Diagnosis and clinical signs of feline infectious peritonitis in the central nervous system

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The diagnosis of feline infectious peritonitis (FIP) in cats remains a challenge in clinical practice. A complete history, physical examination, and adequate selection and interpretation of diagnostic tests remain the cornerstone of antemortem diagnosis. The objective of this review is to familiarize the reader with different aspects of FIP infection of the central nervous system (CNS). This includes signalment, clinical presentation, epidemiology, and diagnostic aids.

Pathogenesis

Feline infectious peritonitis is an immune-mediated disease produced as a result of infection of macrophages by mutant feline coronavirus strains (1). This disease causes severe multisystemic clinical signs in the domestic cat, and other members of the *Felidae* family. Ultimately, FIP results in the death of the affected animal. Feline infectious peritonitis has traditionally been divided into 2 presentations: effusive (wet) form and non-effusive (dry) form. Both forms of FIP have been associated with clinical signs affecting the neurological system, but the non-effusive form appears to more commonly involve nervous tissues (2). The effusive form of FIP is more common than the non-effusive form and FIP has been diagnosed histopathologically in brains of cats without neurological clinical signs (3).

The most likely route of infection of feline corona virus (FeCV) is oral; therefore, cats from catteries and multi-cat household environments, where cats are shedding the virus in feces and sharing litter boxes, are at higher risk of being infected with the virus. A member of the *Cornaviridae* family, FeCV is an enveloped, RNA virus that can be divided into 2 types based on in vitro growth ability, and on antigenic and structural characteristics (4). Type I FeCV is a strictly feline type, whereas Type II FeCV has risen from combinations between FeCV and canine coronavirus. Both types can cause FIP, but Type I is the more prevalent (4). Type II FeCV is more commonly studied because it replicates well in cell cultures and is easier to work with in the laboratory (5).

Traditionally, FeCV has been divided into 2 biotypes based on the clinical signs that they cause: 1) a biotype that can cause FIP based on the ability of the virus to infect mononuclear macrophages (6); and 2) a biotype that induces mild, transient gastrointestinal signs. It is believed that any FeCV can potentially cause FIP in approximately 10% of infected cats (7). An internal mutation theory, in which FeCV mutates leading to the ability to replicate in macrophages and produce FIP has also been proposed (8). A recent study on the genomic RNA sequence of a field-strain FeCV causing FIP found 100% identity of the structural and accessory gene regions between an enteric (jejunum) and non-enteric (liver) FeCV, thus disputing the mutation theory (5). Host and viral interactions and variations may play a role in the development of FIP, but the complete mechanisms remain unknown. Feline coronavirus can mutate in a relatively short period of time giving rise to potentially heterogeneous viral populations with different pathogenicity (5).

Epidemiology

Feline infectious peritonitis is a common etiology of neurological dysfunction in cats. In a retrospective study of 286 cats with neurological disease affecting the central nervous system, 97 cats were classified with inflammatory/infectious disease. Of those cats with inflammatory/infectious neurological disease, 47 cats (48%) were diagnosed histopathologically with FIP (9). Although this disease can affect cats at any age, it was thought to be the most likely cause of CNS disease in cats $<$ 4 y of age in a study that evaluated inflammatory diseases of the CNS (2). Feline infectious peritonitis was also found to be the most common disease affecting the spinal cord of 28 cats (24%) in a group of 84 cats $<$ 2 y of age (10). Another study indicated that FIP was a common disease affecting 10 cats (6%) in a group of 61 middle-aged cats (2 to 8 y old) and 4 cats (2%) in a group of 55 older cats ($>$ 8 y old) (10). The mean time of onset of seizures in a study of cats with FIP was 12 mo (range: 3 to 96 mo) (11) and the median age in another study in cats diagnosed with FIP was also 12 mo (range: 3.6 to 60 mo) (3). Purebred cats have been associated with an increased risk of developing FIP (4,12,13) and male cats are more frequently affected than are female cats (4,13).

Clinical signs

Neurological clinical signs in cats with FIP are reflective of the neuroanatomic location of the primary lesions. Multifocal clinical signs are common, though focal signs may also be found. Seizures, abnormal mental status, abnormal behavior, cranial nerve deficits, central vestibular signs, ataxia, tetraparesis, hyperesthesia, and abnormal postural reactions have all

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been described in the scientific literature (3,10,11,14,15). This spectrum of clinical signs highlights that any part of the CNS can become affected.

In a retrospective study of cats diagnosed histopathologically with FIP, 25% had seizures that were classified as generalized, partial complex, or focal with and without generalization (11). Cervical clinical signs were reported in 29 of 31 cats affected with spinal cord clinical signs caused by FIP (10).

Concurrent, non-neurological signs in cats with FIP include weight loss, weakness, lethargy, fever, pica, anorexia, and ocular lesions mainly characterized by chorioretinitis, uveitis, iritis, keratic precipitates, and anisocoria (2,15).

Differential diagnoses for CNS disease, especially in young cats, should include lymphoma, toxoplasmosis, storage diseases, FeLV, FIV, cerebellar hypoplasia, bacterial meningitis, cryptococosis, or trauma. These possibilities underline the importance of a complete diagnostic workup. Careful physical examination, including a thorough ophthalmologic examination, can be very helpful to increase the index of suspicion of FIP. Abdominal abnormalities, including enlarged mesenteric lymph nodes, and irregular splenic and renal surfaces, were palpated in 11 of 16 cats with neurological FIP; 5 of 15 cats also had respiratory tract clinical signs (15).

Diagnosis

The antemortem diagnosis of FIP remains challenging and it is the combination of signalment, clinical signs, and diagnostic aids that will help the clinician to obtain a diagnosis. As the index of suspicion of FIP increases, the clinician should include diagnostic tests that will help to guide to a more conclusive diagnosis. Limitations of each one of the diagnostic tests needs to be assessed along with the sensitivity and specificity of the diagnostic test selected.

Complete blood (cell) count (CBC) and serum biochemical profile abnormalities of cats infected with FIP include normocytic, normochromic, non-regenerative anemia; neutrophilic leukocytosis with lymphopenia; eosinopenia and monocytosis; hypoalbuminemia and hyperglobulinemia with decreased albumin/globulin (A:G) ratio; and increased α2-, β- and γ-globulin concentrations (16). Cerebrospinal fluid (CSF) analysis is characterized by an elevated protein of more than 2 g/L and leukocytosis ($>$ 100 cells/μL) consisting of predominantly neutrophils (2), or lymphocytes (15). Significant statistical difference has been found between leukocyte counts in CSF in control groups of cats without FIP, cats with non-FIP CNS disease, and cats with FIP not affecting the CNS (3). In the same study 2 of 10 cats with FIP in the CNS had normal CSF leukocyte counts. The CSF protein concentration was only elevated in cats with CNS diseases (FIP and non-FIP diagnosed cats), but there was no statistically significant difference between these 2 groups (3).

Feline infectious peritonitis can only be detected in cats that have been infected with FeCV, but demonstrating its presence does not provide a diagnosis of FIP. Determining the presence of anti-coronavirus antibodies in CSF and serum can also be used as a diagnostic tool, though the presence of antibodies simply demonstrates the animal has been exposed to a coronavirus. As such, the presence of anti-coronavirus antibodies should be interpreted with caution and should be considered in light of signalment, medical history, clinical signs, and other diagnostic test results. In a prospective study of 67 cats, the detection of anti-coronavirus IgG in CSF had a sensitivity of 60% and specificity of 90%. Half the number of cats that were diagnosed as positive were truly positive; while 93% of cats that tested negative were correctly diagnosed. These values vary according to the prevalence of the disease and the selection of the cases tested. When only cats with CNS disease were considered, 75% of the cats that were positive were truly positive and 87% of cats that tested negative were correctly diagnosed (3). This indicates that the appropriate selection of cases increases the value of the diagnostic tests. Cerebrospinal fluid anti-coronavirus IgG was also detected only in cats with high serum titers (range: 1:4096 to 1:16384) (3).

Advanced imaging including computed tomography (CT) and magnetic resonance imaging (MRI) have been used to confirm the neuroanatomical localization of the disease and rule out other diseases affecting the CNS. Despite the lack of availability of advanced imaging in general practice, its use remains a valid alternative when further tests are required to help obtain an antemortem diagnosis. In a study evaluating MRI in inflammatory diseases of the CNS, only 4 of 8 cats with FIP had abnormalities on MRI evaluation. Ventricular dilation and ependymal enhancement after gadolinium injection was noted in 3 of the 8 cats with FIP (17). In another study, ventricular dilation was noted in 3 of 4 cats and periventricular contrast enhancement was present in all 3 cats in which enhancement was administered (15). Despite the small number of cases, it appears that CSF analysis may be more sensitive in detecting inflammatory lesions of the CNS, but MRI can add important information to help distinguish cats with neoplasia or inflammatory disease and possibly differentiate between different inflammatory conditions (17).

Definitive diagnosis of FIP requires examination of the affected tissues, in particular the pyogranuloma that results from immune-mediated phenomena secondary to coronavirus infection of macrophages (1). The lesions of the central nervous system include pyogranulomatous inflammation located around the lateral ventricles or meninges, choroid plexus, with or without evidence of vasculitis or hydrocephalus (3,9). Perivascular inflammation with lymphocytes, plasma cells, macrophages, and neutrophils and necrotizing arteritis are present (11). Difficulties in distinguishing FIP infection from other viral infections of the central nervous system have been recognized. In a study of 286 cats with neurological disease, 8 cats were reclassified as having FIP from an original diagnosis of viral meningoencephalitis. On the other hand, 1 cat originally thought to have FIP was later reclassified to a viral infection of a less specific nature (9). Postmortem diagnosis is facilitated by FIP monoclonal antibody staining of affected tissue and coronavirus-specific polymerase chain reaction (15).

Therapy and prognosis

Feline infectious peritonitis is a fatal disease in cats despite the various treatments attempted, and most patients are either euthanized immediately or within weeks to months, once a

satisfactory diagnosis has been made. The therapeutic goal is to control or reduce the clinical signs caused by the immune-mediated inflammation, and corticosteroids remain the mainstay of therapy. Despite a number of reported treatments for FIP, a systematic review of the literature indicates that most results need to be evaluated with caution due to the lack of placebo controls and lack of diagnosis before treatment was initiated (18). Various medications have been administered including antiviral drugs, immuno-modulators and immunosuppressant drugs (corticosteroids, cyclophosphamide, ribavirin, and feline interferon-ω, among others). The 2006 Feline Vaccine Advisory Panel of the American Association of Feline Practitioners did not recommend vaccination against FIP. This is mainly due to the possibility of antibody-dependent enhancement, a process in which exposure of the virus to antibody increases its uptake by macrophages leading to faster development of clinical signs (19).

It is important to prepare the owners for the unfortunate outcome that inevitably follows the diagnosis of FIP. Supportive care with fluids and nutritional support are recommended as long as the cat's quality of life is not compromised, otherwise euthanasia should be advised.

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