# RHEUMATIC MANIFESTATIONS IN LYME BORRELIOSIS

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## SUMMARY

In the course of Lyme borreliosis which is considered to be a multisystemic disease, rheumatic manifestations are very frequent. In a review of these manifestations four categories can be recognized: 1 - Arthralgias without objective findings, 2 - Arthritis (intermittent or chronic) with objective findings of effusion, 3 - Chronic joint and bone involvement and 4 - Involvement of muscles (myalgias, myositis). In this paper the pathogenesis, clinical findings, diagnosis and differential diagnosis are discussed.



KEY WORDS

*Lyme borreliosis, rheumatic manifestations*


The arthritis caused by *B. burgdorferi* infection was recognized because an epidemic of oligoarthritis occurred in children resident in Lyme, Connecticut (U.S.A.) (1).

Thereafter it became apparent that *B. burgdorferi* was the etiologic agent of a multisystem disease that is now named Lyme borreliosis.

In Europe joint abnormalities were sometimes reported in patients with erythema migrans (EM) or lymphocytic meningitis (2, 3), but the link of articular involvement with cutaneous, cardiac, and neurological disease was recognized only after the description of Lyme arthritis (LA) (4).

Several rheumatological manifestations have been associated with *B. burgdorferi* infection, and probably the clinical spectrum of musculoskeletal involvement is not yet completely delineated.

This paper reviews the rheumatic manifestations of Lyme borreliosis.

## CLINICAL MANIFESTATIONS

**Early manifestations.** After the infection *B. burgdorferi* spreads to the joints, bones or muscles (5). Soon after rheumatic symptoms including arthralgias, myalgias, stiff neck, backache, and stiffness occur.

Since before the discovery of *B. burgdorferi* American patients with EM were not treated with antibiotics there has been the possibility to study

the natural evolution of the infection. Steere (6) reported that twenty percent of patients with EM had no further manifestations of Lyme borreliosis, eighty percent developed rheumatic symptoms and signs. Fifty-four percent of patients with untreated EM had musculoskeletal pain without objective findings (6). Pain was intermittent and migrating, and it affected joints, tendons, muscles, bones and cervical and lumbar spine regions. A median duration of 6 months was reported for the articular symptoms in Europe (7), where most of the patients were treated with antibiotics. American patients, without antibiotic therapy, showed a median duration of arthralgias of 3 years (6). The site most commonly affected by arthralgias, in descending order is shoulder, knee, elbow, wrist, finger, toe, and temporo-mandibular joint (8). Arthralgias may sometimes alternate with frank arthritis and large and small joints are frequently affected in a migratory and polyarticular pattern (9).

**Joint involvement.** Sixty percent of patients with untreated EM were later affected with arthritis, documented by synovial effusion (6). Many of the patients that develop inflammatory arthritis had antecedent arthralgias, and the mean interval between the tick bite or EM is 6 months.

The most common pattern is an intermittent, asymmetric synovitis of one or, less frequently, more large joints. Joints involved, in descending order are the knee, shoulder, ankle, elbow, temporomandibular, joint and wrist. Brief attacks of mono- or oligoarticular arthritis, primarily in the knee, have been emphasized as the characteristic feature of LA by Steere (4). Affected knees are generally very swollen, only moderately warm, but not red, and pain is frequently out of proportion to the amount of effusion. Typically, patients have Baker's cysts. Special emphasis has been given to the occurrence of dactylitis (sausage digits) and to heel swelling, which Herzer indicated as a feature of LA, together with unilateral diffuse hand and finger swelling (10). Polyarticular arthritis is seen in about twenty percent of patients (9), and less than 10% of the cases have symmetric joint involvement that may mimic rheumatoid arthritis. Frequently synovitis remit spontaneously after a few days or a few weeks, and one third of patients have only one attack of joint swelling, while two thirds have recurrent attacks of variable duration and frequency. The frequency and duration of attacks of arthritis gradually fades with time; in North America 15% of patients enter long-term remission each year (6). Chronic arthritis (e.g. persisting synovitis lasting 1 year or longer) occurs in about ten percent of patients (6,9). These patients have frequently only one or two joints involved, and in 85% there are previous arthralgias and arthritis of the affected joints (11).

The knee is the most commonly affected joint also when the arthritis is chronic, followed in frequency by shoulder and hip. If untreated, arthritis may persist for at least 4 years, and patients with the class II HLA phenotypes, DR4 and/or DR2 seem to be at risk of developing a potentially erosive arthritis which frequently is also not responsive to antibiotic therapy (12). These patients may require synovectomy (13).

Acrodermatitis chronica atrophicans (ACA) is a late and characteristic cutaneous manifestation of *B. burgdorferi* infection, and joints and bones may be affected in patients with long standing ACA (14). Subluxation or luxation of joints causes deformity of the fingers and toes, but there are not articular erosive lesions. Periostitis has been described under the affected skin.

**Muscle involvement.** Other rheumatic manifestations associated with *B burgdorferi* infection include myalgias, myositis and fasciitis. Myalgias are very common during the early phase of the disease, characteristically there is no muscle weakness at this time.

In the United States *B. burgdorferi* infection appears to be associated to fibromyalgia (15) in a number of patients, and this has been related to sleep disturbances due to Lyme encephalopathy (16). A myositis, with an interstitial lymphoplasmocytic infiltrate, has been associated to *B. burgdorferi* infection, and in patients with Lyme meningopolyneuritis proximal muscle weakness and elevated creatin kinase have been described (17).

Shulman's syndrome has also been related to *B. burgdorferi* infection by some authors (18,19). Recently, a borrelial dermatomyositis-like syndrome, characterized by involvement of skin and muscles in association with elevated antibodies to *B. burgdorferi*, was reported (20).

## PATHOGENESIS

Current evidence suggests that *B. burgdorferi* spreads to the joints at the beginning of the infection, and that live spirochetes persist during the course of the disease. A confirmation of this is the positive response to antibiotic therapy at any stage of the disease (21). The early immune response is generally restricted to an humoral immune response against the flagellar antigen. Later, when the arthritis becomes localized to one or few joints, at least in American patients (22,23), a strong cellular and humoral immune

response against several spirochetal antigens occurs. The synovial pattern is similar to the lesions observed in rheumatic arthritis (RA) (24), thus suggesting a delayed hypersensitivity response. *B. burgdorferi* induces the production of interleukin 1 (IL-1) (25), and this cytokine plays a major role in the inflammatory destruction of bone and cartilage. Only a small number of patients develop the chronic subset of LA, and this suggests the importance of host factors in the pathogenesis of LA. A role of the class II HLA DR4 and DR2 antigens has been suggested in Americans (26), but it was not confirmed in Europe (27).

The presence of strain differences, and the delineation of three genospecies of *B. burgdorferi* (28) with possible different pathogenicity, suggest that the interplay between the spirochete and the host may be variable, and results in different clinical manifestations.

## SEROLOGY

Serological testing can be very helpful in patients suspected to have LA, as antibodies against *B. burgdorferi* are present in the majority of patients with definite LA. The potential and limits of serology for LA have been reported in detail by Herzer (29). Enzyme-linked immunosorbent assay (ELISA) is the best screening method due to its high sensitivity, and immunofluorescence assay (IFA), with previous absorption with Treponema phagedenis, is a technique with good specificity.

Western blot analysis is commonly used as a confirmatory test, and criteria for defining a positive Western blot have been proposed (23).These topics are covered in deep by Dressler later in this issue. However, a true immune response to *B. burgdorferi* does not necessarily imply that a rheumatic condition is due to active infection (30), as residents in an endemic area may be truly seropositive because of a prior asymptomatic infection (31).

## LABORATORY TESTS

Routine laboratory parameters are often completely normal in patients with LA, and thus not helpful in the differential diagnosis. About half the patients have an erythrocyte sedimentation rate above 20 mm/h (8), and some of them have a slight increase of the white cell count with a shift to the left of the differential count (4). They also can have elevated serum IgM levels, mixed cryoglobulins and circulating immune complexes (32).

Routine synovial fluid analysis (including cell count, total protein, glucose, Gram's stain, crystal) is non-diagnostic, but it should be performed to rule out other causes of arthritis. Synovial fluid findings associated with LA are those found with inflammatory arthritides: the white blood cell count averages 25.000 cells per ml (range 500 to 100.000 cells) with predominant polymorphonuclear leukocytes, glucose is normal and total protein is modestly elevated. Cryoglobulins and abnormal Clq binding (consistent with the presence of immune complexes) are present (33). The synovial biopsy is often not helpful for the diagnosis because the findings are similar to that of rheumatoid arthritis and identification of *B. burgdorferi* by means of staining methods is very difficult.

The polymerase chain reaction (PCR) technique for the identification of spirochetal DNA in synovial fluid or tissue is very promising, and if proven to be sensitive and specific this tool may solve many diagnostic troubles (34).

## RADIOLOGICAL FINDINGS

The spectrum of radiological findings is broad. In North American patients with chronic arthritis several patterns of manifestations have been described (35). In some patients tendons and ligaments were found to be thickened, calcified, or ossified, and calcifications of the articular cartilage were also present. Some cases had typical inflammatory changes as juxta-articular osteoporosis, loss of cartilage, and bone erosions. In a third subset of patients a degenerative pattern, characterized by subchondral sclerosis, osteophytosis and cartilage loss was more prominent. In European series, lesions resembling those of reactive arthritides (dactylitis, heel swelling and calcaneal erosions) were described (8).

## DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

In patients with other typical manifestations of Lyme borreliosis (e.g. EM or lymphocytic meningitis) the diagnosis of LA is not difficult. However, when joint involvement is the only manifestation of the disease, or when there is a long interval between arthritis and other symptoms, the correct assessment may be very difficult. The contribution of diagnostic tests has been dealt with above. Surely there is a great need for a more accurate laboratory aid to the diagnosis. However, several ways of presentation of musculoskeletal involvement require a careful differential diagnosis with many other rheumatic

diseases. When the onset is acute, a monoarticular LA must be differentiated from crystal-induced arthritis and, in some cases, from septic arthritis. Gonococcal and viral arthritis, in particular that, caused by parvovirus B19, may resemble LA when the pattern of arthritis is migratory.

Intermittent Lyme arthritis may be wrongly diagnosed as palindromic rheumatism or as intermittent hydrarthrosis. The most frequent articular pattern of LA is an oligoarthritis. In these patients differential diagnosis with the seronegative spondyloarthropaties is mandatory. In children, juvenile rheumatoid arthritis must be excluded.

Generally, chronic LA is correctly diagnosed, as other symptoms of the disease are frequently present.

In patients complaining of arthralgias only, attention must be paid to the possible existence of fibromyalgia.

## INCIDENCE AND GEOGRAPHIC DIVERSITY

The arthritis of Lyme borreliosis is not influenced by sex, and it affects both children and adults. The appearance of articular involvement, which occurs weeks to months after the infection, does not have a seasonal peak.

The incidence and prevalence of LA vary considerably among different countries. A recent review of this topic (36) concluded that articular involvement seems to be more frequent in the U.S.A. than in Europe, and that differences also exist within European series as arthritis is more frequent in Southern Europe with respect to Northern Europe.

Selection bias, strain-related clinical polymorphism, variation in HLA-related host response and influence of antibiotic treatment are all possible explanations for geographic diversity of Lyme borreliosis. Moreover it is possible that in Europe LA occurs frequently without extraarticular features of *B. burgdorferi* infection, as suggested in Germany (27) and. in Italy (37).

## CONCLUSION

Herzer (27) grouped the spectrum of rheumatic manifestations of Lyme borreliosis in three categories: 1- Arthralgias (musculoskeletal pain) without objective findings, 2- Arthritis (intermittent or chronic) with objective physical findings of effusion, and 3- Chronic bone and joint involvement in ACA. It is advisable to add to these a fourth group, namely the involvement of muscle, either as myalgias, myositis (with or without weakness), or a fibromyalgia-like syndrome.

In conclusion, Lyme arthritis is the best example of a chronic arthritis with a recognized infectious origin (38).

Even if Lyme borreliosis demonstrates that the identification of the causative agent may not solve pathogenetic problems, it is relevant for rheumatologists as it could be studied as a useful model to understand the mechanisms by which an infectious agent can evade the immunologic surveillance, and cause a variety of rheumatic manifestations.

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