# Lyme disease: the present status

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**Abstract**

Lyme disease is a complex multisystemic disorder with a rising incidence worldwide. It is a tick born infectious disease caused by a newly recognized spirochete, Borrelia burgdorferi. Lyme disease may mimic and should be differentiated from other immune--mediated disorders as its symptoms may include neurologic, joint, eye or cardiac abnormalities, as well as the typical skin lesion.

The authors describe some new concepts on epidemiology and clinical characteristics of the disease as well as its diagnosis and treatment.

Key words: Borrelia burgdorferi, Lyme disease, erythema migrans, Lyme arthritis.

## Epidemiology and history

Lyme borreliosis is a multisystemic infectious disease, characterized by different clinical conditions, mainly involving the skin, heart, joints and nervous system. The agent responsible is the spirochete Borrelia burgdorferi,[1,2] which is transmitted to humans by bloodsucker arthropods (Ixodidae).[3,4]

The description of the first cases of the disease, later attributed to Borrelia burgdorferi, dates back to 1908. The typical skin lesion caused by the disease - erythema migrans - was first described by Afzelius[5] in an elderly woman who had been bitten by an Ixodidae. Since then, various cases of "chronic erythema migrans" have been reported[5-7] in several European countries, but the agent responsible for its occurrence was not known.

In 1922, Garin and Bujadoux[8] described the case of a woman with intense radiculalgia and paralysis of an upper limb after being bitten by a tick (most likely corresponding to the neurological involvement in Lyme disease).

However, although the dermatological and neurological manifestations had been known in Europe since the beginning of the century, joint involvement was not recognized in the U.S.A. until 1977, when the disease was first described with identical characteristics to that of rheumatoid arthritis in a group of children in Old Lyme.[9] The rash observed in these patients, similar to that of Afzelius erythema migrans, associated with the bite of an Ixodidae, contributed to the identification of the causative agent. However, it was not until 1982 that spirochetes were isolated from the blood, skin and cerebral spinal fluid of patients with Lyme disease.[1,10,11]

Finally, in 1984 the isolated spirochete was named Borrelia burgdorferi[2] after the scientist Willy Burgdorfer, and a tribute to him who identified it and characterized it for the first time.[1] With the isolation of the spirochete, it was possible to confirm cases of Lyme disease in different regions of the globe such as Australia,[12] Continental Europe,[13] Japan,[14] Soviet Union[15] and China.[16]

It was observed that the geographical distribution of the disease follows that of the vectors and is not restricted only to endemic areas.

## Causative agent

As for the etiological agent, it is agreed that the name Borrelia burgdorferi should be understood today in wider sense, encompassing all the strains isolated so far. In fact, recent studies have contributed to a subdivision of that single species into four new species.[17-20] Borrelia burgdorferi in its strictest sense, which tends to be associated with joint and neurological Lyme disease, Borrelia garinii, which is associated with neurological conditions, Borrelia afzelii, which tends to be associated with skin manifestations, and Borrelia japonica, which appears not to interfere in the aetiology of the disease.[19]

Thus, the antigenic heterogeneity of Borrelia burgdorferi strains, together with the multiplicity of

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Received for publication on the 2nd August 1996

vectors (Ixodidae (I) ricinus, I. persulcatus, I. pacificus, I. scapularis, I. dentatus, I. damnini) and hosts (humans, horses, dogs, deer, reindeers, bears, birds, rats) susceptible to the infection, give this disease increasing importance, which is borne out by the increase in the number of annual cases, the geographical distribution of which exceeds the endemic areas and has become worldwide. It is not surprising, therefore, that this is a disease with marked clinical pleomorphism, with diversified evolution in the infected individual, which makes diagnosis difficult and on which new articles are being published constantly.

## Clinical manifestations

Three main stages with different clinical manifestations have been described. The early infection is stage 1 (erythema migrans), which is followed, within a few days or weeks, by stage 2 (spread of the infection) and within a few months, by intermittent symptoms. Late infection, or stage 3, usually begins at least a year after the onset of the disease.[21]

The distinction between early and late manifestations, though useful, is arbitrary, since it implies a sequential evolution of the disease in terms of duration and clinical symptoms, which is often not the case.

From a clinical point of view, the distinction between localized and disseminated infection seems most important, since it significantly influences the diagnosis and the treatment.

Seeking to standardize the criteria adopted, the following classification was proposed at the 4th International Conference on Lyme Borreliosis (Stockholm 1989):

### *a) Recent or early Lyme disease*

Localized infection: erythema migrans and benign skin lymphocytoma, not accompanied by signs or symptoms of disseminated infection (lymphadenopathy and/or nonspecific signs may be present).

Early disseminated infection: multiple skin lesions similar to erythema migrans, early neuroborreliosis, carditis, arthritis or involvement of other organic structures.

### *b) Late Lyme Borreliosis*

Chronic infection: chronic atrophic acrodermatitis; neurological, rheumatologic or other organ manifestations persisting for at least six to twelve months.

The most common manifestations are:

***1) Cutaneous manifestations*** Erythema migrants is the most characteristic sign of the disease, which generally begins at the site of inoculation of the spirochete anywhere in the body, particularly in the lower limbs and with an average incubation period of one to three weeks. In its classic form, it manifests as a round, erythematous ring-like spot saving the central area. This erythema is usually asymptomatic, but localized itching or even constitutional symptoms may occur. The lesion heals spontaneously within weeks or months.[21-24]

Benign cutaneous lymphocytoma develops mainly in children, generally on the earlobe. It usually takes the form of a bluish red nodular lesion, accompanied by regional lymphadenopathy.[25] Histologically, marked infiltration of the dermis is observed, with lymphocytes, plasma cells, macrophages and some eosinophils.[26]

Acrodermatitis chronica atrophicans occurs after the development of a latent stage of infection, which may last months or years. It is a disease that most often affects the elderly, and is more common in women. It has insidious onset, with the formation of a violet pink macular rash of ill-defined contours, usually located along the limb. The lesions expand, converge, become moderately infiltrated, and after weeks or months, the inflammation is replaced by a skin atrophy.[27,28]

Morphea and scleroatrophic lichen have also been referred to as skin changes associated with Borrelia burgdorferi,[29] although this association remains controversial, since only specific antibodies have been observed so far in these lesions.

***2) Cardiac manifestations*** Cardiac involvement occurs in approximately eight to ten percent of cases[30]. Varying degrees of atrioventricular block have been described, occasionally with syncope and dysfunction of the left ventricle, sometimes requiring the placement of a temporary pacemaker for haemodynamic support.[31] More rarely, myocarditis and pericarditis have been reported,[32] which begin around three weeks after the occurrence of the skin lesion and usually last a few weeks.

***3) Neurological manifestations*** The first signs are observed, on average, four weeks after the tick bite, with or without erythema migrans. The most important neurological manifestation in the early disseminated stage, referred to as Garin-Bujadoux-Bannwarth syndrome,[8,33] corresponds to a clinical entity, the main

symptom of which is intense migratory pain that, in most cases, resolves spontaneously within six months.

However, the neurological symptoms in the Lyme disease are quite varied and include, in particular: meningitis with lymphocytosis in the cerebral spinal fluid (CSF), sometimes accompanied by slightly elevated spinal fluid protein levels, and normal or slightly decreased glycorrhachia, encephalitis, neuromyositis and facial palsy. Changes to other nerves may occur more rarely, including the V, VI, IX and XI nerves.[34,35]

The neurological manifestations in the late stage of the disease are more severe in older age groups. The neurological involvement referred to as progressive Borrelia encephalomyelitis induces severe and permanent lesions of the central nervous system after several years, often with signs of spastic quadriplegia.[36]

It is important to note that changes in the peripheral nervous system, which occur in association with acrodermatitis chronica atrophicans, are present in 40% of cases. Thus, signs of sensory peripheral neuropathy can be observed in the sites where the skin is atrophic.[28]

***4) Joint manifestations*** Months or weeks after the onset of the infection, around 60% of untreated patients develop joint symptoms.[37] Oligoarthritis is usually asymmetric and recurrent, affecting preferably the large joints, especially the knees. The duration of the symptoms varies and they are chronic in about 10% of cases. The joint fluid shows an increase in polymorphonuclear cells and a constant presence of cryoglobulins. Synovial biopsy reveals fibrin deposits, vascular proliferation and marked infiltration of polymorphonuclear cells. The rheumatoid factor and antinuclear antibodies are negative.[38,39]

***5) Ocular manifestations*** Ocular involvement is rare, but may manifest in the early or late stage of the disease.[40] Follicular conjunctivitis, keratitis and inflammatory syndromes such as uveitis and vitritis are described. Neuro-ophthalmological involvement includes neuro-retinitis, optic atrophy and papilloedema. Facial palsy can lead to neurotrophic keratitis.

## Diagnosis

This polymorphic clinical presentation makes it difficult to reach a definite and presumptive diagnosis. Thus, the suspicion of the diagnosis will be based on epidemiological history associated with compatible clinical symptoms, later confirmed by the presence of specific anti-Borrelia burgdorferi antibodies in the serum, CSF or skin, detected by ELISA, indirect immunofluorescence (IIF) or Western Blot. The combination of ELISA with the Western Blot technique for confirming dubious results, allows for greater specificity and sensitivity.[41,42]

Due to the high levels of false positives, particularly with IIF, cross reactions with other spirochetes such as Treponema pallidum,[43] and the significant number of patients who cannot react immunologically with the ELISA method,[44] new methods were sought.[45]

Due to its high sensitivity, the polymerase chain reaction method enables the detection of one infectious agent in a sample. However, although this method provides no information on the capacity of the spirochete to develop in the host (which would enable its virulence to be evaluated), it was able to demonstrate the co-existence, in the same patient, of Borrelia burgdorferi in the wider sense, belonging to different species.[46,47]

## Treatment

Although the symptoms in the early stage of Lyme disease may often resolve spontaneously, it is accepted today that antibiotics should be administered, to prevent future complications. Thus, Borrelia burgdorferi is sensitive in vitro to numerous antibiotics, including penicillin G or V, and their semi-synthetic derivatives, such as amoxicillin, erythromycin and other macrolides, and tetracyclines. However, their effectiveness in vivo is a more delicate problem.[48]

In the early stage, usually tetracycline (250 mg qid), doxycycline (100 mg bid), erythromycin (250 mg qid) or amoxicillin (500 mg tid) is administered for ten to thirty days[49]. In more advanced stages, especially in acrodermatitis chronica atrophicans, chronic arthritis and cases of late neurological involvement, the therapeutic use of penicillin or third-generation cephalosporins is preferred. Although the treatment regimens may vary from one author to another, the following are accepted as effective:[49,50]

Lyme disease with neurological involvement - penicillin G IV (20 million U/day) or ceftriaxone (2 g IV/day) for fourteen days.

Chronic arthritis caused by Lyme borreliosis - penicillin benz. (2.4 million U/week) for three weeks; penicillin G IV (20 million U/day) or ceftriaxone (2 g IV/day) for fourteen days.

Acrodermatitis chronica atrophicans - doxycycline

(100 mg bid), amoxicillin (500 mg tid) or cefuroxime (500 mg bid) per os for three weeks.

Sometimes the use of corticosteroids is necessary, particularly in cases of pericarditis, heart failure or chronic arthritis.

## Lyme disease in Portugal

In 1986, Carvalho de Araújo[51] drew attention to the strong possibility of occurrence of the disease in humans, but it was not until three years later, in 1989, that the first case of Lyme disease was published in Portugal by David de Morais.[52] Later, an isolated case[50] was published in 1990.

The largest case series was reported in Alentejo, the teams of David de Morais and of the Centro de Estudos de Zoonoses de Águas de Moura being the ones that have dedicated the most study to borreliosis in Portugal.[54-62]

However, given the presence of the presumed vector of the disease (Ixodes ricinus) throughout Portugal, it is thought that the disease is under-diagnosed in the Central and North regions of the country.[60]

In a study conducted in 1992 by Sofia Núncio and Armindo Filipe, a prevalence of 11.7% of anti-Borrelia burgdorferi antibodies was found in a rural population in the country's South region.[58] The estimated seroprevalence is similar to that of many European countries. However, the vectors and hosts that are important for the survival of Borrelia Burgdorferi, or Borrelia spp. in Portugal, have not been defined. It would be interesting to define more clearly the antigenic relationships of the national strains with the agents identified in other countries.[63]

The strains of Borrelia that have already been isolated from Ixodidae do not appear to be pathogenic to humans[59]. However, no cases of isolation in the laboratory from infected patients have yet been published. According to David de Morais[60], in the cases described so far, Borrelia burgdorferi in its strictest sense and Borrelia garinii are identified as agents, but not Borrelia afzelii, given the rarity of the cutaneous manifestations normally associated with this strain. ■

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