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A review on the diagnosis of feline infectious peritonitis

Jehanzeb Yousuf[a] | Riyaz Ahmed Bhat[b]* | Shahid Hussain Dar[b] | Alisa Shafi[b] | Snober Irshad[c] | Mohammad Iqbal Yatoo[b] | Jalal Udin Parrah[b] | Amatul Muhee[b] | Abdul Qayoom Mir[b]

[a]Division of Veterinary Medicine, Faculty of Veterinary Sciences and Animal Husbandry, Jammu-181102, Jammu and Kashmir, India.
[b]Division of Veterinary Clinical Complex, Faculty of Veterinary Sciences and Animal Husbandry, Srinagar-190006, Jammu and Kashmir, India.
[c]Division of Livestock Products and Technology, Faculty of Veterinary Sciences and Animal Husbandry, Srinagar-190006, Jammu and Kashmir, India.

Corresponding author: koolriya22@gmail.com

Abstract Feline infectious peritonitis or simply FIP is viral disease caused by coronavirus in cats of less than three years of age. It is manifested as extreme inflammatory reaction in tissues surrounding abdomen, kidneys and brain. This review article discusses various diagnostic tests and their merits in the diagnosis of FIP suspected cases with the purpose of definitive diagnosis. This review can help to compare different diagnostic parameters and also raise awareness about their advantages and disadvantages.

Keywords: acute phase proteins, coronavirus, feline infectious peritonitis, Rivalta's test

1. Introduction

Feline infectious peritonitis (FIP) is a well-known and widely distributed coronavirus (CoV)-induced systemic disease in cats, characterised by fibrinous-granulomatous serositis with protein-rich effusions into body cavities, granulomatous-necrotising phlebitis and periphlebitis and granulomatous inflammatory lesions in several organs (Weiss and Scott 1981; Kipar et al 2005). Feline CoV (FCoV) is spread through the faecal-oral route and enterocytes are primarily infected (Pedersen 1995), but subsequently spreads systemically through a monocyte-associated viraemia (Meli et al 2004; Kipar et al 2005). It has been seen that enhanced viral replicative capacity could be a key feature in the development of FIP and also it is believed that FIP is caused by mutations in a common feline enteric coronavirus (FECV), which is found in cats all over the world and is not a serious infection (Pedersen et al 2009; Healey et al 2022). In around 10% of the infected cats mutations occur, which results in feline infectious peritonitis. In large multi-cat situations, FECV is shed in the faeces of most apparently healthy cats and transmission occurs through direct contact with faeces or contaminated litter and other fomites (Pedersen et al 2004). At roughly 9 weeks of age, kittens become infected (Pedersen et al 2008). The time between the development of clinical signs and death also varies but younger cats and those with effusive disease have a shorter disease course than older cats and with non-effusive disease (Pedersen 2014). Even with severe FIP, some cats can live for months.In multi-cat situations, the feline enteric coronavirus (FECV) is extremely common and highly contagious. Nearly all cats that come into contact with FECV from shedding cats become sick but the infection on the other hand is usually asymptomatic or only causes mild temporary diarrhoea (Pedersen et al 2008; Vogel et al 2010; Ermakov et al 2021). On the other side feline infectious peritonitis virus (FIPV) is not transmitted through faeco-oral route but rather originates from avirulent FECV in a small percentage of infected cats and causes feline infectious peritonitis (FIP) (Pedersen et al 1981; Vennema et al 1998). Anorexia, lethargy, weight loss, pyrexia, ocular and neurological symptoms such gait abnormalities or inappropriate mentation are all non-specific (Giori et al 2011; Kipar et al 2014). Infection exhibits two forms; 'wet' and 'dry'. Dry form causes inflammatory lesions around blood vessels, seizures, ataxia and excessive thirst while as wet form leads to pot-bellied appearance due to excess fluid build-up in the abdomen. Specificity is always the most crucial diagnostic value to consider in preventing mistakenly diagnosing FIP in unaffected cats.

2. Diagnostic tests for feline infectious peritonitis

The age, origin, clinical signs and physical examination of the cat are all taken into account during diagnosis. In cats with either the effusive (wet) or non-effusive (dry) form of FIP, abdominal distension with ascites, dyspnea with pleural effusion, jaundice, hyperbilirubinuria, discernible masses on the kidneys and/or mesenteric lymph nodes, uveitis, and a variety of

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neurological signs associated with brain and/or spinal cord involvement are all common. Ocular lesions are frequently seen in FIP affected cats, retinal changes being the most common ocular lesion. There may occur cuffing of retinal vasculature that appears as fuzzy greyish lines on either side of blood vessels. Granulomatous changes on retina are occasionally seen. It was found that FIPV infection is associated with T cell depletion by apoptosis; although the virus cannot infect CD4+ and CD8+ T cells (Haagmans et al 1996; De Groot et al 2005).The diagnosis of FIP can be made with considerable assurance at this point. Given the high mortality rate, many veterinarians and pet owners are wary of a diagnosis based on "reasonable certainty." The challenge is to decide whether the test raises the likelihood that the clinical indications are caused by FIP (indirect testing) or offers a definitive diagnosis (direct tests). It is vital to remember that the sensitivity and specificity of any indirect test will vary depending on how likely the cat is infected based on other factors. That is, the positive predictive value of a test like complete blood count (CBC) or albumin:globulin (A:G) ratio for predicting FIP will be much higher in cats with FIP-like signalment than in cats with a non-typical FIP signalment. It is worth noting that the results of other indirect tests are only estimates and the results of additional indirect tests have the potential to both confuse and reinforce the diagnostic process.

3. Diagnostic tests

The diagnosis of FIP has an inherent problem in that the non-invasive tests lack reliability. In general, effusion tests have substantially higher predictive values than the blood tests (Stranieri et al 2018; Hartmann et al 2003). As a result, ante-mortem identification of FIP in cats without substantial effusion is particularly difficult. Most useful ante mortem indication is positive anti-corona virus antibody (IgG) titre in cerebrospinal fluid (CSF), high serum total protein and MRI changes like periventricular contrast enhancement, ventricular dilatation and hydrocephalous. However, monoclonal antibodies from affected tissues and coronavirus specific Polymerase Chain Reaction (PCR) are valuable in post mortem assessments (Foley et al 1998). Because a conclusive diagnosis cannot be determined just on the basis of symptoms, history, and clinical and laboratory indicators, these factors should always be considered as a whole, sometimes in combination with other factors such as molecular or even more intrusive diagnostic procedures.

3.1. Analysis of effusion samples

In a suspected case of FIP with effusion, the effusion sample can be incredibly helpful in determining the diagnosis then haematological findings, hence getting effusion samples should always be a top priority. Fluid can be obtained via ultrasound guided fine needle aspiration or by using ‘flying cat’ technique in case of ascites. For the identification of small quantities of fluid in the thorax and abdomen, ultrasonography provides useful guide in locating the effusion pockets in abdomen while evidence of pericardial effusions can be obtained through muffled heart sounds and electrocardiographic changes. Ultrasonography should be used repeatedly to identify any tiny volume effusions, and ultrasonography can also be used to guide sampling of small pockets of fluid. In cats with pericardial effusions, heart auscultation reveals muffled sounds and ECG reveals typical changes.

FIP effusions are often clear, viscous/sticky, straw-yellow, and protein-rich (cytology frequently describes thick eosinophilic proteinaceous backdrops), with a total protein concentration of >35 g/l (>50% globulins). Chylous effusions are described infrequently. FIP effusions are often pyogranulomatous in character, with macrophages, non-degenerate neutrophils, and relatively few lymphocytes. As a result, the effusions are frequently referred to as modified transudates based on cell counts (< $5x10^9$ cells/l) but exudates based on protein concentrations (more than 35 g/l).

Typical FIP effusions have low A:G ratios (see above) and elevated AGP contents, which are similar to those found in serum. AGP concentrations in effusions (>1.55 mg/ml) were found to be more useful (sensitivity and specificity of 93 %) in distinguishing FIP from non-FIP cases than AGP levels in serum or other APPs in a recent study (Hazuchova et al 2017).

Rivalta’s test is a simple assay that can be used to distinguish transudate from exudate in an effusion sample (Barker and Tasker 2020). Positive results simply indicate that the effusion is an exudate and are not specific to FIP; positive for transudate have been documented in situations other than FIP (e.g., bacterial/septic peritonitis and lymphoma) (Fischer et al 2012).

3.2. Serum biochemistry

Although the alterations in blood biochemistry seen in FIP cases are variable and often non-specific, there are a few key anomalies to look for in order to confirm a diagnosis of FIP.

3.2.1. Acute phase proteins

In many inflammatory and non-inflammatory illnesses, acute phase proteins (APPs) are produced in the liver in response to cytokines released by macrophages and monocytes (particularly inter-leukins 1 and 6 and tumour necrosis factor α).

AGP stands for α1-acid glycoprotein, and its testing can aid in the diagnosis of FIP. Although AGP increases (>0.48 mg/ml) are not specific for FIP, FIP patients frequently have considerably high AGP levels (>1.5 mg/ml). As a result, the amount of the

increase may be valuable in assisting FIP diagnosis, with greater levels raising the index of suspicion more effectively (Giori et al 2011; Hazuchova et al 2017).

3.2.2. Hyperglobulinaemia

In 89% of cases, hyperglobulinemia is present; often in conjunction with hypoalbuminemia or a low-normal serum albumin level (seen in 64.5 % of cases) (Riemer et al 2016). Hyperproteinaemia may not always occur because of the existence of hypoalbuminaemia. The albumin:globulin (A:G) ratio is low when hyperglobulinaemia and hypoalbuminaemia (low-normal albumin concentration) are present, and this parameter can be used to assess the likelihood of FIP in a specific instance.

3.2.3. Hyperbilirubinaemia

Hyperbilirubinemia occurs in 21–63 % of FIP cases, and is more common in effusive FIP, where alanine aminotransferase (ALT), alkaline phosphatase (ALP), and γ-glutamyl transferase enzyme activity are commonly high (although these can be moderately elevated in FIP cases). FIP is rarely associated with hyperbilirubinemia due to immune-mediated haemolytic anaemia (IMHA) **(**Norris et al 2012) and cats are frequently not severely anaemic. In the absence of high hepatic enzyme activity or severe anaemia, the presence of hyperbilirubinemia should raise the suspicion of FIP (note that sepsis and pancreatitis can also cause hyperbilirubinaemia in the absence of elevated hepatic enzyme activities). It has been documented that hyperbilirubinemia was more typically recognised in cats right before death or euthanasia than at first presentation, based on a sequential assessment of cats with FIP (Harvey et al 1996). Furthermore, bilirubin levels were observed to be higher in cats soon before death or euthanasia than they were at first presentation in this investigation.

3.3. Haematology

In FIP, haematological alterations are non-specific; however, there are a few abnormalities to check for to help confirm a diagnosis. Lympopenia is the most prevalent alteration (55–77%) of cases, while a recent study (Riemer et al 2016) revealed lymphopenia in only 49.5 % of FIP cases, with neutrophilia (39–57 %), a left shift, and mild to severe normocytic, normochromic anaemia (37–54 %) also being described (Riemer et al 2016; Norris et al 2012). Recently, a link between FIP and microcytosis (with or without anaemia) was discovered. FIP can cause severe IMHA with concomitant regenerative anaemia; however, this is unusual.

3.4. Serology

ELISAs, indirect immunofluorescence antibody tests and fast immunomigration assays are the most common serum antibody tests for FCoV (Addie et al 2015). The majority of the studies use CoV-infected swine or feline cells as a substrate, and titres are measured in multiples of serum dilutions. A positive FCoV antibody test means the cat has been infected with FCoV and has seroconverted (which takes 2–3 weeks from infection). The tests therefore have limited clinical significance. There have been breed-related variances in median FCoV antibody titres discovered, which could indicate disparities in breed response to FCoV infection (Meli et al 2013).

Although FIP cats had greater FCoV antibody titres than non-FIP cats, there is no difference between healthy and suspected FIP cats' median FCoV antibody titres. As a result, the titre in a single animal is only marginally useful in identifying cats with FIP (Bell et al 2006). Many clinically healthy cats (especially those in multi-cat households) have positive and often very high FCoV antibody titres, whereas 10% of cats with FIP are seronegative which could be due to binding of virus to the antibody and rendering it unavailable to the serological test, which also highlights interpretation challenges (Meli et al 2013). A negative FCoV antibody test in a suspected dry FIP case may be more effective in excluding FIP (Addie et al 2009). Nevertheless, negative results have been observed in situations of neurological FIP (Negrin et al 2007). As a result, practitioners differ on whether or not to perform serology in suspected cases, despite the fact that a positive result almost always implies FCoV exposure.

3.5. Recent diagnostic developments

Use of anti-corona virus antibody testing of cerebrospinal fluid (CSF) for diagnosis in cases involving central nervous system is another breakthrough wherein IgG is detected in CSF. However, the antibody in most cases was detected only in cats having high serum IgG titre (Boettcher et al 2007)

Important distinction between feline coronavirus infection and FIP is NSP3c gene behaviour. It was found that infected tissue isolates from the later have disrupted 3c gene while as former showed intact gene. Also, the mutation of the S1/S2 locus and modulation of furin recognition site normally present in the S-gene of enteric corona virus is a critical contributing factor (Levy and Hutsell 2019).

Diagnostic utility of cerebrospinal fluid immunocytochemistry is also exploited for diagnosis of FIP manifesting severe central nervous system affections. Immunocytochemistry staining (ICC) of feline corona virus antibodies within macrophages

of CSF is a highly sensitive test particularly for ante-mortem diagnosis with sensitivity and specificity of 85% and 83.3% respectively (Gruendl et al 2017).

4. Conclusions

Cats suspected for FIP should be correlated with history, clinical signs and clinico-pathological examinations. Dry form is difficult to diagnose than wet form. In wet form, laboratory analysis of fluid can be done such as Rivalta's test. If the test is negative, chances of FIP are scanty but if test is positive, more diagnostic tests should follow to confirm FIP. In FIP A:G ratio is low as hyperglobulinaemia and hypoalbuminaemia (low-normal albumin concentration) are present, and this parameter can be used to assess the likelihood of FIP in a specific instance. FIP patients frequently have considerably high AGP (α1-acid glycoprotein) levels. In distinguishing FIP from non-FIP cases, AGP concentrations in effusions (>1.55 mg/ml) have sensitivity and specificity of 93 %.

Conflict of Interest

The authors declare that there is no conflict of interest.

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