Neuroborreliosis: pathogenesis, symptoms, diagnosis and treatment

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Lyme disease is the most common human tick-borne disease in the northern hemisphere. This article describes the current knowledge of several aspects of Lyme neuroborreliosis. The epidemiology is reviewed first, with special respect to the difference between European and American disease. Then, the current knowledge about the pathogenesis of Lyme neuroborreliosis is presented, with emphasis on immune evasion strategies. Furthermore, the clinical picture of acute Lyme neuroborreliosis and the frequently discussed post-Lyme disease syndrome are critically discussed. The commonly used diagnostic strategies, as well as the relevance of the lymphocyte transformation test, $CD57^+/CD3^-$ cell count and CXCL13, are presented. Finally, the therapeutic options are described to give a balanced overview of all aspects of this disease.

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Learning objectives

Upon completion of this activity, participants should be able to:

- Describe the epidemiology and pathogenesis of Lyme neuroboreliosis (LNB)
- Describe the characteristic symptoms and diagnosis of LNB
- Describe the treatment and management of LNB

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Keywords

■ *Borrelia burgdorferi* ■ CD57 ■ ceftriaxone ■ CXCL13 ■ doxycycline ■ immune evasion ■ Lyme neuroborreliosis ■ lymphocyte transformation test ■ post-Lyme disease

Lyme borreliosis is the most common human tick-borne disease in the northern hemisphere. The responsible pathogen is *Borrelia burgdorferi* sensu lato, a spirochete with a length between 5 and 30 µm (Figure 1). In Europe, at least five species of *B. burgdorferi* sensu lato are pathogenic for human, namely *B. burgdorferi* sensu stricto, *Borrelia garinii*, *Borrelia afzelii*, *Borrelia spielmanii* and the recently discovered *Borrelia bavariensis* [1–3]. *Borrelia valisiana*, *Borrelia lusitaniae* and *Borrelia bissettii* have been detected in either cerebrospinal fluid (CSF) [3,4] or erythema migrans [5,6], but the pathogenicity for humans of these species has not been proven yet [3]. In contrast to this, *B. burgdorferi* sensu stricto represents the only human-pathogenic species in North America.

Epidemiology

The incidence of Lyme borreliosis varies considerably from region to region (an overview is given by Hubalek [7]). In Germany, Lyme borreliosis must legally be notified to local health services in the six eastern states only. Between 2002 and 2009, the reported incidence in these six territories varied between 17.8 and 37.5 per 100,000 inhabitants [8]. In a prospective, population-based study covering the region of Würzburg, the incidence was 111/100,000 per year [9]. The individual probability of becoming infected with *B. burgdorferi* by a tick bite depends on several factors:

- The proportion of infected ticks – a European meta-analysis found 18.6% of the adult and 10.1% of the nymphal ticks to be infected, but the rate varied, depending on the region and the tick stage, from 1.5 to 75% [10]. Notably, there was no differentiation between human-pathogenic and human-nonpathogenic *B. burgdorferi* species.
- The duration of the tick's feeding – while the North American tick *Ixodes scapularis* needs at least 24–48 h of feeding until *Borrelia* are transmitted, experiments with gerbils and *Ixodes ricinus* (endemic to Europe) have shown that after only 16.7 h of feeding, 50% of the animals were infected with *B. burgdorferi* [11–13]. The reason for this discrepancy can be found at the location of *B. burgdorferi* inside of the ticks: while *Ixodes scapularis* harbors the bacteria only in the mid-gut (where they have to detach and migrate to the salivary gland before being injected into the host), a part of the *Borrelia* in *I. ricinus* can already be found directly in the salivary glands [14].
- The borrelial species – skin biopsies from patients with erythema migrans reveal mostly *B. afzelii* (in 70–90% of the cases) and significantly less *B. garinii* (10–20%), while both species can be equally found in the ticks [3,7,10,15]. This suggests that borrelial species vary in their infectivity.

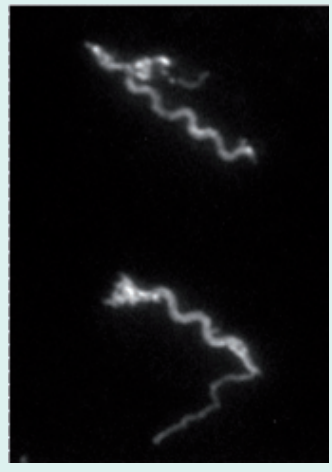

Figure 1. *Borrelia garinii* (dark field microscopy).

Considering the necessary duration of feeding and the proportion of infected ticks, spirochetal inoculation after a tick bite is the exception and not the rule. A study from south-west Germany has shown that only approximately 2.6% of all tick bites lead to a clinically apparent infection [16].

The most frequent manifestation of Lyme borreliosis – accounting for approximately 90% of cases – is erythema migrans, while the CNS is the most frequent destination of dissemination. According to population-based prospective studies performed both in Germany and Sweden, the incidence of Lyme neuroborreliosis (LNB) is approximately 3–11/100,000 per year [9,17].

Pathogenesis

To get from the vector to the host, the *Borrelia* have to penetrate several barriers and survive the vector and host immune system. In unfed ticks, *B. burgdorferi* is mainly located in the mid-gut, attached to the gut by the interaction of the outer surface protein (Osp) A with the corresponding receptor of the tick, TROSPA [18,19]. While human blood streams into the gut during the feeding process, *B. burgdorferi* has to defend itself already against various components of the host immune system (e.g., the complement system

or the leucocytes). To this end, *B. burgdorferi* possesses several mechanisms of defense. For movement from the gut to the salivary glands, they possess so-called endoflagellae, which are located between the outer and inner membrane and enable longitudinal axis rotation. Binding of host plasminogen by OspA and OspC probably enables penetration of barriers (e.g., gut wall and salivary glands).

Antigenic variation

The surface proteins of *B. burgdorferi* are very immunogenic [20] and can induce several pro-inflammatory cytokines [21]. To prevent detection by the host immune surveillance system, *B. burgdorferi* is able to regulate the expression of several surface proteins. During the feeding process, OspA expression ceases, while OspC – most probably due to the rise of temperature and the different pH of the inflowing blood – is upregulated [19,22–25]. OspC appears to play an important role in this early phase of infection. It can bind to the protein Salp15, which inhibits $CD4^+$ T-cell activation [26], protects the *Borrelia* from antibody-mediated killing [27] and prevents the deposition of complement factors on the borrelial surface [28]. Accordingly, the surface protein OspC is necessary for the survival of *B. burgdorferi*, as OspC-negative *Borrelia* are unable to survive in the mammalian host [29]. An example of true antigenic variation can be found in the surface protein VlsE. It has been shown that infection of mice induces sequence changes and thus alters the antigenic properties of VlsE, which consecutively leads to immune evasion [30].

Inactivation of the host immune system

As depicted previously, *B. burgdorferi* is able to bind to tick salivary proteins with protective properties on its own surface. Besides Salp15, the salivary proteins ISAC and IRAC are also capable of inactivating the mammalian complement system [31–33]. In addition, *Borrelia* possess their own anticomplement proteins, the complement regulator-acquiring surface proteins CRASP 1–5, the factor H-binding OspE paralog or the complement-regulating protein CD59, which is also known as 'protectin' [34–36]. The CRASPs appear to play a very important role for complement resistance and might be responsible for the higher complement sensitivity of *B. garinii* compared with *B. afzelii* [37,38]. Furthermore, *B. burgdorferi* induces the production of the anti-inflammatory cytokine IL-10 [39]. Accordingly, IL-10-deficient mice are able to eradicate the *Borrelia* much more efficiently than wild-type mice and the bacterial load is ten-times lower [40]. Finally, *B. burgdorferi* produces soluble antigens that can bind and thus inactivate *B. burgdorferi*-specific antibodies in immune complexes [41–43].

Hiding in a protective niche

Another way to escape from the host immune system is hiding in less accessible compartments, (e.g., the extracellular matrix), also known as immunologically privileged sites [44,45]. *B. burgdorferi* possesses the ability to bind via OspA plasminogen on its surface [46]. Plasminogen can be activated by plasmin, which in turn leads to the degradation of the extracellular matrix as a prerequisite for invasion [47–49]. However, it must be remembered that OspA is known to be downregulated during the early phase of infection [50,51]. Therefore, this mechanism might only play a role for intrathecal pathogenesis, as there are several indications that OspA is upregulated in the CSF of patients with LNB. In addition, there are proteins with degenerating capacities, such as matrix metalloproteinases (MMPs). MMP-9 is upregulated in both erythema migrans skin lesions and the CSF in patients with LNB [52,53]. On the other hand, studies in MMP-9-deficient mice have not shown an impaired dissemination of *B. burgdorferi* [54]. Taken together, while increased levels of MMP-9 have been shown, the functional role of MMP-9 in Lyme disease remains unclear.

After invasion of the extracellular matrix, the *Borrelia* are able to attach to the matrix proteins with their decorin (DbpA und DbpB)- and fibronectin (BBK32)-binding proteins [55,56]. Decorin, for example, is necessary not only for dissemination but also survival in the extracellular matrix [57]. Another potential protective niche could be the intracellular location of *B. burgdorferi*, as is known to be used by other bacteria, such as *Chlamydia* or *Mycoplasma*. However, it must be remembered that these bacteria are approximately 50-times smaller than *Borrelia* and are adapted to intracellular survival. Nevertheless, *Borrelia* have been found in both endothelial, synovial, neuronal and glial cells *in vitro* [58–60], and can be cultivated again once extracted from the mammalian cells [60]. It is tempting to speculate that this might be a location that is protected from the immune system and antibiotic therapy, and thus explaining the etiology of chronic disease. Nonetheless, these findings have not yet been reproduced *in vivo* and, therefore, these findings have to be interpreted very cautiously.

Invasion of the CNS

The most frequent clinical manifestation of Lyme disease is erythema migrans, which, as described previously, accounts for approximately 90% of cases [9]. The expansion of this rash is caused by centrifugal migration of the *Borrelia* from the site of the tick bite [61]. How and especially why the *Borrelia* disseminate to other organs is not well understood. It was recently suggested that in North America, the *Borrelia* disseminate predominantly via the blood, while in Europe, they appear to prefer a migration along other structures (e.g., the peripheral nerves) directly to the nerve roots [62]. This suggestion was based on the higher prevalence of *Borrelia* in the blood and there being more patients with multiple erythema migrans in North America than in Europe [63–68]. In addition, the clinical picture of LNB hints at a different mode of invasion into the nervous system. In Europe, meningopolyradiculitis, with the maximal intensity of the pain close to the site of the tick bite (Bannwarth's syndrome), predominates, but the presentation of CNS disease in North America is more diffuse, with mostly meningitis or encephalopathy [69,70]. A reason for this could be the different borrelial species: while *B. burgdorferi* sensu stricto is the only species found in North America, *B. garinii* and especially the recently distinguished species *B. bavariensis* (formerly defined as *B. garinii* OspA type 4 [2]) are typically found in patients with Bannwarth's syndrome. In a European study, 65% of the patients with *B. garinii* found in the CSF suffered from typical meningoradiculitis, in contrast to none of the ten patients with *B. afzelii* [71]. In the future, analyzing the borrelial genome in more detail might aid in further elucidating the respective species-specific pathogenetic principles [72].

Inflammatory reaction of the CNS

Once inside the CNS, *B. burgdorferi* induces an inflammatory reaction, presenting as a lymphomonocytic pleocytosis in the CSF. Physiologically, the CNS is considered to be an immunoprivileged site, as there are only very few immune cells to be found [73]. While a fairly low number of dendritic and monocytic cells are responsible for the immune surveillance in the CSF/CNS compartment compared with the systemic circulation, neutrophils and components of the complement system are only rarely found, if at all [74]. In addition, the CNS lacks a well-formed lymphatic system, as there are no lymphatic drainage vessels to be found [75]. Therefore, once bacteria have crossed the BBB, the CSF and the CNS are virtually defenseless, as shown by the impressive example of pneumococcal meningitis with high lethality despite antibiotic treatment [76]. By contrast, neuroborreliosis is not such a fatal disease, most probably due to the comparably long division time of *B. burgdorferi* and the lack of classic endotoxins [77]. Therefore, the host organism has enough time to react to the borrelial invasion. *B. burgdorferi* inside the CSF are first encountered by microglial cells [78], perivascular cells [79,80], dendritic cells [81] or astrocytes [82]. In particular, the Toll-like receptors (TLRs) of the innate immune system appear to play an important role in the recognition process. The lipoproteins of *B. burgdorferi* are detected by TLR2 [83–85] and, as recently noted in transfected cell lines, TLR7 and 9 [86]. In addition, it has been observed that astrocyte and microglial TLR1, 2 and 5 are involved in the *in vivo* response of primate glial cells to *B. burgdorferi* [87]. Furthermore, studies have shown that TLRs have an essential role in the control of *B. burgdorferi* burden, because the respective knockout mice have up to 250-fold more spirochetes than wild-type controls [88,89]. For example, TLR2 engagement results in NF-κB nuclear translocation, which not only induces the generation of bactericidal nitric oxide (NO) and superoxide, but also the production and release of cytokines (e.g., IL-1, IL-6, IL-12 or TNF-α) and chemokines [85,90]. The chemokines, in turn, attract further immune cells from the systemic circulation, thus leading to the aforementioned CSF pleocytosis [91].

Using a protein-array as a screening test, the upregulation of four chemokines, the GRO family (equivalent to CXCL1–3 according to the new nomenclature), CXCL8, CXCL10 and CXCL13 has been found in the CSF of patients suffering from LNB [92]. Of particular interest is the high expression of the B-cell-attracting chemokine CXCL13 in LNB, which was not detectable at all or at least in much lower concentrations in most other inflammatory CNS diseases (e.g., pneumococcal or viral meningitis or multiple sclerosis) [92]. Local monocytic cells appear to be the source of this chemokine, as the production of CXCL13 could be induced by cultivating human monocytes with *B. burgdorferi in vitro* [85]. Using the only reliable animal model for LNB – the nonhuman primate – dendritic cells, microglia, endothelial cells and T cells were identified as other potential sources of CXCL13 [93,94]. In one of these studies, the

expression of CXCL13 correlated with the spirochetal load [93]. In addition, a recent study has shown that CXCL13 plays a key role for the immigration of B cells into the CSF in LNB [91]. Taken together, these results fit very well into the observation that B cells are one of the characteristic cells of LNB, as their proportion in the CSF is much higher than in other inflammatory CNS diseases [95,96]. In addition, it explains why an elevated concentration of CXCL13 can be measured days before the intrathecal production of *B. burgdorferi*-specific antibodies (Figure 2) [94,97,98].

Besides B lymphocytes and plasma cells, there is also a clonal accumulation of activated $CD8^+$ T cells in the CSF during early LNB [99]. This lymphocyte subtype could be attracted by the local production of chemokines such as CCL2, CCL4, CCL5, CXCL10 or CXCL11 [94,100], as increased levels of these chemokines have either been found in the rhesus monkey model of LNB or in the CSF of LNB patients [94,101–103]. However, a functional role for the immigration of T lymphocytes, has only been reported for CXCL11 so far [103].

Neuronal dysfunction

Unfortunately, little is known about the pathogenesis of LNB itself (e.g., the neuronal dysfunction evoked by *B.b*). Principally, there are four mechanisms to be discussed: a direct cytotoxic effect of the *Borrelia*; secretion and/or release of cytotoxic mediators by *B. burgdorferi* as, for example, lipoproteins; a result of the host inflammatory reaction – a so-called 'bystander effect'; and autoimmunity through molecular mimicry.

There are several arguments for a direct cytotoxic effect of *B. burgdorferi*. *Borellia* are known to adhere to different murine neuronal or glial cell lines [104,105] and also to primary rat brain cultures [104]. Probably the most relevant observation for European LNB was the adherence of *B. garinii* to dorsal root ganglia cells, as this reflects the presumed pathogenesis of meningoradiculitis (Bannwarth's syndrome) with lancinating, radicular pain [106]. This adherence process appears to be mediated by the borrelial OspA and the proteoglycans [106] or the galactocerebrosides [104]. The adherent *Borrelia* can be cytotoxic for the neural cells [105], and OspA induces apoptosis and astrogliosis [107]. Besides adherence, one study also observed the invasion of *B. burgdorferi* into neuroglial and cortical brain cells, where they were found to be viable without a cytotoxic effect. As this *in vitro* observation has not yet been confirmed *in vivo*, these findings have to be interpreted cautiously and their relevance remains unclear [60].

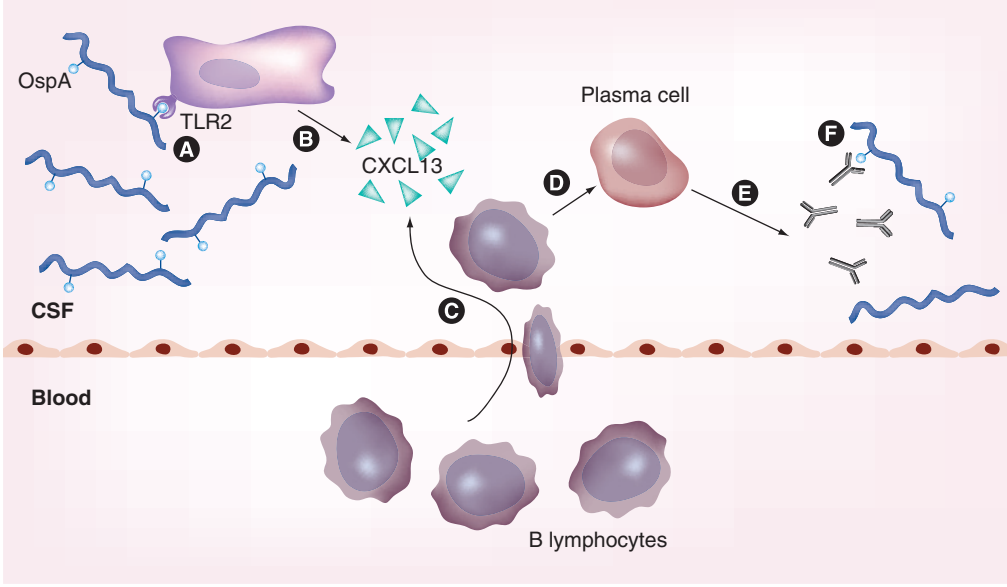

Figure 2. The inflammatory B-cell response in the cerebrospinal fluid in response to the CNS infection. *Borrelia* are recognized by monocytic cells **(A)**, which produce the B-cell-attracting chemokine CXCL13 **(B)**. B cells immigrate into the CSF **(C)** and mature into plasma cells **(D)**. These plasma cells can produce *Borrelia burgdorferi*-specific antibodies **(E)** that can eventually destroy the invading spirochetes **(F)**.
CSF: Cerebrospinal fluid; Osp: Outer surface protein; TLR: Toll-like receptor.
Adapted with permission from [62].

There are only two studies that have shown proteins that are similar to lipopolysaccharide in *B. burgdorferi* with pyrogenic, cytotoxic and IL-1, IL-6 and TNF-α-inducing effects [108,109], while a classical endotoxin has not been identified so far [77]. Therefore, there is only limited evidence for a pathogenic effect of mediators secreted and/or released by the spirochetes. Instead, a bystander effect appears more probable. For example, Schwann cells produce NO in the rhesus monkey model of LNB [110], and the incubation of glial-enriched primary cultures of neonatal rat brain cells with *B. burgdorferi* leads to the release of NO into the culture medium [111]. Macrophages incubated with *B. burgdorferi in vitro* produce quinolonic acid. This agonist of *N*-methyl-D-aspartic synaptic function can be neurotoxic in higher concentrations [112]. Recent experiments with microglia incubated with either *B. burgdorferi* or lipidated OspA *in vitro* found both an inflammatory reaction with the production of IL-6, IL-8, TNF-α and CCL2–5 and apoptosis of cocultured neuronal cells. The authors concluded that the neurotoxic surroundings generated by the microglial cells might have contributed to the neuronal cell damage [113].

Finally, autoimmunity through molecular mimicry is another potential mechanism of neuronal dysfunction in Lyme disease. Antibodies against two homologous OspA peptides generated in rabbits were found to react with neurons in the human brain, spinal cord and dorsal root ganglia by immunohistochemistry [114], and immunization of Lewis rats with *B. burgdorferi* induces ganglioside antibodies [115]. In addition, antibodies against the flagellin of *B. burgdorferi* bind to a human axonal protein [116]. Finally, the serum of patients with Lyme disease contains IgM antibodies to *B. burgdorferi* that crossreact with neuronal antigens [117], and antibodies found in the CSF in LNB patients might not only be directed against *B. burgdorferi*, but also against the CNS parenchyma [118]. In accordance with the concept of molecular mimicry, it has been shown that a patient with an autoimmune neuropathy following acute LNB improved after treatment with intravenous immunoglobulins [119]. Whether autoimmune processes could also be responsible for the frequently debated and not clearly defined 'post-Lyme disease' (PLD) is tempting to speculate. Of interest, a very recent study has found antineuronal antibodies (directed against cortical cells and dorsal root ganglia) in 49.4% of patients with PLD, in contrast to only 18.5% of healthy patients after subsided Lyme disease [120].

Symptoms of LNB & 'post-Lyme disease'

Acute & chronic LNB

In Europe, the most frequent manifestation of LNB is meningoradiculitis, also known as Bannwarth's syndrome. It is characterized by intense, lancinating pain, typically exacerbated by night. The dynamic of the pain during the course of the day is still unexplained. A reason might be the increased alertness to pain during the night time, or the supine position with more warmth in the spine region during bed rest [121]. However, studies on this topic are lacking. Meningeal signs or headache are mostly mild and less common. In particular, if left untreated, the pain is followed by focal neurological signs, such as paresis or paresthesia [122]. The paresis is mostly linked to the location of maximal pain and might affect the limbs, the trunk or the cranial nerves. Typical for LNB are, for example, paresis of the abdominal muscles or bilateral facial palsy. By contrast, an isolated polyneuropathy in LNB without acrodermatitis chronica atrophicans has not been reliably documented in Europe so far. Polyneuropathy in the context of acrodermatitis chronica atrophicans (an isolated polyneuropathy in LNB without an affection of the skin has not been reliably documented in Europe so far) or encephalomyelitis are rare manifestations of LNB and belong to the typical clinical picture of chronic LNB [69,122–124]. In addition, case reports have proposed further CNS manifestations, such as cerebellitis [125] or carpal tunnel syndrome [126], but based on such rare cases, it is difficult to discriminate an incidential coincidence from a real association or cause.

In North America, the manifestation of LNB is less characteristic, with headache and neck stiffness (due to meningitis), subtle sensory polyneuropathy or mild cognitive disturbances in the context of encephalopathy [69,70]. The reason for the different clinical pictures between the continents is most probably the different genospecies, as *B. garinii* and the recently separated *B. bavariensis* (as the typical species found in Bannwarth's syndrome [2]) are only endemic in Europe and not in North America [69]. Even within Europe, there appear to be different forms of LNB depending on the responsible *Borrelia* species. While LNB patients infected with *B. garinii* report radicular pain more often and express meningeal signs, those infected with *B. afzelii* complain more about dizziness [71]. Taken together, LNB should be recognized as a more heterogeneous disease, and it might even be of use to stratify LNB according to the underlying borrelial genospecies.

'Post-Lyme disease syndrome'

There is still an ongoing discussion as to whether PLD really exists. According to proposed diagnostic criteria, it encompasses patients following a treated Lyme disease who suffer from persisting, mostly mild and nonspecific symptoms, in whom other causes have been excluded [127,128]. The onset of the symptoms should be no later than 6–12 months after Lyme disease. On the one hand, there is a large, well-designed American study that did not find an increased incidence of such symptoms in patients after treated Lyme borreliosis compared with the general population [129]. By contrast, a meta-analysis documented persisting symptoms significantly more often – in approximately 5% of patients after Lyme borreliosis [130] – but there may have been a publication bias, as positive studies are often easier to publish. An additional argument against the existence of PLD might be an increased sensitivity to nonspecific symptoms with the knowledge of a borrelial infection in the past, especially as persisting symptoms were found more frequently in those who were misdiagnosed with Lyme disease than in those that had definitely been infected by *B. burgdorferi* in the past [129]. A European study approached this bias problem in a rather innovative way. A large population (n = 505) of young military recruits was screened for *B. burgdorferi*-specific antibodies. After exclusion of those who remembered a subsided case of borrelial infection, or suffered from an active infection with *Borrelia*, the recruits had to fill out a questionnaire without knowledge of the results from the serology. Antibody-positive individuals reported fatigue, general malaise and limb pain significantly more often [131]. This might be an important argument for the existence of PLD. Finally, as already described for LNB, there might be a difference between American and European PLD, and results from either continent are not easily transferred to the other. A study from Norway compared patients who were treated for LNB 30 months ago with a healthy control group and found – besides objective neurological findings – poorer quality of life and, in particular, more fatigue in the treated LNB patients [132]. However, an important drawback of this European study was the selection of the control group, as patients with other inflammatory diseases of the CNS in the past might be more suitable for such a comparison.

The pathogenesis of PLD – if it really exists – is unknown. An ongoing, active borrelial infection is very unlikely, for the following reasons: *Borrelia* have not been cultivated or even identified by PCR from the CSF in PLD patients; the CSF displays no inflammatory changes in these patients; and a resistance of *B. burgdorferi* to the typically applied antibiotics has not been documented to date [127]. Based on these pathogenic considerations, there is no indication for antibiotic treatment of PLD. This is further substantiated by appropriate clinical trials. A large, controlled-treatment trial clearly demonstrated that treatment of PLD (both seropositive and seronegative cases) for 30 days with intravenous ceftriaxone followed by oral doxycycline for 60 days is not more effective than placebo [133]. If only scientifically sound studies that fulfill certain methodological criteria are considered, all other studies on this topic could reproduce these findings [128]. Recently, it was demonstrated that even 10 days of antibiotics are sufficient to treat early Lyme disease, with a 2-year treatment failure-free survival rate of 99% [134]. Therefore, there is no indication for antibiotic treatment beyond the 10–21-day regimen. It must be remembered that a prolonged course of antibiotics leads to increased bacterial resistance and also eliminates the physiological bacterial flora. In addition, there are reports on severe complications, including death, from a prolonged, nonindicated antibiotic therapy for 'chronic' Lyme disease [127].

But what other pathogenic mechanism could account for PLD? In a recent study, antineuronal antibodies against motor neurons and dorsal root ganglia cells have been found in nearly half of patients with PLD, but only in 18.5% of patients after a subsided infection without persisting symptoms [120]. In addition, as described previously, it has been shown that antibodies in LNB are not only directed against the spirochetes themselves, but also against the CNS parenchyma [135]. This would suggest an autoimmune phenomenon triggered by the *Borrelia*, possibly due to molecular mimicry. Another interesting theory is that persisting symptoms after treated LNB are due to disturbances of the hormone axis, as suggested recently, but arguments for an endocrine dysfunction remain very sparse [136]. Nevertheless, PLD has to be distinguished from persisting symptoms due to the harmful effects of the initial borrelial infection (e.g., direct cytotoxicity of the spirochetes). It has to be assumed that remaining complaints after a subsided LNB, which can be found in up to 48% 1 year after the infection [137], are at least in part the result of damage that the *Borrelia* have left behind. An evident example is a remaining facial palsy after cranial neuritis. In addition, other differential diagnoses have to be considered (e.g., chronic fatigue, fibromyalgia or depression) [138].

Taken together, PLD as a disease entity is not yet well defined and its pathophysiology is far from clear. Further studies on this topic are urgently needed, as those patients with persisting symptoms are a diagnostic and therapeutic problem in everyday practice. Often, those patients feel that they are not taken seriously and, due to the unclear diagnosis, therapeutic options are poor.

Diagnosis

The definite diagnosis of LNB is essentially based on three aspects: an appropriate clinical picture, a lymphocytic pleocytosis and the detection of intrathecally produced, *B. burgdorferi*-specific antibodies (as expressed by a positive antibody index AI) [123,139]. Nevertheless, it has to be kept in mind that the intrathecal production of antibodies can take several weeks and, therefore, the AI is positive in only 79–94% of LNB patients in the first 2–3 weeks [122,139–141]. Furthermore, in rare cases, the CSF cell count might even be in the normal range [142]. A study from Slovenia suggested that this is a common phenomenon of *B. afzelii* infection [71], but this has not yet been confirmed by further studies. In such suspected cases without a CSF pleocytosis, a PCR might be of help to confirm the diagnosis, but the sensitivity of this technique for LNB is rather low (10–30%) [139]. The same applies for a CSF culture of *B. burgdorferi*, with a sensitivity of between 10 and 30% [143].

If the intrathecal production of antibodies has not been determined but the CSF cell count is elevated and other diagnoses are virtually excluded, the diagnosis of LNB is not definite, but probable. If no CSF analysis has been performed at all, only a possible LNB can be assumed (Figure 3). Therefore, analysis of the CSF is necessary to confirm a clinically suspected diagnosis [144]. In cases with a very typical clinical picture (e.g., Bannwarth's syndrome with intense, lancinating pain, exacerbating during the night and a recent history of an erythema migrans), the diagnosis is sufficiently definite even without laboratory aid. However, CSF analysis allows the opportunity to perform a follow-up if, for example, a treatment failure is suspected [144].

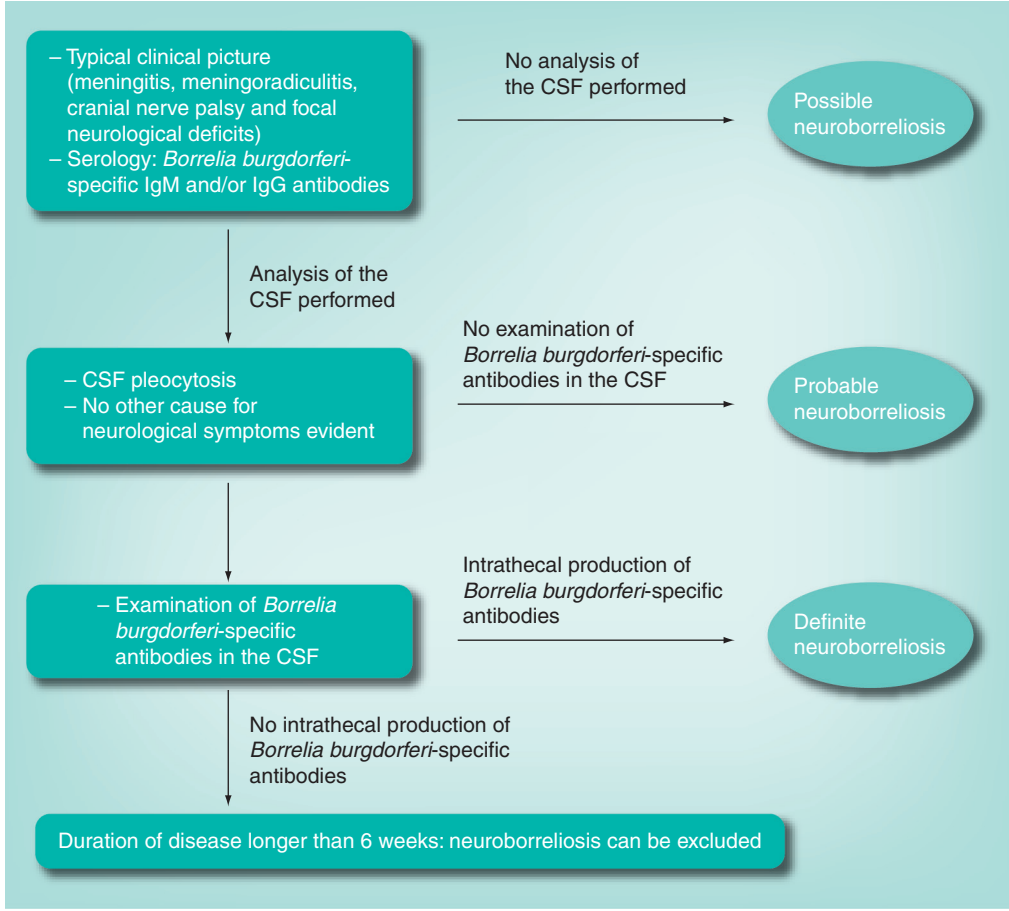

Figure 3. Diagnostic pathway for acute Lyme neuroborreliosis.
CSF: Cerebrospinal fluid.
Reproduced with permission from [121].

A novel biomarker with a high potential is the B-cell-attracting chemokine CXCL13. It is produced upon detection of intrathecal spirochetes by monocytes [85], dendritic cells [93] and several other cell types (as depicted previously) [94] and is a key factor for B-cell immigration into the CSF in LNB [91]. Therefore, the presence of this chemokine precedes the production of antibodies, and the sensitivity in early LNB appears to be higher than the AI [97,98,145]. In the studies published to date, CXCL13 has been found in high levels in the CSF in acute, untreated LNB [92,98,145–147]. In addition, it rapidly decreases under antibiotic therapy, therefore qualifying as an activity or therapy response marker [92,119,146,147]. There are several further studies regarding the diagnostic potency of this chemokine for LNB, which have been presented at the International Conference of Lyme Borreliosis (ICLB) 2010 in Ljubljana, Slovenia, and will presumably be published shortly [148–151]. Taking the results of these published and as yet unpublished studies together, CXCL13 shows a high sensitivity. However, it must be remembered that there are other disease entities, in which highly elevated CXCL13 levels can also be found in the CSF (e.g., neurosyphilis, cryptococcal meningitis, cerebral lymphoma, tuberculous meningitis and HIV meningitis [85,147,148,152]). Due to the low incidence of the aforementioned diseases, the positive and, in particular, the negative predictive value of CXCL13 for acute LNB still appears to be high. A recently published prospective study from Munich found a higher sensitivity of this novel biomarker compared with the AI (94.1 vs 88.8%), with an equal specificity (96.1%). As a conclusion, CXCL13 was proposed to be an additional marker in early cases with a negative AI, in patients with atypical clinical presentation to strengthen the diagnosis and finally as a therapy response marker [147].

In 2007, two studies suggested the lymphocyte transformation test (LTT) to be a potential tool for the diagnosis of LNB in seronegative patients [153,154]. Due to their results, the LTT indicates an active borrelial infection even if the pathogens are not discovered by the humoral immune system and therefore no *B. burgdorferi*-specific antibodies are detectable. Testing the T-cell response is, in general, a very attractive method for the diagnosis of possibly camouflaged infectious diseases. However, both studies lack an adequate control group and reliable case definitions and, therefore, the specificity of the findings remains unclear. The LTT might only reflect a general activation of the immune system, and testing other inflammatory and infectious neurological diseases would be important to confirm these findings. In conclusion, the LTT can not be recommended as a diagnostic tool for the diagnosis of LNB [139].

Stricker and Winger advocated the $CD57^+$ lymphocytes count to be an important marker to diagnose chronic Lyme disease [155]. They found a decreased number of $CD57^+$ cells in patients with chronic Lyme disease, which increased during a month-long antibiotic therapeutic regimen. In this study, no adequate control group was examined, the clinical picture of the patients was not described and their form of chronic Lyme disease is not well defined, thus their results could not be confirmed by other study groups. A recent study even found no alterations of the $CD57^+$ cell count in patients with persisting symptoms after Lyme disease [156]. Taken together, due to the lack of reliable studies, the $CD57^+$ cell count is not recommendable for the diagnosis of chronic Lyme disease [139].

Treatment

While the diagnosis of LNB might be challenging, the therapy is both easy and well defined. Several studies have documented a response to 10–28-day courses of intravenous ceftriaxone (2 or 4 g daily), intravenous penicillin (20 million units daily), intravenous cefotaxime (3 × 2 g or 2 × 3 g daily) and oral doxycycline (200 mg daily). An overview of the treatment trials is reported by Mygland *et al.* [139]. Significant resistance of *B. burgdorferi* to one of these antibiotics is reported to be very rare. A recent Norwegian class I study of 102 LNB patients has shown that oral doxycycline (200 mg daily for 14 days) is noninferior to a 14-day course of intravenous ceftriaxon (2 g per day) [157]. Therefore, as already suggested by a North American meta-analysis [158], both ceftriaxone and doxycycline are equal alternatives and are recommended first-line therapies for acute LNB. Doxycycline has the advantage of an oral route of administration.

The duration of treatment should be 14 days, although there are studies that recommend either a shorter therapy course of only 10 days (with a 2-year treatment failure-free survival rate of 99%) [134], while others discuss the need for 28 days of antibiotic therapy (especially for late LNB). No well-designed study so far could clearly demonstrate the need for prolonged antibiotic treatment beyond 1 month of

treatment, as discussed previously. Therefore, oral adjunct antibiotics are not justified in the treatment of patients with LNB, who initially received an adequate intravenous ceftriaxone therapy [159].

The outcome after antibiotic treatment is generally good. The pain, typical for Bannwarth's syndrome, rapidly decreases under antibiotic therapy, and patients might be free of complaints even after one antibiotic dose [Rupprecht TA, Personal Observation] [160]. Objective findings after 1 year are mostly discrete and can be observed in approximately 16–28% of patients. A delayed treatment initiation in particular is considered a risk factor for these persistent findings [122,132,137]. Persisting, objective symptoms after an adequate course of antibiotics are either due to irreversible damage (e.g., a limb paresis due to axonal loss) or might reflect a misdiagnosis in the majority of cases. Subjective symptoms can be more frequent, and the relevance of this was discussed previously. In rare cases, the borrelial infection might have initiated an autoimmune reaction due to molecular mimicry [119]. To differentiate between both pathogenic mechanisms, the determination of CXCL13 as the most reliable activity and treatment marker can be useful. The serology is not helpful as a follow-up marker: in only approximately 50% of patients does the antibody titer markedly decrease after 12 months [159].

Conclusion & future perspective

The knowledge about this disease, which was clinically described many years before the causative agent – *B. burgdorferi* – had been identified in 1982, is still incomplete [161,162]. In recent years, many aspects of this disease have been elucidated. In particular, immune evasion strategies and mechanisms of dissemination of the pathogen were in the focus of research, and we now know a lot about the pathogenesis of this disease. The discovery of CXCL13 as an early and activity marker for acute LNB has a high potential to improve diagnostic procedures. In addition, the opportunity of an oral antibiotic treatment of early LNB with equal efficiency to the well-established intravenous antibiotics

Executive summary

Epidemiology

- The incidence of Lyme borreliosis varies between regions and was 111/100,000 per year in a population-based study from Germany.
- The probability of infection after a tick bite depends mainly on the rate of infected ticks, the borrelial species and the duration of feeding.
- The CNS is the most frequent destination of dissemination, but Lyme neuroborreliosis (LNB) accounts for only approximately 3–11% of Lyme borreliosis cases in Europe.

Pathogenesis

- *Borrelia burgdorferi* possesses several mechanisms of immune evasion, especially antigenic variation, inactivation of the host immune system and hiding in protective niches of the host.
- Invasion of the CNS appears to vary between the USA (mainly hematogenous spread) and Europe (along structures such as the peripheral nerves).
- CXCL13 appears to play a key role in the B-cell-dominated immune response in the cerebrospinal fluid in LNB.
- The neuronal dysfunction is either the result of a direct process (cytotoxicity of *B. burgdorferi*) or indirectly (e.g., through lipoproteins, inflammatory bystander reactions or autoimmune phenomena).

Symptoms

- The clinical picture of acute LNB is well defined and encompasses meningoradiculitis, cranial neuritis, focal neurological deficits and/or meningitis in the majority of cases.
- Chronic neuroborreliosis is a rare disease with both clinical and laboratory objective findings.
- Post-Lyme disease is a poorly defined syndrome as yet, which applies to treated patients with persisting (mostly subjective) symptoms but without evidence of an ongoing infection.

Diagnosis

- According to the existing guidelines, a typical clinical picture in combination with inflammatory cerebrospinal fluid changes and an intrathecal production of *B. burgdorferi*-specific antibodies is required for a definite diagnosis of LNB.
- CXCL13 appears to be a promising marker for the diagnosis of early cases with negative antibody index, for activity of disease and as a therapy marker.
- Owing to the lack of adequate studies, the lymphocyte transformation test and $CD57^+$ cell counts cannot be recommended for the diagnosis of acute or chronic LNB.

Treatment

- Oral doxycycline and intravenous β-lactam antibiotics appear to be equally effective.
- There is no evidence that antibiotic treatment beyond 21–28 days is more effective, especially in the prevention of persisting symptoms.

offer a reasonable and comfortable method of treatment. However, the clinical dilemma of persisting symptoms after treatment is still unsatisfactorily addressed. Further studies on this topic are urgently needed to better define, diagnose and treat these patients.

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1. Based on the above review by Drs Rupprecht and Fingerle, which of the following statements about the epidemiology and pathogenesis of Lyme neuroborreliosis (LNB) is most likely correct?

- ☐ **A** LNB accounts for about one third of Lyme borreliosis cases in Europe
- ☐ **B** Disseminated Lyme disease seldom affects the CNS
- ☐ **C** Mechanisms of immune evasion for *Borrelia burgdorferi* include antigenic variation, inactivation of the host immune system and hiding in protective niches of the host
- ☐ **D** In the USA, CNS invasion is mostly along structures such as the peripheral nerves, whereas in Europe, CNS invasion occurs mainly through hematogenous spread

2. Your patient is an 8-year-old boy who went camping in the woods with his family and shortly thereafter had influenza-like symptoms for which he received no specific treatment. He now has neurologic symptoms and is thought to have acute LNB. Based on the above review, which of the following statements regarding diagnosis would be most likely correct?

- ☐ **A** Meningitis and focal neurologic symptoms are seldom seen with acute LNB
- ☐ **B** Definite diagnosis of LNB requires a typical clinical picture, inflammatory cerebrospinal fluid changes, and intrathecal production of *B. burgdorferi*-specific antibodies
- ☐ **C** CXCL13 has no value in the diagnosis of acute LNB
- ☐ **D** Lymphocyte transformation test and $CD57^+$ cell counts are needed for definitive diagnosis

3. The patient in question 2 is diagnosed with acute LNB. Based on the above review, which of the following statements regarding treatment and prognosis is most likely correct?

- ☐ **A** Intravenous antibiotic therapy is required
- ☐ **B** To prevent persisting symptoms, antibiotic treatment should be continued for 6 weeks
- ☐ **C** Oral doxycycline and intravenous β-lactam antibiotics appear to be equally effective
- ☐ **D** Few patients have complete neurologic recovery even with appropriate treatment