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A PROSPECTIVE STUDY OF CAT-SCRATCH DISEASE IN LIMA-PERU

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SUMMARY

Cat-Scratch Disease (CSD) is a benign lymphadenitis that may progress to severe or recurrent forms, and it is occasionally associated with morbidity. Between January of 1998 and March of 1999, forty-three suspected CSD patients were assessed in the Hospital Cayetano Heredia and the Instituto de Salud del Niño, in Lima, Peru. Twelve patients had a confirmed diagnosis, 8 of whom were women, and the mean age was 10 years old. The majority (53%) of the cases were encountered in the summer. All patients reported having had contact with cats. Fever, malaise, lymphadenopathy and skin lesions were the most frequent clinical features. Twelve patients had indirect immunofluorescence antibody test titers of between 1/50 and 1/800 for *Bartonella henselae* and *Bartonella clarridgeiae*. Two lymph node biopsies were histologically compatible with CSD. No positive blood cultures could be obtained. This is the first Peruvian prospective study able to identify *B. henselae* and *B. clarridgeiae* in pediatric patients.

KEYWORDS: Cat-scratch disease; *Bartonella*; Emerging diseases.

INTRODUCTION

Cat-Scratch disease (CSD) was first described as a clinical entity in 1931 and since 1950 many case reports have been published with reference to, but without characterization of an etiological agent[8,36]. The association between *B. henselae* and CSD was first made by REGNERY *et al.* in 1992 in a study demonstrating that sera from CSD patients reacted with antigen prepared from the bacterium[28,29]. Subsequently *B. henselae* was recovered from lymph nodes of CSD patients and patients with Bacillary Angiomatosis[34,36]. In 1997, *B. clarridgeiae* was also implicated in the syndrome[18]. Both species, together with a third, *B. koehlerae* (which has yet to be implicated in human disease) have been consistently isolated from the blood of a significant proportion of domestic, feral, stray and wild cats worldwide[6,7,14].

CSD usually manifests as a benign lymphadenitis but may progress to a severe, systemic or recurrent form producing Parinaud's Oculoglandular Syndrome, encephalopathy, convulsions, osteomyelitis, retinitis, arthritis, hepatitis, splenitis, mediastinal masses, erythema nodosum, and pleurisy[2,9,18,30]. CSD is considered as a common infection, and it is occasionally associated to morbidity[11,20,23,32,33]. This condition usually occurs in children and young adults. 80% of patients are younger than 21 years[9,16,20,32]. Clinical manifestations in an immunocompetent host appear approximately two weeks after inoculation (range, 3 to 50 days), and lymphadenopathy is present in more than 90% of the cases. Axillary, cervical, or submaxilar lymph nodes groups are the most commonly involved[9]. Approximately one third of the patients will present a history of fever and tiredness that can persist for a long period of time[20,32]. Lymphadenopathy gradually resolves, but sometimes it may take some months, and in few cases it can be prolonged for as long as 12 to 24 months[2,9]. Epidemiological investigations have revealed that a history of contact with cats is found in 90% of CSD patients and the antecedent of a cat scratch or bite is found in 60% of the patients[9,26,32]. In cats the prevalence of *Bartonella* bacteremia ranges between 15% to 44% in different states of U.S.A[9,10,17,33], where *B. henselae*[17] and *B. clarridgeiae*[10,18] were found; however both species can coexist[10]. Infected cats usually show no signs of illness and, as laboratory studies have shown that infection can be transmitted from one animal to another via fleas, cats are considered as reservoirs for the bacteria[12,17]. TSUKAHARA *et al*.[35] have also suggested that domestic dogs constitute a reservoir of *B. henselae* after this bacterium was detected in peripheral blood, oral swabs and nail clippings using a polymerase chain reaction (PCR)-based method.

Attempts to isolate *Bartonella* species from CSD patients are frequently unsuccessful[2,4,8,13,19]. Usually, samples are inoculated onto rabbit or sheep blood agar and maintained at 35 ºC to 37 ºC during three or more weeks in an atmosphere with 5% CO_2[19,25]. Recovered bacteria are small and coco-bacilliform[19,20]. Due to the frequent failure of culture-based methods, diagnosis often relies of histopathological examination of biopsy material in which organisms may be visualized using Hematoxyline-Eosine (H-E) and Warthin-Starry (W-S) staining methods[3,25,30]. A variety of serological assays have also been described, including an indirect immunofluorescence antibody test (IFAT) for diagnosing CSD and Bacillary Angiomatosis with 84% sensitivity and

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96% specificity[20,21,25]. However, cross-reactions with *Chlamydia psittaci* and other *Bartonella sp*. have been reported[24]. Nonetheless, detection of IgM using IFAT is considered as the first step for the serology diagnosis, with sensitivity comparable with PCR-based tests[5], although in some patients, antibody titers may never reach the detection threshold[5,20]. Detection of *Bartonella* DNA in infected material also serves as a cornerstone of CSD diagnosis, with a number of different assays being described. All appear to perform well, with sensitivity between 86 and 100% depending on the diagnostic criteria chosen[5].

In 1996, the first probable case of non-bacilliformis *Bartonella* infection was described in Peru following a histopathological diagnosis of Bacillary Angiomatosis[3]. In 1999, a retrospective pathological study reported 13 cases of CSD[31]. However, CSD has not yet been described in a prospective study considering epidemiological and clinical characteristics of patients, as well as using serological and microbiological diagnosis methods. The objective of the study was to know the clinical and epidemic manifestations and possible methods for diagnosing CSD in Lima, Peru.

MATERIALS AND METHODS

Patients: Patients were recruited to the study between January of 1998 and March of 1999, in Hospital Nacional Cayetano Heredia (Pediatrics Ward and Transmissible and Dermatology Diseases Department), and Instituto de Salud del Niño (Infectious Diseases Service) in Lima-Peru, with the previous informed consent by parents or attorneys. Patients were suspected of having CSD when fulfilling the following criteria: a history of being scratched or bitten by cats and lymphadenopathy, without another attributable cause, associated with fever, malaise, or other general symptoms, with or without clinical evolution to either encephalitis, retinitis, neuropathy, Parinaud's oculoglandular syndrome, erythema nodosum, osteomyelitis, arthritis, hepatitis, splenitis, mediastinal mass or pleurisy. Patients completed a standard questionnaire and a whole blood, serum and/or a lymph node biopsy was or were collected from each of them when they have been incorporated to the study. Diagnosis was confirmed on the basis of either (i) isolation of *Bartonella* species, (ii) histopathology or (iii) a positive serology to *B. henselae* and/or *B. clarridgeiae.*

Culture of Bartonella species: Whole blood samples were collected into Vacutainer® tubes with ethylendyamintetraacetic acid (EDTA). These were refrigerated at –70 ºC for three days, then an aliquot was inoculated onto Potato Agar and Columbia agar (Difco®) containing 5% fresh sheep or rabbit blood. Plates were incubated at 37 ºC in 5% of $C0_2$ (BBL® Gas Pack CO_2 Pouch System bags) for up to four weeks. If no colonies were observed after this period, plates were discarded and samples considered negative.

Antibody estimations: Serum samples were processed using an in-house IFAT developed and evaluated in the Unité des Rickettsies, Faculté de Médecine, Université de la Mediterranée, France. Agar-grown control bacteria were inoculated into Vero cells, which were harvested and used as antigen. Serum specimen have been fixed on slides with acetone, and diluted in phosphate-buffered saline (pH 6.8). Starting at a 1/25 dilution, a titer of 1/50 is considered the cut-off point; among patients with antibody titers ≥ 1/50, 62.5% definitely or possibly had CSD; among patients with titers ≥ 1/100, 68.2% definitely or possibly had CSD[27].

Histological assessments: Cervical lymph node biopsies were stained with H-E coloration in the Pathology Laboratory of Cayetano Heredia National Hospital (HNCH) and the Instituto de Salud del Niño. W-S coloration was developed only in the HNCH.

Skin tests for CSD: Skin tests for CSD are not available in Peru.

RESULTS

Forty-seven patients with clinical suspicion of CSD were initially included in the study. Of these, two had an eventual histopathological diagnosis of lymph node tuberculosis, one had a microbiological diagnosis of atypical mycobacterial infection and one was diagnosed with lymphoma; all four of these patients were therefore excluded from the study, and their data were neither analyzed nor presented in any of the tables. In the remaining patients, no other diseases could be confirmed during the study or thereafter.

Serum were obtained from 21 suspected CSD patients (Table 1); only one blood sample could be obtained at the moment of the first evaluation. Nine patients had negative titers, four possessed an IgG and IgM titer of 1/50 for *B. henselae*, four patients possessed an IgG titer of 1/100 and IgM titers of between 1/25 and 1/50 for *B. henselae*, three patients possessed an IgG titer of 1/200 to *B. henselae* and an IgG of 1/100 for *B. clarridgeae*, one patient possessed an IgG titer of 1/800 for *B. henselae* and 1/800 for *B. clarridgeiae*. All patients had negative IFAT titers for *B. quintana* and *B. bacilliformis*.

Nine lymph node biopsies were obtained from nine suspected CSD patients, but one case of tuberculosis, one case of *M. kansasii*, and a case of lymphoma were excluded from the study. One sample obtained in the Instituto de Salud del Niño and two others at the HNCH (with W-S coloration) were reported as CSD (Fig. 1), while other three samples obtained in the HNCH were reported as lymphadenitis with caseating granulomata negative for acid-fast bacilli without definitive diagnostic (Table 2).

Using by serology and/or pathology confirmation, a definitive diagnostic of CSD was made in 12 patients. The range of patients ages was between 3 and 30 years old (mean age, 10 years old), 4 were men (33.3%) and 8 were women (Table 1).

Ten of the 12 patients had contact with kittens, and all of them reported having been bitten or clawed by the animals. Summer was the season where most patients were recruited (Fig. 2), 53.5% (23/43) of the patients were included in the study during summer (between December and February in Peru), and nine of them had a confirmed diagnosis. 83.3% of suspected patients had previously visited a physician and were receiving antibiotics at the time samples were collected for this study.

In all confirmed patients, their illness evolved insidiously and the course of the disease was progressive. The mean duration of symptoms was 38 days (range, 7 to 120 days). Among these patients, the most common symptoms were fever (11/12, 91.6%) and malaise (7/12, 58.3%). The most frequently found clinical signs were a cervical lymphadenopathy (7/12, 58.3%), and a scratch or bite lesion (9/12, 75%) (Table 3). Improvement or cure of the illness occurred between 11 to 120 days (mean, 44.6 days of being ill).

Table 1
Results of diagnosis assays in patients with suspicion of CSD

Patient	Age	Time of illness	Pathology	Serology							
				B.henselae 1		*B.henselae 2*		*B.quintana*		*B.clarridgeiae*	
				IgG	IgM	IgG	IgM	IgG	IgM	IgG	IgM
1	35	7									
2*	28	120	CSD	1/100	1/50	1/100	1/50	1/0	1/0	1/100	1/50
3	22	95									
4	19	7		1/0	1/0	1/0	1/0	1/0	1/0	1/0	1/0
5*	6	26	CSD	1/50	1/0	1/50	1/0	1/0	1/0	1/50	1/0
6*	13	20		1/50	1/0	1/50	1/0	1/0	1/0	1/50	1/0
7	20	20									
8	19	90		1/0	1/0	1/0	1/0	1/0	1/0	1/0	1/0
9	16	90									
10	6	7									
11	11	10		1/0	1/0	1/0	1/0	1/0	1/0	1/0	1/0
12	18	365									
13	15	21									
14	9	30									
15	4	27		1/0	1/0	1/0	1/0	1/0	1/0	1/0	1/0
16	7	20									
17*	6	25		1/50	1/0	1/50	1/0	1/0	1/0	1/0	1/0
18*	12	30		1/100	1/25	1/0	1/0	1/100	1/25	1/100	1/25
19	9	30									
20*	3	60		1/800	1/50	1/800	1/50	1/400	1/0	1/800	1/50
21	7	30		1/0	1/0	1/0	1/0	1/0	1/0	1/0	1/0
22	9	365		1/0	1/0	1/0	1/0	1/0	1/0	1/0	1/0
23	10	14									
24*	10	90		1/100	1/50	1/100	1/50	1/0	1/0	1/50	1/50
25*	12	60	CSD	1/100	1/25	1/0	1/0	1/100	1/25	1/100	1/25
26	5	20									
27	21	30									
28*	11	20		1/200	1/0	1/200	1/0	1/0	1/0	1/100	1/0
29	6	60									
30	4	45									
31*	30	60		1/200	1/0	1/200	1/0	1/0	1/0	1/100	1/0
32	20	14									
33	25	10									
34*	8	14		1/200	1/0	1/200	1/0	1/0	1/0	1/100	1/0
35	19	90		1/0	1/0	1/0	1/0	1/0	1/0	1/0	1/0
36	21	45		1/0	1/0	1/0	1/0	1/0	1/0	1/0	1/0
37*	6	7		1/50	1/0	1/50	1/0	1/0	1/0	1/50	1/0
38	5	90		1/0	1/0	1/0 1/0		1/0	1/0	1/0	1/0
39	18	7									
40	23	60									
41	20	30									
42	14	14									
43	12	14									

(*) patient with definitive diagnostic of CSD

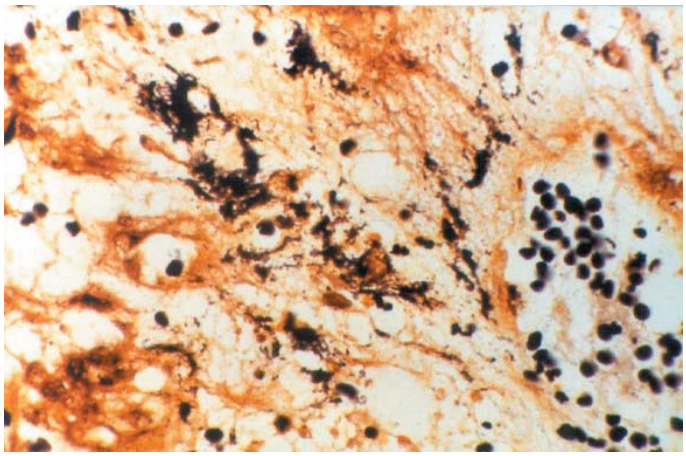

Fig. 1 - Silver-impregnation technique (Warthin-Starry) in a lymph node biopsy showing a conglomerate of black colored *Barthonella* bacillus (40X)

Table 2
Histopathology reports of lymph nodes biopsy

Patient	Histopathologic Reports
2	Fibrous wall defined by histiocytes barrier, granulomatous lymphadenitis, with chronic inflammation and granulation, BAAR negative, suggesting CSD
3	Chronic not casein granulomatous lymphadenitis, BAAR negative
5	Necrosis not casein surrounded by microabscess, W-S suggest CSD
12	Chronic granulomatous lympadenitis, BAAR negative
15	Cortical necrosis, microabscess, BAAR negative
25	Severe hyperplasic follicular lymphoid characterized by germinative centers in way and irregular size severe pericapsular, fibrosis and in a focal and outlying way a reaction chronic inflammatory, BAAR and PAS negative, the possibility of granulomatous lymphadenitis should not be discarded completely; W-S suggest CSD

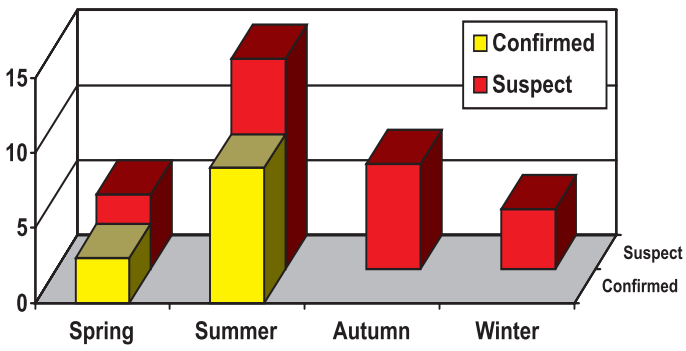

Fig. 2 - Seasonal distribution of patients

Table 3
Clinical characteristics of 12 patients with CSD

Symptoms	Nº	%	Signs	Nº	%
Fever	11	91.6	Lymphadenopathy		
Malaise	07	58.3	Right cervical	05	41.6
Headache	04	33.3	Right axillar	04	33.3
Chills	02	16.6	Left cervical	02	16.6
Hiporexia	02	16.6	Left inguinal	02	16.6
			Right inguinal	02	16.6
			Right epitroclear	01	08.3
			Submaxillary	01	08.3
			Scratch or bite	09	75.0
			Hepatomegaly	01	08.3
			Splenomegaly	01	08.3

Whole blood was collected from all 12 confirmed CSD cases and used for attempted cultivation of *Bartonella* species. No cultures yielded isolates.

In 14 suspected CSD patients a cell blood count was performed and leukocytosis was found with a mean leukocyte count in 12678 cells/µl (range, 7500 to 26000). In 11 patients the hematocrit was in the range between 22% and 43% (mean, 35%). The Erythrocyte Sediment Rate (ESR) of 7 patients was in the range between 12 mm/h and 53 mm/h (mean, 38 mm/h). Toxoplasma and CMV serology studies were performed in all the patients with a confirmed diagnosis.

DISCUSSION

More than 40,000 cases of CSD are annually reported in the USA, resulting in more than 2,000 annual hospitalizations, with a rate of 0.77-0.86/100,000 hospitalizations[12,20,32,37]. It is reported that CSD affects mainly children and young adults with a peak incidence between 2 to 14 years[2,9]. In the present study the average age was 10 years old. Similar results were found by RIVERA[31] in Peru, who found that 69% were younger than 20 years in a retrospective series of 13 patients, and by ABARCA *et al*.[1] in Chile, who found an age range between 6 and 13 years old in a series of 10 patients. In Peru, we do not have information about incidence or morbidity.

Epidemiology studies have determined that CSD is a seasonal illness, affecting the population mainly during autumn and winter, and preferably in regions with warm and humid weather[9,12,37]. In contrast, we found that the majority of patients with suspected (23/43) and confirmed diagnosis (9/12) of CSD were found during summer (Fig. 1), and mainly between December and January (37.77%). This coincides with observations made in our hemisphere proposing as a possible explanation the fact that cats and dogs in our geographical area reproduce mainly between September and November, giving birth to their kittens during Summer[1]. Also, another possible reason is that in our geographical area the season for school vacation is in summer and children spend more time in contact with their pets.

Almost all patients (91.11%) had contact with cats, which coincides with reports indicating that 90% of patients presented this antecedent[8,16];

75.6% of cats were younger than one year, as it was published in the article by CARITHERS[8] who implied kitten in the transmission of the illness. Two of the patients with a definitive diagnosis denied contact with cats but referred contact with dogs, and these animals have been implied as reservoir for *B. henselae*[35].

The clinical features of the disease in patients studied showed that 91.6% had fever. Other frequently reported symptoms were malaise, chills, hyporexia, and headache (Table 3). This clinical presentation is similar with series of cases that described a 59% frequency for fever, 30% with malaise and tiredness, 15% hyporexia, and 14% with headache[8,9,30]. Lymphadenopathy was found in all patients, 58.3% in the cervical region, and 41.6% in the axillary region; an important sign was the lesion due to the cat scratch or bite (Table 2). The range of the duration of illness among patients (mean duration of illness, 44.6 days) was similar to the description by RIVERA[31] in a retrospective study in Peru and by JALIL *et al*.[15] in Argentina.

It is known that 10 to 15% of typical cases feature negative serology studies[24,25,32]. In our series of patients with suspected CSD 9/21 (42.8%) presented negative serology using IFIT. At least in part they may represent false-negative results. This high percentage can be due to the period of illness that had the patients at the time that they were recruited, and there was a delay in obtaining the sample for performing the IFIT, mainly because the diagnosis of CSD is not considered by most physicians. Another possible reason is the limitations of IFIT in comparison to PCR or ELISA[5], the fact that diagnoses titers have not yet been determined in Peru. Additionally, as it is in the case for serotypes Houston and Marseilles of *B. henselae*, perhaps a native serotype could already exist and a specific serotype assay is needed[22]. In addition to possible disadvantages of the IFIT, only a histopathologic confirmation was available during the study. Because cross-reaction has not been demonstrated between *B. henselae* and *B. clarridgeiae*[14,24], the discovery of equal titers for these species may represent coinfection, as has been demonstrated in animals[14]. Unfortunately, we were not able to obtain serum from all 43 patients with clinical suspicion of CSD due to either lack of parental consent for blood sample and difficulties in serum transport; therefore, only 21 serum were processed in a foreign laboratory, allowing 12 serologic confirmations. Additional studies using ELISA or PCR are needed to evaluate the IFIT results.

The histopathologic descriptions during the illness depend on the stage of it. At the beginning a lymphoid hyperplasia with arteriolar proliferation is expected, finally the characteristic description of CSD is a star-shaped conformation with multiple microabscesses will appears, with the particularity of being able to find as much granulomas as microabscesses in a combined fashion; *Bartonella* may be silver stained during the early stages of lymphadenopathy, but not during the later granulomatous stage of inflammation[3,4,25,30,31]. We found histopathological features of CSD in two patients, but most of the findings were described as granulomas negative for acid-fast bacilli. On Fig. 1, a conglomerate of black colored *Bartonella* bacillus are able to be observed with the W-S staining method.

Bartonella are considered organisms with difficult and slow growth in cultures[13,20,23,28]. A sensitivity of 13% for lymph node aspiration and culture compared to 9% in peripheral blood culture has been described[19], as well as that a successful isolation is possible if the sample is collected in an early phase of the illness, since when lymph nodes form abscesses, the likelihood of growth is almost null[2,5,8,23]. Microbiology cultures and subcultures were carried out using EDTA and blood agar under the conditions required for these microorganisms; however, no isolations could be obtained in our blood cultures. In the literature, other diagnostic methods have been demonstrated to be equally or more effective, such as the lysis-centrifugation technique for blood samples, cellular culture media or liquid agar[2,8,25,30]. However, these procedures are more expensive than those used for the present study, and they were not available in our country.

A mean leukocyte count in 12678 cells/µl was found, leukocytosis has already been described by RIVERA[31] and JALIL *et al*.[15] in South America. Additionally, patients possessed mild anemia (mean hematocrit, 33%) and an increase in ESR (mean, 38 mm/h). JALIL *et al.*[15] described the increase in ESR in 57% of the patients in his series. In this respect, it is known that ESR may remain elevated during the first two weeks of illness[16].

RESUMO

Estudo prospectivo da doença da arranhadura do gato em Lima, Peru

A doença da arranhadura do gato é descrita como uma linfadenite benigna que pode progredir para formas recorrentes ou severas, sendo isto ocassionalmente associado com morbidade. Entre janeiro de 1998 e março de 1999, 43 pacientes foram admitidos no Hospital Cayetano Heredia e no Instituto de Salud del Niño, em Lima -Peru. Doze pacientes tiveram o diagnóstico confirmado, sendo 8 mulheres, com uma média de idade de 10 anos. A maioria (53,3%) dos casos foram recrutados no verão. Todos os pacientes relataram ter contato com gatos. Febre, mal-estar, linfadenopatia e lesões cutâneas foram as características mais freqüentes. Doze pacientes tiveram títulos de imunofluorescência indireta (IFI) entre 1/50 e 1/800 para *Bartonella henselae* e *Bartonella clarridgeiae.* Duas biópsias de linfonodos foram descritas como típicas para doença da arranhadura do gato. Nenhuma hemocultura se mostrou positiva. Este é o primeiro estudo peruano prospectivo que foi capaz de identificar *Bartonella henselae* e *Bartonella clarridgeiae* em pacientes pediátricos.

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