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NEWSLETTER

Literature Review: 3 Common Cat Pathogens©

Evelyn E. Zuckerman, Editor **Spring 2018** **Vol. 17, Number 2**

In This Issue:

The Spring 2018 issue of the NVL Newsletter will review literature of the 3 common cat pathogens: *Bartonella*, FeLV and FIV. Among the numerous pathogens that pet cats are exposed to, these 3 are among to most prevalent. A search of the literature on the National Library of Medicine, PubMed site found 6,006 *Bartonella*/CSD, 2,205 FeLV, and 2,244 FIV articles published to date. We will review only 4 of these interesting articles.

Bartonella:

Yanagihara, M. *et. al*., *Bartonella henselae* DNA in Seronegative Patients with Cat-Scratch Disease. Emerg Infect Dis 24: 924-5, 2018.

In this study, real-time PCR (rPCR) was used to detect *Bartonella henselae* (Bh) in 80 patients in Japan with suspected cases of cat-scratch disease (CSD). Eighty immunocompetent patients (73 children, 7 adults) with symptoms consistent with CSD- fever with or without lymphadenopathy, and a history of contact with cats and dogs were tested using IFA serology and rPCR. 17 (21.3%) of the 80 patients were seropositive by IFA for Bh. The remaining 63 patients were seronegative and real-time PCR was used to try to detect Bh DNA in their blood specimens.

Of the 80 patients with suspected CSD, 17 (21.3%) were seropositive. Bh DNA was amplified from peripheral blood of 11 (13.8%) patients by rPCR. Six patients were positive by both IFA and rPCR. CSD was diagnosed in 22 (27.5%) of the 80 patients. After the laboratory diagnosis, macrolides were given to reduce fever. The finding of seronegative CSD suggest that these patients were in the early stages of the disease, before a significant rise in antibodies to Bh, or that the patient's immune responses were insufficient to produce antibodies. Most blood samples were drawn within three weeks after the onset of symptoms, probably too soon for antibody formation in some patients. rPCR alone is not sensitive enough because Bh DNA is not always present in the bloodstream in all patients because of intermittent bacteremia. Bh intermittent bacteremia occurs in cats, dogs, and people. Serology was more accurate in this study whereby 17 of 22 patients were seropositive versus only 11 of 22 patients were reactive by rPCR. We found similar results with Western blot serology versus PCR for Bh in cats.

In conclusion, this study demonstrates that both serology and rPCR testing are useful for the early, noninvasive, screening for CSD, although serology was the most accurate.

Editor's Note:

It remains perplexing to realize than many veterinarians and physicians still do not consider feline *Bartonella* significant pathogens. We hear that some veterinarians **"do not believe in *Bartonella*"** despite the thousands of publications of the diseases caused by these bacteria in cats and humans. Similar opinions have occurred for years with Lyme Disease and *Helicobacter pylori* etiologies in humans. The AAFP and the CDC also seem ambivalent regarding *Bartonella* importance in veterinary and human medicine. In addition, after interacting with thousands of veterinarians during the past 18 years, we still feel that many in our profession do not fully appreciate the importance of *Bartonella* in cats or in people. Likewise, after interviewing more than 500 people infected with *Bartonella*, it is clear that a substantial proportion of physicians do not know much about *Bartonella* or are dismissive of their clinical importance.

Human *Bartonella* Diseases* (Feline Origin):

General Inflammatory Diseases:

- Cat Scratch Disease
  - Fever
  - Papule at scratch or bite site
  - Lymphadenopathy- regional
- Bacillary angiomatosis
- Bacillary peliosis
- Febrile bacteremia
- Lymphadenopathy
- Guillain-Barre Syndrome
- Inflammatory bowel disease
  - Colitis
  - Terminal ileitis
- Chronic fatigue syndrome
- Autoimmune thyroiditis
- Vasculitis
- Pulmonary infiltrates- pneumonia
- Mononucleosis-like syndrome

Ocular Disease:

- Parinaud's oculoglandular syndrome
- Uveitis
- Chorioretinitis
- Neuroretinitis
- Optic nerve neuritis
- Disciform keratitis
- Choroiditis
- Conjunctivitis
- Blepharitis
- Orbital granuloma

Heart Diseases:

- Endocarditis
- Valvulitis- vegetative
- Myocarditis
- Pericarditis
- Thromboembolism (stroke)

Neurologic Diseases:

- Encephalitis
- Encephalopathy- granulomas
- Meningoencephalitis
- Meningoencephalopathy
- AIDS Encephalopathy
- Meningitis
- Fatal Meningitis and Encephalitis
- Seizures
- Status Epilepticus
- Peripheral facial nerve paralysis
- Acute hemiplegia.
- Coma
- Neurologic amyotrophy
- Expressive aphasia
- Transverse myelitis
- Aggression- combativeness
- Headaches- Encephalalgia
- Hemiparesis
- Cognitive dysfunction
  - Brain fog
  - Agitation
  - Dementia

Major Organs Involvement:

Liver:
- Peliosis hepatis
- Granulomatous hepatosplenic syndrome

Spleen:
- Splenic bacillary angiomatosis
- Splenomegaly

Kidney:
- Necrotizing glomerulonephritis

Intestines:
- Inflammatory bowel disease
- Bacillary angiomatosis

Respiratory Diseases:
- Pulmonary granuloma
- Pulmonary infiltrates

Musculoskeletal Diseases:
- Bacillary angiomatosis
- Myositis
- Arthralgia
- Arthritis/polyarthritis
- Juvenile Rheumatoid Arthritis
- Osteomyelitis
- Myalgia

Skin Disease:
- Bacillary angiomatosis
- Cutaneous rash- Henoch-Schenlein Purpura
- Cutaneous granuloma annulare

Other:
- Fever of unknown origin
- Co-infection with Lyme disease
- Mononucleosis-like syndrome
- Pseudo-neoplastic lesions
- Thrombocytopenia
- Anemia
- Autoimmune Hemolytic Anemia

***Many similar diseases have been found in *Bartonella*-infected cats.**

RETROVIRUSES:

Bats Retrovirus:

Retroviruses comprise a diverse group of animal viruses that cause lymphoid cancers, neurologic diseases, and immunodeficiencies in many species. They have a unique replication process involving the production of viral RNA genome into a double-stranded DNA, using the virus encoded reverse transcriptase enzyme. The double-stranded proviral DNA is then inserted into the host cell genome. Some exogenous retroviruses, such as the feline leukemia virus (FeLV), are transmitted horizontally (contagiously).[1] However, they can become endogenous when they enter the host germline cells and result in Mendelian transmission. Many species, including cats and humans, have fossil gammaretroviral sequences in their genomic DNA indicating past contagious epidemics. However, these viral DNA remnants do not produce virus. Retroviruses are classified into Orthoretrovirinae subfamily with the following genera: Alpha, Beta, Delta, Epsilon, Gamma, and Lentivirus and Spumaretrovirinae subfamily containing the single genus Spumavirus. Gammaretroviruses are found in many mammals including cats (feline leukemia and sarcoma viruses), primates, mice, sheep, pigs, cows, koalas, whales, and avians.[2] The evolutionary origin of gammaretroviruses is enigmatic. The following paper gives a possible insight into the origin of mammalian gammaretroviruses from bats.

Bats, the possible origin of viruses such as FeLV

Cui, J., *et al.*, Discovery of Retroviral Homologs in Bats: Implications for the Origin of Mammalian Gammaretroviruses. J. Virol. 86:4288-4293, 2012.

Bats (mammalian order Chiroptera) have the second most species of mammals, after rodents, with 1,116 species.[3] The ability to fly, to hibernate, have a relatively long lifespan, and gregarious roosting behavior, make bats ideal reservoirs for the maintenance of viral pathogens. In this regard, bats harbor more than 60 distinct viruses including the dangerous *Filoviruses*, *Flaviviruses*, *Coronaviruses* amongst others. They often carry many deadly pathogens for long periods without showing any clinical signs. Why bats can harbor such deadly viral pathogens, in good health, is not understood. Analysis of the endogenous "fossil" gammaretroviral sequences in the normal cellular DNA of the greater horseshoe bat *Rhinolophus ferrumequinum*, and its relatives in other bat species, identified a new gammaretrovirus, *Rhinolophus ferrumequinum* retrovirus (RfRV). Phylogenetic analysis of these fossil sequences show they are ancient (basal) to all but the avian REV in the retroviral family tree and this insinuates that gammaretroviruses, such as FeLV, arose in ancient bats and somehow were transmitted contagiously (horizontally) to distant relatives on the ancestral mammalian tree to cats.

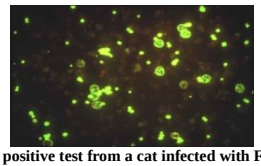
Feline Leukemia Virus:

In the late 1960s and early 1970s, we developed the first FeLV test, an IFA test, to screen cats for the virus and discovered that FeLV was transmitted contagiously among cats.[1] This finding made us concerned about the possibility that FeLV might also be transmissible to cat owners. We recommended a "test and removal" program for multiple cat households whereby any FeLV-infected cat be removed from the household in order to protect the uninfected cats. We received some criticism for this program and later changed the recommendations to "test and quarantine." We then tested several hundred veterinarians and cat owners and found none to be infected with FeLV. We and others also found that our isolate of FeLV (FeLV-A) would not infect human cells in cell culture which alleviated some of our concern for the zoonotic potential of FeLV. However, subsequently it was found that FeLV-B was able to infect cultured human cells.[4]

The following paper is an exceptional study of the infectivity of FeLV-B and the possibility that this FeLV subgroup may have potential for zoonotic transmission. The senior author for this group is James C. Neil, a brilliant virologist from the University of Glasgow Centre for Virus Research and a friend who has been active in FeLV research for decades.

Terry, A., *et al.*, Barriers to Infection of Human Cells by Feline Leukemia Virus: Insights into Resistance to Zoonosis. J. Virol 91:e02119-16 https://doi.org/10.1128/M.02119-16.

FeLV is a gammaretroviruses with 3 subgroups, A, B, and C. All FeLV isolates contain FeLV-A either alone or in combination with B and or C. FeLV-A is the major contagious subgroup for cats.[5] As shown in **Figure 1**, 50% of isolates from cats contain FeLV-B and ~1% FeLV-C. The cat genome contains numerous endogenous FeLV copies that are not replication competent. However, the fossil FeLV genomes are used by infectious FeLV-A, in recombinational mutations of new env gene sequences, to produce new subgroups -B and -C.[6] FeLV-C cause rapidly fatal anemias in cats and thus probably is not transmitted contagiously.



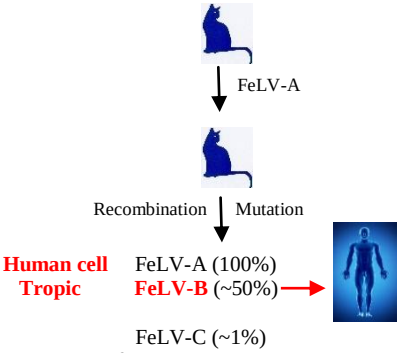
FeLV IFA positive test from a cat infected with FeLV-ABC

The human genome is also rich in fossil genomes of past gammaretroviruses infections but, there has not been any current epidemics, despite exposure to FeLV and to other gammaretroviruses and there is no evidence of infection from cats. This study found that FeLV-A uses the cell receptor THTR1 to infect cat cells but is not able to use the human receptor homolog, hTHTR1 and thus cannot infect cultured human cells. However, in contrast, **FeLV-B** is able to infect numerous cultured human cell types, especially cancer cell lines, although cultured hematopoietic peripheral blood mononuclear cells (PBMCs) are more widely resistant. Even though the PBMCs did not replicate FeLV-B, the viral genome was found to be integrated into the genome of the cells, but no virus was produced. Some of the experiments utilized our FeLV-negative feline lymphosarcoma cell line 3201 as controls. The overall lack of evidence of zoonotic transmission of **FeLV-B** appears to primarily rely on the *in vivo* resistance of the PBMCs, even though in culture they are non-productively infected.

In the paper's discussion, this group asks the question: **"Can the risk of zoonotic infection with FeLV be discounted?**... This study confirms **FeLV-B** as the variant most likely to have zoonotic potential, since virtually all human cells are susceptible, with only limited postentry barriers to infection. The resistance of primary blood cells, at a post-integration step, and potent APOBEC3 induction of mutations in virions released from hematopoietic cells, appear to be significant factors in limiting infectivity for human cells. The possibility that FeLV could evolve to evade these barriers cannot be discounted. It may be interesting to revisit the apparent lack of adaptive immune responses in exposed individuals, e.g., veterinary workers, using more sensitive techniques."

Figure 1

The Recombinational Generation of FeLV-B



Adapted from Terry A., et al. J. Virol

Feline Immunodeficiency Virus:

McDermid, KR., *et al.*, Surveillance for Viral and Parasitic Pathogens in a Vulnerable African Lion (Panthera Leo) Population in the Northern Tuli Game Reserve, Botswana. J Wildl Dis 53:54-61, 2017.

African lion populations are decreasing rapidly in Botswana and infectious diseases may be threatening this population. This paper reports on a survey of various viral and parasitic pathogens during 2012-2014. One lion had antibodies to feline panleukopenia virus, 2 had antibodies to canine distemper virus but 10 of 13 had antibodies to the feline immunodeficiency virus. All lions were negative for all tick-borne agents except for *Babesia* where all were positive. The survey was important as there is an initiative to incorporate this population into a larger lion population in South Africa and Zimbabwe.

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