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Psychosis in *Borrelia burgdorferi* infection – part I: epidemiology, pathogenesis, diagnosis and treatment of neuroborreliosis

Szymon Brodziński, Tadeusz Nasierowski

Medical University of Warsaw, Department of Psychiatry

Summary

Borreliosis is a multisystem, bacterial, zoonotic infectious disease with diversified spectrum of symptoms, which may also include psychotic disorders. Clinical picture of the disease is often unspecific, which makes the diagnosis relatively difficult. Uncharacteristic process of borreliosis is a result of complex molecular strategies used by spirochetes to infect, disseminate and survive in host organism. Part I of the article is focused on the current knowledge about pathogenesis of Lyme Borreliosis (LB), especially neuroborreliosis. Additionally, epidemic situation in Poland and in Europe was presented. Also, typical clinical manifestations of LB were described. In the article, the crucial pathogenic cell mechanisms were depicted. The processes of infection and dissemination of *Borrelia* in the host were presented. The most important strategies of evading the response of host immune system were also discussed. These mechanisms are probable cause of the chronic and uncharacteristic clinical picture of the disease, as they significantly impair host immune response to bacteria. Also, there were presented molecular processes of neural cells impairment, which may lead to observed clinical symptoms of neuroborreliosis. Furthermore, diagnostic methods, treatment guidelines and some of diagnostic problems were discussed.

Key words: neuroboreliosis, pathogenesis, diagnosis

1. Introduction

Lyme borreliosis (LB) is a bacterial disease transmitted by ticks. Its clinical course is diversified and uncharacteristic. Lately, the issue of tick-borne diseases has been extensively discussed in Polish mass media. Borreliosis is also widely discussed on Internet discussion boards, which illustrates vivid public interest in LB [1].

LB might affect numerous systems and organs. The disease may manifest with cardiac, skin, rheumatic or neurological symptoms. In neuroborreliosis both the periph-

eral and central nervous systems might be involved. When the central nervous system (CNS) is affected, there may occur psychotic symptoms similar to those observed in schizophrenia.

2. Epidemiology of borreliosis

Naturally, the disease is noted in areas inhabited by ticks. In Europe, it is between 35° and 60° north latitude and up to about 1,300 meters above the sea level [2]. About 65,000 of new cases of LB are observed every year in the whole Europe [3]. In Poland, average incidence is 22.8/100,000 inhabitants, however, it reaches the level of 80/100,000 inhabitants in the north-eastern parts of the country [4]. In other European countries incidence of LB is diversified. The highest incidence rate was noted in some parts of Slovenia, Germany, Austria, Estonia, Finland, and in the southern coast of Sweden. However, epidemiological data in various countries are not standardized, which makes it difficult to compare them [3].

The factors contributing to the increased incidence of LB are warm winters and humid summers [3]. The risk of LB is higher in people living or working in forest areas [3, 4]. The prevalence of neuroborreliosis (NB) is estimated at 15–40% of confirmed LB cases [5]. It is the most often form of LB in Europe. Meningitis is observed in about 5–15% of cases of LB [3, 5, 6], while the most severe form of the disease – encephalomyelitis – in 0.1% of cases [5].

3. Clinical manifestations

Lyme borreliosis is zoonotic disease caused by bacteria transmitted by ticks. The infectious agent is spirochete *Borrelia burgdorferi sensu lato*, within which several genospecies are distinguished. The following genospecies are pathogenic for humans: *B. burgdorferi sensu stricto, B. garini, B. afzelii, B. bavariensis* [7]. Bacteria are mostly transmitted by *Ixodes ricinus* or *Ixodes persulcatus* ticks. After a bite by an infected tick, spirochetes migrate with tick saliva to the skin of the host. Initially, the infection is limited to the bite area. Typically, in a few days or weeks after the bite characteristic erythrema migrans appears. At this stage, non-specific flu-like symptoms may occur. If the infection is not treated, spirochetes spread in host organism. They may infect various organs, especially joints and the nervous system [5] but also heart muscle and eyes [8]. In a few weeks after the initial infection, the central nervous system (CNS) might be affected. Spirochetes may remain there quiescent for several weeks or even years before producing symptoms [8].

Neuroborreliosis is defined as *Borrelia* infection in which neurological symptoms occur. They may affect both the central and peripheral nervous system. At the beginning symptoms might be mild but when untreated infection spreads, symptoms become more severe. When the central nervous system is affected the following syndromes are distinguished:

– Early-stage syndromes:
  • ‘aseptic’ meningitis;
  • cranial neuritis;
  • radiculoneuropathies.
– Late-stage syndromes:
  • encephalopathies;
  • polyradiculopathies;
  • encephalomyelitis [5, 8].

Most common symptoms during meningitis are: severe headaches, neck stiffness, fatigue, weakness, nausea, vomiting, muscle pains, fluctuating mood, concentration impairment, sleep disorders, and paresthesias. Between the third week and the third month of infection, cranial nerve palsy and radiculopathy may occur [5, 8]. Among the cranial nerves, the facial nerve palsy is the most common [9]. Coexistence of lymphocytic meningitis, radiculopathy and cranial neuritis is called Bannwarth syndrome [5].

The following symptoms may be present at the late stage of the disease: photophobia, emotional lability, irritability, mood disturbances, cognitive and memory impairment [6, 8]. More severe symptoms may occur in the case of encephalomyelitis: consciousness and respiration impairment, hydrocephalus, focal symptoms, and spastic paresis [5]. At this stage psychosis may be observed [10].

4. Pathogenesis

Molecular mechanisms of *Borrelia* infection are still unclear [5, 11–13]. It is not thoroughly known how spirochetes manage to stay unseen for the immune system and then cross the blood-brain barrier. The mechanisms of nerve damage and the exceptional affinity of bacteria to nerve cells and synovial membrane cells are also vague. The currently known mechanisms of infection, evading immune system, reaching the central nervous system and causing damage to neural cells are presented below.

4.1. Infection and evading immune system

These two aspects are inseparably connected. In order to invade the host, spirochetes have to be ready to encounter the immune system yet before entering host tissues. For this purpose *Borrelia* spirochetes use number of mechanisms of evasion of host immune system or decreasing its reactions. The most important of them are: (1) downregulation of expression of surface proteins, which are recognized by the immune system; (2) immune suppression; (3) escape to extracellular space [11, 14].

4.1.1. Role of surface proteins

Borrelia spirochetes produce numerous of surface proteins. Their expression changes depending on environmental alterations. Most significant are following lipoproteins: OspA (Outer Surface Protein A), OspB, OspC, OspD, OspE, OspF, Erp (OspE/F-related proteins), CRASPs (Complement Regulator Acquiring Surface Proteins). They play diversified roles. Function of Osps is adhesion to tick or mammalian tissues, while Erp and CRASPs interact with host complement proteins [13]. Some of lipoproteins activate human immune system intensively [11]. Spirochetes interact with host immune system yet in the tick's gut. Bacteria stay in the tick's intestine for 24–48 hours after a bite, multiplying and preparing to infection [11]. They have contact with host blood flowing into the tick's gut, which might be both opportunity and threat for bacteria. If the blood contains anti-OspA antibodies, spirochetes may be eliminated even before reaching the host [11]. OspA is an important lipoprotein which serves as an anchor for *Borrelia* in the tick's gut, as it binds there with TROSPA (Tick Receptor For OspA) [11, 13].

In vitro studies showed that OspA potently stimulates neutrophils to release proinflammatory cytokines (IL-6, TNF-α, IL-1β) [11]. In order to avoid such an intense immune response, spirochetes rapidly downregulate expression of OspA [11]. Even if OspA-positive *Borrelia* manage to enter the host, they are unable to expand the infection [11]. Moreover, sudden downregulation of OspA in response to contact with host blood, might be an infection trigger, as it causes bacteria 'detachment' from the tick's gut [13].

4.1.2. Immunosupression

Immediately after contact with host blood, *Borrelia* rapidly upregulates expression of some proteins, including OspC. Its synthesis is as rapid as downregulation of OspA [15]. OspA synthesis results from the rise of temperature and pH shifts after contact with host blood [11]. OspC is probably used to gain additional protection against host immune system [11]. Via OspC spirochetes bind to Salp15 (Salivary protein 15), which is present in tick saliva. Salp15 is one of immunomodulators. It inhibits activity of CD4+ cells and leads to decreased production of interleukin 2 (IL-2). It is one of many mechanisms of reducing immune reaction to tick saliva [15]. *Borrelia* spirochetes exploit tick saliva as a cover against recognition by TLR (Toll-like receptors), as it would result with inflammatory reaction of the host [15]. There are also many other immunomodulating proteins in tick saliva, such as, Salp20, ISAC (Ixodes Scapularis Anti-Complement Protein), IRAC (Ixodes Ricinus Anti-Complement Protein). By neutralizing complement protein they form immunosuppressive environment, which is also used by *Borrelia* to evade immune reaction and reach host tissues [11, 15]. Studies show that OspC-negative spirochetes are unable to disseminate [11, 15].

Besides exploiting tick saliva proteins as a protection, *Borrelia* also produces its own proteins which decrease host immune response, e.g.,: CRASPs and Erps. They bind human complement regulators of alternative pathway: factor H and factor H-like protein/reconnectin (FHL-1/reconnectin). It leads to deactivation of C3 convertase and stops complement activation [11, 13–15].

Another way of immune evasion used by spirochetes is stimulating the host to produce anti-inflammatory substances. *Borrelia* induces monocytes to secrete interleukin 10 (IL-10), which is one of the most anti-inflammatory cytokine [11, 14].

Spirochetes also have an ability to release soluble antigens which aggregate with host specific antibodies and form immune complexes antigen-antibody. This strategy impair opsonization with antibodies [11, 14].

4.1.3. Escape to less accessible compartments

Last known mechanism of evading host immune reaction is reaching by *Borrelia* immunologically privileged compartments in human body, i.e., space in which immune system hardly penetrates, for example, extracellular matrix. For this purpose, spirochetes bind via OspA with plasminogen and activate this enzyme to plasmin. Moreover, *Borrelia* activates metalloproteinases. These enzymes digest extracellular matrix and open an escape way for bacteria [11, 12]. Furthermore, spirochetes are able to bind several proteins of extracellular matrix, e.g., fibronectin, some of integrins and proteoglycans. That process enables bacteria to anchor in extracellular matrix and help in hiding from immune cells and molecules [11]. It is also possible that spirochetes can form cysts in order to evade immune reaction, which could also explain antibiotics resistance [14].

4.2. Reaching the central nervous system

It is still unclear how *Borrelia* manages to get to the central nervous system. Further studies are especially required to understand how spirochetes pass the blood-brain barrier [11, 12].

Generally, two ways of dissemination in human host are considered: through the blood stream or along peripheral nerves [5, 6, 11]. Arguments in favor of bloodstream route are based on that *Borrelia* can be cultivated from blood samples taken from patients with LB as well as on that bloodstream pathway is used by many other bacteria and there is no sufficient proof that *Borrelia* is an exception [6, 11]. Nevertheless, the pathway along peripheral nerves has to be taken in consideration as well, due to high prevalence of peripheral nerves impairment (Bannwarth syndrome). It is worth to notice that Bannwarth syndrome is observed often in infections caused by *B. garini* and occurs rarely in LB caused by *B. sensu stricto*. It is therefore possible that particular mechanism of dissemination depends on individual genospecies of *Borrelia* [11].

An intriguing issue is how spirochetes break the blood-brain barrier (BBB). The most probable mechanism is paracellular BBB penetration [8, 12], but transcellular path is also taken into consideration [16]. *Borrelia* does not produce its own substances which could cause capillary permeability changes, although it stimulates host cells (astrocytes, chondrocytes and monocytes) to secrete metalloproteinases [12]. Spirochetes induces expression of plasminogen and metalloproteinases activators, which can result in loosen connections in the BBB [6, 12]. Nevertheless, these mechanisms require further investigation.

4.3. Neural cells impairment

After breaking the BBB, spirochetes reach the cerebrospinal fluid (CSF) where they provoke local inflammation, as a consequence of contact with monocytes, macrophages or dendritic cells. Local immune cells secrete proinflammatory cytokines (IL-6, IL-8, IL-12, IL-18, IFN-γ) and chemokines (CCL4, CCL5, CXCL10, CXCL11). Increased level of these substances attracts other immune cells (especially lymphocytes B). As a result CSF lymphocytosis is observed in people with neuroborreliosis [11, 13].

Three mechanisms leading to neural cells impairment in LB have been described so far: direct cytotoxicity, induced secretion of neurotoxic mediators and immune cross-reactivity [11].

Spirochetes may damage neurons by direct adherence, which is mediated by OspA. This lipoprotein is upregulated when bacteria are in CSF. OspA binds to proteoglycans and galactocerebrosides on neural and glial cells, which can induce apoptosis and astrogliosis [6, 11, 17]. These processes might lead to clinically observed symptoms of LNB [11].

Borrelia does not produce any toxic substances which could damage neurons. However, animal studies show that spirochetes induce host cells to produce potentially neurotoxic substances. Increased secretion of nitric oxide (NO) by Schwann cells, quinolinic acid by macrophages, and IL-6, IL-8, CCL-2, TNF-α has been proved [6, 11, 18]. Increased concentration of these mediators may injure neural cells [17, 19]. In animal models, it was shown that these substances may induce apoptosis of neural and glial cells [6, 19, 20]. The fact that encephalitis in LNB involves more often white matter is also important [19, 21]. An important role is played here by apoptosis of oligodendrocytes, induced by *Borrelia* through increased production of proinflammatory cytokines and chemokines [21].

Finally, spirochetes might cause neural injury by triggering immune cross-reactions [6, 11]. Specific IgM antibodies against flagellin, glycolipid which can be found on the surface of *Borrelia*, have been found in the serum of patients with LNB [6, 22]. These antibodies cross-react with neuronal antigens [6, 22]. Immune cross-reaction was also found between epitopes of OspA and neural cells in the brain, spinal cord

and dorsal root ganglia [23]. Similar reactions were also confirmed between anti-*Borrelia* antibodies and neurons and glial cells in the brain cortex [24]. These immune cross-reactions might lead to injuries of neural tissue and be the cause of long lasting symptoms [5, 23, 24].

5. Diagnostics

Diagnosis of Lyme borreliosis, and especially neuroborreliosis, may be problematic due to the following reasons: uncharacteristic symptoms (except for erythema migrans) and poor diagnostic usefulness of blood or cerebrospinal fluid culture due to a small percentage of positive results of such cultures [9, 25]. Therefore, appropriately gathered medical history is crucial in the diagnostics of borreliosis. Initial diagnosis is based on clinical symptoms. The most characteristic symptom is erythema migrans [7]. However, only 20–30% of patients with LB recalls this symptom [25].

Among laboratory test, the most significant is detecting specific anti-*B.b.* IgM and IgG antibodies in serum and CSF with ELISA method [5, 25]. Unfortunately, method's procedures and results interpretation lack standardization and unification [25]. Moreover, ELISA test shows high sensitivity but low specificity in LNB which causes high false positive results ratio [25]. Furthermore, the usefulness of ELISA test is low in LNB of short duration (less than 6 weeks) due to high false positive results ratio [5, 25]. Therefore, detection of antibodies without any clinical symptoms does not allow to diagnose LNB [7, 25]. Western-Blot method (WB) is useful as a confirmation test only when there is positive result of ELISA test [25]. WB shows high rate of false positive results as well [7]. Polymerase chain reaction (PCR) has minor importance in LNB diagnosis. Despite high sensitivity, this method does not determine whether the infection is active, because alive bacteria are indistinguishable from their lifeless fragments [5].

Analysis of CSF is a key test in LNB diagnostics. LNB is associated with elevated protein level, pleocytosis of 10–1,000 cells/mm^3, with the predominance of lymphocytes and plasma cells [25]. There is, however, risk of misdiagnosis of aseptic or viral meningitis on the basis of CSF analysis, especially in the early stage of LNB when specific antibodies are not present yet [5].

Brain imaging does not play a significant role in LNB diagnostics. Abnormalities in computed tomography (CT), magnetic resonance imaging (MRI) or single-photon emission computed tomography (SPECT) in LNB are rarely seen. If any occur, they are mostly unspecific, hence do not settle the diagnosis [5]. Nevertheless, brain imaging is an useful method to exclude other diseases (e.g., multiple sclerosis, neoplasms).

According to the guidelines of the European Federation of Neurological Societies (EFNS), diagnosis of definite Lyme neuroborreliosis requires all three of the following criteria to be fulfilled:

– neurological symptoms suggestive of LNB;
– cerebrospinal fluid pleocytosis;
– intrathecal production of *B. burgdorferi* antibodies.

When two out of these criteria are fulfilled, possible LNB can be diagnosed. In situation when the third criterion is lacking, then specific anti-*B. burgdorferi* antibodies have to be found in serum after a period of 6 weeks [25].

The only exception to these criteria is a diagnosis of late LNB with polyneuropathy, in which the following should be fulfilled for definite diagnosis:

– peripheral neuropathy;
– clinical diagnosis of *acrodermatitis chronica atrophicans* (ACA);
– anti-*B. burgdorferi* – specific antibodies in serum [25].

6. Differential diagnosis

Table 1 presents selected symptoms of neuroborreliosis, correlated with diseases relevant in differential diagnosis.

Table 1. **Differential diagnosis of selected LNB symptoms**

Symptoms of LNB	Diseases to differentiate from LNB
Facial nerve palsy	– other bacterial meningitis (including syphilis) [26] – thick-borne encephalitis – sarcoidosis – HIV infection – Guillain–Barré syndrome [26] – herpes zoster [27] – ischemic and hemorrhagic brain stroke
Radiculoneuropathy	– mechanical radiculopathies [26] – herpes zoster [27]
Symptoms of meningitis	– viral or bacterial meningitis [26] – thick-borne encephalitis – TB meningitis – neurosarcoidosis [27]
Psychotic disorders	– paranoid schizophrenia – alcohol delirium – psychosis due to substance abuse – bipolar disorder – autoimmune encephalitis

7. Treatment of Lyme borreliosis

Antibiotics are used in the treatment of LB. Depending on the stage of the disease oral or intravenous medications are applied. Table 2 contains current treatment guidelines of the EFNS. Table 3 presents recommendations of the Polish Society of Epidemiology and Infectious Diseases. In early LNB (duration < 6 months) with symptoms confined to peripheral nerves, cranial nerves, nerve roots and without symptoms of CNS infection, the use of penicillin or ceftriaxone, or intravenous cefotaxime or oral doxycycline is recommended [25, 28]. Oral and intravenous antibiotics are equally effective.

Treatment should last 10–14 days according to the EFNS or 14–28 days according to Polish guidelines. In early stage of neuroborreliosis with CNS infection symptoms it is recommended to treat patients with intravenous ceftriaxone (2 g/day) for 14 days [25]. In the case of LNB with some CNS symptoms (meningitis, radiculopathia, cerebral borrelial vasculitis), the recommendations of the Polish Society of Epidemiology and Infectious Diseases allow to use oral doxycycline 200 mg daily or ceftriaxone 2 g intravenously for 14–28 days. Patients with late LNB (duration > 6 months) with peripheral neuropathy and ACA should be treated with oral doxycycline 200 mg daily or intravenous ceftriaxone 2 g daily for three weeks [25]. In the case of late LNB with CNS symptoms, ceftriaxone (2 g daily) for three weeks is recommended. It should be noted that there are no randomized treatment studies of late LNB [25].

Table 2. **Guidelines of the European Federation of Neurological Societies (EFNS) [25]**

Type of LNB	Recommended drug	Daily dose	Way of application	Duration of treatment
Early LNB (definite or possible) confined to peripheral nerves, cranial nerves or nerve roots	Doxycycline	200 mg	Oral	14 days
	Ceftriaxone	2 g	Intravenous	
	Penicillin	20 mln u.		
	Cefotaxime	6 g		
Early LNB with CNS manifestations (myelitis, encephalitis, vasculitis)	Ceftriaxone	2 g	Intravenous	14 days
Late LNB with peripheral neuropathy and ACA	Doxycycline	200 mg	Intravenous	3 weeks
	Ceftriaxone	2 g	Intravenous	
Late LNB with CNS manifestations (myelitis, encephalitis, vasculitis)	Ceftriaxone	2 g	Intravenous	3 weeks

ACA – *acrodermatitis chronica atrophicans*;

Table 3. **Recommendations of the Polish Society of Epidemiology and Infectious Diseases [28]**

Type of LNB	Recommended drug	Daily dose	Way of application	Duration of treatment
Facial nerves palsy	Doxycycline	2 x 100 mg	Oral	14–28 days
Meningitis, radiculopathy, cerebral borrelial vasculitis	Doxycycline	2 x 100 mg	Oral	14–28 days
	Ceftriaxone	2 g	Intravenous	
Encephalomyelitis, Radiculoneuritis, meningitis, occlusive vasculitis, cerebral infarct	Ceftriaxone	2 g	Intravenous	21–28 days

8. Conclusions

Mechanisms of dissemination of *Borrelia burgdorferi* remain unclear. Studies show, however, that spirochetes employ diversified strategies of evading host immune system and use sophisticated mechanisms to invade various human organs. As a result, the disease might develop slowly and uncharacteristically. It is also not fully explained how *Borrelia* manages to break the blood-brain barrier, neither the ways of neural cells injury are clarified. An intriguing fact is that bacteria do not produce any toxic substances, but use cytotoxic compounds secreted by host cells.

Further research on detailed mechanism of spreading the infection, avoiding human immune system, crossing the blood-brain barrier, and injuring neural cells by *Borrelia spirochete* are needed. These studies should result in broadening the knowledge of pathogenesis of borreliosis and therefore help in finding efficient methods of prophylaxis, diagnostics and treatment.

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Address: Tadeusz Nasierowski
Medical University of Warsaw
Department of Psychiatry
00-665 Warszawa, Nowowiejska Street 27
e-mail: tadeusz.nasierowski@psych.waw.pl