Cat-scratch disease

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Summary

Cat-scratch disease (CSD) was first described by Debré in 1950, yet the causative bacterial agent of CSD remained obscure until 1992, when Bartonella (formerly Rochalimaea) henselae was implicated in CSD by serological and microbiologic studies. Bartonella henselae had initially been linked to bacillary angiomatosis (BA), a vascular proliferative disease most commonly associated with long-standing human immunodeficiency virus infection or other significant immunosuppression. Bartonella henselae has also been associated with bacillary peliosis, relapsing bacteraemia and endocarditis in humans. Cats are healthy carriers of B. henselae, and can be bacteraemic for months or years. Cat-to-cat transmission of the organism by the cat flea, with no direct contact transmission, has been demonstrated. Two new Bartonella species have been identified in the cat reservoir, namely: B. clarridgeiae and B. koehlerae. The role of these species in the aetiology of CSD still needs to be confirmed by isolation or DNA identification from lesions in humans. The author discusses the present state of knowledge on the aetiology, clinical features and epidemiological characteristics of CSD/BA, in addition to diagnosis, treatment and prevention.

Keywords

Bacillary angiomatosis – Bartonella clarridgeiae – Bartonella henselae – Cats – Cat-scratch disease – Zoonoses.

Introduction

Cat-scratch disease (CSD) has been clinically identified in humans since the 1930s, but was first described as a clinical entity in 1950 by Debré et al. (40). The disease is typically a benign, subacute regional lymphadenopathy resulting from dermal inoculation of the causative agent (25). One of the common atypical forms of CSD is the Parinaud’s oculoglandular syndrome (25). Several other clinical manifestations have been reported in immunocompromised patients, such as bacteraemia (130), peliosis hepatis (131, 140), altered mental status (55) or dementia (129). In immunocompetent individuals, the clinical spectrum of B. henselae infection has widely expanded to include endocarditis (70), neuroretinitis, aseptic meningitis (26, 142), hepatic and splenic abscesses, pneumonia and pleural effusion, musculoskeletal manifestations, osteomyelitis, and paravertebral abscesses (7). Recent evidence demonstrated that Bartonella (formerly Rochalimaea) henselae (23), a bacterium that has been isolated from patients with bacillary angiomatosis (BA), is associated with CSD (43, 54, 116, 118, 119, 130, 131, 140). Bacillary angiomatosis is a vascular proliferative disease mainly seen in people infected with human immunodeficiency virus (HIV) (119).

Aetiology and historical background

The cause of CSD has long been in question. Initially it was considered to be a possible virus, then a Gram-negative bacterium. However, it is only in recent years that a specific organism has been identified. In 1983, a small bacillus was identified by Warthin-Starry silver deposition stain on lymph node biopsies of thirty-nine patients with CSD (139). In 1988, a pleomorphic, Gram-negative bacterium was isolated from the lymph node of a CSD patient at the Armed Forces Institute of Pathology in the United States of America (USA) (48). Afipia felis was then considered as the most probable agent of CSD. Recently, a report implicated B. henselae and A. felis,
based on polymerase chain reaction (PCR) testing (2). Isolation of \textit{A. felis} was difficult and a very limited number of strains were isolated in only two laboratories. The serology of the bacterium was not highly specific and was difficult to standardise. Isolation of \textit{A. felis} was recently reported from a patient with CSD (57), however, PCR testing of thirty-two lymph node specimens from CSD patients gave no positive results for \textit{A. felis}, whereas all samples were positive for \textit{B. henselae}. \textit{Afpila felis} was concluded to be only a rare cause of CSD (57). Strong evidence demonstrates that \textit{A. felis} is an environment bacterium that lives in water. It is suggested that previous isolations of \textit{A. felis} from lymph nodes could be due to water contamination through ineffectively sterilised fluids used for culture (94).

The identification of \textit{B. henselae} as the agent of CSD was an indirect result of the epidemic of acquired immune deficiency syndrome (AIDS). A new disease known as bacillary angiomatosis (BA), a type of vascular proliferative lesion in immunocompromised hosts (81), was described in HIV-infected patients between 1983 and 1988 (79, 80, 97, 132). The disease was attributed to a new Gram-negative bacillus, which was subsequently named \textit{Rochalimaea henselae} (116, 121, 140). An indirect immunofluorescence antibody test (IFA) was developed in 1992, at the Centers for Disease Control and Prevention, to detect antibodies to this organism (118). Using this test, it was noted that 88% of sera samples from suspected CSD patients had antibodies to \textit{B. henselae}, compared to only 3% of control patient sera (118). \textit{Bartonella henselae} was first isolated directly from the cutaneous lesions of HIV-infected patients with BA in 1991 (80), and thus this organism has been directly cultured from the lesions of both BA and CSD. Bacillary angiomatosis is also caused by \textit{B. quintana}, the agent of trench fever (80). However, \textit{B. quintana} has never been directly associated with a case of CSD. Cases of BA caused by \textit{B. quintana} usually occur in homeless people with a history of low income and alcoholism and are usually associated with exposure to lice, not cats (83). However, two \textit{B. quintana} isolates were obtained in France from two patients with chronic lymphadenopathy who had contact with cats and cat fleas (95).

It was only in the early 1990s that evidence clearly indicated that \textit{B. henselae} was more likely to be the agent of CSD than \textit{A. felis}. \textit{Bartonella} are morphologically very similar to \textit{A. felis} when examined by Warthin-Starrr staining, which may explain the previous confusion. Serological studies and isolation of the organism from the lymph nodes of probable CSD cases demonstrated the major role played by \textit{B. henselae} in the aetiology of CSD (6, 9, 38, 42, 43, 109, 118, 133, 145). Furthermore, amplification of an antigen gene of \textit{B. henselae} by PCR on CSD skin-test material confirmed the presence of \textit{B. henselae} but not \textit{A. felis} DNA (4); and in July 1992, \textit{B. henselae} bacteraemia was reported in a cat with a healthy owner (117).

A case control study to determine the risk factors associated with developing BA revealed that the only statistically significant risk factor was traumatic contact with a cat (scratches or bites) (134). After this study, Koehler et al. identified BA patients who had cats, and performed blood cultures on these animals (82). All seven cats owned by the four patients were bacteraemic with \textit{B. henselae}. Furthermore, 41% of the pet cats and impounded cats that were tested in the San Francisco Bay area were also bacteraemic. Since then, the domestic cat has been shown to be the main reservoir of \textit{B. henselae}. Koehler et al. also demonstrated that peliosis hepatitis and \textit{B. henselae} infection were strongly associated, whereas subcutaneous and lytic bone lesions were more frequently observed in BA cases caused by \textit{B. quintana} (83).

In a few instances, suspected cases of CSD were attributed to \textit{B. clarridgeiae}, based on serological evidence (88, 103). However, \textit{B. clarridgeiae} isolates or DNA have not yet been identified from suspect cases of CSD. \textit{Bartonella clarridgeiae} has been isolated from domestic cats (36, 96), which constitute the main reservoir of the bacterium in the USA (36, 89), Europe (15, 65, 67), Indonesia (104) and the Philippines (34). To date, \textit{B. koehlerae} has only been isolated from two cats in the San Francisco area and has not yet been linked to any human case of CSD (45). The citrate synthase gene sequence of a fourth \textit{Bartonella} species, \textit{B. weissi}, isolated from domestic cats, was published by Marano et al. in GenBank in 1998 (100).

The genus \textit{Bartonella} includes the former \textit{Rochalimaea} (25) and \textit{Grahamella} (18) genera. The spectrum of \textit{Bartonella} species that are human pathogens is still expanding. The isolation of \textit{Bartonella elizabethae} from a human case of endocarditis (39) suggested a possible rodent reservoir, mainly of the genus \textit{Rattus} (47). Similarly, the report of the isolation of \textit{B. vinsonii} subsp. \textit{arupensis} from a cattle rancher suggests transmission to humans by ticks from a probable rodent reservoir (141).

**Epidemiology and biology of the infection**

**Humans**

Limited data are available regarding the prevalence or incidence of CSD world-wide. However, several reports on seroprevalence of \textit{Bartonella} antibodies have been published, mainly from western Europe (Netherlands, Germany, France, Italy), and more recently from Sweden (69), Greece (75), Japan (144) and Australia (50). According to Jackson et al., an estimated 22,000 to 24,000 human cases of CSD occurred in the USA in 1992, 2,000 of which required hospitalisation (71). The estimated total health cost of CSD was over US$12 million in 1992. In the Netherlands, the incidence of CSD was estimated to be 2,000 cases per year (15). In Connecticut, which is the only State in the USA where CSD is
a reportable disease (since January 1992), 246 people met the case definition during the period 1992-1993. A prospective population-based surveillance system reported an average state-wide annual incidence of 3.7 cases per 100,000 persons (66). A survey of an occupational group potentially at risk for Bartonella infection found that the overall seroprevalence was 7.1% (112). Based on these estimates, several thousand cases should occur yearly in most countries of Europe, including France and Germany, where a high percentage of cats have been reported to be infected (32, 67, 124).

Cat-scratch disease occurs in immunocompetent patients of all ages, although the majority (55%-80%) are under twenty years of age. In one study, Jackson et al. reported a higher proportion of cases among children and teenagers than in adults, with 45% to 50% of the patients being younger than 15 years old (71). However, Sander et al. reported a rather high seroprevalence in young adults in Germany (126). Cat-scratch disease is considered to be the most common cause of chronic, benign adenopathy in children and young adults; more cases occur in males than females (71). The incidence of the disease varies by season, with most cases being seen in autumn and winter. Seventy-five percent (184/246) of the cases in Connecticut had developed adenopathy during the period from October to February (66). In the same study, the age-specific attack rate was highest among children under ten years of age (9.3/100,000) and decreased with increasing age (66). The median age of patients with CSD was fourteen years (range: 1-64 years). Eleven percent of patients were hospitalised, but there were no deaths. Risk factors highly associated with CSD include owning a cat of less than 12 months of age, being scratched or bitten by a kitten, or owning a kitten with fleas (145). Several studies have been able to directly associate Bartonella bacteriaemia in cats, especially young kittens, with clinical cases of CSD in humans, resulting from scratches inflicted by these animals (30, 42, 85). Most cases of CSD in humans are thought to result from inoculation of infected flea faeces at the time of the scratch (51). Two cases of Bartonella were reported to be associated with tick bites (99).

Bacillary angiomatosis caused by Bartonella has been associated mainly with exposure to cats (82, 83, 134). A study showed a strong link between the onset of neuropsychological decline or dementia in HIV-infected people and serum immunoglobulin M (IgM) antibodies to Bartonella (129). Cat ownership was associated with neuropsychological decline and dementia. The presence of Bartonella IgM antibodies was also strongly linked to cat ownership, particularly if the cat was acquired less than one year before the measurement of antibody values. Immunosuppressed patients have also acquired BA after renal, liver, cardiac or bone marrow transplantation (37). Bartonella has been shown to colonise vascular tissues and to stimulate vasoproliferative tumour growth. Although the molecular principle of bacterium-induced neovascularisation (angiogenesis) is still unclear, evidence of endothelial colonisation, involving formation, engulfment and uptake of a large bacterial aggregate has been demonstrated (41).

**Cats**

The domestic cat is the main reservoir for the human pathogen, Bartonella. Bacteriaemia in cats was first reported in 1992, in the cat of a healthy owner, by Regnery et al. (117). In northern California, bacteriaemia prevalences of 39.5% (81/205) and 41% (25/61) have been reported (31, 82). Cats below the age of twelve months and impounded cats were more likely to be bacteremic, and flea infestation was also a significant risk factor (31). There was no direct correlation between the level of bacteriaemia and the antibody titre; however, cats with serological titres of 512 or greater were more likely to be bacteremic than cats with a titre of less than 512 (31). More recently, Bartonella has been isolated from domestic cats from many parts of the world, including Europe (e.g. the Netherlands [15], France [32, 65, 67] and Germany [124]), Asia (including Japan [105], Indonesia [104], and the Philippines [34]), Australia (20), New Zealand (74) and Africa (Zimbabwe [77]). In most of these studies, bacteriaemia prevalence ranged from 15% to 55%, depending on whether the feline population tested was made up of pet cats or stray cats.

In Australia, Flexman et al. reported the first isolation of Bartonella from the blood and fleas of a cat belonging to a patient with CSD (49). The patient developed fever, lethargy and anorexia which lasted for three days, followed by the appearance of axillary lymphadenopathy. These symptoms arose three weeks after the patient had removed fleas from his cat. There was no history of a bite or a scratch and no primary lesion on the skin. Therefore, this case could also be one of the first confirmed cases of CSD in humans transmitted by fleas.

In Europe, two different types of Bartonella have been identified by partial sequencing of the 16S rRNA gene from cases of CSD in humans (13, 14, 44, 128) and from bacteremic cats (15, 44). The serotype 'Marseille' reported in France (44) seems to correspond to the type II described by Bergmans et al. (13, 14, 15; M. Drancourt and D. Raoult, personal communication). In most of western Europe, Bartonella type II is more commonly found in cats than type I (15, 65, 67, 124). Conversely, in human cases of CSD in the Netherlands (14, 15) and Germany (128), Bartonella type I was identified most frequently, suggesting that this type may be more infectious for humans than type II. Distribution of Bartonella type I and type II in domestic cats in the USA has not yet been well documented. Bartonella type II appears to be highly prevalent in northern California, whereas Bartonella type II and type I are equally distributed in the cat population of the East Coast (B.B. Chomel, unpublished data). In the Philippines, none of the cats tested carried Bartonella type II, suggesting major regional variations in the prevalence of Bartonella types (34). Isolation of Bartonella clarridgeiae...
from domestic cats is uncommon in the USA; Kordick et al. reported a prevalence of 10% in seventy Bartonella isolates (89). In other regions such as Europe (15, 65, 67), the Philippines (34) and Indonesia (104), B. clarridgeiae accounts for up to 36% of Bartonella isolates.

Several serosurveys have also been conducted in cat populations in the USA. In North Carolina, 21% of 518 sick cats were seropositive for B. henselae (21). Childs et al. reported a prevalence of 28.2% (370/1,314) from cats in various parts of the USA (29), and 14.7% in cats from Baltimore, Maryland (28). Similarly, a seroepidemiologic survey of cats from all over North America identified an overall prevalence of 28% (175/628), with a low range of 3.7% to 6.7% in the Midwest and Great Plains region, to an upper range of 60% in the south-east (72). High seroprevalence appeared to be correlated with warm, humid climates. These warm, humid areas with the largest seroprevalence were also those likely to have the largest number of potential arthropod vectors, including fleas. In Hawaii, of thirty-one kittens involved in human cases of CSD, twenty-three (68%) had positive culture and elevated antibody titres to B. henselae (42). Only one (4%) out of twenty-three adult cats had a positive culture, although eighteen (78%) had elevated antibody titres. In a cluster of CSD encephalopathy in south Florida, 22% of the 124 cats tested were found to be bacteraemic, and 62% (77/124) had B. henselae antibodies (111). Bartonella henselae antibody prevalence in eleven catteries from all over the USA was 35.8%, with six catteries having a low prevalence (between 8.3% and 37.5%) and five catteries showing a high prevalence (above 65%) (52). Flea infestation was the most important risk factor for high B. henselae seroprevalence.

Information on the prevalence of B. henselae antibodies in cats from various parts of the world is also increasing rapidly. Bartonella henselae antibodies have been found in domestic cats in most countries of Europe, in addition to Israel (40%) (8), Egypt (11%) (29), southern Africa (South Africa [21%] and Zimbabwe [23%]) (76), Japan (15%) (137), and Singapore (47.5%) (110).

When experimentally infected, kittens develop a high bacteraemia (up to 10^8 colony forming units per ml) within two to three weeks and usually clear their infection within two to three months (33, 59, 61, 120). In some cases, bacteraemia can last for several months and relapses of bacteraemia at levels much lower than during the initial infection can be observed (1, 53, 61, 87, 90, 91). Cyclic bacteraemia was demonstrated, with the level of bacteraemia fluctuating by as much as 100-fold, and intermittent negative cultures. This suggests that a proportion of infected cats may carry the infection for years. Long-lasting bacteraemia in cats was suggested by Koehler et al. (82) and was well demonstrated by Kordick et al. (85, 90, 91). Co-infection of cats with B. henselae and B. clarridgeiae strains has been reported (15, 64). Furthermore, lack of cross-protection between Bartonella species or B. henselae types was observed in experimentally-infected and heterologously challenged cats (143).

Transmission from cat to human is presumed to occur predominantly by cat scratch, but flea-bite transmission could also be possible. For experimental infection of cats, the intradermal and intravenous routes are highly effective (1, 51, 62, 85, 113). Experimental infection of one- to two-week-old kittens by the oral route has also been reported (63). In an arthropod-free environment, neither direct horizontal transmission from cat to cat, nor vertical transmission from infected queens to offspring appear to occur (1, 62). Zangwill et al. (145) and Koehler et al. (82) suggested that fleas may play a role in the transmission of the infection, as presence of B. henselae DNA was demonstrated by PCR in fleas combed from bacteraemic cats (82). Higgins et al. demonstrated that cat fleas can maintain B. henselae and excrete viable organisms in their faeces for up to nine days after feeding on an infected blood meal (68). Cat fleas (Ctenocephalides felis), transferred from B. henselae bacteraemic cats to specific-pathogen-free (SPF) kittens, were capable of transmitting the infection to all the SPF kittens (33). In an elegant experiment, Foil et al. were able to infect cats by intradermal injection of flea faeces from fleas fed on bacteraemic cats for four days (51).

**Dogs**

Infection of humans following contact with dogs has also been reported. In one study, 95% of patients had a history of contact with cats and 4% had a history of contact with dogs (102). However, a large-scale study of 1,200 cases reported that 99.1% of patients had a history of cat contact and was not supportive for any other animal source (25). In Hawaii, a very limited number of seropositive dogs have been reported, but no bacteraemic dogs (42). A recent report from Japan of a possible case of CSD caused by contact with a dog suggests that dogs could play a role in human B. henselae infection (136). However, such conclusions need further confirmation.

**Clinical signs**

**Humans**

One to three weeks elapse between the scratch or bite and the appearance of clinical signs (56, 102). Between 60% and 93% of patients with CSD develop a small skin lesion (3 mm to 5 mm), often resembling an insect bite, at the inoculation site (usually the hand or forearm). This lesion appears three to ten days after the scratch or bite. The cutaneous lesion evolves from a vesicle to a pustule, and finally to a papule, or more frequently from a macule to a papule (102). The lesions resolve within a few days to several weeks. Inoculation lesions are nonpruritic and heal without scar formation. Lymphadenitis is generally unilateral and commonly appears in the epitrochlear, axillary or cervical lymph nodes (25). In
the study in Connecticut, it was found that younger CSD patients (less than 15 years old) were more likely to present with cervical adenopathy (66). Older patients (15 years old, or more) were more likely to present with inguinal adenopathy and axillary adenopathy. The lymphadenopathy develops approximately three weeks after exposure. Swelling of the lymph node is usually painful and persists for several weeks to several months. In 15% of the cases, suppuration occurs (102). Approximately half of patients show signs of systemic infection, including fever, chills, malaise, anorexia and headaches. Less often, sore throat, rash, conjunctivitis or even arthralgia have been reported. In general, the disease is benign and heals spontaneously without sequelae.

Atypical symptoms of CSD occur in 5% to 25% of cases. The most common of these is Parinaud's oculoglandular syndrome (periarticular lymphadenopathy and palpebral conjunctivitis), but tonsillitis, myelitis, meningitis, encephalitis, status epilepticus, osteolytic lesions and thrombocytopenic purpura may also occur. Encephalopathy is one of the most serious complications of CSD, usually occurring two to six weeks after the onset of lymphadenopathy. However, patients usually make complete recovery with a few or no sequelae. A cluster of five cases of children with acute encephalopathy associated with CSD was reported in south Florida (111). Bartonella henselae infection in immunocompetent people has been associated with new clinical presentations, such as neuroretinitis and bacteraemia as a cause of chronic fatigue syndrome (142), as well as a case of aggressive B. henselae endocarditis in a cat owner (70). Cases of pleural effusion, pneumonia, and granulomatous hepatitis and splenitis have also been reported (10). One case of paronychia was associated with a B. henselae infection in a woman bitten by a cat (125).

In immunocompromised people, the symptomatology of BA is rather different. Also called epithelioid angiomastosis, BA is a vascular proliferative disease of the skin, characterised by multiple, blood-filled, cystic nodules. Infection is usually characterised by violet-coloured or colourless popular and nodular skin lesions that may clinically suggest Kaposi's sarcoma, but histologically resemble epithelioid haemangiomas (119). When visceral parenchyma organs are involved, the condition is referred to as bacillary peliosis hepatitis, splenic peliosis, or systemic BA. Koehler et al. demonstrated the strong association between peliosis hepatitis and B. henselae infection (83). Fever, weight loss, malaise and enlargement of affected organs may develop in patients with disseminated BA.

**Cats**

No major clinical signs of CSD have been reported in cats under natural conditions. Suspicions of lymphadenopathy caused by a CSD-like organism identified by silver-stained section have been reported (78), and more recently, uveitis was associated with Bartonella infection (92).

In experimentally infected cats, some research groups found no clinical signs (1, 120), whereas others reported fever, moderate neurological symptoms and lymphadenopathy. Kordick and Breitschwerdt reported self-limiting febrile illness of 48 h to 72 h duration in six of eight cats, moderate lymphadenopathy in all eight cats and transient neurologic dysfunction in two cats after experimental infection with B. henselae by blood transfusion (87). Guptill et al. (61) also reported mild clinical signs, which included mild fever and anorexia in experimentally infected cats. More recently, O'Reilly et al. (113) reported fever, lethargia, anorexia and cutaneous lesions at the inoculation site associated with lymphadenopathy. A similar observation was made recently in a group of six cats experimentally-inoculated with a feline B. henselae type I isolate, suggesting variability in the pathogenicity of Bartonella strains (B.B. Chomel, unpublished data). A statistical association between presence of B. henselae antibodies and stomatitis and kidney and urinary tract infections was observed in a large serosurvey of cats in Switzerland (58). Ueno et al. also reported an association between B. henselae seropositivity and gingivitis and lymphadenopathy (138). Reproductive disorders (lack of pregnancy or pregnancy only after repeated breedings) have been observed in experimentally-infected queens (62). Similar reproductive disorders were experienced during a trial on experimental transmission between a bacteraemic queen and a non-bacteraemic male (1); stillbirth was observed among the kittens born of bacteraemic queens.

Cat-scratch disease infection is very common in cats, especially in young kittens. Bacteraemia usually lasts from a few weeks to a few months. The organisms have been reported to be intra-erythrocytic (84) and pili may be a pathogenic determinant for Bartonella species (12).

**Dogs**

A survey conducted in Hawaii showed that none of the dogs tested were B. henselae bacteraemic, and a very small percentage 6.4% (2 out of 31 dogs) had seroconverted (42). Experimental inoculation of B. henselae by the intra-dermal route did not result in a bacteraemic phase, although the dogs seroconverted after a few weeks (35). Breitschwerdt et al. (22) and Kordick et al. (86) reported the isolation of B. vinsonii subsp. berkhoffii in a case of endocarditis in a dog. An epidemiological study of 1,920 dogs from North Carolina and Virginia revealed a seroprevalence of 3.6%. Seropositive dogs were more likely to be living in rural areas and have had a history of heavy exposure to ticks (114).

**Diagnosis**

**Humans**

For years, the diagnosis of CSD in humans was based on clinical criteria, exposure to a cat, failure to isolate other bacteria, and/or histological examination of biopsies of lymph nodes. A skin test was developed in the 1950s (102).
However, the antigen prepared from pasteurised exudate from lymph nodes of patients with CSD was not standardised and concerns were raised about the safety of such a product. Since the identification of *B. henselae* as the main aetiological agent of CSD, serological tests, such as the IFA (38, 118, 146) or the enzyme-linked immunosorbent assay (ELISA), using whole bacterium (9, 16, 98, 133) or fraction antigen (6), as well as techniques to isolate the organism from human and cat specimens have been developed (82, 116). Because *B. henselae* is an intra-erythrocytic bacterium (84), cell lysis using a lysis centrifugation technique or freezing-thawing, greatly facilitates bacterial isolation from the blood of bacteremic patients. The technique is appropriate for isolation of *B. quintana* from BA cases or chronic carriers (95), isolation of *B. quintana* from bacteraemic patients. The technique is appropriate for isolation of *B. henselae* from human patients, including people with BA. Isolation of *B. henselae* from the blood of patients with classical CSD is rarely successful. In such cases, DNA extraction from suspect lymph nodes and PCR amplification of the citrate synthases or 16S rRNA genes will allow identification of the organism (5, 17, 19, 73, 106, 108, 117, 122, 123, 127).

Diagnosis of CSD in humans usually employs serological tests to detect anti-*Bartonella* IgM or IgG. Good sensitivity and specificity was reported for *B. henselae* in suspected cases of CSD both in the USA and Europe (3, 13, 38, 133). However, the correct source of *Bartonella* antigen must be used to reduce false negative results, as reported with serotype 'Marseille' (44), or in a series of suspected CSD cases (46). In terms of specificity, cross-reactions have been observed between *B. henselae* and *Coxiella burnetii* (93). It is also important to note that AIDS patients suffering from BA or peliosis hepatitis are often seronegative for *Bartonella* antibodies (115).

Cats

In cats, where bacteremia is common, isolation of feline *Bartonella* is performed by blood culture. A sample of 1.5 ml of blood is drawn into lysis-centrifugation tubes (82), or plastic ethylenediamine tetra-acetic acid (EDTA) tubes. The tubes are kept frozen for a few days to a few weeks at −30°C, or preferably at −70°C (24). Brenner et al. demonstrated that collection of cat blood in EDTA tubes and subsequent freezing improves the sensitivity of detection of *B. henselae* (24). The tubes are centrifuged and the pellet spread onto heart infusion agar plates containing 5% fresh rabbit blood. These plates are maintained at 35°C in a high humidity chamber with 5% CO₂ for three or four weeks. Colonies usually develop in a few days from cat blood, although some strains may require a few weeks. Isolation of *B. clarridgeiae* and *B. koehlerae* is often fastidious, as these species are more likely to take two weeks or more before appearing on agar plates. Furthermore, *B. koehlerae* requires chocolate agar plates, since it does not replicate on fresh rabbit blood medium for primary isolation (45). Identification of isolates of *B. henselae*, *B. clarridgeiae* or *B. koehlerae* is confirmed by DNA amplification using PCR-restriction fragment length polymorphism (PCR-RFLP) analysis using different restriction endonucleases or partial sequencing of the 16S rRNA or citrate synthases genes (15, 31, 82, 87). A commercial PCR test for detecting *B. henselae* bacteremia in cats directly from the blood is now available in the USA (135).

Serodiagnosis of *Bartonella* infection in cats by IFA or ELISA is of limited interest, as a large percentage of the cat population harbour anti-*Bartonella* antibodies. However, testing should be considered by cat breeders to determine the status of their cat colony and for cat owners who may be immunocompromised. Tests for antibodies against both *B. henselae* and *B. clarridgeiae* should be performed. Further epidemiological information is required to determine the prevalence of *B. koehlerae* and the necessity for a systematic screening against this species. In contrast to the results in humans (44, 115), all the cats that were experimentally-infected with either *B. henselae* type I or type II, and that were tested, were seropositive for both type I and type II (K. Yamamoto and B.B. Chomel, unpublished data).

Treatment

Humans

Antimicrobial treatment is indicated for patients with BA, bacillary peliosis or relapsing bacteremia. Treatment with erythromycin (2 g per day per os), rifampin, or doxycycline for at least six weeks, and more likely for two to three months is recommended for immunocompromised people, but relapses can occur (119). In case of peliosis hepatitis, treatment by the parenteral route is initially necessary (81).

For CSD, antimicrobial treatment is not generally indicated, as most typical cases do not respond to antimicrobial administration (101). A retrospective study of 202 CSD patients demonstrated that the most effective antibiotics were rifampin, ciprofloxacin, trimethoprim-sulphamethoxazole, and gentamicin, but that a minimum of four weeks of treatment was required (101). More recently, treatment of typical CSD patients with oral azithromycin for five days afforded significant clinical benefit as measured by total decrease in lymph node volume within the first month of treatment (11, 27). Intravenous administration of gentamicin and doxycycline and oral administration of erythromycin have been used successfully in the treatment of disseminated CSD (60, 107). According to Wong et al., therapy with doxycycline and rifampin appears to be helpful in the treatment of patients with neuroretinitis (142).

Cats

Attempts to clear *Bartonella* bacteremia in cats using antibiotics have had mixed results, most of which were disappointing. Greene et al. reported that antibiotic treatment with doxycycline for one week was effective in suppressing bacteremia in all eight cats under study, but was effective in clearing infection from only four cats (59). However, this
uncontrolled observation has not been corroborated. Regnery et al. reported that antibiotic therapy was incompletely efficacious in terminating cat bacteraemia, as tetracycline hydrochloride (HCL) and erythromycin depressed \textit{B. henselae} bacteraemia, but the duration of bacteraemia remained similar to that of untreated cats (120). Furthermore, Kordick et al. tested the efficacy of enrofloxacin and doxycycline for the treatment of \textit{B. henselae} and \textit{B. claridgeiae} infection in cats (89). Bacteraemia was not eliminated from all the cats treated and a long treatment was required to eliminate infection. The authors stated that they 'would reserve recommendation for treatment to cats owned by an immunocompromised individual or as an alternative to euthanasia of a pet'.

### Prevention

Cat ownership has been increasing in most industrialised countries over the 1980s and 1990s, and now surpasses dog ownership. A large reservoir of \textit{B. henselae} exists among the 60 million pet cats residing in one-third of homes in the USA (56), the 8.4 million pet cats in France, of which approximately 1.5 million could be bacteraemic (B.B. Chomel, unpublished data) or the 2 million pet cats in the Netherlands, of which 400,000 (22%) are estimated to be bacteraemic (15). As the possibility of \textit{B. henselae} infection becomes more widely recognised, there is likely to be negative publicity about the perceived hazards of cat ownership, especially for immunocompromised people. However, cats can be very comforting to the chronically and terminally ill.

Selecting an appropriate companion animal is important. Seronegative cats are more likely not to be bacteraemic and to be safe for ownership, however, 2% of seronegative cats can be bacteraemic (15, 31). Young kittens, especially impounded kittens and flea-infested kittens, are more likely to be bacteraemic. People who own kittens are fifteen times more likely to develop CSD than owners of older cats (145). Therefore, to minimise the risk of infection when acquiring a pet cat, especially if the prospective owner is immunocompromised, a cat raised in a 'clean', flea-controlled cattery should be chosen (52). If possible, the cat should be an adult and should come from a flea-controlled environment. Cats could be serologically tested so that prospective owners could adopt only a seronegative animal. Unfortunately, there is no correlation between seropositivity and bacteraemia. Bacteraemia can also be transient, with relapses.

Declawing cats has also been suggested, but this would have limited value, as infection can be transmitted from cat to cat by fleas (30). Therefore, flea control appears to be one of the major control measures needed to prevent cats from becoming infected and infection being spread from cat to cat.

The most effective means of preventing infection by \textit{B. henselae} are common sense, hygiene and, possibly, changing the behaviour of cat owners themselves. People should wash their hands after handling pets, and clean any cuts, bites or scratches promptly with soap and water.

Development of a feline vaccine to prevent the spread of infection in cat populations and to reduce the risk of infection of humans, will be difficult, given the diversity of \textit{Bartonella} species and types harboured by cats, and the lack of cross-protection between species and types (143).

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Maladie des griffes du chat

B.B. Chomel

Résumé

Mots-clés

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Fiebre de rasguño del gato

B.B. Chomel

Resumen
La fiebre de rasguño del gato fue descrita por primera vez por Debré en 1950, pero su agente causal permaneció en la sombra hasta 1992, cuando estudios serológicos y microbiológicos establecieron un nexo entre la bacteria *Bartonella* (anteriormente *Rochalimaea* henselae) y esta enfermedad. En un principio, *B. henselae* había sido relacionada con la angiomatosis bacilar, una enfermedad vascular proliferante ligada en general a la infección prolongada por el virus de la inmunodeficiencia humana u otras importantes inmunosupresiones. *Bartonella henselae* también ha sido relacionada con la púrpura hepática, bacteriemia recurrente y endocarditis en el hombre. El gato es un portador sano de *B. henselae*, el cual puede permanecer presente en su sangre durante meses o años. *Bartonella henselae* se transmite de gato a gato mediante las pulgas, pero no por contacto directo. Dos nuevas especies de *Bartonella* han sido aisladas en el gato, a saber *B. clarridgeiae* y *B. koehlerae*. Sin embargo, queda por confirmar, mediante aislamiento y análisis del ADN presente en las lesiones, si estas especies juegan un papel en la etiología humana de la fiebre de rasguño del gato. El autor examina el estado actual de los conocimientos sobre la etiología, los
rasgos clínicos y las características epidemiológicas de la fiebre de rasguño del gato y de la angiomatosis bacilar, y discute del diagnóstico, tratamiento y prevención de estas enfermedades.

Palabras clave

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