Feline infectious peritonitis – new developments in pathogenesis, diagnosis, and management

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Introduction

Feline infectious peritonitis (FIP) is a common disease and a frequent reason for referral. Approximately one of every 200 new feline cases presented to American Veterinary Teaching Hospitals represent cats with FIP. FIP is a fatal, immune-mediated disease, triggered by infection with a feline coronavirus (FCoV). FCoV belongs to the family Coronaviridae, which is a group of enveloped, positive-stranded RNA viruses frequently found in cats. In catteries, up to 90% of cats have FCoV-specific antibodies, compared to up to 50% in single cat households. However, only approximately 5% of FCoV-infected cats actually develop FIP in a multi-cat household situation. Since FIP is not only a common, but also a deadly condition and no effective long term management is available, a rapid and reliable diagnosis is critical for prognostic reasons. Difficulties in verifying the diagnosis of FIP are related to nonspecific clinical signs, lack of pathognomonic hematological and biochemical abnormalities and low sensitivity and specificity of tests routinely used in practice. It was initially hypothesized that FIP-causing FCoV strains are different to avirulent enteric FCoV strains. However, a new hypothesis has been accepted in the meantime, that both pathotypes are antigenetically and genetically indistinguishable and represent different pathotypes of the same virus rather than separate virus species. It has been shown that cats are infected with the primarily avirulent FCoV that replicates in enterocytes. In some cats, however, a mutation occurs in a certain region of the FCoV genome leading to virus replication within macrophages, which is the pathogenic key event in the development of FIP.

What is the pathogenesis of FIP?

Today, the „internal mutation hypothesis “has been widely accepted as explanation for the pathogenesis of FIP. Coronaviruses are RNA viruses and as such, particularly prone to mutation. Hence, FIP is caused by spontaneous mutation of FCoV leading to massive replication of FCoV in macrophages. When a cat is infected with FCoV via the oronasal route, the virus first attaches to enterocytes of the small intestine and invades into the cells. The virus then replicates in the cytoplasm and causes apoptosis of the enterocyte. By this mechanism, FCoV can persist in the gastrointestinal tract of cats without causing any clinical signs. The disease FIP is not infectious; it develops within a cat when genomic mutation occurs during replication of FCoV. Several research groups were able to identify gene loci potentially responsible for the pathogenic switch. Mutations in the gene of the spike protein result in a defective spike protein of FCoV. In consequence, the virus becomes unable to bind to surface receptors and to invade enterocytes. As a sequel, mutated FCoV are phagocytized by macrophages. Potentially, another, second mutation in the 3C gene might be necessary for effective replication of FCoV in those macrophages. Factors that favor intensive virus replication increase the probability for virus mutation, such as dose and irulence of the viral strain, age and immune suppression of the cat (caused by e.g. stress, glucocorticoids, infection with FeLV or FIV), genetic predispositions and, in multicat households, predominantly reinfections. Macrophages infected with mutated virus release inflammatory mediators inducing severe systemic inflammation in the organism with formation of antigen antibody complexes which deposit mainly in blood vessels causing vasculitis and body cavity effusion. Hence, the disease FIP is not primarily caused by the virus itself, but by overreaction of the feline immune system to the virus.

Which test should be used to diagnose FIP?

FIP is a lethal condition. This is why a definitive diagnosis is absolutely essential. However, verifying a diagnosis of FIP can be extremely challenging. A weighted score system for FIP diagnosis, taking several parameters into account, including background of the cat, history, presence of clinical sings, laboratory changes, and height of antibody titers, has historically been used. However, this score can only propose a certain percentage of likelihood of FIP and is not a reliable tool for definitive confirmation of the diagnosis. Nowadays, methods of choice for diagnosing FIP utilize techniques for direct virus detection, such as antigen detection in macrophages by immunostaining or reverse transcriptase polymerase chain reaction (RT-PCR). While immunostaining detects intracellular antigen (thus virus protein), RT-PCR detects viral RNA. These two methods are discussed in detail below. Other methods, e.g. detection of FIP-antibodies, are obsolete in the diagnosis of FIP. Detection of FCoV antigen in macrophages (e.g. through immunofluorescence or immunocytochemistry in effusion fluids, by immunohistochemistry in tissues) is often used for intra vitam and also post mortem diagnosis of FIP. Stains reveal large amounts of intracellular FCoV antigen. Massive replication of virus within acrophages only takes place after the crucial mutation. Detection of large amounts of virus in macrophages is therefore
strongly indicative for virus mutation. Tissue immunohistochemistry staining of FCoV antigen in macrophages is considered the gold standard to confirm the diagnosis of FIP. However, tissue is needed for this method which can only be obtained via laparotomy or laparoscopy. If effusions are present, detection of FCoV antigen via immunofluorescence has been considered as method of choice. A high specificity has been documented (mostly 100%) for this method in former studies. However, in one prospective study, false positive results were obtained in 2 cats with diseases other than FIP. Fluids, tissue biopsies, or even tissue imprints can be examined by immunocytochemistry. The latter has the advantage of facilitating evaluation of cell morphology and localization of antigen within the cell besides antigen detection. In one study, diagnostic utility of immunocytopathy using effusion fluids was evaluated. Sensitivity was 85%, and specificity was 72%. Thus, also in this study some false positive results occurred. Those false positive results make immunocytochemistry not sufficiently reliably for confirmation of the diagnosis of FIP. In another study, diagnostic utility of immunocytochemical detection of FCoV antigen in macrophages of cerebrospinal fluid was evaluated. Sensitivity was 70% in cats with histologically confirmed FIP of the CNS, and 91% in cats with non-neurologic FIP. A further study evaluated diagnostic utility of immunocytochemistry using intraocular fluid. In this study, sensitivity was 64%, and specificity was 80%. When using aspirates from lymph nodes, sensitivity was 53%, and specificity was 92%. Thus, in some cats suffering from other diseases, macrophages positive for FCoV antigen were detected in effusion fluid, in cerebrospinal fluid, in ocular fluid, and in lymph node aspirates. It is possible that cross reactions with other antigens occur, or that “harmless” FCoV during a phase of viremia can be detected in samples of from organs and body fluids. It is also possible that these cats suffered from an early stage of FIP that was not yet detected in histology. However, these false positive results in cats without FIP limit the utility of immunocytochemistry and immunofluorescence staining to confirm a diagnosis of FIP.

RT-PCR is frequently used in the diagnosis of FIP. Conventional RT-PCR does, however, not allow differentiation of FIP and “harmless” FCoV. FCoV RNA can also be detected in blood from healthy cats. Many of those RT-PCR-positive cats do, however, not suffer from FIP and also never will. It has been demonstrated that mutations play a central role in the pathogenesis of FIP; however, it is still unclear, which mutations are crucial. The S, 7a, and 3c genes are discussed in this context. It has been shown that 2 point mutations (position 23531 and 23537) in the genome of the spike gene play an important role. In a study from Utrecht, one of these 2 mutations was found in > 95% of cats with FIP, but never in healthy cats. The 2 mutations cause changes in the amino acids of the spike protein which is involved in entrance into enterocytes. The aim of one study was to investigate sensitivity and specificity of a method combining RT-PCR with subsequent sequencing in order to detect the point mutations at the 2 nucleotid positions in the spike gene in effusion fluids and blood samples from cats with confirmed FIP and also from cats with confirmed other diseases. Specificity of this combined method was 100% for both, effusion fluid and blood. Sensitivity was 65% for effusion fluid, but only 7% for blood. Positive results therefore confirm suspected FIP. Negative results are, however, invalid and therefore do not exclude FIP, particularly in cats with no effusions if only blood samples can be examined. A commercial RT-PCR detecting those mutations has recently become available. First evaluations also indicate a high specificity for this commercial assay, although positive results also have been detected in a few cats with diseases other than FIP.

Is any treatment effective in cats with FIP?

Treatment of cats with FIP is almost invariably doomed to failure since all cats with clinical FIP eventually die from the disease. As FIP is an immune-mediated disease, therapy generally aims at controlling the immune response triggered by the infection with FCoV. Immunosuppressive drugs, such as prednisone or cyclophosphamide, can slow disease progression but are not curative. In nearly every published case report, glucocorticoids were administered. However, studies evaluating the actual mechanisms of action of glucocorticoids in FIP are lacking. Some veterinarians use immunomodulators in cats with FIP. However, there is no documented controlled evidence of their efficacy. It has been suggested that these agents might benefit infected animals by restoring compromised immune function, thereby allowing the patient to control the viral burden and recover from clinical signs. However, non-specific immunostimulation might be even contraindicated as clinical signs develop and progress as a result of an immune-mediated response to the mutated FCoV. In the past, many different agents within the class of immunosuppressive, anti-inflammatory, immunomodulators, or platelet function-inhibitory drugs have been tried. However so far, endeavors to find an effective treatment for cats with FIP has unfortunately not been very successful.

Although there are several studies published on the treatment of cats with suspected FIP, results of most of these studies have to be interpreted carefully. Evaluation of data is hampered by the lack of well-controlled clinical trials comparing new treatments against standard treatment protocols or placebo. In most studies, presence of FIP had not even been confirmed before initiating treatment which makes assessing the outcome difficult. The toxicity of drugs that effectively control replication
of FCoV in vitro, like ribavirin, is far too high for feline patients. It might also be too late to start antiviral treatment at a time point when clinical signs of FIP are already present. So far, treatment of cats with FIP still remains frustrating and has to be limited to a small number of cases that responded favorably within the first few days.

In addition to glucocorticoids, cytostatic drugs such as cyclophosphamide have been used for immunosuppression. In the oldest report published, a cat suspected to have FIP was treated with prednisolone, penicillin, and dihydrostreptomycin, and the cat remained alert. However, at this point of time, etiology of FIP was still unknown and the diagnosis of FIP could not be verified. In another study, 2 cats were treated with ozagrel hydrochloride, a thromboxane synthetase inhibitor (5 mg/kg or 10 mg/kg q 12 h, respectively), and prednisolone (2 mg/kg q 24 h). Ozagrel hydrochloride suppresses platelet aggregation by production of thromboxane A2. The cat receiving the lower dose was clinically healthy 2 weeks after initiation of therapy. After 12 months, treatment was discontinued. The cat still remained healthy for the next 6 months. The other cat (receiving 10 mg/kg) was in good clinical condition after 12 days (effusion had also vanished) and stayed healthy until therapy was stopped after 9 months because of the occurrence of nasal bleeding. Ascites recurred and the cat died 11 months after initial remission. Although a likely diagnosis, FIP was also not confirmed in these 2 cases. A group of researchers administered the antiviral drug ribavirin (16.5 mg/kg q 24 h for ten to 14 days PO, IM, or IV) to specific pathogen-free kittens 18 hours after experimental challenge exposure with a FIP-causing virus. All kittens, including ribavirin-treated and untreated kittens, died of FIP. Clinical signs of disease were even more severe in the ribavirin-treated kittens and their mean survival times were shortened. Although ribavirin is active against FCoV in vitro, it has not proven to be effective in treatment of cats with FIP due to the severe adverse effects. In a case series with 3 cases of FIP without effusion (in 2 of them diagnosis of FIP was confirmed), the immunomodulatory drug polypropenyl immunostimulant was used. This compound is a phosphorylated polypropenyl with 10 to 14 prenyl residues, which is a veterinary biologic containing a mixture of phosphorylated, linear polysoprenols, that leads to upregulation of biosynthesis of mRNA of Th1 cytokines and that seems to have some antiviral effect. One treated cat survived 14 months (at necropsy, FIP was diagnosed), one cat was still alive and doing well after 24 months (immunohistochemistry staining of FCoV antigen was positive in this cat), and one cat was still alive and doing well after 28 months (no definitive diagnosis). A controlled treatment trial using various interferons, Propionibacterium acnes (an immunomodulatory compound), a combination, or placebo was performed by another group. Neither prophylactic nor therapeutic administration of high doses of human interferon-α (10⁴ or 10⁵ IU/kg), feline interferon-β (10³ IU/kg), or Propionibacterium acnes (0.4 mg/cat or 4 mg/cat) significantly reduced mortality in treated cats, although cats receiving 10⁶ IU/kg human interferon-α in combination with Propionibacterium acnes, had a mean survival time that was significantly prolonged for a few days. In Europe, Japan, and Australia, feline interferon-ω has been licensed for use in veterinary medicine. Interferons are species-specific (therefore application of the feline product does not cause anti-interferon antibody development in cats). FCoV replication is inhibited by feline interferon-ω in vitro. In a randomized placebo-controlled double-blind treatment trial, 37 cats with FIP were treated with interferon-ω or placebo. In all cats, FIP was confirmed by histology and/or immunohistochemical or immunofluorescence staining of FCoV antigen in effusion or tissue macrophages. All cats received glucocorticoids, either as dexamethasone in case of effusion (1 mg/kg intrathoracic or intraperitoneal injection q 24 h) or as prednisolone (2 mg/kg PO q 24 h) as well as either placebo or interferon-ω at 10⁶ IU/kg SQ q 24 h for 8 days and subsequently once every week. There was no significant difference in the mean survival time of cats treated with interferon-ω versus placebo. Cats survived for a period of 3 to 200 days before they had to be euthanized. Mean survival time was 18 days.

How can FIP be prevented in multi-cat households?

FIP is a problem of cats kept in groups, particularly in catteries and shelters. Vaccination is not effective. Since the most important route of transmission is fecal-oral transmission, hygiene is the foremost method of FIP control in any multi-cat environment. In catteries, FCoV infection is perpetuated by continual cycles of infection and re-infection with the source of infection being the contaminated cat litter. FIP is rarely a problem amongst cats leading a natural outdoor lifestyle. The goal in every cat household is to reduce FCoV load and infection pressure and thus, risk of transmission. This can be achieved by avoiding having too many cats in the household, keeping small group groups of cats of not more than 3 (well-adapted) cats per room, strict hygiene, and outdoor access for the cats to bury their feces. If the latter is not possible, enough litter boxes should be provided, cat litter boxes must be cleaned frequently, and litter trays should be separated from food bowls by placement in different rooms.

What can be done to eliminate FCoV in catteries?

Breeding catteries are at high risk for FIP. In most European countries, there is no cattery in which FCoV is not endemic. Multiple RT-PCR in feces (optimum 4 times over 3 weeks), can be used to identify cats shedding FCoV in high amounts and to separate them from low- and intermediate-shredder cats and from cats
that are not shedding FCoV. Virus shedding occurs over several months, in some cat’s life-long, particularly in multi-cat households. Kitten typically develop FIP in the post-weaning period; therefore, many breeders are unaware of the presence of endemic FCoV infection in their cattery since deaths from FIP usually occur when kittens are already in their new owners’ homes. It has been reported that FCoV infection of young kitten can possibly be prevented by isolating the kitten together with their queens from 2 weeks ante partum, moving them from their mother to a clean environment at the age of 5 to 6 weeks, and keeping them there until they go to a new home (early weaning). The breeder strictly needs to follow strong hygiene methods for success. However, efficacy of this method is controversial. Transplacental transmission of FCoV has been documented in rare cases, but does not appear to be common, but early virus shedding, such as at 2 weeks of age, has been demonstrated using sensitive RT-PCR methods.

What can be done to eliminate FCoV in shelters?
Eliminating FCoV in a shelter is hardly possible. Optimum housing conditions, strict hygiene, and education of people handling the cats is a critical requirement. Ideally, cats should be kept separately. Strict hygiene precautions must be enforced at all times in an attempt to minimize viral spread and in order to keep virus load at a minimum. New shelters should be designed with infectious disease control and stress reduction as important priority.

Suggested Reading References

Other references can be provided by the author on request.