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Clinical evidence for rapid transmission of Lyme disease following a tickbite☆

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Abstract

Lyme disease transmission to humans by *Ixodes* ticks is thought to require at least 36–48 h of tick attachment. We describe 3 cases in which transmission of *Borrelia burgdorferi*, the spirochetal agent of Lyme disease, appears to have occurred in less than 24 h based on the degree of tick engorgement, clinical signs of acute infection, and immunologic evidence of acute Lyme disease. Health care providers and individuals exposed to ticks should be aware that transmission of Lyme disease may occur more rapidly than animal models suggest. A diagnosis of Lyme disease should not be ruled out based on a short tick attachment time in a subject with clinical evidence of *B. burgdorferi* infection.

Keywords: Lyme disease; *Borrelia burgdorferi*; Transmission; Ticks; Coinfections

1. Introduction

Lyme disease is the most common tickborne illness in the world today (Bacon et al., 2008; Hayes and Piesman, 2003; Stricker and Johnson, 2010, 2011). The disease is caused by the spirochete *Borrelia burgdorferi*, which is transmitted to humans by the bite of an infected *Ixodes* tick (Crippa et al., 2002; Falco et al., 1996; Hügli et al., 2009; Kahl et al., 1998; Piesman and Dolan, 2002; Sood et al., 1997). Based on studies in mice and rabbits, transmission of *B. burgdorferi* is thought to require at least 36–48 h of tick attachment (Piesman et al., 1987, 1991; Piesman, 1993). A review from the Centers for Disease Control and Prevention (CDC) states that "virtually no transmission occurs during the first day" of tick feeding (Schwan and Piesman, 2002), and the Infectious Diseases Society of America (IDSA) states that a tick "typically must be attached to the skin for at least 36 hours" to transmit the Lyme bacteria (IDSA Website). Although *B. burgdorferi* is localized primarily in the midgut of the unfed tick and must migrate to the salivary glands during feeding in order for efficient transmission to occur, studies have shown that unfed ticks have spirochetes in their salivary glands and that transmission can occur earlier than 36 h after attachment (Angelov, 1996; Berger et al., 1995; Crippa et al., 2002; Kahl et al., 1998; Lima et al., 2005; Piesman et al., 2001; Piesman, 1995). Furthermore, coinfection with other tickborne agents such as *Babesia*, *Anaplasma*, and *Ehrlichia* species can hasten the transmission of the Lyme spirochete by decreasing host resistance to the infectious agents (des Vignes et al., 2001; Mather et al., 1990; Piesman et al., 1987; Zeidner et al., 2000).

We describe 3 cases in which transmission of *B. burgdorferi* by nymphal *Ixodes* ticks appears to have occurred in less than 24 h based on the degree of tick engorgement, clinical signs of acute infection, and immunologic evidence of acute Lyme disease. The evidence for rapid transmission of Lyme disease following a tickbite is discussed.

2. Case reports

2.1. Case 1

A 59-year-old woman presented with an attached nymphal tick on her neck. She lived in rural Napa County, CA, and had been well except for thyroid disease and

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hypertension, which were controlled with medication. On the day prior to evaluation, her husband had walked their dogs in the evening, and the dogs then slept in the patient's bed overnight. She awoke with flu-like symptoms and went to work, but her coworkers noticed a dark spot and early rash on her neck and she immediately came to the medical office. Evaluation showed a nymphal *Ixodes* tick that appeared to be partially engorged, as assessed by increased coxal width (Gray et al., 2005). There was surrounding erythema on the patient's neck. The tick was removed with difficulty, and the patient was treated with doxycycline for 3 weeks. Testing done after 2 weeks on the antibiotics showed Lyme IgM/IgG immunofluorescence assay (IFA) negative (<1:40), Lyme Western blot IgM and IgG negative, but *B. duncani* IgM IFA positive. The *Babesia* fluorescent in situ hybridization (FISH) test result was also positive. The CD57 natural killer cell level was 126 cells/μL (normal, 60–360 cells/μL), and the C4a was 3656 ng/mL (normal, less than 2830 ng/mL).

The patient continued to have myalgias and arthralgias after doxycycline was discontinued. Because she was unable to tolerate atovaquone, she was treated with azithromycin and artemisinin for 3 months. Repeat testing 10 weeks after tick exposure showed Lyme IFA weakly positive at 1:40, Lyme Western blot IgM positive, Lyme IgG Western blot negative, *B. duncani* IFA negative, and *Babesia* FISH test negative. Despite treatment with azithromycin and amoxicillin for an additional 3 months, her musculoskeletal symptoms persisted. She also complained of sweats, vasomotor symptoms, and fatigue. Repeat testing showed Lyme IFA negative, Lyme Western blot IgM and IgG negative, *B. duncani* IgM IFA positive, and *Babesia* FISH test positive. She is currently taking mefloquine for her persistent *B. duncani* infection.

2.2. Case 2

A 68-year-old woman was evaluated for a tickbite on her chest. She lived in rural Sonoma County, CA, and she had removed ticks from her dog on the previous afternoon. On the morning of evaluation, she awoke with flu-like symptoms, and while getting dressed she noted a tick attached to her left ribcage under her axilla. She removed the tick with tweezers and brought it to the medical office. Examination revealed a nymphal *Ixodes* tick that appeared to be partially engorged, as assessed by increased coxal width. The tickbite location had a punctum and slight erythema but no "bullseye" rash.

The patient continued to complain of flu-like symptoms, and she was treated with doxycycline for 3 weeks. Testing done 1 week after the tickbite showed Lyme IgM/IgG IFA weakly positive at 1:40, Lyme IgM Western blot positive, and Lyme IgG Western blot negative. Testing for coinfections was negative. The CD57 NK level was 114 cells/μL, and the C4a was 4273 ng/mL. The patient became asymptomatic. Repeat testing 3 months later showed that the Lyme IFA and Lyme IgM and IgG Western blots were negative.

2.3. Case 3

A 57-year-old woman was evaluated for a tick attached to her neck. She was a resident of San Francisco who was a competitive swimmer in excellent health, and she was vacationing at a resort in rural San Diego County, CA. On the morning of her first day at the resort, she went for a hike in the woods and then returned for breakfast. A companion noted a tick attached to her neck, and she was immediately seen by medical personnel at the resort. A nymphal *Ixodes* tick that appeared to be partially engorged (as assessed by increased coxal width) was removed from the nape of the neck with difficulty approximately 4 h after the hike in the woods. There was minimal erythema at the site of the tickbite.

The patient developed flu-like symptoms but no rash. She returned to San Francisco and started doxycycline treatment. Testing performed approximately 3 days after the tickbite showed Lyme IgM Western blot positive, Lyme IgG Western blot negative, and coinfection testing negative. The CD57 NK level was 180 cells/μL, and the C4a level was 8793 ng/mL. She continued doxycycline for 30 days, and her symptoms resolved. Follow-up testing 6 months later showed that the Lyme IFA and Lyme IgM and IgG Western blots were negative.

3. Discussion

The attachment time required for a tick to transmit *B. burgdorferi*, the spirochetal agent of Lyme disease, has important clinical implications. Studies in mice and rabbits suggest that a tick must be attached for at least 36–48 h in order for efficient transmission of *B. burgdorferi* to occur, and these studies have been interpreted to mean that removal of a tick within 36-48 h of attachment will prevent transmission of Lyme disease (IDSA Website; Piesman et al., 1987, 1991; Piesman, 1993; Schwan and Piesman, 2002). The animal transmission studies have several significant limitations, however. First, they were performed using laboratory strains of *B. burgdorferi* such as B31, and these strains may have transmission characteristics that differ from wild-type strains (Labandeira-Rey and Skare, 2001; Purser and Norris, 2000). Second, the studies did not factor in tick coinfections that may enhance the infectivity of the Lyme spirochete (des Vignes et al., 2001; Mather et al., 1990; Piesman et al., 1987; Zeidner et al., 2000). Third, the effect of other transmission factors such as tick saliva and host immunity was not evaluated in these animal models (Horka et al., 2009; Hovius, 2009; Ueti et al., 2009; Zeidner et al., 1997). Thus the transmission times derived from these studies may not apply to the clinical situation in humans and may give a false sense of security about the risk of Lyme disease following a tickbite.

Our 3 cases provide clinical evidence that *B. burgdorferi* may be transmitted within 24 h of a tickbite, and perhaps as

quickly as 4 h after tick attachment (Table 1). In each case, a high-risk activity was documented just prior to the tickbite, and ticks were removed within 24 h of that activity. The ticks were observed to have an increased coxal width and a normal idiosomal length, suggesting that feeding had occurred for less than 24 h (Gray et al., 2005). Infection with *B. burgdorferi* was documented with positive Lyme IgM Western blot testing, and coinfection with *B. duncani* was documented in 1 case. The acute nature of the infection was supported by the normal levels of CD57 NK cells, which are decreased in chronic Lyme disease but remain normal in the acute phase of the illness (Stricker and Winger, 2001; Stricker et al., 2002). The presence of acute infection was also supported clinically by the sudden onset of flu-like symptoms in each patient and the elevated C4a level, which has been noted in acute Lyme disease (Shoemaker et al., 2008). Furthermore, symptomatic improvement with antibiotic therapy in patients 2 and 3 was consistent with a clinical response of acute *B. burgdorferi* infection that had occurred within 24 h of a tickbite.

The delay in transmission of *B. burgdorferi* following tick attachment is thought to be due to the need for spirochetes to migrate from the tick gut to the salivary glands, a process that may take up to 60 h (Piesman et al., 1987, 1991; Piesman, 1993). However, studies have shown that spirochetes are present in the salivary glands of unfed ticks, and these organisms presumably are readily transmissible at the start of tick feeding (Lima et al., 2005; Piesman et al., 2001; Piesman, 1995). Furthermore, European strains of *B. burgdorferi* appear to be transmitted faster than North American strains for reasons that are poorly understood (Crippa et al., 2002; Kahl et al., 1998), and coinfection with other tickborne agents such as *Babesia*, *Anaplasma*, and *Ehrlichia* may enhance transmission of the Lyme spirochete (des Vignes et al., 2001; Mather et al., 1990; Piesman et al., 1987; Zeidner et al., 2000). Immunosuppressive factors in tick saliva may also enhance transmission of *B. burgdorferi*, and the quantity of saliva may influence the virulence of the spirochete (Horka et al., 2009; Hovius, 2009; Ueti et al., 2009). In addition, spirochetes may be found in tick feces following the onset of feeding, and these organisms may be transmissible through contact with the bite site or mucous membranes (Angelov, 1996; Patton et al., 2011). Further study of this mode of *B. burgdorferi* transmission is warranted.

The serologic response to *B. burgdorferi* is of interest in our patients. Patient 1 initially had negative Lyme testing 2 weeks after tick exposure while on antibiotic therapy at a time when testing for *B. duncani* was positive. Her Lyme IgM/IgG IFA and Lyme IgM Western blot subsequently became positive at 10 weeks postexposure. Patient 2 had a positive Lyme IgM/IgG IFA and Lyme IgM Western blot 1 week after tick exposure while on antibiotics, and patient 3 developed a positive Lyme IgM Western blot 3 days postexposure at the start of antibiotic therapy. The IgM response to acute infection or immunization has been documented as early as 3–4 days following exposure to the infectious agent, and this response may persist for weeks depending on the infecting organism and host immunity (Anandarao et al., 2006; Moyron-Quiroz et al., 2009; Racine and Winslow, 2009). The IgM response of our patients to acute *B. burgdorferi* infection is consistent with this time frame, and coinfection with *Babesia* in Patient 1 may have extended the immune response. Although coinfection may alter the host cytokine response to *B. burgdorferi* exposure in mice (Zeidner et al., 2000), to our knowledge, the effect of coinfection on the pattern of antibody response to tickborne agents has not been investigated.

Treatment of Lyme disease remains a controversial topic (Stricker and Johnson, 2010, 2011), and the clinical course in our patients is instructive. Patients 2 and 3 had no evidence of tickborne coinfections, and they were promptly treated with doxycycline for 3–4 weeks and recovered completely. In contrast, patient 1 had evidence of coinfection with *B. duncani*, and although she received prompt treatment for *B. burgdorferi* she remained symptomatic. Because she was unable to tolerate the standard *Babesia* regimen, she received an alternative regimen that failed, and she required further treatment for persistent babesiosis. Although *Babesia* infection was originally described as a fulminant illness in immunocompromised patients, more recent studies suggest that the organism may induce a chronic infection requiring extended treatment (Allred, 2003; Barbet, 2009; Krause et al., 1998). The clinical course in patient 1 underscores the importance of testing for tickborne coinfections in patients who fail to respond to standard treatment for Lyme disease.

Table 1
Patient characteristics

Patient (age/sex)	Location where bite occurred	Location on body	Duration of tick attachment (h)	Lyme IFA	Lyme Western blot		CD57 NK cells* (cells/μL)	C4a (ng/mL)**	Coinfection
					IgM	IgG			
1 (59/F)	Napa, CA	Neck	<12	Weak +	+	−	126	3656	*B. duncani*
2 (68/F)	Sonoma, CA	Chest	<12	Weak +	+	−	114	4273	None
3 (57/F)	San Diego County, CA	Neck	<4	ND	+	−	180	8793	None

IFA = Immunofluorescence assay; ND = not done.
* Normal range, 60–360 cells/μL.
** Normal, <2830 ng/mL.

In conclusion, caution should be exercised in ruling out Lyme disease based on a tick attachment time of less than 2 days in a symptomatic patient. Health care providers and individuals exposed to ticks should be aware that transmission of *B. burgdorferi* to humans in the clinical setting may occur more rapidly than animal models suggest.

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