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Bartonellosis: Cat Scratch Disease and Sequelae©

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In This Issue:

In the fall 2010 issue of the NVL Newsletter we will review human Bartonellosis- *Bartonella* diseases, CSD and sequelae, caused by *Bartonella* derived from cats and dogs. On PubMed, there are presently 3,416 *Bartonella* publications including several articles describing unusual sequelae of muscle and neurological complications of *Bartonella* infection in humans.

The Feline *Bartonella* Literature:

Healthy People:

At present there are 30 named *Bartonella* species and 3 subspecies.[1] *Bartonella* are mainly transmitted to mammalian reservoir host species via arthropod ectoparasite vectors such as fleas, ticks, lice and biting flies. An excellent review of the worldwide distribution of the 30 *Bartonella* species was recently published.[1] Interestingly and fortunately, *Bartonella bacilliformis*, the most deadly human *Bartonella* species, is confined to regions of high altitudes of South America, probably due to the restricted range of it's arthropod vector, the sand fly.[2] Untreated cases of *Bartonella bacilliformis* infections in the Andes mountains have a very high mortality of 30%.[2] However, worldwide *Bartonella henselae* is the most common species found in cats, dogs and humans.

Many publications state that "Species of *Bartonella*, which are vector-borne pathogens, cause persistent and asymptomatic bacteremia in their natural hosts."[1] However, there is ample evidence that this is not always the case. For example, *Bartonella bacilliformis* causes Oroya fever and many deaths in humans, the only known natural reservoir host for this species. In addition, there are many publications demonstrating that *Bartonella henselae* in cats and dogs and *Bartonella vinsonii* in dogs cause inflammatory diseases in these "natural host" reservoir species. Such statements have initiated controversy for the past 20 years in veterinary medicine and have caused many veterinary practitioners to dismiss the veterinary and public health importance of *Bartonella* infections in pet animals.

Several papers from China, Japan, Asia, Australia and Jordan report relatively high human *Bartonella* seroprevalence indicating possible current or past infections. In mainland China, Sun and colleagues report 19.6% seropositivity in healthy individuals from 8 areas of Zhejiang Province of eastern China.[3] The range was 32% in Hangzhou to 2% in Jiangshan. Interestingly, the seropositivity was highest for people exposed to dog, rather than cat, bites compared to healthy blood donors. Another publication from Taiwan found 1.7% of 295 healthy veterinary professionals to be seropositive for *Bartonella*.[4] In Japan, 129 veterinary students were tested for *Bartonella* antibody and 10.9% were positive.[5] Another Japanese study of veterinary professionals found 35 of the 233 (15%) were seropositive and females were twice as likely as males to have antibodies. Veterinary assistants and animal groomers were at highest risk.[6] In Thailand, 9 of 163 (5.5%) healthy individuals were seropositive for antibodies to *B. henselae*.[7] Finally, 53 of 482 (11%) healthy Jordanian children were seropositive to *B. henselae*.[8] Children 7-10-years were more likely to be seropositive than younger or older ones.

Editor's Note: Worldwide, cats and dogs are the most common animals that live in close contact with humans. This is probably why the most widely distributed *Bartonella* species in the world is *Bartonella henselae*, since cats and dogs serve as the "natural host" reservoir. Cat fleas are the most common flea species that infest cats and dogs which results in the transmission of *Bartonella henselae* from these pets to humans.

***Ctenocephalides felis*- the cat flea**

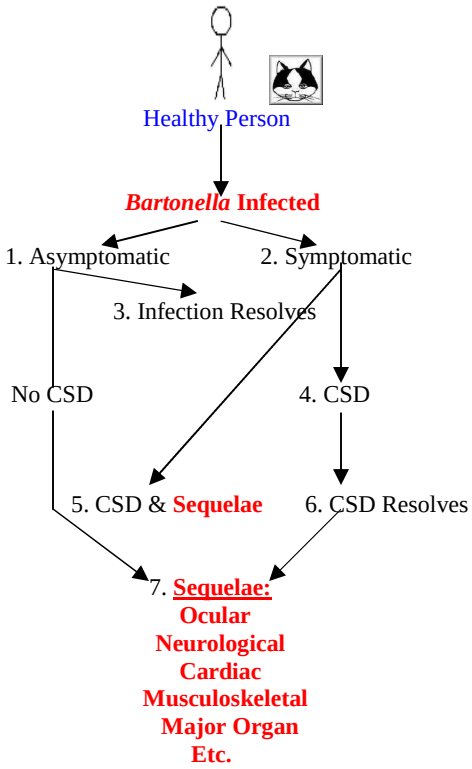
Human *Bartonella* Diseases:

Cat Scratch Disease (CSD):

All *Bartonella* diseases are not cat scratch disease (CSD) (Figure 1). CSD is the prototypical *Bartonella* disease but, in fact, may only represent about 50% of the clinically evident *Bartonella* diseases. CSD is characterized by a prodrome (the earliest consistent sign of a disease) of fever (usually prolonged or intermittent), a papule at the scratch or bite site, and lymphadenopathy.

Most physicians and veterinarians are familiar with classical CSD but are not often familiar with the sequelae that also occur (Figure 1). Sequelae are defined as conditions that follow as a consequence of a disease or infection and may remain long after the initiating disease or infection. An example of a common disease sequela is rheumatic fever following untreated Strep-throat infection of children.

Figure 1. **Bartonellosis**

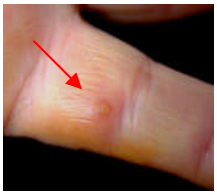
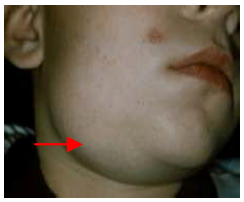


Bartonellosis and CSD have many sequelae including neurologic inflammatory disease, psychotic and cognitive disorders, ocular, heart, musculoskeletal and major organ inflammatory conditions. Thus, CSD may be envisioned as only the tip of the "*Bartonella* disease iceberg."

Figure 1 (stages 1 through 7) gives the possible outcomes of human infection with feline *Bartonella*. A healthy person who becomes infected after contact with a cat may remain asymptomatic (1) and her or his infection may resolve (3). However, an infected healthy person may become symptomatic within 1 to 6 weeks and develop classical CSD with fever, a papule and lymphadenopathy (2). CSD will resolve, without therapy, in 80% of people (6), however, about 20% will develop sequelae after the resolution of CSD (7). Some symptomatic

patients develop classic CSD and sequelae at essentially the same time (5). Similarly, some infected asymptomatic individuals will develop only sequelae weeks after their infection (7). These individuals are difficult for physicians since they present with symptoms different from classical CSD and often there is no mention of cat contact in the patient's history.

Classic CSD:

Papule on finger Cervical lymphadenopathy

Bartonella Sequelae:

The sequelae of *Bartonella* infection and or CSD can involve any tissue in the body since *Bartonella* infect endothelial cells of capillaries. The following recent publications describe unusual sequelae of bartonellosis.

Unknown fever and back pain caused by *Bartonella henselae* in a veterinarian after a needle puncture: A case report and literature review. Lin, J-W, Chen, C-M and Chang, C. Vector-Borne & Zoonotic Dis., 2010.
This is a case report of a 32 year old male veterinarian working in a private veterinary clinic in Taiwan who developed intermittent fever and back pain for 1 month following a needle puncture to his right thumb while preparing medications. No scratch or bite from a cat or dog was reported before the illness began. The back pain was more severe during the periods of fever and he developed a right axillary lymphadenopathy. Blood cultures were sterile, initial PCR tests were negative but the IFA serological tests for IgG, at a 2 week interval, were positive at extremely high titers (1:131,072 and 1:65,536, respectively). An additional dot-blot PCR test was positive for *Bartonella henselae*. The patient was treated with ceftriaxone, doxycycline and azithromycin and recovered rapidly without recurrence. This is an unusual route of transmission by the presumed needle puncture and reinforces the increased risk to veterinary professionals for *Bartonella* zoonoses.

Neuralgic amyotrophy associated with *Bartonella henselae* infection. Stek, CJ. et al. J. Neurosurg. Psychiatry doi:10.1136/jnnp .2009 .191940, 2010 published online.
This is a report of 3 patients with brachial plexus neuropathy diagnosed as neuralgic amyotrophy (NA) that occurred after *Bartonella henselae* infection. NA is a debilitating disease of the brachial plexus characterized by severe shoulder and arm pain with weakness and loss of sensation. The exact cause is not yet understood but there is evidence of an immune cause. The evidence is inflammation in the brachial plexus, the presence of antiganglioside antibodies, and immune-triggering events, mostly infections, preceding the development of NA. Eleven viruses, 13 bacteria, and 1 fungus have been shown to precede the development of NA. The majority of the microorganisms, now including *Bartonella*, are intracellular organisms that are known to trigger a CD+ T cell-mediated immune response which implies a role for T-cell-mediated auto-immunity as the cause of NA.

The 3 patients described in this report were middle-aged men and all lived with cats. The first patient was 48 years old and developed CSD with fever for 1 month, lymphadenopathy and necrotizing liver granulomas. He was serologically positive but PCR negative in liver biopsy tissue for *Bartonella henselae*. Six weeks after the development of CSD the sequelae of acute severe pain in the left shoulder followed by weakness in that arm occurred. There was no mention of antibiotic therapy but the patient gradually recovered over several months.

The second patient was 53 years old and developed CSD with a painful swelling near the left elbow that progressed over 1 year into recurrent abscesses and suppurative axillary lymphadenopathy. Cultures were sterile but PCR and serology were positive for *Bartonella henselae.* A year later the sequela of NA occurred characterized by severe pain in the arm that radiated to several fingers followed by weakness in the right arm, the opposite arm from the original lymphadenopathy. Although no therapy was discussed in the paper, the patient regained full strength in his arm 1.5 years after the initial symptoms of NA.

The third patient was 46 years old who was hospitalized due to sudden severe pain and loss of strength (paresis) in both shoulders and arms. One week earlier he developed signs of CSD with fever, and a painful lymphadenopathy in his groin. He was serologically and PCR positive for *Bartonella henselae* on lymph node tissue. After treatment with rifampin and doxycycline, the inflammation in his groin and fever resolved. However, he still had pain and paresis and was unable to work for 1.5 years.

Expressive aphasia as a presentation of encephalitis with *Bartonella henselae* infection in an immunocompetent adult. Marienfeld, CB, et al. Yale J. Biol & Med. 83:67-71, 2010.
This case report describes severe neurological sequelae that developed in a 59 year-old man. Shortly after adopting several stray kittens he developed classic CSD with a skin papule and right axillary lymphadenopathy for which he was treated with a 5 day course of doxycycline. Ten days later he presented with sudden onset of speech difficulties and a 4mm papule on his right forearm. On neurological examination, he had expressive aphasia (difficulty communicating verbally), word substitution errors, and impaired repetition. An EEG showed moderate generalized slowing but no epileptiform activity. He became more confused as the aphasia fluctuated from paraphasic errors (using wrong words) and expressive aphasia. Then, 18 hours after the onset of symptoms, he had a generalized tonic-clonic seizure. He was negative for HSV, VZV, Enterovirus by PCR, Lyme and West Nile serology, and VDRL and CSF cultures were sterile. The next day his level of alertness worsened and he was aphasic and febrile. Because of the history of stray kittens and the skin papule and lymphadenopathy, the patient was tested for *Bartonella henselae* antibodies. His IgG and IgM titers were high (IgG 1:1,024 and IgM 1:20) and diagnostic. He was treated intravenously with 500mg of Azithromycin. There was an immediate improvement as reported: "The next morning, the patient's symptoms and aphasia had resolved." He was then discharged and switched to doxycycline and rifampin for 14 days. The patient has fully recovered as evidenced by this evaluation: "Today, the patient has resumed his occupation as a musician, singer, and songwriter. He is teaching classes and currently in the recording studio working on an album."

Patients older than 50 years of age with similar symptoms are often thought to have had strokes. These authors caution that when stroke has been eliminated from the diagnosis, *Bartonella* infection should be considered in the differential diagnosis. In this regard, between 0.17 and 2% of *Bartonella* infected patients develop the neurologic sequela of encephalopathy.[9, 10]

Summary:

These reports show that severe sequelae may follow the development of CSD. *Bartonella*, like other intracellular pathogens, may initiate immune attack of patient's tissues and lead to chronic debilitating disease long after the onset of infection and often after the infection has resolved. It is clear that *Bartonella* sequelae are far more severe than the clinical entity known as CSD. Veterinarians should take the lead in educating the public on the dangers of feline *Bartonella* zoonoses.

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