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NEWSLETTER

4th International *Bartonella* Meeting©

Uppsala, Sweden

Evelyn E. Zuckerman, Editor **Winter 2005** **Vol. 4, Number 1**

A Personal Note: **Dr. Hardy, an avid scuba diver and underwater photographer, is very fortunate to have missed being in the path of the recent Indian Ocean tsunami by a mere 28 days. He was scheduled to be the seminar speaker and to be diving with the Society of Aquatic Veterinary Medicine in the Andaman Islands, India beginning January 23, 2005. The Andaman Islands were the first landmass north of the earthquake and were severely damaged by the tsunami.**

In This Issue:

In the winter 2005 issue of the NVL Newsletter we will cover the remaining, non-veterinary, content of the 4th International *Bartonella* Meeting that was held August 26-28 at The Evolutionary Biology Centre, Uppsala University in Uppsala, Sweden. We will cover the human *Bartonella* clinical reports and *Bartonella* genomic and pathogenesis papers.

The remaining scientific presentations comprised 12 papers concerning human *Bartonella* and 15 papers concerning *Bartonella* pathogenesis and their genomes. We will summarize selected papers in each category. Although many of these reports are technical, the observations are very relevant to our studies of *Bartonella* in cats and dogs.

Human *Bartonella* Clinical Reports:

Clinical Manifestations of Bartonella Infection. **JE Koehler, University of California San Francisco, San Francisco, CA**. Dr. Koehler, the leading clinician studying human *Bartonella* diseases, described her work with the occurrence of *Bartonella* induced fevers in HIV infected patients and the development of a primate macaque model of *Bartonella* pathogenesis. Although the classical presentation of cat scratch disease (CSD) lymphadenopathy is usually recognized, the less obvious signs of *Bartonella* infection are often never diagnosed. Dr. Koehler studied 382 HIV infected patients with fever and found *Bartonella* etiology in many more than previously reported. Overall, 18% (68/382) of patients were infected with *Bartonella henselae* or *Bartonella quintana*. She concluded that *Bartonella* infection should be sought in patients with fever of unknown origin. She also reported that there was no adverse outcome for the pregnancy, or to the fetus, in 2 pregnant women infected with *Bartonella*.

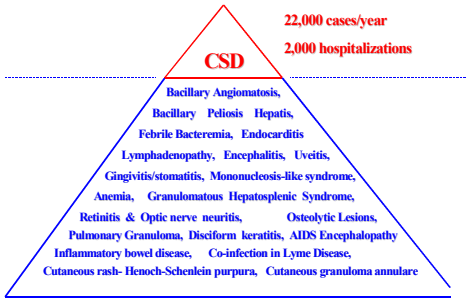
Dr, Koehler also established a macaque model of *Bartonella* infection. She found that only *Bartonella quintana*, and not *Bartonella henselae,* was able to induce a bacteremia when inoculated into macaques. This animal model will allow the study of the natural course and pathogenesis of *Bartonella* infections in primates.

Bartonella koehlerae, A New Human Pathogen Causing Culture-Negative Endocarditis. **B. Avidor, *et al*., Kaplan Medical Center, Rehovot, Israel.** Dr. Avidor and his colleagues reported that *Bartonella koehlerae* was identified for the first time, in the aortic valve, as a human pathogen causing culture-negative endocarditis. The causative agent had been misidentified as *Bartonella henselae* (Schattner, A. et al. 2003 Lancet 361:1786). *Bartonella koehlerae* is a *Bartonella* species carried by domestic cats and has been isolated from several stray cats in Israel.

Cat Scratch Disease Without Lymphadenopathy **M. Tsukahara and H. Tsuneoka, Yamaguchi University School of Medicine, Yamaguchi Kohseiren Nagato Hospital, Nagato, Japan.** A total of 185 patients were serologically positive for *Bartonella henselae*. Of these seropositive cases, 155 (83.8%) had regional lymphadenopathy while the other 30 (16.2%) had no lymphadenopathy. Of the 30 patients without lymphadenopathy, prolonged fever occurred lasting more than 7 days 25/30 (83.3%) and 14 days 11/30 (36.7%). Ten of the 30 (33%) patients without lymphadenopathy had systemic complications including optic neuroretinitis 5/10 (50%), Parinaud's oculoglandular syndrome 2/10 (20%), hepato-spenic granulomas 2/10 (20%), and 1/10 (10%) juvenile rheumatoid arthritis. The absence of lymphadenopathy was significantly associated with both prolonged fever and the presence of severe complications.

Editor's Note: **This is one of the most important observations reported. We have similar data from numerous case studies of the owners of *Bartonella* infected cats who developed severe *Bartonella* disease symptoms without the CSD prodrome of lymphadenopathy (tip of the iceberg below). We feel than many *Bartonella* disease symptoms are misdiagnosed due to the lack of the classic CSD regional lymphadenopathy that is familiar to most physicians.**

Cat Scratch Disease: The Tip of the *Bartonella* Iceberg



High Prevalence of Antibodies to Bartonella in Patients with Infected Cat Bites. **K. Westling, *et el.* Karlinska University Hospital Huddinge, Stockholm, Sweden.** Seventy-four patients with infected cat bites, who were seen in emergency wards, were studied for serological evidence of *Bartonell*a infection. Convalescent sera were available from 35 of the 74 patients. Antibody to any *Bartonella* was found in 44/74 (60%) patients. Seroconversion was observed in 8 patients. Of interest is the fact that only 1-2% of Swedish cats are infected with *B. henselae* whereas 67% are seropositive for *B. grahami*, a species isolated from small rodents in Sweden and Europe. Twenty-six % of the people with cat bites in this study, who were seropositive for *Bartonella,* were reactive to *B. grahami*.

Bartonelloses and Other Louse-Borne Infections in 934 Homeless of Marseilles. **P. Brouqui. Unite des Rickettsies, Universite de la Mediterranee Marseilles, France.** Homeless

people are particularly exposed to ectoparasites. Dr. Brouqui and his medical team found that 22% of the homeless were infested with lice and *Bartonella quintana* was isolated from blood culture of 50 people (5.3%). *Bartonella quintana* was found in the erythrocytes and erythroblasts as well as the dental pulp of bacteremic patients. Interestingly, these chronically bacteremic patients were non-febrile. The uncontrolled louse infestation of this population should alert health professionals to the possible re-emergence of louse-borne infections (*Rickettsia prowazekii, Bartonella quintana, and Borrelia recuuentis*).

Bartonella Infections among Homeless in Sweden. **C. Ehrenborg, *et al.* Uppsala University, Uppsala, Sweden.** This group studied 50 homeless people during a one-year period in Sweden. They found an unusually high *Bartonella* seroprevalence of 62% in the homeless compared to 14% in a matched control group. The 14% prevalence in the control group is also very high. No louse infestations were observed in the homeless people. The species of *Bartonella* seroreactivity was not determined.

A homeless man in Uppsala Sweden.

Editor's Note: *Bartonella quintana* is mainly a human *Bartonella*. It has only been found in people and recently in 1 cat. Humans are the main natural reservoir. The finding of *B. quintana* in the dental pulp is relevant to our observation of the *Bartonella* induced oral inflammatory diseases in cats. *Bartonella henselae* is the prototypic *Bartonella* in cats but has been found in dogs and humans as well.

Evidence of Bartonella sp. In Questing Adult and Nymphal Ixodes ricinus ticks from France and Co-infection with Borrelia burgdorferi sensu lato and Babesia sp. **L. Halos, *et al.* Ecole Nationale Veterinaire, Maisons-Alfort, France.** This group examined 92 questing ticks in northern France for coinfection with *Bartonella, Borrelia burgdorferi sensu lato* and *Babesia sp*. by PCR. *Bartonella* was detected in 9% of the ticks. One tick was infected with all 3 pathogens. Ticks represent a major vector for *Bartonella* transmission to humans and animals.

Bartonella Genomics:

***The Louse-borne Human Pathogen Bartonella quintana is a Genomic Derivative of the Zoonotic Agent Bartonella henselae*.** **SGE. Andersson, *et al.* Uppsala University, Uppsala, Sweden.** Dr. Andersson and her collaborators have sequenced the complete genomes of 2 human pathogens, *Bartonella quintana* (1,581,384 bp) and *Bartonella henselae* (1,931,047 bp). They conclude that *Bartonella quintana* was derived from *Bartonella henselae,* millions of years ago, through the loss of 18% of the genome and genomic islands (bacteriophage regions) and thus genome mobility. These genomic changes may be the reason that *Bartonella quintana* is mainly restricted to humans whereas *Bartonella henselae* is very capable of infecting cats, dogs, and people. In comparison to other Alpha-Proteobacteria, the elimination of a few thousand genes is characteristic of a shift to intracellular animal environments and vector-mediated transmission pathways. This team, and others around the world, is investigating the genes responsible for the pathogenic characteristics of all *Bartonella*. The information is being generated at an extremely rapid pace.

***Sequencing the Bartonella tribocorum Genome*.** **S. Schuster, *et al.* Max Planck Institute for Developmental Biology, Tubingen, Germany.** This group has sequenced the genome of *Bartonella tribocorum,* the *Bartonella species* originally isolated from Norwegian rats. This genome is very large (2.69Mb) compared to *Bartonella henselae* (1.93 Mb) and *Bartonella quintana* (1.58 Mb).[1,2] *Bartonella tribocorum* has genetic sequences derived from an insect virus which may be important in the biology of transmission by insect vectors. In this regard, *Bartonella henselae* can replicate in the flea gut.

Bartonella melophagi: a New Endosymbiont? **M. Vayssier-Taussat, *et al.* Ecole Nationale Veterinaire, Maisons-Alfort, France.** This is an observation that relates to the paper directly above regarding *Bartonella* life cycles in insects. *Bartonella* DNA has been found in the *Hippoboscidae* flies of the genera *Hippobosca*, *Lipoptena* and *Melophagus*. *Melophagus ovinus* flies are a permanent parasite of sheep. Although the *Bartonella* DNA was present in all adult (n=38) and pupae (n=14) *Melophagus ovinus,* no *Bartonella* was recovered in culture. By genome analysis, this *Bartonella* is considered a new species, *Bartonella melophagi*. None of the sheep parasitized by this fly were infected with this new species of *Bartonella*. It appears that this new species of *Bartonella* is an endosymbiont, living symbiotically only within this fly with no transmission to sheep. This is the first example of a *Bartonella* confined to an insect "vector."

Bartonella Pathogenesis:

***Role of the Type IV Secretion System VirB/D4 in Bartonella Pathogenesis*.** **C. Dehio, *et al.* University of Basel, Basel, Switzerland**. Dr. Dehio and his group have made great progress in the elucidation of bacterial virulence factors required for *Bartonella* pathogenesis using cultured human endothelial cells. They have identified the bacterial type IV secretion system (T4SS) VirB/D4 as an essential pathogenicity factor in *Bartonella*.[3] T4SS are multi-component transporters that allow bacteria to transfer protein or DNA into a wide variety of target cell types. VirB/D4 T4SS of *B. henselae* mediates most virulence attributes of this pathogen in endothelial cells.[4] These include: 1) massive rearrangements of the actin cytoskeleton, which results in formation of *Bartonella* aggregates and their uptake into the target cell, 2) NF kappa B-dependent proinflammatory activation, leading to cell adhesion molecule expression and chemokine secretion, and 3) inhibition of apoptotic cell death, resulting in enhanced endothelial cell survival. In total, these factors lead to cell invasion (erythrocyte and endothelial cells), tissue inflammation, prolonged cell survival, and proliferation of endothelial and inflammatory cells (macrophages). In people, this results in bacillary angiomatosis, a tumor-like proliferation of capillaries in the skin and various organs. **Editor's Note: Similar lesions and processes occur in *Bartonella* infected cats.**

***The Role of Bartonella Adhesin A (BadA) and HIF-1 in B. henselae Infections*.** **V. Kempf, *et al.* Institut fur Medizinische Mikrobiologie and Hygiene, Tubingen, Germany.** This group has defined different pathogenic factors induced by *Bartonella*. They have observed, *in vitro* and in bacillary angiomatosis tissues *in vivo*, that *Bartonella henselae* infection activates hypoxia-inducible factor-1 (HIF-1), the key transcription factor involved in angiogenesis, and the secretion of vascular endothelial growth factor (VEGF). *Bartonella henselae* have short hair-like structures in their cell wall called pili that enable the bacteria to move. Pili are similar to flagella but are much shorter. Infection with *Bartonella henselae* variants, that do not possess pili (pilus-negative variants), do not activate HIF-1 nor VEGF secretion indicating the importance of this bacterial surface protein in the angiogenic reprogramming of host cells. This surface protein is a non-fimbrial adhesin of *Bartonella henselae* designated as *Bartonella henselae* adhesin A (BadA). BadA mediates the binding of *Bartonella henselae* to extracellular matrix proteins and to endothelial cells. BadA is immunodominant in the antibody response of humans infected with *Bartonella henselae* and in rodents infected with *Bartonella* indicating it is expressed during *Bartonella* infections. BadA is the largest *Bartonella henselae* protein characterized to date with a size of 340 kD and, in fact, is one of the largest proteins found in any bacterium. The BadA gene is the largest gene in *Bartonella henselae*. Serologic detection of BadA in people may improve the serodiagnosis of *Bartonella henselae* infection.

References:

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