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WHEN, WHY AND HOW TO MANAGE AN INFLAMMATION OF THE NEURO-MUSCULAR SYSTEM?

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The nervous system is divided in two parts: 1- central (brain and spinal cord) and 2- peripheral (nerve, neuromuscular junction and muscle). Inflammation of the nervous system is a frequent cause of neurological manifestations in dogs, less common in cats. The confirmation of an inflammatory origin is usually made during the work-up by cerebrospinal fluid (CSF) analysis for brain, spinal cord or nerve roots involvement. The diagnosis is more difficult for peripheral involvement. A battery of complementary tests must be run once an inflammation is suspected to precise its origin. The treatment is often based on the use of steroids.

When to suspect a nervous system inflammation

Inflammation of the nervous system induces clinical signs that are not characteristic enough to tell with certainty that the patient has neurological signs secondary to such an origin. As always in neurology, the clinical signs are expressed according to the localization rather than the cause of a lesion. The signalment of the patient (breed, age, sex, habitat), the acuteness of occurring signs and a “multifocal” neuro-localization needed to explain these signs, are more in favor of an inflammatory origin. However, very focal signs and a chronic course of the disease cannot rule out an inflammatory origin. Ataxia and paresis may occur with central or peripheral localization. In case of encephalitis however, the patient will express fore brain signs: 1- seizures, disorientation, hemi-inattention syndrome in case of hemispheric involvement; 2- cranial nerve deficits from II to XII and especially vestibular signs in case of brain stem involvement. In case of myelitis, the patient will shows an upper motor or lower motor neuron presentation according to, respectively, a C1-C5/T3-L3 or a C6-T2/L4-S3 involvement. In case of peripheral nervous system involvement (polyneuritis), the paresis/paralysis is associated with hypo or atonia and hypo or areflexia. With neuro-muscular junction immune related inflammation (myasthenia gravis), clinical expression is mainly characterized by generalized weakness although more focal forms exist (oesophagus, ocular muscle). With polymyositis, weakness, reluctance to move and muscle pain are the main clinical signs. However, there is a fair number of cases where the inflammation of the nervous system is mild enough or superficial enough (meningitis); in such cases, the clinical signs will be subtle and not specific for obvious neurological involvement. The owner is complaining that its pet is “not doing right”, usually anorexic, febrile, reluctant to move, or show diffuse poorly localized pain.

How to confirm neuro-muscular system inflammation?

Cerebrospinal fluid collection should be conducted early on in front of patients showing the latest non specific signs or more obvious signs of encephalitis or myelitis. The tap should be performed at the site the closest to the neuro-localization, i.e. lumbar in case of general ataxia/paresis, cisternal in case of cerebral involvement. In front of a non-localized patients, a cisternal tap is preferred: the risk of blood contamination from the needle hub, a drop is put on the protein stamp of a urinary stick. In case of proteinorachia, it will, within seconds, turn positive (normal is less than 0,25 g per liter. If so, 1 to 2 ml of CSF is then collected for further testing. Immediately, the cell count is performed with a Malassez cell allowing for definitive confirmation of the inflammation of the central nervous system (normal is less than 5 nucleated cells per micro liter). False negatives exist if the immune system of the patient is depressed or if high dose of steroids have been given the days prior to CSF collection. CSF should be collected also in front of a rapid generalized lower motor neuron presentation without cranial nerve involvement; coon-hound paralysis or idiopathic polyradiculo-neuritis shows an albumino-cytologic dissociation, i.e. an increased protein content without pleocytosis. Nerve biopsy and identification of an inflammatory infiltration is the only way to diagnose neuritis. Anti-acethyl choline receptor measurement is the most sensitive test to diagnose an immune response directed against the posts synaptic neuro-muscular junction (myasthenia gravis). Creatine phosphokinase measurement is increased in case of polymyositis. The presence of anti 2M muscle antibodies is diagnostic for masticatory muscle myositis.

What other tests must be run once nervous system inflammation has been confirmed?

Pleocytosis and proteinorachia mean that the central nervous system is responding to an aggression. The origin of the inflammation may be secondary to compression (disc hernia, spondylosis, trauma, neoplasia,
1. Aubrey A. Steroid-responsive meningitis-arteritis in dogs with noninfectious, non erosive, idiopathioc, encephalo-myelitis, neuritis or myositis have often a poor prognosis.

2. Intrathecal IgG synthesis can be confirmed by comparing the amount of immunoglobulin in the CSF with the one in serum using albumin as a reference protein. IgG-Index helps to distinguish inflammatory/infectious diseases from other disorders except Distemper in young dogs.

3. IgA can be measured by ELISA. A combined elevation of CSF and serum IgA levels is highly indicative for aseptic suppurative meningitis. Single elevation of IgA in the CSF is rather indicative of primary (infectious or non infectious) or secondary (neoplasia) immune reaction. Other proteins, such as myelin basic protein, S-100 protein and C-reactive protein are not useful in clinical practice; too many disorders are accompanied by an elevation of these proteins.

4. Specific antibodies can be found in the CSF. Pair titers, IgG and IgM titers, Albumin ratio and Immunoglobulin index are run to bypass the possibility of CSF contamination due to blood brain barrier disruption. Canine distemper virus detection can also be performed by indirect immunofluorescent antibody examination.

5. Blood cell count may show a leucocytosis; however it is far from being systematic even with severe meningitis. Eosinophilia may be noted with parasitic origin.

6. Antigen detection is the best test to prove the etiology of an infectious disease. Bacterial or fungal organisms (cryptococcus) may be seen by microscopic evaluation or culture. Polymerase chain reaction (PCR) is becoming a strong sensitive and specific test to confirm or rule out infectious origin. Distemper, Parvovirus, Coronavirus, Feline Immunodeficiency Virus, Feline Leukemia Virus, Toxoplasmosis, Neosporosis, Ehrlichiosis, and other infectious agent are now diagnosed by PCR. Serum and CSF should be tested.

7. Flow cytometry may be requested on mononuclear pleocytosis to confirm monoclonal population. Recently, an association between central nervous system inflammation and polymyralitis has been recognized. Join tap should be performed with CSF collection to confirm a potential multifocal immune connectivitis also associated with renal involvement (detected by proteinuria and confirmed by protein/creatinine ratio). Biopsy may be performed in case of muscle, nerve or even focal brain inflammatory suspicion although it is rarely helpful for a final etiological diagnosis.

How to treat inflammation of the neuro-muscular system?

Encephalitis and myelitis of infectious cause are usually difficult to treat. There is no treatment against Distemper, Feline Infectious Peritonitis or FelV/FIV central nervous system involvement. Interferon is probably the only new drug to try, although antibiotic and steroids may increase the chance of recovery. Toxoplasmosis and Neosporosis should be treated with Clindamycine 10-20 mg/Kg BID. Non infectious encephalitis and myelitis are usually extremely steroid responsive. Immunosuppressive dosage is recommended initially and progressively tapered. An immediate association with other immunomodulating drugs should be proposed systematically to prolong the time of remission on the patient on whom drugs cannot be completely discontinued. Prednisolone, 1 mg/Kg BID initially, tapered to 0,5 mg/Kg every other day within a month, plus either azathioprine, 2 mk/Kg SID progressively tapered, either cytosine arabinosine 100 mg/m2 BID, two days in a row, every 3 weeks are the protocol of choice for the author. Check for neutropenia should be regularly performed the first months.

There is no treatment for the polymyrdiculo-neuritis; steroids do not shorten the recovery time that can last for a few days to a few months, usually with a return of motor function in the opposite way of occurrence, rear limbs last. Steroids are used when a non-infectious polyneuritis or polymyositis has been confirmed by histopathology.

Conclusion

The incidence of inflammatory central nervous system disease and especially non-infectious form is high especially in small breeds of dogs, especially young adult females and in juvenile dogs of large breeds. The majority of peripheral nervous system inflammatory cases are also immune mediated. This explain why steroids is a common drug used in Neurology although it should be used when a tentative diagnosis has been made, not because the clinician expect some blind improvement of its use … The infectious meningo-encephalo-myelitis, neuritis or myositis have often a poor prognosis.

Recommended reading: 1-11


3. Tipold A. Diagnosis of inflammatory and infectious diseases of the central nervous system in dogs: a


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