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Nervous System Involvement in Lyme Borreliosis

Katarina Ogrinc and Vera Maraspin*

Department of Infectious Diseases, University Medical Center Ljubljana, Slovenia

Abstract: Lyme neuroborreliosis (involvement of the central and/or peripheral nervous system due to infection with *B. burgdorferi* sensu lato) is the second most frequent manifestation of Lyme borreliosis in Europe, while it comprises the third most common expression of the disease in North America. Early Lyme neuroborreliosis, which is much better defined and far more common than late Lyme neuroborreliosis, is in Europe caused mainly by *B. garinii* and comprises the classic triad of meningitis, radiculoneuritis and/or cranial neuropathy, while in American patients subacute meningitis with or without cranial neuropathy is the most common manifestation. Among chronic forms of European Lyme neuroborreliosis peripheral neuritis associated with acrodermatitis chronic atrophicans is most frequently observed. A reliable diagnosis of borrelial central nervous system infection requires demonstration of lymphocytic pleocytosis and the evidence of borrelial infection of the central nervous system, established by intrathecal synthesis of specific antibodies and/or isolation of *Borreliae* from the cerebrospinal fluid. Treatment with oral doxycycline, or parenteral penicillin or third generation cephalosporins (most frequently ceftriaxone) for 2-4 weeks is efficient in the majority of patients..

Keywords: *Borrelia burgdorferi* sensu lato, *Borrelia garinii*, chronic meningitis, cranial neuropathy, encephalomyelitis, meningitis, meningo-radiculoneuritis, peripheral neuropathy.

INTRODUCTION

Lyme borreliosis is a multi-systemic infectious disease caused by the spirochete *Borrelia burgdorferi* sensu lato (*B. burgdorferi* s.l.), and is transmitted by *Ixodes* species ticks [1]. The most frequent manifestation of the disease is erythema migrans (EM) - a characteristic erythematous skin lesion, that develops days to weeks after infection at the site of a tick bite, expands over time, often with central clearing and reaches at least 5 cm in diameter [2, 3]. If hematogenous dissemination of the causative agent occurs, EM can be followed by multiple EM skin lesions or by nervous system or heart involvement, and later on by arthritis; late involvement of nervous system, joints, skin or the eye may also occur, but a complete presentation of the disease is extremely rare [4 - 6].

Lyme neuroborreliosis is the involvement of the central and/or peripheral nervous system due to infection with *B. burgdorferi* s.l. Before serodiagnostics was available, the diagnosis of Lyme neuroborreliosis was often missed, but after serological tests became widely available, the disease seems to become overdiagnosed, since the prevalence of seropositivity in endemic regions is high. Therefore, clinical manifestations of Lyme neuroborreliosis and strict diagnostic criteria have to be known and considered.

The aim of the manuscript is to give an overview of the field with special emphasis on clinical manifestations and diagnosis of Lyme neuroborreliosis.

INCIDENCE AND ETIOLOGY

Lyme borreliosis is the most common tick-borne infectious disease in countries with moderate climates in Eurasia and North America. The incidence of the disease is increasing in many countries, reaching up to several hundred per 100.000 inhabitants in some of them [7 - 9].

* Address correspondence to this author at Japljeva 2, 1525 Ljubljana, Slovenia; Tel: +386 1 5222110; Fax.: +386 1 52224564; Email: vera.maraspin@kclj.si

According to the European data, the percentage of patients with Lyme neuroborreliosis, which is the second most frequent manifestation of Lyme borreliosis in Europe [5, 6, 10], differs from 3 [7, 11] to 16 % [10], while in North America nervous system involvement is the third most frequent manifestation of the disease (following skin and joint manifestations), and is reported to occur in 12% of confirmed cases of Lyme borreliosis [8].

In Europe, Lyme borreliosis is caused most often by *Borrelia afzelii (B. afzelii)*, followed by *Borrelia garinii (B. garinii), Borrelia burgdorferi* sensu stricto (*B. burgdorferi* s.s.) and only exceptionally by other *Borrelia* species, which leads to a broader clinical spectrum of the disease compared with North America, where only one species causes the disease in humans - *B. burgdorferi* s.s. [6]. The predominant etiologic agent of Lyme neuroborreliosis in European patients is *B. garinii,* followed by *B. afzelii,* rarely the cause is *B. burgdorferi* s.s. and only exceptionally *B. valaisiana, B. bissettii* or other borrelial species [12 - 20].

It has been found out that different Lyme borrelia genospecies and their geographical distribution are connected with particular clinical manifestations of Lyme borreliosis (most probably owing to their diverse organotropism), leading to some differences between the European and North American clinical picture of the illness [1, 4, 15, 21 - 23].

CLINICAL MANIFESTATIONS

Nervous system involvement usually appears weeks to months after the infection with *B. burgdorferi* s.l. (as a part of early disseminated Lyme borreliosis) and persists for several weeks to months, but may also develop later and persist longer. In some patients, other manifestations of borrelial infection can occur concurrently to Lyme neuroborreliosis, most often EM skin lesion [1, 10].

EARLY LYME NEUROBORRELIOSIS

European early Lyme neuroborreliosis is mostly an acute illness. The classic triad of distinct neurological manifestations consists of lymphocytic meningitis, cranial neuropathy (particularly involving the facial nerve), and radiculoneuritis (sensory or motor or both) [5, 6, 24 - 27].

The clinical picture of **meningo-radiculoneuritis (Garin-Bujadoux-Bannwarth syndrome)** has been a well known entity in Europe for several decades before the discovery of it's spirochetal etiology [28 - 31]. It is defined as a painful meningo-radiculoneuritis with or without peripheral or cranial nerve affection, caused by infection with *B. burgdorferi* s.l. In a substantial number of patients (34-64%) EM may appear prior to or concomitant with neurological impairment [29, 26 - 36] Neurological symptoms typically develop 4-6 weeks after a tick bite or appearance of EM. The most pronounced clinical symptom is severe radicular pain which is burning, biting, boring or tearing in nature, is usually located on trunk, often belt-like, with possible radiation into extremities and almost unresponsive to usual analgesics. It seems to be more severe in elderly and intensifies during the night; patients may be deprived of sleep for several weeks. The location of pain very often matches the site of the tick bite or EM [28, 36, 37], although some reports didn't show any relation of the pain and tick bite and/or EM location [38]. Within 1-4 weeks after the beginning of radicular pain, further neurological complications may develop: cranial nerve palsies with the seventh cranial nerve being most commonly involved (sometimes bilateral), and/or sensory (dysesthesia, hyperesthesia) and/or motor deficit of involved region, which usually results in asymmetric pareses that are not always clinically prominent [32, 38, 39]. Other accompanying symptoms or signs, such as headache, fatigue, loss of appetite, photophobia or meningeal signs may be present [34, 35, 40] but also neuropsychological symptoms, such as agitation, depression, anxiety, and restlessness have been observed [35]. Even in patients not treated with antibiotics, the pain resolves spontaneously after some weeks or months, but late stage of Lyme neuroborreliosis may follow. Meningo-radiculoneuritis is much more often seen in European than American patients, affects predominantly adult population over 40 years of age, and for an unknown reason is extremely rare in children [1, 24, 25].

The course of borrelial **meningitis** in adult European patients resembles mild but protracted viral meningitis with intermittent improvements and deteriorations. Clinically it manifests with mild and intermittent headaches, but in some patients headache may be prominent. Meningeal signs are only mildly expressed or absent, nausea, vomiting and fever are rare [5, 6, 17, 20, 25, 41]. In children, isolated meningitis is more common than in adults [4, 5, 36, 42 - 44].

Among **cranial neuropathies** peripheral facial palsy is by far the most frequent manifestation. It can be unilateral or bilateral, can occur in association with meningo-radiculoneuritis (Garin-Bujadoux-Bannwarth syndrome), or is the first and the only clinical sign of Lyme neuroborreliosis. Clinically it is manifested as facial weakness or paralysis, eye problems (sore eye, lacrimation), taste disturbances, numbness, earache, and increased sensitivity to sound. In the

majority of patients peripheral facial palsy of borrelial origin is associated with lymphocytic pleocytosis, indicating concomitant central nervous system (CNS) involvement, however symptoms and signs of meningitis are frequently absent [1, 6, 45, 46]. Very early in the course of the disease, lymphocytic pleocytosis may be absent, but usually evolves in the following days. In Slovenia, which is a highly endemic country for Lyme borreliosis, borrelial infection was established in 22/114 (19.3%) adult patients who presented with isolated peripheral facial palsy, and among them 12/22 (54.5%) had lymphocytic pleocytosis [45]. Prognosis of borrelial peripheral facial palsy is good in antibiotic-treated and also in untreated patients [1, 24]; full or almost full recovery is expected in over 90% of patients [46]. In children, peripheral facial palsy occurs more often than in adults [4, 5, 43, 47, 48]. Involvement of all other cranial nerves has been described, with the exception of the olfactory nerve, but particularly III (oculomotor), VI (abducens), and VIII (vestibule-auditory) can be affected. These rare abnormalities are clinically manifested with diplopia and hearing loss and/or dizziness, respectively [1, 5, 6, 25, 26, 46].

It should be emphasized, that the above described typical clinical manifestations of early Lyme neuroborreliosis in European patients are due to *B. garinii* infection. However, it has been established, that the majority of patients with the *B. afzelii* infection of the CNS (proved by isolation), doesn't fulfill the diagnostic criteria for the European Lyme neuroborreliosis [17].

American Lyme neuroborreliosis almost always presents as subacute meningitis with or without associated cranial neuropathy (usually facial palsy). The disease develops within a few weeks to a few months after infection or the EM skin lesion. Headache, meningeal signs, migrating numbness or tingling, malaise, fatigue, myalgia and mild cognitive symptoms are common. Radicular symptoms may be present, but painful radiculitis is only occasionally seen in American patients [18, 24, 46, 49].

Some other neurological entities, like meningoencephalitis with cerebellar ataxia, paraplegic meningomyelitis, meningoencephalomyelitis, hemiparesis, exogenous psychosis and extrapyramidal syndrom were also described as possible manifestations of early Lyme neuroborreliosis, but it should be emphasized, that borrelial etiology in these clinical entities is extremely rare.

LATE LYME NEUROBORRELIOSIS

In general, nervous system involvement late in the course of Lyme borreliosis is much less common than in early disseminated stage of the disease [5, 27]; it represents less than 1-2% of all patients with Lyme neuroborreliosis and is described primarily in Europe [36]. Central or peripheral nervous system can be affected.

Chronic borrelial infection of the CNS is a distinct clinical manifestation of the illness, defined as an active and long-lasting (more than 6 months) disease with persistent and marked cerebrospinal fluid (CSF) inflammation. Clinically it is manifested as chronic meningitis, progressive encephalomyelitis, or radiculomyelitis [36, 42, 50, 51].

Chronic meningitis is characterized by headache, malaise, sensorineural hearing loss and considerable weight loss.

Progressive encephalomyelitis, a rare form of chronic parenchymal borrelial infection with white matter involvement, manifests with spastic para or tetraparesis, ataxia, mental disorders, urinary bladder dysfunction, and sometimes with VII/VIII cranial nerve involvement [25, 50, 52, 53].

Acrodermatitis chronica atrophicans associated **peripheral neuropathy**, which is primarily caused by *B. afzelii* is the most common manifestation of late Lyme neuroborreliosis in Europe and occurs in more than half of patients with advanced acrodermatitis chronica atrophicans skin lesions [25, 54, 55]. It involves sensory nerves in affected parts of the skin (typically distal parts of extremities), is usually not associated with CSF inflammation, and is probably a result of direct extension of borrelial infection from the skin to the cutaneous nerves. Patients complain of hypesthesia, paresthesia and pain. The course of the neuropathy is usually mild and chronic, but even with appropriate antibiotic treatment, symptoms often persist. Peripheral neuritis without acrodermatitis chronica atrophicans is probably an extremely rare condition [5, 6, 36].

Lyme encephalopathy is reported predominantly by American authors. It is marked by fatigue, impairment of memory and other intellectual functions, normal imaging and CSF findings, and is not due to direct *Borrelia* CNS involvement, as was often mistakenly thought, but is probably a condition mediated by cytokines and other neuro-immunomodulators in patients with non CNS borrelial manifestations [1, 27, 56 - 61]. Interpretation of this disorder is further complicated by the fact that a marked proportion of the general population experiences similar symptoms in the absence of any medical diagnosis [60].

DIAGNOSIS

The diagnosis of Lyme neuroborreliosis should be based on typical clinical picture and laboratory findings, including CSF pleocytosis, and positive serology, culture and/or PCR result [2, 3, 5, 17, 36, 62, 63].

Clinical diagnosis of early Lyme neuroborreliosis, which typically appears as lymphocytic meningitis, radiculoneuritis and cranial neuropathy, is straightforward, when the triad is complete or when at least one manifestation of the triad is accompanied by EM [1 - 3, 24, 63].

In patients with early Lyme neuroborreliosis, CSF shows pleocytosis up to several hundred leucocytes x 10^6/L, with lymphocytic predominance, normal to moderately raised protein concentration, normal to slightly lowered glucose concentration, and inflammatory disturbances of the blood-brain barrier. In some patients with peripheral facial palsy of a recent onset, CSF pleocytosis may not be present. In chronic progressive encephalomyelitis, CSF lymphocytic pleocytosis, usually with activated B-lymphocytes and intrathecally synthesized specific IgG antibodies in CSF, have to be present to establish the diagnosis of late borrelial infection of the CNS, while in Lyme encephalopathy CSF cell count is normal [56, 57, 59].

Borrelial etiology of CNS infection is proved by demonstration of intrathecal *B. burgdorferi* s.l. antibody synthesis, isolation of *Borreliae* from the CSF and/or demonstration of borrelial DNA in CSF sample [2, 3, 5, 17, 27, 63 - 69]. In everyday European clinical practice, the demonstration of the intrathecally synthesized borrelial antibodies is the most useful method to diagnose Lyme neuroborreliosis. For this purpose, the approach described by Reiber *et al*. is commonly used in which comparison of simultaneously measured serum and CSF concentrations of total and specific borrelial IgM and IgG antibodies is necessary [70 - 72]. The limitations of this approach are the absence of intrathecal *B. burgdorferi* s.l. specific antibody synthesis during the first few weeks of the disease, and persistence of the synthesis for several months or even years, also after appropriate antibiotic treatment [2, 3, 5, 17, 63].

Isolation of the etiologic agent from the CSF is the most reliable microbiologic method for diagnosis of Lyme neuroborreliosis, but is technically demanding, expensive, time-consuming (results are obtained only after several weeks), available only in selected laboratories, and has a rather low sensitivity; in confirmed cases of Lyme neuroborreliosis, CSF culture is positive in 10-15% of patients [17, 20, 73, 74]. PCR detection of borrelial DNA in CSF samples has low sensitivity, can't differentiate between living and dead borrelial cells, and the procedure is not standardized [63]. Seroconversion alone is rarely useful in practice, because at the time of neurological disease, the majority of patients are seropositive. Besides, seroconversion proves recent borrelial infection but not CNS involvement [5].

In recent years, studies of cytokines and chemokines have shown that the level of the CSF CXCL13 is significantly higher in patients with untreated Lyme neuroborreliosis than in patients with other inflammatory or non-inflammatory CNS diseases. CSF CXCL13 level may become a useful biomarker for the diagnosis and follow-up of Lyme neuroborreliosis [75 - 78].

Diagnosis of borrelial peripheral nervous system infection is even more difficult than demonstration of borrelial CNS involvement. Besides an objective evidence of the peripheral nervous system involvement (clinical, neurophysiologic and/or neuropathologic findings), borrelial infection of the involved nerves should be demonstrated; the presence of specific antibodies in serum is not enough for a reliable diagnosis. The proof that the borrelial infection really is the cause of the peripheral nervous system involvement depends upon the presence of concomitant CNS borrelial infection (with characteristic CSF findings) and/or the presence of other typical borrelial manifestations such as acrodermatitis chronica atrophicans [5]. Thus, in acrodermatitis chronica atrophicans associated peripheral neuritis, the diagnosis is established on the basis of characteristic neurological symptoms in the area of typical acrodermatitis chronica atrophicans skin lesion, positive borrelial serology (usually very high levels of specific antibodies in serum) and compatible histologic skin findings [1, 5, 79, 80]. Sometimes additional diagnostic procedures, *e.g.* borrelial skin culture or PCR for detection of borrelial DNA in skin biopsies, may be helpful [81, 82]. Several other diagnostic approaches (*e.g.* blood microscopy, CD57 levels and lymphocyte transformation test) have not been proven to be clinically useful, mainly due to the lack of specificity [83].

DIFFERENTIAL DIAGNOSIS

In early stages, borrelial meningo-radiculoneuritis with or without paresis has to be differentiated from mechanical radiculopathy by characteristic CSF findings and neuroimaging. Painful herpes zoster radiculitis is differentiated by typical rash of shingles. Due to CSF inflammation, other causes of acute, subacute and chronic meningitis must be ruled

out (tick borne encephalitis in endemic areas, other viral, bacterial, tuberculous or fungal meningitis); noninfectious CNS diseases like neurosarcoidosis and leptomeningeal metastases also have to be considered. Facial palsy of borrelial etiology has to be differentiated from idiopathic Bell's palsy, herpes zoster virus infection and, particularly when bilateral, from neurosarcoidosis [6, 25, 36]. Rheumatic polymyalgia is sometimes mentioned in the differential diagnosis of the early Lyme neuroborreliosis. However, rheumatic polymyalgia ("pain in many muscles") is characterized by pronounced pain and/or stiffness in many muscles, and marked fatigue. In addition, in contrast to patients with Lyme neuroborreliosis those with polymyalgia rheumatica as a rule have highly elevated erythrocyte sedimentation rate, high concentration of serum C-reactive protein, anemia and normal CSF findings.

Late Lyme neuroborreliosis may be confused with multiple sclerosis, neurosarcoidosis, intracerebral vasculitis, stroke, psychiatric disorders, pre-senile dementia, and some polyneuropathies. The demonstration of CSF pleocytosis and intrathecal synthesis of borrelial antibodies is crucial to distinguish between these disorders [6, 36].

COINFECTIONS

Concomitant infections of the CNS with *B. burgdorferi* s.l. and tick-borne encephalitis virus are possible in endemic regions. There are indications that in an acute stage of the disease symptoms and signs of tick-borne encephalitis are more pronounced, while later on clinical presentation resembles Lyme neuroborreliosis. However, a limited number of case reports on double infection by *B. burgdorferi* s.l. and tick-borne encephalitis virus of the CNS has been published, and only some of them were based on reliable diagnostic criteria [84 - 87]. In endemic regions patients with double infection should be actively searched for and strict diagnostic criteria for Lyme neuroborreliosis should be followed. Early antibiotic treatment of such patients is required to prevent complications and late manifestations of Lyme borreliosis.

TREATMENT

Antibiotic therapy in patients with Lyme neuroborreliosis shortens the disease duration [88] and decreases the risk of neurological sequelae. Up to some years ago parenteral ceftriaxone was the drug of choice for treating patients with Lyme neuroborreliosis. It is highly active against *B. burgdorferi* s.l. *in vitro*, crosses the blood-brain barrier rather well and has a long serum half-life, which enables once-daily applications. Cefotaxime and penicillin G in high doses are equally effective as ceftriaxone [6], but are rarely used, because they have to be administered several times a day.

There are convincing evidences, that oral doxycycline has excellent results in vitro against Lyme borreliae, good CNS penetration and good clinical efficacy [89 - 93]. A double-blind randomized trial from Norway, published in 2008, showed that oral doxycycline is as efficient as intravenous ceftriaxone for the treatment of adults with Lyme neuroborreliosis [41]. Therefore, the recommended treatment regimens for patients with Lyme neuroborreliosis is oral doxycycline 100 mg two times a day or ceftriaxone 2 g once daily intravenously for 14 days. Ceftriaxone is preferred for cases with parenchymal nervous system involvement (encephalitis, myelitis) in early or late stage of the disease, because of lacking data on doxycycline efficacy in such cases; in the late stage the duration could be prolonged to 28 days. Patients with acrodermatitis chronica atrophicans and peripheral neuropathy could be treated with doxycycline for 21 to 28 days [6]. A more prolonged antibiotic treatment of Lyme borreliosis lacks scientific support but may entail an increased risk for severe adverse events [4, 6, 27, 59, 94 - 97].

PROGNOSIS

Although some early manifestations of Lyme neuroborreliosis would resolve spontaneously, antibiotic treatment speeds up the resolution of symptoms and prevents the development of later complications [6, 88]. Most patients with Lyme neuroborreliosis have very favourable prognosis after adequate therapy [6, 89 - 91], although some reports showed, that a significant number of patients may have residual difficulties, such as fatigue, headache, cognitive impairment, paresthesia, neuropathy, radiculopathy, paresis and residual facial palsy [98 - 100]. Delayed treatment start, more symptoms and findings before treatment and non-complete recovery at 4 months were found as possible predictors for a poorer prognosis in European patients with Lyme neuroborreliosis [101].

CONCLUSION

Lyme neuroborreliosis is the second most frequent manifestation of Lyme borreliosis in Europe, and the third most common manifestation of the illness in North America, with different clinical characteristics between the continents. For the reliable diagnosis strict diagnostic criteria have to be employed. Appropriate antibiotic treatment (usually with

oral doxycycline or intravenous ceftriaxone) is successful in most patients with Lyme neuroborreliosis.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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