CURRENT TOPIC

Lyme disease in paediatrics

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The cluster of 39 children with a presumptive diagnosis of juvenile rheumatoid arthritis in Connecticut, around the town of Old Lyme, initiated the research which eventually led to the arthritis being named Lyme arthritis.¹ The association with a multisystem illness then caused the syndrome to be redefined as Lyme disease. Epidemiologically, an infectious aetiology appeared probable, with ticks as likely vectors for the disease. Clinically, a skin rash, erythema migrans, preceded the development of the arthritis. The skin rash had been first described in Scandinavia in 1913 and associated with tick bites.² Some patients presented with Bannwarth's syndrome, a meningopolyneuritis associated with tick bites, described in Europe as early as 1941.³ A possible causative organism, *Borrelia burgdorferi*, was isolated from a tick in 1982.⁴ This hypothesis was substantiated when the spirochaete was grown from blood, skin lesions, and cerebrospinal fluid (CSF) of patients with Lyme disease, and the disease was reproduced in rabbits, fulfilling Koch's postulates.⁵⁻⁶ Since then the disease has been recognised in many American states, Northern Europe, Russia, China, and Japan.⁷ It has also been reported in the southern hemisphere in Australia.⁷

Transmission

B burgdorferi is transmitted by the ticks of the genus ixodes. *Ixodes dammini* is most frequently implicated in the eastern USA. In the western USA and Japan *I pacificus* predominates. *I ricinus* acts as the vector in Europe with *I persulcatus* in Asiatic and European Russia.⁸⁻⁹ The nymphal ticks become infected by *B burgdorferi* while feeding on small mammals such as the white foot mouse, which act as reservoirs of the spirochaete. The natural hosts of mature ticks are large mammals such as deer. Humans are incidentally bitten when they enter a tick infected area, usually forest or scrub land.¹⁰ Children playing in such areas would be at particular risk of infection. The frequency of infection after a tick bite depends on a number of factors, such as the prevalence of *B burgdorferi* infection in the ticks, the duration of tick attachment, and the number of tick bites. In an English study of forestry workers, 25% had serological evidence of *B burgdorferi* exposure, and 5% symptoms attributable to Lyme disease.¹¹ These workers may have had multiple bites whereas positive Lyme serology was recorded in 20% of Austrian and 7% of Irish

populations who reported single bites.¹²⁻¹³ Another English study reported positive serology in 12% of a population comprising farmers, gamekeepers, and forestry workers.¹⁴

Epidemiology

Since 1982 the number of cases of Lyme disease in the USA has increased from 500 to over 4500 in 1988. The highest incidence is in children of less than 15 years and in adults of 25-44 years.¹⁵ Females were infected in 51% of cases. Data on file at the Charing Cross Lyme Disease Reference Laboratory records approximately 600 cases per year or 0.39 cases per 100 000 people. Most seropositivity is detected in middle aged patients, and the number of males is equal to that of females. In the eastern USA most cases occur in the summer months,¹⁰⁻¹⁵ which follows the period of maximal host seeking activity of nymphal ticks in May and June.¹⁶ In the western USA, cases are most common in spring.¹⁵ At Charing Cross there are two peaks, one in spring and one in autumn. Most Irish cases have come to medical attention in the autumn.

Clinical features

Typically, the clinical features of Lyme disease occur in three stages.¹⁷ There is considerable overlap between stages of the disease, and features of late Lyme disease may develop without any history of early disease. One of the 'unsolved mysteries' of Lyme disease is that there have been no outbreaks of arthritis reported since the initial 'cluster' in Connecticut.

The characteristic rash, erythema migrans, develops 2-30 days after the tick bite. This expanding lesion is centred on the insect bite and spreads outwards over a period of weeks. It is seen in up to 50% of patients and is occasionally due to multiple bites.¹⁸ Non-specific constitutional symptoms may occur at this stage: malaise, anorexia, lethargy, arthralgia, headache, roseola skin rash, abdominal pain, cough, and sore throat are common complaints. Patients, especially children, may be feverish.

The second stage of Lyme disease develops 1-4 months after infection. These patients tend to come to medical attention in the autumn or winter. Lymphocytosis cutis occurs in 1% of European cases but has not been reported in the USA. This lesion is a firm red to purple nodule or plaque. It develops on the ear lobe in children and on the nipple and areola in

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adults.¹⁸ Pathologically there is a dense dermal nodular lymphocytic infiltrate involving B and T lymphocytes. Infrequently, similar lymphocyte infiltrates, at the base of the brain in Lyme borreliosis, have been misdiagnosed in children as B-cell lymphomas.

Central nervous involvement is common. Lymphocytic meningitis, cerebellar signs, cranial polyneuropathy, and radiculopathy have been reported. The differentiation from Guillain-Barré syndrome may be difficult, but in neuroborreliosis the lymphocyte count is usually greater than 50 cells/mm³ and oligoclonal bands may be seen. Encephalitis, often clinically indistinguishable from herpes simplex encephalitis, may occur. Outside the UK one must consider other arthropod-borne encephalopathies in such cases. In an Austrian study of 21 children seropositive for Lyme disease, 17 had central nervous system involvement, three had arthritis, and one had skin symptoms.¹⁹ In this study and in a Swedish report aseptic meningitis and seventh nerve palsies were the commonest neurological features described.^{19 20} Pain in joints and soft tissues and rarely asymmetrical large joint arthritis may occur at this stage. These episodes are brief and recurrent.¹⁷ A self limiting myocarditis, which may necessitate the insertion of a transvenous pacemaker, infrequently presents during this phase of the illness. Bradycardia is not otherwise a feature of the disease. Iritis or panophthalmitis has also been reported, as has isolated inflammation of peripheral muscles.¹⁷

In the third stage, joint disease is most common. As many as 10% of patients may progress to a chronic erosive arthritis.¹ In an American study of Lyme arthritis in 43 children²¹ the mean age was 7.8 years and the male:female ratio 7:1. The knee was involved in 41 patients, the elbow in eight, the hip or ankle in four, and the wrist in two.²¹

At this stage in older patients demyelinating encephalopathy, polyneuritis, and memory impairment may become manifest.¹ Acrodermatitis chronica atrophicans is the characteristic skin rash of this phase of the disease. Initially this is a violaceous and often oedematous area of skin in plaques or nodules, which later atrophies. It resembles but is distinct from scleroderma.^{17 18} Acrodermatitis is unusual in childhood Lyme borreliosis but at least two cases have been described.²² Eosinophilic fasciitis is a rare complication.¹⁷

As many as 30% of patients do not demonstrate erythema migrans or other signs of early disease before presenting with late complications.²³ In European Lyme disease, joint manifestations are reported to be less common than in the USA. Conversely, in Europe nervous involvement tends to be more prominent.^{24 25} In North American Lyme disease, erythema migrans is more often multiple than in Europe. Recent reports suggest that these differences may be less extreme.^{13 26}

The isolation of *B burgdorferi* from the blood has raised the possibility of transplacental transfer of the organism. To date, borreliae have been isolated from one stillbirth and one newborn infant but congenital abnormalities

resulting from Lyme disease during pregnancy have not been unequivocally demonstrated.²⁷ The abnormalities that have been recorded were associated with serological evidence of infection in retrospective studies.²⁸

Laboratory diagnosis

The laboratory diagnosis of Lyme disease is difficult. The organism has been grown from infected tissues such as skin and body fluids, including CSF.²⁹ Culture is an insensitive technique in most hands and not suitable for routine diagnostic use. Visualisation of the pathogen in infected tissue has similar limitations.³⁰ For these reasons serological techniques have been employed as routine diagnostic aids.

Indirect immunofluorescent assay (IFA) techniques were initially used to detect antibodies *B burgdorferi* but recently, as demand for tests has increased, enzyme linked immunosorbent (ELISA) methodologies have become popular. Such tests can be automated, allow objective test reporting, and are easier to standardise than IFA methods.³¹

Initial antibody responses are directed against the unsheathed flagellar proteins.³¹ A rise in IgM antibodies directed against a 41 kDa flagellar antigen can be detected in most patients two to four weeks after infection. This response peaks at six to eight weeks. Assays which detect IgM response to such proteins are very useful early in the disease. ELISAs which use purified flagellae or flagella enriched preparations of whole *B burgdorferi* as antigens have increased sensitivity in early disease.^{32 33} Later in the course of the illness antibodies directed against proteins in the outer surface membranes (OSP), such as the 34 kDa OSP B or the 31 kDa OSP A, are detected.³¹ As *B burgdorferi* shares many antigenic determinants with other bacteria, sera may contain antibodies which cross react in the IFA or ELISA assays described.^{31 32} False positive results can also occur in patients with connective tissue disorders.³⁴ Therefore further definition of the immune response by immunoblotting is a necessary confirmatory procedure if such tests provide positive results. Immunoblot patterns in children are similar to those of adults.³⁵ At the Charing Cross Lyme Disease reference laboratory 11% of the ELISA specimens that are weakly positive and a third of those that are strongly positive are confirmed by immunoblot. False negative results have also been reported: as many as one in three patients with erythema migrans are seronegative on initial testing,²³ and may become seropositive on further testing. Antibiotic treatment early in the illness may abrogate the antibody response to *B burgdorferi*.³⁶

A suitable test system would include a sensitive screening test, such as an ELISA which uses whole *B burgdorferi* or a flagella enriched preparation as the antigen. All positive results would then be checked by immunoblotting. Where clinically indicated, specimen testing would have to be repeated. In most instances serum would be a suitable specimen, but if neurological syndromes are being investigated CSF should also be examined. In one study nine

patients with neurological syndromes suggestive of Lyme disease had serum which was positive by ELISA, but only one had a CSF positive by ELISA and immunoblot and also evidence of intrathecal antibody production.¹³

In interpreting the laboratory results one must be aware that a proportion of the population will have serological evidence of previous exposure to *B burgdorferi* which may be unrelated to their current symptoms. Seropositivity rates of approximately 25% are detected in high risk populations such as forestry workers or orienteers.¹¹⁻³⁷ Clinical symptoms attributable to Lyme disease were detected in 5% of the forestry workers and 0.8% of the orienteers.

Modern advances in molecular genetics and the application of techniques such as the polymerase chain reaction (PCR) may resolve some of these diagnostic problems. A PCR assay using a highly conserved area of *B burgdorferi* chromosomal DNA was able to detect fewer than five copies of complementary DNA. The assay did not cross react with *B hermsi* or eukaryotic DNA.³⁸ The same authors expanded their primer range and were able to differentiate between *B burgdorferi* of European or American origin.³⁹ Using a PCR method, *B burgdorferi* DNA was detected in the urine of four of eight patients with clinical syndromes suggestive of Lyme disease.⁴⁰ If there is a high prevalence of *B burgdorferi* genetic material in the urine of infected patients, detection may simplify the laboratory diagnosis of Lyme borreliosis. By such techniques we may be able to detect these organisms in body tissues and further define the pathogenesis of Lyme disease. Classifying borrelia by PCR may provide valuable epidemiological information which would have especial relevance to vaccine development strategies.

Treatment

The aims of treatment in Lyme borreliosis are (a) to speed the resolution of the patients presenting illness and (b) to stop the progression to major long term sequelae.

It is probably best to avoid prophylactic antibiotics for people who have been bitten by ticks, as the likelihood of an individual developing Lyme disease is small and there is always a risk of an unexpected allergic reaction to antibiotics.⁴¹ Insect repellents to prevent the attachment of the tick are more practical. Nursing and medical staff attending patients with Lyme disease do not require prophylaxis as person to person transmission is unknown.

A particular problem of Lyme disease is that the clinical outcome cannot always be predicted from the sensitivity of the causative bacterium to antimicrobial agents in vitro. *B burgdorferi* is sensitive to a variety of common antibiotics, such as benzylpenicillin, erythromycin, tetracycline, amoxycillin, ceftriaxone, and cefotaxime. Antibiotics such as metronidazole, rifampicin, and sulphonamides have no role in the therapy of Lyme disease. The new quinolones and the aminoglycosides are likewise ineffective at clinical dosages.⁴²⁻⁴⁴

An oral agent is preferable in the treatment

of early Lyme disease. Erythema migrans and its associated symptoms resolved significantly earlier in patients given tetracycline or penicillin than in those treated with erythromycin.⁴⁵ None of 39 patients treated with tetracycline developed major late complications but 8% of the 40 patients given penicillin, and 14% of the 29 erythromycin treated patients did. All drugs were used in a dosage of 250 mg four times daily for 10 days. In a more recent study, no statistically significant differences were detected in the responses to tetracycline or penicillin therapy in erythema migrans. The tetracycline treated patients, however, developed fewer long term major complications, and fewer of them required further courses of antibiotic therapy.⁴⁶

Oral doses of tetracycline, 250 mg four times a day, produce peak serum concentrations four times the minimum inhibitor concentration (MIC), whereas phenoxymethylpenicillin in oral doses of 500 mg four times a day produces serum concentrations equal to the MIC.⁴⁷ Doxycycline in a dosage of 100 mg twice daily may be a convenient alternative. Amoxycillin combined with probenecid has also been used successfully to treat early Lyme disease. A recent study compared amoxycillin and probenecid (500 mg of each three times) to doxycycline (100 mg twice daily). All patients had early skin manifestations of Lyme disease and the duration of therapy was 21 days in each case.⁴⁸ In all patients the erythema migrans resolved and none developed major late sequelae. Symptoms after treatment such as fatigue, headache and arthralgia, developed in 15% of patients and persisted for up to three months. Such symptoms have been noted by other authors and resolve. They are twice as likely to occur in patients with disseminated early disease than in those with single lesions.⁴⁹

The duration of treatment depends on the severity of the illness: 10 days is thought to be adequate in mild cases with skin manifestations but 21 days may be more appropriate in cases of disseminated disease. Longer periods of treatment do not reduce the incidence of major or minor late sequelae.⁴⁹ In children less than 9 years old tetracyclines are contraindicated. In such cases amoxycillin and probenecid orally for 10 to 21 days are the drugs of choice. Erythromycin is a less effective alternative for penicillin sensitive children. In children older than 9 years, oral doxycycline is the most appropriate therapy. Amoxycillin with probenecid is an alternative.

The classical treatment for the neurological signs of Lyme disease was high dose parenteral penicillin.⁵⁰ In patients who manifest an uncomplicated Bell's palsy the outcome is usually favourable, and unless symptoms of meningitis or radiculitis are present oral administration is probably adequate. In a Swedish study of doxycycline treatment for neurological Lyme disease, doxycycline concentrations of 0.2 to 1 mg/l were obtained in the CSF during a regimen of 100 mg twice daily, all patients had a favourable outcome.⁵¹ On a treatment schedule of 200 mg twice daily, CSF concentrations of 0.6-1.9 mg/l were achieved. The MIC of *B burgdorferi* was exceeded in the CSF after the

first day of this dosage, but three to five days of treatment was needed to achieve comparable levels on the lower dosage regimen.⁵²

Treatment for patients with meningitis or radiculitis should be more aggressive. Parenteral penicillin in doses of 20 megaunits daily for 10 days has been used as standard treatment for neuroborreliosis. Results have been disappointing and the isolation of *B burgdorferi* from the CSF of a patient being treated with penicillin underlines the inability of penicillin to kill spirochaetes which may survive under sub-optimal conditions.⁵³ From the results of in vitro studies, third generation cephalosporins appear effective.⁴²⁻⁴⁴ Ceftriaxone has a half life of 8.5 hours.⁵⁴ In the absence of meningitis it crosses the blood-CSF barrier to give CSF concentrations 1.5% of those in serum. Two to four hours after an intravenous infusion of 2 g of ceftriaxone, CSF concentrations three to four times the MIC for *B burgdorferi* may be obtained.⁵⁵ It has been used successfully and proved superior to parenteral penicillin in late neuroborreliosis.⁵⁶

Though experience with ceftriaxone in Lyme meningitis or radiculitis is limited it appears to be a useful agent.⁵⁷⁻⁵⁸ An association has been demonstrated between the use of ceftriaxone and the development of biliary concretions. This antibiotic is as yet unlicensed in the UK.⁵⁹ As an alternative cefotaxime may be used and is equally effective.⁵⁸ The duration of treatment depends on the clinical response and usually varies between 21 and 30 days. In a patient treated for 10 days with parenteral ceftriaxone *B burgdorferi* was isolated from the CSF 7.5 months after treatment.⁵⁶ Recovery from meningitis is relatively rapid but radicular signs may persist for up to 24 months.⁴⁹

Lyme encephalopathy is probably best treated by parenteral ceftriaxone, or by benzylpenicillin as a less effective alternative.⁵⁶⁻⁶⁰ There is a case report of the successful use of cefotaxime in Lyme encephalitis.⁶¹

In patients with Lyme chronic synovitis, treatment failure rates of up to 50% have been reported, especially if erosive changes are present.⁶² Ceftriaxone is superior to penicillin, with therapeutic success rates of over 90%.⁵⁶⁻⁶⁰ Oral doxycycline or, alternatively amoxycillin with probenecid, have been used to treat these patients, with success rates of 72% and 61% respectively.⁶³

The use of corticosteroids in patients with chronic synovitis increases the risk of antibiotic failure and they are best avoided.⁵⁶ The development of chronic synovitis with a poor response to therapy has been associated with HLA DR4 and HLA DR2 alleles.⁶⁴

Jarisch-Herxheimer reactions are encountered in 14% of patients treated for early Lyme disease. They occur within 2-4 hours of starting treatment and are more common in severe disease.⁴⁵ Meptazinol unlike adrenocorticosteroids, has been shown to ameliorate such reactions in relapsing fever.⁶⁵ Meptazinol may be useful in cases of Lyme disease involving vital organs.

In conclusion, Lyme disease is a serious disorder with potential immediate and long

term morbidity and mortality. It occurs in many parts of the world and affects all ages. The diagnosis of Lyme borreliosis should be considered in any unusual neuropathy or arthropathy. Laboratory tests may confirm the diagnosis but must be interpreted with care. Long term complications may occur if it is not recognised and treated effectively. Oral tetracycline, if the patient is older than 9 years, is recommended for early Lyme disease. Younger children should receive amoxycillin and probenecid. In the late stages, ceftriaxone or cefotaxime is more effective than penicillin.

In future, vaccines may provide protection against Lyme borreliosis. Recent evidence in murine models of *B burgdorferi*: infection suggests that outer membrane proteins may be important in this regard.⁶⁶

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