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Lyme Disease and Relapsing Fever

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INTRODUCTION

Lyme disease is a prevalent tick-borne infection in the United States (Roberts et al. 1998). Lyme disease and relapsing fever are caused by various species of genus *Borrelia* causing different pathological problems. The causative agent for Lyme disease is a spirochete bacterium called *Borrelia* (*B.*) *Burgdorferi* (*sensu lato*) strain, while relapsing fever is caused by Relapsing Fever *Borrelia* (RFB), which is a spiral-shaped bacterium (IGeneX Inc 2015). Lyme disease infection is transmitted by tick *Ixodes* (*I.*) *Ricinus.* The most common tick born disease in Europe is Lyme Borreliosis. Spirochetes do not have any effect in the transmission of the disease to humans even though they have been isolated from mosquitoes, flies and fleas. In Europe, deer and rodents serve as the key reservoir for *B. Burgdorferi* on which *I. Ricinus* ticks usually prey (Stańczak et al. 1999). Almost 11 known genostrains of genus *Borrelia* are considered to be pathogenic. The clinical signs of relapsing fever are similar as that of Lyme disease and caused by a species of *Borrelia* called Relapsing Fever *Borrelia* (RFB). Three Lyme disease stages are known; early localized, early dissemination, and late. Erythema migrans which is a red ring-shaped rash at the site of tick bite is the sign for early localized disease (Cervantes 2018). Early localized symptoms might include flu, headache, fever, malaise, myalgia, and arthralgia (Bransfield 2018). Disseminated stage has symptoms similar to early stage, with the most common symptom of several lesions of erythema migrans, flu, lymphadenopathy, arthralgia, myalgia, ophthalmic conditions, lymphocytic meningitis, and palsies of the cranial nerves (Bransfield 2018). Arthritis is the most common pathological condition caused by these pathogens that affects large knees and joints (Arvikar and Steere 2015). The diagnosis of the disease with clinical signs and symptoms are difficult because the signs are not specific (Shapiro 1995). Lyme- disease can be diagnosed by exposure to the bites of ticks, typical signs, serological tests for anti-Bb antibodies and physical findings (Murray and Shapiro 2010). The treatment of the disease includes the use of antimicrobial drugs depending on the age of the patient and the stage of the disease (Antony 2018).

Etiology

Lyme disease or Lyme borreliosis is a vector-borne disease caused by different species of spirochete bacteria known as *B. Burgdorferi sensu lato,* which is transferred by the infected tick bite (Stanek et al. 2012). Different species of ticks transfer the disease, with the *I. ricinus* being the most common vector of the disease (Stańczak et al. 1999). It is a gram-negative, spiral-shaped, slowly growing, micro aerobic, spiral-shaped bacterium. The cells of the bacteria divide about every 12-24 hours (Żarnowska and Prymek 1995; Zajkowska 2005; Oliveira et al. 2010). Among 11 genospecies that are transferred by ticks and affect wild animals, 3 species can infect humans, including *B. burgdorferi sensu stricto, B. garinii, and B. afzelii*, mostly prevalent in European countries. *B. burgdorferi sensu stricto* also exist in North America, while, *B. garinii, B. afzelii, B. bissettii, B. valaisiana* and *B. lusitaniae* appear in the Asian countries which are pathogenic to humans (Aguero-Rosenfeld et al. 2005). The main reason for different clinical manifestations of Lyme disease in Europe and United States is the presence of different spirochete genospecies in these two continents (Wang et al. 1999). Different genospecies of Borrelia attacks different organs and body parts. *B. burgdorferi sensu stricto* affects the joints and causes Lyme arthritis. *B. garinii* is responsible for neuroborreliosis, and *B. afzelli* causes limb dermatitis (Zajkowska 2008).

Epidemiology

Lyme borreliosis is a tick borne and endemic disease in North Asia, Europe and North America (Owecki and Kozubski 2007). The disease is prevalent in areas with high forested geographies including Scandinavia, Germany, Slovenia and Austria (Rydz-Stryczewska 2007). Australia, Africa, South America and southern states of the United States are considered as free from lyme disease (Owecki and Kozubski 2007). Northeastern and upper Midwestern region of the United States is the most common places in the North America for the occurrence of Lyme disease (Berry et al. 2017). Fig. 1 shows the distribution of Lyme disease due to distribution of the *Ixodes* ticks, primarily *I. scapularis* that transmit the causative agent of Lyme disease in the United States (Murray and Shapiro 2010).

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Fig. 1: Reported Cases of Lyme disease -- United States, 2019 (Centers for Disease Control andPrevention 2019).

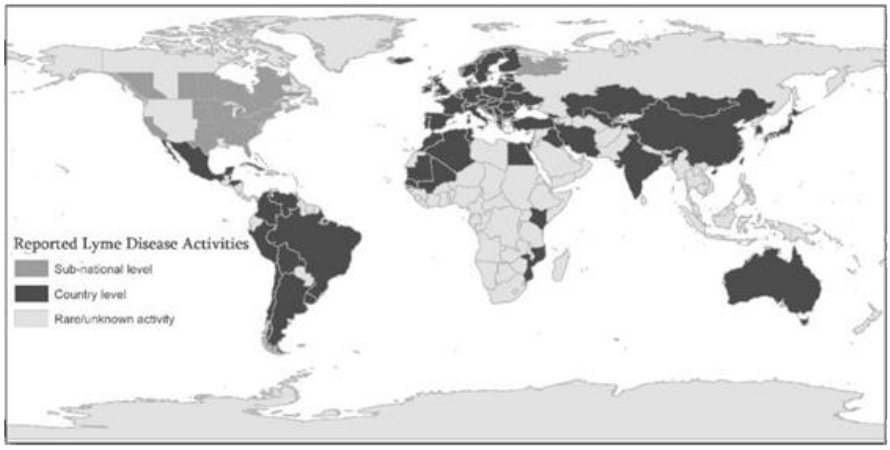

Fig. 2: Geographic Extension of Lyme Disease activities (Ozdenerol 2015).

Lyme disease has also extended into many countries worldwide beyond the endemic foci. Fig. 2 shows Lyme disease activities around the world, which include diagnosed cases of the disease, presence of infected ticks, infected animals, and positive human blood samples for *Borrelia* (Ozdenerol 2015).

Molecular Biology

Immunological study of *B. burgdorferi* (North American strains) shows two surface proteins including outer surface protein A (OspA, 30 to 32 kD) and outer surface protein B (OspB, 34 to 36 kD) (Karami 2012). Like flagellar antigens, the 41-kD antigen is also found in the flagellum. Nowadays, all the isolates have 4 to 9 pieces of extrachromosomal plasmid DNA. Protein may code by plasmid which are crucial for the pathogenicity since the loss of infection of the isolates are abundantly distributed in the laboratory. Thus, they have a relation with the loss of specific plasmid in culture (Barthold et al. 2010). In recent studies, it has been found that similar to relapsing fever, *B. burgdorferi* can differ its antigenicity using different methods and genome modifications (Barbour 1991). Borrelia cells have an average size of 0.2 to 0.5 µm by 4 to 18 µm. The flagella which are periplasmic in nature and have an origination form either end of the spirochete and wind around the protoplasmic cylinder, giving the shape and motility to the organism, in contrast to the peptidoglycan layer that shaped the other bacterial organism (Fig. 3) (Karami 2012). The flagella role is established by inactivation of a gene known as flab that encodes the flagellar protein, filament protein (FlaB) (Karami 2012). The bacterium produced do not have periplasmic flagella and are rod-shaped and non-motile. Alternatively, the motility of bacteria which have external flagella is hindered in viscous substances (Groshong and Blevins 2014).

Pathogenesis of *B. Burgdorferi*

The pathogenicity of *B. burgdorferi* depends on several factors, including the spirochete's motility, cytotoxicity, lymphocyte stimulation and spirochetes resistance to activate completely in the specific antibodies (Sobieszczańska 1994). *B. burgdorferi* can be transferred from the infection site to various parts of the body through blood, lymph and by peripheral nerves. As the tick-bites are the main sources of infection, the inflammatory symptoms are getting visible

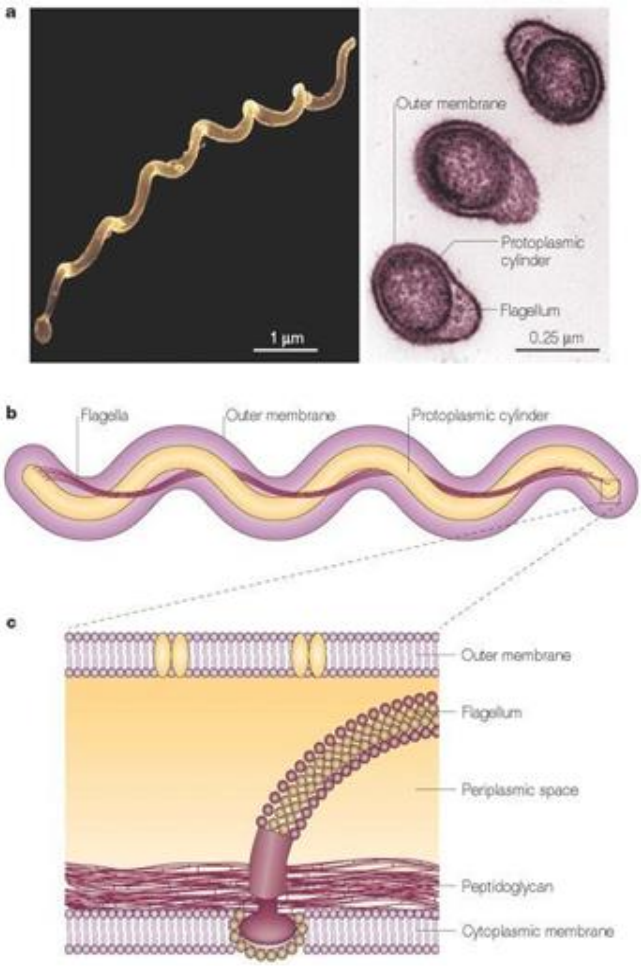

Fig. 3: Structure and morphology of *B. burgdorferi* (Rosa et al. 2005).

more quickly at the site of bite which is an indication that dissemination is more effective in tissues than blood (Fig. 4) (Zajkowska et al. 2000; Zajkowska and Hermanowska–Szpakowicz 2002). *B. burgdorferi* spirochetes can connect to endothelial cells and cross the endothelial layer into the extracellular matrix. The bacteria hide from the defense mechanism of the host as well as antibiotics by localization in the extracellular matrix, utilization of fibrocytes and B-lymphocytes (Zajkowska et al. 2000). The bacteria show tropism to the connective tissue of the heart, synovial membrane, vascular endothelium and to tendon and ligament attachments (Grzesik et al. 2004). Superficial outer surface proteins play an important role in the survival of the bacteria which protect membranous proteins against the action of antibodies (Zajkowska and Hermanowska–Szpakowicz 2002). Bb spirochetes are capable of modifying both cellular and humoral immunological response, and are able to decrease the phagocytotic action of the host. The bacteria disturb cytokines and antibody secretions by aggregation with tissue proteins and fibroblasts. *B. burgdorferi* might attack and destroy T and B lymphocytes (Zajkowska et al. 2000). Complement system can be activated by classical or alternative pathway after the attack of bacteria on the host, while the action of antibacterial is only activated in the existence of specific anti-B antibodies. Microbial adherence might happen independently in the presence of antibodies (Tuchocka 2002). In the Lyme disease pathogenesis, spirochetes fusions with glycosaminoglycans, heparin and heparan sulfate will be able to fuse spirochetes with endothelium. Moreover, decorin which is skin proteoglycan can be figure out by bacterial lipoproteins (Grzesik et al. 2004).

Clinical Manifestation and Infection Course

Chronic Lyme disease has a diverse clinical picture (Rolla–Szczepańska 2007). This disease can be divided into three main stages; early localized, early disseminated, and late stage (Fig. 5) (Tylewska–Wierzbanowska et al. 2008). Early localized Lyme disease is characterized by an expanding, circular red rash known as erythema migrans (EM) which appears around 1 to 28 days after tick exposure in endemic areas (Flisiak and Pancewicz 2008). The second stage which usually develops around 3 to 12 weeks after infection. General malaise, fever, neurological feature such as head ache and cardiac symptoms like chest pain, palpitations and dyspnea are the general features of early disseminated stage (Muhammad and Simonelli 2018). Late Lyme disease appears months or years after infection. The typical characteristics of late stage of the disease include neurological and rheumatological involvements (Yeung and Baranchuk 2018).

Erythema Migrans (EM)

Erythema migrans occurs in nearly 60% of the infected individuals regardless of the age and sex. EM is an oval, red or blue rash that appears at the site of tick bite (Fig. 6). A few weeks after the tick bite, EM starts to increase in diameter. The maximum diameter that EM might reach is as large as 70 centimeters (Nau et al. 2009). Usually, erythema migrans stays for several weeks and then disappears, and this does not mean the eradication of rashes (Flisiak and Pancewicz 2008). Numerous EM appear rarely, and is an indication for the dissemination of the infection. Erythema migrans skin changes might be accompanied by systemic signs such as fever, muscle and joint pains, headaches, meningeal signs and lymph nodes enlargement that may be treated as certificate of spirochetemia (Wormser et al. 2006).

Neuroborreliosis

B. burgdorferi can cause disseminated infection and the most popular and severe form is Neuroborreliosis. The cases of neuroborreliosis commonly found in the Europe. Neuroborrelisis usually involve central as well as peripheral nervous system. It might be caused by all three species of *B. burgdorferi*. *B. garinii* are mostly isolated from cerebrospinal

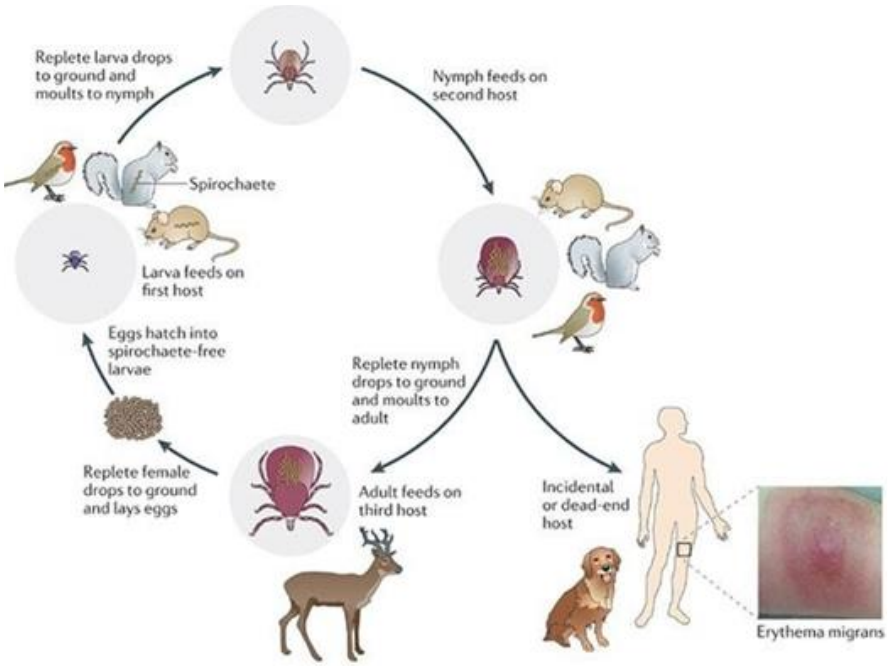

Fig. 4: Borrelia burgdorferi life cycle and transmission from tick to the final host (Radolf et al. 2012)

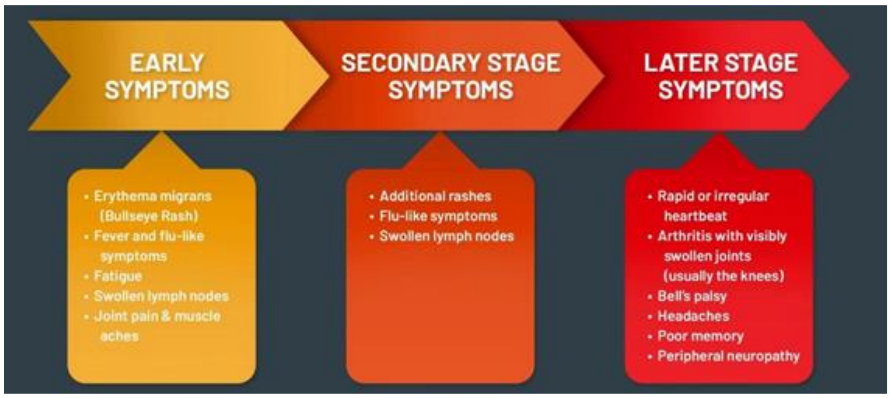

Fig. 5: 3 Stages of Lyme disease (Centers for Disease Control and Prevention 2019)

Fig. 6: Erythema migrans ("classic" Lyme disease rash) (Centers for Disease Control and Prevention2019)

fluid (CSF) than other species in Europe (Flisiak and Pancewicz 2008). In early stages of the disease, neuroborreliosis might proceed with cranial nerve paralysis, most frequently the paralysis of facial nerve. CSF inflammation and changes may cause paralysis. The early stages of neuroborreliosis might cause nerve roots or single peripheral nerves paralysis. Meningitis and encephalomyelitis may also occur. A slow course of encephalomyelitis might appear in the late stage of Lyme disease. It may also proceed to peripheral neuropathy as well as dysaphia and paresteses might appear during the chronic infection. Encephalopathy, dominating memory impairment and dizziness may also appear during the course of disease (Wormser et al. 2006).

Lyme Arthritis (LA)

One of the frequent manifestations of the *B. burgdorferi* infection is Lyme arthritis (LA). In both early and late stage of Lyme disease infection, Lyme arthritis appears. Nearly 10% of Lyme disease patients have persistent arthritis and show resistant to antibiotics, along with the remaining symptoms of disease, despite of using standard antibiotic (Aguero-Rosenfeld et al. 2005). Frequently administered antibiotic might not be effective, because spirochetes can persist in the joints during arthritis despite of elimination of the pathogens. Remains of spirochetes in the joints and arthritis without spirochetes can be differentiated by DNA detection of *B. burgdorferi* in synovial fluid or synovium (Stańczak et al. 1999). Lyme disease could exist with various clinical appearances, for example, muscle ache, arthralgia or periarthritis can persist for months or even years. Most cases of Lyme arthritis attack the knee joint, followed by the humorous and shoulder joints. The temporal and mandibular joints, small joints of hands and legs, elbow, wrist, hip and ankle joints are rarely infected. In rare cases of LA, it may cause permanent damages to the affected joints which are irreversible and also cause permanent immobilization of the joints (Kocbach-Przudzik 2019).

Lyme Carditis

Carditis may appear at the early stage of Lyme disease in 21 days after infection. However, this duration might last from 1 week to 7 months. In *B. burgdorferi* infection, heart problems might be appeared with other forms of Lyme disease such as EM or nervous systems (Afari et al. 2016). One of the features of heart infection in the course of *B. burgdorferi* is the acute onset and atrio-ventricular dissociation as partial or total atrio-ventricular block (Yeung and Baranchuk 2018). Myocarditis, pericarditis, benign cardiac insufficiency, and chronic hemostatic cardiomyopathy are fewer common complications of Lyme carditis. The persistence of *B. burgdorferi* in cardiac muscle during spirochetemia that appears during the early stage of disease, might be the cause of myocarditis (Patton and Phillips 2018). However, the chances of disease progression toward myocarditis and pericarditis are very rare (Shapiro and Wormser 2018).

Acrodermatitis Chronic Atrophicans

After several years of infection with Lyme disease, acrodermatitis chronic atrophicans might appear as red or blue-red stain occurring on the skin of the distal parts of the limbs (Fig. 7) (Stanek et al. 2012). It is a long standing, chronic, and progressive form of Lyme disease that appear more frequently in Europe than in the USA, affecting male patients with older ages. Acrodermatitis chronic atrophicans is mostly caused by *B. afzelii* (Bhate and Schwartz 2011).

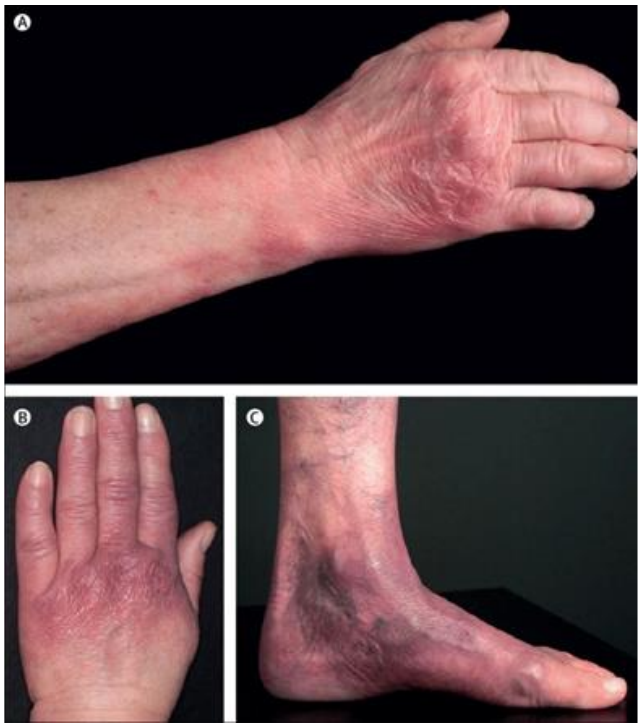

Fig. 7: Acrodermatitis chronic atrophicans (ACA) is typically located on the extensor sites of extremities: (A) ulnar and hand lesions, (B) bluish-red lesion on the back of a patient's hand and waxy appearance of theskin of fingers, (C) lesions on a patient's left foot and lower leg (Stanek et al. 2012).

Diagnosis

The early diagnosis of Lyme disease associated with erythema migrans does not need any serological tests. Erythema migrans appears in between 2-30 days beyond the bite of the infected tick, while anti-Bb antibodies appear in around 2-4 weeks after the initial tick bite. The patients with EM might have negative results for serological test (Flisiak and Pancewicz 2008). In disseminated disease, the diagnosis becomes more difficult and based on careful epidemiological history to confirm any exposure to tick bites, typical clinical signs of the disease and test positivity for anti-Bb antibodies in the patient's serum (MSD veterinary manual).

Two-step diagnosis is needed to detect the pathogen including the first step is based on ELISA (enzyme- linked immunosorbent assay) and then the results must be confirmed by a more specific Western blot assay (Zajkowska et al. 2000). Humoral response starts with immunoglobulin M (IgM) antibodies that usually appear in about 2 to 4 weeks after infection. The level of IgM antibodies peaks 8 to 10 weeks post infection and starts to disappear gradually, which in some patients might remain for several years. Immunoglobulin G (IgG) antibodies can be detected in serum about 6 weeks post infection and reach the peak levels after 4 to 6 months. It can be detectable in serum for many years (Ross Russell et al. 2018). Anti - myelin antibodies are

Table 1: Treatment of Lyme disease (Mark and Klempner 2001).

Clinical picture	Drugs	Dosage	Administration	Duration[days]
	DoxycyclineAmoxicillin	100 mg bid	popo	14-21
	Cefuroxime	500 mg tid	po	14-21
EM		500 mg bid		14-21
	AmoxicillinDoxycycline	500-1000mg tid	popo	14-28
Lyme disease witharthritis	Cefuroxime	100 mg bid	po	14-28
		500 mg bid		14-28
Lyme disease with nervous system, heart, or recurrent joint involvement	Ceftriaxone Ceftriaxone Penicillin G	2000 mg q24h	iv iv iv	14-28
		2000 mg tid		14-28
		3-4 mu q4h		14-28
Acrodermatitis Chronic Atrophicans	Amoxicillin Doxycycline	500-1000mg tid	po po iv iv	14-28
	Ceftriaxone Ceftriaxone	100 mg bid	iv	14-28
	Penicillin G	2000 mg q24h		14-28
		2000 mg tid		14-28
		3-4 mu q4h		14-28

EM – erythema migrans, bid – twice a day, tid–3 times a day, po–per os (by mouth), iv– intravenously, q4h – in each 4hrs, q24h – in each 24 hrs.

detected in the serum and CSF in patients where central nervous system (CNS) borreliosis causes demyelination. The CSF cell count is increased to several dozens or several hundred in cases of meningitis, accompanied by a slight elevation of CSF protein level and specific intrathecal IgG or IgM antibody synthesis, which is detected using ELISA test. CSF abnormalities might be absent or minimal in early stages of the Lyme borreliosis, and limited to a slight increase in the protein levels (Murray and Shapiro 2010). There are difficulties in serological tests and it may be a result of differentiation within individual *Borrelia* species. It is impossible to obtain valid results of serological test by using diagnostic antigen derived from only one strain (Aguero-Rosenfeld et al. 2005). Variable major protein-like Sequence (VlsE) is a recently described marker which can improve the diagnosis of Lyme disease (Aberer 2007).

Treatment and Prevention

The main treatment for the Lyme disease is the use of antibiotics. For the selection of an appropriate treatment, the stage of Lyme disease and the duration of the treatment should be concerned. Antibiotic treatment for Lyme borreliosis lasts a minimum of 21 days (Dybowska 2006). First-line antibiotics used for the treatment purpose includes doxycycline, amoxicillin, ceftriaxone, cefotaxime and penicillin G. Azithromycin or clarithromycin might be used as an alternative for amoxicillin or doxycycline. The combination of antibiotics and long duration treatments with antibiotics is also not recommended (Bockenstedt et al. 2002; Wormser and Schwartz 2009). Table 1 shows treatment protocol of Lyme disease at various stages.

The best way to prevent the infection with *B. burgdorferi* is by prevention of infected tick bites. Removing the ticks as soon as possible after any exposure protects the host against infection with spirochetes. Ticks should be removed with proper care. The possibility of spirochete transmission to humans is increased while removing the ticks carelessly that might regurgitate the tick gut content. Removing of the ticks needs a single movement, and the site of the bite should immediately be cleaned and disinfected. The injured individual should be thoroughly observed for up to 30 days, looking for signs and symptoms of Lyme disease. Active prophylactics of Lyme borreliosis i.e., vaccination is not available. *B. burgdorferi* vaccine based on protein A of the external envelope of spirochete (OspA) was developed and registered in the USA, but the vaccine was removed during 2002 (Piesman and Eisen 2008, Richer et al. 2011).

Conclusion

Lyme borreliosis is the most wide-spread disease transmitted by ticks in Europe and the USA and creates many diagnostic and therapeutic problems. It can either be localized or systemic which can mostly be manifested in the skin as well as musculoskeletal signs. However, it can distribute to other body parts, specifically nervous system and heart. The disease is diagnosed on the basis of clinical signs and then confirmed through serological tests. It can be treated with antibiotic for a period of two to four weeks. The disease might be prolonged in the patients with delayed therapy and can lead to irreversible tissue damage.

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