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MAJOR ARTICLE

Cat Scratch Disease: 9 Years of Experience at a Pediatric Center

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Background. A more complete understanding of the epidemiology, risk factors, and clinical features of cat scratch disease (CSD) in children could help guide patient care.

Methods. We conducted a retrospective analysis of children presenting to a tertiary pediatric hospital system in Atlanta, Georgia between January 1, 2010 and December 31, 2018 who had serology, polymerase chain reaction, and/or cytopathological results consistent with a *Bartonella henselae* infection. We also retrospectively reviewed veterinary diagnostic results performed at the University of Georgia from 2018 to 2020 to ascertain the burden of bartonellosis in companion animals within the state.

Results. We identified 304 children with CSD over 9 years with the largest proportion of diagnoses made during August (41 of 304, 13.5%) and September (47 of 304, 15.5%). The median age of child cases was 8.1 years (interquartile range [IQR], 5.4–12.1); 156 (51.3%) were female; 242 of 262 (92.4%) reported feline exposure; and 55 of 250 (22%) reported canine exposure of those with exposure histories documented in the medical record. Although lymphadenopathy was present on physical examination in the majority of cases (78.8%), atypical presentations lacking lymphadenopathy were also common (63 of 304, 20.7%). Among children with radiographic imaging, 20 of 55 (36.4%) had splenomegaly and 21 of 55 (38.1%) had splenic and/or hepatic microabscesses. Among veterinary data, *Bartonella* seroprevalence was 12 of 146 (8.2%), all among canines, with a geographic distribution that spanned the state of Georgia.

Conclusions. Distinguishing clinical features of CSD included subacute regional lymphadenopathy in school-aged children in the late summer, almost all of whom had cat exposure. Atypical clinical manifestations of CSD were also commonly identified.

Keywords. *Bartonella henselae*; bartonellosis; cat scratch disease; lymphadenitis; veterinary.

Although cat scratch disease (CSD) was first described by Debré in 1950, the Gram-negative bacterium was first isolated in a patient in 1988 and was renamed as *Bartonella henselae* in 1993 [1–3]. Cats are the primary reservoir, and cat-to-cat transmission occurs via the cat flea, *Ctenocephalides felis*. *Bartonella henselae* is transmitted to humans via scratches or bites of infected cats or kittens or through inoculation of flea feces into the mucous membranes. Cat exposure has been reported in up to 90% of cases, although a feline reservoir is not always identified [4]. Approximately 13 000 cases are diagnosed annually in the United States, and children <14 years of age account for 32.5% of all cases with the highest incidence observed among children 5–9 years of age (9.4 cases/100 000 population) [5].

Cat scratch disease can present with a broad range of clinical symptoms ranging from asymptomatic infection to disseminated disease with multiorgan involvement [4–8]. Typical CSD, which is characterized by regional lymphadenopathy in 85%–90% of cases, is a benign self-limited disease [4, 9, 10]. Lymphadenopathy can be accompanied by constitutional symptoms (eg, fever, malaise, headache, nausea, abdominal pain) approximately one third of the time. Less commonly, patients may present with atypical clinical manifestations, such as fever of unknown origin, osteomyelitis, discitis, optic neuritis, Parinaud's oculoglandular syndrome, encephalitis, endocarditis, or hepatosplenic disease [11]. Immunocompromised patients are at additional risk of complications including bacillary angiomatosis and peliosis [12, 13]. Cat scratch disease

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can be difficult to diagnose because the clinical presentation is often nonspecific. In addition, cross-reactivity of serological assays between *B henselae* and other organisms, including *Bartonella quintana*, *Coxiella burnetii, and Chlamydia* species, and the lack of a gold standard diagnostic test make diagnosis difficult [14–16]. Finally, *B henselae* is rarely isolated from cultures, and detection of *B henselae* deoxyribonucleic acid by polymerase chain reaction (PCR) performed on samples obtained from affected organs is not routinely available [14, 15].

Therefore, we conducted a retrospective cohort study using 9 years of data from Children's Healthcare of Atlanta, in a region with known high prevalence of CSD [5]. We aimed to better characterize the patient demographics, spectrum of clinical manifestations, and laboratory, histopathologic, and imaging findings among children with CSD and to define the seroprevalence of *Bartonella* spp in companion animals in Georgia.

METHODS

We conducted a retrospective cohort study of children (less than 18 years of age) who had an inpatient, outpatient, or emergency department (ED) encounter at Children's Healthcare of Atlanta, Georgia between 1 January 2010 and 31 December 2018. Using clinical laboratory records and electronic medical records, we identified patients with serology and/or PCR testing for *B henselae* infection in addition to those with at least 1 *International Classification of Diseases* (ICD) code in the primary and/or secondary discharge diagnosis for CSD or bartonellosis (ICD9 078.3, 088.0 before September 2015 and ICD10 A28.1, A44.9 afterward). In addition, histopathologic specimens were identified using free text search in Sunquest (Tucson, AZ) CoPathPlus 6.3 database using search terms "Bartonella" or "cat scratch" with accession dates January 1, 2010 to December 31, 2018. We then conducted a chart review of each patient using a standardized data collection form to extract information on demographics, associated symptoms (eg, fever, chills, night sweats, weight loss, headache, abdominal pain), duration of symptoms, type of animal exposure (feline or other), physical examination findings (eg, lymphadenopathy, hepatosplenomegaly), imaging results, serology, molecular testing, and histopathology results when available. Antibiotic utilization, duration of antibiotics, follow-up, and overall outcome were also extracted. Study investigators independently reviewed the presenting signs and symptoms (I.Y. and O.A.), histopathology findings (S.C.), and radiological images/findings (B.S.R.) to identify cases with clinical and radiological features consistent with CSD. In our final cohort, we only included patients who presented with clinical features compatible with CSD and had at least 1 positive result from the following: *B henselae* immunoglobulin (Ig)M and/or IgG; and/or *B henselae* PCR from lymph node, purulent debris/abscess fluid, or a tissue sample; and/or radiology imaging findings consistent with CSD; and/or cytopathology results suggesting CSD, including granulomatous inflammation or positive Warthin-Starry staining. *Bartonella henselae* IgM titers >1:20 and IgG titers ≥1:128 were considered as seropositive. *Bartonella henselae* serology testing was performed by a reference clinical laboratory via indirect immunofluorescence. Descriptive statistics were reported as total numbers, percentages, means with standard errors, and medians with interquartile ranges (IQRs) as appropriate. Dichotomous data were analyzed using Pearson χ^2 test and Fischer's exact test. A 2-sided P value of .05 indicated significance. Statistical analysis was performed using SAS software version 9.3.1 (SAS Institute, Gary, IN). The institutional review board of Children's Healthcare of Atlanta approved this study.

To understand the local burden of bartonellosis in companion animals, which is a known risk factor for human disease, we then conducted a retrospective analysis of *Bartonella* spp detected in companion animals among immunofluorescence antibody (IFA) and PCR testing performed at the University of Georgia (UGA) from 2018 to 2020.

Patient Consent Statement

This study was approved by the institutional review board (IRB) at Emory University and conforms to standards currently applied in the country of origin. Informed consent was waived by the IRB due to the retrospective nature of the study and because the study does not include factors necessitating patient consent.

RESULTS

We identified 304 children who presented with clinical and laboratory features compatible with CSD over 9 years from 2010 to 2018. The largest proportion of diagnoses was made during September ($n = 47$, 15.5%), followed by August ($n = 41$, 13.5%), October ($n = 39$, 12.8%), and November ($n = 37$, 12.2%) (Figure 1). The smallest proportion of diagnoses was made in June ($n = 6$, 2.0%), May ($n = 10$, 3.3%), and April ($n = 14$, 4.6%). One hundred thirty-nine (45.7%) patients were diagnosed in an inpatient setting, 125 (41.1%) were diagnosed in the ED, and 40 (13.2%) were diagnosed in outpatient clinics.

Patient Characteristics

Of 304 children, 156 (51.3%) were female. The median age was 8.1 years (IQR, 5.4–12.1 years) and almost all patients (274, 90.1%) were younger than 14 years of age (Table 1). Non-Hispanic/non-Latino children represented 79.6% of all cases. Among those with exposure histories documented in the medical record (262 of 304, 86.2%), 136 of 262 (44.7%) children had exposure to an adult cat, and 73 of 262 (24.0%) had kitten exposure, and 33 of 262 (10.9%) had both adult cat

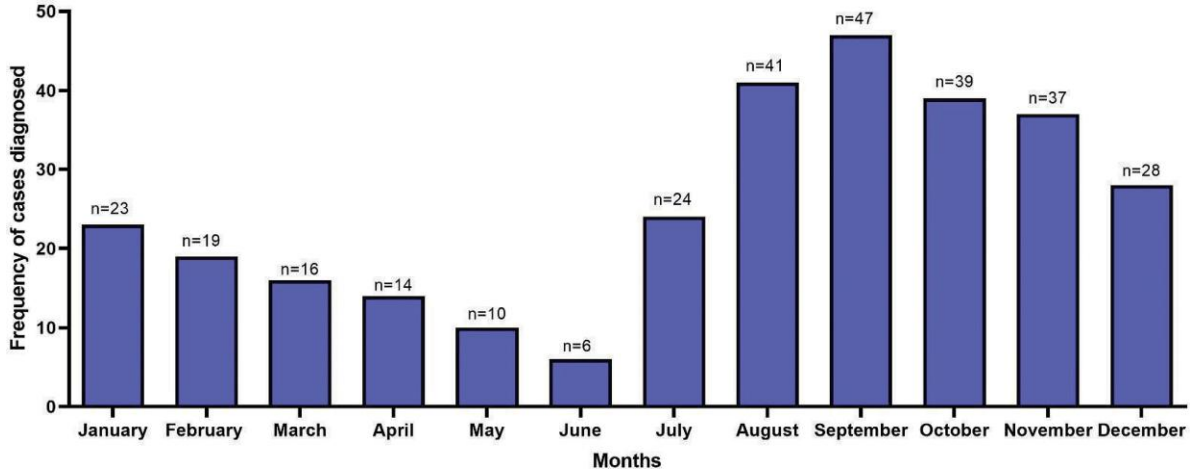

Figure 1. Number of pediatric cat scratch disease cases diagnosed in each month, 2010–2018, $n = 304$.

and kitten exposure. Twenty (7.6%) children did not have known feline exposure. Other animal exposure (eg, canine, bovine) was reported in 65 of 260 (25.0%) children (Table 1).

Clinical and Laboratory Features

Fever was reported in 141 of 304 (46.4%) of the patients, with the majority experiencing a continuous fever pattern (76.0%) (Table 2). The median duration of fever at the time of presentation was 5 days (IQR, 2–12 days). Lymphadenopathy was the most common clinical finding (234 of 297 patients, 78.8%). The median duration of lymphadenopathy at the time of presentation was 9 days (IQR, 6–21 days). More than one third of the patients had cervical lymphadenopathy (104 of 200, 52.0%), 67 of 237 (28.3%) had axillary lymphadenopathy, and 37 of 266 (13.9%) had inguinal lymphadenopathy. Sixty-seven (28.3%) children had lymphadenopathy in other regions including epitrochlear, occipital, submandibular, and submental areas (Table 2). Hepatomegaly was noticed on physical exam in 9 of 284 (3.2%) patients and splenomegaly was found in 23 of 270 (8.5%) cases. Other clinical presentations included osteomyelitis ($n = 9$), ocular abnormalities ($n = 21$), aseptic meningitis ($n = 6$), and pneumonitis ($n = 1$). Overall, atypical manifestations of CSD, defined as those lacking associated lymphadenopathy, accounted for 63 of 304 (20.7%) of cases.

At presentation, the mean hemoglobin was 12.6 (±0.1) mg/dL, mean white blood cell count was 10.1×10^3 ($\pm 0.3 \times 10^3$) cells/per microliter, and mean platelet count was 340.6×10^3 ($\pm 8.8 \times 10^3$) per microliter (Supplementary Figure 1). Erythrocyte sedimentation rate (ESR) ranged from 3 mm/hour to 140 mm/hour, whereas C-reactive protein (CRP) ranged from 0.2 mg/dL to 29.4 mg/dL. Only 12 of 122 (9.8%) children who had available testing had elevations in aspartate aminotransferase or alanine aminotransferase (Supplementary Figure 1). The most common laboratory abnormality in children with CSD were leukocytosis (58 of 218 tested, 26.6%), elevations in ESR (55 of 111 tested, 49.6%), and elevation in CRP (34 of 184 tested, 18.7%).

Serology results were available for 177 of 304 (58.2%) patients: 174 patients had both *B henselae* IgM and IgG, and 3 patients had only *B henselae* IgG testing. *Bartonella henselae* IgM titers were ≥1:20 (seropositive) in 110 of 174 (63.2%) and IgG titers were ≥1:128 (seropositive) in 169 of 177 (95.5%). Five children (2.9%) with seropositive IgM titers had IgG titers <1:128, whereas 62 children (35.6%) with seropositive IgG titers had IgM titers <1:20.

Thirty-six (11.2%) cases had histopathology. A lymph node was the most common specimen type (23 of 36, 63.9%), with necrotizing granulomatous inflammation as the most common finding (13 of 34, 38.2%) followed by normal lymph node (4 of 34, 11.8%). A positive Warthin-Starry stain was infrequently identified (3 of 34, 8.8%). The other samples collected for histopathological examination were as follows: 2 liver tissue, 3 intestinal tissue, 3 bone tissue, and 5 soft tissue/skeletomuscular tissue. Thirteen (4.3%) patients had PCR testing performed (5 cerebrospinal fluid, 5 lymph node and 1 bone, 1 plasma, 1 whole blood); of those, only 3 had detectable *B henselae* by PCR in the lymph nodes.

Radiological Findings

At least 1 radiological study was available in 216 (71.1%) children: 10 with only chest radiograph and 206 with chest radiograph and/or ultrasonography and/or computerized tomography (CT) and/or magnetic resonance imaging (MRI). We identified at least 1 concurrent disease process other than CSD in 9 patients. After excluding these patients, the most common radiological finding was cervical lymphadenopathy (78 of 83, 94.0%), followed by upper extremity (28 of 31,

Table 1. Selected Demographics and Exposures Among Children With Cat Scratch Disease, 2010–2018 ($n = 304$)

Characteristics	$N = 304$	%
Age, years (median, IQR)	8.1 (5.4–12.1)	
Age Groups	…	
0–4 years	63	20.7
5–9 years	108	35.5
10–14 years	103	33.9
15–19 years	30	9.9
Sex	…	…
Female	156	51.3
Male	148	48.7
Race/Ethnicity	…	…
Non-Hispanic White	156	51.3
Non-Hispanic Black	83	27.3
Hispanic	24	7.9
Other[a]	41	13.5
Ethnicity	…	…
Hispanic or Latino	45	14.8
Non-Hispanic or Latino	242	79.6
Unknown	17	5.6
Feline Exposure[b]	…	…
Cat	136	44.7
Kitten	73	24.0
Cat and kitten	33	10.9
None	20	6.6
Unknown	42	13.8
Other Animal Exposure[b]	…	…
Dog	55	18.1
None	195	64.1
Other[c]	10	3.3
Unknown	44	14.5

Abbreviations: IQR, interquartile range.

[a]Other race/ethnicity includes Asian, Native Hawaiian or Other Pacific Islander, multiple races, and unknown.

[b]Self-reported.

[c]Chicken, rabbit, guinea pig, parakeet, horse, monkey, snake, parrot, turtle, cow, donkey, hamster, fish, goat, squirrel, birds, raccoon, opossum, frog, water dragon, and pig.

Table 2. Presenting Symptoms Among Children With Cat Scratch Disease, 2010–2018

Clinical Feature	Frequency	Percent
Fever[a]	141/304	46.4
Fever duration, days (median, IQR)	5 (2–12)	…
Chills[a]	9/293	3.1
Chills duration, days (median, IQR)	3 (2.5–6)	…
Night sweats[a]	11/293	3.8
Night sweats duration, days (median, IQR)	3 (3–6)	…
Weight loss[a]	6/293	2.1
Weight loss duration, days (median, IQR)	1 (1–3)	…
Headache[a]	37/293	12.6
Headache duration, days (median, IQR)	8 (4–14)	…
Abdominal pain[a]	31/293	10.6
Abdominal pain duration, days (median, IQR)	3 (1–4)	…
LAD[a]	234/297	78.8
LAD duration, days (median, IQR)	9 (5.5–21)	…
Neck LAD[a]	104/200	52.0
Axillary LAD[a]	67/237	28.3
Inguinal LAD[a]	38/266	13.9
Other LAD[b]	67/237	28.3
Splenomegaly[a]	23/270	8.5
Hepatomegaly[a]	9/284	3.2

Abbreviations: IQR, interquartile range; LAD, lymphadenopathy.

[a]With available information.

[b]Epitrochlear, occipital, submandibular, and submental.

90.3%) and lower extremity (22 of 25, 88.0%) lymphadenopathy (Supplementary Table 1). Of 55 patients who had at least 1 abdominal ultrasonography, abdominal CT, or abdominal MRI, 5 (9.1%) had abdominal lymphadenopathy, 20 (36.4%) had splenomegaly, and 21 (38.1%) had splenic and/or hepatic microabscesses (Figure 2). Of the 29 children who had neuroimaging performed, 5 (17.2%) had findings suggestive of encephalitis and 8 (27.6%) had optic neuritis. Parotitis was reported in 7 (21.9%) of 32 children who had neck CT. Bone involvement suggesting CSD was identified in 7 of 20 (35.0%) children in various MRI studies, excluding neuroimaging.

Treatment and Outcomes

Sixty-two (20.4%) patients did not receive antibiotics, and 33 of 242 (13.6%) patients who received antimicrobial therapy did not receive a regimen targeting CSD (Supplementary Table 2). Among the 209 of 242 (86.4%) who were treated with antibiotics targeting *Bartonella* infections, 177 (84.7%) initially received antibiotics that have activity against *Bartonella* spp, and 32 (15.3%) had changes in the initial antibiotics to adjust antimicrobial spectrum. Azithromycin was the most commonly used antibiotic (160 [76.6%] as single drug, 7 [3.4%] in combination with rifampin, 2 [1.0%] in combination with doxycycline, and 2 [1.0%] in combination with gentamicin). The median duration of the CSD treatment was 4 days (IQR, 4–10 days). One hundred fourteen (114 of 304, 37.5%) patients had a follow-up visit after diagnosis, and resolution or improvement was achieved in 61 of 114 (53.5%). There was no mortality. There was no statistically significant difference in reported resolution prevalence among patients treated with antibiotics versus those who were not given antibiotic treatment ($P = 0.13$), although multiple confounding factors may have impacted the decision to administer antibiotics and the treatment response.

Bartonellosis in Companion Animals in Georgia

From 2018 to 2020, there were 146 total veterinary diagnostic reports available from companion animals in Georgia that were tested for *Bartonella* by serology (IFA) or PCR at UGA. Thirteen animals ([8.9%] 12 dogs and 1 cat) were positive for *Bartonella* by IFA or PCR. Twelve dogs were positive for *Bartonella* antibody testing (IFA-IgG), whereas 1 cat (1.4%) was positive for *Bartonella* by PCR (Figure 3).

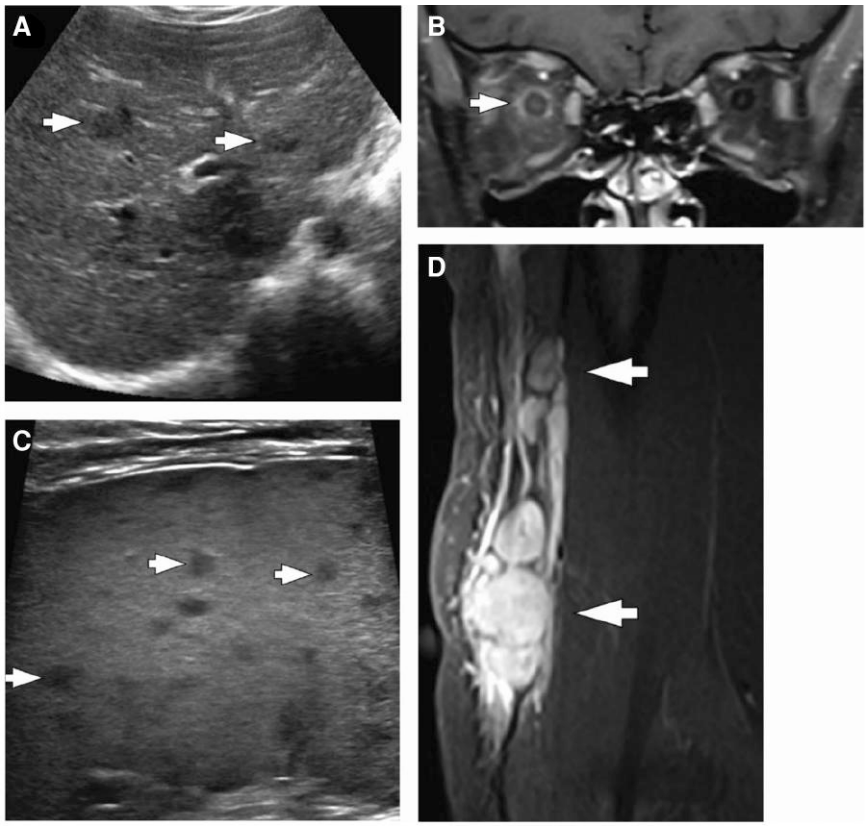

Figure 2. Selected radiological findings among children with cat scratch disease, 2010–2018. (A) Liver ultrasound with 2 hypoechoic lesions compatible with hepatic microabscesses (arrows). (B) Coronal T1 fluid-attenuated inversion recovery (FLAIR) contrast enhanced magnetic resonance imaging (MRI) through the orbits demonstrates abnormal enhancement of the right optic nerve (arrow) consistent with optic neuritis. (C) Ultrasound of the spleen demonstrates multiple hypoechoic splenic lesions consistent with microabscesses. Three of the lesions are annotated (arrows). (D) Coronal short tau inversion recovery (STIR) MRI of the left upper arm demonstrates multiple enlarged lymph nodes (arrows) above the left elbow.

DISCUSSION

We present the epidemiology and clinical features of 304 children with CSD who presented to Children's Healthcare of Atlanta from 2010 to 2018. The South Atlantic region of the United States, which includes Georgia, has one of the highest incidences of clinical human CSD (6.4 of 100 000) [5]. As with other studies, we found that the highest number of cases were diagnosed in the late summer and fall [5, 17, 18]. In Georgia, *Bartonella* spp flea vectors *C felis*, *Ctenocephalides canis*, and *Pulex simulans* peak in abundance at this time [19]. This seasonal variation in human disease is likely driven by a combination of cat flea activity, seasonality in cat reproductive behavior, epidemiology of *B henselae* infection in felines, and the dynamics of cat-flea vector-human interactions. The degree of urbanization and land cover in urban areas also impacts *Bartonella* spp transmission, because higher seroprevalence of *B henselae* has been seen in urban compared to rural cats [20].

Cat or kitten exposure was reported in most of our cases (92.4%), whereas canine exposure was reported in 22% of cases when exposure history was documented. It is interesting to note that our data from diagnostic reports revealed *Bartonella* antibody test positivity in canines with a broad geographic distribution across the state of Georgia. Both dogs and cats can be potential reservoirs of *Bartonella spp* [21]. Although dogs and cats are typically asymptomatic, they may also suffer disease manifestations including endomyocarditis [22], peliosis, systemic granulomatous inflammation, and vascular proliferation, including associations with proliferative vascular tumors [21]. More than 31 million households in the United States have a cat, whereas more than 48 million households have a dog [23]. The prevalence of *B henselae* bacteremia among domestic US cats has been reported to be as high as 47%, with increased risk observed in kittens, stray, and flea-infested cats [24]. Comprehensive environmental and pet flea control, and educational efforts for pet owners, particularly those with children, could reduce the risk of CSD. In addition, clinicians practicing in highly endemic areas such as the US South Central region should maintain high degree of suspicion for CSD, because early diagnostic testing may expedite the diagnosis and facilitate patient care.

A wide spectrum of clinical manifestations was observed among the patients in our study. The most common features

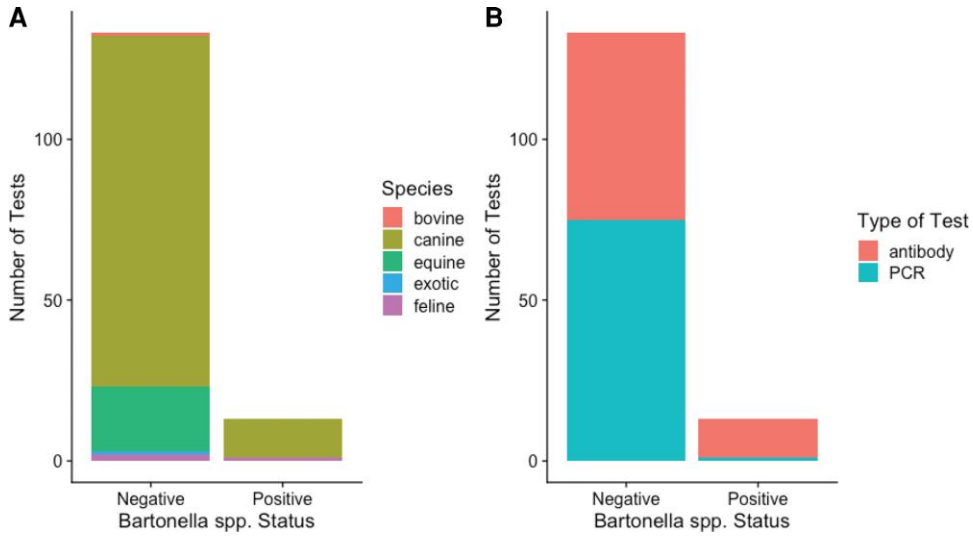

Figure 3. *Bartonella* testing in animal samples submitted to the University of Georgia Veterinary Diagnostic Laboratory, $n = 146$. (A) Results by *Bartonella* status and animal species. (B) *Bartonella* results by testing type (immunofluorescent antibody testing and polymerase chain reaction [PCR]).

were characteristic of typical CSD and included lymphadenopathy (78.8%) and fever (46.4%). It is interesting to note that a significant proportion of our patients (20.7%) lacked lymphadenopathy and presented with atypical presentations, which included hepatosplenic lesions, osteomyelitis, ocular lesions, and meningoencephalitis. A recent study, which was based on a national health insurance claims database using ICD-9 or -10 codes, found that atypical CSD accounted for 1.5% of all cases and occurred most commonly in female patients 10–14 years of age. In that study, ocular disease was the most common atypical clinical manifestation (48.7%), followed by hepatosplenic (24.6%) and neurologic (13.8%) disease [11]. Possible explanations for the higher frequency of atypical manifestations observed in our study include differing definitions of atypical manifestations and diagnostic testing bias, because testing is more likely to be performed for sicker patients with atypical manifestations.

The radiographic findings of CSD in our study included regional lymphadenopathy, hepatosplenic lesions, splenomegaly, encephalitis, optic neuritis, parotitis, and bone lesions. Although literature describing radiographic findings in pediatric CSD is limited, our data are consistent with previously published case reports [25, 26] and series [27, 28]. The findings of bone involvement in CSD are often nonspecific and consist of edematous bone marrow changes. Imaging may play the greatest role in children with atypical manifestations of CSD. In these children, the radiographic diagnoses of complications such as hepatosplenic disease or encephalitis would likely modify the selection of antimicrobials and the treatment duration. Thus, judicious imaging of children with suspected atypical CSD may be beneficial to guide patient management.

Regarding treatment, most recommendations depend on the specific disease manifestations. In general, CSD in immunocompetent patients is a benign disease with self-limiting symptoms, and the benefits and choice of antibiotics are often debated [29]. It is still not clear whether antibiotics can prevent progression of localized CSD into systemic disease. Bass et al [30] published the only prospective, double-blinded, placebo-controlled study, which showed that the use of azithromycin in uncomplicated CSD resulted in decrease in 80% of the initial lymph node volume in treated patients compared to those in the placebo group; however, there was no reduction in the duration of symptoms. For patients with severe or disseminated disease, multiple antibiotic regimens have been used including ciprofloxacin, rifampin, gentamicin, and trimethoprim/sulfamethoxazole [14]. Azithromycin was the most frequently used antibiotic in the treatment of CSD in our patient cohort. Of those with follow-up data available, we did not observe significant differences in outcomes between patients who received antibiotics versus those who did not. However, we were unable to control for the various confounding factors that may have influenced treatment outcome due to the retrospective nature of the study.

Our study has several limitations. First, this is a single-center, retrospective study using existing data collected over 9 years. The case definition is based on diagnosis codes and testing ordered by providers, and thus it is subject to variability in sensitivity and specificity of the test and ascertainment bias. We also did not have access to diagnostic results that were performed on specimens not collected within our healthcare system. In addition, we did not capture any information that was not recorded in the medical records, such as additional symptoms or exposures. We also do not have information on comorbidities such as

immunocompromising diseases that may have relevance to the clinical presentation and outcome. The size of the animal cohort was also small, and clinical data for the animals were not available.

CONCLUSIONS

In conclusion, we describe the epidemiology, clinical, laboratory, and radiographic features of CSD in a cohort of children from one of the largest pediatric centers in the US South Atlantic region. Cat scratch disease caused regional lymphadenitis in the majority of cases, but it also caused a spectrum of atypical clinical manifestations in a significant minority of children. Clinicians must maintain a high index of clinical suspicion for the diagnosis of CSD, especially for atypical presentations among children in highly endemic areas, where exposure to cats and dogs is frequent. Prospective clinical trials would be beneficial to guide therapeutic clinical decision making in children affected by both typical and atypical CSD in the future.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

Author contributions. I. Y. and M. G. conceived and designed the study. I. Y. created clinical data collection instruments, coordinated and supervised data collection, managed datasets, and conducted statistical analysis. O. A., M. E., T. S., O. S., E. Q., and I. Y. contributed to clinical data collection. B. A. B., N. L. G., and J. J. W. contributed to veterinary data collection and analysis. S. C. provided cytopathological data. B. S. R. provided the radiological data. M. G. designed and maintained the microbiology data collection instruments and provided data. O. A., C. A. R., and I. Y. drafted the manuscript. All authors critically reviewed the manuscript for important intellectual content and approved the final manuscript.

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