DISCUSSION PAPER

Lyme Disease – A Brief Review And Report Of A Case In Hong Kong

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Abstract

In a search for the spirochetes responsible for Lyme disease in Hong Kong, a sixty year old female, with a clinical diagnosis of arthritis, was found to have a rising antibody titre against Borrelia burgdorferi by indirect immunofluorescent assay (IFA).

This paper presents a brief review of Lyme disease, its epidemiology, clinical features, diagnosis, prevention and treatment, followed by a report of this first case of Lyme disease in Hong Kong.

Key words: *Borrelia burgdorferi*, indirect immunofluorescent antibody (IFA), Lyme disease, rheumatoid factor, *Treponema pallidum* haemagglutination assay (TPHA).

History

For Americans, a discussion of the history of Lyme borreliosis usually begins with the story of two persevering women, Polly Murray and Judith Mensch of Old Lyme, Connecticut. In the early 1970s, they were concerned about the occurrence of arthritis in members of their families and in families of the neighbouring towns of Lyme and East Haddam. Severe headaches, skin lesions, and subsequent recurring arthritic and neurologic symptoms suggested to them that the physicians' diagnosis of "juvenile rheumatoid arthritis" was wrong. Their suspicion that something unusual was happening was made known to the Connecticut State Health Department, which sought help from Dr. Allen Steere of the Rheumatology Department at Yale University Medical School. In October 1975, he started a retrospective study that eventually led to the description of Lyme arthritis,[1] which was later changed to Lyme disease,[2] a new complex multisystem disorder of unknown etiology.

Unknown to most Americans, however, is the earliest reference to manifestations of what today is known as Lyme borreliosis. In as early as 1909, the Swedish physician, Dr. Arvid Afzelius, reported an elderly woman who had a ringlike skin lesion where she had been bitten by the sheep tick, *Ixodes ricinus*.[3] This characteristic expanding skin lesion, erythema chronicum migrans (ECM), has long been associated with sheep tick bites,[4,5] and with tick-borne meningopolyneuritis in Europe.[6,7] The association between Lyme Disease and Ixodid ticks is now well recognized in Europe and the United States

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of America;[8] it is noted as the most prevalent tick-borne illness in the coastal regions of North America;[9] and is of world-wide distribution, including China.[10,11] These syndromes are now often subsumed under the name Lyme disease.

Although many theories have been proposed to explain its etiology,[12-17] the causative agent of Lyme disease remained elusive until 1982, when Burgdorferi and associates[18] isolated the spirochete that bears his name *Borrelia burgdorferi* from *Ixodes dammini* in New York, and linked it serologically to patients with Lyme disease. In the following few years, numerous workers confirmed the spirochete nature of the disease.[19-23] Because it is infectious in origin but inflammatory or "rheumatic" in expression, Lyme disease, beyond its intrinsic interest as a new nosologic entity, presents a unique human model for an infectious etiology of rheumatic disease.

Epidemiology

Lyme disease has now been recognized as a worldwide tickborne borreliosis of public health importance. It has become the leading vectorborne infectious disease in the United States, with more than 40,000 cases reported to the Centers for Disease Control in the 10-year period 1982 to 1991.

The Pathogen

Borrelia burgdorferi, the causative agent of Lyme disease,[18] is a newly discovered microaerophilic spirochete that is 2 to 20 μm long but only 0.18 to 0.25 μm wide, belonging to the family Spirochaetaceae. *B. burgdorferi* occurs mainly in wild white-footed mice, in deer, and in ticks of the genus *Ixodes*. The ticks can transmit the spirochete to humans by bites at any stage of the tick's life cycle (i.e. larval, nymph and adult). *B. burgdorferi* is injected into the skin of an human victim either by infective tick saliva during biting, or by infective tick faecal matter that is deposited on the skin and rubbed into the bite. The spiral organisms of medical significance include *Leptospira*, which causes human leptospirosis; *Treponema*, responsible for the diseases known as treponematoses, such as syphilis;[24] and *Borrelia*, which causes relapsing fever.[25]

Tick Vectors

Ticks are not insects, but related to spiders, scorpions and mites, and placed in the class Arachnida.[26] There are two families of ticks, the Ixodidae (hard-bodied ticks) and the Argasidae (soft-bodied ticks), which differ morphologically and behaviourally. *Ixodes* is one of the thirteen genera of Ixodidae, and the principal vector of *B. burgdorferi* worldwide.[27]

The Hosts

The *Ixodes* vectors of *B. burgdorferi* that feed on humans as incidental hosts also parasitize a large number of small, medium and large wild and domestic animals, including hundreds of species of mammals, reptiles and birds.[28-30]

Global Distribution

Lyme disease is endemic in North America, across Europe to Asia, including the British Isles, western Europe and Russia (from the Baltic States to the Pacific Coast),[31-33] China and Japan.[10,11,34,35] Although not yet confirmed by isolation, the disease has also been reported from Africa, South America, Australia and India.[33,36-38]

Clinical Features

Lyme disease is an illness having protean manifestations with symptoms that include:

(1) an erythematous expanding red annular rash with central clearing;

(2) fever, headache, stiff neck, nausea, and vomiting;

(3) neurologic complications such as facial nerve (Bell's) palsy and meningitis; and

(4) arthritis in about 50% of untreated patients.

These symptoms occur most frequently from May to November, when ticks are active and numerous, and people are engaged in many outdoor activities. The most characteristic feature of early Lyme disease is a skin rash, often referred to as erythema chronicum migrans (ECM), which appears shortly (3-32 days) after a bite from an infected tick. The lesion typically expands almost uniformly from the centre of the bite and is usually flat or slightly indurated with central clearing and reddening at the periphery. It is noteworthy, however, that many Lyme disease victims do not recall being bitten by a tick or do not develop classic ECM. Indeed one third of the patients may not develop ECM. On the other hand, at various intervals after the initial rash, some patients develop similar but smaller multiple secondary annular skin lesions that last for several weeks to months. In approximately half of the patients, the first sign to appear is a slowly expanding red rash at the site of the bite. Beginning as a small flat or raised lesion, the rash increases in diameter in a circular pattern and over a period of weeks the diameter may reach 10-15 inches. It has an intense red border and a red centre resembling a bull's eye. It can vary in shape and is usually hot to touch. The initial tick bite may be distinguished from a mosquito bite because the latter itches, while a tick bite does not.[39] Biopsy of these skin lesions reveals lymphocytic and plasmacytic infiltrates. Various flulike symptoms such as malaise, fever, headache, stiff neck and arthralgias are often associated with ECM. The spirochete eventually reaches the brain, and within several weeks or months about 15% of the patients develop meningitis, which may be accompanied by excruciating headaches and neck pain. There may be abnormalities of the nervous system that last for years, ranging from a mild tingling sensation in the limbs to encephalomyelitis, partial paralysis, or even mental deterioration. Within several weeks after the onset of the disease, approximately 8% of patients show cardiac involvement indicated by heartbeat irregularity, dizziness or shortness of breath. Within 2 weeks to 2 years after the beginning of the disease, 80% of patients develop recurrent arthritis, and eventually the knees or other large joints may become swollen and painful.

Much of the damage to the body caused by *B. burgdorferi* has been attributed to the endotoxin in the outer membrane of the spirochete. The endotoxin is believed to stimulate macrophages to produce interleukin-1, a regulator of the body's immune response. Over-production of this regulator accounts for the fever, skin rash and recurrent arthritis that are characteristics of Lyme disease.[40] The late manifestations of Lyme disease may include migratory and polyarticular arthritis, neurologic and cardiac involvement with cranial nerve palsies and radiculopathy, myocarditis and arrhythmias. Lyme arthritis typically involves a knee or other large joint. It may enter a chronic phase, leading to destruction of bone and joints if left untreated. Interestingly, Lyme arthritis is less common in Europe than in the USA, but neurologic complications are more prevalent in Europe. Unique strain variations expressing antigenic subtypes between European and North American isolates of *B. burgdorferi* probably explain these dissimilarities.

Diagnosis

Like syphilis, Lyme disease produces a diverse number of clinical symptoms that can be confused with many other disease entities.

In many cases the clinical differential is often complex resulting in heavy reliance on the laboratory to provide diagnostic evidence.[1-2,41-42] However, successful isolation and culture of *B. burgdorferi* from skin lesions, blood and joint and cerebrospinal fluid in suspected cases of Lyme disease is rare,[19,42] and most common nonspecific laboratory tests are not helpful in the differential diagnosis. Thus, serologic tests provide the most important confirmatory evidence of all stages of Lyme disease and may be the only way of diagnosing atypical cases. The most commonly used serologic tests are the enzyme-linked immunosorbent assay (ELISA) and indirect fluorescent-antibody assay (IFA) which detect the specific antibody against *B. burgdorferi*. Since antibodies to other spirochetes, including *Treponema pallidum*, can cross-react, differential diagnosis must be undertaken using tests such as VDRL, TPHA or RPR for all specimens showing a positive reaction towards *B. burgdorferi*.

In serum, specific IgM antibody titres against *B. burgdorferi* usually reach a peak between the third and sixth week after the onset of disease; specific IgG antibody titres rise more slowly and are generally highest months later when arthritis is present.

On 19 October 1990, the CDC defined case criteria for reportable disease.[43] Lyme disease is one of the diseases for which the CDC established diagnostic clinical and laboratory criteria, as follows:

Clinical case definition – Erythema migrans, or at least one late manifestation.

Laboratory criteria for diagnosis – isolation of *B. burgdorferi* from clinical specimen, or demonstration of diagnostic levels of IgM and IgG antibodies to the spirochete in serum of CSF, or significant change in IgM or IgG antibody response to *B. burgdorferi* in paired acute and convalescent-phase serum samples.

Treatment and Prevention

For early stage treatment, in order of preference, oral tetracycline 250mg four times a day, phenoxy-methyl penicillin 500mg four times a day, or erythromycin 250mg four times a day each for 10 to 20 days depending on the response, is suggested.[44]

For meningitis and cranial or peripheral neuropathies, intravenous penicillin G 20 million U a day in six divided doses for 10 days is effective therapy.[45]

For established Lyme arthritis, treatment with intra-muscular benzathine penicillin 2.5 million U weekly for 3 weeks has been proven to be successful.[46] The affected joint should be at rest, and accumulated fluid should be removed by needle aspirations.

In vitro and *in vivo* susceptibility tests have suggested that cefuroxime may be an effective alternative therapy for Lyme disease.[47]

A few simple precautions will help reduce possible exposure to *Borrelia*-infected ticks and increase protection against Lyme disease. These include wearing clothing that fully protects the body and using repellents that contain DEET (diethyltoluamide).[48] People should be made aware of the typical early symptoms of infection, such as the characteristic skin rash. The potential for human contact with *Ixodes* ticks as a cause of occasional cases of locally acquired spotted fever must not be overlooked.

The Current Investigation

The incidence of Lyme disease has been increasing considerably world-wide since 1975, but it has never been documented in Hong Kong; and the local situation regarding the disease is unknown. In an attempt to investigate its

occurrence in Hong Kong, since August 1992, a survey of seroprevalence has been conducted in patients with a clinical diagnosis of arthritis.

Blood samples of patients with a clinical diagnosis of arthritis were collected from ten different clinical laboratories in Hong Kong. Whole blood specimens were centrifuged to obtain sera for assay by indirect immunofluorescent antibody (IFA) titre to *Borrelia burgdorferi* (Lyme-spot IF, Ref. 75941 Bio Mérieux, France); to rheumatoid factor by agglutination of IgG coated latex particles (RA80, Eiken Chemical, Japan); and for antibodies against *Treponema pallidum* by haemaglutination assay (TPHA, Fujirebio Inc., Japan) and the rapid plasma reagin card test (RPR reditest, Biokit, Spain) following the manufacturers' instructions. Other clinical and laboratory data relating to the patients were also collected and recorded as additional information.

For a potential patient to be defined as positive for antibody to *Borrelia burgdorferi*, the patient had to have a clinical diagnosis of arthritis, a titre of 1:160 or greater for antibody to *Borrelia burgdorferi* by indirect immunofluorescent antibody (IFA), together with non-reactive results in the remaining three assays, namely: (a) rheumatoid factor (RA), (b) *Treponema pallidum* haemaglutination assay (TPHA) as well as (c) rapid plasma reagin (RPR).[49]

Case Report

In September 1992, a sixty year old female patient recruited into the scheme mentioned above with joint pains but no other symptoms of arthritis was found to provide the results shown in **Table 1.** The patient, who had travelled to the US and Australia prior to seeking medical assistance, had no previous history of skin lesions, etc. She was later treated only with a two weeks course of tetracycline 250mg q.i.d. and has since recovered from her arthritis. The *Borrelia burgdorferi* antibody titre (IFA) in her blood sample has fallen from 1:320 to less than 1:160 nine months after the treatment.

Table 1: Laboratory results of the first reported Lyme disease patient in Hong Kong

Test	Result (unit)	Reference range
Haemoglobin	13.8 (g/dL)	12.0 - 16.0
Haematocrit	41 (%)	36 - 48
Red cell count	4.4 (x 10^{12}/L)	4.0 - 5.0
White cell count	7.4 (x 10^{9}/L)	5.0 - 10.0
ESR	35 (mm/hr)	0 - 20
Hepatitis B surface antigen	Negative	Negative
Uric Acid	45 (mg/L)	25 - 75
Rheumatoid factor (RA)	Negative	Negative
TPHA	Negative	Negative
RPR	Non-reactive	Non-reactive
ANA	Negative	Negative
Borrelia burgdorferi antibody titre (IFA)		
First sample	Positive 1:160	
Second sample (4 weeks apart)	Positive 1:320	< 1:160
Nine months after treatment	Negative < 1:160	

Discussion

The situation regarding Lyme disease in Hong Kong is unclear. Although little is known about the prevalence of the *Ixodes* ticks in this area, there are several possible routes for Lyme disease to gain entrance into Hong Kong.

1. Domestic animals, such as dogs and cats, are found to be commonly infested by *B. burgdorferi* carrying *Ixodes* ticks in endemic areas.[50-52] But pets imported into Hong Kong are not known to have been de-ticked before entrance. *Ixodes* ticks have been noted in pets visiting local veterinarians.[53]
2. 49 species of birds have been found to be infested by *Ixodes* ticks,[29] and migrating birds have already been suspected to be a route of transmitting Lyme disease.[54]
3. Other than *Ixodes* ticks, possible transmission of *B. burgdorferi* to humans by blood-sucking insects such as fleas, mosquitoes and horse flies has been reported.[55,56]
4. The tremendously high volume of visitors, re-immigrants, and travellers to and from endemic areas each year has increased largely the possibility of Lyme disease infection.

Like syphilis, Lyme disease has been called a "great imitator" and is often difficult to diagnose clinically. Less than one third of patients presenting with ECM recall having been bitten by ticks.[57,58] Up to 50% of patients presenting with Lyme arthritis may not recall the pathognomonic ECM rash, flulike illness, or tick bite.[59] The ECM rash may be unrecognized or mistaken for another annular dermatosis. Even in endemic areas of the United States, such as eastern New York and Connecticut, ECM went unrecognized by most physicians until the early 1980s. In children, the rash can be totally missed, when occurring in the scalp area or other unobserved locations.[2,60]

In almost all clinical bacteriological investigations, laboratory culture of causative microorganisms is the prime tool for diagnosis; however, for the screening of Lyme disease, laboratory culture is not a practical option. Isolation of *Borrelia burgdorferi* from blood serum, joint fluid, cerebrospinal fluid, or tissue has proven to be very difficult, if not impossible. Successful positive cultures have been reported in less than 5% of patients with otherwise proven Lyme disease.[22]

Nearly all patients with Lyme arthritis have antibodies to *Borrelia burgdorferi* detectable in their sera. Antibody screening, therefore, remains the most practical method for the detection of the disease, pending the discovery of a better, more reliable, faster methodology. False-positive results, attributable to antibodies cross-reactive to *Borrelia burgdorferi*, can also be seen, however, in the serum of patients with other spirochetal infections.[57] Thus, confirmation of the diagnosis of Lyme disease is only possible if results obtained from the TPHA and RPR test are negative.

Routine laboratory testing is often not helpful in the differential diagnosis of Lyme disease, since some patients with Lyme disease may not have laboratory abnormalities. Table 2 summarizes laboratory findings during early Lyme disease, where rheumatoid factor (RF) and ANA are typically absent from the sera of Lyme disease patients[1] and, as can be seen from the results, less than 60% showed any abnormality.

Table 2: Laboratory Findings in Early Lyme disease.[23]

Test		Number of patients (%) with abnormal values*	Median (range) of abnormal values
Haematocrit		37 (12)	35 (31 - 36)
Leukocytes	>10 cells x $10^3/mm^3$	24 (8)	12 (11 - 18)
ESR	>20 mm/hr	166 (53)	35 (21 - 68)
IgM	>250 mg/dL	104 (33)	310 (252 - 930)

*Total number of patients = 314

Lyme Disease

The availability of laboratory tests and the awareness of clinicians for ordering the test therefore play the most important roles in diagnosing the disease. However, most clinical laboratories in Hong Kong do not carry out the test for Lyme disease and it is not included in "arthritis profile test". A recent survey of eight local laboratories revealed that clinicians ordered the test for Lyme disease less than once per year per laboratory. It is not surprising that, although Lyme disease is such a worldwide illness, previously there has not been one single case officially reported in Hong Kong.

It has been reported that Lyme disease is endemic in China in the forested northeastern regions, particularly in Hailongjiang and Jilin Provinces;[10] yet little is known about Ixodid ticks in Hong Kong. It is not known whether this first reported case of Lyme disease is due to a local infection or not. However, the clinical manifestations together with a seropositive rising titre of antibody to *Borrelia burgdorferi* by IFA has already met the criteria for national reporting of Lyme disease in the United States.[43] The Department of Health of the Hong Kong Government has confirmed with the authors that no cases of Lyme disease have been reported in Hong Kong[61] and, therefore, we consider the present investigation to be the first. The possible reservoirs of the vectors for the spirochete – *Borrelia burgdorferi* – are now being studied.

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