# Neurological and ocular FIP

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**Background**- Many owners of cats with FIP have turned to the Chinese black market to obtain GS-441524. This black market is not entirely profit motivated as the FIP problem in China is horrendous. Pets are the in-thing in China, and expensive pedigreed Western breeds of cats produced locally are imported from abroad are especially valued. As a result of the associated FIP problem, Chinese were producing, selling, and applying drugs like GC376 and GS-441524 months before we were even able to publish our results. The reality is that the immediate need for drugs like GS-441524 has outpaced the official approval and commercialization process, which takes years. The result is a wild-west with new producers and suppliers entering the market weekly. Ultimately the black market will disappear as official suppliers come forward and patents are finally enforced. In the meantime, it is not beneficial for FIP anti-viral drug therapy to be given a bad name. Therefore, the purpose of this article of this communique is to discuss one of the main problems that has arisen, i.e., what to do with cats that have the neurological and/or ocular forms of FIP. This group of cats is increasingly a focus of my communications and also the type of cat that is most difficult to treat and requires a lot more clinical research.

**The blood-to-brain and blood-to-eye barriers**-The eye and nervous system are protected from harmful substances/agents by what is called the blood-to-eye and blood-to-brain barriers. These barriers have great evolutionary significance because they protect both brain and ocular functions from the effects of systemic toxins and infectious agents. Such barriers evolved over millions of years by positive selection for the fittest. The blood-to-brain barrier in cats will exclude around 80% of most drugs, while the blood-to-eye barrier excludes about 70%. Therefore, if a given dose of drug such as GS-441524 achieves an effective blood (plasma) level of 10 uM, the levels in the brain (cerebrospinal fluid) will be only 2 uM and the level in the eye (aqueous humor) only 3 uM.

There are several other aspects of these barriers that need to be considered. First, their efficiency at excluding unwanted substances and agents varies between individuals. Second, the efficiency of this barrier will decrease in inflamed tissues and increase as inflammation subsides. This is good for treatment in the early stages of disease but bad for treatment in the final stages when the inflammation is gone and only the virus is left. Thirdly, there is no simple, safe or effective means to decrease these barriers and the only way to increase drug levels in brain or eyes is to increase their levels in blood plasma with higher dosages.

**How these barriers cause disease-** Paradoxically, the ocular and neurological forms of FIP are also a result of these same barriers, but in this case of neurological and/o ocular FIP, the impediment is to the entry of antibodies and immune lymphocytes. The phenomenon of neurological disease following a common systemic virus infection is well known in humans and

animals. The prime example is polio-encephalomyelitis in people and canine distemper in dogs. The polio virus is a common enteric pathogen and usually causes an inapparent or mild intestinal infection. However, in some people the virus also escapes to the brain and spinal cord. People mount a vigorous systemic immune response to the polio virus, which is highly effective in eliminating the virus in parts of the body except for the nervous system, where the blood-to-brain barrier limits is an impediment to immunity. These unfortunate people will develop the classical neurologic form of the infection. A similar phenomenon occurs with canine distemper. The canine distemper virus, which is closely related to the human measles virus, causes an acute respiratory infection in young dogs that manifests 7-14 days after exposure and lasts for a week or two. Most of these dogs will completely recover, but a proportion will develop neurological disease three or more weeks later. This highly fatal secondary form of canine distemper is caused by virus that escaped into the brain and spinal cord during the respiratory phase of infection and is shielded from the host's immune system by the blood-to-brain barrier.

**What is FIP? -** FIP is ultimately caused by a common and a largely innocuous enteric coronavirus, similar to coronaviruses causing diarrhea in humans, foals, calves and poultry. In about 10% of cats, mainly kittens, the enteric coronavirus will undergo specific mutations that allow it to escape the cells lining the lower intestine and infect the most basic cell of the immune system, the macrophage. This macrophage infection is eliminated in all but 0.3-1.4% of cats, which for unknown reasons are unable to develop the required protective immunity. The disease that occurs in this unfortunate small group of cats can clinically manifest within days, several weeks, sometimes months, and rarely a year or more. The form of disease that is manifested is referred to simply as wet (effusive) or dry (non-effusive). These two forms are easily distinguishable, although there may also be transition forms between the two. Some cats may present with signs of dry FIP but later develop wet FIP, or vice versa. Overall, about 75% of cats will present with wet FIP and 25% will present with dry FIP. Less than 5% of cats, usually those with milder forms of dry FIP to start, will survive longer than one year with the best symptomatic care.

**Clinical manifestations of FIP-** The clinical manifestations of wet (Table 1) and dry (Table 2) FIP vary according to the main site(s) of disease in the body. Wet FIP is characterized by the accumulation of large amounts of inflammatory fluid either in the abdominal cavity and/or chest cavity. Involvement of the central nervous system (CNS) and eyes is relatively uncommon in the wet form of FIP. The dry form of FIP is characterized, not by diffuse inflammation and fluid effusion, but rather by less numerous and larger tumor-like lesions (i.e., granulomas) in organs (e. g., kidney, cecum, colon, liver, lung, lymph nodes) within the abdominal or thoracic cavities, or in the eyes and brain. Whereas the brain and/or eyes are only involved in 9% of the cases, neurological and-or ocular disease is seen as the main presenting clinical sign in 70% of cats with dry FIP.

Table 1. Variability in clinical signs of effusive (wet) FIP from cats necropsied at UC Davis

| **Signs referable to:** | **% affected** |
|---|---|
| **Peritoneal cavity** | **58.0** |
| **Peritoneal & pleural cavity** | **22.0** |

| | |
|---|---|
| **Pleural cavity** | **11.0** |
| **Peritoneal cavity, eyes** | **2.8** |
| **Peritoneal cavity, CNS*** | **1.9** |
| **Peritoneal and pleural cavity, CNS** | **0.9** |
| **Peritoneal and pleural cavity, eyes** | **0.9** |
| **Pleural cavity, CNS, eyes** | **0.9** |
| **Peritoneal cavity, CNS, eyes** | **0.9** |

***Central nervous system (brain, spine)**

Table 2. Variability in clinical signs of non-effusive (dry) FIP from cats necropsied at UC Davis

| **Signs referable to:** | **% affected** |
|---|---|
| **Peritoneal cavity** | **30** |
| **CNS** | **22** |
| **Eyes** | **14** |
| **CNS & eyes** | **8** |
| **Peritoneal cavity, eyes** | **7** |
| **Peritoneal & pleural cavities** | **4** |
| **Peritoneal & pleural cavities, CNS** | **3** |
| **Peritoneal & pleural cavities, eyes** | **2** |
| **Peritoneal cavity, CNS, eyes** | **2** |
| **Pleural cavity** | **1** |

The FIP virus spreads to sites outside of the body cavities through infected macrophages that have gained entry to the bloodstream. The main clinical signs of neurological FIP are fever, inappetence, weight loss, and incoordination (most intense in posterior). Some cats may also develop seizures and varying degrees of dementia. Ocular disease often accompanies neurological FIP due to the intimate relationship of eyes and brain. Ocular disease is most often manifested by inflammation of the anterior uveal tract (iris and ciliary body) with discoloration of one or both irises, precipitates on the back side of the cornea, and cloudiness of the aqueous humor. Ophthalmoscopic examination may also demonstrate inflammation in the retina and optic nerve.

**Diagnosis of neurological and/or ocular FIP-** The neurological and/or ocular forms of FIP can be confused with feline systemic toxoplasmosis, which is why so many cats with these forms of FIP are tested for toxoplasmosis and treated with Clindamycin or other antibiotics. However, systemic toxoplasmosis is an exceedingly rare disease of cats, especially when compared to FIP. FIP can be easily differentiated origin (cattery, foster/rescue, shelter), signalment (age, gender, breed), and basic blood test results. Deep fungal infections (coccidioidomycosis, blastomycosis, histoplasmosis) can cause similar clinical signs to dry FIP but are still uncommon even in their endemic regions. Lymphoma may also be a differential diagnosis for dry FIP, but this disease is usually sporadic and in older cats. The diagnosis of neurological and/or ocular

disease is ultimately based on where a cat comes from the clinical signs, age, common changes in complete blood count (anemia, lymphopenia), serum protein changes (high total protein, high globulin, low albumin, low A:G ratio). The diagnosis may be confirmed if there is still doubt, by characteristic changes in cerebrospinal fluid (CSF) and aqueous humor (high protein, high cells, neutrophils, lymphocytes, macrophages), suggestive lesions on MRI, PCR or immunohistochemistry on CSF, or high serum coronavirus antibody titer by IFA (>1:3200). One must be careful, however, to follow the 70% rule, i.e., no single typical laboratory abnormality will occur 100% of the time. The rapid response of FIP to GS-441524 is in itself a diagnostic indicator.

**Treatment of neurological and/or ocular FIP**- The only effective treatment for neurological and/or ocular FIP is an antiviral drug such as GS-441524. The minimum dosage regimen for this form of FIP should be 5 mg/kg, SC, q24 h for at least 12 weeks. We have found this treatment to cause a rapid reversal of clinical signs within days, a return to near normal within two weeks, and a return to full normalcy within 8 weeks or so. The best gauges of normalcy are weight gain, growth if retarded by the disease, and the ability to once again jump to previous heights without hesitation. Although GS-441524 is highly effective in reversing abnormal clinical signs in cats with neurological disease, it is not always curative. Relapses of disease following cessation of treatment have occurred within days to several weeks after stopping treatment and the relapse rate appears to be much higher than for cats suffering other forms of FIP. We have treated only six cats with neurological disease (four also with ocular disease). One cat relapsed with neurological disease after completing treatment at a dosage of 2 mg/kg, SC, q24h and was cured at a dosage of 4 mg/kg, SC, q24 h, while a second cat was treated twice at 2 mg/kg and relapsed each time. A third and fourth cat was treated at a dosage of 5 mg/kg and cured, while a fifth cat relapsed after two identical treatments at the same dosage. A sixth cat relapsed at 5 and 8 mg/kg and is now being treated at a dosage of 10 mg/kg. Cats that cannot be cured of FIP can be kept in a state of normalcy with indefinite treatment, but this can be a costly endeavor and with unknown long term side effects and the spectrum of drug resistance.

**Can most cats with neurological FIP be cured?** - The bottom line is that we do not know whether all cats with neurological FIP can be cured and in this regard, people treating cats with neurological FIP are definitely in a research mode. We feel that increasing the blood levels may be part of the solution based on very few cases. It is also interesting that ocular lesions in cats with neurological involvement are more amenable to treatment. We found that ocular disease signs can be eliminated at a dosage that is not sufficient to cure brain disease. This may reflect the greater permeability of the blood-to-eye barrier compared to the blood-to-brain barrier in cats.

The ability of drugs like GS-441524 to inhibit inflammation caused by FIPV infected macrophages may also be a two-edged sword. Increased vascular permeability in lesions may allow more drug to pass into tissues in the initial stages of treatment, while resolution of the inflammation may re-instate the barrier and prevent sufficient drug levels later in treatment.

Finally, the problem of drug resistance of FIP virus in brain has to be considered. We know from our field trial experience, and from the published research of others, that drug resistance occurs in a very small proportion of naturally infected cats and can be also induced by repeated passage in cell culture. There is

additional evidence from the literature that different forms of the infecting virus can evolve in different tissues, so that virus in the brain may respond different to GS-441524 than virus in other parts of the body. The long-term exposure of variant viruses in the brain to low levels of drug could be conducive to the evolution of drug resistance. If drug resistance is present naturally or occurs after long term treatment, increasing drug dosage will not succeed.