Inflammatory CNS Diseases

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Objectives:

1. Identify common infectious and sterile/auto-immune causes of CNS inflammation
2. Identify typical breeds associated with sterile inflammatory CNS disease
3. Appreciate the difference between canine and feline species when considering the cause of inflammatory CNS disease
4. Understand the diagnostic approach for animals suspected to have inflammatory CNS disease
5. Be able to outline a treatment and follow-up plan for affected pets

Terms and definitions:

Meningitis: Inflammation of the meninges (covering of the spinal cord). This is a source of pain that can be very severe.
Encephalitis: Inflammation of the brain parenchymal tissues. This causes signs of encephalopathy (specific signs depend on the location affected).
Myelitis: Inflammation of the spinal cord parenchymal tissues. This causes signs of myelopathy (specific signs depend on the location affected).
Meningoencephalomyelitis: We can combine terms if multiple parts of the nervous system are affected. This indicates that the brain, spinal cord, and meninges are all inflamed.
Pleocytosis: Increased white blood cell count in the CSF.

Inflammatory disease can affect the brain and/or spinal cord of both dogs and cats. "Inflammatory" disease is a broad category that can be further divided into two categories: infectious or non-infectious/sterile (usually presumed to be auto-immune) types of inflammation.

In dogs, in 85-95% of cases with confirmed inflammatory disease, the cause is ultimately presumed to be of the sterile/autoimmune category. The opposite is true in cats – non-infectious inflammatory disease is very uncommon.

Inflammatory CNS diseases are common and can be stressful for some veterinarians for a few reasons:

- Severely affected animals can be frightening to see, especially when the disease is progressing rapidly over hours or days.
- There is not a single "best" approach for every inflammatory case – each patient is an individual.
- Specialists might have strong, differing opinions on how inflammatory cases should be managed
- Inflammatory CNS disease feels "nebulous" because it is invisible without advanced diagnostics and can be hard to track progress accurately. This can make it harder for owners to understand because they cannot "see" the cause of the disease.
- Infectious disease tests are not absolute and we can often get "gray-area" results that are hard to interpret.
- Some infectious organisms are drug-resistant which can make it harder to know if we have an incorrect therapy plan for the correct diagnosis or an incorrect diagnosis.
- Some non-infectious diseases can be aggressive and drug resistant which can make it harder to know if we have an incorrect therapy plan for the correct diagnosis or an incorrect diagnosis.
- Prognosis is highly variable, so at the time of diagnosis, it makes it very hard to predict how the individual pet will do in the long-run.

Every neurologist may manage inflammatory CNS diseases a little differently. It is important to remember that there can be many ways to address the same problem. I encourage you to try not to worry about choosing the "right" plan, but to instead follow some general principles. These notes reflect some of the guidelines I like to use when managing these diseases in my patients. I follow a typical methodical case management approach with signalment, history, physical and neurologic exams, diagnostics, therapeutic, and follow-up planning.

Signalment:
Pets of any age and breed can be affected with infectious and non-infectious inflammatory diseases. There is a greater incidence of non-infectious inflammatory CNS disease in young to middle-aged dogs. Very young animals (<4-6 months of age) are more likely to have an infectious cause.

History:
Progression of untreated inflammatory disease is typically over days to weeks. This might be a more slow or "relapsing and remitting" course in cases with incomplete or improper management. I like to ask about any recent travel history, exposure to other animals, time outside in the woods or near stagnant water, vaccines within two weeks of the onset of clinical signs, recent illnesses like GI or upper respiratory signs, etc. If the pet has been on medications, what was the response on the medication? After stopping medication?

Physical exam:
This is performed to look for signs of multisystemic disease. Animals with multiple body systems affected with new disease (ie pulmonary and CNS or brain signs with uveitis) are more likely to have infection or cancers like lymphoma.

Neurologic exam:
This is a crucial step toward identifying a lesion localization. Inflammatory disease can be focal, but is very often multifocal disease. Multifocal CNS localizations indicate one of two scenarios:

1. The same disease in more than one place. This usually means infections, non-infectious inflammation, or cancers like metastatic disease or lymphoma.
2. More than one problem occurring at the same time (like a residual head tilt from an old ear infection and new neck pain from IVDD).

Diagnostics:
I separate diagnostics into "general practitioner level" and "specialist level" testing. At the general practitioner level, tests are tailored to the pet and the clinical signs that you are seeing. Some tests that we might consider include:

1. CBC/chemistry/urinalysis assess general body health in pets of any age. This also offers an opportunity to look for multisystemic involvement (shifting infectious disease higher on your differential list).
   This will also give you an idea of baseline organ function before adding new medications to the plan and seeing the pet's progress over time.
2. Radiographs can be performed of any affected body area to look for pulmonary involvement, masses in the belly or gastrointestinal signs, or areas of pain or lameness.
3. Senior pets might also have hormone evaluations like T4 levels and blood pressure assessments.
4. Cultures or aspirates and cytology of suspicious lesions.

This is the stage when you decide if this is a pet that will need to see a specialist for advanced diagnostics or if it will continue to be managed at the general practitioner level. If seeing the specialist next, then I allow the specialist to determine next reasonable tests based on results from advanced diagnostics. I do this because a dog with a surgical disc herniation causing neck pain does not need extensive costly infectious disease testing.

5. Advanced imaging can be performed to look for structural changes in the brain or spinal cord. MRI is the best test to provide detail of the soft tissues and is the imaging test of choice for inflammatory CNS disease.
6. Cerebrospinal fluid (CSF) analysis is performed in conjunction with advanced imaging to try to strengthen the diagnosis of inflammatory disease. We are looking for signs of increased white blood cell counts (pleocytosis) and protein. If we are lucky, we might see infectious organisms on cytology. The CSF can also be used for special infectious disease tests in addition to blood and urine.
7. In cases in which we find evidence of inflammatory CNS disease in our advanced tests (or if the pet is being managed at the general practitioner level without advanced diagnostics), infectious disease testing can then be performed. This can be tailored to the individual pet considering species and risk factors. Some common CNS infectious diseases include:
    a. Dogs
        i. Distemper, Toxoplasma, Neospora, Blastomycosis (or other regional fungal organisms for areas lived or traveled), various bacterial infections (local invasion versus systemic spread), tick-borne diseases like Ehrlichiosis or Rocky Mountain Spotted Fever
        ii. Don't forget rabies in unvaccinated pets!
    b. Cats
        i. FIV, FeLV, FIP, Panleukopenia virus, Toxoplasma, Neospora, Blastomycosis, Cryptococcus (or other regional fungal organisms for areas lived or traveled), various bacterial infections (local invasion versus systemic spread)
        ii. Don't forget rabies in unvaccinated pets!

<u>Therapy</u>:
Some infectious disease test results come back immediately (like snap tests on the 4Dx or FeLV/FIV), while most take a couple of days or up to a couple of weeks to come back. We are often in the position of having to choose an empirical treatment while we wait for our final infectious disease test results. In these cases, I have to consider both infectious and non-infectious, auto-immune-type inflammatory disease. Because both can be very serious in early stages, I tend to treat for both conditions together until I can narrow my focus with positive infectious disease test results or the test of time and clinical progress. When taking this approach, I tell families that we are trying to "treat for the more easy-to-treat" diseases. This will mean using a steroid and antibiotic combination for a few weeks. Some diseases may resolve with this plan (like a susceptible bacterial infection or limited inflammatory disease), while others may need chronic management or may only be managed for a while (like a difficult inflammatory disease). The following are examples of plans that I choose for dogs and cats. These include anti-inflammatory steroids that are tapered over a few weeks as well as antibiotic combinations that penetrate well into the nervous system and treat a relatively broad spectrum of bacterial and some protozoal diseases.

- **Dogs**
  Prednisone 1-2mg/kg/day to start, then taper off over 4-8 weeks
  Doxycycline at 5-10mg/kg BID for 3-4 weeks
  Clindamycin 12-25mg/kg BID OR sulfadimethoxine 15mg/kg BID for 3 weeks
- **Cats**
  Prednisolone 1-2mg/kg/day to start, then taper off over 4-8 weeks
  Clindamycin 12-25mg/kg BID
  +/- Doxycycline at 5-10mg/kg BID for 3 weeks
  +/- Capstar (for cuterebra candidates) use the label dose every 48 hours for 2-3 doses

**When there is a strong suspicion for non-infectious inflammatory disease, especially in a dog with more rapidly progressing signs and a breed prone to more aggressive autoimmune disease (like a pug or Yorkshire terrier), then I may start prednisone at 2-4mg/kg/day for at least 1-2 weeks before reducing the dose.*

When choosing to start a steroid *before advanced diagnostics*, I also warn owners that if they change their minds about pursuing further testing later, this can make it harder to find certain diseases like sterile inflammatory disease or lymphoma that might become "hidden" with steroid use. For example, if we sample the spinal fluid while on prednisone and it is abnormal, then we know it would probably be more abnormal off of the medication. However if the spinal fluid is normal or border-line then we cannot be sure if it would have been normal anyway or if there is disease being hidden by the prednisone. For that reason, we will ideally do these tests before we start a steroid or when an animal has been off of the drug for a few weeks. That being said, if a pet is already on steroids and cannot function without it, then we can only do our best to interpret tests in light of the needed medication.

If we identify an infection, then treatment is targeted to the specific organism.

What does it mean when infectious disease tests are negative?
About 85-95% or more dogs with active inflammation in the nervous system will have a negative infectious disease test panel result, so this is a common situation. Many doctors will take these results to simply mean we are dealing with an auto-immune disease, however I like to consider a few possibilities:
1. The dog truly does not have an infection and has an autoimmune disease or something similarly unrelated to an infectious agent. This may resolve with the initial medication plans or may prove to be a persistent problem needing longer-term medications to keep controlled. This is the most common situation.
2. The dog has an infection of one of the diseases we tested for and we got a false negative test result. There are many ways to test for the same disease. Even in cases in which we ultimately definitively identify an infectious agent, some of the ways we test for that agent end up negative anyway.
3. The dog has an infection, but we did not run a specific test for it. We can test for many diseases that have the potential to end up in the nervous system. We choose more limited options that are more common or more likely for the individual pet when deciding how to best use the body fluid samples. That being said, it is possible we didn't choose the right diseases to test for.
4. The dog can have an infection that doesn't have a test yet. For every test that is currently available, there was a time in which this test didn't exist and we were trying to figure things out.

When we have negative infectious disease results, this means that there is not a clear SPECIFIC diagnosis for the pet so far from the results - the two most likely categories are an infection that we haven't identified yet and an autoimmune central nervous system inflammation disease (meningitis/encephalitis/meningomyelitis, etc). So, because so many of these options consider the possibility of infection in the face of negative or confusing test results, I often continue a 3-4 week course of antibiotics to be on the safe side in animals that were feeling better with the initial treatment. We then make decisions over time about further tests or ongoing treatment based on progress (including how the pet responds to us stopping certain medications).

Longer-term case that is dependent on prednisone

I like to change one medication at a time to try to provide some logical clarity on what is driving the pet's progress. In these cases, I will usually reduce the prednisone dose at least once before stopping the antibiotics. If doing well a week later, then I might stop the antibiotics after about 3 weeks. If still doing well a week later, then I reduce the prednisone dose again. I reassess the case and make decisions based on progress at each stage.

When I have cases that initially do well in the first few weeks, but then cannot go to lower doses or off of the steroid with relapsing neurologic signs, then I have to consider if this might be a non-infectious/ autoimmune-type disease. In these cases, I increase the prednisone dose back up to at least the lowest effective dose and then I like to add a secondary immunomodulatory medication like Cytarabine or Atopica. Other commonly used drugs include leflunomide, mycophenolate, and azathioprine. This is intended to better control the disease in the hopes that we might have a better chance of reducing the prednisone further. I keep the combined steroid and secondary immunomodulatory agent at the same doses for 1-2 months with stable neurologic condition, before reducing the prednisone dose again. As long as the pet is doing well (balancing neurologic function and drug side effects), I reduce the prednisone dose every 4-8 weeks until either totally weaned off or at least reduced to the lowest effective dose. I will then keep the lowest effective prednisone dose and secondary immunomodulatory agent at the same doses for another 3-6 months. If stable, then I might start to reduce the secondary immunomodulatory agent until either weaned completely off or at least reduced to the lowest effective dose.

This can be a long process and your careful re-evaluations and close communication with the owner will be crucial to making sure you are on the right path for this pet. I give owners some expectations in the beginning for what I want for minimal long-term follow up. This might look like:

If your pet is relapsing on lower doses of prednisone and we are looking at a much longer term (sometimes life-long) treatment plan with chronic prednisone and/or adding secondary immunosuppressive medications, we have to see your pet more often for examination and blood testing to be sure the medication is having the effect we want and that there are no concerning changes in organ function. Animals must be examined and have periodic blood tests according to the MINIMUM schedule if things are going well. This will be advised more frequently if your pet has bloodwork abnormalities or is not feeling well. Your pet should return to a veterinarian sooner than scheduled if not doing well.

Baseline exam and CBC/chemistry before starting the drug:
2 weeks – recheck exam
4 weeks – recheck exam and CBC/chemistry (sometimes additional tests like cyclosporine drug levels)
6 weeks – recheck exam
8 weeks – recheck exam and CBC/chemistry
12 weeks – recheck exam
16 weeks (4 months) – recheck exam and CBC/chemistry
24 weeks (6 months) – recheck exam and CBC/chemistry
Then full examination and bloodwork every 6 months after that if your pet is stable.

Prognosis:
Time will ultimately tell you if a non-infectious CNS inflammatory disease is a good disease or a bad disease. In the early stages, we are trying to determine if this is a limited disease or if the pet will require a much longer course of treatment. We can expect the following scenarios as being most likely:

1. The pet does very well on medication, returns to more normal over several weeks, and does not relapse off the medication. In that case, we are hopeful to have treated an infection or more limited inflammatory disease. About 1/5 of canine cases might fall into this category.
2. The pet is difficult to manage and we can't seem to get the disease controlled well. These cases can continue to progress no matter what we do. In those cases, I wonder about a drug resistant infection, an infection we are not actively treating for (like a fungal disease), or an aggressive drug-resistant non-infectious inflammatory disease. About 1/3 of canine patients might fall into this category longer term, though I find it is not common for me to have patients unable to leave the hospital at the time of diagnosis.
3. Most dogs with non-infectious inflammatory CNS disease fall somewhere between scenario #1 and #2 with disease that may get worse on lower doses of steroids or off the drug. These cases may need medication for over a year, or sometimes a lifetime to keep controlled and allow animals to feel more normal. This is a disease that behaves like multiple sclerosis in that regard - every patient may respond a little differently and we have to tailor the treatment plan to that individual's progress over time.

The above approach is a generic application that can be used for many types of inflammatory CNS disease. There are several separate disease entities which I will outline below. All of these require a similar diagnostic and therapeutic approach. For all of these, the key diagnosis is obtained via biopsy or necropsy. This is obviously invasive (or unreasonable!) testing for an otherwise functional dog. We therefore try to use clues from the signalment, history, MRI findings, and CSF results to help guide us toward one of these diseases. Without a definitive diagnosis, we use the term “meningoencephalitis of unknown origin, MUO” or “meningoencephalitis of unknown etiology, MUE”.

Necrotising meningoencephalitis

- "Pug dog encephalitis" – pug predisposition, though other small breeds can be affected like maltese, Pekingese, chihuahua, and shih tzu
- Juvenile to young adult dogs: Median age is 18 months
- Cerebrum signs only (gray and white matter effacement)
- Can be one of the more aggressive and challenging to treat inflammatory diseases

Necrotizing leukoencephalitis

- "Necrotizing Encephalitis of Yorkies" – yorkies and frenchies are predisposed
- Can occur in the cerebrum or brainstem (white matter)
- Can be similarly aggressive and challenging to treat

Granulomatous meningoencephalitis

- Small dogs are predisposed, but can affect dogs of all sizes. Increased prevalence in small terriers, miniature poodles, maltese, dachshund, chihuahua.
- Young to middle-aged dogs are most common – youngest reported is 6 months of age.
- Can occur in any part of the brain and spinal cord. Can also affect the optic nerves.
    - Ocular (optic neuritis)
    - Focal (a single mass-like lesion)
    - Multifocal is the most common form
        - Only 8% will have only spinal cord signs
- Young to middle-aged dogs are most common – youngest reported is 6 months of age.
- Can occur in any part of the brain and spinal cord. Can also affect the optic nerves.

Idiopathic Generalized Tremor Syndrome/Idiopathic cerebellitis

- "Little White Shaker Syndrome"
- Can be any breed – not just little white dogs!
- Predominantly cerebellum, but can include parts of the forebrain or brainstem
- Good chance of resolving over several months

Steroid-Responsive Meningitis-Arteritis

- "Beagle Pain Syndrome" – beagles, boxers, Bernese, bulldogs most common but can occur in any breed
- Tend to be younger to middle-aged dogs – range of 4 months to 7 years
- Spinal cord disease – primarily the meninges
    - Usually severe pain with normal strength and proprioception, though hemorrhagic lesions can cause paresis and proprioceptive ataxia
    - Can also see a polyarthritis
    - Can see a systemic response with fever and increased WBC's in the CBC
- Good chance of resolving over several months – 60-80% of cases are weaned off of medication long-term

References

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