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Steroid Responsive Meningitis-Arteritis: A Retrospective study of 37 dogs from Hungary and Norway

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1. Preface

As most veterinary students I love dogs, and in 2014 I adopted my second shelter dog from Hungary. It was the happiest moment of my life when I picked the 2-year-old Beagle, Nala. But the happiness didn't last for too long. Only one month after I adopted Nala, she became very sick. We thought it was due to the fact that she was castrated the week she was adopted, but the symptoms didn't correlate with the clinical findings. She was in severe pain, and she was reluctant to move or eat. Also she had a fever (40,2 °C) lasting for days. My veterinarian took a thorough clinical examination of the dog, including blood test, ultrasound and x-rays without any findings leading to what could cause the pain. She was given both antibiotics and NSAIDs for a week, without improvement. As the time went by, Nala became so ill that she was referred to the Small Animal Clinic at the Veterinary University in Budapest. They suspected 'beagle pain syndrome' or 'steroid-responsive meningitis-arteritis' and a CSF sample was taken. The result revealed neutrophil pleocytosis in the CSF and the diagnosis was therefore finally concluded to be SRMA.

As a veterinary student, eager to learn, I started to read and research online for articles about this syndrome. But the knowledge and experience about the treatment of this disease was vague. Therefrom I started to work out my very own treatment regimen to suit my dog. It was not an option to keep the dog on high dose prednisolone each time she got a relapse as the treatment recommendation was in the books, because she was relapsing many times. There were too many side effects, and the dog had a reduced life quality with the on and off prednisolone mega-dose. So instead of euthanizing the dog, I tried one last thing; combining prednisolone with other immunosuppressive drugs, with the goal to reduce the side effects. The dog is still happily alive today, two years later, even though she's permanently on medications.

This personal experience made me wonder what happens to other dogs diagnosed with steroid-responsive meningitis-arteritis? How are they treated and are they treated again with new drugs if they relapse after a prednisolone tapering, or are they euthanized?

2. Abbreviations & Definitions

APP: Acute phase protein

CNS: Central nervous system

CRP: C-reactive protein

CSF: Cerebrospinal fluid

GME: Granulomatous meningioencephalitis

IgA: Immunoglobulin A

MRI: Magnetic resonance imaging

NSDTR: Nova Scotia Duck Tolling Retriever

PCR: Polymerase chain reaction

SAA: Serum amyloid-A

SLE: Systemic lupus erythematosus

SRMA: Steroid-Responsive Meningitis-Arteritis

WBC: White blood cells

AUTOIMMUNE DISEASE: When the dogs own immune system attack one or more organs in its own body.

LEFT SHIFT: an increase in the number of immature leukocytes in the peripheral blood, particularly neutrophil band cells.

MENINGITIS: Inflammation of the meninges: The pia-, arachnoid- and dura mater; protective membranes covering the brain and spinal cord.

MONONUCLEAR PLEOCYTOSIS: refers to a predominance of lymphocytes and macrophages in the CSF.

PLEOCYTOSIS: Increased nucleated cell counts in the CSF

SIGNALMENT: that part of the veterinary medical history dealing with the animal's age, sex and breed.

SPORADIC DISEASE: a disease which occurs in single and scattered cases.

STAB CELLS: Also called band cells. Young granulocytes.

3. Introduction

Steroid-responsive meningitis-arteritis (SRMA) is a non infectious inflammatory disease of the meninges and its arteries. It is most likely immune mediated, but the etiology is still unknown. In fact, it is one of the most important and common inflammatory diseases in dogs.[1,2] The disease was first described as juvenile polyarteritis syndrome (JPS) in young laboratory Beagles used for toxicological studies, and the first case study was published already in 1973.[1, 3, 14] The disease is well known in small animal clinics, and have been described world wide. In human medicine, the clinical picture of SRMA is similar to the Kawasaki Syndrome which was already described in Japan in 1967.[15]

There are several different studies regarding the etiology, pathogenesis and treatment regimen of this disease, hence all these different names of the very same condition; juvenile polyarteritis syndrome, necrotizing vasculitis, beagle pain syndrome, canine pain syndrome, and now today steroid-responsive meningitis-arteritis. The term SRMA is probably the most commonly used name today, and it indicates both the pathology and the treatment.[3] The disease shows up in an acute form and if not treated properly, a chronic form may develop. The acute form occurs with a quick onset, and usually starts between 6-18th months of age. After steroid treatment it usually disappears. The chronic form will develop after an acute form is unsuccessfully treated, and it may require lifelong treatment.

Genetic predisposition has been question, and it seems like genes play a role in some breeds. It occurs most often in medium and large-breed dogs, less than 2 years of age, but it is reported to occur in dogs over 7 years old, so potentially, it can occur in any age. The most predisposed breeds are Beagles, Bernese Mountain Dogs, Nova Scotia Duck Tolling Retrievers, Boxers and German shorthaired pointers, but it may affect any other breed as well. There's no data on gender predisposition.[5]

Despite the fact that this disease has been known for years and that it is quite frequently seen in small animal practice, there are still unanswered questions concerning the disease today; there is no known definite etiology, pathogenesis and no permanent treatment proven to be effective for all dogs.

Like the name of the disease indicates, the most effective drug-group used to treat this syndrome is corticosteroids, like prednisolone. Treatment results have been reported to have varying outcome. Acute cases have better prognosis than the chronic ones.

The aim of this retrospective study is to evaluate statistically the cases administered to the Veterinary University of Budapest between January 2004 and June 2016 with beagle pain as a possible diagnosis. Additionally, four similar cases from a small animal clinic in Norway was added to the studies. We describe certain aspects of the disease like breed predisposition, age, gender. We also collect and resume the standpoints of examination and treatment.

4. Literature review

4.1. CNS diseases – A general overview

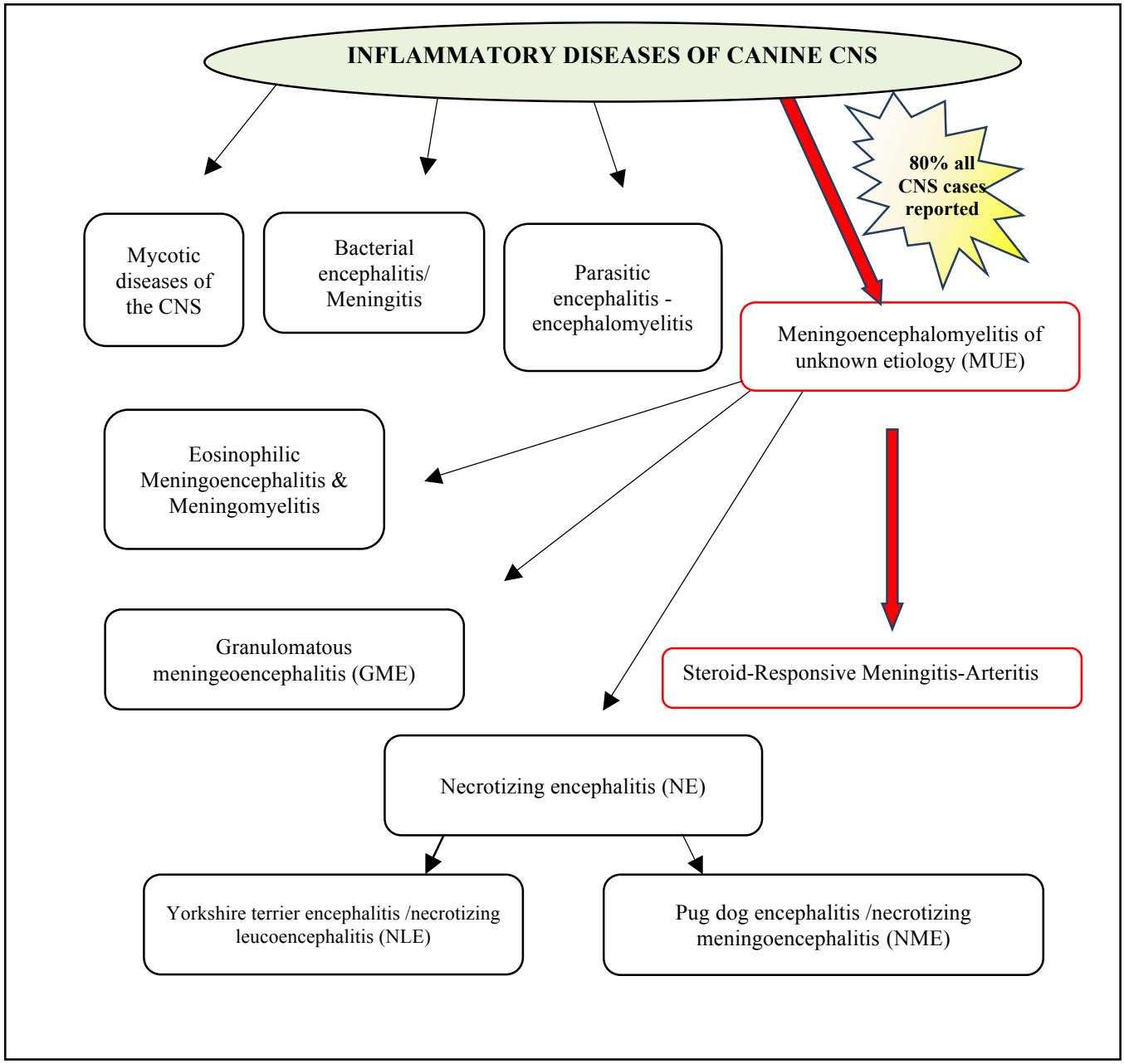

Fig. 1: An overview showing the related Inflammatory diseases of the CNS.[5]

The inflammatory CNS diseases in general is classified into two main etiologies; infectious and noninfectious etiologies, with the latter being related to a potentially immune system dysfunction. Around 80% of the cases in Europe and USA goes under this category, the so called meningoencephalomyelitis of unknown etiology (MUE).[2]

Although there are characteristics that differs these disease conditions from each other, there are also cases that blur the lines between these diagnoses. Therefore, researchers and clinicians are divided on wether to "collect" or "split" these conditions in Figure 1.[10] The most common MUE is SRMA, with all its different name changes over the last years. Among the names used about this one single condition are beagle pain syndrome, canine pain syndrome, corticosteroid-responsive meningisti/arteritis (CRMA), corticosteroid-responsive meningomyelitis, necrotising vasculitis, polyarteritis, panarteritis, juvenile polyarteritis syndrome, primary periarteritis, necrotizing vasculitis and aseptic suppurative meningitis. All these names reflect not only the dearth of knowledge about this condition but also the important clinical signs such as pain resolved with corticosteroid therapy, and histologic involvement of the meninges and arteries. [2]

4.2. The SRMA diagnosis

The diagnosis of inflammatory CNS diseases in small animal patients is based on many factors combined in signalment data, clinical signs, and results of diagnostic testing like hematology, CSF and MRI. The most useful test are MRI and CSF analysis.[9]

4.2.1. Signalment data

Age: SRMA is considered a juvenile disease and clinical signs typically starts at 6-18 months of age, although any age may be effected. There is reported animals already from four months of age but symptoms can emerge even at 7 years.[2] One study have suggested that resistance to relapse develop around 2 years of age.[3]

Breeds: Beagles (especially, but not exclusively those in laboratory-bred colonies, appears to be at risk)[2], Bernese Mountain dogs, Boxers, German shorthaired Pointers, Nova Scotia Duck Tolling Retrievers (NSDTR), Weimaraners and sporadically other breeds like Whippets [4, 5] are concerned.

Gender: There is no specific gender predisposition reported from the cases in the articles.

4.2.2. Clinical signs

From the owner's point of view, the first complaint is usually inappetence, listlessness and the dogs seems to move differently, or doesn't want to move at all (due to pain along the entire spinal cord).

Both the chronic and the acute forms of SRMA have the very same clinical signs, but they differ in insensity and duration. The most common finding at clinical examination is the marked pyrexia. The fever will wax and wane in the beginning of the disease (40-41'C). [4] Other findings include rigid cervical region incapable of being bent, short-strided and creeping gait, arching of the back with a lowered held head, back pain on palpation, spontaneous yelps when touched, due to hyperesthesia. The pain in neck region and through the whole length of the vertebral column tend to reoccur as the disease progresses. A more prolonged, chronic, form of the disease may be seen following inadequate treatment, including more frequent relapses. Although neurologic deficits are uncommon in these dogs with SRMA, ataxia, paresis, paralysis may develop as a result of concurrent myelitis, spinal cord hemorrhage, or infarction.[4]

4.2.4. Hematology

Blood work results can be normal or peripheral neutrophilia with a left shift can be seen, especially in the acute cases.[11] There is also reported increased erythrocyte sedimentation in the majority of dogs with either acute or chronic disease, and an increased IgA serum concentration can be seen.[16] Also several acute phase proteins have been found to be consistently elevated in the patients with this disease. [11] CRP is the primary major canine acute phase protein (APP) and has been shown to respond immediately to both the onset and resolution of inflammation. Other APPs include elevated serum amyloid-A (SAA), haptoglobulin, alpha-1-acid glycoprotein (AGP)[16] and alpha-2-globulin fraction.[2] Serum CPR levels have been reported to be significantly higher in dogs with SRMA compared to dogs with other neurological diseases.[16] A recent study of 9 dogs diagnosed with SRMA reveals a significant increase in all serum APPs, which all decreased (with the exception of haptoglobin) in response to corticosteroid treatment.[16] Serum CRP and SAA were also found to be consistently elevated in all dogs exhibiting clinical signs consistent with a relapse during treatment in the presence of normal CSF and leucograms.[16] But, as with the IgA elevation, the CRP is also considered to be nonspecific, as this can also occur in case of other inflammatory conditions, and can only be used as a supportive diagnostic test.[16]

4.2.5. CSF

The sample can be collected either from the atlanto-occipital site or from caudal lumbar site. 1ml per 5 kg bodyweight can be safely collected from most dogs. Evaluation of a CSF is made based on detection of deviations from the normal findings:

Characteristics	Normal findings
Assessment of gross physical characteristics: colour and clarity	Colourless and transparent
Total protein	Cisternal tap: 14-30 mg/dl Lumbar tap: 30-45 mg/dl
Cell count	Red blood cells: 0/μl (excluding iatrogenic blood contamination) White blood cells: <5/μl
*Microsco*pic examination with differential leucocyte count	Lymphocytes: 60-70% Monocytes: 30-40% Neutrophils: <1% (excluding iatrogenic blood contamination) Eosinophils: <1% Ependymal lining cells: rare

Fig. 2: Normal findings from CSF.[16, 19]

*The CSF sam*ple may show false if it is not evaluated within 1 hour after taken, but if stored in a fridge, it can safely be stored for 8 hours without affecting the diagnostic interpretation.[16]

According to some authors the most important diagnostic tool, which can be even the gold standard of SRMA is the cytological examination of CSF.[9]

Analysis of CSF in SRMA patients typically reveals elevated white blood cell amount (pleocytosis), usually with marked neutrophil and protein elevation.[16] Netrophilic pleocytosis is defined as >50% neutrophils.[19] However, the degree of pleocytosis can be variable, but it often exceed 100 cells/μL where more than 75% are neutrophils.[4, 9] The neutrophils are non-degenerative and less in number, compared to those seen in bacterial meningitis. In case of suspect of bacterial infection, a culture should be made from the CSF sample.[16]

High immunoglobulin A concentrations can be found in both CSF and serum (>90% of the dogs), aiding diagnosis, but this finding lacks specificity, because it is seen in connection with other inflammatory CNS diseases aswell.[4, 16] The elevated IgA levels are true for both the acute and the chronic disease. The sensitivity for IgA concentration in the CSF and serum was 91% with a specificity of only 78% in a study that evaluated 311 dogs with SRMA.[16] Total protein concentration is usually elevated with values around 100 mg/dl.[19] A single dose of prednisolone can change the picture of a CSF analyses within 24 hours. [7]

Acute cases: The CSF results usually show a severe pleocytosis, mainly consisting of mature non-degenerative neutrophils and increased protein content.[2,11]

Chronic: In chronic cases the CSF is often less dramatic. Mononuclear cells are often overrepresented without elevated protein concentration.[11] This have been suggested to develop from a later recognition of the disease or inadequate treatment like premature taper of steroids.[5]

4.2.7. Diagnostic imaging

Diagnostic imaging includes radiograph, CT, MRI. It is often unremarkable in this condition, but may show meningeal enhancement. [9] It is mostly used in connection with differential diagnosis.

4.2.8. Differential diagnosis of neck pain

4.2.8.1. Degenerative diseases

Intervertebral disc disease (Hansen type I and II): Spinal cord compression due to intervertebral disc extrusion or protrusion is one of the most common clinical neurological disorders. Disc herniation can cause pain, without obvious neurological deficits; the severity of the pain may mimic the symptoms of SRMA. Diagnostic imaging like radiography, myelography, CT or MRI can help to establish the diagnosis.[16]

Cervical spondylomyelopathy (Wobbler syndrome): Most common in Dobbermans and Great Danes, but many other breeds have been recognized with similar abnormalities. Pain may be the only clinical sign, but pelvic limb ataxia, pelvic limb paresis and ambulatory tetraparesis are commonly associated with the discomfort. The diagnosis is based on imaging (myelography, CT, MRI).[16]

Spinal synovial cyst: Extradural spinal synovial cysts, originating from articular facet joint capsules, that cause compression of the spinal cord have been described in dogs. They are most commonly found in cervical vertebrae in giant-breeds with cervical spondylomyelopathy, but can occur in the lumbosacral spinal canal. All the reported dogs with cysts located in the cervical region had cervical pain. This is not the case with the thoracolumbar cysts. The diagnosis is based on imaging (myelography, CT, MRI).[16]

Spondylosis deformans: Spondylosis deformans is a degenerative, non-inflammatory, proliferative disease. Usually the formation of osteophytes is without any clinical signs, but sometimes the osteophytes compress the nerve roots and can cause pain along the vertebral column. The diagnosis is based on spinal radiography, but demonstrating soft tissue and neural tissue involvement requires advanced imaging such as MRI. [16]

4.2.8.2. Developmental anomalies

Atlantoaxial instability: Atlantoaxial instability can lead to subluxation of the first and second cervical vertebrae; the cranial aspect of the axis often rotates dorsally with respect to the atlas, into the vertebral canal. Subsequent spinal cord compression results in a variety of neurological signs, but may just cause neck pain. The signs usually starts in

young animals and can develop acutely or gradually, and waxing and waning of signs is often reported. The diagnose is based on radiographs.[16]

4.2.8.3. Inflammatory conditions

Infectious diseases

Meningitis/Meningomyelitis: Infectious diseases include canine distemper virus, protozoal, rickettsial, algal and fungal diseases. This condition is also often associated with a neutrophilic pleocytosis. Neutrophils associated with infectious disease are more likely to degenerate that those in the case of SRMA and other noninfectious disorders.[11]CSF sample is used to diagnose these diseases, and a culturing of the fluid is highly recommended in order to distinguish this disease from SRMA.

Discospondylitis/osteomyelitis: Discospondylitis is due to infection of the intervertebral disc and adjacent vertebral endplates. If the infection is confined to the vertebral body, it is called osteomyelitis or spondylitis. Coagulase positive Staphylococcus spp. are the most common etiological agents associated with canine discospondylitis. A definite diagnosis is usually made with spinal radiographs, although radiographic changes may not be evident in the first 2-4 weeks of infection. [16]

Non-infectious - Granulomatous meningoencephalitis (GME): GME is a non-suppurative CNS inflammatory disease of undetermined aetiology in dogs. It is suggested to be the result of a T cell-mediated delayed-type hypersensitivity.[16] This condition may involve the spinal cord at any level; however, lesions appear to be most severe in the cervical spinal cord. The clinical findings include neck pain, rigity, inappetence, hyperestesia and neurological deficits. The cytologic picture from the CSF can be similar or the same in SRMA as in case of GME. They can both typically show a moderate to severe mononuclear or neutrophil pleocytosis. And in some very rare cases the cytology for both diseases can be normal. Therefore, MRI is necessary to differentiate SRMA from GME. This condition, in similarity to SRMA, responds well to corticosteroids. [16]

Idiopathic polymyositis: The main clinical sign of disease affecting skeletal muscles is weakness; however, muscle pain (myalgia), can sometime affect the neck region and be expressed as spinal pain. A stiff, uncomfortable gait in all limbs is usually accompanied

by an arched thoracolumbar spine (kyphosis) and ventroflexed neck. Pyrexia may be feature of the disease, just like in SRMA. Diagnosis is based on multiple findings; appropriate clinical signs, elevated serum creatinine kinase concentration, negative infectious disease titers and muscle biopsy sample showing signs of inflammation. This condition is often responsive to prednisolone treatment in similarity to SRMA.[16]

Polyartheritis: Polyartheritis is generally classified as either infectious or non-infectious, where the latter is related to an immune-mediated problem. The disease can affect multiple joints, hence the name. Immune-mediated can be either erosive or non-erosive. Typical clinical signs are spinal pain, but there is also appendicular joint pain. Typically, animals appear to be 'walking on eggshells', and are reluctant to lie down or rise once down.[16]

4.2.8.5. Trauma

Vehicle-related accidents is the most common exogenous cause of trauma of the spine in small animals; however, falling from heights, kicks from horses and hitting objects. Depending on the type of force, the area of impact and the strengths and weakness of the vertebral column, any spinal trauma can lead to spinal cord compression due to vertebral fracture, subluxation or luxation. In this case diagnostic imaging together with the history is most informative to differentiate the trauma from SRMA.[16]

4.3. Etiology

Even though a definite known etiology is not found yet, there are many different suggestions. Among them are the immune mediated etiology, the infectious and the genetic predisposition the most frequently suggested causes. The disease is most probably a multifactorial disease. Some dogs may be more genetically predisposed to handle environmental challenges in a different way that then leads to disease.[12]

4.3.1. Noninfectious (Immune mediated due to IgA)

From more recent studies, it appears that an immune event, specifically directed to the CNS occurs in the affected dogs. This is indicated by the serum and CSF IgA concentration. The increase of IgA indicates that there is an autoimmune reaction

involved.[5] No specific pathogen found in the serum and CSF and the good response to immunosuppressant drugs also underbuilds this etiology.

4.3.2. Infectious

It is possible that an unidentified infectious agent may be involved in the development of the disease, although today, no virus or bacteria are associated with the disease. However, a recent report shows DNA from *Anaplasma phagocytophilum* in 4 out of 23 cases of dogs diagnosed with SRMA.[5] The pathogen is not thought to be in direct cause of the disease, but according to a hypothesis it is a combination of the environment and genetics, that elicit the inflammatory response. The geographical relation of this case study is not specified.[5] Also activated T-cells have been found in some dogs, indicating the cells have been in contact with some kind of pathogen.[2] Antibiotics are not proven to be effective in the treatment of SRMA yet.

4.3.3. Genetic or not?

Autoimmune diseases are more frequently seen in a population if it is rather small, with narrower gene pools. This is the case for the NSDTR breed, which has its origin from only a handful of dogs when it got approved as breed in Canada in 1945, where the breed originates from. The Norwegian Kennel Club estimates that about 5% of the NSDTR dogs will be affected by an autoimmune disease, and this is mainly the SRMA, but also the Systemic Lupus Erytematosus.[8]

Dogs diagnosed with SRMA is forbidden to use in breeding, since the disease is suggested to be hereditary.[8]

In the UK, there have been done some research on the Nova Scotia Duck Tolling Retriever, since it is reported to be a breed predisposed to develop SRMA. The aims of the study were;

1. To establish the incidence of the disease in the UK population of NSDTR's.
2. To investigate the etiologic factors involved in the condition developing this condition.
3. To find the possibility of SRMA to be an inherited condition in this breed.

By this study they were able to establish firstly that dogs identified in the study confirmed with the disease were less in-bred than the control group of healthy dogs, and secondly

that there is most likely a simple autosomal recessive inheritance pattern in NSDTR's with SRMA.[7]

In Beagles a study at the Canine Genetics team, UK was carried out in 2010. A whole genome association scan was carried out on DNA samples from 47 Beagles, where 26 of them were suffering from SRMA and 21 of them were control cases with healthy Beagles. This type of scan allows to compare the genomes of dogs affected with SRMA to the genomes of healthy dogs and to pinpoint any regions where a clear difference can be seen. Such regions are likely to be associated with the disease and may contain mutations in genes that are involved with SRMA.[18] The author concluded; "Although the genotyping was carried out successfully, the study failed to identify any regions of the genome which were clearly and significantly associated with the disease. The genotyping data we generated was of high quality, so the likely explanation of our failure to identify a region of the genome associated with SRMA is because the disease is more complex than was originally thought. Either because SRMA is caused by more than one gene, or the interaction between genes and the environment. In either of these cases the solution is to collect and genotype more samples, and any new data can be added to what we already have, thus increasing the chances of success. This is a disappointing result in some ways, but as a result of this investigation we now can say fairly confidently that SRMA in the Beagle is not inherited as a simple autosomal recessive disease with a high degree of penetrance, and that more samples need to be analyzed to identify a genomic region associated with the disease. "[18]

4.4. Treatment and management

As for any CNS inflammatory condition, corticosteroids are a mainstay of therapy in CNS inflammatory diseases of unknown origin. Dogs presenting in the acute stages usually responds completely to immunosuppression with corticosteroids, and additional immunosuppressive drugs are rarely required. However, it is recommended to give additional analgesics, e.g., tramadol.[11] If there is concern about an infectious etiology, antibiotic able to cross the blood-brain-barrier can be co-administered for 2-4 weeks. The generally most accepted treatment protocol among small animal practitioners is the one described in Figure 3. It includes prednisolone given in tapering doses.

Chronically affected dogs may require additional immunosuppression.[9] This may be seen following inadequate treatment, including relapses. It is reported that approximately half

of the treated dogs will require a long-term immunosuppressive therapy or additional immunomodulatory drugs for this disorder (e.g., azathioprine, cyclosporine). Especially for relapsing cases, these other drugs are recommended, to minimize the side effects of corticosteroids.[11, 12]

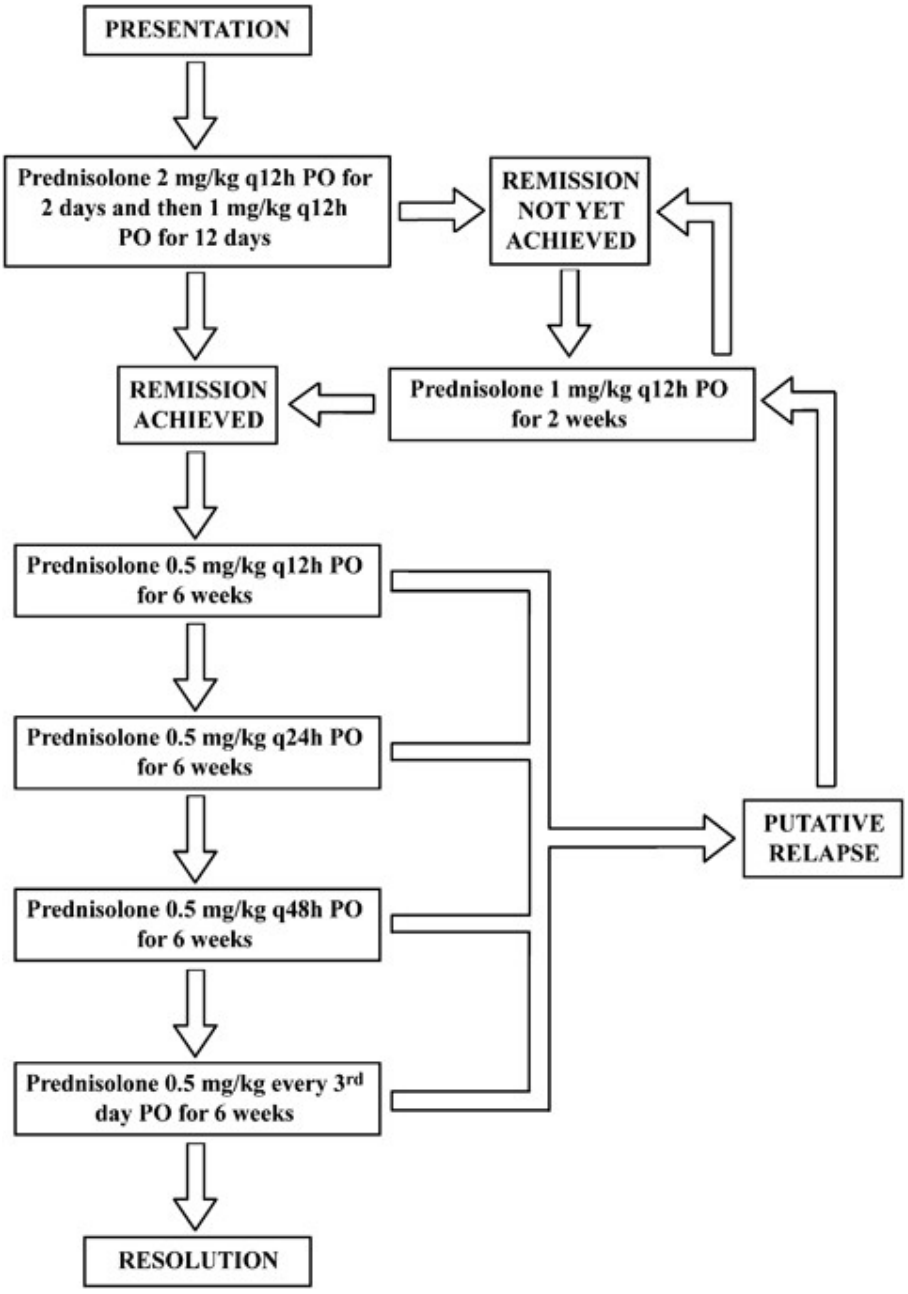

Fig 3. Treatment schedule for canine patients with steroid responsive meningitis-arteritis commencing with immunosuppressive doses of prednisolone using a schedule adapted from other studies. (q12h: twice daily; q48h: every other day; PO: per os; q24h: once a day). [3]

4.5. Prognosis

In the acute disease, the prognosis is considered favorable, if the patients are treated appropriately and promptly using immunosuppressive doses of corticosteroids aggressively to begin with, following a 6-8 months long tapering period. In dogs with a chronic or untreated situation the dogs tend to have a remitting and relapsing course and the prognosis is fair to guarded.[2,11] Owners of dogs with persistent disease or frequent relapses are often discouraged, both by the side effects of the treatment as well as the cost of diagnostic workups. Death due to complications of the condition, or euthanasia due to the prominent side effects of the glucocorticoids.[12]

4.6. Pathology

As the name of the disease indicates, Steroid-Responsive Meningitis-Arteritis, causes inflammation in both the meninges of the brain and its arteries. Some of the affected animals show lesions of vasculitis elsewhere, like the joints, coronary arteries, skin and testicles. Another lesion reported is hemorrhages within the spinal canal.[12] A Hungarian autopsy report of a Beagle with SRMA reveals apparent mediastinal lesions. Well circumscribed greyish-white, firm nodules were seen around the extramural coronary arteries. Similar nodules appeared in other organs as well. In the same report necropsy findings included spinal subdural, extra-medullary hemorrhages in the cervical region (Figure 4). In the brain stem multiplex hemorrhages was found which was varying in size from a dot-like to a cherry sized. The largest hemorrhage caused apoplexy of the brain tissue (Figure 5).[13]

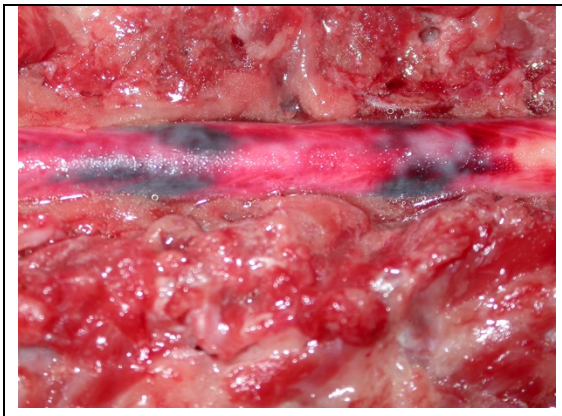

Figure 4.[13]

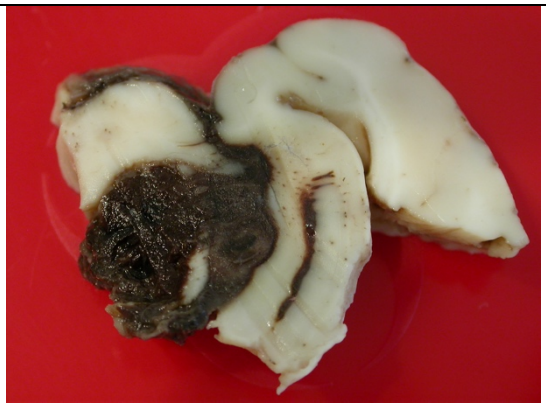

Figure 5.[13]

Histologically the report describes the examination of suppurative and nectrotizing vasculitis affecting multiple arteries in several organs (Fig. 6). Some of the lesions appeared as progressive fibrinoid necrosis in the wall of the small and medium-sized arteries frequently with dense inflammatory cell infiltration (Fig. 7)[13] The report further describes the infiltration cells found; "The infiltrating cells were predominantly neuthrophils with closely the same amount of lymphocytes, few monocytes, macrophages and plasma cells. High number of neutrophils in the adventitia and fewer in the tunica media was seen. Insudation, accumulation of substances derived from the blood in the arterial wall, could be recognized in the tunica intima in the epididymis. Neither eosinophils nor mast cells were observed to any significant degree. Thrombus formation with partial or total occlusion of the vessel lumen was also seen."

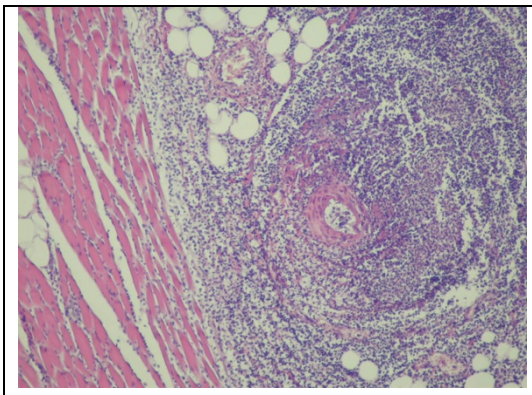	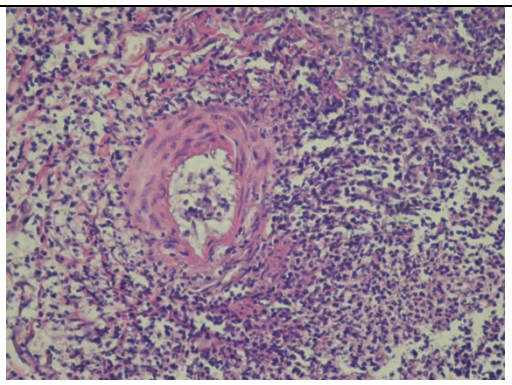
Figure 6.	Figure 7.

5. Material and Methods

5.1. Collection of the Hungarian cases

The data evaluated were selected from the electronic data base (DOKI system) at the small animal clinic at the University of Veterinary Medicine Budapest, Hungary.

63 dogs were collected that had 'beagle pain' as diagnosis or differential diagnosis in the system between January 2004 and June 2016. After thorough evaluation of all the available records (history, physical findings, laboratory results, reaction to treatment) of each dog, 33 cases were confirmed as beagle pain cases. The available data of the selected cases regarding nationale (breed, gender), age at disease onset, physical findings (fever, inappetence, pain at mouth opening, stiff gait), laboratory findings (hematology, CSF results) were statistically evaluated. Hematology and cytological examination of the cerebrospinal fluid was made by the central laboratory of the university.

5.2. Collection of the Norwegian cases

We collected all the SRMA cases from Tromsø Veterinary Hospital between January and December 2014. Four cases were collected from the hospital's computer system, VetServe. The hematologic examination was all done on the clinic with QBC hematology analyzer by the treating veterinarians.

5.3. Processing of the data

After careful and detailed evaluation of all the 67 dogs on the basis of the available data we selected 37 cases that were regarded as real beagle pain cases.

For the selection the history, clinical signs, laboratory results of blood- and CSF samples were used.

6. Results

67 dogs were collected from the databases between 01.2004 - 06.2016 from both Hungary and Norway. The number of confirmed cases suffering from SRMA were 37 dogs all together (33 Hungarian and 4 Norwegian case).

During the same period 64087 new patients were registered in the Small Animal Clinic of the University of Veterinary Medicine in Budapest. 1057 of them were beagles and 13 beagle mixes.

Beagles and Beagle mixes represented 1,7% of the new patients. 2,5% of Beagles and Beagle mixes was presented to the clinic with beagle pain. Beagle pain represented 0.05% of the admissions at the Veterinary University in Budapest, Hungary during the given period.

6.1. Signalment and History

The signalment data are age, gender and breed. The age of onset is defined as the age when the dog was brought in to the clinic for the first time in connection with the disease. The findings were like the literature indicates; SRMA most often affect young dogs, but the condition may occur at any age (between 3 months and 6 years), like seen in Figure 8. The median age at time of presentation was 11 months.

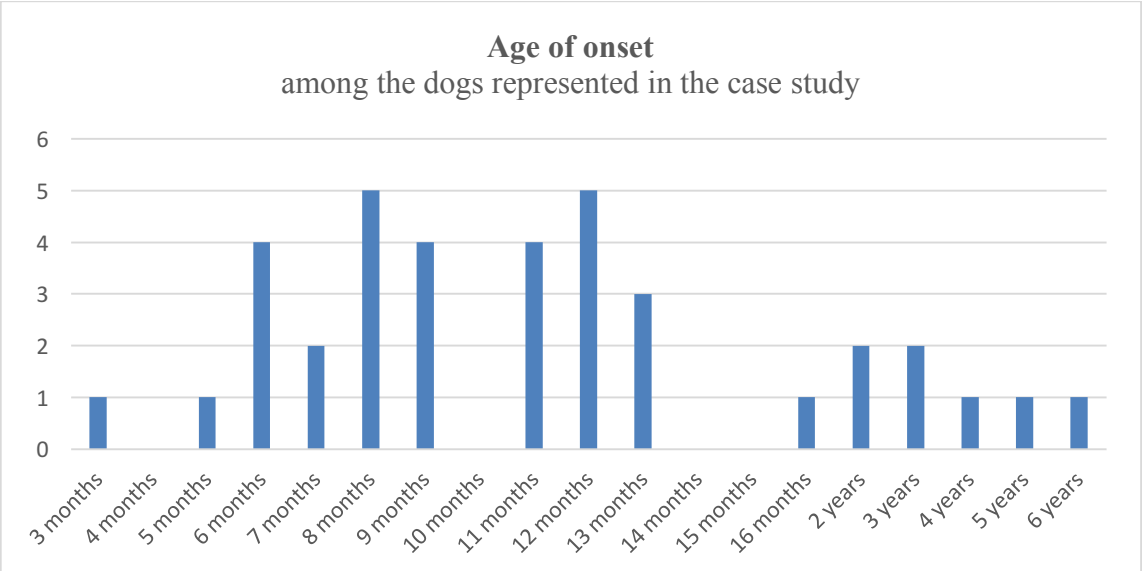

Fig. 8: The number of dogs (y) distributed at the certain age (x). The total number of dogs was 37.

The gender ratio reveals that the genders were equally represented when added together (figure 9). There is no gender predisposition indicated.

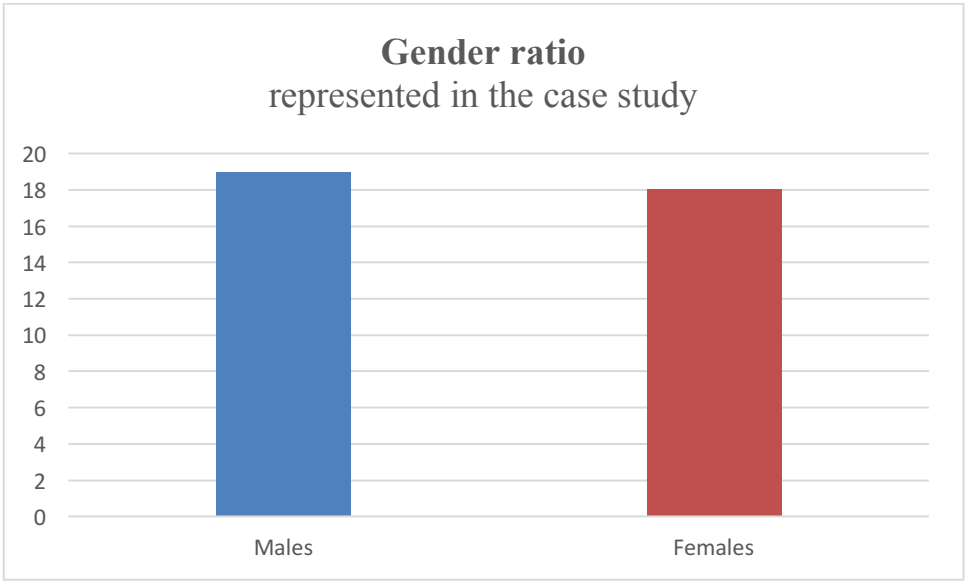

Fig. 9: The gender ratio among the 37 dogs; 19 males and 18 females.

7 different breeds were included in this study. Breeds represented involves 28 Beagles and 4 Nova Scotia Duck Tolling Retrievers and 1-1 of each of the following breeds: Whippet, German Shorthaired Pointer, Hungarian Vizsla, Bernese Mountain dog and mixed dog (Fig. 10).

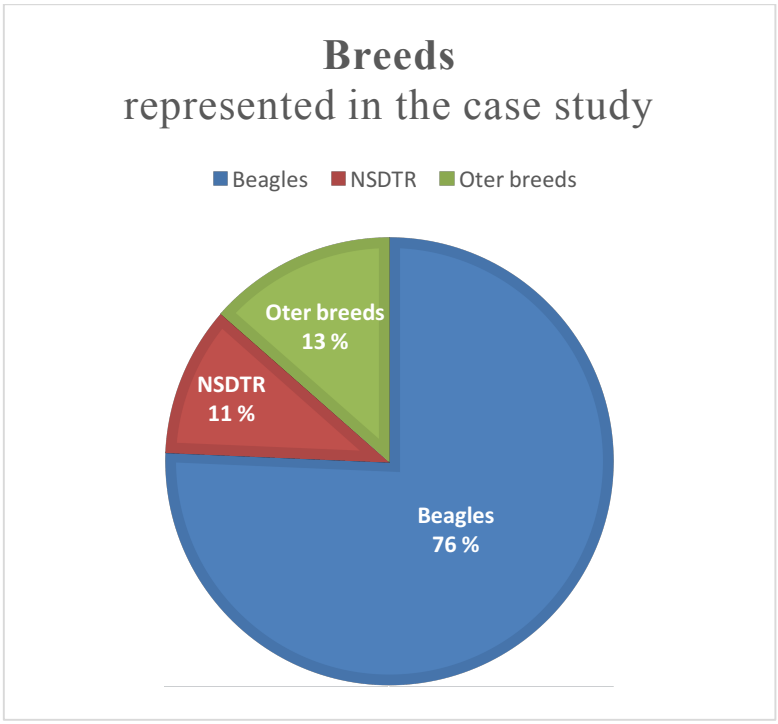

Fig. 10: Breed distribution among the 37 dogs in the case study.

Relapse – 19 out of the 37 dogs (51,3%) suffered from putative relapses. Some during tapering, others after finishing the treatment in Figure 3. 3 out of these dogs was subsequently treated with additionally with the immunosuppressive drug Azathioprine.

6.2. Clinical signs

Like indicated in Figure 12, 23/37 dogs (62,1%) had pyrexia (defined as temperature >39,5°C), 19/37 dogs (51,3%) were inappetent, 15/37 dogs (40,5%) had jaw pain, 31/37 dogs (83,7%) had stiff gait (Fig. 11) and 3/37 dogs (8,1%) experienced excessive salivation. Neck pain was one of the inclusion criteria, so it considered to occur in 100%.

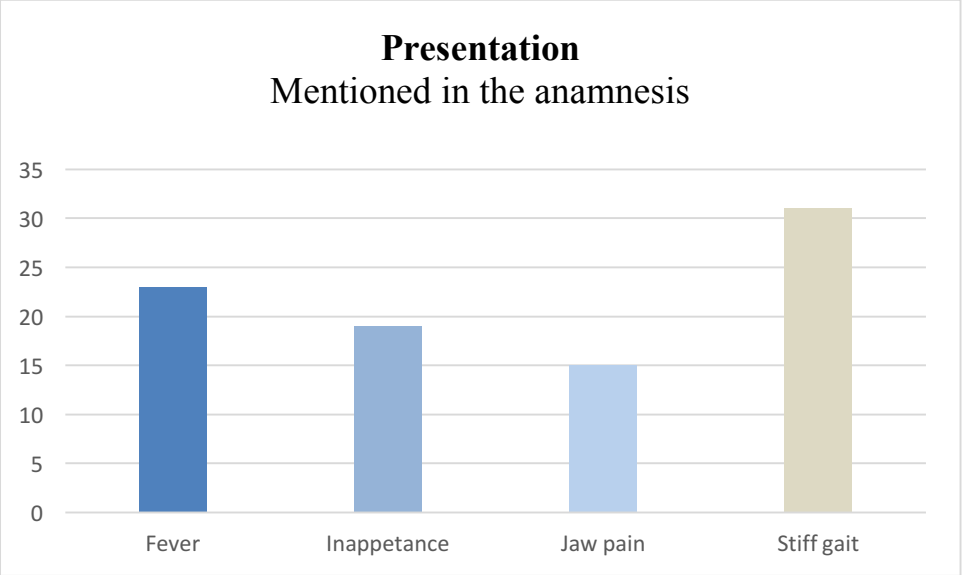

Fig. 12: The clinical signs mentioned in the anamnesis of the 37 dogs.

Fig.11: One of the Hungarian dogs in this case study. Presented with typical clinical signs. Low held head, arched back and stiff gait (Photo: Maylene Johansen)

6.3. Hematology

Blood samples was taken from 29/37 dogs (78,3%). 27/29 dogs (93,1%) had a leukocytosis at the admission. The reference range is 6-12 x 10^9/L. The results from the 27 patients were ranging from 12,2 x 10^9/L to 37 x 10^9/L (Figure 12), with stab cells above the reference value (0-5%) seen in 12/29 dogs (41,4%). The stab cells are young neutrophil cells, so if there is an increased presence of stab cell % there is an indication for an acute ongoing process. Therefore, stab cell concentration will change regarding the course of illness.

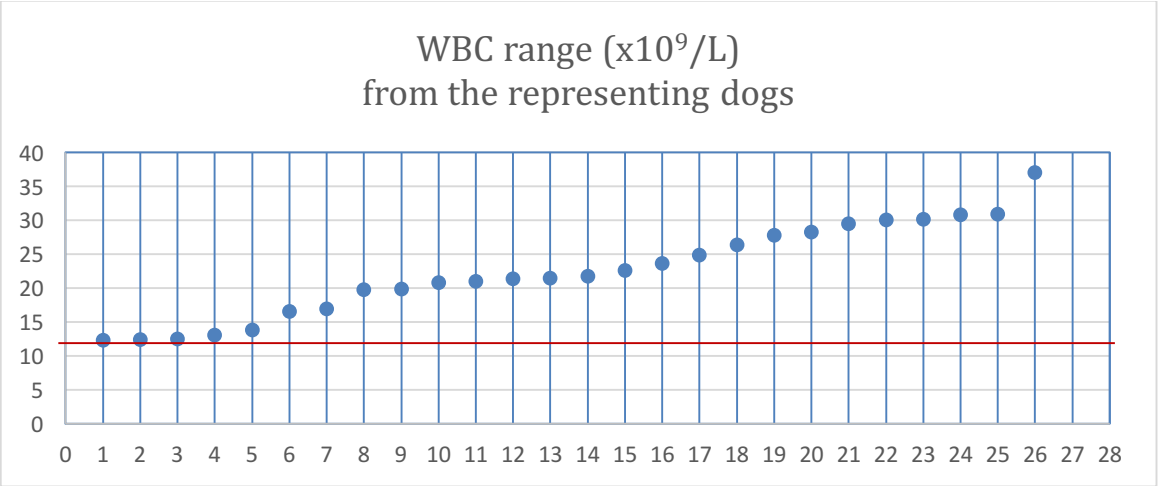

Fig. 12: Each dot indicates a dog (x) and its WBC-count in G/L (y). The red line indicates the reference value of WBC count in dogs (12 x10^9/L).

6.4. CSF results

CSF sample was taken from 9/37 dogs (24,3%) (Fig. 13). Increased total protein g/l was seen in 2/9 dogs (22,2%). All 9/9 dogs revealed elevated nucleated cell count. Neutrophilic pleocytosis is reported in 8/9 dogs (88,8%), where one of the dogs had lymphocytic pleocytosis instead. During the course of SRMA neutrophilic pleocytosis later can develop into a picture predominated by monocytes.

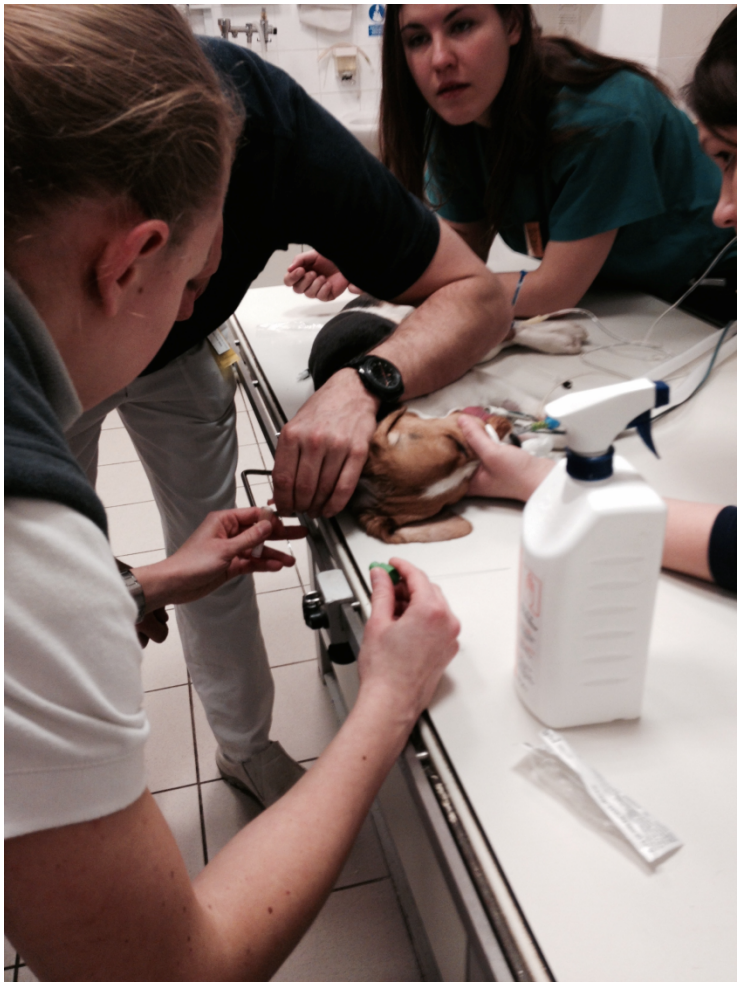

Fig. 13: CSF sampling from one of the Hungarian dogs with beagle pain, at the University of Veterinary Medicine Budapest, Hungary (Photo: Maylene Johansen)

6.5. CRP and ANA

C-reactive protein (CRP) was used as diagnostic approach in all of the 4 dogs from Norway. The reference range was based on previous studies and was 0.46-9.6 mg/l.[3]

At presentation all 4 dogs had CRP values above reference range, ranging between 40 mg/l – 210 mg/l. After treatment with corticosteroids the CRP went down to <10 mg/l in 2/4 dogs. ANA test were analyzed in 5/37 dogs, all of them were negative.

6.6. Treatment protocol

33/37 dogs (89,2%) were treated with corticosteroids (Prednisolone, Medrol) in accordance with Figure 3. This involves a 6-month long follow-up period. 19/33 dogs (57,6%) treated with corticosteroids suffered from putative relapse. 3/19 (15,8%) relapsing cases added azathioprine (2 mg/kg/day) to treatment for 8-16 weeks. If relapsing again, the result was lifelong treatment with lowest responsive dose of prednisolone alone or an even lower dose prednisolone combined with azathioprine. One of the beagles was treated lifelong with a combination of 12 mg azathioprine and 2,5 mg prednisolone every other day, since treatment with the same dose every third day gave clinical signs of putative relapses. The 4 Norwegian cases was treated with prednisolone and additionally with pentoxifylline.

8. Discussion

8.1 Signalment and History

The number of dogs that didn't fulfill the criteria to be classified as true SRMA cases includes 30 dogs. Some of these dogs are cases that had other diagnoses confirmed, and SRMA only as a differential diagnosis. The reason why almost half of the dogs was SRMA negative is because all cases with the name 'beagle pain' written in its journal was involved in this study. However; the fact that 30 dogs had beagle pain as differential diagnosis or were misdiagnosed, implies that neck pain can be complex when it comes to the ruling out process. Recognition of the signs of spinal pain in animals can be difficult by the different reactions to pain seen between individuals.[16]

The age of onset findings was like the literature indicates; SRMA most often affect young dogs, but the condition may occur at any age. The median age at time of presentation was 11 months, which is the same result as found in a previous article about SRMA in 2009.[3]

It is usual that the clinical signs start some time before the presentation at the clinic, what we took it into consideration, in case data was presented.

The gender ratio reveals that there is no gender predisposition indicated, and this was also described in the very same article as above, from 2009.[3]

Most of the breeds represented in the study had previously been described as breeds at risk of become affected with SRMA, except the Vizsla and Whippet.

Age of onset: 29 dogs (78,4%) were under 14 months out of the total 37 dogs.

8.2 Clinical signs

Just above half of the dogs was suffering from pyrexia. This could be explained by the characteristics of the course of the disease. The fever will wax and wane in the beginning.[4] In some cases, the symptoms start even weeks earlier than the diagnosis is made or the dog is taken to the vet. Other signs found, like stiff gait, inappetence, fever is mentioned in literature, but pain at mouth opening is not. This can be because the act of opening of the mouth is coming with some neck manipulation, eliciting the pain.

8.3 Laboratory diagnostics

According to literature[4] there was a marked elevation in white blood cell count in the hematology of the dogs. Left shift was seen in 41,4% of the samples. The dogs presumably were in different phases, so the stab cell count probably would have been higher if all the samples were taken in the acute phase.

ANA was measured in 4/37, and was proposed several times. It is not mentioned in the literature as an indicative test for SRMA, but in breeds at genetic risk of systemic lupus erythematosus (SLE) e.g. the Nova Scotia Duck Tolling Retrievers, an ANA test will exclude the SLE from the list of differential diagnosis. The sensitivity is low, and the test is not recommended, unless the breed is as risk.

CSF sample was only taken from 24,3% of the patients and the result reveals both neutrophilic pleocytosis and lymphocytic pleocytosis in different patients. Conclusion is hard to draw regarding the course of disease and differences in CSF cytology. But CSF cytology reveals abnormal cell population and number in the liquor which is crucial in SRMA diagnosis. Moreover, this makes CSF the most important tool in the diagnosis of SRMA and a help in differential diagnosis, for example CSF results in discus prolapse are not altered.

8.5 Treatment protocol

In general, the treatment protocol, given above should be used, but as the disease unfolds differently among most of the dogs, one cannot follow one certain protocol for every patient and therefore individual adjustments should be made in many of the cases. Each dogs' individual response and sensitivity to prednisolone is independent from the treatment protocol suggested in the literature review. It seems like the treatment is most efficient if combined with regular monitoring. The tapering process is crucial in order to have a successful outcome. The symptoms can resolve quickly but at the same time the premature tapering can cause relapse.

Keep to the protocol, adjusting it individually and following changes in laboratory data, as CRP, WBC count is recommended to control the inflammation as liquor sampling is more invasive than blood sampling and CRP are demonstrated to have a significant positive correlation with CSF WBC count.[3]

The administration of pentoxifylline after recommendation from veterinarian Helene Hamlin, which has SRMA as research field in Sweden. Pentoxifylline (Trental) is a useful supplement in combination therapy when it comes to immune mediated diseases in general. The main indication of pentoxifylline is vasculitis, and SRMA is a severe form of arteritis. Pentoxifylline is able to treat milder to moderate vasculitis alone, but it is excellent to be used a transition drug when tapering the dose of prednisolone. In most cases it is indicated to use corticosteroids before using pentoxifylline. Pentoxifylline is a safe drug when it comes to side effects and can only contribute in favour of the dog's health. It takes 4-6 weeks before it reaches its full effect. There are no studies or articles to refer to when it comes to this drug indication in SRMA dogs, but the experience from the Swedish colleague, Hamlin.

The combination of pentoxifylline and cyclosporine was tested in a relapsing dog where azathioprine caused a problematic bone marrow suppression. The dog treated with this combination supports the effect of pentoxifylline, since cyclosporine do not cross the blood brain barrier and could not have done the effect alone.

8.6. Conclusion

SRMA is a frequently emerging disease in Beagles and in other dogs in young age. Clinical signs are revolved around the meningitis giving hyperesthesia involving the axial skeleton, the resulting neck pain is the main clinical sign. Blood test results mostly show elevated WBC count, but not specific for the disease.

The diagnosis of Beagle pain is based on CSF analysis. As the treatment means a long, sometimes lifelong immunosuppressive therapy, an exact diagnosis is important before we start the treatment regime.

9. Summary

As an owner of a dog with Steroid-Responsive, I experienced this disease on a close hold. But as a veterinary student I also wanted to know as much as possible about the diagnosis, so I started to search for literature. I found it hard to find anything certain about the different aspects of the disease, and realized that there still are some unknown questions about SRMA. This awakened my interest in learning more about the condition and maybe find answers to some of the parts that are unclear about it.

Steroid responsive arteritis-meningitis (SRMA) is the most common form of meningitis in dogs. The etiology is most likely autoimmune, causing vasculitis/arteritis of the meningeal vessels in the spinal cord and the brain. The disease has changed names over the years, like aseptic meningitis, suppurative meningitis, necrotizing vasculitis. The disease affects mostly younger dogs between 6-18 months, but middle-aged and older medium to large breed dogs like Beagles, Bernese Mountain Dogs, Boxers, German Shorthaired Pointers and Nova Scotia Duck Tolling Retrievers may also be affected. Clinical signs of the disease include fever, reluctance to move, cervical pain. Neurologic deficits are uncommon. Laboratory diagnostics reveals neutrophilic leukocytosis with or without a left shift. Cerebrospinal fluid (CSF) analysis shows an increased protein concentration and neutrophilic pleocytosis. As the treatment means long, sometimes lifelong immunosuppressive therapy, an exact diagnosis is important before starting the treatment regime.

The aim of this retrospective study is to evaluate statistically the cases administered to the Veterinary University of Budapest between 01.2004 and 06.2016 with beagle pain as a possible diagnosis. Additionally, four similar cases from a small animal clinic in Norway was added to the studies.

2,5% of Beagles and Beagle mixes was presented to the clinic with beagle pain. Beagle pain represented 0.05% of the admissions at the Veterinary University in Budapest, Hungary during the given period.

89,2% were treated with corticosteroids (Prednisolone, Medrol), and 57,6% treated with corticosteroids suffered from putative relapses.

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Also I would like to award a big thank to Dr. Gerd Brandvoll for supplying me with the Norwegian dogs used in the case study. She also willingly provided me with information on her experience with the treatment.

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