Lyme Disease

Subjects: Anatomy & Morphology

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Lyme disease, or Lyme borreliosis, is an increasingly prevalent illness caused by several bacteria in the Borrelia genus. Lyme disease is an increasingly common bacterial illness that exists throughout the world. Current diagnostic methods for Lyme disease are ineffective at detecting the illness during its early stages - when it is easiest to treat; thus, the improvement of Lyme diagnostics is a popular area of research in many scientific fields.

Lyme disease | Infectious disease | Diagnosis

1. Introduction

While several species can cause Lyme disease, *Borrelia burgdorferi* is the predominant pathogenic species in North America; *B. garinii* and *B. afzelii* are responsible for most infections in Europe and Asia. The transmission of *Borrelia* is facilitated by ticks within the *Ixodes* genus, which serve as the primary vector and reservoir host for the bacterium. *Borrelia* is transferred to a mammalian host when an infected tick attaches to and feeds on the blood of the host. During blood-feeding, *Borrelia,* located in the salivary glands of the tick, enter the mammalian host via the tick's saliva, transmitting the Lyme bacteria and causing the disease. By exploiting the natural feeding relationship of ticks on mammals, *Borrelia* is easily transmitted to deer, livestock, and humans.

Since Burgdorfer's seminal paper realizing *Borrelia* as the causative agent of Lyme disease[1], the wide range and inconspicuous nature of the disease have become clear. According to the Centers for Disease Control and Prevention (CDC), there are approximately 30,000 reported cases of Lyme disease in the United States each year; however, more recent estimates place this number as high as 300,000, owing to frequent misdiagnosis and under-reporting[2][3][4]. Not only is Lyme disease the most common vector-borne illness in the US, but recent studies suggest that it is on the rise in other locations as well. With climate change leading to the northern expansion of temperate conditions, reservoir and vector hosts of Lyme disease stray further and further from their original habitats. Because of this, *B. burgdorferi* is expected to expand its territory northward by 250–500 km in the next 30 years[5]. Increases in Lyme disease incidence are already occurring in many parts of Canada and are expected to continue into the next decades[6][7]. As well, Lyme disease continues to rise steadily throughout Europe (e.g., Germany, Sweden, Austria) and is beginning to take hold in Asia, particularly in regions of China[8][9][10].

The earliest manifestation of Lyme disease is the appearance of a typically bullseye-shaped rash, known as an erythema migrans, at the site of infection. While this rash is generally sufficient for Lyme diagnosis, it only occurs in 70–80% of cases, making it unreliable as a main indicator[11]. Other than the erythema migrans, the most common symptoms are headaches and arthralgia, but these are far too general to indicate Lyme disease[12]. As the disease

progresses, *Borrelia* disseminate from the site of tick attachment and travel throughout the body, causing early disseminated symptoms that can include multiple erythema migrans, carditis, and meningitis[3]. If left untreated for a prolonged period, Lyme disease may progress to a more severe late stage that can include encephalitis and arthritis, among other serious symptoms. While Lyme disease is easily treated with antibiotics if caught early, delayed diagnosis and/or treatment can prove more difficult to treat and lead to more serious health effects[13].

2. Current Methods of Diagnosis

In cases where an erythema migrans is not present or proves inconclusive, a global consensus of guidelines recommends the use of a standard two-tiered (STT) serology approach for the diagnosis of Lyme disease[14]. This approach involves an initial enzyme immunoassay (EIA) or immunofluorescence assay (IFA) to measure antibody response to *Borrelia* antigens — often in the form of a whole-cell *Borrelia* sonicate[12]. If this EIA/IFA returns a positive or equivocal result, then a follow-up Western blot is used to verify the presence of antibodies for a panel of specific *Borrelia* proteins. A meta-analysis of thirteen two-tiered serology studies across North America estimated the sensitivity of the approach at 46.3% for those with early-stage Lyme disease (symptoms for less than 30 days), 89.7% for those with early disseminated Lyme disease (30+ days), and 99.4% for those with late-stage Lyme disease[15]. Specificity estimates for the two-tiered methodology were approximately 99% for all disease stages.

Recently, a modified two-tiered (MTT) approach, in which the western blot of the STT is replaced with a second immunoassay, was approved for use in the United States[16]. Compared to the STT, the MTT demonstrates increased sensitivity for early Lyme disease, similar or slightly higher sensitivity for later stages of the disease, and similar specificity for all stages[17]. A comparison of the STT and MTT approaches on several collections of sera from patients with erythema migrans and early Lyme disease estimated the sensitivity of the MTT test to be approximately 50%, while the sensitivity of the STT test on the same samples was approximately 40%[18].

While the sensitivity of the current two-tiered serology approaches is very high for disseminated Lyme disease, it remains quite difficult to detect the disease in its early stages. The development of anti-*Borrelia* antibodies can take upwards of three weeks to reach sufficient detection levels in the blood[19]. Since the current standard relies on these antibodies, it is evident that a more direct method of detection is necessary to diagnose Lyme disease prior to its dissemination. The necessity of improved diagnostics is underscored by the recent and expected increases in Lyme disease, the potential for serious health difficulties, and the current diagnosis difficulties (e.g., misdiagnosis, false positives)[3].

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