The Clinical Spectrum of Lyme Neuroborreliosis

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Abstract
Lyme disease is a multisystem infectious disease, endemic in parts of Europe, including the West of Ireland. Neurological manifestions (neuroborreliosis) are variable. Presenting neurological syndromes include meningitis, cranial neuropathies, myeloradiculitis and mononeuritis multiplex. A lack of specificity in serological diagnosis may add to diagnostic confusion. We reviewed thirty cases of acute Lyme disease in the West of Ireland and found neurological syndromes in 15 (50%), with painful radiculopathy (12 patients; 80%) and cranial neuropathy (7 patients;46%) occurring frequently. Neuroborreliosis needs to be considered in the differential diagnosis of these neurological syndromes in the appropriate clinical context.

Introduction
Lyme disease is a multisystem infectious disease caused by the Borrelia spirochaete genus. The predominant species in North America is Borrelia burgdorferi sensu stricto, and in Europe the predominant species are B. afzelli and B. garinii. Deer and other mammals are the intermediate hosts [1]. Lyme disease is the most frequently reported arthropodâ borne infection of the nervous system in Europe and the USA1. Erythema migrans (EM) is regarded as the most common clinical marker of infection and is estimated to occur in 60-80% of patients [1]. Neurological manifestations of Lyme disease (neuroborreliosis; NB) comprise an array of both central and peripheral neurological syndromes, mimicking a variety of common disorders [2]. Typical neurological presenting syndromes include include meningitis, cranial neuropathies (with a predilection for the facial nerve), myeloradiculitis and mononeuritis multiplex [3,4]. Difficulties in the diagnosis and management of patients with Lyme NB may be compounded by a lack of specificity and sensitivity of serological tests in active disease [5].

Seroprevalence studies report the Republic of Ireland as having one of the highest rates of Lyme disease in Europe [6]. Lyme disease is considered endemic in the West of Ireland [7,8]. However, few studies have explored the clinical presentation and natural history of Lyme NB in Ireland [9-11]. We therefore undertook a retrospective analysis of the clinical characteristics of Lyme NB in the West of Ireland. We conducted a retrospective review of the clinical presentation of patients with serologically confirmed Lyme disease diagnosed over a five-year period at a single referral centre in the West of Ireland. We identified the proportion of patients presenting with NB, we define the neurological syndromes at presentation, and report the clinical outcomes.

Methods
The study population included those patients who had serological testing consistent with Lyme disease, based on referrals to the Department of Medical Microbiology, University Hospital Galway. The study period extended from January 1999 to August 2004. During that period, approximately 2100 sera were tested using the screening ELISA. A two-tier diagnostic process was utilized in accordance with international standards [12], comprising an initial screening enzyme-linked immunosorbant assay (ELISA) for anti Borrelia antibodies. In those patients who had positive screening ELISA tests, antibody positivity was confirmed by a positive IgG and/or IgM immunoblot assay at the Lyme Borreliosis Unit, Southampton, UK. We identified 42 samples over the sixty-six month study period with serology consistent with Lyme disease.

After obtaining Ethics Committee approval and written informed consent from the referring physician, we then obtained clinical data for 32 patients. Data was collected by chart review and included demographic characteristics, potential exposure to tick bite, clinical presentation and results of imaging and cerebrospinal fluid analysis. Patients were included in the study in whom there was a clear temporal relationship between the onset of a clinical syndrome known to be associated with Lyme disease, (such as EM) and serological testing. Exclusion criteria were equivocal serological results or positive tests that were deemed to represent convalescence serology. Two patients were excluded; both had IgG anti B. burgdorferi antibodies but their clinical presentation and imaging studies were compatible with alternative diagnoses (multiple sclerosis and brain neoplasm). Data on the remaining 30 patients was analyzed as pooled data.

Results
Baseline characteristics
Antibody subtypes directed against B burgdorferi in the thirty patients included in the study were detected as follows: seventeen patients (57%) had both IgM and IgG antibodies; six patients (20%) exhibited anti IgM antibodies only, and seven patients (23%) had only IgG anti-Borrelia antibodies. Patients ranged from 26 to 80 years of age, with a mean of 52.5 years; 60% were male. Twenty patients (67%) were resident of western counties of Ireland. Only one patient was resident outside the state. Recent travel outside Ireland was documented in seven cases. Nine patients (30%) had documented potential exposure to heavily wooded areas due to occupation or leisure activities. A history of tick bite was elicited in only one third of the patients. Lyme serology was requested by the patientâ s general practitioner in twelve cases, by a consultant physician in thirteen cases and by a neurologist in five cases.

Clinical Presentation
The majority of patients (25/27, 93 %) presented between the months of May and October. While twenty-two patients (71%) had a rash at presentation, only 43% of patients presented with EM rash. Fatigue was a prominent symptom in more than half of the patients (16/30), but fever >38 degrees C was reported in only four patients (13%). Seven patients (23%) had polyarthralgia at presentation; one patient had anterior uveitis. None of the patients had cardiovascular symptoms.

Neurological Manifestations
Fifteen patients (50%) had neurological manifestations at presentation (Table). The most common symptom was radiculitis (12/15 patients; 80%). Cranial neuropathy occurred in seven patients, among whom unilateral facial palsy was present in six patients (40% of patients with neurological manifestations). Bilateral facial palsies were documented in only one patient. Four patients had headache at presentation. Psychiatric disturbances, in the form of marked irritability and reduced concentration, were noted in one patient.

Laboratory Findings in NB patients
Eleven patients with Lyme NB had both anti-Borrelia antibodies for IgM and IgG; two patients were IgM positive only, and two were IgG positive only. Cerebrospinal fluid (CSF) analysis was carried out in five of the fifteen patients with NB and was abnormal in all five (Table). All had raised CSF protein levels ranging from 0.6 g / l to greater than 1g/l. Four had CSF pleocytosis (>6 white cells/mm ^{3}), predominantly a lymphocytosis. Oligoclonal bands were present in one patient. Lyme serology in CSF was positive for IgM and IgG antibodies in the only patient in whom it was requested. MRI brain scans were abnormal in two out seven cases in which it was performed. In both cases, the abnormalities found were considered to be incidental findings (acoustic schwannoma; hypertensive leukoencephalopathy).

Treatment and Follow up
Doxycycline was used in three patients; seven patients received intravenous cefotaxime/ceftriaxone, and two patients received oral amoxicillin, one patient received vibramycin while treatment was not documented in two patients. Follow up of the fifteen patients with Lyme NB was as follows: four patients showed definite clinical improvement, defined as complete resolution of symptoms (three had received intravenous ceftriaxone/cefotaxime and one had received oral doxycyline; five patients showed partial improvement or relapse (two patients received oral doxycyline, two received oral amoxicillin and one received oral vibramycin); five patients were lost to follow up and one patient who had received only steroids showed no response.

Discussion
We identified forty-two patients with serological evidence of acute Lyme disease over a five-year period presenting to a single referral laboratory in the West of Ireland. Fifty percent of the patients on whom clinical data was available had evidence of Lyme NB. Both the incidence of Lyme disease as well as the proportion of patients with NB in our study appears to be higher than in previous reports [9-11]. The first reported cases of Lyme disease in Ireland appeared in the late 1980s [9]. The West of Ireland has been identified as a high-risk area because of high rates of sero-prevalence among asymptomatic adults [6]; the highest seroprevalence was documented in the western area of Portumna (8.7%) compared to a national average of 3.4% [7]. In a retrospective seroprevalence study, only 13 of 483 serum samples were seropositive for Lyme antibodies, mainly from patients attending Dublin hospitals, but Galway area patients formed the second largest group despite its much smaller catchment population [10]. Given the apparent high incidence of Lyme disease in Ireland, information regarding Lyme NB in this region is sparse. Reilly and Hutchinson in 1991 described the clinical presentation of six cases of NB diagnosed in Ireland over a 4 year period, five of whom contracted the disease in the West of Ireland [11]. The authors recommended further epidemiological studies to establish the prevalence and pattern of infection with B. burgdorferi in Ireland. The larger number of patients in our study may reflect a combination of higher awareness among physicians, as well as more reliable serological diagnostic techniques.

The proportion of patients with Lyme NB in our cohort is high, amounting to 50% of patients presenting with confirmed Lyme disease. Although estimates vary, previous studies in Ireland and Europe report rates of neurologic involvement in Lyme disease ranging from 18% -31% [13]. Sensory or sensory-motor radiculitis and facial palsy were the two most common neurological presentations in these patients; we have recently reported perineuritis as a pathological finding in one of this cohort [4]. Lymphocytic meningoradiculitis (Bannwarth's syndrome) is a radicular neuralgia associated with a chronic lymphocytic pleocytosis in cerebrospinal fluid and frequently with unilateral or bilateral peripheral facial palsy) is one of the commonest neurological manifestations of Lyme disease in clinical studies conducted in Ireland and other parts of Europe [13]. Truncal neuralgic pain in one of our patients was severe enough to prompt investigation for a cardiac cause. All patients with Lyme facial palsy in our cohort had additional neurological symptoms, and 87% reported constitutional complaints. This highlights the fact that while NB may be responsible for up to 10% of cases of facial palsy [ ], Lyme disease should be considered in a patient with facial palsy when it is associated with other signs or symptoms of borreliosis.

A relatively small number of our patients had symptoms of meningism. Meningitis in NB seems to cause less pronounced meningitic symptoms than aseptic meningitis [14]. Only one third of our patients with symptoms suggestive of NB had a lumbar puncture and cerebrospinal fluid analysis; however, CSF was abnormal in all of these cases. Oligoclonal bands were present in cerebrospinal fluid and not serum in one case. Current guidelines consider the presence of intrathecal specific antibodies as essential laboratory evidence for the diagnosis of early Lyme NB and the presence of specific CSF oligoclonal bands as supporting evidence [15]. Given the relatively high yield of CSF for identification of Lyme antibodies physicians should be encouraged to carry out CSF analysis in all patients with symptoms suggestive of NB even in the absence of meningism.

This study has some inherent limitations due to its retrospective design and potential for ascertainment bias. However the potential for overestimation of disease incidence through the use of serology as part of patient selection is more than offset by the fact that only about 40-60% of patients with early disease EM have positive serology [5]. Moreover, serology may not be requested in these patients as current guidelines recommend diagnosis and treatment of EM on clinical grounds [15]. However in patients in whom the duration of illness is 4 weeks or more, the sensitivity and specificity of IgG response is very high (range of 95%-99%) as determined by the 2 test approach [12], and thus a single test (for IgG only) is usually sufficient for diagnosis if the clinical picture is compatible [1]. We believe our results indicate a relatively high incidence of neurological complications in patients with Lyme disease, particularly in patients with serologically confirmed disease. There is a high incidence of Lyme NB among patients with Lyme disease in the West of Ireland, higher than that suggested by previous studies. The absence of a history of tick bite, potential exposure to ticks or EM is not reliable in the exclusion of the diagnosis. CSF analysis and serology testing is recommended in all suspected cases of neuroborreliosis, even in the absence of meningeal symptoms.

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Comments:
