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Borrelia Burgdorferi Sensu Lato Infection-induced Autoimmunity – A Decennary Literature Review

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Abstract

Borrelia burgdorferi sensu lato is a Gram-negative spirochete that causes Lyme disease (Lyme borreliosis). The signs and symptoms of Lyme disease are a consequence of the immune response to spirochete in soft tissues, and it is debated if said immune response can become an autoimmune disease of the body over time due to bacterial and HLA/MHC molecular mimicry. Continual Lyme Disease (CDL) also known as Post-Treatment Lyme Disease Syndrome (PTLDS) is a broad group of rapidly appearing flu-rash symptoms and cognitive difficulties combined with chronic fatigue that is observed after at least six months after completing treatment. This review contains scientific collections throughout the last 10 years of studies related to alleged post-infection auto-immunogenicity.

Key words: *Borrelia burgdorferi, autoimmunity, lyme, lyme disease, lyme arthritis, auto-immunogenicity*

Purpose and methods

Purpose

The purpose of this article is to review the latest scientific publications from 2012 to 2022, which cover the medical debates on the auto-immunogenicity of Borrelia infection and digressions on the possibility of borreliosis being both pro-inflammatory and pro-immunogenic.

Methods, materials

A decennary literature review regarding Lyme disease immunogenicity was performed using the PubMed, Google Scholar, and ScienceDirect databases with the search terms borrelia, borreliosis, immunogenicity, PTLDS, CLD, immunity and autoimmunity, lyme. Out of numerous articles 46 met the search criteria and were analysed and used as references in this review.

Literature review

Introduction

Borrelia burgdorferi sensu lato is a Gram-negative spirochete. It is the causative factor of Lyme disease, which has spread mostly on the Northern side of the world. The saliva of infected Ixodes ricinus complex nymphal ticks contains the spirochetes mostly from B afzelii and B garnii and spreads widely among human habitats. Borrelia burgdorferi sensu stricto is responsible for most cases of Lyme disorder in North America. Around 476,000 cases are found and treated yearly in the United States and less than 200,000 cases a year in western Europe (with 12,934 cases in Poland alone in 2020), making the disease widespread throughout the world [1, 2]. The risk of acquiring Borrelia infection after a tick bite is 5% [3]. The signs of Lyme disease depend on the time frame between the tick bite and the professional treatment. The most common symptoms of infection are the erythema migrans rash, which can resolve without any treatment, arthritis (usually in major joints like knees, but wrists and ankles are also commonly affected), and facial palsy with neuropathies [4]. Due to molecular mimicry, there has been widespread speculation about autoimmune reactions related to the early and late stages of Lyme infection.

Autoimmunity is a set of immune responses to organisms' own cells. Autoimmunity might be induced by a rapid immune response when foreign antigens are present in amounts that may limit the response – i.e., the early degrees of the infection.

Molecular mimicry is a consequence of the structural similarity of hosts and exogenous antigens. As a consequence, during an immune reaction, the organism creates antibodies that will bind both host and unfamiliar antigens which leads to the amplification of the inflammatory and immune reaction. In contradiction, this case might be a part of the usual development course of the disease [5].

There is an unresolved hypothesis that B. burgdorferi elicits an antibody to Borrelia enolase that cross-reacts with human γ enolase [6, 7]. There is a proven similarity in the amino acid structure of the outer surface protein – OspA – and

human Lymphocyte function-associated antigen 1 (LFA-1) [8]. Officially no human vaccines for Lyme disease are currently available [9].

Lyme disease diagnose is confirmed after finding specific symptoms, objective physical signs (such as erythema migrans, facial palsy, or arthritis), history of possible exposure to infected ticks, and laboratory tests [10, 11].

In the absence of erythema migrans or a history of tick exposure, Lyme diagnosis depends on laboratory confirmation. The number of IgM antibodies usually decreases 4–6 months after infection, while IgG antibodies can remain detectable for years [12].

Differential diagnosis

The most common misdiagnoses are erythema migrans as spider bite rash, cellulitis, or shingles; facial palsy as Bell's palsy and viral meningitis; Lyme radiculopathy as a nerve root compression; Lyme arthritis as juvenile rheumatoid arthritis [13, 14].

Treatment

There is no available vaccine approved to protect communities, research is still ongoing. Several spirochetes' molecules were found as possible vaccinal prototypes [15]. Two recombinant OspA vaccines that were proven effective are under further clinical development [16].

The only U.S. Food and Drug Administration-approved vaccine LYMErix targeted only Borrelia burgdorferi sensu stricto and was created for 15–70-year-old patients. However, it was withdrawn from the market in 2002. Its efficacy ranged from 49% to 76% after three doses [17]. A new vaccine – VLA15 – is under clinical development and gives promising protection against six OspA serotypes [9].

The disease in its early stages is treated with antibiotics such as doxycycline, amoxicillin, cefuroxime, axetil, and azithromycin [18].

The most recent trials prove that azlocillin can be a new candidate against drug resistant Borrelia burgdorferi sensu stricto [19]. It is believed to kill 99––100% of spirochetes' cells at concentrations of 20 and 40 μg/mL [20].

Joint pain connected to Lyme arthritis is treated with non-steroidal anti-inflammatory drugs. When it is refractory to antibiotics, disease-modifying antirheumatic drugs (DMARDs) and arthroscopic synovectomy are used in addition to the therapy [21].

Literature overview

The presence of an assumed immune-mediated reaction might be explained by an occurrence of antibiotic-resistant borreliosis. This end result is connected to human leukocyte antigen (HLA)-DR alleles, immoderate joint inflammation, an imbalance between the CD41 effector and regulatory T lymphocytes (Teff: Treg) cell ratio, and autoimmunity caused by infection.

Interestingly, there were reports of patients developing de novo systemic autoimmune diseases – including rheumatoid arthritis and spondyloarthritis, a few months after the occurrence of Lyme disease [22].

It might have happened incidentally, yet it is considered that latent immunity could be induced in a non-specific way by adjuvant Borrelia infection effectors or conditions triggered by other autoimmune diseases spread systematically [23]. Lyme disease research showed T and B cell autoimmunity towards the joints in drug-resistant borrelia arthritis [24].

These spirochetes have a major potential for antigenic variation and expression of antigenic proteins upregulated at different stages of infection. The correlation between immune recognition of other B. burgdorferi antigens and chronic disease has not been explored in a systematic classification and could reveal other candidates for molecular mimicry [25]. Moreover, recent research associating xenodiagnosis to PTLDS backs up the thesis that PTLDS probably has an autoimmune background [26].

Lyme disease and autoimmune diseases:

Facial nerve palsy: a facial nerve paralysis, appearing with one-sided muscular weakness, taste bud hypoesthesia, sensitivity to noise, and low tear and saliva production. B. burgdorferi – caused disease is one of the most prevalent causes of pediatric facial nerve palsy in endemic areas [27].

Localized morphea: Borrelia-associated morphea may represent post-infectious sequelae resulting from infection-induced autoimmunity [27].

It manifests itself with skin sclerosis and extracutaneous formations. Lichen sclerosus, lichen atrophicus, and morphea have documented case reports on disease remissions after antibiotic treatment toward borrerial infection [28].

Lyme-associated uveitis: Applied antibiotic and steroid treatment are widely effective in most cases [29].

Lichen sclerosus (LS): Appears with white patches on the skin, hyperkeratosis, itchy skin pains, frequent skin cracking, and bruising. There is no discovered etiology of LS, but autoimmune and infection-triggered etiologies were discussed as possible causes for LS [30].

Data sources indicate no correlation between Borrelia infection and the development of fibromyalgia, celiac disease, and alopecia areata [31, 32, 33].

Lyme disease-associated thyroiditis (LDAT): causation of LDAT in predisposed patients by the infection cannot be ruled out [34, 35].

Neurologic diseases: Patients suffering from neuroborreliosis are in an increased-risk group of Guillain-Barré syndrome and seizures [36].

Post-treatment Lyme Disease Syndrome: Studies have shown no direct connection, yet Burgdorferi spirochetes have shown resistance and tolerance to antibiotics in vitro in non-human primate studies, indicating a possibility of an autoimmune response not only by initial immune response to borrelial infection but also in response to borrelial persistence secondary to antimicrobial tolerance [37].

Any joint inflammation and autoimmune arthritis that has appeared after borrelial infection: Non-functional FcγRIIb allele owners are more inclined to arthritis while being simultaneously less prone to develop Borrelia infection. Animal models prove that cationic external proteins of the spirochete can bind itself to the surface of cartilage, directing more and more studies to chronic synovial diseases. Patients' joint fluid has marked elevated levels of apoB-100 protein, which may connect with its auto-antigenicity [38, 39, 40].

The combination of immune dysregulation and activation of MMP-10-specific T cells may induce an IgG antibody response to an immunoreactive state, leading to increasing autoimmune influence [41].

Conclusions

No studies can officially confirm the auto-immunogenicity of Borrelia burgdorferi sensu lato. Despite that, it is firmly believed there is such a connection, as it has been proved by clinical observations and experiences [42, 43].

Disclosure

The authors declare no conflict of interest.

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