Lyme neuroborreliosis in cases of non-specific neurological symptoms

BACKGROUND Analysis of cerebrospinal fluid is required in order to diagnose Lyme neuroborreliosis. We investigated the symptoms of patients in a highly endemic area who were referred for evaluation of possible Lyme neuroborreliosis, and explored whether cerebrospinal fluid analysis confirmed or ruled out the diagnosis.

METHOD We reviewed the medical records of all patients who underwent lumbar puncture at Sørlandet Hospital Arendal in the period 1 January 2013 to 31 December 2013.

RESULTS A total of 140 patients were referred with suspected Lyme neuroborreliosis. Of these, 110 patients had non-specific neurological symptoms (e.g. fatigue, dizziness and headache), only one of whom received a diagnosis of possible Lyme neuroborreliosis. Thirty patients had symptoms typical of the condition (such as radiculitis or peripheral facial nerve palsy). Six of these were diagnosed with definite Lyme neuroborreliosis, and one with possible Lyme neuroborreliosis. None of those diagnosed with Lyme neuroborreliosis had had symptoms lasting more than six months.

INTERPRETATION The probability of Lyme neuroborreliosis is low in the absence of typical symptoms of the condition, even when anti- *Borrelia* antibodies are detected in serum and especially when the symptoms are of long duration.

Lyme disease is a vector-borne zoonosis that is caused by infection with the spirochete *Borrelia burgdorferi* following a tick bite (1). Early localised disease manifests as erythema migrans, and approximately half of those infected have non-specific symptoms such as fever, myalgia, lymphadenopathy and headache (2).

Lyme neuroborreliosis is the most widespread form of disseminated borreliosis in Europe. The condition is reported in 3–12% of those with untreated early localised disease, usually four to eight weeks after a tick bite, but both earlier and later onset occur (3–7). The most common clinical manifestation of Lyme neuroborreliosis is Bannwarth’s syndrome, which consists of peripheral facial nerve palsy or ocuolomotor nerve palsy, radiculitis with symptoms including radiating pain, changes in sensation and/or paralysis, and the presence of lymphocytes in the cerebrospinal fluid (7, 8). In children, typical presentation is facial nerve palsy with low-grade meningitis symptoms without radiculitis (9). In rarer cases of Lyme neuroborreliosis, there may be peripheral neuropathy, cognitive impairment, cerebellar ataxia, encephalitis and myelitis (1, 7).

In Norway, Lyme neuroborreliosis is diagnosed on the basis of European guidelines. These require neurological symptoms consistent with the disease, as well as lumbar puncture showing pleocytosis and a positive antibody index as evidence of intrathecal anti- *Borrelia* antibody production (Box I) (10). In 10–30% of those with symptom duration of less than six weeks, *Borrelia* antibodies are not detected in the cerebrospinal fluid (CSF) or in serum, which makes early diagnosis challenging (11).

Between 28 and 50% of those who undergo treatment for Lyme neuroborreliosis develop post-treatment Lyme disease (PTLD), which is marked by fatigue, neuropsychological symptoms and reduced quality of life (12, 13). Diagnostic criteria have been proposed for this condition, but its aetiology, diagnosis and clinical significance remain uncertain and controversial (14–16).

In 2015, a total of 425 cases of disseminated borreliosis, neuroborreliosis, Lyme carditis and Lyme arthritis were recorded in Norway (17). The coastal regions of the Agder counties are considered highly endemic for *Borrelia*, with up to 31.1% of ticks being carriers of *Borrelia* species (18).

At Sørlandet Hospital the number of referrals for possible Lyme neuroborreliosis has increased in recent years. We have investigated the symptoms shown by these patients and the duration of those symptoms, the results of CSF analysis, and the final diagnosis.

Material and method

Patients

The medical records of all outpatients and inpatients who underwent lumbar puncture in the Department of Neurology, Sørlandet Hospital Arendal in the period 1 January 2013 to 31 December 2013 were reviewed.

There was a low probability of Lyme neuroborreliosis in cases of prolonged non-specific neurological symptoms, including when anti- *Borrelia* antibodies were detected in serum.

Lyme neuroborreliosis should be suspected in patients with painful radiculitis that worsens at night, especially when accompanied by numbness in a dermatomal distribution and peripheral facial nerve palsy.

Patients with symptoms of Lyme neuroborreliosis should be assessed with lumbar puncture.
Interpretation

3 of 3 criteria: Definite Lyme neuroborreliosis
2 of 3 criteria: Possible Lyme neuroborreliosis
1 of 3 criteria: Negative for Lyme neuroborreliosis

Results

Of the patients who did not receive a diagnosis of Lyme neuroborreliosis, 52% had myalgias, 43% tiredness/fatigue and 42% non-specific paraesthesias. Eight per cent had been bitten by ticks within the last three months and 5% had had a rash suspected of being erythema migrans. In this group, 45% had had symptoms for less than three months and 30% for more than 12 months (Table 2). Of the eight who received a diagnosis of definite or possible Lyme neuroborreliosis, 63% had peripheral facial nerve palsy, and 50% had radiculitis and paraesthesias in a dermatomal distribution. None reported a history of erythema migrans. Two of the eight described tick bites within the last three months.

In all, 24% of patients who were referred for evaluation of possible Lyme neuroborreliosis on the basis of new-onset peripheral facial nerve palsy received a diagnosis of definite or possible disease. All six patients who were diagnosed with definite Lyme neuroborreliosis tested positive for Borrelia IgG antibodies in serum, with values exceeding 650% of cutoff.

Discussion

Our study revealed that 79% of those referred for lumbar puncture upon suspicion of Lyme neuroborreliosis did not have typical symptoms of the disease – they were referred because of non-specific neurological symptoms such as prolonged tiredness, non-specific paraesthesias, difficulties with concentration, and myalgias. Patients in this group were unlikely to be diagnosed with Lyme neuroborreliosis.

Many of those who were diagnosed with definite or possible Lyme neuroborreliosis had had symptoms for less than three months, and none had had symptoms for more than six months. This may indicate that prolonged non-specific symptoms render a diagnosis of Lyme neuroborreliosis less likely. The symptoms of the disease are often such that patients seek medical assistance relatively quickly. A large percentage of the patients with non-typical symptoms had had them for more than a year, and none received a diagnosis of Lyme neuroborreliosis.
Whether lumbar puncture is necessary to diagnose Lyme neuroborreliosis is subject to international debate. Lumbar puncture is not required in the USA, whereas positive CSF results are required in Europe (7, 10, 20, 21).

Certain doctors and patients argue that Lyme neuroborreliosis can be diagnosed on the basis of symptoms alone, including non-specific symptoms such as tiredness, myalgias and headache, and with the use of non-validated tests (15, 22). However, non-specific symptoms are common in the general population and there is little evidence that these are necessarily caused by Lyme neuroborreliosis; such diagnostic criteria are therefore not accepted by the major international academic communities (8, 14–16, 23, 24). An increased focus on the possible under-diagnosis of Lyme neuroborreliosis in persons with medically unexplained symptoms may have led to the increased use of lumbar puncture observed in recent years.

In our dataset, we found that all patients with definite Lyme neuroborreliosis had relatively high titres of *Borrelia* IgG antibodies in serum. Similar values were seen in 27 % of those who did not receive the diagnosis. In Sogn og Fjordane county, 10 % of healthy blood donors are *Borrelia*-IgG-seropositive – without this being associated with health problems (24, 25). In Vest-Agder county, 18 % of the population have serum antibodies (26). Exposure to *Borrelia* can lead to seropositive status for several years, for both IgM and IgG (27). A number of those with non-specific neurological symptoms may have been referred for evaluation for Lyme neuroborreliosis after testing positive for *Borrelia* antibodies at their GP surgery. The detection of anti-*Borrelia* antibodies in serum does not necessarily mean that a patient’s health problems are caused by Lyme neuroborreliosis, but a positive result may support the diagnosis in those who do have symptoms of the disease (24).

Peripheral facial nerve palsy was present in 63 % of patients with possible or definite Lyme neuroborreliosis, and 24 % of those assessed for peripheral facial nerve palsy received a diagnosis of either possible or definite Lyme neuroborreliosis. None of the eight patients with definite or possible Lyme neuroborreliosis had had a rash suspected of being erythema migrans, and only two recalled a tick bite within the last three months. It is known that about half of patients with Lyme neuroborreliosis do not recall either a tick bite or erythema migrans (7, 28).

Lyme neuroborreliosis is thus an important differential diagnosis in cases of new-onset peripheral facial nerve palsy, irrespective of whether the patient can recall a tick bite or erythema migrans. Sørlandet Hospital has introduced lumbar puncture for all patients with peripheral facial nerve palsy, and our results support this practice in an area highly endemic for *Borrelia*. None of those who received a diagnosis of possible or definite Lyme neuroborreliosis had symptoms of meningitis (headache with hypersensitivity to light and sound, and nausea or vomiting). The symptoms of *Borrelia* meningoencephalitis may be pronounced but often resemble those of viral meningitis – headache of varying severity and fluctuating fever, but with no other signs of meningitis (29).

One limitation of this study is that it is based on a review of medical records and not on direct discussions with, and examination of, patients. The dataset is relatively small, with only six patients with definite Lyme neuroborreliosis. Most of the records and referrals provided a good picture of symptoms and medical history, but it was not possible to resolve any ambiguities in the self-reported medical history and clinical results. We assumed that if a symptom was not described in the referral or medical records, then the patient had not had that symptom – however, this cannot be ruled out for certain. The individual who recorded symptoms was not formally blinded with respect to the results of the CSF analysis.

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The author has completed the ICMJE form and reports no conflicts of interest.

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<th>Symptoms</th>
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<th>Negative for Lyme-neuroborreliosis (n = 132)</th>
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ORIGINAL ARTICLE

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References

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