SCIENTIFIC INFORMATION DOCUMENT

Feline infectious peritonitis

FELINE infectious peritonitis (FIP) is a systemic, fatal, immune-mediated vasculitis caused by a feline coronavirus (FCoV). Historically, FIP was considered to be caused by FIP virus (FIPV) and feline enteritis by a feline enteric coronavirus (FECV). Recent studies have shown that there is essentially only one FCoV in the field, although laboratory strains may vary in virulence.

FCoV readily mutates but genomic studies have failed to show a consistent mutation distinguishing FIP strains from FECV strains. Nevertheless, it is believed that a mutation in the virus alters its cell tropism from enteric epithelial cells to macrophages, resulting in FIP.

Alternatively, since FIP usually follows an episode of stress (rehoming, surgery, kittening and so on), it is possible that disease is related to virus dose and a non-protective immune response.

FCoVs are serologically related to canine coronavirus (CCV), transmissible gastroenteritis virus of pigs, porcine epidemic diarrhoea virus and human bronchitis virus 229-E, and belong to one of two distinct serotypes; most field infections are caused by serotype I FCoV, whereas most laboratory isolates are type II. Serotype II isolates evolved more recently than serotype I through recombination between type I FCoV and CCV. The role of CCV in causing FIP is unclear, although McArdle and others (1992) have shown that CCV administered parenterally to cats will cause FIP-like disease.

Epizootiology

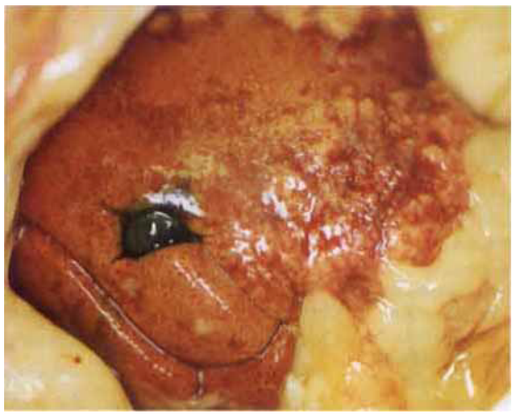
All cats are susceptible to FIP, but the disease is seen primarily in cats aged between three months and two years old, with a second peak in cats over 10 years of age, possibly associated with a decline in immune responses. Kittens are protected from FCoV by maternal antibodies up to approximately six weeks of age.

FCoV is very infectious. Over 90 per cent of cats exposed to it will seroconvert and, of these, approximately 10 per cent will develop signs of FIP.

The seroprevalence of FCoV is approximately 25 per cent in single-cat households and up to 100 per cent in multicat households in which the virus is endemic. Approximately half the cat breeders in the UK are thought to have FCoV endemic among their cats, compared with only about a quarter of multicat households where the cats are kept simply as pets. The main predisposing factors to FIP in multicat groups are greater environmental virus levels with consequent higher infective doses and increased stress levels which may reduce immunity.

FCoV is shed in the faeces and transmission occurs mainly via the sharing of litter trays with an infected cat. Horizontal transmission (direct cat-to-cat infection) can occur, although virus is shed in the saliva for only about one month after infection. The virus is fragile and can be destroyed by household disinfectants, particularly sodium hypochlorite (bleach). However, some strains can survive for up to seven weeks in the environment and thus fomite transmission is a real risk in specific pathogen-free, rescue and breeding catteries. Transmission on clothing from house to house (for example, by a visiting veterinary surgeon) is extremely unlikely unless clothing is contaminated with particulate faeces. Transplacental transmission, although rare, has been documented.

The incidence of feline leukaemia virus has been shown to be no higher in cats which develop FIP than in the general cat population and the incidence of feline immunodeficiency virus even less.



Granulomas on the liver of a cat with FIP

Pathogenesis

There are many different laboratory strains of FCoV, with varying pathogenicity for causing FIP. However, in the field it has been shown that wherever FCoV infection occurs there is the potential for FIP to develop (ie, there are probably no naturally occurring 'avirulent' strains). Lack of FIP within certain breeders' households where FCoV infection is endemic, occurs because all the adult cats are immune, not because the virus is avirulent, and around 10 per cent

This article, one of a series published in the *BSAVA News*, has been prepared by the BSAVA's Scientific Committee

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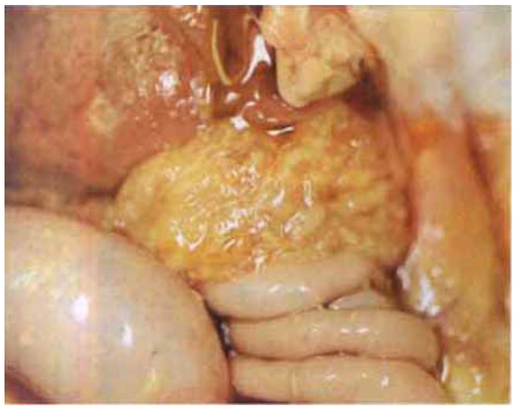

Fibrinous peritonitis associated with FCoV infection involving the serosal surfaces of abdominal organs

High protein exudate obtained from the abdominal cavity of a cat with FIP

of kittens sold from such households will develop FIP. The likelihood of developing FIP following infection with a FCoV depends upon virus dose and the cat's genetic make-up. It has been shown that first-degree relatives of FIP-affected cats are more likely to be affected by FIP than unrelated cats.

In 90 per cent of infected cats, FCoVs infect the intestinal epithelial cells causing a mild or asymptomatic enteritis and, in at least 25 per cent of these, virus can also be detected in blood. Most of these infected cats will mount a successful immune response and eliminate the virus, although a few will remain healthy carriers. In the remaining 10 per cent of infected cats disseminated vasculitis ensues.

Vasculitis may occur because virus-infected macrophages leave small blood vessels and an inflammatory response develops around them, or because circulating immune complexes attract an inflammatory response. A pyogranuloma develops around the blood vessel and the blood supply to the organ is affected.

In effusive ('wet') FIP, many blood vessels are affected and a protein-rich exudate of the same composition as plasma leaks out into the body cavities. In non-effusive ('dry') FIP, only a few blood vessels are affected and the body attempts to 'wall off' the lesions by forming pyogranulomata which may become quite large (up to 2 cm). One theory is that non-effusive FIP occurs where there has been a partially successful cell-mediated immune response. The course of non-effusive FIP is much more chronic, with the cat being ill for weeks to months. In some cases, non-effusive FIP may develop into the effusive form terminally.

Clinical findings

FCoV in the gastrointestinal tract may cause a mild pyrexia, small or large bowel diarrhoea and sometimes vomiting. Transient upper respiratory tract signs have been reported when FCoV first enters a cattery. These signs may be seen weeks or even months before the onset of the first case of FIP. However, in the majority of FCoV infections no clinical signs are observed.

FIP (effusive and non-effusive forms) is characterised by a low-grade fever (39·0 to 39·5°C) unresponsive to antibacterial drugs, weight loss, anorexia and lethargy, and often a particularly palpable mesenteric lymph node. With the effusive form of FIP a high-protein exudate develops in the abdomen causing ascites and in around 25 per cent of these cases exudate also develops in the thorax, causing dyspnoea and tachypnoea. Entire male cats may show scrotal swelling. Vomiting and diarrhoea may also develop as a consequence of peritoneal inflammation.

Non-effusive FIP is characterised by the development of granulomas in a variety of organs, including the liver, kidney, spleen, omentum, lymph nodes, lungs, eye and central nervous system. The ocular signs include anterior uveitis (hypopyon, hyphaemia, aqueous flare and miosis), retinal haemorrhage and linear retinal detachment. Up to 25 per cent of cats with non-effusive FIP eventually develop multifocal progressive neurological signs (eg, seizures, vertical or rotatory nystagmus, tremors, hyperaesthesia, changes in temperament and proprioceptive deficits).

Clinicopathological findings

Haematological findings are variable and non-specific, and include a normocytic, normochromic, non-regenerative anaemia, neutrophilia and lymphopenia. Leucopenia may develop terminally. Serum biochemistry and urinalysis abnormalities relate to specific organ involvement; thus cats with renal involvement may show proteinuria, although azotaemia develops only in advanced disease. Hyperbilirubinaemia and elevated alanine transaminase and alkaline phosphatase concentrations reflect hepatic involvement. Hyperglobulinaemia is present in more than 50 per cent of cats with effusive FIP and 75 per cent with non-effusive FIP, and is a polyclonal gammopathy. Analysis of cerebrospinal fluid in cats with non-effusive FIP demonstrates elevated protein concentrations and neutrophilic pleocytosis.

Effusions contain high protein concentrations due to protein leakage from plasma, are often yellow and contain fibrin clots, with non-degenerate neutrophils the predominant cell type.

Serology

Serology can be performed on plasma, serum or effusion. Testing for FCoV antibodies is usually performed for one of the following reasons:

A diagnosis of FIP is suspected

● *Non-effusive FIP.* The anti-FCoV antibody titre should be 1280 or higher. A titre of less than 320 usually rules out non-effusive FIP. Ocular lesions, an albumin:globulin ratio of less than 0·7 and alpha-1 acid glycoprotein (AGP) result of greater than 1500 mg/ml should also be present before making a diagnosis of FIP.

Note that healthy cats with FCoV antibody titres do not have non-effusive FIP.

● *Effusive FIP.* Antibody titres vary from zero to more than 1280. The reason why a few cats have a titre of zero is that antibody is bound to virus in immune complexes during the pathological process and is undetectable by the test.

The total protein content of the effusion should be greater than 35 g/litre, the albumin:globulin

ratio of the effusion should be less than 0·7 and the AGP of the effusion or plasma should be greater than 1500 mg/ml.

If in doubt, have reverse transcriptase-polymerase chain reaction (RT-PCR) technology performed on the effusion.

Remember that cats with other conditions can have anti-FCoV antibodies coincidentally, especially those from multicat households, or those that have been acquired from a cat breeder/rescue organisation within the previous six to 12 months.

Cat(s) which have been in contact with a case of FIP or a FCoV excretor

Serology in these instances is usually carried out for one of the two reasons discussed below. In either case, make it clear to the owner before testing that it is very likely that the cat will be seropositive. Almost all cats exposed to FCoV become infected. Reassure the owner that this does not indicate a poor prognosis for the cat as approximately nine out of 10 cats infected with FCoV will not develop FIP and many will eventually become seronegative.

● *The owner wishes to obtain another cat.* If the cat is seronegative (ie, has an antibody titre of zero) it is not shedding virus and it is safe to get another cat. However, if the cat is seropositive (ie, has an antibody titre of 10 or over) there is a 1 in 3 chance that it is shedding FCoV so it would be unwise to get another cat (unless it also has antibodies), although cats with antibody titres of 20 or less are unlikely to be infectious.

Wait three to six months and retest to determine if the cat's antibody titre has fallen. Most uninfected cats will lose their antibodies in periods of three months to several years. If there are several cats (eg, five or more) mixing together and at least half of them are seronegative then the seropositive cats cannot be shedding virus.

● *The owner wants to know the prognosis for the exposed cat.* If the cat is seronegative, it will not develop FIP; however, if the cat is seropositive, there is a low probability (about 1 in 10) that the cat will develop FIP.

Screening breeding cats

Cat breeders often request that their cats be screened for FCoV before mating. If the cat is seronegative it is not excreting FCoV and can be mated safely. Be sure to find a seronegative mate for it.

If the cat is seropositive it would be wise to find a seropositive mate so as not to risk introducing FCoV into a FCoV-free cattery. Kittens of such a mating should be prevented from becoming infected by isolation and early weaning (see below).

Screening a household/cattery for FCoV

If there are many cats mixing together, then a random sampling of three or four cats will determine whether FCoV is endemic (because FCoV is very contagious). Households of fewer than 10 cats and those where the cats are isolated from each other in groups of three or less often lose their FCoV infection eventually. Testing every six to 12 months will establish when this is occurring as antibody titres fall and an increasing proportion of cats becomes seronegative.

Screening a cat for introduction into a FCoV-free household

The only safe antibody titre in this circumstance is zero.

Testing for virus

FCoV genome may be detected using RT-PCR technology. The genomes of the avirulent or enteritis-inducing laboratory strains of FCoV are indistinguishable from those of FIP-inducing strains. Thus it is not possible to determine whether a cat will or will not develop FIP using this test.

Use of RT-PCR tests

● *Diagnosis of FIP.* RT-PCR is useful in the diagnosis of effusive FIP when used on the effusion. It is not however useful when used on blood samples because healthy infected cats may contain FCoV RNA in plasma and FCoV RNA has been demonstrated in cats with other diseases (eg, cholangiohepatitis). In addition, cats with FIP may not have FCoV RNA in the bloodstream.

● *Monitoring virus excretion.* RT-PCR can also be used to detect FCoV in the faeces of cats which are shedding virus in households where shedders and non-shedders are being separated in an attempt to eliminate FCoV infection.

Virus isolation

Virus isolation can be attempted but is often unrewarding due to the difficulty in encouraging wild virus to adapt to cell culture. Work in this field is currently being undertaken at Bristol veterinary school.

Pathology

Histopathological examination of biopsy samples of lesions is the only absolutely conclusive method of making an antemortem diagnosis. Characteristically there are disseminated pyogranulomata around small blood vessels. In dubious lesions, immunohistochemistry can be performed.

Antemortem diagnosis

With the exception of immunohistochemistry of a pyogranuloma, there is no one test or clinical finding that can diagnose FIP definitively. However, various studies have looked at combinations of indications and reported a high predictive value. These are summarised by McReynolds and Macy (1997). For example, a cat with clinical signs consistent with FIP, a lymphopenia, a FCoV titre of greater than 160 and a hyperglobulinaemia was found to have an 89 per cent probability of having FIP confirmed postmortem. If a cat showed signs of FIP but did not have all three of the above results, there was a 99 per cent probability that it did not have FIP.

Several studies have recently shown that protein electrophoresis may be of value in cats with appropriate clinical signs and other positive indicators. Gamma globulin levels in excess of 32 per cent of the

total protein content have a 100 per cent predictive value, while an albumin concentration greater than 48 per cent of the protein content has a 100 per cent negative predictive value (prevalence rate 21 per cent), thus ruling out the diagnosis.

Treatment

Treatment for cats suffering from FIP is symptomatic, with fluid replacement and nutritional support of paramount importance. In view of the immunological nature of the disease, treatment with immunosuppressive doses of corticosteroids (2 to 4 mg prednisolone/kg/day) is a rational approach, along with broad spectrum antibiotics. There may be a place for immunosuppressive drugs such as cyclophosphamide, although no treatment has been shown to affect the clinical outcome. FIP is invariably fatal and euthanasia is therefore a treatment option.

Control

FCoVs are difficult to control in multicat environments due to:

- the potentially long and unpredictable incubation period;
- the difficulty inherent in identifying carriers which are shedding the virus;
- the ability of FCoV to survive in the environment;
- the infectious nature of the virus, which infects 96 to 100 per cent of in-contact cats.

If FIP is confirmed in a cattery, the serological testing of other cats is useful if the owner requests a prognosis for these cats or wishes to add further stock. It must be emphasised at the outset that it is very likely that most, or all, of the cats will be seropositive. This does not necessarily indicate a poor prognosis as FIP is only likely to develop in 12 to 16 per cent of cats following initial exposure to the virus and in 3 to 4 per cent of cats which have encountered it at some time previously.

A recent survey showed that over 33 per cent of seropositive cats will become seronegative provided no new infection is introduced. This loss of antibody can take from three to 25 months, with approximately one-third of the cats becoming seronegative within one year. Housing of the cats has the biggest influence on whether they become seronegative. Those housed in groups of three cats or less are more likely to become seronegative than those housed in larger groups. Age, breed and gender have no influence on the loss of FCoV antibodies.

Seronegative cats should not be introduced into seropositive catteries. Kittens and new cats should not be introduced into a cattery until the existing resident cats have become seronegative. To maintain a seronegative household, cats which have been to shows, or left the premises, should ideally be isolated on their return and antibody tested two weeks later.

Prevention of infection of kittens

Approximately 1 in 3 seropositive queens excrete virus regardless of the antibody titre.

To prevent infection of kittens from a seropositive queen, the queen should be isolated with her kittens from birth. The litter should be weaned at five weeks old (as protective maternal antibody wanes) and isolated from all other cats in the household, including their dam and the kittens from other litters. If possible, test the kittens at 10 to 12 weeks of age to ensure that they have not been infected. This method has been found to be completely effective in producing FCoV-free kittens. However, some breeders prefer to isolate seropositive queens and retest every six to 12 months until they become seronegative, before breeding again.

Seropositive kittens have a 1 in 10 chance of developing FIP. They can be rehomed where no other cats are present, and the owners warned of the 10 per cent chance of FIP, or they can be kept in total isolation and tested monthly until they either become seronegative or develop the disease.

Seronegative queens can be left with their kittens indefinitely.

Vaccination

An intranasal vaccine (Primucell; Pfizer) has been launched in the USA and parts of Europe, providing encouragement for the control of FCoV. The vaccine causes seroconversion and stimulates mucosal and cell-mediated immunity. Its efficacy is around 50 to 75 per cent when used on cats which have not been exposed to FCoV. It is not yet available in the UK.

Acknowledgements

The section on the uses of serology has been reproduced with kind permission from the Feline Virus Unit, University of Glasgow Veterinary School. The illustrations were supplied by Dr Bryn Tennant.

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