



NATIONAL VETERINARY LABORATORY

P.O. Box 239, 1Tice Road

Franklin Lakes, NJ 07417

877-NVL-LABS (877-685-5227)

www.natvetlab.com

NEWSLETTER

Bartonella Association with Autoimmune Diseases[©]

Evelyn E. Zuckerman, Editor

Spring 2015

Vol. 14, Number 2

In This Issue:

The Spring 2015 issue of the NVL Newsletter will review the association of *Bartonella henselae* with autoimmune diseases, mostly in humans, but some in dogs and cats.¹⁻¹⁶ Autoimmune *Bartonella* diseases are not common but can be severe.

Basic Concepts:

Bartonella are widely known to cause cat scratch disease (CSD) which, in typical cases, are characterized by fever, a papule on the site of a scratch or bite from a cat, and lymphadenopathy. Atypical CSD is characterized by inflammation in various sites and organs in the body and rarely can induce autoimmune disease. In general, the pathogenesis of autoimmune diseases in all species is not fully understood and is multi-factorial, including genetic and environmental parameters.¹ The pathogenic mechanism(s) by which *Bartonella* cause autoimmune disorders may include direct infection or, indirectly, by molecular mimicry, polyclonal T cell activation by bacterial superantigens, induction of autoantibodies such as antierythrocyte, antithrombocyte, antinuclear, activation of classical complement cascade, and production of proinflammatory cytokines. Immune complexes of such antibodies may be precipitated in various tissues resulting in inflammation and



Components of immune system

clinical signs. *Bartonella* induce very high antibody titers in cats and some humans, as well as cellular immune stimulation resulting in granuloma formations and lymphocyte and neutrophil accumulations in various tissues. *Bartonella* cause chronic immune stimulation that can last for months and even years in various animals including humans.

Humans:

In humans, infections with viruses, bacteria and fungi are known to cause autoimmune diseases during or after the infections have been cleared. *Bartonella* infections are associated with several autoimmune diseases in humans¹⁻¹³ including, autoimmune thyroiditis,² systemic juvenile rheumatoid arthritis,^{3,4} vasculitis,⁵ glomerulonephritis⁶ autoimmune hemolytic anemia,⁷ transverse myelitis,⁸ Henoch-Schonlein purpura,⁹⁻¹¹ and Guillain-Barre syndrome.¹²

Autoimmune Thyroiditis²

An 11-year-old boy was seen due to the development of a goiter, diarrhea and weight loss.² He had mild tachycardia, a mild tremor and agitation. He also had the prodrome of CSD with a mildly tender right subclavicular lymph node and an erythematous papule on the side of his neck. He was diagnosed with autoimmune hyperthyroidism (Hashitoxicosis). The family had a 9 month old cat but they could not remember any scratches or bites from the cat. The child's *B. henselae* serology showed an IgG titer of 1:100. He was treated with tapazole and clarithromycin and showed a gradual improvement in thyroid function, resolution of the tachycardia, weight gain, reduction in goiter size and regression of the lymphadenopathy and neck papule. After 5 months he was able to stop the tapazole therapy and made a complete recovery.

Juvenile Rheumatoid Arthritis (JRA)^{3,4}

JRA was diagnosed in a 4 year old girl who presented with a persistent fever and myalgia in spite of prolonged multiple antibiotic therapy.³ There were no other symptoms including arthralgia or joint swelling. Hypergammaglobulinemia, elevated complement, and antinuclear antibody (ANA) were found by laboratory analysis.



Abdominal ultrasonography showed several low echoic lesions (granulomas) in the liver and spleen. A month before this illness, the child was scratched on a finger by a cat. There were no prodromal signs of cat scratch disease (CSD) such as a papule or lymphadenopathy. *B. henselae* IFA serology was negative for IgM whereas the IgG titer was high at 1:4096. *Bartonella* PCR of peripheral blood was negative. The patient was treated with aspirin for 41 days and her symptoms and visceral granulomas all resolved. There was no mention of additional antibiotic therapy.

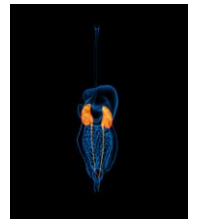
Vasculitis⁵

A 65-year-old woman presented with fever, purpuric plaques with hemorrhagic blisters and necrosis on both lower legs 3 days after being bitten and scratched by a stray cat.⁵ There were no classic prodrome signs of CSD such as lymphadenopathy or a papule. The erythrocyte sedimentation rate and C-reactive protein were

elevated. An IgA nephropathy was diagnosed by elevated creatinine, proteinuria, swollen glomeruli with IgA deposition and hyperechogenic lesions in the renal cortex by ultrasonography. *Bartonella* serology was positive for IgM 1:20 and IgG 1:128. The patient was treated with azithromycin and the skin purpura resolved within 1 week and the renal failure resolved with the additional use of methylprednisolone IV and oral prednisone for 6 months. The serologic evidence of acute *Bartonella* infection resulting in the acute clinical syndrome, and the rapid resolution of the extensive dermal purpura with azithromycin therapy, demonstrated the etiologic role for *Bartonella*-induced autoimmune disease.

Glomerulonephritis⁶

A 13-year-old boy presented with hematuria and intermittent low-grade proteinuria at the time he was diagnosed with CSD with fever, a right axillary lymphadenopathy and vertebral granulomas.⁶ He was treated with amoxicillin/clavulonic acid but was then changed to rifampin and azithromycin. Three weeks after presentation, his lymphadenopathy had decreased and he was restarted on rifampin twice daily for 3 days and azithromycin daily (duration not indicated). Six months later he noticed painless tea-colored urine during a short course of URI. Renal biopsy showed IgA, C3 and albumin deposition in the glomeruli. The mild symptoms of glomerulonephritis persisted for more than 8 months. The *B. henselae* titers were: IgM 1:128 and IgG 1:256. The authors concluded that, with the boy's genetic parameters, a large IgA stimulus induced by the *Bartonella* infection may have overwhelmed the immune clearance of IgA resulting in its deposition in the kidneys. The patient eventually fully recovered.



Autoimmune Hemolytic Anemia⁷

A 60-year-old man was seen due to severe Coombs-negative hemolytic anemia.⁷ He had been treated at a previous hospital with amoxicillin/clavulanic acid and doxycycline for 5 days. Blood smears revealed spherocytosis and polychromatophilia with a markedly elevated absolute and relative reticulocyte count. Free plasma hemoglobin was 4 times normal. Direct and indirect antiglobulin tests and cold

agglutinins were negative. Taken together these finding indicated severe hemolysis. Exclusion of other known mechanisms for infectious anemias, a diagnosis of Coombs-negative autoimmune hemolytic anemia was made. Antibiotics were discontinued and the patient was treated with methylprednisolone and 2 units of concentrated red cells. The anemia rapidly improved within 4 weeks.

A similar severe acute Coombs-negative hemolytic anemia syndrome (Oroya Fever) has been known for decades caused by *B. bacilliformis* in parts of South America. Due to the history of exposure to a cat before the illness began, *B. henselae* serology was performed on day 8. Results were IgM 1:64 and IgG 1:512 indicating recent infection. This finding, along with the response to doxycycline antibiotic therapy, and decrease in IgM concurrent with clinical improvement, strongly indicated the etiology of this condition to be *B. henselae*.

Transverse myelitis⁸

Transverse myelitis is an inflammation occurring across one level, or segment, of the spinal cord. Myelitis means inflammation of the spinal cord and transverse describes across the width of the spinal cord. Inflammation of nervous tissues can damage or destroy the myelin cover of nerve cell fibers. This inflammation damages nervous tissues which can interrupt transmission between nerves in the spinal cord. Inflammation can be caused directly by viral or bacterial infections or indirectly by abnormal immune reactions against the infectious agents. In post-infectious cases of transverse myelitis, immune system mechanisms, rather than active viral or bacterial infections, play an important role in causing damage to spinal nerves. The mechanism by which this occurs is unknown but stimulation of the immune system in response to infection indicates that an autoimmune reaction may be responsible.

Baylor *et. al.* reported 2 cases of transverse myelitis in a 46-year-old man and a 13-year-old boy with concurrent CSD.⁸ Both patients were serologically positive for *B. henselae* IgM and IgG. No antibodies to *B. henselae* were found in the CSF of either patient. Both patients fully recovered from the CSD and transverse myelitis. Including these cases, there are a total of 8 cases reported in the literature. Although not proven, some cases of transverse myelitis appear to be an autoimmune disease caused by *B. henselae* infection.

Henoch-Schönlein Purpura⁹⁻¹²

Henoch-Schönlein purpura (HSP) is a vasculitis where IgA and complement 3 are deposited on arterioles, capillaries, and venules. Serum levels of IgA are high in HSP. HSP is a systemic disease involving the skin and connective tissues, joints, gastrointestinal tract and kidneys. The etiology of HSP is unknown but insect bites, foods, and a number of infectious agents, viruses and bacteria, have been implicated.



Henoch-Schönlein purpura on the legs of a child.

Reproduced with permission: Okwikikim at the wikipedia.

In 2 studies, 12 of 18 and 17 of 28 patients with HSP were seropositive for *B. henselae* antibody.^{9,10} The authors concluded that *B. henselae* is a significant causal factor in some cases of HSP.

Guillain-Barre Syndrome¹³

Guillain-Barré syndrome (GBS) is a rare autoimmune disorder in which a person's own immune system damages their nerve cells, causing muscle weakness and sometimes paralysis. A 10-year-old girl presented with loss of movement of her legs. She became irritable, had severe myalgia, and tests found axonal damage.¹³ There was no history of cat scratches or bites but *B. henselae* serology was positive for IgG 1:1024 and IgM. After immunoglobulin treatment she fully recovered.

Dogs:

Immune-Mediated Hemolytic Anemia¹⁴

The diagnostic criteria for dogs with immune-mediated hemolytic anemia (IMHA) are anemia with PCV <37%, positive saline agglutination and direct Coombs' tests or moderate to marked spherocytosis on a peripheral blood smear. Perinuclear antineutrophil cytoplasmic autoantibodies (pANCA) are most often IgG antibodies reactive to cytoplasmic antigens in neutrophils and other granulocytes that have been used as markers for autoimmune diseases such as glomerulonephritis, vasculitis, IBD and Crohn's disease in people. A recent study found an association of (pANCA) in dogs infected with vector-borne pathogens including *B. henselae*. Thirteen of 29 dogs (45%), with pANCA, were seropositive for *B. henselae*.¹⁴

Cats¹⁵⁻¹⁷

B. henselae and 5 other *Bartonella* species induce chronic inflammatory diseases in cats.¹⁵ To date, we have found 47.9% of 5,010 cats with anemia and 50% of 208 cats with thrombocytopenia to be seropositive for *B. henselae* by western blot.¹⁶ Although practitioners submitting the samples did not define the type of anemia, some may have been autoimmune in nature. Cats with thrombocytopenia had epistaxis, petechia and ecchymosis. However, the anemias and thrombocytopenias were not tested for autoimmune markers.

B. henselae infections are chronic in cats and, untreated, can last for months to years. Cats produce very high antibody titers, some as high as 1:2,048,000, against the more than 15 immunogenic *B. henselae* proteins.¹⁷ It is possible that some of these antibodies may form complexes with soluble *B. henselae* proteins resulting in immune complexes that may be deposited in the walls of blood vessels or in the renal glomeruli leading to autoimmune disorders. In addition, some of the antibodies against *Bartonella* structural proteins may react with closely related cell surface antigens (proteins and glycoproteins) causing cellular damage. Further studies are needed to elucidate whether or not *B. henselae* do induce autoimmune diseases in cats.

References:

1. Maritsi DN, Zarganis D, Metaxa Z, Papaioannou G, Vartzelis G. *Bartonella henselae* Infection: An Uncommon Mimicker of Autoimmune Disease. Case Reports in Pediatrics 2013;2013:726826. doi: 10.1155/2013/726826. Epub 2013 Jan 17.
2. Chiuri RM, Matronola MF, Di Giulio C, Comegna L, Chiarelli F, Blassetti A. *Bartonella henselae* infection associated with autoimmune thyroiditis in a child. Horm Res Paediatr. 79:185-8, 2013.
3. Tsukahara M, Tsuneoka H, Tateishi H, Fujita K, Uchida M. *Bartonella* infection associated with systemic juvenile rheumatoid arthritis. Clin Infect Dis. 32(1):e22-3, 2001.
4. Rigante D, Bosco A, Esposito S. The Etiology of Juvenile Idiopathic Arthritis. Clin Rev Allergy Immunol. Nov 12. [Epub ahead of print] 2014.
5. Cozzani E, Cinotti E, Ameri P, Sofia A, Murialdo G, Parodi A. Onset of cutaneous vasculitis and exacerbation of IgA nephropathy after *Bartonella henselae* infection. Clin Exp Dermatol 37:238-40, 2011.
6. Hopp L, and Eppes SC. Development of IgA nephritis following cat scratch disease in a 13-year-old boy. Pediatr Nephrol. 19:682-4, 2004.
7. Van Audenhove A, Verhoef G, Peetermans WE, Boogaerts M, Vandenberghe P. Autoimmune haemolytic anaemia triggered by *Bartonella henselae* infection: a case report. Br J Haematol. 115:924-5, 2001.
8. Baylor P, Garoufi A, Karpathios T, Lutz J, Mogelof J, Moseful D. Transverse myelitis in 2 patients with *Bartonella henselae* infection (cat scratch disease) Clin Infect Dis. 2007 45:e42-5, 2007.
9. Ayoub EM, McBride J, Schmiederer M, Anderson B. Role of *Bartonella henselae* in the etiology of Henoch-Schönlein purpura. Pediatr Infect Dis J. 21:28-31, 2002.
10. Robinson, JL, Spady, DW, McColl, D, Artsob, H. *Bartonella* seropositivity in children with Henoch-Schönlein purpura. BMC Infect. Dis. 5:21, 2005.
11. Emilio Palumbo, Federica Sodini, Giuseppe Boscarelli, Giuseppina Nasca, Maurizio Branchi, Guido Pellegrini. Immune thrombocytopenic purpura as a complication of *Bartonella henselae* infection. Infez Med. 16:99-102, 2008
12. Borcker, A and Gardner, R. Severe thrombocytopenic purpura as a complication of cat scratch disease. Clin Pediatr (Phila) 41:117-8, 2002.
13. Massei F, Gori L, Taddeucci G, Macchia P, Maggiore G. *Bartonella henselae* infection associated with Guillain-Barre syndrome. Pediatr Infect Dis J. 25:90-1, 2006.
14. Karagianni AE, Solano-Gallego L, Breitschwerdt EB, Gaschen FP, Day MJ, Trotta M, Wieland B, Allenspach K. Perinuclear antineutrophil cytoplasmic autoantibodies in dogs infected with various vector-borne pathogens and in dogs with immune-mediated hemolytic anemia. Am J Vet Res. 73:1403-9, 2012.
15. Hardy, WD, Jr., Zuckerman, E, Corbishley, J. Seroprevalence of *Bartonella*-infection in healthy and diseased cats in the United States and Caribbean: Evidence for *Bartonella*-induced diseases in cats. International Conference of the American Society for Rickettsiology, Big Sky, MT, August 17-22, 2001.
16. Hardy, WD, Jr., Zuckerman, EE, Petcher, SP and Raclyn, P. Atypical *Bartonella-associated* Diseases of Cats and Dogs: Platelet and Pancreatic Disorders. 6th International Conference on *Bartonella* as Emerging Pathogens, June 21, Chester, UK, 2009.
17. Hardy, WD, Jr, Zuckerman, EE, Gold, JWM, Baron, P, Kiehn, TE, Polsky, B, and Armstrong, D. Immunogenic proteins of *Bartonella henselae* defined by western immunoblot with naturally infected cat sera. 95th General Meeting, American Society for Microbiology, Washington, D.C., May 21-25, 1995.

Bartonella references can be obtained at:

www.nlm.nih.gov/or/natvetlab.com

©National Veterinary Laboratory, Inc., 2015