Arch Pediatr Infect Dis. 2016 January; 4(1): e28272. doi: 10.5812/pedinfect.28272

Published online 2016 January 2. **Case Report**

Atypical Cat-Scratch Disease in Children: Report of Seven Presentations Ranging From Hepatosplenic Disease to Horner Syndrome

Olivier Gilliaux,[1] Valerie Ghilain,[2] Dimitri van der Linden,[2] Jean Philippe Stalens,[3] Catherine Heijmans,[4] Jacques Louis,[5] Christiane Vermylen,[2] and Christophe F. Chantrain[6,*]

[1]Department of Pediatrics, Hôpital Civil Marie Curie, Charleroi, Belgium
[2]Department of Pediatrics, Cliniques Universitaires Saint-Luc, Université catholique de Louvain (UCL), Brussels, Belgium
[3]Department of Pediatrics Centre, Centre hospitalier Wallonie Picarde, Tournai, Belgium
[4]Department of Pediatrics, Centre hospitalier de Jolimont, Haine-Saint-Paul, Belgium
[5]Department of Pediatrics, Grand hôpital de Charleroi, Charleroi, Belgium
[6]Department of Pediatrics, Division of Pediatric Hematology Oncology, Clinique de l'Espérance, Centre Hospitalier Chrétien, Montegnée, Belgium

*Corresponding author: Christophe F. Chantrain, Department of Pediatrics, Division of Pediatric Hematology Oncology, Clinique de l'Espérance, Centre Hospitalier Chrétien, 447 Rue St-Nicolas - 4420 Montegnée, Belgium. Tel: +32-42249141, Fax: +32-42249148, E-mail: christophe.chantrain@chc.be

Received 2015 February 28; **Accepted** 2015 April 30.

Abstract

Introduction: Cat scratch disease (CSD) is an infectious disease caused by the Gram-negative rod Bartonella henselae (BH). It usually leads to subacute loco-regional lymphadenitis occasionally associated with fever. In most of the cases, it resolves spontaneously within 4 - 6 weeks. However, CSD has also been associated with other atypical presentations.

Case Presentation: We reported a series of seven children with unusual symptoms of CSD. In particular, we described the case of a child with ptosis, miosis and enophtalmy, suggesting Horner syndrome, associated with cervical lymphadenitis. Cat scratch was mentioned in only one patient, while four of them mentioned a recent contact with cats. We reviewed and discussed the incidence of these atypical presentations of CSD as well as the therapeutic approaches recommended and the available diagnostic tools.

Conclusions: This paper highlighted the need to exclude CSD in children with unexplained symptoms such as prolonged fever, hepatosplenic lesion and osteomyelitis.

Keywords: Bartonella Henselae, Cat-Scratch Disease, Horner Syndrome, Osteomyelitis, Atypical Presentation, Systemic Manifestation

1. Introduction

Cat-scratch disease (CSD) is an infectious disease caused by the Gram-negative rod Bartonella henselae (BH). It is usually benign and self-limited. It affects children or young adults in contact with infected cats. Cats, especially under one year old, get infected by cat fleas (Ctenocephalides felis). Humans are contaminated by cat saliva or by scratch. However, the absence of cat in the direct environment of patient and the lack of history of scratch does not exclude the diagnosis of CSD. Transmission by dogs has also been rarely reported (1).

Typically, CSD leads to subacute regional lymphadenitis, possibly associated with mild fever. Symptoms occur between 14 days to several weeks after the inoculation. Scratch lesion is rarely found. Lymphadenitis tends to resolve spontaneously within 4 - 6 weeks, although surgical drainage of necrotic collection is indicated in 12 - 16% of the cases (2). Less specific symptoms such as prolonged fever, hepatosplenic lesions, osteomyelitis, radiculopathy or neuroretinitis have also been associated with CSD (1). In this paper, we reported a series of seven children with atypical presentations of CSD. We reviewed and discussed the incidence of these unusual manifestations, the therapeutic approaches recommended, and the biological tools available to confirm the diagnosis of CSD.

2. Case Presentation

Seven children with a broad spectrum of atypical symptoms were diagnosed with CSD in several pediatric centers in Belgium. The clinical histories of these patients are summarized in Table 1. Four children mentioned the presence of cats at home, but only one patient reported a history of cat scratch. Five children (patients 1 to 5) presented abdominal pain associated with systemic symptoms such as persistent fever and loss of weight. In these patients, the radiological evaluation revealed liver and/or spleen nodular infiltrations. Bone lesions (in thoracic or lumbar vertebrae) were detected in three patients (patients 3 to 5) with back pain. A systemic infection without localized lesion was identified in patient 6 who presented prolonged fever and diffuse muscle pain. Patient 7 presented preauricular and cervical lymphadenopathy associated with ptosis, miosis and enophtalmy, suggestive of Horner syndrome.

Table 1. Clinical, Biological and Radiological Presentations of Seven Children With Atypical Cat Scratch Disease

Patient, Age, Gender	Clinical Symptoms	Evocating History of Cat Scratch	Imaging	Serological Testing and Other Investigations	Treatment and Evolution
Patient 1, 7 y, female	Abdominal pain for 72 hours; high fever	No contact with cats reported	US: hypoechogenic mass in the liver associated with enlarged lymphadenitis. MRI: unique lesion in the liver associated with lymphadenitis	Day 0: IgG > 1/320, IgM > 1/100 Day 10: IgG > 1/1280, IgM > 1/100	Treated by rifampicin and azithromycin; disappearance of all lesions in one month
Patient 2, 14 y, male	Weight loss (15% in 7 weeks); abdominal pain, vagal discomfort (twice); painful axillary lymphadenitis	No contact with cats reported	US: multiple hypoechogenic lesions in the liver. Tomodensitometry: multiple lesions in the liver (qualified as micro-abscesses) + multiple lesions in the spleen not seen on US. MRI: multiple lesions in the liver and in the spleen (qualified as abscesses)	Day 0: IgG 1/320, IgM negative Day 7: IgG > 1/1280, IgM > 1/100	Treated by ciprofloxacin; disappearance of all lesions in one month
Patient 3, 15 y, male	Left lumbar area pain (brutal appearance); left low thoracic pain; irradiation of pain to the left testis; mictalgia; fever; weight loss (8% in 1 week); enlarged painful lymphadenitis in the pre-auricular area; painful palpation of the left iliac area; painful splenomegaly reaching 3 cm below the costal edge	No contact with cats reported	US: numerous nodular hypodense lesions in liver and spleen + enlarged lymphadenitis in the liver. PET scan: hypermetabolic lesions in a lymphadenopathy in the right parotid gland and another in the right spinal area. Numerous hypermetabolic lesions in the liver and spleen. Hypermetabolic lesion in a lumbar vertebrae (L3-no traduction in tomodensitometry)	Day 0: IgG > 1/1280, IgM > 1/100	Treated by azithromycin followed by ciprofloxacin; disappearance of all lesions
Patient 4, 3 y and 9 mo, female	10 days fever; back pain; granulomatous lesion on the left index	Presence of kitten at home; patient regularly scratched	US: hypoechogenic lesion in the liver. Tomodensitometry: no bone lesion. MRI: bone lesion seen on L3. Bone scintigraphy: hyperfixation on L3	Day 0: IgG > 1/1280, IgM negative	Treated by azithromycin; disappearance of all lesions
Patient 5, 14 mo, male	Recurrent fever for 6 weeks; faint with cyanosis of the extremities	In contact with cats, no scratch reported	US: multiple hypoechogenic lesions in liver and spleen. MRI: *Abdominal: multiple lesions in the liver and in the spleen. *Vertebral spine: inflammatory lesion on the pedicle of T4. Minimal infiltration of the soft tissues surrounding. PET Scan: hypermetabolic lesion on a vertebra (T4). Some other lesions in the axillary area, in the liver and in the spleen. US: normal Lumbar MRI: normal	Day 0: IgG > 1/1280, IgM > 1/100. Day 14: IgG > 1/4000, IgM > 1/100	Treated by azithromycin; disappearance of all lesions
Patient 6, 10 y, female	Shoulders, back and inferior limbs pain for 6 weeks (probable radiculitis); fever for 6 weeks	In contact with cats, no scratch reported	US: normal. Lumbar MRI: normal	Day 0: IgG > 1/1280, IgM negative Day 14: IgG 1/320, IgM negative. Day 60: IgG 1/640, IgM negative	Treated by clarithromycin; complete regression within 1 month
Patient 7, 14 y, female	Preauricular painful tumefaction; miosis, ptosis, enophtalmy evocating Horner Syndrome	In contact with cats, no scratch reported	US: Enlarged lymphadenitis inside the left parotid. MRI: A specific nodulary tumefaction of the parotid	Day 0: IgG 1/320, IgM negative. Day 21: IgG > 1/1280, IgM > 1/100. Biopsy: granulomatous lymphadenitis	Treated by azithromycin; disappearance of all signs included Horner syndrome

Abbreviations: MRI, magnetic resonance imaging; PET, positron emission tomography; US, ultrasonography.

3. Discussion

These series illustrated that CSD induces symptoms that surpass the classical subacute lymphadenitis associated or not with slight fever. Those symptoms can occur independently on the immune status of the host. The frequencies of these atypical presentations of CSD are listed in Table 2. In immunodeficient patients, CSD is rather associated with specific manifestations such as bacillary angiomatosis and peliosis hepatis (1). As found in our series, prolonged fever and hepatosplenic CSD are the most common signs of disseminated BH infection. In pediatrics, CSD is considered as the third cause of fever of unknown origin (FUO) after infection by Epstein Barr virus and osteomyelitis, and before urinary tract infection (1, 3). Fever can last for several weeks and may be associated with headaches and diffuse muscle pain. Hepatosplenic lesions, often revealed by abdominal pain, have been described in 10 - 14% of CSD patients (1). They consist of parenchymal micro-abscesses resulting from a hematogenous spread of the pathogen (1, 2). Hepato- and/or splenomegaly have been clinically detected in some, but not all cases. The dissemination of BH may also result in osteomyelitis (4). The most frequent bones involved are vertebrae, pelvis and ribs. Patients present with localized pain possibly along with inflammatory signs in the adjacent soft tissues, although some bone lesions are asymptomatic and are only detected by scintigraphy and/or radiology (4, 5). Magnetic resonance imaging (MRI) allows early detection prior to tomodensitometry or X-ray (5).

The neurological manifestations of CSD are very rare and reported in only 1 - 2 % of CSD cases. These symptoms include encephalopathy (90% of neurological manifestations), neuroretinitis (acute visual loss due to optic nerve edema and macular exudate), radiculitis and transverse myelitis (7). The Parinaud oculoglandular syndrome, characterized by unilateral conjunctivitis with conjunctival granuloma, has also been associated with preauricular and/or submaxillary CSD lymphadenopathy. It is attributed to the inoculation of BH in the conjunctiva (1). Patient 6 presented with back and inferior limbs pain which may correspond to radiculitis. While bone lesions were excluded by radiological workup, no further examination was performed to investigate the presence of neurological lesion in this patient. Patient 7 presented with miosis, ptosis and enophtalmy, suggesting Horner syndrome. It was the first time that this syndrome was associated with CSD. It is usually due to a lesion along the sympathetic pathway in the area of neck, head or eye. Our hypothesis was that enlarged lymphadenitis probably compressed the sympathetic nerve and induced Horner syndrome. This syndrome completely disappeared concomitant with lymphadenitis regression.

Table 2. List of Atypical Presentation of Cat Scratch Disease Reported in the Literature

Incidence	Value, %	Reference
More Frequent	30 – 65 of CSD	
Fever	30 - 65	(1, 2, 6)
Malaise	~ 44	(6)
Less frequent	5 – 15 of CSD	
Myalgia/arthritis/arthralgia	5 - 10	(5, 6)
Hepatosplenic involvement	~ 10 - 14 (present in 30 of FUO due to CSD)	(1)
Parinaud syndrome	~ 5	(1)
Dermatologic lesions (other than inoculation site papule): maculopapular and urticarial eruption, erythema nodosum, erythema marginatum, etc.	~ 5	(1)
Rare	Less than 5 of CSD	
Neurological involvement	1 - 2, (90 encephalitis)	(1, 7)
Osteomyelitis	0.1 - 0.3	(4)
Endocarditis	3 of children with previous valvular disease	(1)
Glomerulonephritis	rare case reports	(1)
Hematological manifestations: hemolytic anemia, prolongation of the activated partial thrombin time, etc.	rare case reports	(1)

Abbreviations: CSD, cat scratch disease; FUO, fever of unknown origin.

Since BH is difficult to culture from human specimens, the diagnosis of CSD mainly resides on serological investigations. Two techniques are available to detect antibodies against BH. The immunofluorescent antibody assay (IFA) is considered more reliable and more sensitive than the enzyme-linked immunosorbent assay (EIA) (6, 8). The sensitivity and specificity of immunoglobulin (Ig) G detection by IFA have been reported respectively around 88% and 97%. IgM detection is slightly less sensitive and specific (respectively around 70 - 90% and 87.5 - 100%) (6, 8). The timing is also important for the interpretation of these analyses. IgM and IgG occur within 1 - 8 weeks after the onset of the disease. IgM lasts for three months while IgG remains increased up to two years after infection. An increase of both IgM and IgG confirms the diagnosis of CSD (6). However, an isolated elevation of IgM or IgG, in particular in the context of atypical presentation, needs to be interpreted with caution. A second analysis repeated after 3 - 6 weeks may be useful in the interpretation. A delayed elevation of IgM level on the second sample concomitant with IgG increase is considered as a proof of CSD. Likewise, an amplified increase of IgG level on the second sample (above 1/512 or at least four times the previous level) confirms the diagnosis of CSD (6). In our series, all the patients but two had an increase in both IgM and IgG levels. The high level of IgG (> 1/1280) in patients 4 and 6 and the presence of lymphadenopathy possibly with a cat scratch on the finger in patient 4 led us to establish the diagnosis of CSD. Polymerase chain reaction (PCR) is also useful in the detection of BH (8). This analysis can be performed on any possibly infected tissue (i.e. lymph, liver, bone, etc.). PCR allows early detection, prior to seroconversion, with a high specificity and a better sensitivity than serological investigations. When combined, these analyses reach a sensibility of more than 92% (2). The major limitation of PCR is the requirement of invasive tissue sampling. On blood, PCR has a lower sensitivity and its use in clinics remains controversial (1, 7). None of our patients was diagnosed using PCR.

As for typical CSD lymphadenitis, the role of antibiotics in the management of uncomplicated fever and/or hepatosplenic lesions is controversial and most authors only recommend symptomatic treatment (1, 2). While drugs such as azithromycin, doxycycline, rifampicin, gentamicin, ciprofloxacin or trimethoprim-sulfamethoxazole have a potential interest, only azithromycin (with a dose of 10 mg/kg on day one, followed by 5 mg/kg from days 2 - 5) has demonstrated its efficacy on lymphadenitis (9). There has been no randomized trial on atypical CSD. In CSD osteomyelitis, prolonged antibiotherapy up to six weeks is recommended, but the drug and the duration of treatment remain debated (5). Azithromycin has good bone diffusion and no significant toxicity in children (5). Trimethoprim–sulfamethoxazole, ciprofloxacin or rifampicin are also characterized by good bone diffusion and could therefore be used against BH. No pediatric recommendation has been offered for neurological manifestation of CSD. In adults, a combination of doxycycline and rifampicin has been proposed (10). In the absence of response, the use of corticosteroids has also been suggested while there is no published data in this regard. We acknowledge that the therapeutic approach in our patients was quite variable. This was due to the fact that patients were diagnosed and treated in several centers. All of them were treated with antibiotics despite the absence of consensus in the approach of uncomplicated forms of CSD. Their clinical outcomes were favorable, although it was not necessarily correlated to the initiation of antibiotherapy.

This report underlines that CSD should be evocated not only in front of loco-regional lymphadenitis, but also in a broad spectrum of presentations in children. In this context, history and clinical examinations looking for cat scratches are often not contributive. In addition, serological workup represents a widely available tool for the diagnosis of CSD. Therefore, we suggest including this testing in the routine evaluation of children with prolonged fever of unknown origin, or unexplained liver, spleen or bone lesions. We also highlight that, when unclear, a second delayed serological assay and/or a PCR on the possibly infected tissue may be useful to precise the diagnosis of CSD. Further investigations are required to better understand the natural progression of BH infection in human, identify the factors leading to self-limited or systemic dissemination, and define the most efficient therapeutic approach of this disease in children.

Footnote

Authors' Contribution: Study concept and design: Olivier Gilliaux and Christophe F Chantrain; acquisition of data: Olivier Gilliaux, Valerie Ghilain, Dimitri Van der Linden, Jean Philippe Stalens, Catherine Heijmans, Louis, Christiane Vermylen and Christophe F Chantrain; analysis and interpretation of data: Olivier Gilliaux; drafting of the manuscript: Olivier Gilliaux; critical revision of the manuscript for important intellectual content: Christophe F Chantrain; statistical analysis: Olivier Gilliaux; administrative, technical, and material support: Christophe F Chantrain; study supervision: Christophe F Chantrain.

References

1. Florin TA, Zaoutis TE, Zaoutis LB. Beyond cat scratch disease: Widening spectrum of Bartonella henselae infection. *Pediatrics.* 2008;**121**(5):e1413–25. doi: 10.1542/peds.2007-1897. [PubMed: 18443019]
2. Abgueguen P, Chennebault JM, Achard J, Cottin J, Pichard E. [Cat scratch disease. Clinical study of 26 patients. Role and importance of PCR]. *Rev Med Interne.* 2001;**22**(6):522–9. [PubMed: 11433560]
3. Jacobs RF, Schutze GE. Bartonella henselae as a cause of prolonged fever and fever of unknown origin in children. *Clin Infect Dis.* 1998;**26**(1):80–4. [PubMed: 9455513]
4. Hajjaji N, Hocqueloux L, Kerdraon R, Bret L. Bone infection in cat-scratch disease: A review of the literature. *J Infect.* 2007;**54**(5):417–21. doi: 10.1016/j.jinf.2006.10.045. [PubMed: 17140668]

5. Roubaud-Baudron C, Fortineau N, Goujard C, Le Bras P, Lambotte O. [Cat scratch disease with bone involvement: A case report and literature review]. *Rev Med Interne.* 2009;**30**(7):602–8. doi: 10.1016/j.revmed.2009.01.015. [PubMed: 19303175]
6. Metzkor-Cotter E, Kletter Y, Avidor B, Varon M, Golan Y, Ephros M, et al. Long-term serological analysis and clinical follow-up of patients with cat scratch disease. *Clin Infect Dis.* 2003;**37**(9):1149–54. doi: 10.1086/378738. [PubMed: 14557957]
7. Rondet B, Sarret C, Lacombe P, Rouveyrol F, Chenel C, Romaszko JP, et al. [Neurological symptoms with Bartonella henselae infection: report on 2 pediatric cases]. *Arch Pediatr.* 2012;**19**(8):823–6. doi: 10.1016/j.arcped.2012.05.011. [PubMed: 22749487]
8. Sander A, Berner R, Ruess M. Serodiagnosis of cat scratch disease: Response to Bartonella henselae in children and a review of diagnostic methods. *Eur J Clin Microb Infect Dis.* 2001;**20**(6):392–401.
9. Margileth AM. Antibiotic therapy for cat-scratch disease: Clinical study of therapeutic outcome in 268 patients and a review of the literature. *Pediatr Infect Dis J.* 1992;**11**(6):474–8. [PubMed: 1608685]
10. Rolain JM, Brouqui P, Koehler JE, Maguina C, Dolan MJ, Raoult D. Recommendations for treatment of human infections caused by Bartonella species. *Antimicrob Agents Chemother.* 2004;**48**(6):1921–33. doi: 10.1128/AAC.48.6.1921-1933.2004. [PubMed: 15155180]