The Neurological Form of Feline Infectious Peritonitis and GS-441524 treatment

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Introduction - Neurological involvement occurs in about 5-10% of FIP cases. This may vary between regions, as Turkish street cats appear to have a greater incidence based on this author's experiences. The age of onset parallels that of other forms of FIP, with most cases occurring under 3 years of age.

Neurological FIP is considered a form of dry FIP and typical lesions of dry FIP are also observed in abdomen, thorax, or eyes in about one-half of neurological FIP cases.[1] In contrast, neurological signs are only seen in about 5% of cats presenting with wet FIP.[1] However, there has been a significant increase in neurological FIP in cats on GS-441524 treatment for other forms of FIP. Neurological FIP is also a common cause of relapse in cats that have completed treatment for non-neurological FIP.

Clinical signs- Neurological FIP presents in two forms, primary and secondary. Cats with primary disease present for evaluation of abnormal neurological signs. However, generalized signs of ill-health are common, including failure to thrive, weight loss, lethargy and inappetence. Fever may be apparent or inapparent. About one-half of cats with primary neurological FIP will also have identifiable lesions outside of the central nervous system (CNS) and blood tests will be more typical of systemic FIP. However, cats with no apparent extra-CNS signs will frequently have normal or near normal blood values on CBC and serum chemistry tests.

Early neurological signs, when recognized prospectively or retrospectively include licking at floors or walls, sporadic muscle twitches, anisocoria, and vague behavioral and cognitive abnormalities. The suspicion of neurological FIP grows as the neurological signs effect movement. The earliest sign is usually a progressive loss of coordination and balance (ataxia). This is often preceded by a reluctance to jump up or down from high. Incoordination is most noticeable at first in the rear legs but rapidly becomes more generalized. Seizures of the grand mal or psychomotor type may also occur in some cases. Grand mal seizures are manifested by a brief loss of consciousness, severe rhythmic muscle spasms involving the entire body. Psychomotor epilepsy is associated with varying degrees of consciousness and uncontrolled or partially controlled body movements.

Cats with secondary neurological FIP present with the usual systemic signs of disease and CNS involvement appears at a later point in the disease. Neurological disease is a frequent occurrence during antiviral drug treatment for other forms of FIP and is a common cause of relapse in cats treated for the common systemic forms of FIP. These relapses usually occur within the first 1-4 weeks after what appeared to be a successful treatment.

Spinal cord involvement is frequently overlooked in neurological FIP, although over 50% of cats with inflammatory spinal cord disease have FIP.[2] Spinal cord involvement leads to fecal and/or urinary incontinence of varying severity. Paralysis of tail or hindlegs are also signs of spinal cord disease. Spinal cord involvement is more likely to lead to permanent neurological deficits then disease in the brain.

Diagnosis- The sudden appearance of neurological abnormalities in cats < 5-7 years of age is strong evidence for FIP based on odds alone, as few other diseases will produce similar signs in this age group. However, there is a tendency among veterinarians to put systemic toxoplasmosis higher on their diagnostic list, especially when ocular or CNS signs are observed. Systemic toxoplasmosis in cats is a rare disease compared to FIP and often occurs in immunocompromised hosts, including those with FIP.[15-17] This is understandable, because cats are the definitive host for *Toxoplasma gondii* in nature and have evolved a state of facultative symbiosis. Furthermore, the major clinical manifestation of systemic toxoplasmosis is a characteristic pneumonia, sometimes associated with hepatitis, pancreatic necrosis, myositis, myocarditis and dermatitis.[3-8] Uveitis, which resembles that of FIP, is seen in about 10% of cats with systemic toxoplasmosis,[4] and encephalitis is even less common.[7,17] The diagnostic test for systemic toxoplasmosis is based on comparing IgG and IgM antibody titers by the indirect fluorescent antibody (IFA) procedure.[3] High IgG titers in the absence of IgM antibodies indicates previous exposure to toxoplasma, which can be as high as 50% among feral cat populations.[4] The presence of high IgM antibody titers is an indication for systemic spread of the organism from the intestine to other tissues and is one requirement for diagnosing systemic disease. <u>However, many cats with ocular and neurological signs are inappropriately treated for systemic toxoplasmosis based only on high IgG titers. FIP and toxoplasmosis have also been described in the same cats.[15-17]</u>

The diagnosis of the typical systemic forms of FIP is usually made by coupling information on the age and origin of the cat, historical and physical signs (e.g., ill-health, fever, typical abdominal or thoracic effusions, palpable masses in abdominal organs) with certain laboratory abnormalities in a complete blood count (anemia; high white blood cell, low lymphocyte, and high neutrophil counts), serum chemistry panel (high total protein, high globulin, low albumin, and low A:G ratio), examination of effusions when present (exudate or modified exudate, yellow-tinged) and playing the odds that these findings can best be explained by FIP. A definitive diagnosis can be obtained by identifying coronavirus proteins or RNA within effusions or samples of diseased tissues by PCR or immunohistochemistry. However, cats that develop neurological FIP either during or after treatment for extra-CNS FIP, will often lack many or all of these clinical features.

Diagnosis of neurological FIP, especially in the primary form, is usually made in three ways: 1) consider all the historical, clinical and laboratory findings and play the odds that it must be FIP, 2) examine the brain for characteristic signs of FIP by magnetic resonance imaging (MRI) and/or cerebrospinal fluid (CSF) analysis,[8,9] and 3) treat based on odds that it is neurological FIP and hope for positive response to antiviral drug therapy.

Magnetic resonance imaging with contrast enhancement has become increasingly a test of choice in diagnosing neurological FIP. Dilatation (hydrocephalus) of one or more ventricles is a common lesion in the brain.[8,9] Similar dilations in the form of syringomyelia may also be seen within the spinal cord. Dilatations are secondary to inflammation of the surrounding ependyma. The ependyma secretes, circulates, and maintains homeostasis within the CSF pool. Therefore, the severity of the secondary obstructive hydrocephalus of FIP is proportional to the degree of ependymal inflammation and associated contrast enhancement. Discrete parenchymal lesions are not identified. MRI adds greatly to the expense of diagnosis, the required anesthesia adds to the risk of death in severely ill cats, and the expertise and equipment are not always available. Therefore, the ultimate diagnosis often falls to response to specific antiviral drug therapy. The drug of choice for neurological cases of FIP is GS-441524.[9,12]

CSF analysis is an alternative way to quantify the nature and severity of the inflammation in the ependyma and meninges. CSF protein levels and cell count are both elevated in cats with FIP, and it is often possible to get appropriate samples to

detect infected macrophages either by IHC or PCR.[10,11] CSF analysis also carries a small risk from anesthesia as well as needle puncture into the cisterna magna.

Treatment- Neurological FIP can be cured if sufficient anti-viral drug passes the blood-to-brain barrier and the virus has not acquired drug resistance.[9,12] Field tests with the viral protease inhibitor GS376 were the first to show that neurological signs can be greatly suppressed but the infection not cured. The reason was assumed to be the inability to get high enough levels of GC376 into the CNS. Greater success in curing cats with neurological FIP was obtained with the nucleoside analog and viral RNA transcription inhibitor GS-441524.[9,12] GS-441524 was shown to enter the cerebrospinal fluid (CSF) at levels ranging from 7-21% of the blood (compared to 3% for GC376), depending on the cat tested.[13] This variation in the blood-to-brain barrier between cats is the probable explanation for the variable dosages of GS-441524, from 4 to 10 mg/kg daily, required to cure naturally occurring cases of neurological FIP.[9,12]

The present starting dosage for GS-441524 has been set at 10 mg/kg daily by the subcutaneous route based on a recent report.[7] Although, it is possible to treat some cats at lower dosages,[9,12] there is no easy way to measure the strength of the blood-to-brain barrier, so the lowest dosage that will be curative for the most cats is used. The success of treatment is measured by both improvement in clinical signs and when present, improvement in critical abnormal blood test values. Weight gain and quality of coat are also important qualitative signs to monitor. Sequential MRI and CSF analyses will provide more direct evidence of treatment response,[9] but are impractical in most cases.

Improvement in general health and neurological signs usually occurs within 24-48 hours and most cats destined for a full recovery will return to normal function in 4-6 weeks. However, a significant proportion of cats will respond slower and require a re-evaluation of their clinical and blood test status every 4 weeks. A slow down in progress, either clinically or in reversal in initial blood test abnormalities will require increases in drug dosage from +2 to +5 mg/kg daily.[9,12]

The end of treatment, which is usually 84 days, is not always easy to confirm. Typical blood test abnormalities that are used in most other forms of FIP are either not present at the time of diagnosis or returned to normal before the treatment ends. Permanent neurological abnormalities may persist even after the infection has been cured and confuse the clinical evaluation. Without MRI and/or CSF analysis to

confirm whether the disease as gone, the only remaining option is to stop treatment and hope that a relapse will not occur.

Complications of neurological FIP- Relapses in cats treated for neurological FIP usually occur within days following the end of treatment and are due to either inadequate dosage and/or the acquisition of drug resistance. The incidence of relapses somewhat higher than following treatment of extra-CNS forms of FIP. Under-dosing may result from stronger blood-to-brain barrier in some cats than others, poor quality antiviral drug, or miscalculation of the dosage. However, most cats can be cured on retreatment providing drug resistance has not developed.

The acquisition of drug resistance is well known for antiviral drugs used in humans for diseases like HIV/AIDS. It has also been recognized for both GC376[11,14] and GS-441524 in cats.[12] Drug resistance can occur by mutations in either the parent FECV or in its mutant FIP biotype in nature[14], and manifest by a poor initial response to treatment, but this is uncommon.[12] Resistance is more likely to occur during treatment and is facilitated by both chronic exposure to the drug and lower sub-inhibitory drug levels. Drug resistance is usually partial and can often be overcome by increasing the dosage. Drug resistance can occasionally increase over time, negating any effect of the higher dosage.

Cats with neurological FIP may be left with residual damage to brain and/or spinal cord and permanent disabilities. Disabilities include varying degrees of incoordination, behavioral changes, and dementia. The most troublesome disabilities result from involvement of the spinal cord. The spinal cord is encased in a boney tube that does not allow for much expansion in cases of inflammation or a form of syringomyelia. Spinal cord involvement in FIP is frequently manifested by varying degrees of fecal and/or urinary incontinence. Paralysis of the rear legs and tail are also observed. Unfortunately, these clinical abnormalities are often permanent, especially when the neurological disease goes untreated for a long time.

One of the most common negative outcomes of antiviral drug therapy in cats with neurological FIP is a failure to achieve a cure, even though continued treatment at a high dosage still allows a sustainable quality of life (i.e., control of disease signs without a cure). This situation indicates that inhibiting virus replication with antiviral drugs may be insufficient to cure an infection and that an effective immune response is also required. This phenomenon of "treatment without cure" has led many owners to continue treatment at all costs for periods over a year in

some cases. It has also led to much experimentation with ultra-high dosages of GS-441524 (>15 mg/kg daily), split doses, switches from injections to oral treatment, simultaneous oral and injectable treatment, combined antiviral drug therapy (e.g., GS-441424 plus GC376), and augmentation of the antiviral drug treatment with high dosage corticosteroids and other immunosuppressives. A cure is occasionally claimed for such treatments, but the outcome for most of these cats has been bad.

There is indirect evidence that host immunity to FIP is compartmentalized between CNS and extra-CNS parts of the body. The incidence of CNS involvement appears to increase when extra-CNS infection is inhibited by GS-441524.[12] Therefore, active extra-CNS disease appears to have an inhibitory effect on disease in the CNS. Cats presenting with pure neurological disease often do not have abnormal blood test values in both CBC and serum chemistry panel, even with significant inflammatory changes in the CSF.[8] Cats with neurological FIP often have the highest serum, and hence CSF antibody titers, by IFA than other forms of FIP.[8] These are all evidence for "compartmentalization" of infection on one or the other side of the blood-to-brain barrier.

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