A positive antibody response may lead to more confusion than clarification.

Could it be Lyme neuroborreliosis?

Borrelia bacteria can be transmitted to humans through tick bites and give rise to Lyme neuroborreliosis. Disease manifestation varies in terms of symptoms and time course. Most patients experience subacute onset of neurological symptoms weeks or months after infection, the most common being facial nerve palsy or focal neurogenic pain owing to radiculitis (1, 2). Other symptoms may include diplopia, hearing impairment, paralysis, altered sensation, difficulty in walking or cognitive impairment. In rare cases, patients show prolonged neurological symptoms that progress over months or years: so-called late-stage disease. Clinical neurological examination usually reveals objective findings, but in the early stages radiculitis may manifest purely as pain. Analysis of cerebrospinal fluid reveals signs of inflammation with an elevated lymphocyte count (3). The vast majority of patients who have had symptoms for more than two months have antibodies against the *Borrelia* bacterium in their serum and cerebrospinal fluid (2). However, detecting *Borrelia* antibodies is insufficient to diagnose Lyme neuroborreliosis. Up to 18 % of healthy persons also have serum antibodies (4), and some show antibody production in their cerebrospinal fluid without an elevated lymphocyte count. Some of these individuals may have undergone previous treatment for the disease or had an infection that resolved spontaneously.

Chronic and diffuse pain and fatigue disorders with non-specific neurological symptoms are common in the general population. Such symptoms are not typical of neuroborreliosis, but an article in this issue of the Journal of the Norwegian Medical Association shows that patients are often evaluated for this disease (5). In Aust-Agder in 2015, 140 individuals were referred for lumbar puncture to test for possible Lyme neuroborreliosis. Approximately one in four tested positive for *Borrelia* antibodies in serum. Only 30 of the 140 had typical symptoms of Lyme neuroborreliosis. Non-specific symptoms were present in 110 patients, half of whom had had them for more than six months. This liberal approach to testing patients for Lyme neuroborreliosis may reflect the strong focus on tick-borne diseases in general. Media coverage of individual cases may create the impression that *Borrelia* infections are a common cause of otherwise unexplained chronic symptoms.

In the Aust-Agder study, none of those with prolonged non-specific symptoms were diagnosed with Lyme neuroborreliosis following lumbar puncture. The fact that clinical neurological examination was not performed systematically prior to lumbar puncture is a limitation of the study, as is the fact that the number of patients was too small to allow any firm conclusions to be drawn about diagnostic value. But the result is in line with broad clinical experience suggesting a low probability of Lyme neuroborreliosis in patients with prolonged non-specific symptoms (6, 7). In this patient population, lumbar puncture to rule out the disease is unnecessary if *Borrelia* antibodies cannot be detected in serum. In the event of a positive serum test, lumbar puncture should be performed if clinical examination fails to exclude neurological affection.

Liberal assessment practices mean that we often find ourselves faced with patients with non-specific symptoms and a positive antibody test. In such cases the diagnosis is uncertain, and it is important to convey this to the patient. First, there is a small possibility of active *Borrelia* infection in the early dissemination phase in which symptoms may be predominantly non-specific. Many choose to administer a two-week course of antibiotics to cover this possibility, but there is little justification for this in cases with prolonged symptoms. Second, the positive antibody test may be a chance finding. A study of approximately 1200 Norwegian blood donors, for example, found no correlation between subjective health complaints and *Borrelia* antibodies in serum (8). Third, the antibodies may be a marker of late effects of a previously treated or unrecognised *Borrelia* infection: so-called post-treatment Lyme disease. This term arose due to a number of patients reporting persistent non-specific health problems after completing treatment (6, 9), but the incidence of post-treatment Lyme disease is controversial and its mechanisms unknown (7). While this possibility should be considered in individual patients, it is important to communicate to patients that the symptoms are not due to active infection and that long-term antibiotic treatment is ineffective (10).

It is thus very unlikely that chronic non-specific neurological symptoms in the absence of objective findings upon clinical neurological examination are due to active Lyme neuroborreliosis, even when *Borrelia* antibodies are detected in serum, or in the cerebrospinal fluid without an increased cell count. Patients should be informed about other more likely explanations for a positive antibody result in order to avoid uncertainty and inappropriate treatment with antibiotics.

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References
1. Ljøstad U, Skogvoll E, Eikeland R et al. Oral doxycycline versus intravenous ceftriaxone for European Lyme neuroborreliosis: a multicentre, non-inferiority, double-blind, randomised trial. Lancet Neurol 2008; 7: 690–5.
2. Stanek G, Wormser GP, Gray J et al. Lyme borreliosis. Lancet 2012; 379: 461–73.
3. Mygland A, Ljøstad U, Fingerle V et al. EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis. Eur J Neurol 2010; 17: 8–16, e1–4.
4. Mygland A, Skarpaas T, Ljøstad U. Chronic polyneuropathy and Lyme disease. Eur J Neurol 2006; 13: 1213–5.
5. Roaldsnes E, Eikeland R, Berild D. Lyme-nevroborreliose ved uspesifikke nevrologiske symptomer. Tidsskr Nor Legeforen 2017; 137: 101–4.
6. Hu LT. Lyme Disease. Ann Intern Med 2016; 165: 677.
7. Koedel U, Pfister HW. Lyme neuroborreliosis. Curr Opin Infect Dis 2017; 30: 101–7.
8. Hjetland R, Reiso H, Ihlebæk C et al. Subjective health complaints are not associated with tick bites or antibodies to Borrelia burgdorferi sensu lato in blood donors in western Norway: a cross-sectional study. BMC Public Health 2015; 15: 657.
9. Eikeland R, Mygland A, Herlofson K et al. European neuroborreliosis: quality of life 30 months after treatment. Acta Neurol Scand 2011; 124: 349–54.
10. Berende A, ter Hofstede HJ, Vos FJ et al. Randomized Trial of Longer-Term Therapy for Symptoms Attributed to Lyme Disease. N Engl J Med 2016; 374: 1209–20.