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Feline infectious peritonitis (FIP) – an update

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Approximately 1 – 3% (1) or 5 – 12% (2, 3) of cats infected with feline enteric coronavirus (FECV) develop feline infectious peritonitis (FIP). Feline coronavirus (FCoV) is the term used to refer to FECV and its mutated form – feline infectious peritonitis virus (FIPV).
To date, not all stages of the pathogenesis of FIP have been clarified and finding a diagnosis is only possible by invasive methods or by including several laboratory tests, especially for the non-effusive or dry form of FIP.

Epidemiology and shedding of FECV

FCoV can be found in many households (4) or animal shelters worldwide, especially in multi-cat households (2, 5). Cats younger than 12 months are 2.5 times more likely to shed FECV in the faeces than cats aged 1 – 5 years (4). Most cats get infected at 6 – 10 weeks of age (usually via the mother). Normally, faecal excretion does not occur before the age of 9 weeks, but shedding from 4 weeks of age onwards has also been proven (4).

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FECV may spread through the faeces for a period of 18 months after infection. In general, approximately 10 – 13% of cats become chronic carriers (chronic viral shedding) after infection, 70 – 80% of cats have a transient infection, i.e. they are intermittent shedders, 5 – 10% of cats develop resistance (1, 6). Cats that are chronic carriers of FECV may help to spread the virus within the cat population but appear to be less likely to develop FIP themselves (1).

FCoV mutation

RNA viruses usually have a very large genome and their polymerase is prone to reading errors during viral replication, so, in general, they are very likely to mutate (5).
According to current knowledge, the amino acid sequences of mutated (FIPV) and non-mutated (FECV) strains of FCoV only differ in very few individual sequence positions (2). Yet, these few changes in the amino acid sequence can still lead to a change in cell tropism of FCoV. It is assumed that FIPV, unlike FECV, does not invade intestinal enterocytes, but rather infects macrophages and monocytes where it replicates. As a result, after the mutation, it is no longer shed in the faeces. Thus, a cat suffering from FIP cannot transmit the mutated virus to other cats.
So far, no mutation is known which reliably leads to FIP when infected. Four regions are thought to be responsible for possible FCoV gene mutations causing the change in viral cell tropism. These include the open reading frame (ORF) “3a-c ORF” (the significance of the mutation is not yet clear; a virus with mutations in this sequence region is no longer excreted in the faeces), the “7a-b ORF” (the significance of the mutation is not yet clear; however, it is detected discontinuously in cases of FIP), the M gene (which is responsible for a membrane protein of the virus) and the S gene for the so-called “spike protein” (this protein is responsible for the ability of the virus to “enter” the cells) (5).

The main focus of research is currently on the detection of mutations in the spike protein, as this is thought to be the main reason for the change in cell tropism. Although a mutation in the spike protein was found in 91% of the tissue samples from cats with clinical FIP, 9% of the cats with clinical FIP had no mutation in the spike protein. Furthermore, a mutation in the spike protein was also detected in 89% of the tissue samples from cats without clinical FIP (3). It was therefore concluded that a mutation in the spike protein can more likely be used as a marker for systemic virus spread than for confirming the diagnosis of FIP (3, 7). A PCR result negative for mutations must be critically assessed, as there may still be a mutation of FCoV. A possible reason could be that the mutation is located at a different sequence site or it is just not present in the supplied material. PCR results which are positive for mutations must also be viewed critically, since cats without clinical disease can also carry an FCoV mutation, as described above.
There are other studies which suggest that several mutations must be present for the cat to develop the clinical picture of FIP (5). Thus, the exact mutation mechanisms and their effects resulting in FIP, and eventually the benefits and methods of mutation detection are not fully understood.

Risk factors for the development of FIP

In the literature, various risk factors are described that may be related to the development of FIP. The age of the cat is considered to be the most important one. Cats younger than 2 years have the highest risk of developing FIP (4, 5). After that, the risk for FIP, especially the dry form, only seems to increase again at an older age (6).
Stress in any form, e.g. change of owner, transfer to a shelter, surgery or changes in hierarchy, is another factor which is certain to have an impact. Moreover, many cats with FIP come from households with a high population

density (5). According to studies, the excretion of FECV in a cat's faeces increases 10-fold after changing its home (change of owner or shelter) – in some cats even up to 10^6-fold (1). Intact males have a higher risk, whereas neutered cats are less likely to develop FIP (6). Furthermore, a genetic factor is being discussed, more precisely the number of alleles encoding the feline leukocyte antigen (FLA), which is supposed to vary in different breeds. For example, Burmese cats are said to have fewer alleles than other breeds (1). This could result in a loss of FLA diversity and could consequently cause these cats to develop a poorer immune defence (1). However, there are many different studies on breed-specific FIP, with sometimes contradictory statements about the same breeds or in which a breed predisposition could not be replicated (1, 4, 6). The theory suggesting that the interferon-γ-gene and its variants are associated with the risk of developing FIP has not yet been confirmed (4).

Diagnosis of FIP

So far, the gold standard of FIP detection remains staining the viral antigen in macrophages, which are surrounded by pyogranulomatous lesions, by means of histopathology or immunohistochemistry (7). Unfortunately, the high degree of certainty of this method is contrasted by the invasive nature of obtaining tissue samples.
As a further diagnostic component, PCR can be performed to detect FCoV (typically, real-time PCR on fluids from body cavity effusions has the highest sensitivity). According to current knowledge, all fluid or tissue samples which are PCR-positive for mutations also have a positive FCoV PCR (3, 7). Since in case of FIP, FECV is no longer excreted in the faeces due to the mutation of the virus, and since a cat can be reinfected with non-mutated FCoV at the same time despite suffering from FIP (7), FCoV PCR from faecal samples is of little help in making a diagnosis.
In general, the result of the FCoV PCR must always be assessed together with the results of other tests. Thus, for example, the Rivalta test, serum protein electrophoresis, cytology of CSF or of body cavity effusions and possibly an ultrasound scan continue to be important building blocks for the diagnosis of FIP (1, 6).

Diagnosis of FECV (non-)shedders

When identifying chronic and intermittent shedders, it is important to note that after an initial infection with FECV, the virus can be shed for over 18 months. FCoV PCR can therefore be positive over a long period of time without the cat necessarily being a chronic carrier.
There is no general recommendation on how long the test period should be (i.e. in which time frame repeated FCoV PCR tests on faeces should be carried out) through which the cat can be identified as a non-shedder. Different information can be found on this, ranging from more than 5 – 30 days (4) to at least 5 months (6) or even 9 months (1).
Of course, the general rule is: the longer the period chosen, the more certain the status of the animal.

Treatment

So far, there is no therapeutic option to avoid the fatal outcome of FIP. Only few data is available on treatment attempts with e.g. corticosteroids, chlorambucil and cyclophosphamide, polyprenyl immunostimulant or pentoxifylline (6). Furthermore, for many drugs, there are no suitable control studies or sufficient numbers of cases (6).
A small molecule from the group of nucleoside analogues, GS-441524, is currently being discussed as the most promising therapeutic option. Its mechanism of action is that this molecule is incorporated as an alternative substrate into the viral RNA chain during replication, thereby stopping the elongation of the RNA chain, as no further ribonucleic acids can be added. According to first studies,

effective levels can also be achieved in the ocular chamber and the CSF. In vitro and after initial infection trials, a daily subcutaneous injection of GS-441524 seems to reduce the clinical signs of FIP, improve the general condition of the cats and significantly increase their lifespan by 8 to 17 months after diagnosis (8, 9).

Prevention

The best and only safe prevention of FIP is to prevent the cat from becoming infected with FCoV.
If a new FCoV-negative cat is supposed to join the household after a cat has died, it is best to wait for 3 months to ensure that any remaining FCoV in the household has lost its infectivity (6). In a dry environment, FCoV can be infectious for at least 7 weeks. The virus is, however, sensitive to almost all common detergents. Bleach has been described as particularly suitable (1).
Another recommendation to reduce the viral load is to clean the litter trays daily; if possible, the litter trays should be in different rooms than the food and water bowls (6).
Recent studies have shown that the choice of cat litter can help to reduce the viral load and viral transmission. According to these studies, cat litter variants that are based on clay minerals prevent, in vitro, the infection of cells with FECV and reduce the virus titre (10). However, these results are rather attributed to virus-binding properties (since clay mineral usually binds proteins and fats) than to any virus-neutralising capacity (10). It is questionable whether these virus-binding properties are also fully effective if a cat does not completely cover its faeces with cat litter. Those types of cat litter whose raw material is based on sawdust do not seem to have any virus-binding or virus-neutralising properties. Further field research is needed to determine the effectiveness (10).
Possibly, adapted feeding, i.e. a reduction of unsaturated fatty acids and a reduction of the omega-6 to omega-3 ratio, can contribute to a less pro-inflammatory environment in the intestine and in the animal. If the animal's condition is less pro-inflammatory, monocytes and macrophages show a lower tendency to adhere and migrate, so that the contact between virus and immune cells decreases and, thus, possible penetration and virus replication in monocytes or macrophages is reduced (1).

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