

Multiple sclerosis and Lyme borreliosis

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Summary. In a deductive approach the two disease entities of multiple sclerosis and chronic progressive neuroborreliosis are discussed. Various clinical features, seroepidemiology, neuroimaging, CSF findings, CSF serology, specific proteins within the CSF and antibodies against neuronal structures as well as the most recent findings of different dendritic cells within the CSF are discussed as a means of differentiating these two disease entities.

Key words: Neuroborreliosis, progressive borreliar encephalomyelitis, multiple sclerosis.

Introduction

Multiple sclerosis is a relapsing/remitting or chronic/progressive disease of presumably autoimmune origin affecting mainly or exclusively the CNS, leading to demyelination and remyelination. Many pathogenic agents have been incriminated in being either directly involved in the pathogenesis or indirectly, i.e. by triggering an autoimmune process within the CNS [50].

Gay and Dick were the first to discuss spirochetes as the possible causative agents of multiple sclerosis [15], and Kurtz et al. proposed both relapsing fever and Lyme disease borreliae as having the capacity to cause a central nervous system disease equal or similar to multiple sclerosis [24]. Although these medical hypotheses have never been substantiated by biological, biochemical or molecular-biological findings, other authors have continued to postulate a causative relationship between multiple sclerosis and spirochetes [4, 10, 15, 27].

The etiology of multiple sclerosis is still a subject of controversial discussion and it continues to cause considerable uncertainty in the medical community, reflected by a very recent Polish publication in which a causal relationship between the agent of Lyme borreliosis and multiple sclerosis is postulated [5].

We aim here to clarify this confusion within the medical community by contrasting epidemiologic, clinical and diagnostic findings of neuroborreliosis, and in particular chronic neuroborreliosis, with multiple sclerosis. In addition we discuss the most recent developments in molecular biology and neuroimmunology with respect to these two diseases. Using deductive methods we believe we have achieved conclusive results, i.e. we hope to clarify the relationship between these two diseases.

Materials and methods

A thorough search in Pubmed and Medline libraries was done using the two entry codes of multiple sclerosis and Lyme borreliosis (or neuroborreliosis respectively): 60 entries were found in which both terms were keywords of the publications.

Results

Ten topics were identified as being usable and helpful in the deduction of the causative relationship between these two diseases. They are listed in Table 1.

Seroepidemiology

Whereas several authors [4, 10, 15, 24, 27] suggested a hypothetical causal link between Lyme disease and multiple sclerosis on epidemiologic grounds, Schmutzhard et al. [40, 42, 43] and Coyle [6] clearly showed, both in controlled studies and in a series of consecutive patients, that MS patients had positive serology in serum less frequently when compared with well matched control persons. However the frequency of recalled tick bites and the frequency of potential tick exposure (frequencing grassland, edges of woods etc.) was significantly higher in control patients compared with multiple sclerosis patients [43]. Only 1/50 of MS patients had an intrathecal production of borrelia antibodies [42], and because this study was done in the mid-eighties it cannot now be determined whether the specific *Borrelia burgdorferi* IgG antibodies were produced intrathecally or if they merely reflected the disruption of the blood brain barrier.

Table 1

Seroepidemiology
Clinical presentation
Neuroimaging
Cerebrospinal fluid
CSF serology
Kynurenines
Matrix metalloproteinases
Cross reactivity of <i>B. burgdorferi</i> and myelin basic protein specific antibodies
Dendritic cells
Molecular mimicry

These studies [6, 40–43] were accepted as clearly indicating that, on seroepidemiologic grounds, a causative link between multiple sclerosis and any form of Lyme borreliosis was not to be suspected. However, only recently, Chmielewska-Badora performed another seroepidemiologic study comparing the serology of 26 MS patients with 743 rather poorly defined “non MS” patients [5]. Whereas in our study [43] 14,2% of the MS patients, compared with 25,2% of the very well matched (age, sex and ecologic exposure) controls were seropositive (103 patients in each group), the rather unbalanced study of Chmielewska-Badora showed 10/26 MS patients (38,5%) being seropositive compared with 145/773 (19,4%) of “non MS” patients. The authors do not elaborate on the frequency of tick bites, exposure to tick-infested environment, or age and sex matching. However, despite this recent finding seroepidemiology clearly indicates that the relationship between MS and the presence of anti-*Borrelia burgdorferi* antibodies is highly unlikely to be causal.

Clinical presentation of multiple sclerosis and the various forms of neuroborreliosis

There is little doubt about the clinico-neurological presentation of MS with either a relapsing/remitting course of disease or a chronic/progressive form [39, 50]. It is only the latter that – in a very rare instance – could be mistaken for a progressive borrelial encephalomyelitis [2, 13, 18, 44, 53]. Whereas the progressive form of MS in most instances is confined to a chronic myelitis, with frequent relapses and remissions in the early days of disease before finally becoming progressive [13, 50], the progressive borrelial encephalomyelitis, as defined by Ackermann et al. [2], begins with a progressive (chronic) myelitic disease [18]. In contrast to progressive borrelial encephalomyelitis, early neuroborreliosis, as seen in Bannwarth’s syndrome includes the clinical entities of meningitis, radiculoneuritis and peripheral polyneuritis cranialis [30, 39]. None of these 3 syndromes is ever seen in MS. In recent years neuroophthalmic manifestations of Lyme disease have been discussed [3, 29, 38], however both the oculomotor presentations and manifestations involving the optic nerve are clearly different in MS, presenting either as optic neuritis or as a pontomesencephalic nuclear lesion of the oculomotor system leading to double vision [50]. In contrast, Rothermel et al. [38] and Balcer et al. [29], describing neuroophthalmic manifestations of Lyme disease, saw in children either peripheral oculomotor disturbances or compression of the optic nerves. Gold et al. (1990), Lyon-Caen et al. (1994) and Karussis et al. (1999) published, rather outspokenly, clear guidelines to delineate the two disease entities of MS and Lyme borreliosis [16, 23, 26].

Neuroimaging

No larger series has been published on the neuroimaging presentation of either acute or chronic neuroborreliosis. Nevertheless both cranial computed tomography (cCT) and magnetic resonance tomography (MRT) have been performed on children and adults with neurological Lyme disease [11]. Demaerel et al. described ring enhancing lesions as one possible MRT-feature [8]. This finding

added to differential diagnostic confusion as patchy areas, not localized periventricularly, were previously thought to be more frequently seen in patients with chronic neuroborreliosis i.e. progressive borrelial encephalomyelitis. In MS-patients a typical periventricular distribution pattern is regularly found. In addition to the size of the hyperintense lesions seen on T2 weighted images, their distribution is a further, possible way of distinguishing multiple sclerosis from chronic borrelial encephalomyelitis [50]. It must be stressed that the study on the 3 cases of neuroborreliosis, appearing similar to multiple sclerosis on MRT, was performed on children. Since it never has been repeated in adults, this finding might be a feature seen only in young neuroborreliosis patients. As early as 1990, Egerter et al. were able to show that central nervous system borreliosis is clearly mirrored by MRT pathology [11]. However, it was not until 1998 that Triulzi and Scotti published an MRT algorithm with which they were able to differentiate various diseases from multiple sclerosis [48]. In addition to conventional MR images (T1 and T2 weighted images) they used the FLAIR technique, which adds only little to differential diagnostic accuracy; however, when they calculated the magnetisation transfer ratio (MT ratio) they were able to provide a useful tool for the characterization of both multiple sclerosis and other white matter diseases such as vasculitis and chronic neuroborreliosis as well as acute disseminated encephalomyelitis (ADEM) [39, 50]. When employing additional imaging techniques such as diffusion and perfusion weighted MR, further differentiation from chronic borrelial encephalomyelitis and vasculitis is easily possible [39, 50]. Thus, by means of neuroimaging, i.e. various magnetic resonance techniques, the appropriate differentiation of several diseases, including multiple sclerosis, from chronic progressive neuroborreliosis seems to be possible, and obviously easier in the appropriate clinical/neurological setting.

Cerebrospinal fluid findings

Pohl et al. described the cerebrospinal fluid findings in various neurological manifestations of Lyme disease [33], Schmutzhard et al. adding CSF characteristics in chronic neuroborreliosis [41]. It is mainly the plasmacellular pleocytosis, increased intrathecal production of IgG, IgM and – in most instances – IgA which give the first indication of a possible borrelial origin of the neurological infectious/inflammatory disease. Typically, the range of CSF glucose is within normal limits, but CSF protein is highly elevated. Differing from other infections of the CNS, plasmacellular pleocytosis is seen in the early phase of the disease and does not subside over a prolonged period of time (at least 6 months, own observation). In almost all acute and subacute infectious diseases of the nervous system intrathecal IgM and IgG production can be observed. In contrast to this, intrathecal IgA production, demonstrated by a positive IgA index [35], is rarely seen in purely infectious diseases. However, in autoimmune disease, and in [or such as?] acute transverse myelitis, acute disseminated encephalomyelitis (ADEM) or acute hemorrhage leukoencephalitis (Hurst) such an intrathecal IgA production can be observed [39, 50]. Neuroborreliosis is one of very few infectious diseases of the

nervous system in which from the early stage of disease onwards throughout the prolonged course of chronic manifestations, i.e. progressive borreliac encephalomyelitis, intrathecal IgA production may continue to be observed [39]. It seems justified to add the constellation of a pathological/inflammatory CSF finding with mainly plasmacellular pleocytosis and intrathecal IgM, IgG and IgA production to the list of typical diagnostic features in neuroborreliosis, including chronic neuroborreliosis. Both plasmacellular pleocytosis and intrathecal IgA production are virtually never seen in patients with multiple sclerosis. On the other hand a patient with chronic neuroborreliosis – being clinically similar to multiple sclerosis – virtually never shows the typical MS pattern in his/her CSF, i.e. no pleocytosis (or very low pleocytosis $<15/\text{mm}^3$) with isolated intrathecal IgG production (no intrathecal IgM production).

CSF serology

It is well accepted that intrathecal production of specific *Borrelia burgdorferi* antibodies is one of the hallmarks of diagnosis of neurological Lyme disease. Only rarely is a “negative Lyme serology” seen in acute neuroborreliosis patients, and is most likely to be found in acute neuroborreliosis patients who had have early antibiotic treatment [39]. In chronic neuroborreliosis the intrathecal production of borrelia-specific IgG, IgM (and IgA) antibodies is typical. Since polyclonal stimulation may cause a mild increase of various nonspecific antibodies, including *Borrelia burgdorferi* antibodies (IgG), commercially available tests may yield positive results. This aspect has been addressed and discussed at length by Coyle et al. [7] and Lana Peixoto [25], finally reaching the conclusion that in MS patients a reactive Lyme serology might test positive. However, this represents the breakdown of the blood brain barrier and never indicates an autochthonous intrathecal production of specific *Borrelia burgdorferi* antibodies [19]. Various methods of identifying intrathecal (autochthonous) production of specific *Borrelia burgdorferi* antibodies have been employed, such as the equilibration of CSF and serum (to bring the albumin levels to equal concentrations by means of diluting the serum appropriately) or the detection of specific oligoclonal bands within the CSF by CSF electrophoresis. These methods are extremely helpful in diagnosing chronic neuroborreliosis and differentiating it from multiple sclerosis [20, 41]. Within the correct clinico-neurological setting, Lyme serology should be an appropriate method of differentiating the two diseases of multiple sclerosis and chronic/progressive neuroborreliosis. This is particularly important since antibodies for neuronal proteins have been thought to exist in patients with neuroborreliosis, although the pathogenic relevance of these “was never clearly determined” [22]. As in any other progressive disease of the central nervous system finally leading to destruction of neuronal cells, it is conceivable that also in patients with neuroborreliosis antibodies to neuronal proteins released from degenerating neuronal cells are eventually formed. Therefore, the specificity of such antibodies against neuronal proteins clearly needs to be elucidated and validated, particularly with respect to the time

course of a subacute or chronic inflammatory disease of the nervous system.

Cross-reactivity of *Borrelia burgdorferi* and myelin basic protein specific antibodies

As outlined above, antibodies against neuronal proteins have been shown to exist in patients with both multiple sclerosis and neuroborreliosis [22, 47]. In the latter, myelin basic protein specific antibodies have been found and have been considered to be specific for multiple sclerosis [47, 50]. Pohl-Koppe et al. did not find cross-reactivity of intrathecal antibodies to *Borrelia burgdorferi* and myelin basic protein [34]. This means that the detection of myelin basic protein-specific antibodies might be an additional means of differentiating multiple sclerosis from chronic/progressive neuroborreliosis. In addition to antibodies against myelin basic protein, typically found in multiple sclerosis, antibodies against oligodendrocytic glycoprotein have also been found to be present in the CSF of MS patients [36]. In a comparative study these antibodies (against oligodendrocytic-glycoprotein) could not be found at a comparable level in neuroborreliosis patients when compared with MS patients [36]. This, therefore, justifies the assumption that antibodies against both myelin oligodendrocytic-glycoprotein and myelin basic protein may exist at a low level in all patients in whom neuronal cells degenerate, either by necrosis or apoptosis, but they are typically seen – at higher levels – in patients with multiple sclerosis. However, it has to be accepted that a clearcut discrimination of the two diseases, multiple sclerosis and progressive borreliac encephalomyelitis, by measuring the levels of antibodies against myelin-oligodendrocytic-glycoprotein and/or myelin basic protein is not easily possible.

Kynurenines and matrix metalloproteinases in CSF

Neuroactive kynurenines have been shown to occur in CSF in both the acute and chronic forms of neuroborreliosis [14, 17]. These kynurenines, reflecting excitotoxicity, have never been shown to be upregulated in multiple sclerosis.

Matrix metalloproteinases have been shown to be induced by *Borrelia burgdorferi* in neural cultures [32]. Very recently these molecules have been implicated in the pathogenesis of multiple sclerosis [12]. Their suggested role includes the disruption of the blood brain barrier, immune cell transmigration into the central nervous system and myelin degradation. Therefore, these molecules can be detected in virtually all inflammatory diseases leading finally to neuronal cell degradation [12]. However, Yushchenko et al. could clearly show that certain matrix metalloproteinases (e.g. MMP-9) are strongly correlated to the CSF cell count [54]. Very recently, Galboiz et al. showed that MMP 9 levels were not different in the CSF of patients with multiple sclerosis and in healthy controls [12]. However, elevated levels of MMP-7 and MT1-MMP were detected.

To our knowledge, no prospective study has addressed the issue of using various matrix metalloproteinases and/or their respective tissue inhibitors to differenti-

ate the two disease entities of multiple sclerosis and progressive borreliac encephalomyelitis.

Molecular mimicry

Molecular mimicry is the concept that antigenic determinants of micro-organisms resemble antigenic determinants of the host. It is frequently cited as a plausible mechanism to account for the association of infections and autoimmune disease [49, 53].

The currently controversial issue of molecular mimicry in Lyme borreliosis might definitely be an important issue in chronic neuroborreliosis [1, 21, 28], although Rose and Mackay looked critically at various human diseases and the role of molecular mimicry [37]. They concluded that, based on analogous sequences of aminoacids or on cross-reactions of monoclonal antibodies, numerous examples of molecular mimicry have been reported, but to date there has been no clear example of a human disease caused exclusively by molecular mimicry [37]. In view of recent findings in Lyme arthritis, where molecular mimicry was demonstrated at the single cell level [49], the statement by Rose and Mackay [37] must at least be reconsidered.

Dendritic cells

Steinman et al. [46] and Dittel et al. [9] stipulated that dendritic cells may be crucial in inducing and regulating immune responses not only against pathogens but also against autoantigens. Very recently, this issue was addressed by Pashenkov et al. who found two subsets of dendritic cells within the human cerebrospinal fluid [31]. Whereas myeloid dendritic cells, one of the two subsets, were found to be elevated in various neuroinflammatory conditions including MS, optic neuritis, and to some extent also in septic meningoencephalitis and neuroborreliosis, the other subset of dendritic cells – the plasmacytoids – were found to be significantly elevated in the CSF of Lyme neuroborreliosis compared with other neuroinflammatory conditions. The initially elevated number of dendritic cells in the CSF drops dramatically over a few weeks in acute neuroborreliosis and appropriate antimicrobial chemotherapy.

Conclusion

From this approach of deductive argumentation it is without doubt that acute neuroborreliosis is a clearly distinct disease entity. Similarly without doubt is the fact that any form of chronic neuroborreliosis, e.g. progressive borreliac encephalomyelitis, may present as an MS-like disease; however, there are many ways to clearly differentiate multiple sclerosis from any form of chronic neuroborreliosis. It is not the task of this deductive outline to discuss either the treatment protocols for the various forms of multiple sclerosis or the distinct treatment protocol for neuroborreliosis (the reader is referred to the published practice guidelines for the treatment of Lyme disease by Wormser et al. [52] and Steere et al. [45]).

Since both treatment options and prognosis are different in these two disease entities (multiple sclerosis and chronic neuroborreliosis) it is necessary to distinguish them as early as possible and with maximum possible

certainty, keeping in mind the treatment options and their prognostic aspects.

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