

Review for the Generalist

Lyme borreliosis (disease) in children and adolescents

Prof. Dr. med. Hans-Iko Huppertz

Hans-Iko Huppertz

Klinikum Bremen-Mitte

Professor-Hess-Kinderklinik

Sankt-Jürgen-Strasse

28205 Bremen, Germany

huppertz.bremen@t-online.de

Introduction

Lyme borreliosis is a vector borne disease transmitted by ticks of the *Ixodes* genus. These ticks include *Ixodes ricinus* (Western Europe), *I. persulcatus* (Eastern Europe and Asia), *I. scapularis* (Northeast and Central US), and *I. pacificus* (Western US). [1-2] The disease affects several organs including skin, central nervous system and joints. [3] It is caused by the spirochete *Borrelia burgdorferi sensu lato*. [4] It is the most common vector borne disease of the northern temperate climate zones. [2,5] So it is an infectious disease, but not contagious. Although the disease is usually not fatal, it has attracted a lot of attention. In my opinion this heightened attention may be due to the fear of a long lasting infection acquired in an environment perceived as healthy by a blood-searching small animal and the fascination of scientists that this bacterium is able to persist within the human body in the presence of a functioning immune system. Lyme disease is named after the small town of Old Lyme, Connecticut, USA, where it has been first described in 1975. A young rheumatologist Alan Steere noted an epidemic of oligoarthritis in children occurring after a skin rash. [6] However, the disease had already been described extensively in Europe. In 1883 the German physician Herxheimer first described acrodermatitis chronica atrophicans, a chronic skin disease which is now known to be part of the clinical spectrum of Lyme borreliosis. [7] In 1910 erythema migrans was first described as being tick borne. [8] In 1941 the physician Bannwarth described a disease with meningitis, radiculitis and rheumatism. [9] Later successful treatment with penicillin was described in 1946 [10] and transmission by skin biopsies of erythema migrans to healthy volunteers were reported in 1955. [11]

However, it was only after the description of Lyme disease in the U.S., that within a few years the full spectrum of the disease, the etiology, *Borrelia burgdorferi*, named after the Swiss-American microbiologist Burgdorfer, methods of diagnostics including serology, treatment by antibiotics and modes of pathogenesis were described. [3] Lyme borreliosis is also one of the “emerging” infectious diseases, an example that infectious diseases remain important causes of morbidity in spite of the enormous changes brought about by hygiene, nutrition, vaccinations, antibiotics and other interventions. [2-3]

Transmission of Lyme borreliosis

Ixodes ricinus and other species, the transmitting ticks, evolve by metamorphosis through three stages. The smallest one is the larva which feeds on small mammals, for example mice, and then develops in the humid ground to a nymph which, after another blood meal, develops in the ground to an adult animal. The adult animals are bisexual, survive in the fur of large animals like deer during wintertime, and then, after another blood meal, copulate in spring and the female lays eggs in the ground, which then develop into larvae. *Borrelia burgdorferi* is not transmitted transovarially, but is transmitted transstadially. So when larvae get infected with *Borrelia burgdorferi*, nymphs and adults will be infected as well. The larva usually acquires the infection from mice in which *Borrelia burgdorferi* maintains spirochetemia. Often larvae feed in late summer, while nymphs feed in early summer. So mice have gotten the infection with *Borrelia burgdorferi* from nymphs and transmit it to larvae later in the year. Human beings are usually bitten by nymphs and sometimes by larvae and rarely by adult ticks. [2-3,12-14]

The tick bite is often not recognized, in part because the animals are so small. [12] Other reasons are the special components found in tick saliva. Although it is called tick “bite”, it is more like a sting, when an elongated part from the tick’s mouth is pushed through the epidermis into the skin where it is rotated to form a lake of ruptured vessels. The tick’s saliva contains local anesthetics, so that the host does not feel pain. Since saliva also contains antihistamines, anti-C3, anti-TNF- α and anti-neutrophil substances, there is neither an allergic nor an inflammatory reaction against the tick or its products. In addition, saliva contains antithrombotic substances so that the tick can suck blood for a long time; usually it feeds between 3 and 5 days. [15]

Etiology

Borrelia burgdorferi is a spirochete which, due to its small size, is not visible by microscopy, except for phase contrast microscopy, when *Borrelia* can be seen because of its ability to move. Several genotypes have been described including *Borrelia burgdorferi* sensu stricto (in a strict sense), *Borrelia afzelii* and *Borrelia garinii* all of which are part of *Borrelia burgdorferi* sensu lato (in the broad sense). Although *Borrelia burgdorferi* sensu stricto is associated with arthritis, *Borrelia garinii* with central nervous system involvement and *Borrelia afzelii* with acrodermatitis chronica atrophicans, all species may also lead to other manifestations and the distinction between the different species is of limited clinical importance. [4]

Clinical manifestations

Clinical manifestations in children and adolescents vary from what is described in adult humans (Table 1). [12-14]

Table 1: Clinical manifestations of Lyme borreliosis in children and adolescents.

Early (days, weeks)	Late (months, years)
Erythema migrans Lymphocytoma	Acrodermatitis chronica atrophicans

Lymphocytic meningitis	Radiculoneuritis
Facial palsy	Encephalomyelitis
Myopericarditis	Cardiomyopathy
Conjunctivitis	Uveitis, Keratitis
Summer "flue"	Episodic arthritis
Arthralgias	Chronic arthritis

The most frequent pediatric manifestations are printed in bold letters.

Pediatric Lyme borreliosis usually is divided into early and late manifestations. Early manifestations occur days to weeks after the infection, are self-limiting and do not lead to permanent organ damage. Late manifestations occur months to years after infection; they may become chronic and may lead to permanent organ damage. Early manifestations can disappear by itself without any further disease, but they may also progress to late manifestations. Late manifestations may occur in the absence of early manifestations. Although some patients have several manifestations of the disease, usually patients have just one of the late manifestations. [2-3,12-13]

The most frequent manifestation of Lyme borreliosis is erythema migrans, an expanding reddish lesion starting at the site of the tick bite. The erythema enlarges during the next days to an oval or round spot of several cm of diameter with a black point in the middle, the site of the tick bite, and an accentuated margin and a pale centre of the lesion. Figure 1 Erythema chronicum migrans rash on a child's legs



In some patients, several erythemata migrantia occur, which are not due to several tick bites but due to early spread of *Borrelia burgdorferi*. (Figure 1) These children often have lymphocytic meningitis in addition to multiple erythemata migrantia. Lymphocytic meningitis with or without facial palsy is the most frequent neurological manifestation in children and adolescents. Other cranial nerves may be involved as well. In spite of lymphocytic pleocytosis, often, the patient has an only marginally stiff neck, but headaches, nausea and constitutional symptoms. [12-13]

The most frequent late manifestation of Lyme borreliosis is arthritis, in 2/3 of the patients as episodic arthritis. In episodic arthritis, the patient has arthritis for a few days to 2 weeks and then it disappears by itself. After a symptom free interval of a few weeks to months, arthritis recurs, usually in the same joint. After several episodes, arthritis may disappear or become chronic (duration of uninterrupted arthritis of 3 or more months). Nearly all patients with Lyme arthritis have involvement of the knee joint during their disease; 2/3 have monoarthritis. Often there is a large effusion with little pain. Most patients do not remember a tick bite and very rarely there is a preceding erythema migrans. This is a consequence of early antibiotic treatment of patients with erythema migrans which prevents progression of the disease to late Lyme borreliosis. [16-17]

Sometimes patients with Lyme arthritis may also have eye disease. The iridocyclitis may be indistinguishable from what is seen in patients with juvenile idiopathic arthritis. Uveitis intermedia may lead to severely impaired vision. More frequently, eye disease occurs in the absence of arthritis and encompasses conjunctivitis as an early manifestation and, in addition to the above mentioned manifestations, keratitis as a late manifestation. [18-20]

Epidemiology

The disease is prevalent in nearly all European countries, in some areas of North-America and in parts of Asia. [2,5] The incidence varies in different countries and different parts of countries and is highest at the east coast of the United States, southern Sweden, Germany and central European countries where it may exceed 100 per 100,000 inhabitants per year. [21-24] This high incidence translates into a lifetime risk of more than 7%. [24] The disease may be acquired in humid areas with grass, bushes and shrubs but usually not in the center of dark forests. [12-13] The incidence is highest during the first 15 years of life and between 60 to 70 years of age. [23-24] Children are more likely than adults to have manifestations other than erythema migrans alone including arthritis, neuroborreliosis or lymphocytoma. [24] The disease is acquired in spring, summer and autumn, usually when surface temperature is above 10 – 15 degrees Celsius. [2,4,24-25] Most patients, up to 90 %, have erythema migrans. [2-3,13-14] Therefore the disease is most prevalent in spring to autumn. However, some cases start in wintertime. They usually have late Lyme borreliosis like Lyme arthritis which has a long and varying incubation period. In contrast to tick borne central European encephalitis, a viral disease, which is transmitted by the same ticks, Lyme borreliosis is not acquired at special, sometimes remote, sites during leisure time, but is acquired during daily life-activities close to the sites where patients live. It may be acquired also in municipal parks and in the front garden of town houses. [13,25]

Diagnosis of Lyme borreliosis

Diagnosis is made by clinical evaluation alone or with support of additional laboratory results. Laboratory values should not be obtained in the absence of a clear clinical suspicion of Lyme borreliosis. Available laboratory methods include culture of borrelias, which is rarely efficient due to the fastidious nature of *Borrelia burgdorferi*, the long culture period of 4 – 6 weeks and the low number of organisms present in body fluids. Tissue staining with monoclonal antibodies is rarely efficient because of the low number of organisms. Lymphocyte transformation assay has been shown to be less sensitive and less specific than serology. [5,12,13]

So far polymerase chain reaction (PCR) is difficult to handle outside research laboratories. Usually it is recommended to analyze more than one body fluid with several primers including bacterial chromosome and plasmids. In addition, tissue specimens, for example from the joint, might be a better medium for PCR than synovial fluid. PCR under these conditions has been found positive in patients with Lyme arthritis in synovial fluid in up to 80% and in lymphocytic meningitis from cerebrospinal fluid in up to 25%. So serology cannot be substituted by PCR. A positive PCR from a good laboratory supports the diagnosis Lyme borreliosis, a negative PCR is of no consequence. [3,12-13]

The usually performed serological tests are enzyme-immuno-assays for IgG and IgM antibodies to *Borrelia burgdorferi*. Since they are screening assays, they are often false positive. Therefore, if enzyme-immuno-assays are positive, they have to be confirmed by immunoblot-/Western blot-assays. There are no standardized rules for interpretation; however, in whole-cell blots, 2 bands of the IgM blot and 6 bands of the IgG blot usually are required to confirm positivity. [26-28]

Erythema migrans is diagnosed by clinical means only and there is no need for serological confirmation. Indeed, serologic tests often are still negative in the presence of early infection and thereby might confuse physician and patient alike. In rare cases of atypical presentation, PCR from skin biopsy could be considered. In my opinion, this skin biopsy is more invasive than a therapeutic attempt with a short course of antibiotic treatment. In all other manifestations, laboratory confirmation of the clinical suspicion of Lyme borreliosis should be sought. [29]

In the case of Lyme arthritis, a clinical score has been developed for the diagnosis. [30] Comparing clinical data of patients with Lyme arthritis with those of patients presenting with other causes of arthritis, it was found that patients with Lyme arthritis more frequently remember a tick bite, more frequently have episodic arthritis, more frequently start with arthritis of the knee joint and less frequently complain of arthralgias initially. In addition, they are older and have a smaller number of large joints involved. By combining these six items, a score has been elaborated which allows for the exclusion of Lyme arthritis or confirmation of Lyme arthritis in 2/3 of cases, in the absence of the knowledge of serological results. This example of a clinical score, based solely on data obtained by history and physical examination, shows the importance of the clinical evaluation of a child when assessing the patient for the presence of Lyme borreliosis. Only in the presence of clinical evidence for Lyme borreliosis, serological tests for antibodies to *Borrelia burgdorferi* should be performed. [30]

Treatment

While diagnosis of Lyme borreliosis may be difficult in some cases, treatment usually is easy. Erythema migrans is treated for 2 – 3 weeks by doxycycline 200 mg/day in children 9 years or older. In younger children amoxicillin 50 mg/kg in 3 doses is given. When erythema migrans disappears rapidly, 2 weeks of treatment are sufficient. If disappearance is slow, the treatment should be prolonged for a week. If it is still present after 2 weeks of treatment, the diagnosis should be questioned. [31-33]

All other manifestations can be treated by ceftriaxone 50 mg/kg/day (maximum 2 g/d) for 14 days by intravenous route. Since it is applied just once per day, we continue treatment in the outpatient department if the patient's social context allows this or when the patient has recovered from neuroborreliosis. While neuroborreliosis should always be treated by intravenous means, Lyme arthritis may also be treated by oral antibiotics, amoxicillin for 4 weeks or doxycycline for 4 weeks at the same doses as mentioned above. It is important to assure a good compliance which might be difficult using amoxicillin because 3 doses per day have to be given for 28 days at predefined time points. We have had favorable experiences with the combination of roxythromycin (5mg/kg) plus cotrimoxazol (6 mg/kg) in 2 doses for 4 weeks, when patients did not respond to ceftriaxone. Although 1 antibiotic treatment should be sufficient for eradication of borrelias, we recommend 2 courses, usually with different drugs, if the first treatment is not effective within 6 weeks of initiation (see table 2). [34]

Table 2: Antibiotic treatment of Lyme borreliosis

Drug	Dosage per day in doses	Maximum dose/day	Duration [weeks]
Amoxicillin	50 mg/kg in 3	2 g	EM: 2-3; LA: 4
Doxycyclin ¹	200 mg in 1	200 mg	EM: 2-3; LA: 4
Ceftriaxone	50 mg/kg in 1	2 g	2
Cefotaxime	150 mg/kg in 3	6 g	2
Roxythromycin; Cotrimoxazol ²	5 mg/kg in 2; 6 mg/kg in 2	300 mg; 360 mg	4
EM: erythema migrans; LA: Lyme arthritis amoxicillin, doxycycline, and roxythromycin + cotrimoxazol are given by mouth, ceftriaxone and cefotaxime are given intravenously. Neuroborreliosis should always be treated intravenously.			
1: Not to be used in children younger than 9 years of age or during pregnancy			
2: Combination used as second line drug for Lyme arthritis. [34]			

Not all children with Lyme arthritis respond to antibiotic treatment. One year after initiation of antibiotic treatment, between 10 and 20% of patients still have arthritis or arthralgias, mostly in the joints that have been affected previously by arthritis. Risk factors for an antibiotic refractory course are treatment with steroids, especially intraarticular steroids, prior to initiation of antibiotic treatment, older age (10 years or older in comparison to younger age), female gender and long duration of arthritis before initiation of antibiotic treatment, i.e. more than 6 months. [32]

When antibiotic treatment fails in patients with Lyme arthritis, antirheumatic treatment may be initiated. Intraarticular steroids may be tried, while non-steroidal antirheumatic drugs usually are of little help. In case of failure of intraarticular steroids, methotrexate or other second line antirheumatic drugs may be tried. Finally synovectomy in combination with intraarticular steroids remains an option for refractory cases. [35]

Prognosis in general is excellent and finally arthritis will disappear. However, we have observed relapses for up to 3 years after disappearance of arthritis. Antibodies may remain high in spite of lasting clinical remission; therefore induction of remission is not assessed by serology but by clinical means only. [36]

Pathogenesis of chronic Lyme arthritis

The histological picture of chronic Lyme arthritis is indistinguishable from changes found in juvenile idiopathic arthritis: Synovial hypertrophy, lymphocytic infiltration and high vascularization. [37] Although it is close to impossible to culture *Borrelia* from joint tissue, the organism has been demonstrated by tissue staining and PCR. [38-39] In an in vitro model, synovial cells could be infected by *Borrelia burgdorferi* and *Borrelia* persisted intracellularly even in the presence of antibiotics in the surrounding medium. [40]

If *Borrelia burgdorferi* is an intracellular bacterium, CD8+ cytotoxic T-cells should be present in patients with Lyme arthritis. In fact, CD8+ HLA class I-restricted T-cells, specific for particular antigens of *Borrelia burgdorferi*, could be found. However, lytic activity of these cells appeared only after disappearance of arthritis. As a consequence the authors suggested that CD8+ cytotoxic T-cells are necessary for eradication of *Borrelia burgdorferi*. However, these cells are suppressed in case of ongoing arthritis either by persistent infection or by purely immunological means. [41]

There are several theories trying to explain the pathogenesis of chronic and treatment-resistant Lyme arthritis. Besides persistent infection, the most probable theory is autoimmunity. One proposed autoimmune mechanism is molecular mimicry of *Borrelia* OspA, a bacterial surface antigen, and human LFA-1, a T-cell antigen. [42] Recently, some authors who had put up this theory several years ago have backed away from it. Moreover, immunopathological reactions due to lipoproteins, abundant at the surface of *Borrelia burgdorferi*, might be responsible for chronic arthritis. [42]

Prevention

Several means of prevention have been proposed. While it is possible to avoid states and areas with a high incidence of Lyme borreliosis in the United States, the disease is prevalent nearly everywhere in many parts of Europe. Proposals to use repellents or to wear proper clothes are unrealistic in Europe, where the disease may be acquired in everyday life close to the patient's home and in inner city parks. [1] A vaccine, developed in the United States and marketed for some time, was withdrawn for economic reasons. Due to strain variations, it would not have been useful in Europe.

Therefore, the best means of prophylaxis is to remove an attached tick as early as possible. The reason for the prophylactic value of early removal of the tick is as follows: *Borrelia burgdorferi* lives in the midgut of the tick. Only when the host's blood enters the tick's midgut, after the beginning of a blood meal, *Borrelia burgdorferi* starts to proliferate, perforates the gut wall and enters the hemolymph, a kind of blood

of the tick. *Borrelia burgdorferi* then enters the salivary glands of the tick, and finally, borreliae are excreted via these glands into the host. This process takes some time, in an animal model nearly 36 hours. So prompt removal of the attached tick within 24 hours of attachment is the best available protection against Lyme borreliosis. If children are assessed each night before going to bed, the time of attachment in most cases is very short. Removal of ticks should not be performed with nail polish, glue, rotation of the tick or other manipulations, but by drawing slowly with instruments or finger nails without compressing the animal's body. It may take up to 90 seconds till the tick withdraws its mouthparts from the host and then comes off the skin. After tick removal the bite site should be disinfected. [1]

Summary

Lyme borreliosis (disease) is a complex disease with cutaneous, articular, neurologic, and other organ system disease. It occurs due an infection in an individual of the spirochete *B. burgdorferi*. The child or adult develops the infection after being bitten by a tick of the genus *Ixodes*. Each manifestation of this illness may be seen as a single presenting problem in a person without other clinical features or in combination. Prevention is possible in endemic areas with aggressive tick surveillance and removal but no viable, affordable vaccine is yet available. Diagnosis can be challenging but treatment easier. Children can do well with early diagnosis of Lyme and appropriate antibiotic treatment.

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