

ORIGINAL ARTICLE

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Cat scratch disease: analysis of 130 seropositive cases

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Abstract To clarify the clinical manifestations of cat scratch disease (CSD), we evaluated a total of 130 seropositive patients with CSD. The patients' ages ranged from 1 to 68 years; 103 (79.2%) were under 18 years of age. CSD occurred predominantly in the fall and winter months. Regional lymphadenopathy was noted in 110 (84.6%) of the cases, and the most common sites were the neck (33%), axillary (27%), and inguinal (18%) regions. One hundred of the patients (77%) had general symptoms, such as fever, headache, and malaise. The clinical manifestations of CSD showed a wide spectrum from typical or classical CSD, with regional lymphadenopathy, to atypical or systemic CSD. Of the 130 cases, 103 (79.2%) were typical CSD and 27 (20.8%) were atypical CSD. Atypical cases of CSD were commonly reported as fever of unknown origin (37.0%), neuroretinitis (22.2%), encephalopathy (14.8%), hepatosplenic granuloma (11.1%), and Parinaud's oculoglandular syndrome (7.4%). Fever of unknown origin or prolonged fever lasting more than 14 days was evident in 27 (20.8%) of the 130 cases in this study. Eleven of the 27 cases lacked lymphadenopathy. Our findings suggest that CSD is not a rare disease in Japan. The indirect fluorescent antibody (IFA) test to detect *Bartonella* species may provide a prompt diagnosis of CSD and facilitate appropriate therapy.

Key words Cat scratch disease · *Bartonella henselae* infection · Indirect fluorescent antibody (IFA)

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Introduction

Cat scratch disease (CSD), caused by *Bartonella henselae*, is a worldwide zoonosis that is associated with a variety of clinical manifestations.¹ The epidemiological and clinical characteristics of CSD have been well delineated in countries other than Japan.²⁻⁶ However, epidemiological and clinical study of CSD in Japan has been limited. We report here 130 cases of CSD with serological diagnosis.

Materials and methods

Case ascertainment

Between May 1, 1997, and March 31, 2002, a total of 393 patients (287 children and 106 adults) suspected of having CSD because of lymphadenopathy or fever of unknown origin, as well as pet ownership, were referred to Yamaguchi University for serological and molecular studies. Blood samples and/or biopsied specimens from 84 hospitals located in the central and southwestern areas of Japan were included in this study. Referred patients also were accepted from pediatricians, physicians, surgeons, orthopedists, otolaryngologists, ophthalmologists, dentists, radiologists, plastic surgeons, and pathologists. The referring doctors were requested to provide the following patient information: age; sex; history of contact (scratch, bite, or touch) with a cat, dog, or other animal; clinical signs and symptoms; laboratory values, physical findings; and diagnostic procedures (Table 1).

Serological study

Serum from each of the referred patients was tested for antibodies to *B. henselae* by the indirect fluorescent-antibody (IFA) method.^{7,8} The specificity and sensitivity of the IFA method were 100% and 62%, respectively. Serological cross-reactions among *Bartonella henselae*, *Bartonella*

Table 1. Summary of clinical findings in 130 seropositive cases

Features	No. (%)
Age	
Child	103 (79.2)
Adult	27 (20.8)
Sex	
Male	60 (46.2)
Female	70 (53.8)
History of contact with animal	
Cat	120 (92.3)
History of trauma by a cat	88/120 (73.3)
Dog only	3 (2.3)
General symptoms	100 (76.9)
Fever	93 (71.5)
Lymphadenopathy	110 (84.6)
Occipital	2 (1.8)
Neck	36 (32.7)
Pre- or postauricular	7 (6.4)
Submandibular	17 (15.5)
Axillary	30 (27.3)
Clavicular	3 (2.7)
Elbow or upper arm	7 (6.4)
Intraabdominal	1 (0.9)
Inguinal	20 (18.2)
Thigh	2 (1.8)

quintana, other *Bartonella* species, *Chlamydia pneumoniae*, and *Coxiella burnetii* have been described.⁹⁻¹² A serological diagnosis, using IFA, was made on the basis of either evaluated titers of immunoglobulin M (IgM) ($\geq 1:20$) antibodies or immunoglobulin G (IgG) ($\geq 1:256$) antibodies, or the presence of a fourfold rise in the serum IgG titer between the acute phase and the convalescent phase.

Results

One hundred thirty (33.1%) of the 393 patients had positive titers of antibody to *B. henselae*. The epidemiological and clinical manifestations of the 130 positive-IFA cases were further analyzed.

Table 1 summarizes the clinical findings of the 130 positive-IFA referred cases. The patients' ages ranged from 1 to 68 years (mean, 16.0 years); 103 (79.2%) were under 18 years of age. There were 60 males (49 children, 11 adults) and 70 females (54 children, 16 adults). Familial occurrence was observed in 3 (2.3%; 2 families) of the 130 cases. One hundred twenty patients (92.3%) had a previous history of contact with a cat, and 3 (2.3%) had a history of contact only with a dog. The patient reportedly was scratched, bitten, or both scratched and bitten in 88 (73.3%) of the 120 positive-IFA patients who had contact with a cat. Of the 88 cases, the dates of injury by the cat were obtained in 26 cases (29.5%). The mean duration of the onset of CSD after injury was 37.7 days (range, 4 to 180 days; less than 1 week in 4 cases, from 1 week to 1 month in 7 cases, from 1 month to 3 months in 13 cases, and more than 3 months in 2 cases). One case (0.7%) was caused by cat flea bites. The prevalence of CSD was highest in the fall and winter and lowest in the spring (Fig. 1).

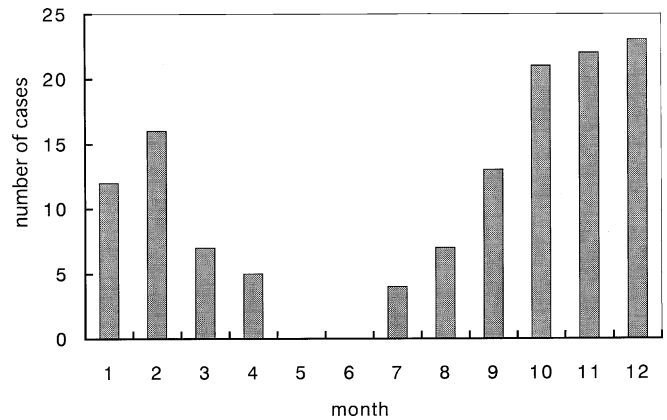


Fig. 1. Number of reported cases by month. CSD predominantly occurred in the fall and winter months

One hundred ten (84.6%) of the 130 patients developed lymphadenopathy within 2 to 240 days after being touched or injured by a cat or a dog. The most common sites of swollen lymph nodes were the neck (36 cases), followed by the axilla (30 cases), the inguinal region (20 cases), the submandibular region (17 cases), the pre- or postauricular region (7 cases), the elbow or upper arm (7 cases), the clavicular region (3 cases), the occipital region (2 cases), the thigh (2 cases), and the intraabdominal region (1 case). The lymph nodes were swollen, tender, or painful in 81 (73.6%) of the 110 patients in whom lymphadenopathy developed.

Of the 130 patients, 100 (76.9%) had general symptoms, including fever, fatigue, headache, edema, and convulsion. Fever was the most common symptom reported, occurring in 93 (71.5%) of the cases.

The mean reported duration of fever was 9.8 days (range, 1 to 40 days), with a maximum temperature of 41°C. Table 2 summarizes the association of lymphadenopathy with duration of fever in the 130 cases. The fever lasted for 1 to 6 days in 48 cases, 7 to 13 days in 18 cases, and more than 14 days in 27 cases. Eleven of the 27 patients (10 children and 1 adult) did not have lymphadenopathy. Two patients who had neither lymphadenopathy nor fever had neuroretinitis. Other clinical symptoms were fatigue (38 cases), headache (20 cases), edema (4 cases), convulsions (4 cases), and abdominal pain (1 case).

One hundred three patients (79.2%) had typical clinical features of CSD, with regional lymphadenopathy and general symptoms. Atypical CSD was found in 27 patients (20.8%). Twenty-one of the atypical CSD cases (77.8%) were pediatric cases. The 27 cases of atypical CSD included fever of unknown origin (10 cases), neuroretinitis (6 cases), encephalopathy (4 cases), hepatosplenic granuloma (3 cases), Parinaud's oculoglandular syndrome (2 cases), facial nerve palsy (1 case), and juvenile rheumatoid arthritis (1 case). Twenty of the atypical CSD cases (74.0%) were not accompanied by lymphadenopathy. It is noteworthy that 10 patients (all children) with fever of unknown origin had no lymph node swelling, even though they had fever for 7 to 24 days.

Table 2. Association of lymphadenopathy with duration of fever in 130 seropositive cases

Features	Duration of fever (days)				Total
	No fever	1–6	7–13	≥14	
Lymphadenopathy	35	47	12	16	110
No lymphadenopathy	2 ^a	1	6	11	20
Total	37	48	18	27	130

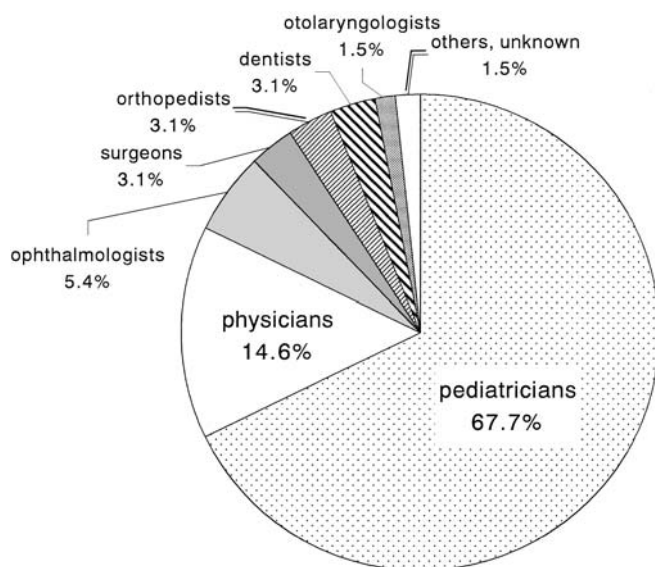
^aNeuroretinitis**Fig. 2.** Specialties of referring doctors

Figure 2 shows the specialty of the referring doctors. The reported specialists in descending order were pediatricians, physicians, ophthalmologists, surgeons, orthopedists, dentists, and otolaryngologists. Pediatricians and physicians referred 82.3% of the patients.

Discussion

In this study, a total of 130 positive-IFA cases with CSD were evaluated. The seasonal distribution of CSD was found to peak in the fall and the winter. CSD was found to occur in persons of all ages and both sexes. Significantly more persons under 18 years of age (79.2%) had CSD than adults. This finding may reflect selection bias on the part of pediatricians toward their patient population.

Most CSD cases were associated with exposure to a cat infected with *B. henselae*. However, CSD caused by contact with a dog and with cat fleas was also reported. These findings suggest that CSD may be acquired from pets other than cats.^{13–19}

The clinical manifestations identified in the 130 CSD cases were similar to those reported in countries other than Japan. Regional lymphadenopathy, the most common clinical feature of CSD, was noted in 84.6% of the 130 cases. A

broad range of clinical manifestations of CSD, from typical or classical CSD with regional lymphadenopathy to atypical, systemic, or disseminated CSD, was found among the patients in this study. Typical or classical CSD was occurred in 79.2% of the cases. The incidence of atypical CSD, which was noted in 20.8% of our patients, was higher than that previously described.^{1,2,20} The manifestations of atypical CSD, in descending order of frequency, were fever of unknown origin, neuroretinitis, encephalopathy, hepatosplenic granuloma, Parinaud's oculoglandular syndrome, facial nerve palsy, and juvenile rheumatoid arthritis. It should be emphasized that a fever of unknown origin or prolonged fever lasting more than 14 days was found in 27 (20.8%) of the 130 cases, and 11 of the 27 cases lacked lymphadenopathy. These findings support previous studies, which have shown that *B. henselae* infection was the third most common cause, accounting for 4.8% of the cases, among patients with fever of unknown origin.²¹ The fact that bacteremia is not rare in immunocompetent healthy individuals with CSD may also indicate a higher rate of systemic involvement.²² The *Bartonella*-host interactions causing at one end typical or classical CSD and at the other end atypical or systemic CSD remain unknown. Further investigation will be necessary to clarify the situation. It is interesting to note that a case of CSD was associated with juvenile rheumatoid arthritis.²³ Chronic polyarthritis,²⁴ chronic (autoimmune) fatigue syndrome,²⁵ and non-Hodgkin's disease¹⁷ also have been reported in Japan. Chronic inflammatory diseases or cancer of unknown etiology could result from various microbial agents through the elicitation of an autoimmune response.²⁶ Further research is necessary to determine the role of *B. henselae* in the pathogenesis of chronic inflammatory disease or cancer.

To our knowledge, a total of 618 cases of CSD, 130 in our study and 488 from 260 publications, have been reported in Japan since the first description of CSD in 1953.²⁷ The number of reported cases of CSD in Japan has been increasing (Fig. 3). This may be due to one of the following two explanations. First, serological diagnosis was introduced in 1995 in Japan, resulting in an increase in the number of CSD cases diagnosed. Fifty-nine percent of all cases were reported after 1995. Before 1995, clinical diagnosis fulfilling three of the four criteria for CSD²⁸ 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 lymphadenopathy 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 24000 cases of CSD annually in the United States.²⁹ Our recent retrospective population-based survey in a city with a population of 110000 revealed that at least 10000 people were estimated to be infected with CSD yearly. According to a survey conducted by the Prime Minister's Office in Japan in 2000, more than 10% of the population own a cat and more than 23% own a dog. A prospective population-based surveillance would be

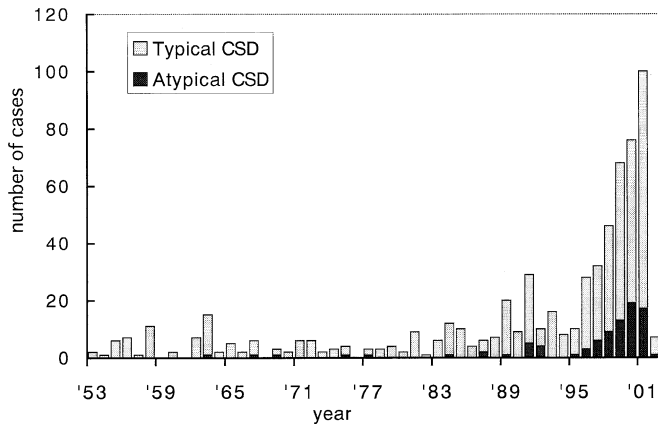


Fig. 3. Number of reported cases of CSD. Fifty-nine percent of the cases were reported after serological diagnosis was introduced in 1995, and atypical CSD cases have been increasing

necessary to characterize the epidemiology of CSD in Japan.

In conclusion, our study found that CSD is not rare in healthy individuals. Physicians need to inquire about recent contact with and injury from animals when a patient presents with or without lymphadenopathy. Performing the IFA test and/or a polymerase chain reaction (PCR) on blood and examining aspirated or biopsied material to detect *Bartonella* species may provide a prompt diagnosis of CSD, both classical and atypical, and facilitate appropriate therapy.

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