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SHORT REPORT
Neuroborreliosis in the South West of England

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SUMMARY

Although Lyme borreliosis is increasingly diagnosed in the United Kingdom, few systematic studies have been performed there. UK data suggest that the commonest complications are neurological, but inadequate information exists about their nature and the incidence of late neuroborreliosis. Local data are necessary because clinical presentations may show geographical variation. This study aimed to provide data on clinical manifestations in an area of South West England and to estimate treatment delay. We reviewed clinical records of 88 patients in the Royal Devon and Exeter Hospital catchment area who had positive *Borrelia* antibody tests during a 5-year period. Fifty-six (64%) reported tick bites. The commonest presentations were erythema migrans (65%) and arthralgia/myalgia (27%). However, 22 patients (25%) had neurological symptoms other than headache alone. Fourteen had facial palsy, eight had confusion/drowsiness, four had meningism, five had radiculopathy, two had sixth nerve palsies, and two had peripheral neuropathies. No late, progressive or atypical neurological syndromes were found. Neurological manifestations were generally predictable and usually included either (or all) of meningoencephalitis, facial palsy or radiculopathy.

Reports of Lyme borreliosis, a tick-transmitted infection caused by spirochaetes of the *Borrelia burgdorferi sensu lato* group, are increasing in the United Kingdom. The annual reported incidence in England and Wales rose from 0·38/100 000 in 1997–2000 to 1·46/100 000 in 2006 [1]. Several factors may have contributed to this rise. These include increased awareness, enhanced surveillance, rising popularity of outdoor recreational activities (both in the United Kingdom and abroad), new housing in rural areas, and increased tick numbers due to expanded deer range and population and possibly climate change.

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Despite this rise in reported incidence, there have been no recently published or detailed systematic studies of Lyme borreliosis in the United Kingdom. Some clinical information is available from small case series. For example, one study published in 1988 described eight New Forest neuroborreliosis cases [2]. Most information about clinical presentations comes from experience in Europe or North America where larger case series have been studied [3–5]. However, clinical features of disseminated infection vary geographically depending on variations in distribution of *B. burgdorferi* genospecies. For example, Lyme arthritis is mainly associated with infection with *B. burgdorferi sensu stricto*, a genospecies common in the United States. This genospecies is uncommon in the United Kingdom, where the common pathogenic genospecies are *B. garinii* and *B. afzelii*, and the available data

suggest that the commonest complications are neurological [1, 6].

With the rising incidence of Lyme borreliosis, UK clinicians are increasingly involved in the diagnosis and management of neuroborreliosis, and in the controversy surrounding chronic neurological symptoms of Lyme disease. Misconceptions exist because many published reports have associated *B. burgdorferi* infection to diverse chronic neurological presentations [7]. Although studies in other countries have helped to clarify the natural history of borreliosis and its responsiveness to treatment [8, 9], more systematic and comprehensive local data are required. Detailed clinical information on the relative frequencies of Lyme presentations in the United Kingdom is needed so that clinicians can identify patients who have this treatable condition early, and avoid inappropriate treatment of patients who are more likely to have an alternative diagnosis. Our study, conducted in an area where Lyme borreliosis is relatively common (second only to the New Forest region in the UK) [6], had two aims. First, we aimed to provide detailed and systematic data on clinical manifestations of Lyme borreliosis presenting to hospital and primary care in an area of South West England. Second, we aimed to determine how quickly and appropriately patients were treated.

We studied all inhabitants of the Royal Devon and Exeter Hospital (RDEH) catchment area (a population of 350 000), who were identified from RDEH microbiology records as having a first positive *B. burgdorferi* antibody test using the internationally recommended two-stage procedure [10] during the 5-year period 2000–2004. First-stage screening tests were carried out at RDEH. Detailed serology tests, including immunoblots, were performed by the Health Protection Agency Lyme Borreliosis Unit in Southampton General Hospital. Patient data were collected from hospital and general practitioner (GP) records, and from detailed questionnaires sent to GPs. The data included patient's age, sex, tick exposure risk and tick bite history, nature and timing of symptoms and signs, results of investigations, and nature and timing of treatment. These data were collated anonymously and with the approval of the local ethics committee (ref: 04/Q2012/152). Patients were considered to have neuroborreliosis if they had neurological symptoms or signs other than headache alone. Clinically apparent meningoencephalitis was defined as the presence of meningism, drowsiness or confusion without other cause.

Table 1. *Characteristics of 22 patients with neuroborreliosis, defined as having positive* Borrelia burgdorferi *serology and neurological clinical features other than headache alone*

Characteristic	Patients (%)
Children (⩽16 years)	9 (41)
Bite reported	10 (45)
Rash thought to be erythema migrans	8 (36)
Headache	7 (32)
Arthralgia/myalgia	4 (18)
No bite, rash, headache, fever or arthralgia/myalgia	6 (27)
Neurological findings	
Facial palsy (unilateral or bilateral)	14 (64)
Bilateral facial palsy	3 (14)
Isolated facial palsy	6 (27)
Meningoencephalitis	11 (50)
Radiculopathy	5 (23)
Bannwarth's syndrome	2 (9)
Other peripheral neuropathy	2 (9)
Sixth nerve palsy	2 (9)

The patient numbers for each category represents the total number of patients with that feature or combination of features except for 'isolated facial palsy' where the number of patients with no other neurological feature is given.

B. burgdorferi antibody tests were carried out on 2825 serum samples at RDEH during the 5-year study period. Ninety-eight new cases of Lyme borreliosis were serologically confirmed, but ten patients who had been managed in primary care were excluded because the GP records were unavailable, usually because the patient had moved away. Therefore, we studied 88 patients (58 % male, age range 5–82 years) of whom 71 (81 %) were diagnosed by GPs.

Of the 88 patients, 56 (64 %) reported a preceding recent 'insect' bite, and three (3 %) gave a history of recent foreign travel. Fifty seven (65 %) had a rash suggestive of erythema migrans, 24 (27 %) reported arthralgia or myalgia, and 20 (23 %) had either a demonstrated or reported fever. No patient had demonstrable Lyme arthritis or carditis. Headache was the only neurological feature in eight (9 %) patients. A further 22 (25 %) had significant neurological presentations other than or in addition to headache.

The characteristics of the 22 patients with neuroborreliosis are shown in Table 1. Twenty (91 %) had either facial palsy, radiculopathy, or clinically apparent meningoencephalitis. Six (27 %) patients had two of these features: four with meningoencephalitis and

facial palsy, one with radiculopathy and facial palsy, and one with radiculopathy and meningoencephalitis. Two (9%) patients had all three characteristics and therefore fitted the classic description of Bannwarth's syndrome [3]. Facial palsy was the most common cranial neuropathy, occurring in 14 patients, and was bilateral in three. Facial palsy was the only neurological symptom in six patients and occurred without a rash or any other systemic symptoms in three. A painful radiculopathy (diagnosed clinically) was the most common cause of limb weakness or parasthesiae (five patients). Two patients had peripheral sensory symptoms which could not be classified.

Nine (69%) of the 13 children (aged $\leqslant$16 years) had neurological symptoms. Of these, eight had facial palsy, six had meningoencephalitis, and one had a radiculopathy.

Six of the 22 patients with neuroborreliosis were managed entirely in primary care, and 15 (68%) were admitted to hospital, including all nine children. Five patients (four adults) underwent cerebrospinal fluid (CSF) examination. All had an elevated CSF lymphocyte count (range 14–370 cells/μl, mean 150 cell/μl) and 4/5 had an elevated CSF protein (range 0·39–2·5 g/l, mean 1·3 g/l).

In the 22 patients with neuroborreliosis, the median time from onset of first symptoms (neurological or non-neurological) to serological testing was 20 days [interquartile range (IQR) 10–32 days]. The median time from onset of symptoms to treatment was 26 days (IQR 9–41 days). In 16 patients, antibiotics were given either before or within 3 days of the serological test, but in the remaining six patients there was a delay of between 13 and 20 days. All patients with neurological symptoms received an appropriate antibiotic (cefotaxime, ceftriaxone, doxycycline or amoxycillin) for between 14 and 30 days [10]. Complete resolution of symptoms was reported by 18 (82%) of the 22 patients. Residual symptoms were reported after the completion of treatment in four patients (residual weakness from facial nerve involvement in three and from radiculopathy in one patient). However, this retrospective study included no standardized follow-up data and the eventual number of patients with long-term residual symptoms is unknown.

Our study includes 5% of all Lyme borreliosis cases (and about 8% of neuroborreliosis cases), which were serologically confirmed in England and Wales during the 5-year study period (2000–2004) [1]. We have shown that neuroborreliosis, defined as neurological symptoms or signs other than headache alone, is the most common presentation of disseminated *Borrelia* infection in the South West of England, occurring in almost one quarter of serologically confirmed cases. The proportion of cases with neuroborreliosis is higher than the 15% previously quoted for England and Wales overall [6]. This may represent a true geographical variation, but our results may also be influenced by our methods of patient selection.

Inclusion of patients into this study was based on laboratory criteria. This was important because our aim was to study the range of clinical presentations. If clinical inclusion criteria had been used, patients with atypical clinical presentations might have been excluded. However, bias may exist either because included patients could have had false or incidental positive serology, or because patients could have been missed because they never had a positive antibody test. We minimized the risk of false-positive serology by only including patients with clear positive results in both stages of the internationally recommended two-stage procedure. It is possible that a few patients had true positive results which were incidental to their symptoms. However, this might be expected to overestimate the incidence of atypical symptoms. Our finding that most patients presented with stereotypical features suggests that this was not a large problem, although it is impossible to be certain because patients with apparently typical symptoms may be more likely to be selected for serology testing. More importantly, however, we could not include patients who did not undergo serology testing because they were undiagnosed or treated without testing, or patients who had false-negative test results. Negative *B. burgdorferi* antibody test results are not uncommon in patients with early erythema migrans, because the antibody response may take several weeks to develop. Clinicians in Lyme-endemic areas, such as ours, are encouraged to diagnose erythema migrans clinically and avoid possible delay in treatment that reliance on serology might cause [10]. However, most patients with acute neuroborreliosis are seropositive at the time of presentation, and seroconversion usually occurs quickly in those who are initially seronegative. These biases would result in an apparent higher proportion of complicated Lyme borreliosis, but it is also present in other case series which included patients selected by a similar or an even more restricted fashion. For example, the largest previous study of neuroborreliosis only included patients if they were admitted to hospital and were shown to

have evidence of intrathecal *Borrelia* antibody production [3].

Demonstration of intrathecally produced *Borrelia* antibodies is required for the European Union Concerted Action on Lyme Borreliosis (EUCALB) case definition of neuroborreliosis [11] and it is a potential weakness of our study that we did not use CSF findings as part of our inclusion criteria. There are two main advantages of CSF analysis. First, it may reduce false inclusion because other causes of neurological symptoms are more effectively excluded, and second, it may reduce false exclusion because an antibody response may be detected in the CSF earlier than in the serum in neuroborreliosis. However, we felt that if CSF testing were part of the clinical inclusion criteria this would have unnecessarily excluded a significant number of patients with neurological symptoms and signs who did not have a lumbar puncture. Consequently, we would have been much less able to accurately estimate the overall frequencies of neurological findings in Lyme disease. Although the majority of patients (and all of the children) with neuroborreliosis in our study were admitted to hospital (68%), only five (23%, one of whom was a child) underwent a lumbar puncture. In the remaining patients, the diagnosis of Lyme disease was felt to be clinically certain without any alternative cause found for the neurological findings, and it was considered that further invasive investigation of all these would not have been ethical or appropriate.

Although neurological complications were common in our study, they were predictable, acute, and most resolved after treatment. Almost all patients had part or all of the classic triad described by Bannwarth of facial palsy, meningoencephalitis and radiculopathy. Despite a high awareness for neuroborreliosis amongst local hospital clinicians, GPs and many patients, we found no cases of late, progressive or atypical neurological syndromes in our region, where almost 600 Lyme antibody tests are requested annually. Although our study was retrospective, we feel that these findings support those of earlier studies in other countries, that true late encephalomyelitis or chronic meningitis is rare. Encephalomyelitis was shown to occur in only 0·3% of all clinically evident Lyme cases in a prospective Swedish epidemiological study ($n=1471$) [5]. Only 6% of 187 neuroborreliosis cases studied in an early Danish study had evidence of either chronic meningitis or encephalomyelitis [3]. Late manifestations of Lyme borreliosis have declined throughout Europe and North America because of early diagnosis, effective early treatment regimes, and most importantly, public education about effective personal measures for infection prevention.

All our patients with neuroborreliosis were treated with appropriate antibiotics according to international guidelines [10], but most patients had symptoms for several weeks (median 20 days) before treatment was given. Furthermore, there was a significant treatment delay of between 13 and 20 days after serology was taken in 27% of cases. These delays in treatment may be due to late presentation, delayed recognition of symptoms, or a delay while waiting for serology tests to become available. We think that our results suggest that education about the stereotypical presentations of Lyme neuroborreliosis is necessary, allowing cases to be identified and treated earlier and without the need to wait for the results of serology tests, and thereby permitting a reduction in anxiety about 'chronic Lyme disease'.

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DECLARATION OF INTEREST

None.

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