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When Lyme Neuroborreliosis Mimics Multiple Sclerosis. Challenges and Advances in Differential Diagnosis

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1. Introduction

Lyme neuroborreliosis (LNB) and multiple sclerosis (MS) are two separate entities that exhibit comparable neurological symptoms.[1] LNB, a complication of *Borrelia burgdorferi* infection spread through tick bites, can present both acute (meningitis, radiculitis, cranial nerve palsy) and chronic (encephalopathy, polyneuropathy) neurological symptoms.[2] MS, on the other hand, is an autoimmune demyelinating illness of the central nervous system that mainly affects young people. It is categorised into three types: Relapsing-Remitting MS (RRMS), Secondary Progressive MS (SPMS), and Primary Progressive MS (PPMS).[3] Because of the overlapping features—such as paraesthesia, exhaustion, gait problems, cognitive impairment,[1] and demyelinating lesions found on MRI[4]—the differential diagnosis is frequently complicated and may cause therapeutic delays.[5,6]

The classical diagnostic approach to LNB is based on clinical evaluation and detecting intrathecal *Borrelia*-specific antibodies.[7] Conversely, MS is often diagnosed based on MRI demyelination patterns, the presence of CSF oligoclonal bands, and clinical evolution.[8] However, both diseases may match some of these characteristics simultaneously, resulting in a misdiagnosis.[1]

The actual situation in Romania hampers diagnosis. The rising incidence of Lyme disease in this area, along with restricted access to modern CSF analyses, leads to both underdiagnosis and overtreatment.[9]

The purpose of this paper is to analyse and compare the diagnostic criteria for Lyme neuroborreliosis and multiple sclerosis, assess clinical and paraclinical overlap, and establish clear criteria for differential

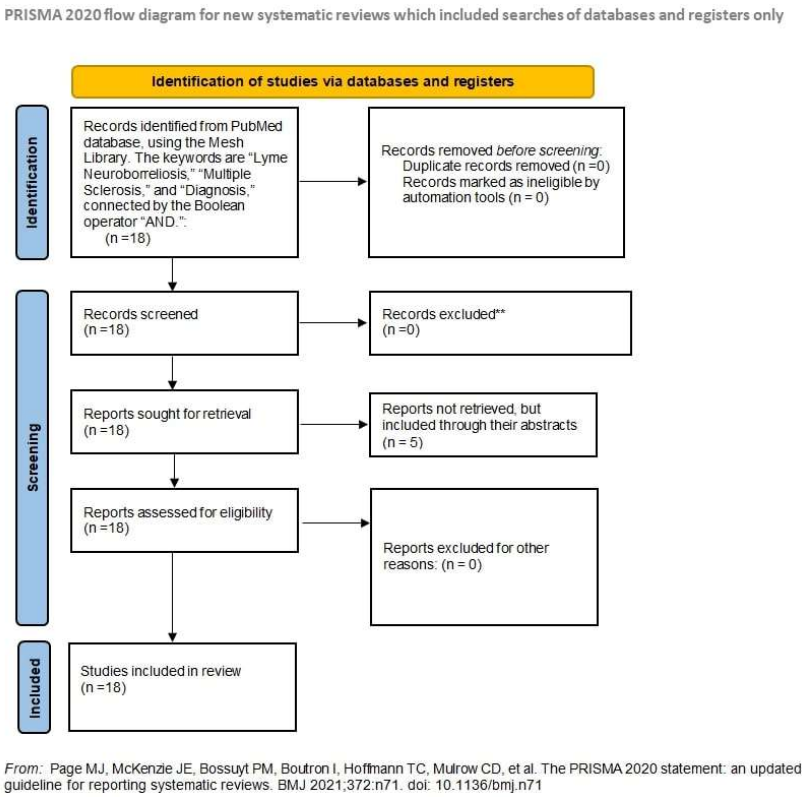
diagnosis between LNB and MS in terms of clinical manifestations, imaging techniques, and blood/cerebrospinal fluid (CSF) markers.

2. Methods

A systematic review was conducted using the PubMed database, selecting articles using MeSH terms "Lyme Neuroborreliosis," "Multiple Sclerosis," and "Diagnosis," connected by the Boolean operator "AND". This search method returned 18 items and we included all of them.

The study selection followed the Preferred Items for Systematic Reviews and Meta-Analysis (PRISMA) reporting guidelines; thus, all papers were screened twice, once using the Title/Abstract keywords search algorithm and again using the Full-text. Due to the scarcity of research on this topic, we also considered publications for which we only had access to the abstract, because they provide a broader perspective on the subject, but their contribution to the final study is limited. For Data Extraction and Synthesis, variables were collected based on the full-text, with an emphasis on clinical symptoms, imaging modalities, blood/cerebrospinal fluid (CSF) markers, and histological characteristics.

Figure 1: PRISMA flow diagram



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Additionally, clinical data from case observations at the Neurology Department in Cluj-Napoca were reviewed, with a focus on patients with ambiguous presentations who met partial diagnostic criteria for both disorders.

3. Results

A. Inaccuracy of the levels of intrathecal/serum antibodies

We can state that when a patient presents with a clinical presentation that could be attributable to both diseases, or unclear symptoms that cause differential diagnosis challenges, we have four possible possibilities to consider:

- The patient could have MS with Anti-*Borrelia* antibodies. In this scenario, we must assess if the antibodies are true positive or false positive.
- If results are false positive, the patient may have MS that mimics LNB.
- True positive results indicate either LNB imitating MS or LNB associated with MS.

As a result, the problem is to determine whether the Anti-*Borrelia* antibody analysis is true or false positive. This challenge is based on a number of facts, including:

- Serum IgM antibodies are useful in patients with a disease of less than 4 weeks[1]
- Intrathecal Bb antibody production has limitations:
    A. It is absent during the first 6 weeks post-infection;
    B. It persists even after the bacteria disappeared, thereby being false positive;
    C. A positive test does not discriminate between actual and past infection.[7]

B. Clear diagnostic criteria

Studies have shown that most patients with LNB present the following features:

a. New neurological symptoms and objective findings suggestive of LNB;
b. Lymphocytic pleocytosis (> 5 leucocytes/mm3);
c. Intrathecal *Borrelia* antibody production at presentation or during follow-up with values of the Antibody Index > 2.[7]

C. Clinical and Imaging Overlap

Even though each disease has distinct symptoms, their association with other signs and ambiguous symptoms makes it difficult to distinguish between them. Imaging techniques can be useful most of the time, however in rare situations of LNB, the lesions can resemble those in MS. [4]

- **LNB Presentation:** Common symptoms include headache, radiculitis, facial nerve palsy, fatigue, cognitive impairment, and peripheral neuropathy. Patients should have a tick bite or rash as a result of their encounter with the vector. The disease has a geographical distribution.[2]
- **MS Presentation:** Typical symptoms include optic neuritis, ataxia, and brainstem disorders. The first symptoms usually appear around adolescence, and the patient is generally afebrile.[8]
- **MRI Findings:** Demyelinating lesions can appear in both disorders. MS lesions usually occur in the periventricular area and are gadolinium-enhanced during relapses.[10] In some cases of LNB, they are more variable and less specific.[11]

D. Laboratory Findings

- **Serology:** Serum IgM is only reliable within the first 4 weeks of LNB.[1] Intrathecal antibody index (AI) >2 suggests LNB but may remain elevated long after infection, reducing specificity.[7]
- **CSF Analysis:**
    - LNB: Lymphocytic pleocytosis and increased Bb-specific antibody index.[7]
    - MS: Oligoclonal bands.[2]

E. The Role of CXCL13

CXCL13 is a B-lymphocyte-attracting chemokine that has been demonstrated to be highly accurate in the early diagnosis of acute LNB, as it is significantly higher than MS and returns to normal levels following therapy.[7,12] Ljøstad et al. found that increased CSF CXCL13 and positive CSF Bb AI had a pre-treatment sensitivity of 100% (95% CI = 91-100) and 78% (95% CI = 75-96), respectively ($p = 0.053$). Mean CSF CXCL13 levels were significantly greater in LNB (3524 ng/g CSF protein) compared to MS (27 ng/g) ($p<0.001$).[7]

4. Discussion

The overlapping characteristics of LNB and MS highlight the necessity for a defined differentiated diagnosis methodology.[1] Reliance on MRI and antibody levels is insufficient because:

1. Persistently positive intrathecal antibodies post-LNB resolution.[7]
2. Lack of serum antibodies during the first 4 weeks post-infection.[1]
3. Variable MRI findings that lack disease specificity.[4, 11]

In contrast, CXCL13 provides a dynamic, quantitative marker with great sensitivity and specificity.[7] Furthermore, its quick rise and fall after treatment make it important not only for diagnosis but also for monitoring treatment efficacy.[12] However, many health systems, including Romania, do not currently use this marker in regular testing. This is why more research is necessary. In Romania, for

example, the implementation of a similar experiment will be beneficial to evaluate the role of CXCL13 as a supplement in the early detection of LNB. This can be accomplished through collaboration between the Neurology and Infectious Diseases departments in Cluj-Napoca. The study will compare the gold standard diagnostic criteria (the three aforementioned criteria: new neurological symptoms and objective findings suggestive of LNB; lymphocytic pleocytosis (> 5 leucocytes/mm3); and intrathecal *Borrelia* antibody production at presentation or during follow-up with Antibody Index values > 2) to the CXCL13 value. The data will be evaluated based on the patient's symptom remission and progression. A cut-off value for CXCL13 analysis (using the ROC curve) can be determined for the Romanian population. Finally, the findings will be published, with the hope of changing diagnostic and treatment guidelines (in accordance with the protocol described by Ljøstad et al.).[7]
Furthermore, a differentiation in the populations of lymphocytes, dendritic cells and CD markers in CSF for each disease was observed, but larger studies are to be conducted. As a result, while immunophenotyping is still in its early stages, it has the potential to pave the way for new diagnostic assays.[13,14,15]

The results we found were promising:

Table 1: Populations of lymphocytes, dendritic cells and CD markers in CSF

	Adam et al. (13)	Heinrich et al. (16)	Pashenkov et al. (17)
LNB	CD19 and/or CD138 B-cells	highest proportion of CD38 and lower CD25+ T-cells	Plasmacytoid dendritic cells elevated
MS	CD4+ and CD8+ T-cells	higher proportions of CD38 and CD25 T-cells	Increased number of CSF dendritic cells, especially Myeloid

Interestingly, studies have described the relationship of LNB with Parkinsonism[10], Toxoplasmosis[4], and monolateral neurosensory hearing loss[18], demonstrating once again the wide range of symptoms that this disease can cause. However, measles (M), rubella (R), and varicella zoster (Z) viruses (MRZ reaction) have been linked to MS. The MRZ reaction was found to be a statistically significant marker in the differential diagnosis of MS and NB, increasing several times in patients with MS.[19]

5. Conclusions

Despite their distinct causes, Lyme neuroborreliosis and multiple sclerosis have comparable symptoms that complicate diagnosis and delay beginning of appropriate treatment.[1,20] The conventional triad for LNB remains the gold standard;[7] however it has considerable limitations, particularly in terms of anti-*Borrelia* antibody levels.[1,7,21] CXCL13 has demonstrated significant potential as an early, accurate biomarker and should be included in conventional diagnostic techniques, particularly in endemic

areas.[7,12] Immune cell profiling is a promising future direction that deserves additional research.[13,16,17] Implementing these findings on a broader scale, either by running both tests and comparing the results, or even by replacing the antibody analysis with CXCL13, could significantly enhance diagnosis accuracy and therapeutic success.

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