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Cat-scratch disease: Experience in a tertiary care children's hospital

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ABSTRACT

Introduction. *Bartonella henselae* is the etiologic agent in cat-scratch disease. It affects children and young adults. The clinical spectrum is wide; the most common clinical presentation is a solitary lymphadenopathy. The objective of this study was to analyze the epidemiology, clinical features, and course of this disease in a tertiary care hospital in Argentina.

Population and methods. Retrospective, descriptive, and observational study conducted at a tertiary care pediatric hospital from January 1st, 2019 to June 30th, 2021. Children aged 0 to 16 years with compatible clinical signs and symptoms and positive serology were included.

Results. A total of 150 patients were included; their mean age was 7.9 years ± 3.68. Of them, 68.7% reported having contact with cats. The most common reason for consultation was the presence of solitary lymphadenopathies (84.7%) in the head and neck. Febrile syndrome without source was the reason for consultation in 15.5% of cases, with a pathological abdominal ultrasound scan in 85.7%. IgM and IgG were positive in 88%. With the result of a positive serology test, 44% received antibiotic treatment. Protracted lymphadenopathy was the main reason for antibiotic treatment; the agent most commonly used was azithromycin (42.4%). Fourteen percent (n = 21) required hospitalization.

Conclusions. Diagnosis is based on clinical suspicion, epidemiological history, and complementary testing. Its typical presentation is a solitary enlarged lymph node in the head and neck. Due to the high frequency of hepatosplenic involvement, an abdominal ultrasound scan would be indicated in children with fever.

Key words: Bartonella henselae, *cat-scratch disease, child, lymphadenopathy, spleen diseases.*

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INTRODUCTION

Bartonella henselae is a Gram-negative bacillus and is the etiologic agent in cat-scratch disease (CSD). It affects children and young adults with a peak between 2 and 14 years old.[1,2] Domestic cats are the main reservoir hosts. They get the disease through an anthropod (flea) vector. Infection may be acquired from cat scratch or bite, most often kittens.[3]

The most common clinical hallmark in immunocompetent individuals is a solitary lymphadenopathy associated with fever. In 85% of cases, a single lymph node is involved; being the axillary and epitrochlear lymph nodes the most frequently involved.[3]

CSD has a wide clinical spectrum. There are less common forms of presentation (10% of cases),[1,2] most of them consisting of protracted febrile syndrome and hepatosplenic disease.[4] Bone,[2] eye,[5] nervous system,[6] and heart[7] involvement has also been described.

Considering the wide spectrum of manifestations, no single criterion should be regarded as the gold standard for diagnosis. Clinical criteria, epidemiological history, and complementary testing are taken into account for the diagnosis.[3] Serological techniques based on the detection of specific immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies have been developed.[8,9]

According to reports from the American Academy of Pediatrics, the prevalence among children under 18 years of age ranges from 54% to 87% in the United States.[10] In our country, the prevalence is unknown since it is not a notifiable disease.

In the pediatric clinical practice, it is common to see patients with (solitary or multiple) lymphadenopathy of an insidious clinical course that, after performing complementary tests, are attributed to *B. henselae*. Due to the high prevalence of CSD in medical consultation, associated with the few publications reported locally, it is important to determine the different forms of presentation, the reason for consultation, and the need for antibiotic treatment and/or hospitalization.

The objective of this study was to analyze the epidemiology, clinical features, and course of this disease in a tertiary care hospital in Argentina.

POPULATION AND METHODS

Children aged 0 to 16 years old with compatible clinical symptoms and positive serology attending the Low Risk and Evening Low Risk Sectors of Hospital de Pediatría Juan P. Garrahan from January 1st, 2019 to June 30th, 2021 were included. The diagnosis was serological when one of the following parameters was observed by indirect immunofluorescence (IFA): a) positive IgM, b) negative IgM with significant IgG levels (cut-off point 1/256) or c) IgG seroconversion at 15–21 days. Children with primary and/or secondary immunodeficiencies were excluded.

Ethical aspects

The research protocol was approved by the Teaching and Research Committee of Hospital Juan P. Garrahan. The development of the protocol was based on the Guidelines for Good Clinical Research Practice. For diagnosis and treatment, the standards of care of our institution were followed. Results were reported to each patient and their parents and/or guardians and the corresponding treatment or follow-up was indicated.

Access to the information of the present study was in accordance with all legal and ethical principles regarding research confidentiality (Act no. 25326 for the Protection of Personal Information). Data collected may not be used for purposes other than those for which they were obtained.

Statistical analysis

A data collection sheet was created in the RedCap database that belongs to Hospital Juan P. Garrahan. For the description of the sample, proportions were used for categorical variables, and mean and standard deviation, or median and interquartile range (IQR), for numerical variables, based on their adjustment or not to normality.

Data were processed using the R i386 version 3.5.0. software.

RESULTS

A total of 150 patients were included; their mean age was 7.9 years ± 3.68. Of them, 55.3% (n = 83) were male.

During case taking, most of them (68.7%) reported having contact with cats; 77.5% were kittens, and 88.3% were household pets.

The most common reason for consultation was lymphadenopathy (84.7%). Most were found on a single region (91.3%) of the body; mainly on the head and neck (*Table 1*). The median time to consultation was 7 days (IQR: 4–15 days). Fever was present in 24.4%; only 2 had

spleen enlargement. A soft tissue ultrasound scan was performed in 54.3%; abscessed lymphadenopathies were found in 37.7%; 8 (21.1%) required drainage procedures. An abdominal ultrasound scan was requested in 39.4%; it was pathological in 30%. The most common lesions were splenic microabscesses (73.3%). Leukocytosis was present in 91% and thrombocytosis in 18.2% of patients.

Febrile syndrome without source was the reason for consultation in 15.5% (n = 23). The median duration of fever was 13 days (IQR: 7–16 days). Most patients (n = 18) had protracted febrile syndrome. A complete blood count was performed in 22 children; leukocytosis was detected in 6 and thrombocytosis in 5 of 22. CRP level was measured in 20 children; it was found to be elevated in 19. Due to lack of supplies, erythrocyte sedimentation rate was measured in only 10 patients; it was high in 100%. Liver function test was performed in 19 children, but only one had elevated liver enzymes. Abdominal ultrasound scan was performed in 21 children; it was pathological in 18 (85.7%); splenic microabscesses were found in 94.4% (*Table 2*). Two children had abdominal pain associated with febrile syndrome, both with splenic microabscesses.

IgM and IgG were positive in most of the children (88%). As for the rest of the serological pattern, in 8% (n = 12) IgM was positive and IgG was negative; in 3.3% (n = 5) IgG seroconverted, and only 1 child who consulted for protracted 21-day long febrile syndrome with neck lymphadenopathy had high IgG titers (1/5120) with negative IgM results.

With the result of a positive serology test, 44% received antibiotic treatment. Protracted lymphadenopathy was the main cause of antibiotic treatment; the agent most frequently used was azithromycin (*Tables 3 and 4*).

Fourteen percent (n = 21) required hospitalization. Systemic involvement led to the hospitalization in 11 children and abscessed adenitis in 10; 8 out of them required drainage procedures; a residual fistula was found in 1. The median length of stay in days was 6.6 (IQR: 3–17 days).

No major complications or sequelae were observed.

Table 1. Location of solitary lymphadenopathies

Location	n (%)
Head and neck	76 (65.5)
Axillary	26 (22.4)
Inguinal	9 (7.8)
Epitrochlear	5 (4.3)

Table 2. Pathologic ultrasound findings in children with febrile syndrome without source

Ultrasound finding	n (%)
Splenic microabscesses	10 (55.5)
Splenic and hepatic microabscesses	7 (39)
Hepatic microabscesses	1 (5.5)

Table 3. Antibiotic prescribed with a positive serology result

Antibiotic prescribed	n (%)
Azithromycin	28 (42.5)
Trimethoprim/sulfamethoxazole	23 (34.8)
Clindamycin	9 (13.6)
Clarithromycin	5 (7.6)
Cephalexin	1 (1.5)

DISCUSSION

Household cats are the main reservoir hosts of *B. henselae*; half of them have antibodies against this bacterium. Transmission to humans usually occurs through cat saliva or scratch.[2,3,11] In our study, a high prevalence of contact with household kittens was observed. However, the absence of this epidemiological history among children with clinically and serologically diagnosed disease could be due to a sporadic contact, overlooked or not prioritized by the family, or to some other form of infection that has not been determined yet. Some publications report that the flea (*Ctenocephalides felis*), vector responsible for the horizontal transmission of the disease among cats, can, through its bite, infect humans. It is also mentioned that tick bites could transmit the bacteria.[12] Although more common among felines, 10.1% of healthy dogs and 27.2% of sick dogs in the southeast of the United States have

Table 4. Reason for prescribing an antibiotic treatment

Antibiotic prescription	n (%)
Protracted lymphadenopathy	40 (60.6)
Febrile syndrome	13 (19.7)
Systemic involvement	8 (12.1)
Systemic involvement associated with fever	4 (6.1)
Lymphadenopathies associated with fever	1 (1.5)

antibodies against *B. henselae*.[13] At present, it is unclear whether its presence in canines is of clinical significance to humans.[14]

When analyzing the forms of presentation, differences between our local experience and publications were observed. According to Florin et al.,[3] the most common clinical presentation in immunocompetent individuals is a solitary lymphadenopathy associated with fever. In most cases a single lymph node is involved; being the axillary and epitrochlear lymph nodes the most frequently involved.[12] This is scientifically supported by a case series of 1200 patients published by Carithers et al.[15]

In our study, 65.5% had a solitary lymphadenopathy in the head and neck with a high incidence of splenic microabscesses. This would justify performing an abdominal ultrasound scan in this population. Inoculation papules close to the lymphadenopathy site were detected in 8 children. The difference in the location of lesions could be due to the local habit of holding the animals in our arms and sleeping with them. This would lead to the presence of lesions in the head and neck with the development of regional lymph node enlargement. Due to the high rate of patients with CSD and lymphadenopathy in our hospital, at the Department of Imaging Studies, when suspicious ultrasound features are observed, an abdominal ultrasound scan is performed to confirm or rule out the presence of hepatic and/or splenic microabscesses. This would account for the high frequency of splenic lesions.

A high prevalence of abscessed lymphadenopathies requiring drainage was observed in 21.1%, while that described in the literature is 10%.[16] *B. henselae* is increasingly recognized as a cause of protracted febrile syndrome (PFS) and clinically evident fever without source (FWS) in children.[3] A study identified *B. henselae* as the third leading infectious cause of PFS after Epstein-Barr virus. *B. henselae* was found to be responsible for 5% of cases out of 146 children with PFS. The history of exposure to cats was not consistently observed, suggesting that it should be taken into account in the initial assessment of PFS, regardless of the epidemiological history.[17]

It is worth noting that the number of children with PFS observed in our population (12.6%) was high, probably due to the high rate of clinical suspicion motivated by consultation in a tertiary care hospital after visiting primary care centers. It is important to consider the high prevalence of splenic microabscesses to determine the need for complementary testing and treatment, since it is higher than that published so far. Jacobs et al.,[17] found that 30% of PFS cases caused by *B. henselae* had hepatosplenic involvement. Nawrocki et al.,[11] conducted a retrospective search from 2005 to 2014 for patients with CSD; it was found that 4759 children were less than 14 years old. This population represented 36.2% of the diagnoses of atypical disease and had a higher risk of hepatosplenic involvement (RR: 1.76; 95% CI: 1.04-2.99) compared to those older than 15 years.

Based on the above, *B. henselae* should always be considered as a possible diagnosis in children with PFS and FWS, as well as in patients with fever and abdominal pain.[3,9] Liver or splenic involvement can be identified by abdominal scans. Although computed tomography is the recommended study, an ultrasound scan performed by qualified medical personnel has a high yield and is useful for follow-up.[9]

The isolation of *Bartonella* in culture is difficult. Because of the slow growth and low sensitivity, it is of little use in clinical practice.[3,8,9] Serological techniques based on the detection of specific IgG and IgM antibodies have been developed. The main methods used are the indirect fluorescence assay (IFA) and enzyme-linked immunoassay (ELISA).[3,8] Sensitivities vary according to the antigen, test procedures and cut-off point. The U.S. Centers Disease Control and Prevention recommend IgG detection by IFA, with a reported sensitivity of 88-100% and a specificity of 92-98%.[8] The recommended cut-off point is 1:64; some consider titers greater than 1:256 as an indicator of acute disease. IgM sensitivity ranges from 71.4% to 95%. Sensitivity is lower with ELISA technique than with IFA (73% vs. 93%).[8,18]

Timing of serological detection of antibodies is important to determine acute infection. A positive IgM (IFA) result will suggest an acute infection, but IgM production is brief (about 3 months) and the sensitivity of the test is low compared to the excellent IgG sensitivity and specificity. Therefore, a negative IgM result does not rule out acute disease. If the sample was taken within the first 10 to 14 days from the onset of symptoms, with high clinical and epidemiological suspicion, a new test should be performed.[2,8,18] IgG titers also decrease over time. In early stages, IgG and IgM titers may be low, hence a second sample is required for diagnosis (15–21 days apart).[18]

Consistent with our observations, in a series

published by Armitano et al.,[18] the most commonly observed serological pattern was the double-positive (IgG- and IgM-positive). Since Abarca et al.,[8] found that 21 of 37 children were IgG positive and IgM negative, a positive IgM result could be useful for diagnosis, but a negative IgM result does not preclude it. Therefore, IgM does not yet meet the requirements to replace IgG for the diagnosis.

In immunocompetent patients, CSD has a favorable, self-limited prognosis. Treatment is a matter of discussion.[2,3,9] Typical CSD usually resolves in 2 to 6 months.

In our series, 44% of patients were prescribed antibiotic treatment, an impressively high percentage. However, consultations occurred in a tertiary care hospital and this is a bias, since those who usually seek consultation are the ones who do not follow the expected course. The main causes for treatment initiation were persistent lymphadenopathies for at least 30 days and febrile syndrome. Considering the natural course of the disease without complications and the risk of adverse effects of antimicrobials, antibiotic treatment is not recommended in typical CSD.[3] Antibiotic treatment would be beneficial in severe cases and in those with immunological disorders.[19]

For mild to moderate infections in immunocompetent patients, the most appropriate treatment consists of analgesics, local heat applications, and periodic clinical follow-up. Excess fluid can be removed from lymph nodes to ease pain. Incision and drainage are not recommended due to fistula formation.[3] In our series, only 8 children required drainage due to abscedation and pain. A marked short-term improvement was observed.

When analyzing the type of antimicrobials used, publications mention an efficacy ranging from 58% to 87% with rifampicin, ciprofloxacin, gentamicin, azithromycin, and trimethoprim-sulfamethoxazole.[3,20] A study showed an 80% decrease in lymph node volume in 50% of those patients treated with azithromycin compared to 7% of those treated with placebo. There was no difference in the clinical outcome between the groups and no efficacy was demonstrated for disseminated disease.[21]

According to Margileth, in those patients with significant lymphadenopathy, a 5-day long treatment with azithromycin should be considered.[22] Trimethoprim-sulfamethoxazole, ciprofloxacin or rifampicin could be effective.[3,12]

Consistent with these publications, in our series, azithromycin and trimethoprim-sulfamethoxazole were the most commonly used agents. It was not possible to accurately determine their efficacy, nor was it possible to measure the decrease in lymph node volume.

In analyzing the strengths of our study, we consider that the high number of cases is fundamental, with an accurate diagnosis based on epidemiology, clinical criteria, and complementary testing. It is essential to remember that the local evidence is scarce. When analyzing the weaknesses, the most important one is that the study was conducted at a tertiary care hospital, which is often not the first place of consultation. Mid- and long-term course and follow-up could not be evaluated.

Although there are differences, much of the data obtained is consistent with the publications. Further research is needed to obtain more scientific evidence.

CONCLUSIONS

CSD diagnosis is based on clinical suspicion, epidemiological history, and complementary testing. The main form of infection would correspond to contact with kittens. Typical CSD consists of subacute lymph node enlargement mainly in the head and neck. Based on the high incidence of hepatosplenic involvement, an abdominal ultrasound scan would be indicated in children with CSD and fever, especially if they have abdominal pain and/or liver or spleen enlargement. ■

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