Coronavirus infection in cats – feline infectious peritonitis and COVID-19

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Summary

Coronaviruses comprise a large family of RNA viruses that infect a wide variety of mammalian and avian hosts causing severe disease in some of them, such as the recent pandemic of COVID-19 caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). The feline coronavirus (FCoV) is an excellent example for shifting virulence and cell tropism by mutation. It occurs in 2 different biotypes, a harmless enteric variant that develops into a deadly biotype causing the fatal disease feline infectious peritonitis (FIP). Our research focuses on the epidemiology of FCoV infection as well as on pathogenic aspects, on the diagnosis of FIP and recently on new antiviral therapy for both FIP as well as COVID-19, as the FIP/cat model can serve as an excellent natural model for further treatment approaches for severe coronavirus-associated syndromes.

Research Objectives

Coronaviruses possess a single-stranded, positive-sense RNA genome and are particularly prone to mutation and recombination, and this property significantly contributes to their existing diversity. The consequence is a sudden emergence of new coronaviruses transmitted from animal hosts, such as severe Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and most recently SARS-CoV-2 causing the disease COVID-19. Shifts in tissue or cell tropism and resulting changes in virulence are a unique feature of coronaviruses, so that a seemingly innocuous infection can also be turned deadly by changing viral tropism. The best example for such a virulence change is FCoV that occurs in 2 different biotypes: a harmless enteric variant (sometimes called "feline enteric coronavirus (FECV)") that changes its cell tropism and pathogenicity through mutations and thereby develops into a deadly biotype (sometimes called "feline infectious peritonitis virus (FIPV)") causing the fatal disease FIP. The emergence of the worldwide pandemic of SARS-CoV-2 has focused research on the development and advancement of antiviral drugs. In the context of COVID-19, a syndrome has been described in children with SARS-CoV-2 infection, the paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-

TS). Astonishing parallels between PIMS and FIP can be found. PIMS is a hyperinflammatory immune response similar to FIP. Affected children often initially only show gastrointestinal signs, while in the course of the disease further symptoms appear, such as persistent fever, circulatory shock, ascites, pleural and pericardial effusion. Therefore, FIP can provide a useful natural model for insights into the pathogenesis but also potential treatments of PIMS.

Infection with non-pathogenic FCoV is widespread among cats worldwide, especially in multi-cat environments and usually remains asymptomatic or only causes mild diarrhoea with little clinical consequence. However, a small proportion of FCoV-infected cats (7-14% in multi-cat environments) develops FIP, triggered by mutation of the virus gaining tropism for macrophages in individual cats, although the immune system ofinfected cats also plays an important role in the pathogenesis. FIP is the most common infectious cause of death in cats with a fatality of virtually 100% and a median survival time of 8 to 9 days if untreated.

However, the pathogenesis of FIP is still not fully understood and diagnosis of FIP is challenging, as all non-invasive clinical tests have limitations. Thus, our research focuses on the epidemiology of FCoV infection as well as on pathogenic aspects. Goals are to determine FCoV prevalence and risk factors for FCoV infection in catteries, as well as to evaluate a possible correlation between FCoV antibodies and virus shedding and between FCoV infection and diarrhoea. Viral pathogenesis is studied on a cellular level by in-situ-hybridization. In addition, we work on the development and evaluation of newly established diagnostic assays for the ante mortem diagnosis of FIP. The aim is to establish and evaluate diagnostic tests with high sensitivity and specificity for the diagnosis of FIP and to compare these different diagnostic tools using different sample material from cats with and without FIP. Current research focuses on the treatment of cats suffering from FIP with novel nucleoside analogues (specifically those that can be used orally) and on the investigation of their safety and efficacy with regard to clinical and clinicopathological parameters, virus load, and survival. Additionally, the development of gene expression and immunologic parameters will be evaluated in the course of antiviral treatment. These findings can be crucial for the development of effective treatment strategies for FIP but also for COVID-19 and especially SARS-CoV-2-infected children with PIMS. If efficacy of such oral treatment in cats with a deadly disease could be consistently proven, this also could be a promising approach for treating other severe coronavirus-associated diseases, such as COVID-19.

Key Findings

According to our studies, the prevalence of FCoV infection in German breeding catteries is extremely high. None of the German catteries are free of FCoV infection. Younger cats are at a higher risk of being infected and shedding FCoV with their faeces. We were able to show a correlation between the antibody titre of cats infected with FCoV and the likelihood, frequency, and amount of faecal virus shedding. Thus, measurement of the FCoV antibody titre can assist in identifying cats shedding large amounts of FCoV, which is important for the elimination of FCoV infection from multi-cat households. However, since not all antibody-positive cats shed FCoV and some FCoV shedders do not have antibodies, measurement of the antibody titre cannot replace faecal quantitative RT-PCR.

We could demonstrate that immunocytochemistry can detect FCoV antigen within macrophages in effusion, aqueous humour, cerebrospinal fluid, and fine-needle aspirations of mesenteric lymph nodes, which can be obtained minimally invasive and ante mortem in cats suspected of having FIP. However, this method was shown not to be sufficiently specific for FIP and additionally lacked sensitivity in most of the sample materials. Thus, it cannot be used as a sole test to reliably diagnose FIP. RT-PCR detecting mutated FCoV could identify FCoV with spike gene mutations in all of the cats with FIP in at least one body fluid or tissue, which confirms an association between the presence of spike gene mutations and systemic spread of FCoV. However, when evaluating RT-PCR detecting mutated FCoV as a diagnostic test in blood, effusion, aqueous humour, and cerebrospinal fluid, specificity was not 100% and sensitivity was only acceptable in effusion but very poor in blood samples. Although the detection of FCoV with spike gene mutations via RT-PCR initially appeared rather specific for FIP, few false positive results occurred

and our further research will focus on investigating the presence of FCoV with spike gene mutations in multiple body fluids and tissues from FCoV-infected cats without FIP. Additionally, the reason for the occurrence of false positive results will be further investigated by simultaneously applying immunocytochemistry and in-situ-hybridization.
Future research will also focus on the treatment of cats suffering from FIP with novel nucleoside analogues to investigate their safety and efficacy with regard to clinical and clinicopathological parameters, virus load, and survival. Additionally, the development of gene expression and immunologic parameters will be evaluated in the course of antiviral treatment. These findings are not only important for cats suffering from FIP, but also could be crucial for the development of effective treatment strategies for SARS-CoV-2-infected children with PIMS.

Selected Publications

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