



## ***Bartonella henselae* and *Coxiella burnetii* Infection and the Kawasaki Disease**

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**ABSTRACT:** It was reported that *Bartonella henselae*, *B. quintana* and *Coxiella burnetii* was not strongly associated with coronary artery disease but on the basis of geometric mean titer, *C. burnetii* infection might have a modest association with coronary artery disease. Serum antibodies to *B. henselae* from 14 patients with acute phase of Kawasaki disease were determined by the indirect fluorescence antibody assay. Serum antibodies to *C. burnetii* were also tried to detect. However, no positive results were obtained. I also examined 10 children and 10 pregnant women who had serum IgG antibody to *B. henselae* or to *C. burnetii*. No one showed abnormal findings of coronary artery. @JASEM

Several *Bartonella* species cause illness and asymptomatic infection in humans. *B. henselae* has been associated with an increasing spectrum of clinical syndromes including cat scratch disease. Although the clinical spectrum has not been completely clarified, *B. quintana* may cause blood-culture negative endocarditis in children (Barbe *et al*, 2000). *Coxiella burnetii* causes in humans a widespread zoonosis, Q fever, though in many cases infection is asymptomatic and confirmed by serologic diagnosis only (Kafetzis *et al.*, 2001). Endocarditis is the most common presentation of chronic Q fever. *B. henselae*, *B. quintana* and *C. burnetii* also can adhere to and enter endothelial cells and cause local inflammation (Sawyer *et al.*, 1987). Inflammation clearly plays an important role in the atherosclerotic process, and chronic intercellular infections due to these organisms were speculated to play an important role in this inflammatory pathogenesis (Ender *et al.*, 2001). Vasculitis has some kind of role in the pathogenesis of atherosclerosis. Bacteremia or presence of infectious agents in blood stream has been associated vasculitis and endocarditis. An association between *C. burnetii* infection and long-term vascular complications was suggested (Dehio, 1999). Ender and colleagues (2001) prospectively evaluated 155 consecutive patients undergoing coronary angiography for evidence of *Bartonella* species and *Coxiella burnetii* infection. They reported that *B. henselae*, *B. quintana* and *C. burnetii* was not strongly associated with coronary artery disease but on the basis of geometric mean titer, *C. burnetii* infection might have a modest association with coronary artery disease.

### **MATERIALS AND METHODS**

Coronary artery disease is an inflammatory condition

associated with several infections, including *Chlamydia pneumoniae*, cytomegalovirus, *Helicobacter pylori* and other intercellular bacteria (Danesh *et al.*, 1997). Previous studies supported the possibility of certain populations having an association of infections and coronary artery disease Kawasaki disease (KD). KD with characteristic complication of coronary arteries in children has long been considered to have an infectious cause, but no association has been reported with *Rickettsia conorii*, *Rickettsiae typhi*, *C. burnetii*, or *Ehrlichia phagocytophilia* (Lovey *et al.*, 1999).

Serum IgG and IgM antibodies to the Houston-1 isolate of *B. henselae* (ATCC 49882) from 14 patients with acute phase of KD were determined by the indirect fluorescence antibody assay (IFA) as described previously (Numazaki *et al.*, 2000). Serum antibody titers greater than 1:64 for IgG and 1:16 for IgM against *B. henselae* were considered positive. Serum IgG and IgM antibodies to *C. burnetii* Nine Mile phase II were also tried to detect. Serum antibody titers greater than 1:16 for IgG and IgM against *C. burnetii* were considered positive.

### **RESULTS AND DISCUSSION**

Fourteen patients with acute phase of KD had serum antibodies neither to *B. henselae* nor to *C. burnetii*. I also examined 10 children and 10 pregnant women who had positive serum IgG antibody to *B. henselae* or to *C. burnetii*. No one showed abnormal findings of coronary artery.

Although Ender and colleagues (2001) postulated that *Bartonella* species may play a role in the pathogenesis of coronary artery disease, they did not find a statistically significant association between seropositivity to *Bartonella* antigens and coronary

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artery disease. Intracellular infection with one of these organisms or with others may still play a role in the development of coronary artery disease. The involvement of several organisms may be additive or synergistic. A complex relationship of several infections that leads to coronary artery disease may make a clear association with a single specific organism more difficult to identify.

Previous studies of *Bartonella* infection reported less than 5% seropositivity in the general population (Numazaki et al., 2000; Regnery et al., 1992). The rate of *Bartonella* seropositivity in population of Enders and colleagues (2001) is higher than previous results. Although they used only serological assays, the diagnosis of *Bartonella* species infection can be established by isolating the agents from clinical specimens. PCR assay for genomes also provides a rapid, sensitive and specific method to diagnose active infection.

On the other hand, the IFA reminds the reference technique for the serological diagnosis of *B. henselae* or *C. burnetii* infection. A differential diagnosis is established when antibody titers against both phase I and phase II *C. burnetii* antigens are determined. Although the positive association of *C. burnetii* phase I antibody detection (a marker of chronic infection) with coronary artery disease was shown (Ender et al., 2001), cross-reactivity of antibodies between *C. burnetii* and *C. pneumoniae* should be considered.

Multivariable logic regression analysis revealed no association between seropositivity to *B. henselae*, *B. quintana*, and *C. burnetii* phase I, and II. In a prospective, cross-sectional study, it was unable to detect a significant association between infection with *Bartonella* species and atherosclerotic coronary artery disease that was diagnosed by coronary angiography (Ender et al., 2001).

In general vascular or coronary arterial infection of *B. henselae* or *C. burnetii* is recognized as a rare condition. Since the clinical manifestations of *B. henselae* or *C. burnetii* vascular infection are nonspecific, the disease has been recognized only when serology was done systemically. Infectious agents may be one of the nonspecific for the pathogenesis of coronary artery disease associated with KD. Well standardized sensitive and specific tests are definitely needed to further analyze the potential association between *B. henselae* and *C. burnetii* infection and KD.

## REFERENCES

Barbe KP, Jaeggi E, Ninet B, Liassine ND, Cosima.

G, Alain SS (2000). *Bartonella quintana* endocarditis in children. N Engl J Med 342: 1841-1842.

Danesh J, Collins R, Peto R (1997). Chronic infections and coronary heart disease: is there a role? Lancet 350: 430-436.

Dehio C (1999). Interactions of *Bartonella henselae* with vascular endothelial cells. Curr Opin Microbiol 2: 78-82.

Ender PT, Phares J, Gerson G, Taylor SE, Regnery R, Challener RC, Dolan MJ (2001). Association of *Bartonella* species and *Coxiella burnetii* infection with coronary artery disease. J Infect Dis 183: 831-834.

Kafetzis DA, Maltezou HC, Constantopoulou I, Antonaki G, Liapi G, Mathioudakis I (2001). Lack of association between Kawasaki syndrome and infection with *Rickettsia conorii*, *Rickettsia typhi*, *Coxiella burnetii* or *Ehrlichia phagocytophilia* group. Pediatr Infect Dis J 20: 703-706.

Lovey P, Morabia A, Bleed D, Peter O, Dupuis G, Petite J (1999). Long-term vascular complications of *Coxiella burnetii* infection in Switzerland: cohort study. BMJ 319: 284-846.

Numazaki K, Ueno H, Yokoo K, Muramatsu Y, Chiba S, Morita, C (2000). Detection of serum antibodies to *Bartonella henselae* and *Coxiella burnetii* from Japanese children and pregnant women. Microbes Infect 2: 1431-1434.

Regnery RL, Olson JG, Perkins BA, Bibb W (1992). Serological response to "*Rochalimaea henselae*" antigen in suspected cat-scratch disease. Lancet 339: 144-145

Sawyer LA, Fishbein DB, McDade JE (1987). Q fever: current concepts. Rev Infect Dis 9: 935-946.