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BARTONELLOSIS IN HUMANS AND IN DOMESTIC AND WILD CARNIVORES

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La maladie des griffes du chat fut décrite cliniquement en France en 1950, mais ce n'est que récemment que son étiologie a été clairement identifiée. Une nouvelle bartonelle, Bartonella henselae, agent de l'angiomatose bacillaire, une maladie vasculo-proliférative sévissant principalement chez les sujets infectés par le virus du SIDA, fut aussi incriminée comme le principal agent de la maladie des griffes du chat sur des critères épidémiologiques, sérologiques, bactériologiques et de biologie moléculaire. Le chat domestique représente le principal réservoir de l'agent infectieux. Les chats sont porteurs sains et peuvent être bactériémiques pendant des mois voire des années, sans aucune expression clinique de leur infection. L'infection se transmet de chat à chat essentiellement par l'intermédiaire des puces. Les connaissances actuelles concernant l'étiologie, les manifestations cliniques et l'épidémiologie de la maladie des griffes du chat et de l'angiomatose bacillaire sont présentées.

INTRODUCTION

Cat scratch disease (CSD) in humans is typically a benign, subacute regional lymphadenopathy resulting from dermal inoculation of the causative agent. Recent evidence demonstrated that *Bartonella* (formerly *Rochalimaea*) *henselae*) a bacterium that has been isolated from patients with bacillary angiomatosis (BA) is associated with CSD. BA is a vascular proliferative disease mainly seen in HIV-infected persons. Several other clinical manifestations are reported, such as bacteremia, peliosis hepatis, endocarditis, neuroretinitis and aseptic meningitis. Although cat scratch disease was first described in France by Debré in the 1950s, the causative agent remained obscure until 1992, when *B. henselae* was implicated through a serologic study.

ETIOLOGY

In 1983, a small bacillus was identified by Warthin-Starry (WS) silver deposition stain on lymph node biopsies of 39 patients with CSD. In 1988, a pleomorphic, gram-negative bacterium was isolated from the lymph node of a CSD patient at the Armed Forces Institute of Pathology (AFIP) in the United States. However, its isolation was not easy and limited to a few strains. Serology was not highly specific and difficult to standardize. For several years, *Afipia felis* was then considered as the most probable agent causing CSD. Identification of CSD agent as *B. henselae* was an indirect result of the AIDS epidemic. A new disease known as bacillary angiomatosis (BA), a type of vascular proliferative lesion in immunocompromised hosts, was described in HIV-infected patients in 1983-88. It was attributed to a new gram-negative bacillus subsequently named *Rochalimaea henselae*. A new IFA test was developed in 1992 at the Centers for Disease Control and Prevention to detect antibodies to this organism. Using this test, it was noted that 88% of a cohort of CSD patient sera had antibodies to *B. henselae* as compared with only 3% of control patient sera. *Bartonella henselae* was first isolated directly from the cutaneous lesions of HIV-infected patients with BA in 1991, and thus this organism has been directly cultured from the lesions of both BA and CSD. Bacillary angiomatosis is also caused by *B. quintana*, the agent of trench fever, which has never been associated with a case of CSD. It is only in the 1990s that evidence clearly indicated that *B. henselae* was more likely to be the agent of CSD. *Bartonella* are morphologically very similar to *A. felis* when examined by WS staining, which may explain the previous confusion. Serological studies and isolation of the organism from lymph nodes of probable CSD cases substantiate the major role played by *B. henselae* in the etiology of CSD. Furthermore, utilizing the methodology of amplifying an antigen gene of *B. henselae* by polymerase chain reaction (PCR) on CSD skin test material confirmed the presence of *B. henselae* but not *A. felis* DNA. In 1992, *B. henselae* bacteremia was reported in a cat with a healthy owner. A case-control study to determine risk factors associated with developing BA revealed that the only statistically significant risk factor was traumatic contact with a cat (scratches or bites). Koehler et al. identified BA patients with cats, performed blood cultures on these cats and found that all 7 cats were bacteremic with *B. henselae*. *B. clarridgeiae* was isolated from a healthy cat in Texas in the recent years. No human case has been yet associated with this bartonella.

EPIDEMIOLOGY

IN HUMANS

According to Jackson et al., there were an estimated 22,000 human cases of CSD in the USA in 1992, some 2,000 of whom were hospitalized for an estimated health cost of CSD over $12 million per year. In Connecticut, (the only State where CSD is a reportable disease,since January 1992), a prospective population based surveillance system found an average statewide annual incidence of 3.7/100,000 persons. CSD occurs in immuno competent patients of all ages, with 55% to 80% being less than 20 years of age. Proportion of cases is higher among children and teenagers than adults, with 45% to 50% of the cases being less than 15 years old. It is considered the most common cause of chronic, benign adenopathy in children and young adults; more cases occurring in males than females. Incidence varies by season, most of the cases being seen in fall and winter, such as 75% (184/246) of the

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cases in Connecticut who developed adenopathy during the period October through February . Zangwill et al. reported that CSD patients are more likely than healthy cat-owning control subjects to have at least one kitten £ 12 months, to have been scratched or bitten by a kitten and to have at least one kitten with fleas. Of 45 patients, 38 (84%) had antibodies to *B. henselae* compared to 4 (3%) of 112 controls. Interestingly, 81% (39/48) of the cats of these patients had also antibodies to *B. henselae*, as compared with 11 (38%) of 29 control cats. Several studies have been able to directly associate *B. henselae* bacteremia in cats, especially young kittens, with clinical human CSD cases resulting from scratches inflicted by these cats. Bacillary angiomatosis caused by *B. henselae* have been mainly associated with cat exposure. A study also showed a strong assocation between recent onset of neuropsychological decline or dementia in HIV-infected persons and serum IgM antibodies to *B. henselae*.

IN CATS

The domestic cat is a major reservoir for the human pathogen, *B. henselae*. Bacteremia in cats was reported for the first time by Regnery in the cat of a healthy owner. The cat had been detected positive by serology (IFA) a few weeks earlier. Koehler et al., and Chomel et al. reported a bacteremia prevalence of respectively 41% (25/61) and 39.5% (81/205) in pet and impounded cats from Northern California. Among the various risk factors, age <12 months and being an impounded cat were strongly associated with being bacteremic, and flea infestation was also significant. Various serosurveys in cat populations have been conducted in the USA giving prevalence rates from a few percent to more than 60%. High seroprevalence appeared to correlate with warm, humid climates, which also would have the highest number of potential arthropod vectors, including fleas. Information on the prevalence of *B.henselae* in cats from other parts of the world is still limited. In Japan, Ueno et al. reported a 15.1% (30/199) prevalence among domestic cats, and Maruyama et al. isolated the agent from about 15% of the cats tested. In Australia, Flexman et al. reported the first isolation of *B. henselae* from the blood and the fleas of a cat of a patient with CSD. The patient had developed fever, lethargy and anorexia for 3 days followed by the appearance of axillary lymphadenopathy, 3 weeks after he 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 flea-transmitted cases of CSD in humans. In the Philippines, more than 50% of the cats we cultured blood from were bacteremic. En Israel, Baneth et al. found antibodies in 39.5% of the 114 cats tested. In Europe, Allerberger et al. reported a 33% *B.henselae* antibody prevalence in Austrian cats (32/96). In Germany, 135 of the cat testes were found to be bacteremic. In France, we isolated *B. henselae* and *B. clarridgeiae* from 16% (71/436) of a convenience sample of cats tested in the Paris area. Heller et al. isolated *B. henselae* and *B. clarridgeiae* from 54% (51/95) of stray cats in Nancy. In the Netherlands, Bergmans et al. reported a prevalence in isolation of 22% (25/113) and 50% were seropositive.

The mode of transmission from cat to human is presumed to occur predominantly by cat scratch, but the method of transmission from cat to cat is unknown. We demonstrated the best efficacy of the intradermal route for experimental infection. Kittens develop after inoculation a high bacteremia within 2 to 3 weeks and usually clear their infection within 2 to 3 months. In some cases, bacteremia can last for several months and relapses of bacteremia at much lower levels that during the initial infection can be observed. Long term bacteremia and stable antibody titers were documented in both naturally and experimentally infected cats. Cyclical bacteremia was demonstrated with fluctuations in the level of bacteremia by as much as 100 fold with intermittent negative cultures, suggesting that a proportion of infected cats may carry the infection for years. Neither horizontal nor vertical transmission were observed in experimental infections that we performed. Susceptible cats housed in an arthropod-free environment in prolonged intimate contact with infected cats remained non-bacteremic and seronegative. As suggested by Koehler et al., fleas may play a role in the transmission of the infection. Viable *B. henselae* organisms were cultured from cats with *B. henselae* bacteremia, and presence of *B. henselae* DNA was demonstrated by PCR in fleas combed from infected cats. We studied 47 cats from one cattery over a period of 12 months to determine the longitudinal prevalence of feline *B. henselae* bacteremia, the prevalence of *B. henselae* in the fleas infesting these cats (detected by PCR), and whether *B. henselae* bacilli could be transmitted experimentally from cat to cat via the cat flea (*Ctenocephalides felis*). Bacteremia was detected in 89% of the cats and *B. henselae* DNA was detected in 29% to 80% of the fleas collected from the cats. Fleas removed from bacteremic cats were allowed to feed on 5 SPF kittens in a controlled environment. All of the experimentally exposed kittens became bacteremic within 2-6 weeks. Based on molecular epidemiology data, cats are the main reservoir for *B. henselae*, but also of some other new *Bartonella* species, such as *B. clarridgeiae*. We isolated new strains from California wildlifeand found a high seroprevalence in bobcats (50%) and cougars (30%).

CLINICAL SIGNS

IN HUMANS

From 1 to 3 weeks elapse between the scratch or bite and the appearance of clinical signs . In 50% of the cases, a small skin lesion, often resembling an insect bite, appears at the inoculation site, usually the hand or forearm, and evolves from a papule to a vesicle and partially healed ulcers. These lesions resolve within a few days to weeks. Lymphadenitis is generally unilateral and commonly appears in the epitrochlear, axillary or cervical lymph nodes. The lymphadenopathy develops approximately 3 weeks after exposure. Swelling of the lymph node is usually painful and persists for several weeks to several months. In 25% of the cases, suppuration occurs. The large majority of the cases show signs of systemic infection: fever, chills, malaise, anorexia, headaches. In general, the disease is benign and heals spontaneously without sequelae. Atypical manifestations of CSD occur in 5%-10% of the cases, such as Parinaud's oculoglandular syndrome (periauricular lymphadenopathy and palpebral conjunctivitis), but also meningitis, encephalitis, osteolytic lesions and thrombocytopenic purpura may occur. CSD encephalopathy is one of the most serious complications of CSD. It occurs 2-6 weeks after the onset of

lymphadenopathy. Usually, complete recovery occurs with few sequelae. New *B. henselae* clinical presentations have been reported in immunocompetent persons, such as neuroretinitis and bacteremia as cause of chronic fatigue syndrome-disease, and a case of aggressive *B. henselae* endocarditis in a cat owner.
For bacillary angiomatosis in immunocompromised persons, the symptomatology is rather different. BA, also called epithelioid angiomatosis, is a vascular proliferative disease of the skin characterized by multiple, bloodfilled, cystic tumors. BA is usually characterized by violaceous or colorless papular and nodular skin lesions that clinically may suggest Kaposi's sarcoma, but histologically resemble epithelioid hemangiomas. When visceral parenchymal organs are involved, the condition is referred to as bacillary peliosis hepatis, splenic peliosis, or systemic BA. Fever, weight loss, malaise, and enlargement of affected organs may develop in people with disseminated BA. Endocarditis has also been reported.

IN CATS

No clinical signs of CSD have been reported in cats in natural conditions. Suspicion of lymphadenopathy caused by a CSD-like organism identified by silver staining has been reported. Breitschwerdt et al. reported self-limiting febrile illness of 48 to 72 hours' duration and transient neurologic dysfunction in two cats experimentally infected with *B. henselae* by blood transfusion. In all our experimentation, we never observed such clinical manifestation, but had not used blood transfusions for the cat infection. In cats, infection is very common, especially in young kittens. Bacteremia usually lasts a few weeks to a few months. The organisms have been reported to be intra-erythrocytic and pili may be a pathogenic determinant for *bartonella* species. Cats can yielded more than one million colony forming units (CFU) per ml of blood.

IN DOGS

Surveys have been conducted in dogs in California and in Hawaii. None of the dogs were found to be *B. henselae* bacteremic, and a very small percentage 6.4% (2/31 dogs tested from Hawaii) seroconverted. Experimental inoculation of B. henselae by intra-dermal route did not created any bacteremic phase, but the dogs seroconverted (Chomel, unpublished data). Breitschwerdt et al. reported the isolation of a new subspecies *B. vinsoni* var. *berkoffii* in a case of endocarditis in a dog.

REFERENCES

Available from the author upon request.