Role of Cat-Scratch Disease in Lymphadenopathy in the Head and Neck

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Bartonella henselae is the causative agent of cat-scratch disease (CSD), which usually manifests as acute regional lymphadenopathy. The causes of cervical lymphadenopathy, with special regard to CSD, were investigated in a study of 454 patients who presented with unclear masses in the head and neck from January 1997 through January 2001. Sixty-one patients (13.4%) experienced CSD; 54 (11.9%) had primary lymphadenopathy due to other infectious agents, and 41 (9.0%) had lymphadenopathy that occurred in association with primary infections of other organs. For 171 patients (37.7%), the cause of the cervical lymph node enlargement could not be found. Bartonella henselae DNA was detected in extirpated lymph nodes only during the first 6 weeks of lymphadenopathy, which indicates that the results of polymerase chain reaction strongly depend on the duration of illness. CSD should be included in the differential diagnosis of adenopathy in the otorhinolaryngologic patient population, to avoid unnecessary treatment.

Bartonella henselae, a fastidious gram-negative bacterium, has been known as the principal causative agent of cat-scratch disease (CSD) only since 1992 [1]. Thereafter, a broad spectrum of various clinical manifestations, including Parinaud oculoglandular syndrome, bacillary angiomatosis, peliosis hepatitis, bacteremia, endocarditis, and aseptic meningitis, were recognized as Bartonella henselae infections [2–4]. The clinical manifestation of a Bartonella henselae infection highly depends on the immune status of the patient. Immunocompetent hosts usually present with typical CSD, which is characterized by a primary granulomatous skin lesion that develops 3–10 days after contact with an infected cat. Development of this lesion is followed by enlargement of the regional lymph nodes.

Lymphadenopathy is the most common clinical manifestation of CSD and is described in >80% of all cases [5, 6]. Atypical manifestations of CSD (with or without lymphadenopathy) occur in 5%–25% of all cases, and many different organs can be affected, including—but not limited to—the eyes, liver, CNS, skin, and bones [2, 3, 7–14]. The location of the lymphadenopathy in CSD depends on the site of inoculation. In an overview of a study of 1200 patients with CSD, Carithers [5] reported that the axillary lymph nodes were most often affected (in 586 patients [48.8%]). The cervical or submandibular regions were involved in 30 (28.3%) of all patients. In a study of 246 patients with CSD, Hamilton et al. [15] reported that the most commonly infected site was the neck (43% of patients), followed by the axilla (38%) and groin (20%), and that 37% of the patients reported having enlarged lymph nodes at ≥1 site. Typical CSD is seldom found in immunocompromised individuals. In these patients, Bartonella infections manifest as bacillary angiomatosis, peliosis hepatitis, and bacteremia [2, 3].

Even today, many cases of CSD remain unrecognized. In the study reported here, our aim was to systematically evaluate patients with unclear cervical masses who were referred to the Department of Otorhinolaryngol-
ogy–Head and Neck Surgery at the University of Freiburg (Freiburg, Germany) from January 1997 through January 2001 and to determine the infectious and noninfectious causes of these diseases, with special regard to CSD. Increasing recognition of CSD in the otorhinolaryngologic population makes it necessary to improve the detection of this infection caused by *B. henselae*, an emerging human pathogen.

**PATIENTS AND METHODS**

**Patients.** From January 1997 through January 2001, a total of 454 patients with unclear masses in the head and neck were included prospectively in this study. All patients underwent clinical examination and were assessed for symptoms and signs of infection (e.g., fever, swelling of the lymph nodes, adynamia, pharyngitis, laryngitis, skin rash). For documentation of lymph node enlargement, all patients were assessed by B-scan ultrasonography. For selected cases, power Doppler ultrasonography, color-coded Doppler ultrasonography, and CT and MRI were performed. Patients who obviously had neoplasms were not included in the study.

**Case definition for CSD.** CSD was diagnosed when at least 2 of the following 3 criteria were fulfilled: (1) presence of clinical symptoms typical of CSD; (2) serological detection of antibodies against *B. henselae* (as described in the following subsection), including negative results of serological tests for the detection of other infectious diseases; and (3) detection of *Bartonella* DNA in the extirpated lymph nodes.

**Serological investigations.** Serum samples were obtained from all patients at the time of admission, and additional convalescent-phase serum samples were available for most patients with CSD. All serum samples were tested for IgG and IgM antibodies against *B. henselae* (Houston 1; ATCC [American Type Culture Collection] 49882) by an immunofluorescence antibody test (BIOS; BIOS GmbH). Titers \( \geq 1:64 \) indicated seroreactivity to *B. henselae* [16]. The serological criteria used for the diagnosis of CSD have been either the detection of a single high IgG titer \( \geq 1:512 \), a 4-fold increase in the titer of a second serum sample obtained from the same patient, or a low positive IgG titer (range, 1:64 to 1:264) in combination with detection of IgM antibodies against *B. henselae*.

For detection of lymphadenopathy due to other infectious causes, all patients’ serum samples were also assessed for antibodies against *Toxoplasma gondii*, cytomegalovirus, Epstein-Barr virus (EBV), mumps virus, and *Borrelia burgdorferi*. The serum samples obtained from the first 200 patients were also tested for antibodies against *Brucella abortus* and *Francisella tularensis*. Screening for tuberculosis was performed using the tuberculin skin test.

**Detection of Bartonella DNA in tissue specimens.** Fine-needle aspiration or extirpation of the affected lymph nodes was performed for patients who developed lymph node suppuration and for patients for whom a malignant or benign noninfectious disease was suspected on the basis of results of physical examination or other results (e.g., ultrasonography results). The extirpated lymph nodes were assessed histopathologically and microbiologically, as well as by molecular methods.

Extraction of DNA from the lymph node specimens and amplification of *Bartonella* DNA by use of PCR methods (with primers p24E and p12B) were performed as described elsewhere [17]. In each experiment, purified DNA obtained from a cultured *B. henselae* strain (ATCC [American Type Culture Collection] 49882) and DNA-free water were used as positive and negative controls, respectively. A PCR protocol for detection of the \( \beta \)-globin gene in the extracted DNA sample was used as an internal control [18].

**Culture methods.** Extirpated lymph node specimens obtained for microbiological investigation were homogenized and incubated in brain-heart infusion broth and were plated onto Columbia agar, chocolate agar, and, for anaerobic growth, blood agar that contained glucose–yeast extract–cysteine. All cultures were incubated either at 37°C in a humid atmosphere that contained 5% CO\(_2\) or anaerobically, and the cultured bacteria were identified by standard biochemical methods.

**Histopathological investigation.** The lymph node specimens were fixed in 4% formalin, embedded in paraffin, cut to a size of 2–3 \( \mu \)m, and routinely stained with hematoxylin-eosin. Warthin-Starry silver staining was performed on all lymph node specimens obtained from patients with histopathologically suspected CSD.

**Statistical analysis.** Results are presented as mean values (± SD) and median values. Data were analyzed with Kruskal-Wallis 1-way analysis of variance. \( P \leq 0.05 \) was considered to be statistically significant. Analyses were performed with SPSS software for Windows, release 10.0.5 (SPSS), and Microcal Origin software, version 6.0 (Microcal Software).

**RESULTS**

**Diagnostic spectrum of patients with lymphadenopathy in the head and neck.** Of the 454 patients with enlarged lymph nodes, a total of 156 patients (34.4%) had infectious diseases, 75 (16.5%) had benign disorders, and 52 (11.5%) had malignant diseases; 171 (37.7%) remained undiagnosed (table 1). Sixty-one patients (13.4%) fulfilled the diagnostic criteria for CSD, and, in a total of 95 patients (20.9%), the enlarged lymph nodes were found to be caused by other bacterial, viral, or protozoal infections. The primary infections in this group comprised serologically diagnosed cases of toxoplasmosis (\( n = 15 \)), EBV (\( n = 5 \)), varicella-zoster virus (\( n = 4 \)), mumps (\( n = 2 \)), Lyme borreliosis (\( n = 1 \)), and tularemia (\( n = 1 \)). Antibodies
against *Brucella abortus* were not found in any of the serum samples tested, and no acute infections with cytomegalovirus were diagnosed.

By culture of lymph nodes, we found *Streptococcus pyogenes* (7 isolates), *Staphylococcus aureus* (6 isolates), *Mycobacterium tuberculosis* (5 isolates), anaerobic bacilli (5 isolates), and *Haemophilus parainfluenzae, Haemophilus aphrophilus, Streptococcus anginosus*, and *Actinomyces israelii* (1 isolate each). For 41 patients, swollen lymph nodes were accompanied by non-CSD infections, such as tonsillitis, sinusitis, parotitis, mastoiditis, and otitis media (secondary infections; table 1).

Malignant neoplasms were found in 52 patients (11.5%). Of these malignant neoplasms, 26 were squamous cell carcinomas of the head and neck, 6 were malignant Hodgkin lymphomas, 14 were malignant non-Hodgkin lymphomas, 2 were melanomas, and 4 were other neoplasms. Benign neoplasms were found in 60 patients (13.2%). Of these benign neoplasms, 20 were adenomas, 14 were cystic lesions, 14 were cases of lymph node hyperplasia, and 2 were carcinomas; in addition, there was 1 case each of neurofibroma, hemangioma, and lymphangiolipoma, and 7 other benign neoplasms were noted.

Benign disorders were found in 15 patients (3.3%). Four of these patients had Sjögren syndrome, 3 had sarcoidosis, and 2 had thrombotic veins. Furthermore, we found 1 case each of Melkersson-Rosenthal syndrome, stenosis of the glandular papilla, myosclerosis, chronic cicatrization along a thrombotic internal jugular vein, cystic structure, and chyle fistula.

**Clinical findings for patients with CSD.** On the basis of the criteria presented in the Patients and Methods section, CSD was diagnosed in 61 (13.4%) of all patients assessed (table 1). Of the 61 patients with CSD, 33 (54%) were women or girls and 28 (46%) were boys or men. Of the 393 patients without CSD, 230 (58.5%) were women or girls and 163 (41.5%) were boys or men. The average age of the patients with CSD was 4–89 years (median, 33.9 years), and that for the non-CSD group was 2–90 years (median, 35.0 years). The spectrum of clinical findings for the 61 patients with CSD is shown in table 2. We diagnosed acute lymphadenopathy in 39 patients (64%); in 11 (18%) of these patients, we found suppuration of the affected lymph nodes or, even, an abscess, and the remaining 11 patients presented with chronic lymphadenopathy (defined by a duration of illness of >3 months). A total of 36 (59%) of all patients with CSD had bilateral lymphadenopathy as detected by ultrasonography. Of the patients with unilateral lymphadenopathy, 18 (30%) were found to have left-side disease and 7 (11%) were found to have right-side disease. Of interest, 11 patients with CSD had concomitant pharyngitis, and 1 female patient developed perichondritis of the auricle with regional lymphadenitis after sustaining a cat scratch on her ear.

Although, to date, cats are the only known reservoir for *B. henselae*, only 35 (57%) of the 61 patients with CSD had contact with cats. Fifteen patients (25%) denied having any contact, and an additional 11 patients (18%) could not definitely remember whether they had been exposed to cats or not.

The interval from the onset of symptoms to a patient’s first presentation at the Department of Otorhinolaryngology–Head and Neck Surgery at the University of Freiburg varied enormously (average interval, 41 days). For patients with acute lymphadenitis and for patients with supplicative lymph nodes, the average interval was 25 days; for patients with chronic lymphadenopathy, it was 117 days. Most of the patients with CSD got sick in fall and winter (between September and April) (figure 1).

**Serological findings.** *B. henselae* infection could be proven serologically in all 61 patients. In 23 patients (38%), we found only low IgG titers of <1:512 at the time of the first examination. For patients with CSD, the IgG titers against *B. henselae* at the time of admission, with regard to the onset of the illness, are shown in figure 2. The highest titers (up to 1:8192) were found 2–16 weeks after the onset of illness. Kruskal-Wallis 1-way analysis of variance was used for statistical analysis of the IgG titer in association with the time of onset of illness (3

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### Table 1. Diagnoses for 454 patients with lymphadenopathy in the head and neck.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Bartonella henselae seropositivea</th>
<th>Bartonella henselae seronegativeb</th>
<th>Total no. (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cat-scratch diseaseb</td>
<td>61</td>
<td>0</td>
<td>61 (13.4)</td>
</tr>
<tr>
<td>Other primary infections</td>
<td>15</td>
<td>39</td>
<td>54 (11.9)</td>
</tr>
<tr>
<td>Secondary infection</td>
<td>11</td>
<td>30</td>
<td>41 (9.0)</td>
</tr>
<tr>
<td>Malignant neoplasm</td>
<td>16</td>
<td>36</td>
<td>52 (11.5)</td>
</tr>
<tr>
<td>Benign neoplasm</td>
<td>18</td>
<td>42</td>
<td>60 (13.2)</td>
</tr>
<tr>
<td>Other benign disorders</td>
<td>5</td>
<td>10</td>
<td>15 (3.3)</td>
</tr>
<tr>
<td>Undiagnosed</td>
<td>46</td>
<td>125</td>
<td>171 (37.7)</td>
</tr>
<tr>
<td><strong>Total, no. (%) of patients</strong></td>
<td>172 (37.9%)</td>
<td>282 (62.1%)</td>
<td>454 (100)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. of patients, unless otherwise indicated.

a IgG titer against *B. henselae*, ≥1:64.

b Including 4 patients with malignancy.
groups: those tested at 0–10 days of illness [19 patients], 11–55 days of illness [24 patients], or >56 days of illness [18 patients]). Findings showed that patients who underwent testing within the first 10 days of illness had a significantly lower IgG titer than did those who were tested at a later stage (P = .021). A total of 111 (28.2%) of 393 patients without CSD had low titers of antibody against *B. henselae*. The serological results for patients with and without CSD are compared in figure 3.

For 46 patients (75%), IgM titers against *B. henselae* were negative at the time of the first serological investigation; for 8 patients, the titer value was 1:64, and, for another 6 patients, the titer value was 1:128. Only one patient had an initial IgM titer of 1:256. Four patients, who had Sjögren syndrome, EBV, the titer value was 1:128. Only one patient who had an initial IgM titers without detectable IgG antibodies. However, no increase in titer was noted, and CSD could not be confirmed in these patients. Of all 61 patients with CSD, only one 34-year-old woman was shown to have CSD and toxoplasmosis simultaneously, and a 37-year-old woman had CSD and an EBV infection.

**PCR detection of Bartonella DNA in lymph node specimens.** Lymph node specimens were obtained from 21 of the 61 patients with CSD. By use of PCR analysis of the β-globin gene as an internal control, DNA amplification could be obtained for all lymph node specimens evaluated. For 10 (48%) of these 21 patients, we could confirm the diagnosis of CSD by detection of *B. henselae* DNA with PCR (table 3). Relating our positive (n = 10) and negative (n = 11) PCR results to the time interval after onset of illness, almost all lymph nodes removed (9 of 10) had positive PCR results up to the sixth week of the illness. Thereafter, *B. henselae* DNA could be detected in only 1 lymph node (obtained from an HIV-positive patient) at 17 weeks after the onset of lymphadenopathy. *Bartonella* DNA was not detected in any of the 11 patients without CSD who we evaluated. Although part of all extirpated lymph nodes was also plated onto agar, *B. henselae* could not be cultured from any specimen.

**Histopathological findings.** Whole lymph nodes were extirpated from 12 patients with CSD because of initially suspected malignant disease or because the lymph nodes were suppurative. In 8 patients, we found a reticular granulomatous abscess. One case each of nonspecific follicular, paracortical, and sinusoidal hyperplasia, epithelioid granulomatous lymphadenitis with sarcoidosis-like granulomas, and epithelioid granulomatous giant-cell reaction in a lymph node with focal suppuration was found. In all 12 patients, CSD bacilli were not detected by Warthin-Starry silver staining.

In 4 patients, histological examination of the lymph node was performed, despite the presence of high IgG titers (1:1024) against *B. henselae*, because the patients’ histories and the findings of physical examination and ultrasonography made an infectious etiology unlikely. In 2 of these patients, we found a squamous cell carcinoma, and 2 patients had malignant B cell lymphoma.

**Antimicrobial therapy for patients with CSD.** Thirty-four (56%) of the patients with CSD were treated in an outpatient setting, and 27 (44%) were admitted to the hospital. A total of 48 patients (79%) had received empiric antibiotic therapy before serological investigation for CSD was performed. Twenty-one patients had received cephalosporins; 14, penicillins; 7, doxycycline; and 5, clindamycin. One patient was treated with trimethoprim-sulfamethoxazole. None of those treatments was successful, as history-taking, physical examination, and ultrasonographic studies revealed.

After CSD was diagnosed, we initiated antibiotic treatment only for patients who had painful or abscessed lymph nodes; 33 patients were treated with antibiotics (27 were treated with macrolides and 6 were treated with quinolones). For those patients, the pain subsided within a few days, although it took several weeks to months until the lymphadenopathy had subsided ultrasonographically. Nine patients with CSD did not

![Figure 1.](https://academic.oup.com/cid/article-abstract/35/6/643/377924/646)
Figure 2. IgG titers against *Bartonella henselae* at the time of admission of 61 patients with cat-scratch disease, in relation to the onset of symptoms.

require any antibiotic treatment, and, for 14 patients, antibiotic therapy was discontinued after CSD was diagnosed.

**DISCUSSION**

Lymphadenopathy in the head and neck is common, and the causative agents are numerous. Infections caused by bacterial, viral, fungal, and protozoal agents remain the most common etiologic group for localized lymphadenopathy, but malignancies or lymphoproliferative diseases are often found as well, especially in elderly patients. A careful history and physical examination combined with a few laboratory tests (complete blood count, sedimentation rate, tuberculin test, and specific serological tests) will narrow the spectrum of diagnostic consideration [19, 20]. Nevertheless, a considerable percentage of cases remain undiagnosed. The discovery, in 1992, of *B. henselae* as a causative agent of CSD provided an additional diagnostic tool.

CSD of the head and neck was first described in 1985 in 4 patients [21]. Thereafter, few similar cases were described in the literature. Hamilton et al. [15] showed that the neck is the site most commonly involved in CSD. CSD may also cause deep, fascial neck-space infections with adenitis and swelling of the parotid gland [22, 23]. We previously reported one case of CSD that mimicked a hypopharyngeal tumor in a 67-year-old farmer [12]. The present study demonstrates that CSD is indeed one of the most common causes of lymphadenopathy in the head and neck, with a frequency of 13.4% in our patients. However, only the patients with the most severe cases were admitted to the Department of Otorhinolaryngology at the University of Freiburg, probably because many physicians do not include CSD in their differential diagnosis. Therefore, the real incidence is likely higher than our results indicate.

CSD occurs at any age. Because early studies reported that the disease mostly affects children and adolescents, CSD has been ignored as a differential diagnosis of lymphadenopathy in adults for a long time. In the present study, the mean age of patients with CSD was 33 years (age of the oldest patient, 89 years). In the United States, 24,000 cases of CSD are reported per year (9.3 cases per 100,000 population), and >2000 (0.86 per 100,000 population) of these cases require patient hospitalization [24]. Comparable data for Germany are not yet available. Twenty-seven (44%) of our patients were hospitalized. This relatively large percentage might be explained by the selected group of patients included in our study. It is likely that we have only seen patients with more severe illness: patients with milder cases probably either did not seek medical treatment at all or were treated by physicians outside the hospital.
Clinically suspected CSD usually is confirmed serologically by antibody titers ≥1:512 [1, 16, 25]. IgM antibodies against *B. henselae* are seldom found even in the early stages of CSD, and negative results do not exclude the presence of acute disease. Our data demonstrate that, in the early stages of disease, antibody titers of both IgG and IgM might still be low, and diagnosis can only be confirmed after increasing titers have been noted in a second serum sample. In addition, 111 (28%) of 393 patients without CSD in our study had low antibody titers against *B. henselae* or even a non-specific reaction. In instances in which serological results fail to confirm the diagnosis of CSD, lymph node excision and the performance of histopathologic and molecular diagnostic procedures are recommended. As indicated in Table 3, PCR results strongly depend on the duration of illness; in the present study, we detected *B. henselae* DNA only in lymph nodes extirpated during the first 6 weeks of illness. We could confirm these results in an animal model of CSD as well (data not shown), and this phenomenon will be further investigated.

Table 3. Results of PCR analysis and Warthin-Starry silver staining of 21 lymph nodes, in relation to the onset of illness in patients with cat-scratch disease and serological results at the time of lymph node extirpation.

<table>
<thead>
<tr>
<th>Patient</th>
<th>No. of weeks after onset of illness</th>
<th>Result of PCR</th>
<th>Result of silver staining</th>
<th>IgG titer</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>1</td>
<td>−</td>
<td>ND</td>
<td>1024</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>+</td>
<td>−</td>
<td>8192</td>
</tr>
<tr>
<td>13</td>
<td>3</td>
<td>+</td>
<td>−</td>
<td>1024</td>
</tr>
<tr>
<td>11</td>
<td>4</td>
<td>+</td>
<td>ND</td>
<td>256</td>
</tr>
<tr>
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<td>29</td>
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<td>18</td>
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<tr>
<td>61</td>
<td>40</td>
<td>−</td>
<td>ND</td>
<td>256</td>
</tr>
</tbody>
</table>

**NOTE.** ND, not done; +, positive; −, negative.

a Detection of *Bartonella henselae* DNA.

b HIV-positive patient.
ably much more common cause of unclear masses in the head and neck than has been previously reported. CSD should no longer be considered a disease of children; it occurs in individuals of any age. The clinical symptoms of CSD range from painless lymphadenopathy to large cervical abscesses, even in immunocompetent patients. Therefore, to avoid unnecessary treatment or surgery, CSD should be considered in the differential diagnosis of unclear masses and lymphadenopathy of the cervicofacial region.

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References


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