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Bartonella Henselae Infection

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Abstract *Bartonella henselae* infection is a zoonosis found worldwide. Clinical manifestations of *B. henselae* infection occur on a wide spectrum from typical or classical cat scratch disease (CSD), with regional lymphadenopathy, to atypical or systemic complications. Atypical *B. henselae* infections include: neuroretinitis, Par inaud's oculoglandular syndrome, hepatosplenic granuloma, and fever of unknown origin. *B. henselae infection* is not a rare disease in Japan. Performing an indirect fluorescent antibody assay (IFA) to detect antibodies against *Bartonella* species may provide a prompt diagnosis of *Bartonella* infection and facilitate appropriate antibiotic therapy.

Key words: *Bartonella*, cat scratch disease, clinical manifestations

Introduction

Bartonella henselae infection is a worldwide zoonosis, although its prevalence and impact differs among different geographical areas. It is associated with a variety of clinical manifestations.[1] The author briefly reviews here the clinical manifestations of *B. henselae* infection.

Bartonella species

Bartonella are small, curved, pleomorphic, gram-negative bacilli which are found in cats and dogs around the world. A characteristic feature of *Bartonella* is their adherence to and invasion of erythrocytes. *Bartonella* infection stimulates neurovascular proliferation in tissues by causing endothelial-cell proliferation and migration. To date, 21 different species of *Bartonella* have been identified and of these, seven have been implicated in human disease (Table 1).

Epidemiology of *B. henselae* infection

The epidemiological and clinical characteristics of *B. henselae* infection have been well delineated in countries other than Japan.[2,3] Since epidemiological and clinical studies of *B. henselae* infection have been limited in this country, we reviewed cat scratch disease (CSD) cases, the representative of *B. henselae* infections.[4]

The literature reviewed, including those involving our own 110 cases, revealed that a total of 561 patients with CSD have been reported since 1953 in Japan. The seasonal distribution of CSD in Japan was found to peak in the fall and the winter, and to occur in all ages and both genders. Most reported CSD cases were associated with exposure to a cat infected with *B. henselae*. However, CSD was also reported to have been caused by contact with a dog,[5] and a hamster, cat fleas, and human scratches have also been reported.[4] These findings suggest the possible contribution of CSD from pets other than cats. Given that dogs or other pets might also be implicated in the reservoir of *B. henselae*, the name of "cat scratch disease" may lead to misunderstandings that only cats carry *B. henselae*. Therefore it is suggested that name of *Bartonella henselae* infection, instead of CSD,

Table 1 *Bartonella* species

Human pathogens (7)	
B. henselae	Cat scratch disease Endocarditis Bacillary angiomatosis
B. quintana	Trench fever Endocarditis Bacillary angiomatosis
B. elizabethae	Cat scratch disease Endocarditis
B. bacilliformis	Carrion's disease (Oroya fever, verruga peruana)
B. clarridgeae	Cat scratch disease
B. grahamii	Neuroretinitis
B. vinsonii spp. Vinsonii	Endocarditis
Non-human pathogens (14)	
B. alsatica, B. birtlesii, B. bovis, B. capreoli, B. doshiae, B. koehlerae, B. peromysci, B. schoenbuchii, B. talpae, B. taylorii, B. Tribocorum, B. vinsonii spp. arupensis, B. vinsonii spp. berkhoffii, B. washoensis	

would be more appropriate for better understanding.

A review of literature found that CSD is not rare in Japan, and that the number of reported cases of CSD has been increasing since1995. This may be due to the following two possible explanations. First, serological diagnosis using the IFA method was introduced in 1995 in Japan, resulting in increased diagnosis of CSD cases. Fifty-five percent cases of all cases were reported after 1995. Before 1995, clinical diagnosis fulfilling three of the four criteria for CSD was difficult because skin test solution was not readily available, and biopsy of lymphadenopathy, a painful and invasive procedure, was difficult to perform. In addition, it was difficult to diagnose a case of CSD lacking lymphadenophathy without a reliable diagnostic test. The development of an IFA test for detection of antibodies against *Bartonella* species has greatly enhanced serological diagnosis. Second, physicians became more aware of CSD with the increased number of case reports. There are an estimated 24,000 cases of CSD annually in the USA.[1] Our recent retrospective population-based survey, in a city with population-size of 110,000, revealed that at least 10,000 individuals yearly were estimated to be infected with CSD.[4] According to a survey conducted by the Prime Minister's Office in Japan in 2000, over 10% of the Japanese population have a cat as a pet, while over 23% have a dog. A prospective population-based surveillance would be necessary to characterize the epidemiology of CSD in Japan.

Serological and molecular diagnosis

The diagnosis of *B. henselae* infections is made based on the clinical features, serological or molecular studies. We developed a IFA method to measure antibodies to *B. henselae* in 1998.[6] Briefly, serum samples were analyzed by IFA for IgM and IgG antibodies to *B. henselae* ATCC 49882. *B. henselae*, grown on rabbit blood agar based on the heart infusion medium (BBL, Becton Dickinson, Cockeysville, USA) for seven days at 35℃, was prepared for the detection of IgM antibodies to *B. henselae*. In addition, the cultivated *B. henselae* was co-cultivated with Vero cells for three days at 35 ℃ in an atmosphere containing 5% CO_2 for the detection of IgG antibodies to *B. henselae*. A serological diagnosis using IFA was made on the basis of the patient having elevated titers of either immunogloblin M (IgM)(≧1:20) or immunogloblin G (IgG) (≧1:256) antibodies or having a fourfold rise in the IgG titer between their acute-phase and convalescent-phase sera. The sensitivity and specificity of our IFA method were 87% and 97.7%, respectively.

PCR analysis is performed by using peripheral blood cells, cerebrospinal fluid, bio-

psied materials, and buccal swab of a cat or a dog.[5)7)] Performing an IFA test and/or a PCR method on blood and examining aspirated or biopsies materials to detect *Bartonella* species may provide a prompt diagnosis of CSD, both typical and atypical, and facilitate appropriate therapy.

Clinical manifestations

Bartonella henselae infection is associated with a variety of clinical manifestations.[1)]

Typical *B. henselae* infection

Cat-scratch disease (CSD) is a representative of typical *B. henselae* infection. Immunocompetent individuals tend to develop the CSD presenting with regional lymphadenopathy at the site of scratch injury, a short period of self-limiting fever, and general symptoms. The lymph node swellings are noted in the axillary, neck, elbow or upper arm, inguinal, submandibular, pre- or post auricular, clavicular, thigh, occipital, hilar, and other areas. The fever of CSD is usually absent or lasts a few days. General symptoms include chills, headache, malaise, loss of appetite, nausea, abdominal pain, diarrhea, and arthralgia.

Atypical *B. henselae* infection

Atypical *B. henselae* infections are defined as those with prolonged fever (≧ 37.5 ℃, for more than 7 days), or with systemic complication, or without lymphadenopathy. Immunocompromized individuals tend to follow an atypical course characterized by prolonged fever and various systemic complications with or without lymphadenopathy. Atypical *B. henselae* infections are prevalent in 13-15% of the reported cases. These include neuroretinitis, Parinaud's oculoglandular syndrome, hepatosplenic granuloma, fever of unknown origin, encephalopathy, paresthesia, facial nerve palsy, idiopathic thrombocytopenic purpura, leukemoid reaction, acute progressive glomerulonephritis, chronic (autoimmune) fatigue syndrome, chronic polyarthritis, an association of non-Hodgkin's disease, and juvenile rheumatoid arthritis. Chronic inflammatory diseases or cancer of unknown etiology could result from various microbial agents through the eliciting of an autoimmune response. Further research is necessary to determine the role of *B. henselae* in the pathogenesis of chronic inflammatory disease or cancer. *B. henselae* infection should be considered in the initial evaluation of a fever of unknown origin (FUO). Jacobs and Schutze[8)] explained that *B. henselae* infection was the third most common infectious disease among children with FUO. Our study also confirmed that the duration of fever was significantly associated with both the absence of lymphadenopathy and the presence of complications.[9)] Patients suffering from *B. henselae* infection without lymphadenopathy or with complication tend to have prolonged fever.[10)] Conversely, when patients have prolonged FUO, the possibility of *B. henselae* infection should be considered, and a search for underlying systemic complications is recommended for prompt diagnosis and appropriate treatment.

Treatment

Though *B. henselae* infection is self-limiting and symptoms subside spontaneously within 6-12 weeks, antibiotic therapy is recommended to eradicate *B. henselae* and to prevent systemic dissemination after diagnosis. *Bartonella* species are sensitive to erythromycin, azithromycin, doxycycline, rifampicin, and minocycline. Since prompt diagnosis and antibiotic therapy may prevent systemic complications, physicians need to inquire about recent contact and injury caused by animals when a patient presents with FUO.

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