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Chronic coinfections in patients diagnosed with chronic Lyme disease: a systematic literature review

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Abstract

Purpose—The controversial diagnosis of chronic Lyme disease is often given to patients with prolonged, medically unexplained physical symptoms. Many such patients are also treated for chronic co-infections with *Babesia*, *Anaplasma*, or *Bartonella* in the absence of typical presentations, objective clinical findings, or laboratory confirmation of active infection. We have undertaken a systematic review of the literature to evaluate several aspects of this practice.

Methods—Five systematic literature searches were performed using Boolean operators and the PubMed search engine.

Results—The literature searches did not demonstrate convincing evidence of 1) chronic anaplasmosis infection, 2) treatment responsive symptomatic chronic babesiosis in immunocompetent persons in the absence of fever, laboratory abnormalities and detectable parasitemia, 3) either geographically widespread or treatment responsive symptomatic chronic infection with *Babesia duncani* in the absence of fever, laboratory abnormalities and detectable parasitemia, 4) tick-borne transmission of *Bartonella* species, or 5) simultaneous Lyme disease and *Bartonella* infection.

Conclusions—The medical literature does not support the diagnosis of chronic, atypical tick-borne coinfections in patients with chronic, nonspecific illnesses.

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Keywords

Lyme disease; coinfection; *Borrelia burgdorferi*; *Bartonella*; *Babesia*; *Anaplasma*

Introduction

Lyme disease is the most commonly reported vector-borne infection in the United States with over 30,000 confirmed and/or probable cases in 2011.(1) Lyme disease is caused by infection with the spirochete *Borrelia burgdorferi* and transmitted by *Ixodes* spp. ticks.

While many aspects of Lyme disease are well accepted by the mainstream medical community, considerable controversy surrounds “chronic Lyme disease”, an ill-defined diagnosis that some clinicians give to patients with alternative diagnoses or medically unexplained symptom complexes. In many instances these patients are also diagnosed with chronic coinfection with *Anaplasma*, *Babesia*, or *Bartonella*. In the context of chronic Lyme disease these pathogens are often diagnosed in the absence of typical presentations or objective clinical findings, and without laboratory confirmation.

In this systematic review we address several major questions relevant to the diagnosis of coinfections in patients with a diagnosis of chronic Lyme disease. These questions are the following:

1. Is there evidence of persistent human granulocytic anaplasmosis (HGA)?
2. How is relapsing or persisting babesiosis identified and diagnosed?
3. Has chronic *Babesia duncani* infection been described?
4. Is there convincing evidence for tick-borne human *Bartonella* infection?
5. Is there convincing evidence for simultaneous Lyme disease and *Bartonella* infection?

Methods

In order to identify relevant articles we performed the following Boolean searches of the indexed medical literature using the PubMed search engine.

Search 1

For evidence of chronic human anaplasmosis:

(anaplasma OR anaplasmosis OR ehrlichia OR ehrlichiosis OR phagocytophilum) AND (chronic OR persistent OR recurrent OR relapse)

Search 2

To characterize chronic or relapsing babesiosis:

(babesia OR babesiosis) AND (chronic OR persistent OR recurrent OR relapse)

Search 3

For the role of Babesia duncani in human disease:

babesia AND (duncani OR WA1)

Search 4

For tick-borne *Bartonella* infection:

(tick OR Ixodes) AND (bartonella OR bartonellosis)

Search 5

For simultaneous Lyme disease and bartonellosis:

(Lyme OR borrelia OR borreliosis) AND (bartonella OR bartonellosis)

Case reports, case series, and primary scientific studies were selected from among the search results. Review articles, correspondence, and editorials were excluded. We limited our search to studies with human subjects. This was done by manually reviewing the papers and excluding those in which the subjects were non-human (rather than adding a search function limit to the PubMed query). Because *Anaplasma phagocytophilum* was formerly categorized as *Ehrlichia*, we included *Ehrlichia* and ehrlichiosis in the search terms for this query.

Results

Search 1: Persistent, chronic, or recurrent human granulocytic anaplasmosis

This search yielded 252 articles. The vast majority of scientific articles yielded by these search terms were animal studies. Many addressed microorganisms other than *A. phagocytophilum*. Ultimately only two studies were appropriate for further review based on our inclusion criteria. In the first two febrile asplenic patients were diagnosed with HGA based on blood smear examination.(2) One developed neurologic symptoms including left-sided weakness, left hemi-neglect, and delirium within 12 days of an admission in which HGA had been diagnosed and treated. His blood smear examination was negative at this second visit and he was apparently afebrile, so recurrent HGA was not definitively established; nonetheless he received doxycycline and promptly improved. The second asplenic patient was treated uneventfully with ten days of doxycycline and suffered no relapse. A second study reported HGA in three recipients of pancreas transplantation.(3) While all of the patients had overall complicated medical courses, none had evidence of recurrent or chronic HGA. This study was reported from Kentucky, a state where HGA is not known to be endemic.

Search 2: Persistent or relapsing human babesiosis

This search yielded 200 articles. Of these 31 were retrieved for further analysis after screening as described in the Methods. A large number of these studies documented relapsing or persistent babesiosis or babesiosis whose diagnosis was delayed; complicated disease predominantly affected asplenic or otherwise immunocompromised patients. Fever, laboratory abnormalities such as anemia, and direct evidence of parasitemia such as a

positive blood film examination or polymerase chain reaction (PCR) assay were nearly universal among the reported patients.(4-23)

The literature search did not yield evidence of cryptic babesiosis resulting in a less overt syndrome. A study of patients with chronic fatigue syndrome found seroreactivity to *B. microti* in two controls but not in any of the study subjects with chronic fatigue.(24) A case series of three patients attributed panic attacks to infection with multiple tick-borne pathogens including babesiosis.(25) In two of the three cases presumption of babesiosis was based solely on antibody titers – an IgM titer of 1:80 in one case and a “low positive” titer in the other. A third patient in this series reportedly had *B. microti* DNA detected by PCR. Details of the PCR reaction were not provided, there was no report of a blood film examination, and no report of laboratory testing to evaluate hemolysis; the article reports that the patient's panic attacks were eliminated after 9 months of “increasingly aggressive antimicrobial therapy for tick-borne diseases”. None of the antibiotics listed in the article has known efficacy for human babesiosis.

Search 3: *Babesia duncani* infection

This search yielded twenty-six articles. Of these we identified thirteen case reports, case series, or human studies for further review. The remainder was comprised of review material or animal studies. Two instances were reports of a *Babesia divergens*-like pathogen, and infection with *B. duncani* was excluded.

Infection with *B. duncani*, formerly designated WA1, has been described in 8 patients in the medical literature.(26-32) Three of these cases were transfusion-associated. Fever was a predominant symptom in seven of these cases; this was not the case in that of a premature infant with transfusion-associated disease. In all published cases infection was directly confirmed by blood smear examination, direct amplification of pathogen DNA, or by inoculation of a laboratory animal. One additional subject from Australia with no history of travel was reported to be positive by PCR for *B. duncani*.(33) His clinical presentation was not described in this publication.

Seropositivity to *B. duncani* appears to be common in asymptomatic individuals. In northern California 3.5% of all individuals and 16% of higher risk subjects were seropositive. This was corroborated by a separate study from northern California showing a seroprevalence of 17.8%.(34) Finally, a private reference laboratory reported that 27% of clinical specimens and 2% of specimens from prospective blood donors had titers to *B. duncani* of at least 1:256.(35)

In no published report was *B. duncani* directly detected in afebrile patients who lacked other objective clinical or laboratory signs of disease.

Search 4: Evidence of tick-borne human *Bartonella* infection

A total of 200 articles was identified, the great majority of them reporting the detection of *Bartonella* within ticks. Nine articles were reviewed further for direct evidence of human *Bartonella* infection transmitted by a tick bite, or the vector competence of ticks to transmit *Bartonella* spp. to a host. The most direct evidence of tick-borne human bartonellosis comes

from a study of three patients from southern France investigating the "scalp eschar and neck lymphadenopathy after tick bite" (SENLAT) syndrome.(36) The eschars from two of these patients were positive by PCR for *B. henselae*. These patients, however, did not have an identified tick bite, and had other risk factors for *Bartonella* infection (including cat exposure). A third patient had an eschar that was negative by PCR for *B. henselae*. He did, however, provide an ornate sheep tick, *Dermacentor marginatus*, that was retrieved from the site of the eschar; this tick was positive for *B. henselae*. Our search did not yield other articles demonstrating tick transmission of *Bartonella* to humans. Three studies have demonstrated transmission of *Bartonella* spp by ticks using artificial feeding systems and murine transmission models. One study demonstrated that the brown dog tick, *Rhipicephalus sanguineus*, could become infected with *B. vinsonii* subsp. *berkhoffii* when feeding using a capillary tube system.(37) A second study found that *I. ricinus* ticks could acquire *B. henselae* after feeding on infected blood using a membrane feeding system. Neither of these studies demonstrated transmission of the organism from the tick to a mammalian host. The only study to do so found that *B. birtlesii* could be transmitted to mice by *I. ricinus*.(37-39) This study has not been corroborated by evidence that transmission occurs in nature. No study has yet investigated transmission of *B. henselae* by *I. scapularis*.

Search 5: Evidence of simultaneous Lyme disease and *Bartonella* spp. infection

This search yielded 155 articles, of which 8 were appropriate for further review based on the criteria described in the Methods. Three of these publications presented patients with putative *Bartonella*/Lyme disease coinfection.(40) One patient had several months of nonspecific symptoms, then sudden vision loss that was attributed to neuroretinitis. Titers were strongly positive to *B. henselae* (> 1:1024). The patient had detectable peripheral and cerebrospinal fluid IgM antibodies to *B. burgdorferi*, but had a negative *B. burgdorferi* IgG by established interpretive criteria. The second publication reported four symptomatic patients in whom DNA from both *B. henselae* and *B. burgdorferi* were found in the cerebrospinal fluid. (41) Only one of these subjects was seropositive to *B. burgdorferi*. Very little clinical information was given about these patients, including whether there was CSF evidence of meningitis. Amplicons from PCR reactions were not sequenced. Finally, a third publication reported testing results from two patients from Poland with meningitis; no further clinical details were provided in the study. (42) Of these patients one had *B. henselae* DNA in the CSF; this individual was seronegative for antibodies to *B. henselae*, but had detectable IgG antibodies to *B. burgdorferi*. A second patient was found to have equivocal levels of antibodies to *B. henselae* and equivocal levels of IgM antibodies to *B. burgdorferi*. Serologic evaluation for Lyme disease in this study did not correspond to current recommendations for two-tier testing.

A number of other studies have suggested that occupationally-exposed individuals are frequently seropositive for antibodies to both *B. burgdorferi* and *Bartonella*. A serosurvey of at-risk individuals in Lublin, Poland (forestry workers and farmers) found that 8.9% of individuals had antibodies to both *Bartonella* spp. and *B. burgdorferi*.(43) A separate study from the Warsaw region found seropositivity to both organisms in 10% of forestry workers. (44) A study of patients with a variety of rheumatic disease manifestations from a Lyme disease-hyperendemic region found antibodies to *Bartonella* in 62% of subjects and direct

detection of the organism in 41.1%; none of these patients, however, had documentation of Lyme disease.(45) Finally, in an Australian study two patients were described as having evidence of simultaneous *Bartonella* infection and Lyme disease. The clinical syndromes from these patients were not described; their seropositivity to *Bartonella* was an isolated IgM titer of 1:40, and these subjects only had IgM seroreactivity to *B. burgdorferi*.(33)

Discussion

There is no debate in the scientific community that *Ixodes* spp. ticks transmit a number of important human pathogens, and sometimes in combination. In addition to *B. burgdorferi*, the causative agent of Lyme disease, *Ixodes* ticks may transmit *B. microti* and other human *Babesia* species, *A. phagocytophilum*, tick-borne encephalitis virus, Powassan virus, and emerging pathogens such as *Borrelia miyamotoi*. These infections may occur in isolation or in various combinations, and it is well-established that coinfections have important clinical, diagnostic, and therapeutic implications. Active infection is characterized by objective clinical findings (e.g., fever or laboratory abnormalities). Practitioners who frequently offer the diagnosis of chronic Lyme disease often do not rely on more accepted standards of clinical and laboratory testing. In such circumstances many patients also receive spurious diagnoses of chronic anaplasmosis, babesiosis, and bartonellosis.

We have performed a systematic review of the medical literature in order to evaluate whether published science supports chronic, cryptic infections with these pathogens. Because of basic biological, clinical, and epidemiologic differences among HGA, babesiosis, and bartonellosis different search terms were required for each pathogen.

A. phagocytophilum, the causative agent of HGA, is a rickettsial organism that produces an acute febrile systemic illness within about 2 weeks of an infectious tick bite. Infection is characterized by fever, constitutional symptoms, and laboratory abnormalities such as leukopenia, thrombocytopenia, and elevated levels of hepatic transaminases. While HGA is potentially fatal, the infection will be self-limiting in survivors regardless of whether they are treated. As HGA is an infection of circulating leukocytes, both blood film examination and PCR of the blood can establish the presence of infection. Our search did not yield any reports of chronic, relapsing, or refractory HGA in humans. Persistent infection in domestic and wild ruminants, and persistent veterinary infections with related microorganisms (e.g., *A. marginale*) cannot be assumed to predict the plausibility of chronic HGA in humans. To date there is no basis upon which to diagnose a human patient with chronic HGA.

Babesiosis is a malaria-like protozoal infection of erythrocytes that is transmitted by *Ixodes* spp. ticks. It may also be acquired from blood transfusions. Several species of *Babesia* are capable of causing human disease; the most important of these are *B. microti* in the northeastern and Midwestern United States and *B. divergens* in Europe. Lyme-*Babesia* coinfection has been well-established and may result in greater disease severity.(10) Clinical babesiosis is nearly always dominated by fever and characteristic laboratory abnormalities, and the infection can be proved by direct visualization of the parasite on blood smear or detection of its DNA by blood PCR.

Relapsing or persistent infection can occur in immunocompromised patients, particularly those with lymphoma who are asplenic and received treatment with rituximab. Persistent babesiosis produces the same clinical and laboratory abnormalities that are seen in acute babesiosis, and patients remain both PCR and blood smear positive. In fact, immunocompromised patients who are at risk of persistent or recurrent babesiosis often have higher parasitemias and generally more severe disease. This is the only group of patients for whom there is evidence that a course of anti-babesia drug therapy that exceeds 10 days duration is beneficial.(21) We found no evidence that active babesiosis, as demonstrated by a positive PCR or blood smear, produces purely subjective complaints (e.g., fatigue, pain, cognitive symptoms) that are unaccompanied by fever or by laboratory abnormalities. Asymptomatic blood donors have been the index cases for transfusion-associated babesiosis, so it may be the case that patent infection can actually be subclinical or nonspecific. If PCR negative patients with purely subjective symptoms due to babesiosis exist, there are no published data on whether anti-babesia therapy might be beneficial for them. The current standard of care is to treat only those individuals who can be shown by direct molecular or microscopic testing to have active babesiosis.(46) Seroprevalence to *B. microti* clearly exceeds the incidence of clinically evident infections, suggesting that many individuals experience subclinical and asymptomatic infections. Thus, reliance on serology in the absence of direct demonstration of the organism could lead to erroneously attributing coincident symptoms to active infection.

This is particularly true for *B. duncani*, a pathogen responsible for a small number of human cases in the Pacific northwest. Like other human babesias *B. duncani* produces fever and hemolysis. Among the limited case reports there was no evidence of cryptic infection resulting only in subjective complaints. The high rates of background seropositivity to *B. duncani*, including in supposedly nonendemic areas according to one report, raise the question of whether there are cross-reactive antibodies in the population at large. This underscores the importance of directly demonstrating intraerythrocytic infection when pursuing a diagnosis of active babesiosis. Unlike HGA and babesiosis, which in nature are exclusively transmitted to humans by *Ixodes* spp. ticks, we have found no convincing evidence that this is a natural or even plausible mode of transmission for *Bartonella* spp. Our search yielded no case in which tick-borne bartonellosis was unequivocally established. Not only is tick-borne human bartonellosis unfounded to date, but there is very little literature to support Lyme disease-*Bartonella* coinfection at all, regardless of the means of acquisition. Moreover, appropriate seroepidemiologic studies have not even been attempted in Lyme disease patients in the United States to evaluate the seroprevalence of *B. henselae* in such individuals. While several small case series and reports in the literature purport to describe simultaneous Lyme disease and *Bartonella* infection, in no case did the laboratory corroboration of Lyme disease correspond to established diagnostic standards.

The putative association between ticks, Lyme disease, and *B. henselae* infection is ultimately derived from two problematic sources of data. The first is a limited number reports of mostly European subjects in whom clinical infection with *B. henselae* and *B. quintana* has been temporally associated with a tick bite.(47-49) The second source of data is the observation that many tick specimens contain *Bartonella* DNA when subjected to PCR

analysis.(50-54) This has been demonstrated primarily in the Eurasian ticks *I. ricinus* and *I. persculatus* and to a lesser degree in the North American tick *I. scapularis*. Nonetheless, it should come as no surprise that ticks would contain *Bartonella* DNA – ticks feed on a variety of mammalian hosts that may be reservoirs for *Bartonella* spp. The presence of *Bartonella* DNA in the tick does not prove that the tick is a competent vector for transmission to a second mammalian host. Vector competence of *I. scapularis* ticks for *B. henselae* has never been demonstrated in an animal system.

Conclusion

The *Ixodes* spp. ticks that transmit *B. burgdorferi* are capable vectors of several human pathogens. In all cases, however, these infections produce defined clinical syndromes that are corroborated by objective clinical and laboratory findings. This is true for well-established *Babesia*-Lyme and *Anaplasma*-Lyme coinfections. Treatment and diagnosis of chronic coinfections, however, is clearly not justifiable in the absence of convincing objective evidence that these infections are present and active.

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Clinical Significance

- There is no evidence to support a diagnosis of chronic anaplasmosis in humans
- Persistent or relapsing babesiosis is accompanied by fever and demonstrable parasitemia
- There is little evidence to support tick-borne *Bartonella* infection or *Bartonella*-Lyme coinfection