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Retrovirus Infections in Cats – an ongoing problem?

The two most important retrovirus infections found in cats, **FIV and FeLV**, are encountered daily in practice and in the laboratory. Hardly a day passes on which you do not carry out an in-house test or send a sample to the lab.

But what do we know about these viruses?

The first “Leukaemia viruses” were discovered in chickens in 1904.

Retroviruses are enveloped RNA viruses with three characteristic main structural protein genes: *gag-env-pol*.
The “advantage” of an envelope is that it consists of a protein-lipid double membrane incorporating important envelope proteins. This envelope can influence the course of infection, but also make the virus much more susceptible to disinfection than non-enveloped viruses such as Parvo- and Calicivirus.

This means they have a lower tenacity, and are susceptible to soaps and detergents as well as common disinfectants.

During the replication of RNA viruses, there is no proof-reading step, so that frequent mutations allow for rapid evolution, which can have medically relevant consequences. These viruses can rapidly adapt to their host cell organism and therefore secure survival advantages for themselves.

This makes the development of vaccines difficult and can lead to difficulties in diagnosing these infections.

Feline Leukaemia Virus (FeLV)

FeLV was first described in 1964 and is directly transmitted from cat to cat. The main source of infection is saliva. Bite wounds also carry a high risk of transmission, since these can lead to the direct introduction of saliva into the blood stream. In most cases, initial infection is oropharyngeal. The virus enters through the mucous membranes and replicates there as well as in the tonsils and the retropharyngeal lymph nodes within two days. The virus spreads into the blood stream and then the bone marrow after about twelve days via infected lymphocytes and monocytes.

The development of a lymphopenia is due mostly to a loss of CD4+ T-lymphocytes. Initially, the number of CD8+ cells is also reduced, but these recover over time. The loss of T-cells leads to a reduction in cellular immunity. The remaining T-cells have a reduced activity.

The envelope or transmembrane protein p15E is responsible for viral entry into the cell. Corresponding neutralizing antibodies prevent this and probably also prevent persistent infections!
Current research on the detection of antibodies against p15E have shown promising results for diagnosis and prognosis.

The primary results of infection include tissue damage resulting from virus replication, particularly FeLV-associated bone marrow depression. This is due to infection of mitotically active cells of the hematopoietic cell line. The early viraemic phase is cha-

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racterized by bone marrow hypoplasia with various degrees of anaemia, leukopenia, and thrombocytopenia. Anaemia is found in almost 50% of FeLV infected cats and leads to death in about 8%. This is usually an aplastic anaemia caused by disturbance of erythropoiesis. A low number of reticulocytes is an indicator for a non-regenerative anaemia.

In about 45% of the time, a cat infected with FeLV will develop a **transient, abortive infection**. The immune system is able to eliminate the virus. The cat does not become ill. Research on whether or not the virus neutralizing antibodies produced are capable of generating a resilient immunity has shown contradictory results.

A sufficient immune response to prevent virus replication is mounted in about 30% of infections. However, virus elimination is not possible. The result is a **latent infection**, with latency residing in the fibroblasts of the bone marrow. This is also known as a **regressive infection**. Provirus can be detected in affected cats, but they are p27, i.e. antigen-ELISA, negative.

Other infectious diseases or stress can lead to virus reactivation and viraemia.

All other cases develop **persistent infections**, which are usually associated with a severe and short course of disease.

The diagnosis of FeLV is usually carried out using an ELISA for antigen detection. One problem is detection during latency, as no antigen is detectable during this period. This can lead to confusion and discrediting of vaccines especially in those cases in which an animal is vaccinated following a negative test and then, often years later, develops a viraemia and becomes positive.

Vaccinations against FeLV are very safe and confer relatively good protective immunity, as these are genetically engineered vaccines. *As these are not full-pathogen vaccines, they do not interfere with diagnostic detection methods*.

The detection of proviral FeLV-cDNA (provirus) by PCR is very useful to confirm a positive antigen test.

This is, however, somewhat problematic during the initial phase of infection. Studies have shown that even vaccinated cats can be PCR positive for up to 100 days following experimental infection without ever producing antigen.

Latently infected cats are persistently positive when tested for provirus by PCR. These animals are a high risk when used as donors for blood transfusions!

In a recent study, blood was transfused from antigen negative but provirus (PCR) positive cats to SPF cats. All 15 recipients remained provirus positive for more than 15 weeks, and two cats also remained persistently antigen positive. This proves that infection can be transmitted by blood transfusion.

Feline Immunodeficiency Virus (FIV)

FIV is also a member of the family *Retroviridae*, but belongs in the genus *Lentivirus.* The virus is closely related to HIV, but is not infectious for humans. It was first described in California in 1987, shortly after the discovery of HIV.

Husbandry and environmental conditions as well as gender play a role in the epidemiology of FIV infections. Since FIV is transmitted mostly by bites, the incidence of infected animals is highest in non-castrated tomcats five years or older. Intrauterine infection or infection via colostrum lead to abortion or so called “Fading Kitten Syndrome”.
FIV occurs worldwide and is also found in wild felids. In Germany, the prevalence is around 3-5%. Infection with FIV generally occurs long before the cat develops initial grave clinical signs.

Initial signs of infection are generally unremarkable and can include short-term fever and reduction of neutrophil granulocytes in the peripheral blood over a period of several

weeks. Significant, however, is the occurring lymphadenopathy, which may be detectable over several months. Rarely, more severe forms occur during this phase.

The immune system is slowly depleted due to the infection of the immunocompetent cells.

The virus persists for life. It has a clear tropism for T-lymphocytes and macrophages, with the T-lymphocytes most severely damaged, whereby both qualitative and quantitative damage to the T-helper cell population predominate. This leads to a percentage and then absolute reduction in the number of CD4 cells. The CD4+/CD8+ ratio is reduced over the course of the infection. The function of the humoral immune system is only reduced relatively late during the infection. The cats then demonstrate a wide range of clinical signs and combinations of signs, depending on secondary infections. Most common are diseases of the respiratory tract such as rhinitis, bronchitis, laryngitis, and pneumonia. Diseases of the oral cavity are observed in 30 to 50% of cases. Rarely, the virus itself causes damage of the CNS leading to clinical signs and ocular lesions. FIV positive cats may have a disturbed sense of balance. Recent research has also shown that the plasma concentration of hormones may be influenced by infection, which can lead to increases in T4 and fT4.

FIV is generally diagnosed by antibody detection using ELISA. Since it is a persistent infection, antibodies can be detected about 2-3 weeks post infection.

The detection of antigen is particularly difficult during the persistence phase due to the low viral replication rate and is therefore not performed in routine diagnostics.

The virus itself can be detected using a qualitative or quantitative polymerase chain reaction (PCR). This determines the viral load (number of virus particles in the plasma) or the proviral load (number of DNA copies of the viral genome per defined number of lymphocytes).
Unfortunately, this detection of the viral genome by PCR can be problematic, since there are numerous subtypes and variants that can make genome detection difficult. Rare strains may not be detectable. Treatment with antiretroviral medication (e.g. Zidovudine, AZT, CART [combined anti-retroviral therapy], etc.) leads to inhibition of the infection of new cells or prevents virus release from infected cells. In these cases, a quantitative PCR can be used to determine the viral load and to monitor the effectivity of the therapy.

Another good prognostic indicator is the **cellular immune status**, in which the number of CD4, CD8 and B-cells as well as the CD4+/CD8+ ratio are determined. Many cats may have values within the reference ranges over a period of years. Only in the late phase of infection, the cell population is noticeably reduced. This can even lead to a situation in which antibodies are no longer produced and antibody detection via FIV-ELISA will be negative.

The life expectancy of a cat with FIV infection is now not significantly shorter than that of a non-infected cat. Although the owner should try to minimize the time spent outdoors, two studies from Scotland have shown that the risk of transmission within a single household with an integrated cat group is minimal.

Infections with retroviruses like Feline Leukaemia Virus (FeLV) and Feline Immunodeficiency Virus (FIV) occur with a prevalence of 1.5% and 3.5% in the German cat population. The percentage of positive samples in our laboratory is much higher, though, as most of the submitted samples are from cases in which infections are suspected. Here we see a prevalence among submitted samples between 5 and 7%.