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Cat Scratch Disease in Children

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Abstract
The aim of this paper is to provide information on the clinical manifestations, diagnosis and treatments of *Bartonella henselae* infection in children. Cat scratch disease (CSD) is a zoonosis caused by *Bartonela henselae*. Cat fleas are responsible for spreading the bacterium among cats. Bacteria can be transmitted to humans from the site of a cat bite or scratch. The typical manifestation of CSD is regional lymphadenopathy with a pustule at the site of inoculation, usually self-limiting. Atypical CSD has a wide range of clinical manifestations (hepatosplenic disease, pulmonary infiltrates, encephalitis, skin or bone involvement, endocarditis), some of which are life-threatening. Atypical presentations mainly occur in immunocompromised children, but have also been described in immunocompetent children. Conclusion – In recent years the number of households with a pet is growing and the number of children visiting a pediatrician with CSD is growing.

Key Words: Cat Scratch Disease ▪ Children ▪ *Bartonella Henselae* Infection.

Introduction

Cat-scratch disease (CSD) is an infectious disease caused by the *Bartonella henselae (B. henselae)* which is distributed worldwide, but the incidence is highest in regions with a warm, humid climate (1).

The first patients with clinical CSD were described in 1931 in Paris. The causative agent of CSD was identified in 1983, after finding bacteria in the lymph nodes of patients with clinical CSD (2). Cat fleas are responsible for spreading the bacteria among cats, then it is transmitted to humans from the site of a bite or scratch (1, 2). The disease is more common in children than in adults. According to one large study in the United States the highest rates of CSD occur among children 5–9 years of age (3). In a study from Japan, 79.2% patients with CSD were under 18 years of age (4), and a study from Greece reported significantly more CSD cases (62.5%) in children than in infants and adults (5). The disease has a wide range of clinical manifestations. Immunocompetent people have mild systemic nonspecific symptoms and spontaneous resolution in a few weeks. In 5%–20% of cases the infection is disseminated, with various complications (1, 6). Diagnosis of atypical CSD is often delayed. Sometimes symptoms confuse doctors. In 2014-2015 a study on clinical load assessment, treatment, and prevention of CSD was conducted in the United States among primary care staff: family physicians, internists, pediatricians and nurses. The research showed that the knowledge of pediatric staff is somewhat better, but overall knowledge is insufficient (7).

The aim of this review is to summarize the different spectra of clinical manifestations of CSD in children, to contribute to faster recognition and treatment.

Method

We searched for articles on CSD published between 2000 and 2022 in two international databases (Medline/Pub-Med and Google scholar). For the search we used the key words: cat scratch disease, children, *B. henselae* infection, clinical manifestations, etiopathogenesis, diagnosis, and treatment. Only articles published in English were included. We did not limit the type of article. Original studies with a large sample and review articles contributed to drawing a conclusion about the diagnosis and treatment of CSD. Case reports of rare manifestations were important for faster recognition of the disease.

Pathogenesis

Genus *Bartonella* consists of almost 50 different species that are small, intracellular, Gram-negative aerobic bacilli. Literature data showed that 16 species are correlated with human infections, especially *B. qiuntana, B. bacilliformis* and *B. henselae* (2, 8). The *Bartonella* species is fastidious, slow growing intracellular bacteria, which infect human erythrocytes and endothelial cells. Since erythrocytes are cells without adequate immune surveillance, they serve as reservoirs for prolonged and recurrent bacteremia and relapsing infections. Bacteria replicate in vacuoles inside infected erythrocytes for prolonged periods without hemolysis, enabling this intracellular pathogen efficient vector transmission and immune evasion. It is possible that intracellular invasion also leads to failure of antibiotic therapy. Another explanation for unsuccessful therapy treatment is the ability of this pathogen to form a bacterial community on the surface of endothelial cells, known as biofilm (8). Biofilm is a bacterial defense mechanism which allows them to resist the immune system and the action of antibiotics, leading to chronic or recurrent infections. Inside the biofilm, bacteria are protected by a self-produced exopolysaccharide envelope, preventing penetration of antibiotic molecules and immune cells (9). Infected patients produce significant levels of antibodies, but humoral immunity can only prevent the spread of extracellular bacteria and reinfection from the primary infection niche. Antibodies have no effect on the intracellular pathogens settled either inside endothelial cells or in erythrocytes, or on the bacteria protected by the biofilm. Cellular immunity is a key element in the eradication of this pathogen and the healing of an infected person. Immunocompetent patients will develop a strong cellular immune response, manifesting in lymphadenopathy as a common and the most frequent symptom of this disease. In immunocompromised patients, reduced cellular response will result in a prolonged infection, with unique angiogenic lesions that are the consequence of the production of angiogenic cytokines by infected cells of innate and adaptive cellular immunity (8, 9).

Epidemiology

CSD occurs worldwide, with the highest rates in regions with a warm climate, and most cases between July and January (1, 6). In the United States, data on national insurance claims indicate a minimum incidence of 4-6 per 100,000 population, with the highest rates in children aged 5-9 years, and 9.4 cases/100,000 population (3, 6). A study conducted in Montenegro, which is one of the Balkan countries, shows that CSD is present in this Mediterranean region. The data from 2007-2017 show 42 confirmed cases (10). The available literature data for Spain show 781 in-patients in 1997-2015, and for France 493 positive lymph node biopsy specimens over a 10 year period (11, 12). Serological studies all over the world show various results, ranging from 3.1% to 61.6% positivity in the general population (13). People become infected after a bite or scratch by an infected animal. Infection by contact of damaged mucosa with the saliva of an infected cat is also possible. *B. henselae* reservoirs are domestic animals, mostly cats. Cats with chronic bacteremia are usually asymptomatic carriers of *B. henselae* (8). The cat flea (*Ctenocephalides felis*), is the vector responsible for horizontal transmission of the disease from cat to cat. Also, it is speculated that *B. henselae* form biofilm in the gut of the cat flea, which is excreted in

the fecal matter, where it forms a biofilm that protects the bacteria for several days on the feline skin or claws (8, 9). A new potential transmission vector of *B. henselae* is *Ixodes ricinus*, the most widespread ixodid tick in Western Europe, which is frequently associated with bites in humans (1).

Clinical Presentations

Typical CSD is generally a benign self-limiting disease, with spontaneous resolution of symptoms within 2–4 months. Papules develop (single or group) at the site of inoculation and last days or weeks, with proximal regional lymphadenopathy that lasts weeks to months. Some patients may also experience fever, headache and malaise (14, 15). According published studies (6, 14) lymphadenopathy is observed in 80-95% patients with typical CSD, and is most common in the axillary and epitrochlear nodes (46 %), head and neck (26 %) and groin (17.5 %). The lymph nodes are painful and movable, with solid consistency. In 20% of patients, inflamed lymph nodes produce suppuration with purulent fistulas to the skin. Approximately 10% of nodes require drainage (14, 15).

Fever of unknown origin (FUO) is fever that lasts 2 weeks without diagnostic signs or symptoms of an obvious clinical disease. *B. henselae* is an agent increasingly recognized as the cause of chronic FUO, especially in children (15). Approximately 30% of cases of FUO are caused by *B. henselae* (16). The study by Liao et al. found that systemic CSD should be included in the differential diagnosis of children with prolonged fever associated with abdominal pain or other symptoms (weight loss, chills, headache, myalgia) (17).

Cutaneous manifestations in atypical CSD are most often maculopapular exanthem and erythema nodosum. Other, but extremely rare, cutaneous manifestations also described in Bartonella infection are: erythema multiforme, purpura, febrile morbilliform rash, erythema marginatus, granuloma annularis, and leukocytoclastic vasculitis (6, 18). The histopathology of cutaneous lesions mimics those in the lymph nodes, with the formation of granulomas with a central necrotic area, surrounded by lymphocytes, and histiocytes and with a neutrophilic infiltrate (18, 19).

Hepatosplenic disease is an unusual clinical presentation occurring in only 0.3% to 0.7% of patients, mostly in children. Patients present with fever, abdominal pain and weight loss (20, 21). Single or multiple lesions in the liver and spleen may mimic more serious disorders such as malignancy, histoplasmosis, tuberculosis, mononucleosis or immunodeficiency (21). In one recent study of 142 patients with CSD (younger than 16 years of age), 34.5% had hepatosplenic involvement (14),and similar data were obtained in a study by Nawrocki et al. (6). Visceral involvement in atypical CSD, such as lesions in the liver, spleen, lungs or kidneys, are also described (22, 23). Abdominal imaging is an important diagnostic step in patients with suspected hepatosplenic CSD. Liver biopsy and histopathological analyses of the lesions are sometimes necessary to confirm the diagnosis (22).

Atypical CSD with pulmonary manifestations may present as pneumonia, pulmonary nodules, interstitial pulmonary infiltrates or pleural effusion (24, 25). Patients with pulmonary infiltrates present with fever, regional lymphadenopathy and respiratory symptoms. This may be associated with infiltrates in other organs, where other symptoms can also be present (26, 27). The diagnostic process includes the evaluation of systemic infectious and noninfectious disease-causing mediastinal lymphadenopathy, such as tuberculosis, sarcoidosis, lymphoma or metastatic disease. Chest imaging is an important diagnostic step in patients with suspected pulmonary CSD (27). Biopsy of the mass is necessary for appropriate diagnosis (24-27).

Cardiac signs and symptoms in atypical CSD were present in only 3.6% of cases (6, 16). Presentation is nonspecific with fever, dyspnea, abdominal pain, cardiac failure and cardiac murmur. Echocardiography confirmed the presence of mitral and aortic regurgitations, and also revealed several prominent mitral-valve vegetations. Atypical CSD should be suspected in children with blood culture negative for endocarditis (28).

Unilateral lymphadenopathy in pediatric patients should be included in the differential diagnosis of CSD. Other infectious causes most often accompanied by lymphadenopathy in children are: infections by cytomegalovirus, Epstein-Barr virus and human immunodeficiency virus (HIV), adenitis caused by *Streptococcus pyogenes*, *Staphylococcus aureus* and *Toxoplasma gondii* (29). In the large study by Riva et al. patients with neck masses were divided into six groups: congenital/developmental lesions, tumors, acute and subacute lymphadenopathies, chronic nonspecific lymphadenopathies, cat-scratch disease, and mycobacteriosis. The symptoms of prolonged fever and a painful mass were typical for CSD. Clinical features with serological exams and imaging findings should drive the physician to an appropriate diagnosis (30). Most patients, especially children with CSD have a self-limiting lymphadenopathy lasting two to eight weeks and do not require antibiotics (6, 15). Lymph node biopsy is appropriate in patients whose lymph nodes fail to involute, and in whom diagnosis is uncertain (15).

Bone involvement during CSD is a rare manifestation accounting for 0.17–0.27% of all CSD cases. Following a review of published case studies of osteomyelitis associated with CSD, fever and osteoarticular pain were the most common clinical findings (31). The median age was 7 years, similar data were obtained in the study by Erdem G. (32). The most commonly affected bones were vertebral bones (51.9%) followed by limbs (32.7%). Skull localization is even more unusual. All patients showed radiological abnormalities. Most patients had a solitary bone lesion. Antibiotic therapy was combined in most cases with a duration of 3–4 weeks (31, 32). In some cases, despite antibiotic therapy, bone lesions require surgical debridement (33).

Ocular bartonellosis is a common manifestation in atypical CSD. Neuroretinitis and granulomatous follicular conjunctivitis are the most common ocular findings in children (6). Symptoms include redness, ocular discomfort, unilateral or bilateral vision loss and scotoma. Unilateral granulomatous conjunctivitis, associated with locoregional lymphadenopathy and fever, is Parinaud's oculoglandular syndrome which was mostly present in the younger age group (34). Early antimicrobial treatment may speed recovery and improve the final visual outcome. Systemic corticosteroids were recommended in patients who had significantly poor vision. The visual prognosis of ocular bartonellosis is generally good (34, 35).

Neurological manifestations in atypical CSD may be present in 1-7% of patients, more frequently in children between 7 and 12 years old (6, 36). Neurological manifestations in atypical CSD may be in the form of convulsions, status epilepticus, meningitis, encephalitis, myelitis, radiculitis or peripheral neuropathy. Encephalopathy is the most common neurological manifestation (36). Patients usually have persistent headaches, with or without fever, and may develop seizures, nuchal rigidity to pupillary dilatation or aphasia and hemiplegia. Cat-scratch encephalopathy must be considered in the differential diagnoses when pediatric patients present with unusual neurological symptoms. The spinal fluid is usually normal, although there are some reports of pleocytosis. EEGs are usually consistent with encephalopathy. Computed tomography (CT) and magnetic resonance imaging (MRI) are usually within normal range, and there are few reports of focal changes. Recovery takes months, and persistent neurological deficits are possible (36, 37).

Bacillary angiomatosis (BA) is a rare angioproliferative disease of immunocompromised patients that usually presents as vascular tumors in the skin and subcutaneous tissues. It resembles Kaposi's disease, epithelioid hemangioma and pyogenic granuloma. It most often occurs in people with HIV infection (38).

Peliosis hepatis (PH) is a rare reactive vascular process which radiologically resembles liver tumors. In children, PH has been reported mostly with underlying chronic conditions, neoplasia, acute bacterial and *B. henselae* infection, and exposure to certain drugs and toxins. Reported mortality in pediatric cases is high (6, 39).

Diagnosis

The diagnosis of *B. henselae* infection is based on a combination of patient history, clinical manifestations, microbiological analysis and histological examinations (15). Patients with unilateral lymphadenopathy and a history of cat exposure need a diagnostic evaluation of CSD (29, 30). Laboratory findings of CSD are variable, high levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), leukocytosis and anemia have been described most (14, 40). Microbiological analyses involve classical culture methods, and serological and molecular testing. Cultivation of bacteria is always the gold standard for detection of live pathogens in human samples. Since *Bartonella* species are fastidious, biochemically inert and slow growing bacteria, classical culture techniques on solid agars are not sensitive enough and should be supplemented with serological and molecular methods (40). Novel approaches combine liquid *Bartonella-Alphaproteobacteria* growth medium for pre-enrichment growth of bacteria sampled in human specimens, such as blood or tissue biopsy, followed by molecular polymerase chain reaction (PCR) testing. Such liquid media contain a higher number of bacteria after proper incubation compared to the direct sample from the patient, which allows precise detection by molecular techniques. Although molecular testing is most sensitive analysis for most intracellular pathogens. A direct PCR test from the blood of CSD patients is of limited value for patients with a very low bacteremia level, while in the case of tissue specimens, the sample collection requires invasive medical procedures that are often avoided by doctors (40, 41). The most common and readily available method for diagnosis of SCD is serological testing of *B. henselae* in blood samples of infected patients (41). Elevated antibodies for *B. henselae* can be detected by two serological diagnostic methods: enzyme linked immunosorbent assay (ELISA) or indirect fluorescent assay (IFA). ELISA could be an automated method, which is more preferable in routine laboratory testing. On the other hand, the sensitivity and specificity of IFA testing are higher than ELISA, but the production of *B. henselae* IFA antigen is complicated. The production of antigen by liquid medium for ELISA testing is easier and faster (40). A titer of immunoglobulin G (IgG) greater than 1:256 strongly suggests an active or recent infection. A *Bartonella* serology titer ≥ 1:512 or four-fold titer rise in paired serum samples taken 2–4 weeks after the first titer is the most useful predictor of acute infection (41, 42). A positive immunoglobulin M (IgM) test suggests acute disease, but IgM production time is very short and transitory. Given all the shortcomings of serological assays, negative serology does not rule out CSD in a patient with typical epidemiological and clinical features (40-43). Radiological imaging diagnostic methods are important for patients with suspected atypical CSD with bone or visceral involvement (32). Histopathological examination is an invasive method but sometimes necessary to confirm diagnosis (1, 25).

Treatment

Prevention measures include: avoiding rough play with cats, treating cats for fleas, and washing hands after animal bites and scratches with soap and water (7). Typical CSD is a self-limiting disease that resolves within 2 to 4 months. Most symptoms of typical CSD, such as fever and swollen lymph nodes, are the result of an immune response to the presence of bacilli, and do not require antimicrobial therapy. For mildly ill immunocompetent patients antibiotics are not usually recommended, because antibiotic therapy adds the risk of adverse drug reactions and the generation of resistant flora (44, 45). Monitoring of the patient and symptomatic therapy with analgesics and applying warm compresses to the affected area are recommended. The lymph node may suppurate and drainage is necessary, where needle aspiration is preferred (1, 3). According to the recommendations given by the Infectious Diseases Society of America (IDSA) in their practice guidelines, antibiotics are indicated for patients with moderate to severe CSD, extensive lymphadenopathy, and immunocompromised patients (45). The recommended antibiotic is

azithromycin at doses of 10 mg/kg on day one and 5 mg/kg per day on days 2-5 (43-45). Most patients treated with azithromycin had a significant reduction in the volume of the affected lymph nodes. It is also effective in treating atypical forms of CSD due to its ability to penetrate human cells such erythrocytes, where bacteria multiply (14, 34, 43). Also, macrolides have a better safety profile for children compared to tetracyclines and aminoglycosides. If azithromycin is contraindicated, an effective alternative may be trimethoprim-sulfamethoxazole (TMP-SMX). In the small study by Shorbatli et al. the effectiveness of azithromycin and TMP/SMX was comparable in improving symptoms and reduction of the volume of the affected lymph node (46).

There is no consensus about the type of antimicrobial drug and the duration of therapy for a diagnosis of systemic CSD. Treatment and combinations of antimicrobial therapy vary from case to case (22, 33, 44). Antibiotic options for atypical or complicated forms of CSD include TMP-SMX, rifampicin, ciprofloxacin and gentamicin. In vitro, most of the antibiotics tested had bacteriostatic activity against *Bartonella*, but only aminoglycosides showed bactericidal activity (44). Doxycycline is most commonly used in the treatment of ocular bartonellosis (34). The combination of doxycycline with rifampicin has been successful in treating patients with endocarditis, central nervous system (CNS) disease, retinitis and visceral forms (22-28, 44). Doxycycline treatment in children requires caution due to possible side effects, and macrolides are a good alternative. Treatment of hepatosplenic CSD and FUO with azithromycin, plus rifampicin or rifampicin and gentamycin for 2–3 weeks has been shown to be effective (22, 23). In the study by Sandoval et al. (14) ciprofloxacin for 14 days plus azithromycin for 7 days was effective. Erythromycin for 2 weeks to 2 months is recommended for treatment of BA and PH, with longer treatment for immunocompromised patients (44, 45). For osteomyelitis in CSD, antibiotic therapy was mostly combined, where the combination of rifampicin and TMP-SMX was more effective than azithromycin alone, with a duration of 3-4 weeks (31-33). Intracellular localization of this bacteria or possible biofilm production are the most likely reasons for the failure of single drug treatment, and suggest prolonged drug combination therapy with two or more antibiotics (9). Published studies show experience in treating cases with similar clinical manifestations (14, 33, 44). The duration of treatment, choice and combination of antibiotics are different, depending on the manifestation of CSD, previous recommendations and clinical experience. Prospective controlled studies with guidelines for the treatment of atypical forms of CSD would be useful.

Conclusion

Cat scratch disease has a wide spectrum of clinical manifestations. Education of primary care physicians about CSD is important. Careful medical history and serological testing usually can confirm typical CSD. Radiological imaging examinations and pathohistological analysis of the sample are sometimes necessary to confirm systemic CSD. There is no uniform treatment protocol and it varies from case to case. Systemic CSD has a high morbidity rate in immunocompromised children. The prognosis for immunocompetent patients is good. The disease leaves lifelong immunity.

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