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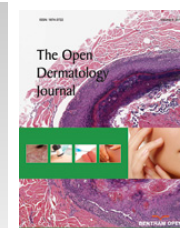
Impact of Co-Infections in Lyme Disease

Giuseppe Stinco[*] and Serena Bergamo

Department of Experimental and Clinical Medicine, Institute of Dermatology, University of Udine, Italy

Abstract: Lyme disease is one of the most frequent tick-borne diseases worldwide, it can be multi-systemic and insidious, in particular when it shows a chronic course.

In recent years co-infections represent an emerging issue in Lyme disease spectrum because in addition to *Borrelia burgdorferi sl* many other potential pathogens may be transmitted by hard ticks Ixodes species. The main co-infections found in Lyme disease described in this review are represented by *Anaplasma phagocytophilum, Babesia species, Bartonella species, Rickettsiae species and tick-borne encephalitis virus*. For each single co-infecting micro-organism, clinical features, diagnostic issues and therapeutical approaches are discussed.

Co-infections represent an emerging problem because they might exacerbate Lyme disease clinical features, they can also mimic Lyme borreliosis sharing common manifestations, and eventually they can change the course of the disease itself.

The presence of one or more co-infecting agent during the course of Lyme disease may represent an issue especially in endemic areas for tick-borne diseases and in people occupationally exposed.

The aim of this review is to summarize the more important co-infections in patients with Lyme disease and to discuss their importance in the disease process.

Keywords: Anaplasma phagocytophilum, Babesia species, Bartonella species, Borrelia burgdorferi, Co-infections, Lyme disease, Rickettsiae species, Tick-borne encephalitis virus.

INTRODUCTION

Lyme disease (LD) is one of the commonest vector-borne infections worldwide, caused by a spirochete, *Borrelia burgdorferi sensu lato (Bb)*, and transmitted to humans through hard tick (*Ixodes spp.*) bite [1, 2]. In addition to *Bb*, other human pathogens may be transmitted by *Ixodes* ticks [3]. A concomitant infection of more than one agent is named co-infection. The risk for human co-infections with multiple pathogens after an *Ixodes* tick bite differs by geographic location and depends on the prevalence of pathogens within the reservoir host and *Ixodes* ticks [4 - 6]. The more relevant co-infections in LD are caused by *Anaplasma phagocytophilum, Babesia species, Bartonella species,* primary *Bartonella hensalae and tick-borne encephalitis virus (TBEV)* [5]. *Bartonella henselae* is the aetiologic agent of cat scratch disease, which is not transmitted to humans by ticks.

The clinical and pathological impact of co-infections was first recognized in 1990, about ten years after the discovery of LD and they are thought to be the main reason for treatment failures [7].

Co-infections might exacerbate LD as well as they can induce similar clinical manifestations or change the course of the disease [3, 4, 7, 8]. However the actual burden of co-infections in the natural disease history has not been unravelled yet. When two or more pathogens infect a patient, clarifying which is the major responsible of the clinical pictures can be challenging, since LD can share common clinical features with other conditions transmitted by Ixodes ticks bite especially in early stages [3, 9, 10]. The difficulties in diagnosis and management of co-infections in LD are more related to late and chronic LD since co-infecting agents might cause chronic forms of diseases too [3, 7].

* Address correspondence to this author at the Institute of Dermatology, "Santa Maria della Misericordia" University Hospital, Piazzale Santa Maria della Misericordia, 15, 33100-Udine, Italy; Tel: (+39) 0432559822; Email: giuseppe.stinco@uniud.it

In such cases an accurate anamnestic report in early stages may be useful to recognize the chronic course of the co-infection together with LD.

The diagnosis of co-infections is based on patient's history, the course of the disease, results of medical technical tests, physical examination and the exclusion of differential diagnoses.

Laboratory tests for diagnosis of LD and co-infecting agents are available both for serology, culture and indirect detection by lymphocyte transformation test [11, 12]. The most widely used and reliable test is the two-step serological diagnosis with the confirmation by Western blot in case of positive or doubtful serology. Serological findings, especially in endemic areas, are not always signs of the current infection and a negative serology is not sufficient to exclude the disease [13, 14]. The positive serological result only proofs that infection has taken place, but cannot prove the disease and there may be seronegativity in case of co-infection with long lasting chronic disease.

Since the treatment of the infections caused by various tick-borne pathogens differs from one another, concomitant infections are becoming a serious epidemiological and clinical problem [15].

The aim of this review is to summarize the most important co-infections in patients with LD and to discuss their importance in the disease process.

ANAPLASMA PHAGOCYTOPHILUM

Tick-borne *Rickettsiae* in the genera *Ehrlichia* and *Anaplasma* are intracellular bacteria that infect wild and domestic mammals and humans. They can cause human granulocitic anaplasmosis (HGA), an acute febrile illness ranging from asymptomatic to severe disease in humans [16]. The main features of HGA are fever, headache, joint and muscle pain and laboratory findings such as leukopenia, thrombocytopenia and high liver enzymes levels in peripheral blood. Usually the infection is mild and self-limiting, even if it can be life-threatening with the development of meningitis and other central nervous system disorders. The incubation period is about 7 days from the tick bite and the development of symptoms. Co-infection between LD and HGA ranges from 2% to 11% in three studies [4, 3, 17, 18]. In a recent study Strle *et al.* demonstrated that in Slovenia, a country endemic for LD, TBE and HGA, none of 67 patients involved in the survey with typical erythema migrans was found to be co-infected with *A. phagocytophilum*, even if only serology was performed by the Authors as diagnostic tool [19].

In 2007, Grab *et al.* found that the infection of *A. phagocytophilum* may be responsible of a more severe form of LD with enhanced dissemination and possible long-term complications because co-infection causes reduction in transendothelial electric resistance and increased production of metalloproteinases, cytokines and chemokines [20, 21].

Recently, Horowitz *et al.* analysed patients having erythema migrans and a positive blood culture for *Anaplasma phagocytophilum* living in Valhalla, New York. They found that the total number of symptoms was not significantly different in patients with LD alone and patients with LD and HGA. In addition to that, the Authors interestingly noted that patients having HGA alone experienced a shorter duration of illness compared with those co-infected by *Bb* and *Anaplasma phagocytophilum*, maybe because they went sooner to the doctor. In this study leukopenia and thrombocytopenia were reported more frequently in HGA alone than in co-infections, even if this difference was not statistically significant [15]. In Literature conflicting data about the severity of co-infection compared to LD or HGA alone are available [7, 10, 17, 18].

The diagnosis of HGA is mostly based on serology findings: specific antibodies can be detected two to three weeks after the onset of the illness. *Anaplasma phagocytophilum* can also be amplified by means of PCR from the blood or it can be cultured from blood as well. Eventually intragranulocitic morulae can be directly detected from peripheral blood stained with Giemsa and observed under microscope [4, 15, 22].

Doxycycline 100 mg twice a day is found to be the most effective therapy, it can be the treatment of choice also in children [3, 4]. Usually it is prescribed orally for 14 days, but no universal data are available [4, 15, 23].

Rifampicin and possibly levofloxacin may be second choice treatments: they showed good antimicrobial activity *in vitro*, but clinical studies are poor or lacking. *Anaplasma phagocytophilum* has found to be resistant to several classes of antibiotics such as amoxicillin and other beta-lactams, erythromycin, azithromycin, clarithromycin, clindamycin, trimethoprim-sulfamethoxazole [3, 24, 25].

BABESIA SPECIES

Human babesiosis is a tick-borne disease, caused primarily by the intraerythrocytic protozoan *Babesia microti* and

by other *Babesia species*. In the United States *Babesia microti* has found to be more often detected in ticks, whether in Europe *Babesia divergens* seemed to be prevalent [6, 8, 11, 26]. It can be transmitted either by *Ixodes* ticks or less often with blood transfusions and by perinatal infection. The clinical spectrum of the infection ranges from asymptomatic or moderate disease to rapidly progressive and sometimes fatal [4, 11]. Acute Babesiosis usually shows as fever and flu-like symptoms such as myalgia, chills, gastro-intestinal features. Since *Babesia* causes an intra-erythrocytic infection, haemolysis ranging with different severity can be detected as well. Immunocompromised subjects as oncologic, asplenic and undergoing immunosuppressive therapy patients could develop a more severe disease form which might become chronic and relapsing [27].

Babesia infection can be proved with DNA amplification by means of PCR. It can be detected also with direct confirmation of the protozoan on blood smear, but this technique is not straightforward and usually requires multiple examinations. Serology is not helpful because it is poorly associated with clinical symptoms, especially in endemic areas [28, 29].

Studies of clinical outcomes suggest that patients with acute *Babesia* co-infection have more severe symptoms and a longer duration of illness than patients with LB alone, but the risk of spirochete dissemination seems to be similar [7].

Concomitant infections may be difficult to diagnose since both LD and Babesiosis have overlapping symptoms *e.g.* flu-like illness with fever and fatigue [20].

In Literature atovaquone, azithromycin, clindamycin with or without quinine are found to be effective [15]. Clindamycin 600 mg every 8 hours taken orally plus quinine 650 mg orally every 8 hours for 7 to 10 days have efficacy proven in Literature in milder forms of disease [30, 31], while the intravenous use of clindamycin is preferred in more severe disease forms. Alternative and similarly effective treatments are atovaquone 750 mg twice daily taken orally plus azithromycin 250 mg daily except for the fisrt day of treatment (500 mg) for 7 days as well. These therapies have to be associated with an adequate anti-Borrelial drug regimen (*e.g.* doxycycline) [8].

In immunocompromised patients there are some evidences for a more prolonged anti-*Babesia* therapy (*e.g.* more than 10 days) to be prescribed [32]. In patients severely ill with haemolysis and organ failure with high levels of *Babesia* in blood, transfusions may be sensible [33, 34].

According to data available, it seems that babesiosis represents a minor health hazard and can cause little consequence as a co-infection in LD [3].

CONTEMPORARY INFECTION WITH ANAPLASMA PHAGOCITOPHILUM AND BABESIA SPECIES

Bb sensu lato, *Anaplasma phagocytophilum* and *Babesia* share very similar epidemiology and trasmission cycles, having hard ticks as vectors and white-footed mice and white-tailed deer as reservoir hosts [11].

Since *Bb, Anaplasma phagocitophilum* and *Babesia* may be co-transmitted by Ixodes ticks bite, the clinical features of acute and chronic disease can be atypical, complex and variable [10].

In an original study, Krause *et al.*[10] analysed clinical and laboratory features as well as short-term complications in 192 people living in New England who experienced infections due to Bb and or Babesia and Ehrlichia. The Authors found that erythema migrans is very peculiar of LD alone, whereas flu-like symptoms are more suggestive of LD concurrent with babesiosis and/or HGA. However, LD itself in small percentage (about 10%) can present with fever, chills and headache. Such an epidemiologic report is confirmed also in Europe: in an Italian study conducted on more than 700 people living in an endemic area for LD, flu-like symptoms as fever, myalgia and headache preceded, accompanied or were the only clinical sign of LD in 16.88% of patients [35].

From the study by Krause *et al*, it seems that patients having only LD experienced a fewer number of symptoms and a shorter time of illness compared to those with babesiosis, HGA or co-infection between LD and babesiosis or HGA. The Authors suggest performing serological laboratory tests for *Babesia* and *Ehrlichia* in suspected LD patients having prolonged flu-like symptoms and poorly responding to an appropriate antiborrelial therapy.

In contrast with other reports [33, 36, 37], Krause *et al.* found that the presence of a co-infection does not help *Bb* to spread more rapidly into blood, skin, joint, nervous system and heart [10].

BARTONELLA SPECIES

Bartonella species are vector-transmitted, blood-borne, intracellular, gram-negative bacteria that can induce

prolonged infection in the host. Persistent infections in domestic and wild animals result in a substantial reservoir of *Bartonella* organisms in nature that can serve as a source for inadvertent human infection. A wide spectrum of disease has been described in immunocompetent individuals, including bacillary angiomatosis, peliosis hepatitis, lymphadenitis, and aseptic meningitis with bacteremia and cat-scratch disease [4, 38]. Human bartonellosis main features are represented by infected skin lesions and lymphadenopathy. It can be a multisystemic disease with involvement of spleen, liver, central nervous system and eye [39].

Even if *Bartonella henselae* has been found in *Ixodes* ticks in USA, Europe and Russia, there are no proven data in Literature for a tick-born transsission of human bartonellosis [40 - 42].

Bartonella infection can be detected by serologic findings (controversial), PCR amplification (either in blood or in tissue) and culture (difficult) [4, 43].

The main treatment suggested is azithromycin 500 mg single dose orally on day one, followed by 250 mg every 6 hours for 4 days [44].

RICKETTSIA SPECIES

Ixodes tick bites might transmit *Rickettsia species* as well. Some *Rickettsia* species are known to cause human diseases, whereas some others are not fully identified as pathogen to humans [45].

Usually the co-infection between *Borrelia* and *Rickettsia* does not represent a diagnostic challenge because the acute *Rickettsia* infection is dominated by a typical generalized exanthema, high fever, abdominal symptoms, prostration and potentially central nervous system impairment.

The main-stray treatment for Rickettsiosis is doxycycline [4].

TICK-BORNE ENCEPHALITIS (TBE)

In endemic areas, TBE and LD are equally transmitted by *Ixodes* ticks. TBE and neuroborreliosis share common clinical features such as lymphocytic meningitis, meningomyelitis, limb weakness, cranial nerve impairment [46]. Differentiating between TBE and LD is important because of the different therapeutic approaches.

TBE is a febrile illness, which develops within 1 month after a tick bite and has typically a biphasic course: a flu-like symptoms prodromic period ranging from 1 to 2 weeks after the tick bite is followed by a 2 to 10 day asymptomatic period. After that, about one out of three patients experience the second phase of the disease with aseptic meningitis. Some of them later will develop a post-encephalitis syndrome [47, 48]. In a paper by Logina *et al*, the Authors focused on common clinical features shared by LD and TBE, suggesting that physician should have a low-threshold for prescribing antibiotics against LD in patients with TBE [44].

Infection by TBE virus can be detected by specific antibody titre in cerebrospinal fluid (ELISA). Serology in this case is found to be sensitive and specific for the diagnosis [49].

Any specific antiviral therapy for TBE is not available yet. In endemic areas, vaccination against TBE virus is accessible and strongly recommended.

CONCLUSION

In recent years co-infections in LD spectrum represent an emerging issue, even if they are less frequent compared to the report of micro-organisms found in ticks. Such a problem is more evident in endemic places with significant differences among different geographic areas, according to natural habitat which may foster the vital cycle of pathogen. Humans, as occasional hosts, may be infected, though concomitant infections with more than two organisms are rarely reported.

Only a single paper describing four co-infecting pathogens detected in forestry workers in an endemic area can be found in Literature [50]. The actual role of these infections in asymptomatic people is not unravelled yet, as well as the possible effect on clinical history of disease; also the therapeutical approach in such cases is not well defined.

LD is a highly complex condition and still partially controversial as regards late and chronic phases. Possible explanations to clinical features of such phases have been searched in co-infections in LD, even if studies on adequate records did not support this hypothesis. In a convincing review Lantos and colleagues' main purpose was to answer several questions about the relevance of co-infections in chronic LD; they found that Literature does not sustain the diagnosis of chronic and atypical co-infections in patients with chronic unspecific LD [7].

On the other hand, more and more reports of single clinical cases or case series point out the role of co-infections as worsening or trigger factor in late LD picture. Recently a correlation between cutaneous B-cell lymphomas and *Bb* has been supposed [51 - 53]. In our experience, in primitive cutaneous B-cell lymphomas we found that in 100% of cases the presence of *Bb* and *Anaplasma phagocytophilum* could be detected by means of PCR (unpublished data).

In front of such controversies, in endemic areas for tick-borne diseases, it is sensible that co-infections are searched and noticed especially in potentially exposed people (either for working or for travelling reasons). Prospective studies on wide records are needed to prove the actual burden of this issue.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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