15]. It is usually of B-cell immunophenotype but cases of T-cell lineage [14] and/or natural killer cell immunophenotypes have been described. As opposed to the general poor outcome of this disease patients achieving complete remission have been described [15].

An increased risk of non-Hodgkin lymphoma in patients, who had a history of autoimmune diseases such as MS [8], association with Epstein-Barr virus infection in both entities, the significance of Lyme borreliosis in etiopathogenesis of MS and lymphomas as well as CSF findings in Lyme borreliosis mimicking malignant lymphoma suggest that further studies are needed in order to determine association between these three separated but still related entities.

In order to confirm or dispute our hypotheses and to exclude the possibility of central nervous system primary effusion lymphoma, we suggest additional methods to be undertaken in the patients suspected for the diagnosis of MS and Lyme borreliosis. Additional methods should be performed on CSF of these patients including: immunocytochemistry, morphometry, flow cytometry, and cytogenetic/molecular genetic methods (PCR, in situ hybridization, and Southern blotting).

References