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Feline infectious peritonitis (FIP)—the present state of knowledge

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ABSTRACT

This paper gives a summary of our present knowledge of the aetiology, clinics, diagnosis, pathology and pathogenesis of feline infectious peritonitis. Special emphasis is given to the participation of the immune system in the development of the condition. A therapy protocol is proposed and an extensive list of original literature for further study is presented.

INTRODUCTION

During the last decade, the frequency of feline infectious peritonitis (FIP) has increased considerably. At the same time, the importance of the cat as a companion animal has grown, which could be observed by any veterinary practitioner. These are the reasons why veterinarians are faced increasingly with questions concerning the clinical picture, diagnosis, pathogenesis, prophylaxis and therapy of FIP. This short review is intended to provide the necessary information. Those of our readers who are interested in the experimental details on which much of our present insight is based are referred to a recent review article by Pedersen (6) and to the literature listed at the end of this article.

HISTORICAL REVIEW

Feline infectious peritonitis was first described in the early sixties in the USA as a disease picture *sui generis* (1, 2). In 1966 Wolfe & Griesemer recognized that FIP is infectious and also coined its name (3). On the basis of serological cross-reactions with coronaviruses and the characteristic coronaviral morphology shown by electron microscopy, FIP virus (FIPV) was classified as a member of the family Coronaviridae (4, 14).

In Europe FIP was first described in England in 1968 (5). Meanwhile reports of clinical FIP have been obtained from all European countries and all continents (for a recent review see ref. 6). FIP does not only occur in domestic cats but has also been recognized in exotic cat species in zoos (7–10). From seroepidemiological studies Horzinek *et al.* concluded that coronavirus infections in cats are encountered worldwide (11).

THE AGENT

FIP is caused by a coronavirus which is related to transmissible gastroenteritis virus (TGEV) of pigs, an enteric coronavirus of dogs and a respiratory coronavirus of man (strain 229E) (12–15). Apart from FIPV another feline coronavirus has been described which does not lead to FIP and causes only a mild diarrhoeal disease (16). This feline enteric coronavirus (FECV) replicates mainly in the intestine. So far it cannot be distinguished from FIPV by morphological or immunological methods (16, 25).

FIPV was first grown in macrophage culture in 1976 (17); other groups succeeded in multiplying the virus in organ cultures or lines of foetal cat cells *in vitro* (18–22). In addition, Horzinek and collaborators succeeded in adapting FIPV to brain cells of newborn mice, rats and hamsters (23, 24).

From the fact that different feline coronaviruses with differing *in vitro* growth conditions have been isolated it was anticipated that different disease pictures can be produced by them. *In vivo* FIPV was demonstrated by electron microscopy in macrophages within inflammatory foci (4, 17).

FIPV has a diameter of about 100 nm and is pleomorphic. The viral nucleocapsid is surrounded by a lipoprotein membrane containing glycoproteins and carrying projections (peplomers) which form the so-called corona. Due to its lipid-containing envelope FIPV is relatively unstable and susceptible to the action of current disinfectants (17). It appears, however, that the virus is relatively resistant to drying. This can be concluded from an unintended experiment in which a group of specified pathogen-free cats were infected by an FIPV-contaminated litter pan (27).

CLINICAL PICTURE

FIP appears in two different forms: the wet or exudative form which is characterized by peritonitis and/or pleuritis accompanied by ascites and/or pleural effusions and the dry or parenchymatous form which is characterized by granulomatous inflammation of different organs and no or little exudate (28, 29). Both forms can occur together. Once clinical symptoms are seen FIP usually takes a fatal course. The diseased animals show elevated body temperatures exceeding 39°C which may prevail for several weeks. The animals do not eat well and lose weight. The wet form of FIP is easily recognized by the typical exudate in the body cavities. Pleural effusions lead to dispnoea which is sometimes the only symptom the owner recognizes. Quite often the patients do not appear to be unwell irrespective of the presence of ascites. In the wet form, disturbances of the central nervous system (CNS) are encountered in about 10 per cent and ocular symptoms in about 4 per cent of the cases (see below). The dry form is often difficult to diagnose. In emaciated animals the pyrogranulomatous lesions may be palpable in the kidneys and mesenteric lymph nodes. The inflammatory nodules in the spleen, liver, pancreas and omentum are chance findings upon laparotomy. Inflammation

of the pleura, lungs and heart recognized in most cases by auscultation and X-ray. Massive involvement of the liver may lead to bilirubinaemia and jaundice. About the most important signs of the dry form are the CNS disturbances and ocular symptoms. Central nervous symptoms are recorded in about 40 per cent of the cases (6) and appear as nystagmus, torticollis, wavering gait, paralysis of the fore and/or hind legs, paralysis of the *N. trigeminus* and *facialis*, convulsions and a changed behaviour (6, 31, 32). With an incidence of about 35 per cent ocular symptoms are reported—they may be the only clinical symptoms in about 20 per cent of the cases (20). Ocular symptoms in dry FIP are inflammations of the iris and the ciliary body, turbidity of the *humor aqueus* and *corpus vitreum* and inflammatory reactions of the retina (31, 33–35).

LABORATORY FINDINGS

The red blood picture does not show any dramatic changes but sometimes a low to moderate anemia has been found which should be taken as an expression of chronic inflammation. Leucocytosis is very common in FIP and is due to neutrophilia with normal or lowered lymphocyte counts.

In most FIP cases plasma protein values of and above 80 g/l have been measured. These increased concentrations are due mainly to the immunoglobulins but also to fibrinogen (in about half of the cases exceeding 4 g/l) and the beta-globulins (36). Liver damage leads to augmented transaminase values, sometimes accompanied with increased concentrations of bilirubin. Enhanced urea and kreatinin reflect the renal damage. In the wet form of the disease especially a disseminated intraversal coagulopathy (DIC) may occur. Weiss *et al.* were able to show experimentally that in the course of DIC the bleeding time, prothrombin time and partial thromboplastin time are increased. As a consequence of increased consumption these cats show low platelet counts and high concentrations of fibrin katabolites (37). The mechanisms leading to DIC are not known in detail; important factors seem to be the formation of immune complexes followed by complement activation and a lacking capacity of the liver to secrete coagulation factors (38).

The ascitic and pleural fluids are viscous and of (brownish) yellow colour. It is an exudate with an increased specific weight (above 1,017 g/l) and protein concentrations above 50 g/l (36, 39).

As mentioned above, a clinical FIPV infection leads to an increase of the immunoglobulin fraction in most cases and to high titres of antiviral antibody (11, 40). For antibody titration, the immunofluorescence test as developed by Osterhaus *et al.* is being used routinely, where cells infected with TGEV serve as an antigen substrate (41). The titre values are often useful for the diagnosis of FIP: about 80 per cent of the cats where the disease had been diagnosed by (histo)pathology possess titres of >400 whereas less than 20 per cent show titres of <100. In sick cats where no signs of FIP have been found histologically, titres of >400 have been

detected only in exceptional cases (42). It should be underlined that in contrast to the situation in diseased animals, titre values give no clues for the diagnosis of developing FIP in healthy cats.

PATHOLOGY

FIP is a disease of younger cats: 71 per cent of the cases in the section material of the Veterinary Pathology Institute at Zurich University were between 3 months and 2 years of age, with no difference in frequency between both sexes. The exudative form is slightly more prevalent than the dry form (60 per cent). The wet form is characterized by large quantities (up to 1 l) of ropy yellowish exudate in the abdominal, pleural and/or pericardial cavities. The serosae of the affected body cavities are usually covered by a detachable greyish-white matter and disseminate white necrotic plaques. The typical dry form lacks the exudate and the fibrinous adhesions; instead the miliary plaque-like serosal lesions are more numerous and additional greyish foci of varying size occur in the renal cortex, liver, parenchyma and, although less frequently, in the lymph nodes and the lungs. Occasionally fine greyish-white nodules are macroscopically visible in the meninges. Not infrequently the wet and dry form occur together.

Histologically the wet form appears as a fibrinous inflammation of the serosal membranes accompanied by accumulations of neutrophilic granulocytes and macrophages. Karyorhexis in part of these leucocytes is characteristic. The greyish-white foci which have been mentioned in the dry form of the disease appear to be composed of macrophages, neutrophilic granulocytes, lymphocytes and plasma cells enclosing a central fibrinous necrosis. In the dry form the lesions are often localized around the smaller vessels (venules, arterioles and lymph vessels) where they are the expression of a vasculitis and thrombovasculitis. In most cases of dry FIP histology reveals a pyrogranulomatous meningitis, less frequently encephalitis, iridocyclitis and chorioiditis (29, 40, 43, 44).

In the necrotic foci immune complexes, FIPV antigen and IgG as well as the third component of complement (C3) have been demonstrated. Also circulating immune complexes have been evidenced which, when activating the complement cascade, may induce glomerulonephritis (37, 40, 44–46).

PATHOGENESIS

Under field conditions the infection with FIPV can be subdivided in a primary and a secondary reaction: during the primary phase, i.e. upon the first contact with FIPV or FECV some animal show a nasal (and sometimes ocular) discharge which disappears after several days or weeks; other cats are asymptomatic during this period (36). Only a small fraction of the animals proceeds into the secondary phase which leads to the proper picture of FIP. The number of animals succumbing to

FIP is small in comparison with cats showing serologic evidence of coronavirus infection; estimates of a few percent have been reported.

From experimental studies it was learned that upon oronasal or intratracheal inoculation FIPV multiplies first in the epithelial cells of the upper respiratory tract and the intestine (21, 47). This explains the symtoms observed during the first phase of the infection. Clinically apparent FIP occurs only when the virus crosses the mucosal barrier. Weiss & Scott were able to demonstrate viraemia where the virus does not float free in the plasma but stays associated with blood monocytes (44). Crossing of the mucosal barrier and appearance of FIP symptoms are dependent upon the infectious dose (21). Under field conditions additional factors must be responsible for virus spread in the feline organism. Differences in the biological properties, e.g. the protein structure of the virus envelope are likely to occur by mutation which would lead to viral subtypes of different virulence. There can be no doubt that differences in virulence exist: in addition to FECV which causes only diarrhoea (16) FIP strains with different biological properties have been isolated (25).

In addition to the infectious dose and the virulence of the infecting virus strain individual properties of the host, e.g. genetic factors, stress due to environmental conditions (like a change of owner) certainly play an important role. A decisive factor in FIP pathogenesis, however, is the immune reaction of the host. The following observations made during the recent years indicate that FIP is an immune-mediated disease:

(1) In the inflammatory foci immunoglobulins and C3 were demonstrable in addition to viral antigen (40, 44–46).

(2) In the course of experimentally induced FIP increasing titres of coronaviral antibodies were demonstrated (40, 46).

(3) In seropositive cats experimental infection led to disease and death significantly quicker than in seronegative animals (40, 44).

(4) Passive immunization (using serum or purified immunoglobulin of sero-positive animals) of SPF cats made them more susceptible to experimental challenge with FIPV (40).

In the course of FIP increasing concentrations of circulating immune complexes were recorded paralleled by an initial rise and a dramatic decrease ante-mortem of complement components (46). Therefore, complement activation is attributed an important role in the pathogenesis. In a pilot experiment it was shown that decomplemented cats survived an otherwise fatal infection with FIPV (41). Together with the observations that complement is encountered in the inflammatory lesions these observations support the hypothesis of an immune-mediated pathogenesis of FIP.

Even though important information, especially with respect to the cellular immune mechanisms are still lacking, the following events during FIP pathogenesis can be postulated: under natural conditions the virus first colonizes the epithelia of the upper respiratory tract and the intestine where it occasionally causes transient

symptoms. Only rarely the virus succeeds in crossing the mucosal barrier and spreads throughout the feline organism via infected monocytes and macrophages. Since the macrophage is one of the cell types where various complement components are synthesized (49) this may lead to increased synthesis and/or release of complement. Simultaneously, activated macrophages also produce interleukin 1 which, apart from its stimulating influence on the B and T cell system, is a potent pyrogen and may be responsible for the febrile reaction (50). Viral antigen is expressed on the surface of infected macrophages; this may stimulate specific B- and T-cells and lead them to the production of virus-specific antibodies. These antibodies on one hand bind to the viral antigens thereby inducing the formation of circulating immune complexes (Horzinek *et al.*, in press). On the other hand the antibodies also attach to the surface of the infected macrophages. Both the circulating immune complexes and the antibodies bound to the macrophages activate the complement cascade cuasing release of anaphylatoxin and cytolysis. The macrophages liberate more virus which in turn can infect more macrophages or be phagocytized as immune complexes. Again more macrophages are infected and the vicious circle is closed.

PREVENTION AND THERAPY

Protective active immunization against FIP is not possible so far. On the contrary, immunization led to earlier and more pronounced disease symptoms upon challenge infection (40, 52, 54). For the time being only hygienic measures and the avoidance of stress can be recommended. In a single cat household where an animal has died from FIP the floors, carpets, etc. should be cleaned and disinfected. A new animal should not be introduced into the premises earlier than 2 weeks after disinfection. The situation is different in multicat households. Here the question arises which of the other animals are infected and may shed virus. Unfortunately it is not yet possible to identify these virus carriers. Serology is of no help since most of the cats kept in larger groups are seropositive (42). A stress-free environment (avoidance of crowding) seems to be one of the most important prophylactic measures. When introducing a new animal into a seronegative cattery this cat should be tested for FIPV antibodies. If the test results in a positive titre, the animal should be kept in quarantine for 2–3 weeks. If the animal is seronegative, the risk of introducing a viral carrier is small and quarantine is considered unnecessary. As with other viral infections, catteries and animal hospitals pose a special problem. In these establishments hygienic measures are crucial, e.g. regular disinfections of floors, tables, etc., hand disinfection before handling a cat, regular cleaning and disinfection of food bowls, litter pans etc.; since the cat is a territorial and solitary predator, crowding is to be avoided at all cost.

Once FIP symptoms are recognized the prognosis is bad. When considering the immune pathogenesis, treatment of the FIP symptoms should aim at a suppression

TABLE 1. Therapeutic protocol (Zürich)

Drug	Application + dosage
Dexamethasone-21 isonicotinate (Voren†)	2 mg, i.m., day 1 and day 5
Ampicillin	20 mg/kg, oral, 3 times daily, during 10 days
	or
Prednisolone (tablets)	10 mg, oral, 2 times daily, day 1–7; 5 mg, oral, 2 times daily, day 8–14; 2·5 mg, oral, 2 times daily, day 5–18; 1·25 mg, oral, daily, day 29–22.
Ampicillin	20 mg/kg, oral, 3 times daily until day 25

* Repetition of the protocol upon reappearance of the symptoms can be considered.
† Boehringer, D-Ingelheim, West Germany.

of the immune system and the inflammatory processes; these measures, however, would not influence replication of the virus itself. An experimental therapy can be considered in selected FIP patients which are not emaciated, show no neurological symptoms and eat normally. We have been able to induce remissions which sometimes lasted for several months using the protocol presented in Table 1. Also cytostatic drugs in connection with corticosteroids have been recommended (53). When using corticosteroids and cytostatics virus excretions is probably not affected. Before attempting a therapeutic experiment the risk for other cats should be considered and corresponding measures (quarantine of the patient) should be taken. Other therapeutic possibilities are presently explored. The use of lymphokines should certainly be considered in the future.

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