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Leader

Lyme arthritis

Lyme disease is a multisystem disorder caused by the spirochaete *Borrelia burgdorferi* and transmitted by the Ixodid tick. It was first described in 1977 following an outbreak of arthritis in Lyme, Old Lyme and East Haddam, Connecticut, USA.[1] It seems likely, from phenotypic analysis of the different spirochaete isolates[2] and previous reports of the dermatological[3] and neurological[4 5] manifestations that the disease originated in Europe. It was not, however, until the outbreak of arthritis in Lyme and subsequent isolation of a new spirochaete[6] that the exact cause was identified. Lyme disease is a cause of considerable morbidity in the Northern hemisphere and continues to be the focus of intense research. There are more than 2500 articles published on the condition to date and recently, the Second European Symposium on Lyme disease was held in this country.[7 8]

Epidemiological aspects of Lyme disease

Surveillance for Lyme disease in the United States was initiated by the Centres for Disease Control (CDC) in 1982 when there were 497 reported cases. Since then the incidence in the USA has increased to 9344 cases in 1991[9] and it is now the most common vector-borne disease in the United States. In addition to an increase in incidence, heightened physician and public awareness and more frequent laboratory testing have led to increased reporting of the disease. Lack of diagnostic criteria initially resulted in incorrect diagnosis, however, the recent adoption of a uniform case definition for Lyme disease surveillance has now standardised reporting.[10 11]

Lyme disease appears to be less common in Europe, particularly in the UK, where there are approximately 200 cases per year.[12] Endemic areas include the New Forest (Hampshire), Thetford forest (Norfolk) and parts of Scotland.[13] Ixodes ticks infected with *B burgdorferi* have also been found in Richmond and Bushey parks, London[14] and we have recently found clinical and serological evidence of Lyme disease in workers from these parks.[15]

Although Ixodes ticks infected with *B burgdorferi* (detected using the polymerase chain reaction), are widespread throughout the UK (fig 1), the organism appears to be present in ticks in this country in lower numbers than in continental Europe and isolation of the spirochaete from UK ticks has proved difficult.[16] The same laboratories, however, have readily isolated the organism from ticks collected in Switzerland and the Czech republic. Further studies have shown that in vitro growth requirements of UK *B burgdorferi* differ significantly from strains from other parts of Europe[16] and it is likely that the lower incidence of Lyme disease in the UK reflects inherent pathogenic differences in the causative organism.

Clinical manifestations

Much concern has been expressed over the diversity of clinical manifestations in Lyme disease, which has been

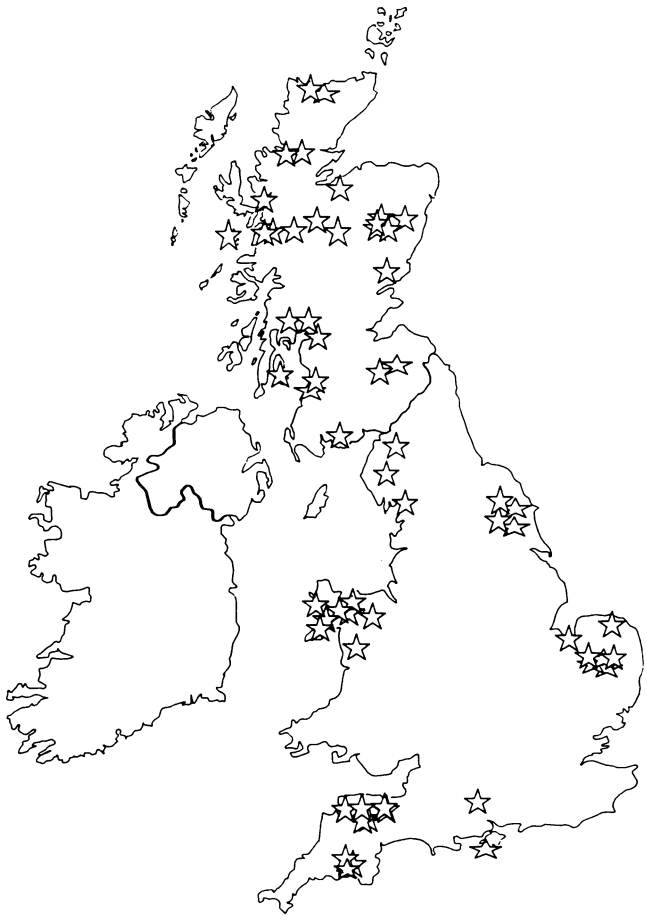

Figure 1 Distribution of Ixodes ricinus *ticks collected between 1990 and 1992 and identified as polymerase chain reaction (PCR) positive for* Borrelia burgdorferi. *Location of PCR positive tick collections are indicated by a star. (figure reproduced with kind permission of Dr P Nuttal)*

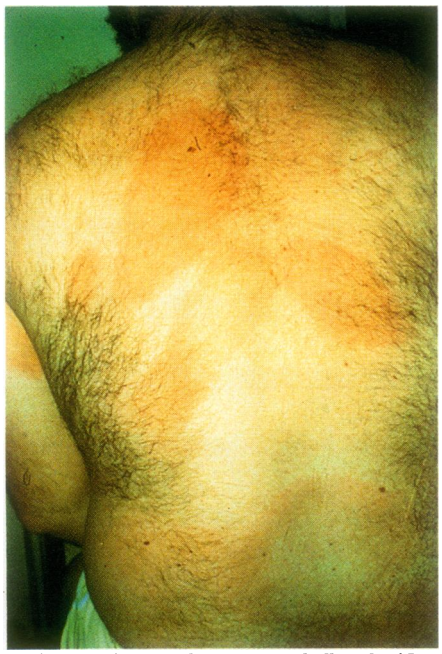

Figure 2 Erythema migrans, *the cutaneous hallmark of Lyme disease, initially occurs at the site of innoculation, usually three days to one month after the tick bite with a peak incidence in the summer and autumn months. It is a red expanding annular rash which clears from the centre and may be itchy or painful. It generally resolves spontaneously within a few weeks to months. Following dissemination of the spirochaete, multiple* erythema migrans *lesions may occur as shown in this figure (reproduced with kind permission of Professor Allen Steere)*

described as 'The great imitator'.[17–19] In fact, clinical reports characterise the condition quite specifically. The initial manifestations of the disease are the characteristic skin lesion, erythema migrans (fig 2), and general malaise (stage 1). This may be followed weeks to months later by fever, arthralgias, lymphocytic meningitis, facial palsy, cardiac conduction disorders and myocarditis (stage 2). Months to years later intermittent or continuous attacks of mono- or oligoarthritis, chronic neurological manifestations and the skin rash, acrodermatitis chronica atrophicans may occur (stage 3). Nearly half of all patients with stage 2 and 3 Lyme disease do not report a preceding skin rash or tick bite,[20] but a carefully taken history covering details of residence, employment, recreational activities and travel will usually reveal previous exposure to tick habitats.

Musculoskeletal manifestations in Lyme disease vary in incidence between countries, being particularly common in the USA. In the most informative study to date, fifty five North American patients with erythema migrans, seen before the infectious aetiology of Lyme disease was elucidated, and who did not receive antibiotic therapy, were followed prospectively for several years.[21] Of these, 18% developed arthralgias without objective joint swelling, 51% developed one or more episodes of intermittent mono- or oligoarthritis lasting less than one year and 11% developed chronic synovitis in one to three large joints for greater than one year, more than a third of whom had radiographic evidence of erosive disease. In continental Europe, arthritis is less common, occurring in approximately 30% of patients with Lyme disease[20 22] and has only rarely been reported in the UK. An early review of 68 UK patients with serological evidence of Lyme disease, identified only one possible case of Lyme arthritis,[13] although in a more recent report of 170 patients with serological evidence of LD, 14 (8%) had arthritis; eight (5%) of whom acquired the infection within the UK.[23] Since 1991, we have seen a further four cases of arthritis complicating Lyme disease, two of whom acquired the infection within the UK and in three of the four patients, arthritis was the only manifestation of the condition.[24]

B burgdorferi has recently been delineated into three separate genospecies,[25] all three species are present in Europe, whereas only group I isolates are found in North America. Increased reactivity on immunoblot is seen against group I organisms in patients with arthritis and against group II organisms in patients with neurological manifestations. It is therefore likely that the regional variations seen in the clinical manifestations results from pathogenic differences in the causative organism.[26]

Pathogenic mechanisms in Lyme arthritis

INFLAMMATORY RESPONSES

Infection with *B burgdorferi* can cause widespread tissue damage, although the precise mechanism by which this occurs is not entirely clear. Spirochaetes have been isolated from or visualised directly in all affected tissues other than the peripheral nerve,[27–31] although, other than in erythema migrans, they are usually present in small numbers. The organism itself does not appear to be directly toxic[32] and evidence suggests that tissue damage may sometimes result from a delayed hypersensitivity response.[33 34] Furthermore, *B burgdorferi* is a potent inducer of interleukin-1 (IL-1) a pro inflammatory cytokine and high levels of synovial fluid IL-1β are associated with more prolonged episodes of arthritis.[35]

HUMORAL AND CELL-MEDIATED IMMUNE RESPONSES

The initial specific humoral immune response to the spirochaete is usually minimal with early responses often restricted to the 41 kD flagellar antigen, the 21 kD outer surface protein (osp C) and the 58 kD and 66 kD heat shock proteins.[36] Months later, when the disease localises to a few joints there is a strong humoral immune response to 12 or more spirochaetal polypeptides.[36] The final point in expansion of the antibody response is often the recognition of the outer surface proteins A and B (OspA and OspB) and interestingly, this often coincides with the beginning of the most prolonged episodes of arthritis, a median of 18 months after disease onset.[37] Most patients with Lyme disease also develop an early and strong cellular immune response to *B burgdorferi*[38] and in Lyme arthritis this is considerably more marked and specific in synovial fluid than blood mononuclear cells. A poor correlation is found between in vitro T Cell responses and antibody responses and of particular interest is that, unlike antibodies, T cells respond to ospA, (the major outer surface protein of *Borrelia burgdorferi*) early in the disease. This dissociation of the humoral and cellular immune responses in Lyme disease may partly be due to selective activation of a TH 1 T cell subset producing a restricted pattern of cytokines unable to activate B cells.[34]

EVIDENCE FOR AUTOIMMUNITY IN LYME ARTHRITIS

Lyme arthritis often begins many months to years after initial infection and in some cases does not respond to antibiotic treatment.[39 40] In this subgroup of patients there is an increased frequency of HLA DR4,[41] the haplotype associated with rheumatoid arthritis.[42] A recent study, using the polymerase chain reaction (PCR), detected *B burgdorferi* in the synovial fluid of 96% of patients with Lyme arthritis which was either untreated or only treated with short courses of antibiotics but in only 30% of patients with persistent Lyme arthritis treated with prolonged courses of appropriate antibiotics. *B burgdorferi* is capable of surviving within mouse macrophages in vitro,[43] however,

it is unlikely that spirochaetal antigen persisted undetected within the joints, as the PCR technique used was a highly sensitive multitarget method. Thus it appears that in approximately 70% of patients with chronic Lyme arthritis, spirochaetes are successfully eradicated from the joint and a reactive arthritis develops, though the mechanism for this remains unclear. One possible explanation for the continued inflammation is that, in genetically susceptible individuals, an autoimmune response develops, as a result of similarities between spirochaetal and synovial proteins. Possible candidates for this antigen mimicry are the outer surface proteins A and B of *B burgdorferi*, antibodies to which, in combination with HLA DR4 are strongly associated with prolonged resistance to treatment.[44] Furthermore, raised levels of IgA and IgM rheumatoid factors have been found in some patients with neuroborreliosis and Lyme arthritis (unpublished observation and reference [45]) and antibodies to cardiolipin and normal human axons have been detected in patients with neuroborreliosis.[46 47] No other autoantibodies have been detected in Lyme arthritis, however, MHC class II autoreactive T cells (to irradiated, autologous peripheral blood lymphocytes) have been found.[48] We have also demonstrated increased expression of idiotype 16/6 (a public idiotype which is expressed on antibodies in a variety of autoimmune conditions) on IgA antibodies in patients with Lyme arthritis but not in patients with other manifestations of the disease.[49]

Diagnosis and treatment of Lyme disease

DIAGNOSTIC CRITERIA

The diagnosis of Lyme disease requires exposure to tick habitats in an endemic area and either the finding of the pathognomonic rash of erythema migrans or laboratory evidence of *B burgdorferi* infection, along with otherwise unexplained articular, neurological or cardiac manifestations consistent with the condition.[11 24] Laboratory diagnosis can be made by histological demonstration of silver-stained spirochaetes in skin biopsy specimens,[50] culture of the organism from blood,[29] cerebrospinal fluid[30] and skin[51] or more recently by detection of *B burgdorferi* DNA using the polymerase chain reaction (PCR).[52] In the absence of direct detection of the spirochaetes by these methods the diagnosis may be supported serologically by enzyme linked immunosorbent assay (ELISA)[53] and immunoblotting.[54] In practice, culture of the organism is difficult and PCR is not routinely available. Much reliance has therefore been placed on serological tests. However, the presence of raised antibodies to *B burgdorferi* does not necessarily indicate active infection and these serological methods lack both sensitivity in early disease and specificity (particularly ELISA) as a result of cross reacting antibodies produced in other spirochaetal and some bacterial infections,[55] infectious mononucleosis and rheumatoid arthritis.[56] Serological testing for Lyme disease therefore should only be carried out in patients with symptoms compatible with the condition along with a history of exposure to tick habitats in an endemic area. Testing patients who do not meet these criteria is of no value and may lead to incorrect diagnosis and inappropriate treatment.[24]

CURRENT TREATMENT RECOMMENDATIONS

The vast majority of patients with Lyme disease are successfully treated with antibiotics and treatment of the early manifestations usually prevents later complications of the condition.[57] The antibiotic regime used depends on the stage of the disease and current recommended antibiotic schedules[58] are shown in the table. In Lyme arthritis the response may be slow with several months sometimes required for complete resolution of the arthritis and in those patients who fail to respond at all to antibiotic treatment, arthroscopic synovectomy has been shown to be of benefit.[59] Recently, it has become apparent that a small percentage of patients with Lyme disease, despite adequate treatment with antibiotics, develop fibromyalgia or chronic fatigue.[60] There is no evidence that this results from persistent infection or any immunological abnormality and these patients do not respond to further courses of antibiotics.

Manifestation		*Treatment*
Erythema migrans		Penicillin V 1 gm qds po × 10 days
	or	Amoxycillin 500 mg tds po × 10 days
	or	Doxycycline 200 mg od po × 10 days
Neuroborreliosis		Benzylpenicillin 3 gm qds iv × 14 days
	or	Doxycycline 200 mg od po × 14 days
	or	Cefotaxime 2 gm bd iv × 14 days
Lyme arthritis		Doxycycline 200 mg od po × 21 days
	or	Amoxycillin 500 mg + probenecid 500 mg tds po × 21 days
	or	Cefotaxime 2 gm bd iv × 14 days

Current antibiotic treatment recommendations for Lyme disease in adults; bd = twice daily, tds = three times daily, qds = four times daily, po = orally, iv = intravenously.

PROPHYLAXIS

Recent interest has focused on preventing cases of Lyme disease. Simple measures such as checking for and removing ticks after walking through grassy land are of benefit, though antibiotic prophylaxis following a tick-bite in an endemic area is of little value.[61] Mouse studies suggest that a protective polypeptide vaccine from OspA/OspB could be developed,[62 63] however, the humoral and cellular immune response differ between mice and humans, in particular antibodies to OspA occur late in human disease and there is concern that in genetically susceptible individuals this vaccine could trigger arthritis.

Conclusion

- Lyme disease is an important, treatable condition and early treatment with antibiotics prevents later complications of the condition.
- The disease is uncommon in the UK and in some patients, arthritis may be the sole manifestation of the disease.
- Serological testing for Lyme disease should only be carried out in patients with clinical manifestations compatible with the condition as well as a history of exposure to tick habitats in an endemic area.
- The pathogenesis of Lyme disease is complex and partly immune mediated. Possibly some cases of chronic Lyme arthritis result from autoimmune response, though this mechanism requires further study.

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