FIP and infectious neurological diseases of the cat

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INTRODUCTION
Inflammatory and infectious diseases of the cat's Nervous System (NS), despite the great progress made by veterinary neurology in the feline species over the last few decades, is still a relatively unknown field, which maintains various debated aspects. The aim of these notes is to address the updated, systematic and consequential approach to inflammatory / infectious neurological diseases affecting the cat.

In the cat, inflammatory diseases of NS are mainly due to viral etiologies. Beside the Feline Infectious Peritonitis (FIP), which plays a primary role, there are various forms of supposed viral etiology. These latter, in the absence of a clearly identified etiologic agent, show neuropathological signs compatible with viral infection (so called “viral non-FIP encephalitides”). Bacterial and protozoal forms are rarer, although toxoplasmosis is a well-known cause of cat encephalitis, and so-called "sterile" forms are, differently from the dog, rarely reported. As for dogs, also in the feline species are meningoencephalitis with mycotic etiology. Among the inflammatory/Infectious diseases of the cat SNC, FIP has a dominant role and, for this reason, will be thoroughly discussed.

CLINICAL FEATURES OF INFLAMMATORY/INFECTIONOUS DISEASES OF THE NERVOUS SYSTEM OF THE CAT
In neurology, clinical signs are usually linked to the affected neuroanatomic region and, consequently, they may be very different depending on the anatomic structures involved in the pathological process. It is therefore difficult to trace a common symptomatic profile of inflammatory-infectious diseases since they may affect different SN structures. The same FIP can exhibit extremely different clinical features due to the different areas of the affected central nervous system (CNS).

In the presence of NS inflammatory/infectious diseases, the neuroanatomic localization of the lesion is usually multifocal, although it is not uncommon to document signs indicating "focal lesions". Nevertheless, it is possible to identify some common traits for this category of illnesses. Inflammatory/infectious diseases, while favouring younger subjects, can affect cats of all ages and, typically, show a subacute/acute onset and a progressive course. On the neurological examination, frequent findings are represented by alterations in the functions of the brain stem, forebrain and spinal cord, including deficits of the cranial nerves, gait, proprioception, seizures, behavioural changes, and menace response.

DIFFERENTIAL DIAGNOSIS
In the case of a multifocal localization and suspicion of an inflammatory/infectious etiology, clinical differential diagnosis should consider a variety of diseases, which are not always easy to be identified. If bacterial and protozoal meningoencephalitis is poorly represented in the feline species, viral diseases have a relevant role. In this abstract, the main cat infectious diseases are synthetically described essential parts.

Feline Infectious Peritonitis
Aetiology – Feline Infectious Peritonitis (FIP) has been described for the first time in 1963, and is currently considered one of the most important neurological diseases of the cat. The FCoV generic name (Feline Coronavirus) was applied without particularly stringent criteria to define all the serotypes and biotypes of the feline Coronavirus. In this context, the Feline Enteric Coronavirus (FECV), responsible for the benign enteric form of the cat, is considered to be a FCoV biotype (Figure 1)

The etiologic agent responsible for FIP is the Feline Infectious Peritonitis Virus (FIPV), a Feline Coronavirus (FCoV) or, more correctly, Feline Enteric Coronavirus (FECV) mutant strain. For long time the common belief
was that of two different types of feline coronavirus, namely the FECV and the FIPV. Only in relatively recent times, it was found that FIPV represents a spontaneous mutation of FECV in cats previously infected with the virus.

![Figure 1 – Electronic microscope image of Feline Coronavirus](image)

**Epizootiology** (science that deals with the character, ecology, and causes of outbreaks of animal diseases) – FIP is not considered a contagious disease but a sporadic event caused by a virus mutation that occurred in a given cat in the presence of particular host conditions. Virtually, FIP can manifest everywhere the FECV is present and, for this reason, can be considered widespread throughout the world in the feline population. Thus, the FIP epizootiology (ie the study of factors that determine the frequency and distribution of infectious disease in animals) is closely related to FECV. The FECV is present in virtually all farms and shelters that accommodate more than six cats and is eliminated by about two-thirds of cats living in groups in private residences. Elimination of FECV may be transient, recurrent or chronic. Although several studies point to predispositions of certain breeds to developing the disease in certain geographic areas, it is more likely that predisposition is more due to certain bloodlines within a breed rather than to the breed itself. Losses due to illness are more frequent in young cats aged between 3 and 16 months. FIP in cats over 5 years of age is considered a sporadic event. FIP is an enzootic disease, but sometimes may have epidemic features within a cattery. Factors associated with the development of FIP epidemics are to be found mainly in overcrowding, in the high presence of newborns or genetically predisposed kittens or in the introduction of new FECV variants.

**Pathogenesis** – As mentioned above, FIP is not a per se contagious disease. The most scientifically accredited hypothesis states that FIP develops for a virus mutation under a FECV infection. The FECV mutation occurs spontaneously in a given region of the viral genome. The possibility that virus can mutate is proportional to the amount of virus present and its persistence in the host. Viral transmission usually occurs via the oro-nasal route through contact with infected cats from FECV. Unchanged FECV is replicated in enterocytes, causing asymptomatic infection or, at most, a mild diarrhoea, while the mutated variant replicates in macrophages, causing FIP. Therefore, all factors that increase the replication of the virus, such as immune system depression, young age, stress, glucocorticoid therapies, and surgeries, increase the likelihood that mutation occurs. The key factor in understanding the pathogenesis of FIP is the ability of the mutant virus to replicate itself in macrophages and, therefore, to spread to other tissues. The genetic basis for explaining the different tropism for macrophages between FECV and FIPV is not fully clarified, but seems to derive from a mutation within the 3c gene.

Replication of the virus in macrophages appears to be very slow in the first two weeks, and then dramatically increases over the next ten days, in conjunction with the appearance of specific antibodies. These antibodies are neutralizing the virus in vitro, but in vivo seem even to facilitate the replication.
Physiopathogenesis of the lesions – Antibodies against the virus, as stated above, are not only not useful but also have a harmful role. FIP is indeed a disease whose lethal effects are not caused directly by the virus but rather by the series of reactions of the immune system of the host. The typical feature in the so-called "antibody" phase of the infection is inflammation of the serous membranes, where around small calibre venules increased replication and release of the virus from infected degenerating macrophages occurs with subsequent infection of other approaching macrophages. This lesion appears as the typical pyogranuloma, surrounded by proteinaceous oedema, neutrophils and plasma cells. Pyogranuloma relates to an Arthus-type hypersensitivity reaction. The activation of the complement and the resulting vasculitis produces microhaemorrhage, Coagulating Intravascular Dissemination (CID; usually not clinically appreciated) and an abundant serosal effusion. Pyogranulomas, characteristic of the effusive form of FIP, are prevalent in the abdomen, are microscopic or a few millimetres in size and, by confluence, they can literally cover the serous surfaces of the abdominal organs, assuming the appearance of a fibrinous coat.

It is well known that FIP can be present in two clinical forms: the exudative ("wet") form and the non-exudative ("dry") form, probably linked to the development of two different responses by the host immune system. While the exudative form is only related to the production of circulating antibodies that cannot protect the host, the dry form appears to be the result of partially protective immunity. Protective immunity is cell-mediated and is linked to the ability of macrophages to respond differently to the virus, destroying it instead of acting as incubators. Likewise, the immune system becomes capable of destroying infected macrophages. It is believed that this immune response, if premature and robust, can lead to healing or, at least, blocking the replication of the virus without evidence of clinical signs.

In the event that the cat can develop a robust humoral response and a moderate cell-mediated response, the development of the dry form occurs, typically more prolonged in time and characterized by the formation of true granulomas disseminated in various organs and systems including the CNS (Figure 2). These granulomas, much less numerous and scattered than the pyogranulomas of the exudative form, tend to deepen from the surfaces to the underlying parenchyma of the affected organs. This typical positioning adjacent to the surfaces is in accordance with their origin as pyogranulomas. For example, in CNS the lesions of the dry form are typically oriented from the surfaces and deepen in the surrounding parenchyma (eg by the ependymal layer and periventricular tissue).

Figure 2 – Histopathology: sections of the nervous tissue of a cat affected by FIP. On the left side is the characteristic granulomatous lesion: on the left notice the blood vessel and the marked pyogranulomatous perivascular inflammation. On the right, specific staining with immunohistochemical techniques shows the presence of viral antigen within the lesions. Photo: dr. Carlo Cantile, University of Pisa
Clinical presentation – The clinical features of the disease reflect the pathogenesis of the lesions and the signs are variable depending on the ability of the patient to react immunologically. Classically, there is an exudative (wet) form, a non-essudative (dry) form, and a mixed form. In fact, this distinction is more for didactic purposes than found in the reality, as it has been shown that the two forms can coexist and represent one transition to the other and vice versa.

FIP may be characterized or preceded by very vague and non-specific clinical signs, such as delayed growth and progressive weight loss. Persistent and non-responsive hyperthermia may be an early sign of FIP. The "exudative" form is characterized by ascites (Figure 3) and thoracic and/or pericardial effusion. On abdomen palpation typically enlarged and indolent, fluctuating intestinal loops or enlarged lymph nodes may be felt. This form does not usually involve clinically relevant neurological sequelae, although histopathologically microscopic lesions have been documented in the CNS. If pleural and/or pericardial effusion is marked, it is possible to appreciate paradoxical breathing and signs of right heart suffrance. Typically, peritoneal and pleural effusion consists of a modified trasudate or a high-protein exudate due to the high concentration of γ-globulin. The cellularity of the effusion is relatively mild.

The "dry" form, as from the name, is characterized by the presence of granulomatous lesions in different organs. In 40% of the cases, the abdominal cavity is affected and, on palpation, enlarged mesenteric lymphnodes, bumpy kidneys (Figure 4) and thickened intestinal loops can be detected.

Figure 3 – Abdominal distension due to ascites in a cat with exudative FIP

Figure 4 – Macroscopic section of a kidney of a cat with neurological signs affected by the non-exudative form of FIP
About 60% of cats with dry FIP present CNS ocular signs. The most common findings in the eyes of affected cats are those of uveitis and corioretinitis. Sometimes it is possible to appreciate discoloration of the iris, abnormalities in the shape of the pupil and visible precipitates on the back of the cornea. Haemorrhage in the anterior chamber (Figure 5) and retinal detachment are not uncommon.

![Figure 5 – Hemorrhagic discharge into the front chamber in a cat affected by the non-exudative form of FIP. (Photo Dr. Manuela Crasta - Bologna).](image)

The neurologic signs are different and, in their expression, reflect the injuries in the various parts of the CNS. Among the most commonly encountered, there are brain stem, cerebellar and spinal cord signs. In particular, abnormal mentation, ataxia of the four limbs, pathological nystagmus, tetra- and paraparesis, intention tremors and balance alterations are reported. Seizures, both generalized and focal, are considered a bad prognostic sign due to the progressive involvement of the cortex.

Diagnostic work-up - The ante-mortem diagnosis is not always easy and is based on the presence of sufficiently specific clinical and laboratory signs, unfortunately none of them pathognomonic. Along with the previously highlighted signalment data, cats with dry FIP usually exhibit typically progressive, multifocal neurological and ocular signs. In laboratory tests, in addition to the non-specific leucocytosis and possible non-regenerative anaemia, the most significant data consist of marked hyperproteinemia (up to 12 g / dL) due to α2- and γ-globulin increase, sometimes associated with hypoalbuminemia, the latter due to glomerulopathy and consequent proteinuria.

In effusive FIP forms, peritoneal fluid analysis can be of great help. The peritoneal fluid is characterized by the yellow/ pale yellow colour, high protein content (from 3.5 to 9.8 g/dl), mild cellular content (103-105 WBC) and sterility.

The results of serology, aimed to assess the concentration of antiviral antibodies should be related to other data. Positive titles do not necessarily confirm FIP but, simply, the contact with a coronavirus. However, it should be emphasized that especially the dry forms are characterized by particularly high antibody titers. In some cases of FIP, serology, due to the formation of circulating immune complexes, can be falsely negative. At present, PCR techniques do not allow us to derive particularly useful information, basically because of the difficulty of distinguishing the FIPV from the FECV from a genomic point of view.

Some authors have emphasized the possibility of obtaining a FIP diagnosis by the determination of some acute phase proteins, and in particular of the alpha-acid protein (AGP). Although high AGP levels are strongly suggestive of FIP, this determination is not unfortunately specific either.

The neurological form of FIP has marked alterations in cerebrospinal fluid (CSF) expressed in terms of relevant increase in protein concentration (50-350 mg / dL) and marked mixed pleocytosis (> 100 cells / µl) (Figure 6). Often, in cats affected by FIP, CSF collection may be extremely problematic for the high viscosity of the fluid itself.
On the left, you can appreciate a pattern of mixed pleocytosis (neutrophils, granulocytes, lymphocytes and monocytes); On the right, strongly positive Pandy's test: you can notice the dense cloud obtained by pouring a drop of CSF into Pandy's solution.

On Magnetic Resonance Imaging, the presence of granulomas, obstructive hydrocephalus and contrast enhancement at the level of periventricular tissue, meninges and ependyma may be detected (Figure 7).

Prognosis is invariably poor despite therapeutic attempts to reduce abnormal immune response using immunosuppressive doses of corticosteroids. Several studies have been carried out on antiviral drugs such as ribavirin, human α-interferon, and feline ω-interferon, with discouraging results.

Feline Immunodeficiency Virus (FIV)
The feline immunodeficiency virus (FIV), although cases characterized by specific neurological deficits have been described, is a weakly neurotropic virus that normally produces subclinical infections. Among these, behavioural abnormalities, abnormal aggression, disorientation, hyperactivity and convulsions have been documented. The virus, under experimental conditions, is able to produce nervous tissue lesions, modeled for AIDS study in humans. It is commonly believed that clinical forms of nervous FIV are due to the action of opportunistic agents, such as toxoplasma or FIP virus, rather than the FIV virus itself. Mild alterations of the CSF (mild mononucleated pleocytosis) have been reported both in spontaneous and experimentally induced forms.

Feline leukemia Virus (FeLV)
In veterinary literature, there are only sporadic reports of neurological lesions directly attributable to FeLV infection. These rare neurological forms are characterized by myelopathy, which occurs with hyperesthesia,
paraparesis and ataxia. However, it is worth remembering that one of the most common intracranial neoplasms in the cat is lymphoma, which is often associated with FeLV.

“non-FIP” viral encephalitides, Borna disease and Feline Polioencephalomyelitis
Many neurological cases with supposed inflammatory/infectious aetiology but non confirmed diagnosis fall into the so-called "non-FIP viral encephalitis" group. This category includes those cases where the CNS histopathology confirms the typical signs of viral encephalitis. These cases, described in different countries of different geographic areas are grouped, based on histopathological features in two groups:
Group 1: Cats showing signs of non-suppurative encephalomyelitis;
Group 2: cats showing signs of polioencephalomyelitis or polioencephalitis
Cats belonging to the first group have a particularly wide range of age and show acute onset signs and progression of neurological disease, which is characterized mainly by fever, ataxia, nystagmus, head tremors, depression and seizures. Antemortem diagnosis can be supported by the presence of an abnormal CSF with mild mononuclear pleocytosis and the MRI may show multifocal contrast signs of contrast enhancement on T-1 weighted sequence.

Several authors, after exclusion of known viruses such as FIV, FeLV and FIP, believe that a Borna-like Virus (Borna Disease Virus) may cause the non-suppurative encephalomyelitis associated with Group 1. The disease is caused by a RNA virus affecting mainly the horse and sheep and reported in many other species including the cat. In the feline species, the disease appears histopathologically as a non-suppurative polioencephalomyelitis characterized by fever, loss of appetite, progressive ataxia of the back limbs, loss of balance, nystagmus, behavioural changes and seizures. The disease has also been termed "staggering disease". Although the CSF examination may be mildly altered, the diagnosis is made histopathologically. The disease is progressive and generally fatal. The difficulty in attributing the responsibility of the signs to the virus derives from the fact that antibodies against BDV are also found in healthy cats.

Cats categorized in Group 2 have slower progression of the disease which may last for several months and, in some cases, allows partial recovery. The clinical signs described include mainly ataxia, paresis, and altered postural reactions. Lower motor neurons signs, hyperesthesia, focal-complex seizures have also been reported. Some authors use the term "feline polioencephalomyelitis" to include in a single disease this second group of cases; Although the clinical and histological characteristics are quite different, it is currently not possible to exclude that these forms may represent a variant of the Borna Disease Virus.

Toxoplasmosis
Toxoplasmosis is typically a multisistemic disease, occurring both in acute and chronic form. Although toxoplasmosis has always been associated with cats because they are definitive host of the parasite, it does not frequently produce CNS clinical signs in the feline species. When neurological disease occurs, often it is the expression of an "awakening" of the Toxoplasma or a secondary protozoal infection in a cat with FIV or other immunodeficiency conditions. These forms develop with neurological and ocular signs, in the absence of multisystemic signs. Central neurological signs are, once again, the expression of the affected region and include alterations in behaviour and mentation, blindness, anisocorosia, central vestibular signs, ataxia and paresis.

Diagnosis is not always easy and includes, in addition to the evidence of clinical signs, the presence of positive antibody titers (important the detection of IgM) and the findings of a CSF examination characterized by increased protein content and moderate mixed, predominantly mononuclear, pleocytosis. MRI findings are non-specific and usually show granulomatous lesions that must be placed in differential diagnosis with neoplasia.

Treatment of toxoplasmosis consists of administration of Clindamycin at a dose of 10-15 mg / kg BID per os or parenterally for at least 4 weeks.

Cerebral abscesses and bacterial meningoencephalitides
Cerebral abscesses and bacterial meningoencephalitides represent a sporadic occurrence be due to metastatic diffusion (endocarditis, pneumonitis outbreaks), extension of a septic process from the middle ear, eye and sinuses and traumatic events like the penetrating bites of other animals. In the presence of an abscess (Figure
8), the diagnosis results from the visualization of a lesion typically characterized by a necrotic core and a peripheral ring normally enhancing after contrast medium administration on both CT and MRI.

In the absence of bacterial culture and antibiogram, the treatment involves the use of massive antibiotic therapy, using those antibiotics having a wide spectrum, bactericidal activity and facility in the penetration of the blood-brain barrier (BBB; although the inflamed BBB permits the passage of molecules that in normal conditions would not partially or totally be able to cross). Therapy should be given intravenously, at least in the first few days, and continued for about three weeks. Surgical decompression can be considered in all cases where medical therapy has not yielded the expected results.

**Figura 8** – Immagine TC post contrasto dell’encefalo di un gatto con una lesione settica a livello dell’angolo cerebello pontino destro derivante dall’estensione di un’otite media-interna. Da notare la presa di contrasto a livello dell’anello periferico della lesione.

**DIAGNOSTIC WORK-UP**

The diagnostic steps aimed at confirming the suspicion of CNS inflammatory disease and identifying its aetiology include blood tests, serological investigations, cerebrospinal fluid examination and Magnetic Resonance Imaging.

Complete cell blood count (CNC) examination and biochemistry profile usually do not show relevant abnormalities, as most CNS inflammatory diseases of the cat do not produce appreciable systemic involvement. FIP is an exception since a number of blood alterations can be detected, representing important parts of the demonstration of the etiological diagnosis. In the course of FIP, it is usual to find a significant increase in serum proteins, mainly due to an increase in beta and gamma globulin fractions. This increase in total protein is often associated with hypoalbuminemia, resulting from concomitant glomerulopathy, commonly found in FIP affected cats.

During infectious NS disease in the cat, serology tests are of particular importance, being extremely useful in detecting the presence of antigens (such as FeLV) or antibodies (in the case of FIV, FIP and toxoplasma). It should be emphasized that the finding of anti-coronavirus antibodies does not confirm the presence of FIP.

CSF tap and analysis is one of the most important diagnostic tools in approaching inflammatory diseases of the CNS. These diseases are characterized by possible in the BBB and infiltration of leukocytes from the bloodstream into CNS. Both of these aspects produce altered CSF, particularly the increase of both proteins and cells. In the majority of cases, the presence of an increased number of cells (pleocytosis) in the CSF, usually associated with an increase in proteins, confirms at first the suspicion of a CNS inflammatory disease and, subsequently, orients further investigation for the diagnosis of a specific disease.

For this purpose, it is important to assess the quantity and type of cells in the CSF. Marked pleocytosis usually reflects not only the involvement of the nervous tissue but also the meninges. Viral diseases, with the exception of FIP, are characterized by a mononuclear pleocytosis. Examination of the CSF is particularly helpful in
confirming the suspect of FIP. In this case, the CSF is cloudy due to the high presence of proteins (especially globulins) and the marked mixed pleocytosis, consisting of neutrophils and mononucleates cells and, in some sporadic cases, eosinophils. Recently, several PCR kits have been developed to detect the DNA presence of the etiologic agent. These methods can integrate CSF analysis for the detection of toxoplasma and feline coronavirus.

**FOLLOW-UP AND THERAPEUTIC OPPORTUNITIES**

Despite the progresses made in the last decade, the diagnosis and, consequently, the therapy of infectious/inflammatory diseases of the cat CNS still can be very frustrating. Bacterial meningoencephalitis and toxoplasmosis offer concrete therapeutic possibilities, as above described. By definition, in the absence of adequate therapy, the progression of clinical signs is continuous and worsening. It should be emphasized that the prognosis in case of encephalitis of any nature is always guarded. In addition, the lack of an aetiologic diagnosis prevents an adequate treatment, often based on non-conclusive diagnostic findings.

**References:**