Lyme disease in a British referral clinic

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Summary

Background: Concerns about over-diagnosis and inappropriate management of Lyme disease (LD) are well documented in North America and supported by clinical data. There are few parallel data on the situation in the UK.

Aim: To describe the patterns of referral, investigation, diagnosis and treatment of patients with suspected LD referred to an infectious disease unit in Liverpool, UK. Previous management by National Health Service (NHS) and non-NHS practitioners was reviewed.

Design: Descriptive study conducted by retrospective casenotes review.

Methods: Retrospective casenotes review of adults referred with possible LD to an infectious disease unit in Liverpool, UK, over 5 years (2006–2010).

Results: Of 115 patients, 27 (23%) were diagnosed with LD, 38 (33%) with chronic fatigue syndrome (CFS) and 13 (11%) with other medical conditions. No specific diagnosis could be made in 38 (33%). At least 53 unnecessary antibiotic courses had been given by non-NHS practitioners; 21 unnecessary courses had been prescribed by NHS practitioners. Among 38 patients, 17 (45%) with CFS had been misdiagnosed as having LD by non-NHS practitioners.

Conclusions: A minority of referred patients had LD, while a third had CFS. LD is over-diagnosed by non-specialists, reflecting the complexities of clinical and/or laboratory diagnosis. Patients with CFS were susceptible to misdiagnosis in non-NHS settings, reinforcing concerns about missed opportunities for appropriate treatment for this group and about the use of inappropriate diagnostic modalities and anti-microbials in non-NHS settings.

Introduction

Lyme disease (LD) is the most common human tick-borne infection in Europe and North America. It is caused by several pathogenic genospecies of the spirochaete Borrelia burgdorferi, transmitted by hard-bodied ticks of the Ixodes ricinus complex. Clinical manifestations include skin lesions (notably erythema migrans), neurological abnormalities, musculoskeletal symptoms and cardiac dysrhythmias. The incidence of infection appears to be increasing in the UK and the rest of Europe. More than 1000 serologically confirmed infections are reported annually in the UK, 15–20% of which are acquired overseas. In addition, 1000–2000 unconfirmed cases are estimated to occur in the UK each year. Infection with B. burgdorferi may be asymptomatic. Erythema migrans is the presenting complaint in ~90% of symptomatic cases, occurring from a few days to about a month after the tick bite. An expanding, homogeneous, annular or target-like erythema develops, centred on the bite. It may be accompanied by fever, myalgia, arthralgia and headache. In some cases, borreliae disseminate to other organs and tissues, mainly the nervous system, joints and, rarely, the heart. Early LD can therefore present with cranial nerve palsy, meningitis, radiculoneuritis, mono- or oligoarthritis (usually

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affecting the knee or other large joints) and myopericarditis (usually presenting with atrioventricular conduction defects).

A minority of untreated or inadequately treated patients develop late manifestations of LD, usually from 6 months to years later, involving the skin (acrodermatitis chronica atrophicans), musculoskeletal or nervous systems. Late Lyme arthritis commonly involves the knee, causing synovitis, effusion and pain. Late neurological sequelae include cerebral vasculitis, a chronic encephalitis or encephalomyelitis, radiculopathy and mononeuropathy.6

Serological testing for antibodies to *B. burgdorferi* remains the mainstay of laboratory diagnosis. Reference laboratories use a two-stage technique, with a sensitive enzyme immunoassay followed by a more specific immunoblot. Properly validated interpretive criteria must be applied to ensure maximum specificity.1,5,7,8 Negative serology does not exclude a diagnosis of recently acquired infection as antibodies may take several weeks to develop and may be abrogated by early treatment.5 In a recent review of 65 patients diagnosed with LD in a London teaching hospital, reference laboratory immunoblots were negative in 31%, principally those with early infection.9 It is rare for patients with long-standing infection to have negative serology.7 Positive serology persists indefinitely in some patients even after treatment and does not per se indicate ongoing disease; serological patterns should always be interpreted in the clinical context of each patient.5,10 The background rates of seropositivity in areas with high endemicity may exceed 4%.1

The number of British patients referred for specialist assessment of suspected LD has risen over recent years.9 This is likely to reflect an increase in recreational exposure in rural parts of Europe and North America, as well as heightened public anxiety. The latter has been fuelled by information available in the media and on the internet relating to ‘chronic Lyme disease’. The term ‘chronic Lyme disease’ is confusingly used to describe different patient populations that should not be grouped together.8 These include patients with objective manifestations of untreated late LD (as described earlier) as well as patients with persistent subjective symptoms following treatment for LD (‘post-Lyme syndrome’). The term has also been applied to patients with chronic pain, fatigue and/or neurocognitive symptoms which are attributed to persistent *B. burgdorferi* infection, with or without clinical or serological evidence of previous LD.11–13 Laboratory support for diagnosis in this context is often based on unvalidated tests14,15 and many of these patients are treated for months to years with multiple anti-microbial agents, against current evidence-based guidelines.

The Tropical and Infectious Disease Unit (TIDU) at the Royal Liverpool University Hospital receives increasing numbers of referrals for patients who are suspected of having LD or who are themselves concerned about the diagnosis. Some of these patients give a history of having received prolonged and unorthodox treatments for LD. Some have received treatment for alternative infectious diseases of questionable significance. We conducted a descriptive study of all patients referred to the TIDU with possible LD between the start of 2006 and the end of 2010 in order to evaluate the patterns of referral and final diagnosis.

Patients and methods

Clinical assessment and diagnosis

The clinics of the TIDU provide secondary and tertiary referral services for a wide variety of infections, including travel-related disease and zoonoses. In addition, we provide an assessment referral service for ~400 patients per year with chronic fatigue syndrome (CFS).16–18 In clinic, history-taking, clinical examination and investigations are used to formulate a diagnosis and management plan for each patient. The diagnosis and classification of LD follows internationally accepted criteria.1,5,7 We accept results of serological tests for LD performed at national reference laboratories such as the English Health Protection Agency Lyme Borreliosis Unit in Southampton, which use fully validated and CE-marked methods, in accordance with international recommendations. The results of other tests for Lyme borreliosis and zoonoses possibly related to LD are also noted, when available. Diagnosis of CFS is based on clinical features, using internationally accepted criteria.19,20 Other conditions are diagnosed using similar international standards of practice.

Casenotes review

Patients were identified by reading through referral letters and performing an electronic search of discharge summaries and clinic letters held in the databases of the TIDU, using the terms ‘Lyme’ and ‘borreliosis’. Patients referred between 1 January 2006 and 31 December 2010 were included. Referral letters, casenotes and electronic files were used to collect descriptive data about each patient, including: demographic details; referral pathway; clinical presentation; reference laboratory results; diagnosis ascribed by TIDU specialist; experience
of non-National Health Service (NHS) clinics, including investigations, diagnoses and treatments. The data (compiled in an Excel spreadsheet) were then anonymized before further analysis, using simple descriptive methods. The study was approved by the Information and Audit Officer of the hospital and data were held in accordance with current Information Governance guidelines. In accordance with local and national guidance, formal ethical board review was not required for a retrospective descriptive study on casenotes of our own patients.

Results

Demographics

Review of referral letters and electronic files identified 115 patients referred over the 5-year period for consideration of LD. Their age ranged from 16 to 81 years (median 42 years) and 64 (56%) were female. Referrals increased in number from 18 in 2006 to 33 in 2010. A total of 93 (81%) referrals were generated by general practitioners and 17 (15%) by NHS hospital specialists. One patient self-referred, one was referred by a walk-in centre and in three cases the referral pathway was unclear. A total of 96 (83%) referrals came from North West England, including Merseyside, Cheshire and Cumbria and 12 (10%) came from Wales. Five (5%) came from elsewhere in the UK and two were unknown.

Clinical presentation

The presentation was acute in 31 (27%) and chronic in 82 (71%) of patients (unknown in 2 cases). The commonest reasons for referral were fatigue in 51 (44%) patients and rash in 37 (32%). Other symptoms, in order of frequency, were: neurological (19); rheumatological (17); non-specific (13); cardiac (1); asymptomatic tick bite (1) (some patients had more than one symptom complex, so the total exceeds 115). None of the 115 patients were considered at risk of LD. Other symptoms included rheumatological complaints in six, neurological symptoms in six and fatigue in one. Nineteen patients had an acute presentation (associated with rash in 16/19), while 8 had chronic symptoms. Reference laboratory serology was positive in 16/27 (59%) and negative in 11/27 (41%).

None of these 27 patients were assessed or treated in an alternative practice setting. Eleven had been previously treated for LD in NHS settings with appropriate antibiotics, albeit using slightly longer regimens than necessary in some cases. A further 15 patients received treatment from the TIDU, 1 of whom had previously received treatment overseas.

Thirty-eight of the 115 patients (33% of referrals) were diagnosed as having CFS. None of these patients had clinical features suggestive of active LD. Reference laboratory serology was known for 29 of these 38 patients and was negative in all. One patient was thought to have had previous infection with LD, which had been adequately treated in primary care. A further five had previously been treated for suspected LD by an NHS practitioner. And, 17 (45%) more of the 38 patients with CFS had been diagnosed in non-NHS settings as having LD and 13 had received treatment as a result.

No specific diagnosis could be made for 38 patients (33%). Their presenting features included a wide variety of symptomatology, acute in 7, chronic in 29 and unknown in 2. Reference laboratory serology was known for 31 patients. It was negative in 30/31 (97%) and positive in 1 patient. Of these 38 patients, 7 (18%) had received treatment for LD in NHS settings and 4 (11%) had received treatment for Lyme in non-NHS settings. A further three patients had been treated for LD overseas.

A small proportion of patients (13/115) were diagnosed with a non-Lyme, non-CFS condition (Table 1). Of these, nine presented with rash and none with fatigue. Five patients had acute symptoms, eight had chronic symptoms. Reference serology was requested in 10 of these 13 patients and was negative in all. Among these 13 patients, 6 (46%) had received treatment for suspected LD in an NHS setting.

‘Non-NHS’ management

Twenty-six (23%) patients had consulted non-NHS clinics. All had chronic symptoms and 21 (81%) of them presented with fatigue. A total of 22 (85%) patients had received a diagnosis of LD and 9 of these 22 had also been diagnosed with co-infections such as babesiosis, bartonellosis, ‘cryptostrongylus’ infection, chlamydia or chronic candidiasis. Diagnoses were based on unvalidated tests, such as direct or video-assisted light microscopy of blood, CD57 counts and immunological test panels performed overseas. Among 22, 15 also
had Lyme serology performed in a reference laboratory, with a negative result in all cases. None of these 22 patients were considered to have LD at the TIDU, where 17 of them were diagnosed as having CFS.

Some details of anti-microbial regimens previously administered were available for 16 of the 22 patients with an unsubstantiated diagnosis of LD. These 16 patients had received at least 53 courses of antibiotics prescribed in non-NHS clinics, including at least 4 intravenous courses. Five patients had received five or more different anti-microbial agents and one had received eight different anti-microbials (Table 2). In some cases, antibiotic regimens were excessively prolonged, with up to 20 weeks of doxycycline in one instance.

### Discussion

Only 27 (23%) of 115 referred adults were thought to have been infected with *B. burgdorferi*. Thirty-eight (33%) patients were diagnosed as having CFS and another third had unexplained symptoms. Our experience mirrors that reported by referral centres in areas of North America of known high endemicity for Lyme borreliosis (Table 3).
Similar findings have been reported in paediatric cohorts in North America.27–29 Our results reinforce concerns raised by previous authors regarding the diagnosis of ‘chronic Lyme disease’ being applied increasingly to patients with persistent pain, fatigue or neurocognitive symptoms, in the absence of clinical or serological evidence of previous LD.11 Fatigue was a presenting complaint in 51 (44%) of 115 patients referred to the TIDU with suspected LD. Of these 51 patients, 17 had been previously diagnosed as having chronic LD by a non-NHS centre based on unvalidated tests, but reference laboratory Lyme serology was negative in all 11 of these 17 in whom it was checked.

Table 3  Descriptive studies of adults referred to specialist centres for assessment of suspected LD

<table>
<thead>
<tr>
<th>Cohort, N, Place, Years, (Reference)</th>
<th>Diagnosis of LD</th>
<th>Diagnosis of CFS or fibromyalgia</th>
<th>Previous antibiotic administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 patients, NJ, USA, 1988–1989, (21)</td>
<td>28 (28%) active LD, 9 (9%) previous LD (excludes 18 patients also diagnosed with fibromyalgia)</td>
<td>25 (25%) fibromyalgia (15 had history of previous LD, 3 with coincidental LD)</td>
<td>Half of the 91 antibiotic courses given were inappropriate</td>
<td>22 (22%) alternative diagnosis (non-Lyme, non-CFS), 14 (14%) no specific diagnosis, 2 lost to follow-up</td>
</tr>
<tr>
<td>788 patients, MA, USA, 1987–1991, (22)</td>
<td>180 (23%) active LD, 156 (20%) previous LD and another current illness. 49 of these developed CFS or fibromyalgia within a few months after LD; 23 developed CFS or fibromyalgia or headache or depression ≥1 year after LD</td>
<td>Of 452 patients patients with no evidence of LD, 142 (31%) diagnosed with CFS, 84 (19%) diagnosed with fibromyalgia</td>
<td>409 patients had been treated with antibiotics, of whom 322 (79%) did not have LD</td>
<td>452 patients (57%) did not have LD. 45% of these had positive Lyme serology in other labs. All were seronegative at centre</td>
</tr>
<tr>
<td>65 patients, Vancouver, Canada, Years unspecified, (23)</td>
<td>2 (3%) active LD</td>
<td>Of 63 patients with no evidence of LD, 11 (17%) diagnosed with CFS or fibromyalgia</td>
<td>19 courses of IV antibiotics; 30 courses of ≥10 days’ oral antibiotics</td>
<td>48 (74%) alternative diagnosis (non-LD, non-CFS/fibromyalgia), 4 (6%) no specific diagnosis</td>
</tr>
<tr>
<td>209 patients, CT, USA, 1994–1995, (24)</td>
<td>44 (21%) active LD, 40 (19%) previous LD. 21 of these (53%) had ‘fatigue-arthralgia-myalgia syndrome’</td>
<td>Of 125 patients with no evidence of LD, 39 (31%) diagnosed with ‘fatigue-arthralgia-myalgia syndrome’</td>
<td>94 (75%) of patients with no evidence of LD reported previous use of antibiotics for LD (232 courses in total)</td>
<td>125 (60%) had no evidence of LD. Of these, 61% had a positive test result for LD elsewhere. None had a positive Western blot at centre</td>
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<td>240 patients, NJ, USA, 2002–2007, (25)</td>
<td>46 (19%) active LD, 25 (10%) previous LD</td>
<td>Of 169 patients with no evidence of LD, 72 (43%) had fibromyalgia</td>
<td>114 of 169 (68%) patients with no evidence of LD had received ≥1 course of antibiotics</td>
<td>53 (22%) had identifiable alternative medical condition, 42 (18%) had unexplained symptoms, 2 healthy</td>
</tr>
<tr>
<td>115 patients, Liverpool, UK, 2006–2010 (current report)</td>
<td>23 (20%) active LD, 4 (3%) previous LD, 1 of whom was diagnosed with CFS</td>
<td>38 (33%) had CFS, 1 with previous LD.</td>
<td>Among 88 patients not diagnosed with LD: ≥33 anti-microbial courses given to 16 patients in non-NHS settings; 21 courses given to 18 patients in NHS settings; 3 patients treated overseas.</td>
<td>13 (11%) had identifiable alternative (non-Lyme, non-CFS) condition, 38 (33%) had unexplained symptoms</td>
</tr>
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Adapted from Marques.26
Among these 17 patients, 14 were diagnosed with CFS at the TIDU. There were similar concerns about the other five patients diagnosed as having LD in non-NHS clinics, and about the diagnoses of co-infections (some imaginary such as ‘cryptostrongylus’) in nine patients with no credible evidence of any of these conditions.

NHS practitioners prescribed antibiotics for 41% of 27 confirmed and 20% of 88 other suspected cases of LD. They generally used an appropriate agent, although for a longer duration than recommended in some cases, with nine patients receiving antibiotics for ≥6 weeks (36 weeks in one case). Our findings reinforce concerns that patients who have been mislabelled as having chronic LD may receive multiple, inappropriate anti-microbial agents over extended periods (Tables 2 and 3). At least 53 anti-microbial courses had been prescribed by non-NHS practitioners for 16 patients with an unsubstantiated diagnosis of LD; details of anti-microbial regimens were not available for a further 6 patients. This non-evidence-based practice can expose patients to serious adverse effects of antibiotics including *Clostridium difficile* associated diarrhoea and colitis, colonization with multi-drug-resistant bacteria, and intravascular catheter-related complications; deaths have also been reported as a consequence. In one American centre, 94 (75%) of 125 patients without evidence of borrelial infection reported previous antibiotic treatment for LD. These 94 patients had received a total of 232 antibiotic courses (171 oral and 61 parenteral). Seven patients developed a major adverse drug event: *C. difficile* colitis in three, neutropenia in two, septic thrombophlebitis in one and serum sickness in one. In a more recent study of 240 patients referred to a specialist LD centre in New Jersey, 169 (70.4%) had no evidence of borrelial infection, but 114 (67.5%) of them had received at least one course of oral or intravenous antibiotics. Twelve patients had received repeated courses of intravenous antibiotics, often over months or years.

The limitations of this study include those associated with any retrospective case note review. In particular, precise details of investigation and management in centres other than our own were often incompletely recorded, so the results presented here will underestimate the true extent of health care use by this patient group. In addition there may be referral bias, particularly of patients with alternative diagnoses made elsewhere, for whom primary care practitioners request a further opinion.

We suspect that our experience is similar to that in other referral units in the UK, and this raises a number of issues. The majority of patients referred did not have LD. A small number (11%) of patients had other specific diagnoses made in our clinic, allowing targeted management for those conditions. One-third of referred patients had CFS that is potentially amenable to evidence-based management strategies, although almost half (17/38) of them had been labelled as having ‘chronic Lyme disease’ by alternative practitioners and had been advised to take multiple and prolonged courses of antimicrobials. A further third of referred patients had a constellation of medically unexplained symptoms.

The frustration expressed by these patients is compounded by the substantial costs of repeated attendances at non-NHS settings, of unvalidated investigations (often sent overseas) and of multiple lengthy courses of anti-microbial agents, with potential for toxicity and hence concurrent prescription of various ‘detoxification’ regimes. Many are further disheartened by disputes with NHS purchasers if they refuse to underwrite these costs.

This situation leads to conflict between patients, their primary NHS carers and secondary and tertiary care clinicians. This conflict is counterproductive to a patient’s recovery. In a thoughtful editorial earlier in 2011, Kullberg and colleagues emphasized the need for the medical profession to adopt a more open approach to the acknowledged difficulties of clinical diagnosis and interpretation of laboratory test results for LD. The challenge for the medical profession, in partnership with patients and their advocates, is to rise above current disputes and find mutually acceptable and pragmatic approaches to successful management of the different groups of patients described in this and other reports. In the meantime, medical practitioners have a professional and moral obligation to avoid the promotion of unnecessary and potentially harmful modalities of diagnosis and treatment, and not to encourage patients to avoid therapeutic approaches that have a good evidence base for clinical effectiveness.

**Conflict of interest:** None declared.

**References**


