Relationship between the clinical findings, MRI findings and the efficiency of the prescribed drugs in Cavalier King Charles Spaniels with Chiari-like malformation and syringomyelia (CM/SM)

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Introduction

Chiari-like malformation (CM) is a combination of malformation of the hindbrain and the surrounding caudal cranial fossa (CCF) and a consequential herniation of part of the cerebellum and brainstem into or through the foramen magnum reported in small breed dogs (1) (2)(3). Syringomyelia is currently defined as a condition that results in the development of fluid-containing cavities within the parenchyma of the spinal cord as a consequence of abnormal cerebrospinal fluid movement (3). The estimated prevalence of CM is 95% in the Cavalier King Charles Spaniel (CKCS) (4)(5)(6). In dogs without clinical signs the prevalence of SM is ranging from 25% of CKCS's aged 12 months old, increasing to 70% in CKCS's aged 70 months or more (7).

Clinical signs of CM/SM are generally recognized between 6 months and 3 years of age, although dogs of any age may be presented (8). By far the most significant clinical sign of SM is pain, commonly localized to the cervical region (9). Both CM and SM are associated with pain. Signs of discomfort such as ear and facial rubbing/scratching can be observed in dogs that have CM alone, it is hypothesized that this pain is due to abnormal cerebrospinal fluid (CSF) flow and abnormalities in medullary sensory processing (10). Dogs with SM can show neuropathic pain syndromes, the symptoms are suspected to be caused by damage to one or both spinal cord dorsal horns. The clinical signs that are often seen are an oversensitive skin on the head, neck, shoulder and sternum, phantom scratching, pain attacks, dysaesthia and allodynia (10)(5)(9).

There are two aims in this study; the first is to investigate the association between the findings on magnetic resonance imaging (MRI) and the reported clinical signs observed by the individual owners, the second is to do a retrospective study to investigate the effect of prescribed drugs.

Materials and methods

Earlier, veterinary student Wieteke Eggelmeijer investigated the incidence and described the MRI findings of 848 CKCS's scanned in the Netherlands. For the description of the MRI findings a newly developed scheme was used. All owners of the scanned dogs were asked to submit information on their scanned dog using a hard paper questionnaire. This information will be used to study the relation between the reported clinical signs by the owner and the MRI findings. The same information will also be used to do a retrospective study to investigate the effect of the prescribed drugs.

The evaluation of Chiari-like malformation is divided into four degrees (figure 1). No CM, an indented cerebellum, a cerebellum that is misshaped but without herniation or the cerebellum is impacted into, or herniated through the foramen magnum.

Figure 1: Assessment schedule Chiari-like malformation.

Grade 0	No CM
Grade 1	Cerebellum indented
Grade 2	Cerebellum is misshaped, but there is no herniation
Grade 3	Cerebellum is impacted into, or herniated through the foramen magnum.

The evaluation of syringomyelia is divided into five degrees (figure 2). It is based on the central canal dilation (CCD) in millimetres and the existence of a syrinx.

Grade 0	No abnormalities
Grade 1	CCD less than 1 mm in diameter
Grade 2	CCD less than 2 mm in diameter
Grade 3	CCD more than 2 mm in diameter
Grade 4	Syringomyelia (CCD which has an internal diameter of 2 mm or greater), or separate syrinx

Figure 2: Assessment schedule syringomyelia

Because syringomyelia is a progressive disease it is useful to divide dogs in different age groups (figure3).

A	Age over 5 years
B	Age between 3 and 5 years
C	Age between 0 en 3 years

Figure 3: Different age groups

Results

One of the 844 dogs that were scanned did not have chiari malformation. 704 dogs were diagnosed with chiari malformation grade 2 (CM2) and 139 dogs were diagnosed with chiari malformation grade 3 (CM3). These results are presented in table 1 combined with information about the dogs having complains or not.

	Total	Complaints	No complaints	Unknown
No CM	1			0
CM 2	704	35	157	512
CM 3	139	10	31	98

Table 1: CM degree combined with complaints

555 of the 844 scanned dogs did not have syringomyelia. 9 dogs were diagnosed with syringomyelia grade 1 (SM1), 106 dogs were diagnosed with syringomyelia grade 2 (SM2), 10 dogs were diagnosed with syringomyelia grade 3 (SM3) and 164 dogs were diagnosed with syringomyelia grade 4 (SM4). These results were combined with information about the dogs having complaints or not.

	Total	Complaints	No complaints	Unknown
No SM	555	14	138	403
SM1	9	0	2	7
SM 2	106	11	21	74
SM 3	10	0	1	9
SM 4	164	20	26	118

Table 2: SM degree combined with complaints

Chi-Square Test

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	32,569[a]	4	,000
Likelihood Ratio	31,070	4	,000
Linear-by-Linear Association	30,055	1	,000
N of Valid Cases	233		

233 completed surveys were returned. According to the owners 45 dogs have complaints (19,3%) and 188 dogs do not have complaints (80,7%).

The next data are all about dogs with complaints according to the owner

	No SM	SM2	SM 4
CM 2 (35)	11	9	15
CM 3 (10)	3	2	5

Table 3: Dogs with complaints according to the owner

Chi-Square Test

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	,198[a]	2	,906
Likelihood Ratio	,201	2	,904
Linear-by-Linear Association	,076	1	,783
N of Valid Cases	45		

The survey consisted of 40 questions. Not all these questions are processed in the next pages because some of them are about the prescribed medication. In most of the questions the owners were asked to what extent the complaint is present, they could choose 1-10 where 1: not present and 10:extremely present. These choices are clustered in three groups: not-little(answers 1-4), somewhat (answers 5-7) and evident-extreme (8-10).
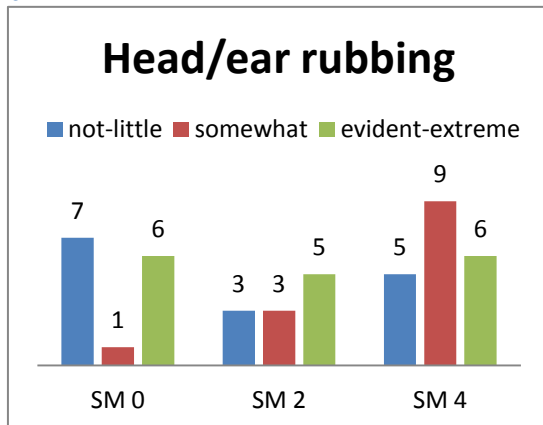
Question 1

Scratching (with or without skin contact)

not-little ■ somewhat ■ evident-extreme

	SM 0	SM 2	SM 4
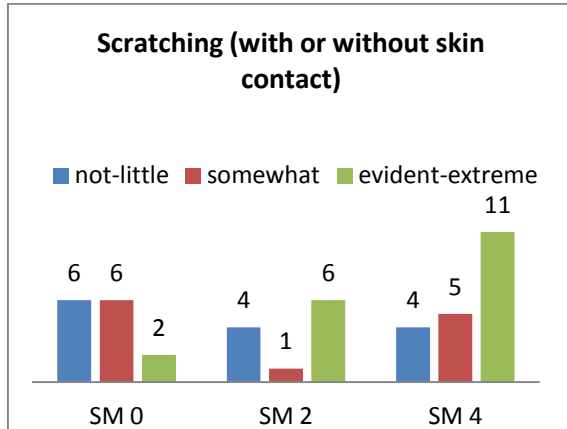
Chi-Square Test

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	7,940[a]	4	,094
Likelihood Ratio	9,008	4	,061
Linear-by-Linear Association	4,362	1	,037
N of Valid Cases	45		

Because the P-value is >0,05 there is no significant relationship between the grade of SM and the extent of presence of the complaint.
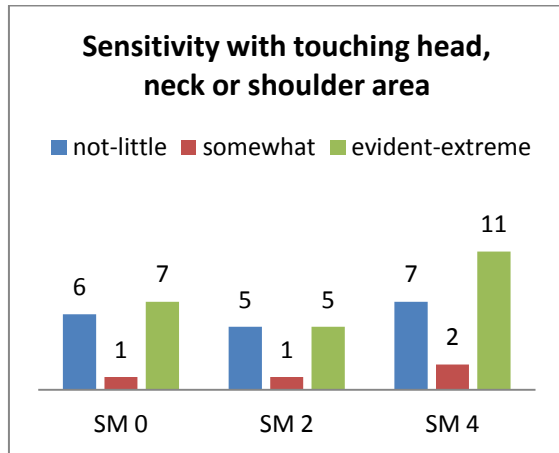
Question 2

Head/ear rubbing

not-little ■ somewhat ■ evident-extreme

	SM 0	SM 2	SM 4

Chi-Square Test

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	6,391[a]	4	,172
Likelihood Ratio	7,031	4	,134
Linear-by-Linear Association	,125	1	,724
N of Valid Cases	45		

Because the P-value is >0,05 there is no significant relationship between the grade of SM and the extent of presence of the complaint.

Question 3
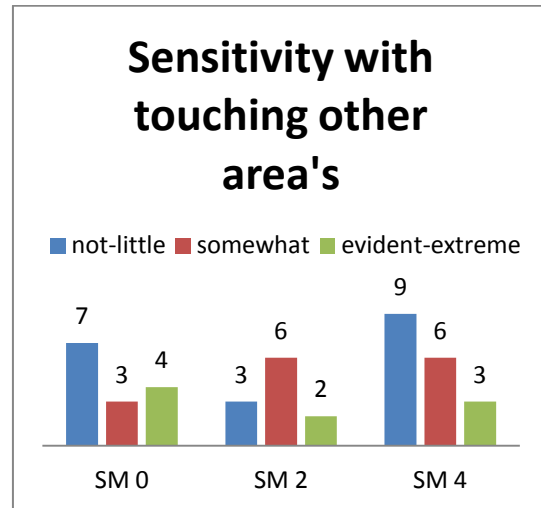

Sensitivity with touching head, neck or shoulder area

Chi-Square Test			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	,443[a]	4	,979
Likelihood Ratio	,448	4	,978
Linear-by-Linear Association	,178	1	,673
N of Valid Cases	45		

Question 4

Sensitivity with touching other area's

Chi-Square Test			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	6,391[a]	4	,172
Likelihood Ratio	7,031	4	,134
Linear-by-Linear Association	,125	1	,724
N of Valid Cases	45		

Because the P-value is >0,05 there is a significant relationship between the grade of SM and the extent of presence of the complaint.

Different weather circumstances can change the grade of the neuropathic pain symptoms in CKCS's. Some dogs show more extreme symptoms during cold weather or low barometric pressure. The diagrams below show the sensitivity of the dogs during different weather types. 1: not present and 10: extremely present.
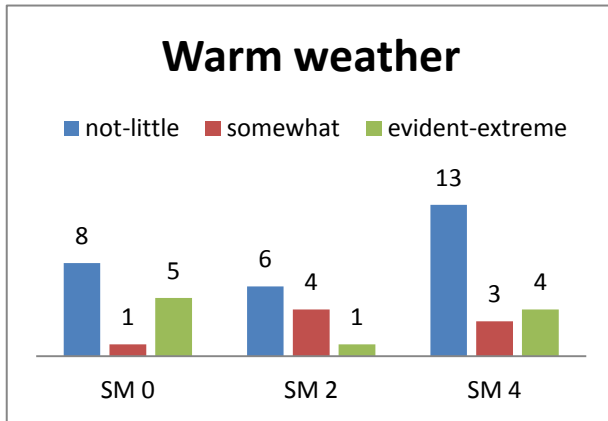
Question 5

Cold weather
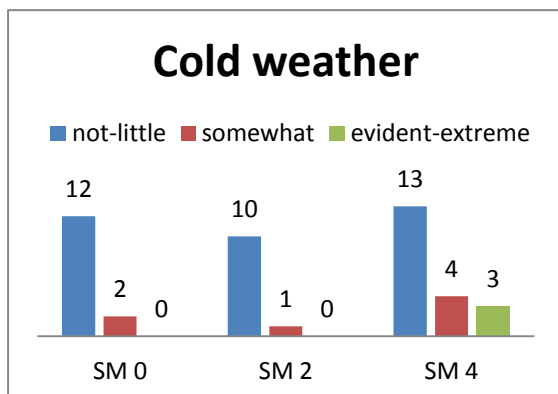
Chi-Square Test			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	5,091[a]	4	,278
Likelihood Ratio	6,247	4	,181
Linear-by-Linear Association	3,414	1	,065
N of Valid Cases	45		

Because the P-value is >0,05 there is no significant relationship between the grade of SM and the extent of presence of the complaint.
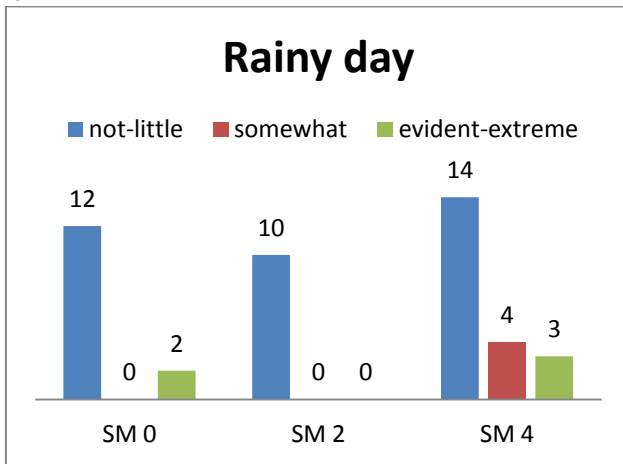
Question 6

Warm weather

Chi-Square Test			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	$5,317^a$	4	,256
Likelihood Ratio	5,153	4	,272
Linear-by-Linear Association	,604	1	,437
N of Valid Cases	45		

Because the P-value is >0,05 there is no significant relationship between the grade of SM and the extent of presence of the complaint.
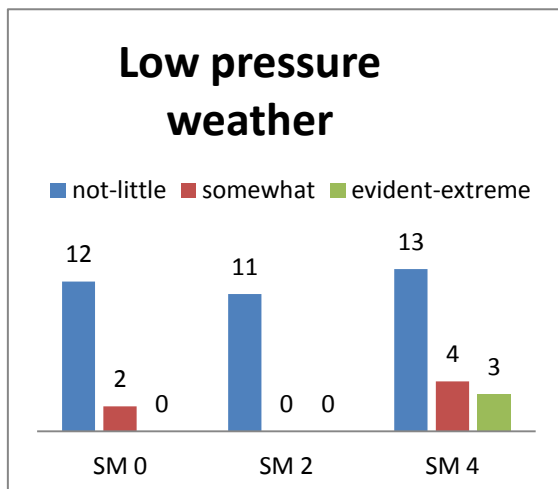
Question 7

Rainy day

Chi-Square Test			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	$4,177^a$	4	,383
Likelihood Ratio	6,464	4	,167
Linear-by-Linear Association	,662	1	,416
N of Valid Cases	45		

Because the P-value is >0,05 there is no significant relationship between the grade of SM and the extent of presence of the complaint.
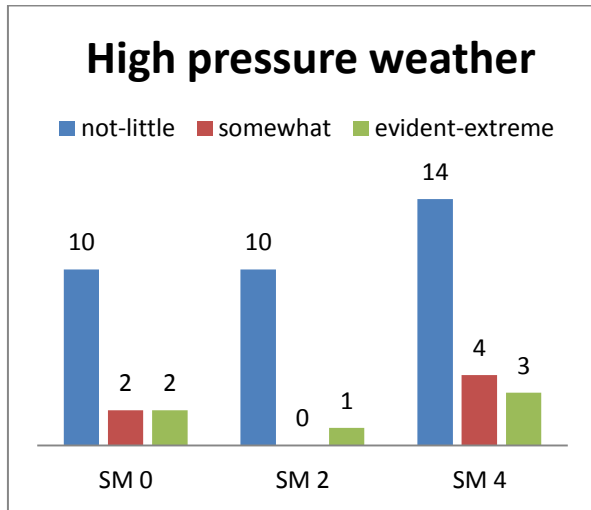
Question 8

Low pressure weather

Chi-Square Test			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	$7,063^a$	4	,133
Likelihood Ratio	9,552	4	,049
Linear-by-Linear Association	3,668	1	,055
N of Valid Cases	45		

Because the P-value is >0,05 there is no significant relationship between the grade of SM and the extent of presence of the complaint
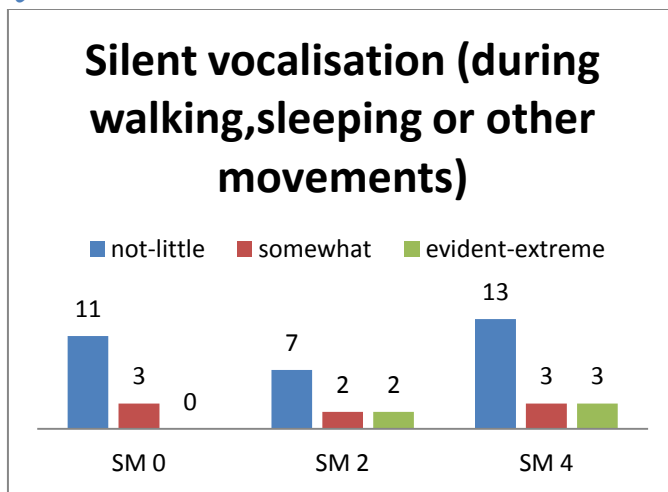
High pressure weather

■ not-little **■ somewhat** **■ evident-extreme**

Chi-Square Test			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	3,722[a]	4	,445
Likelihood Ratio	5,221	4	,265
Linear-by-Linear Association	,035	1	,852
N of Valid Cases	45		

Because the P-value is >0,05 there is no significant relationship between the grade of SM and the extent of presence of the complaint.

Question 10

Silent vocalisation (during walking,sleeping or other movements)

■ not-little **■ somewhat** **■ evident-extreme**

Chi-Square Test			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	3,581[a]	4	,466
Likelihood Ratio	5,301	4	,258
Linear-by-Linear Association	1,008	1	,315
N of Valid Cases	45		

Because the P-value is >0,05 there is no significant relationship between the grade of SM and the extent of presence of the complaint.

Question 11

Seemingly sudden pain expression

■ not-little **■ somewhat** **■ evident-extreme**
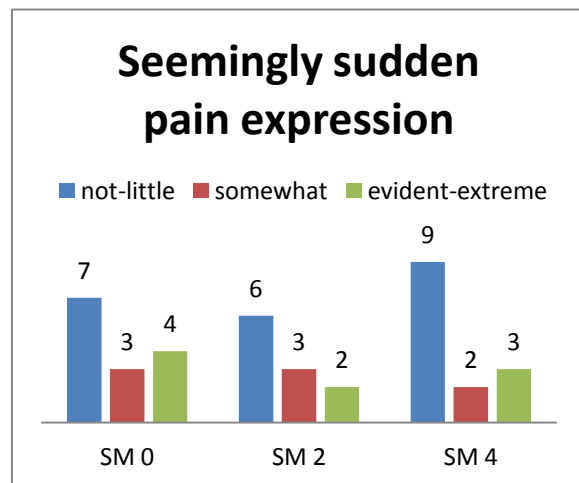
Chi-Square Test			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	3,150[a]	4	,533
Likelihood Ratio	3,267	4	,514
Linear-by-Linear Association	,571	1	,450
N of Valid Cases	45		

Because the P-value is >0,05 there is no significant relationship between the grade of SM and the extent of presence of the complaint.

The next questions are about activity level and sleeping

Question 12

Activity/liveliness
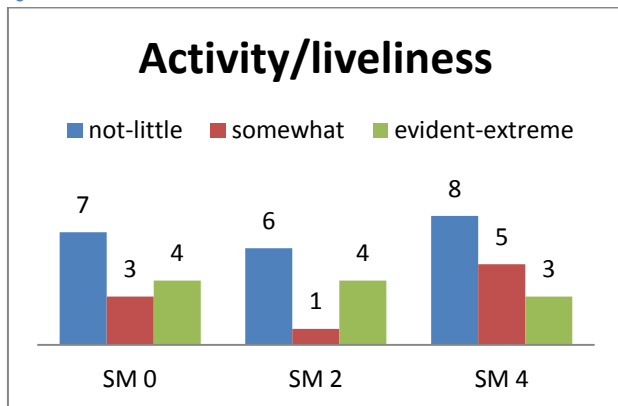
Chi-Square Test			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	1,431[a]	4	,839
Likelihood Ratio	1,586	4	,811
Linear-by-Linear Association	,295	1	,587
N of Valid Cases	45		

Because the P-value is >0,05 there is no significant relationship between the grade of SM and the extent of presence of the complaint.

Question 13

Sleep pattern
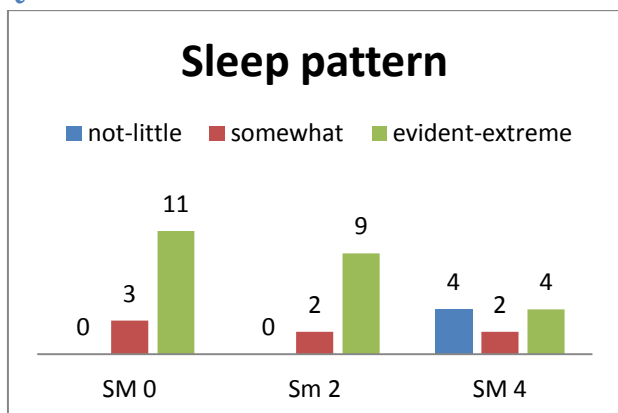
Chi-Square Test			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	5,912[a]	4	,206
Likelihood Ratio	7,422	4	,115
Linear-by-Linear Association	1,841	1	,175
N of Valid Cases	45		

Because the P-value is >0,05 there is no significant relationship between the grade of SM and the extent of presence of the complaint.

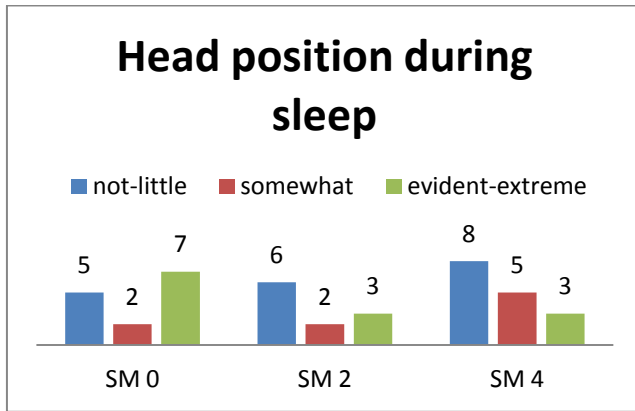Some dogs tend to sleep with their head in an abnormal position (higher or in between objects).

1: no abnormal head position during sleep and 10: constantly an abnormal head position

Head position during sleep

■ not-little ■ somewhat ■ evident-extreme

SM 0	SM 2	SM 4

5 2 7 — 6 2 3 — 8 5 3

Chi-Square Test

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	1,972^a	4	,741
Likelihood Ratio	1,938	4	,747
Linear-by-Linear Association	,276	1	,600
N of Valid Cases	45		

Because the P-value is >0,05 there is no significant relationship between the grade of SM and the extent of presence of the complaint.

The next diagram is about dogs having a headache according to the owner.

**1: no symptoms of headache and 10: a lot of symptoms of headache**

Headache

■ not-little ■ somewhat ■ evident-extreme

8 3 3 — 6 0 5 — 5 5 3

	SM 0	SM 2	SM 4
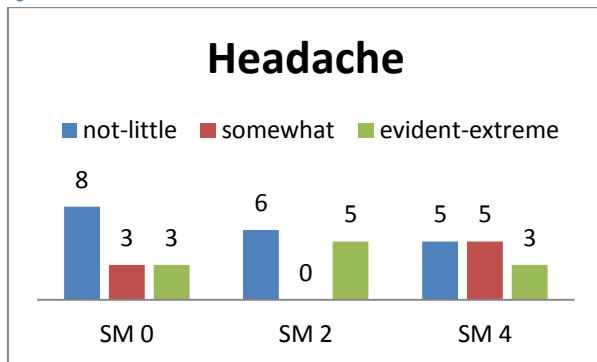
Chi-Square Test

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	6,975^a	4	,137
Likelihood Ratio	9,200	4	,056
Linear-by-Linear Association	3,680	1	,055
N of Valid Cases	45		

Because the P-value is >0,05 there is no significant relationship between the grade of SM and the extent of presence of the complaint.

The next diagram is about dogs being oversensitive for light (photophobia).
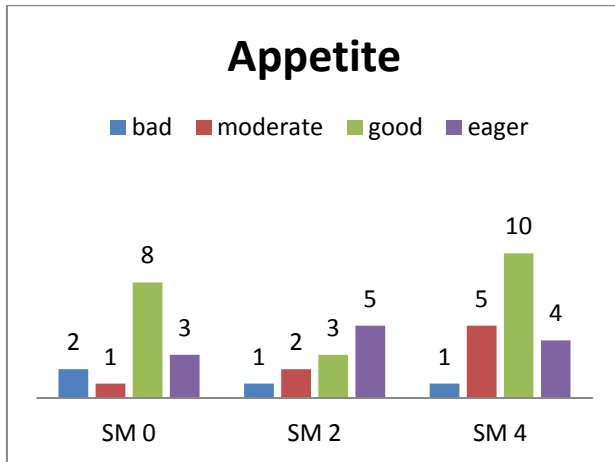
1: not sensitive and 10: evident
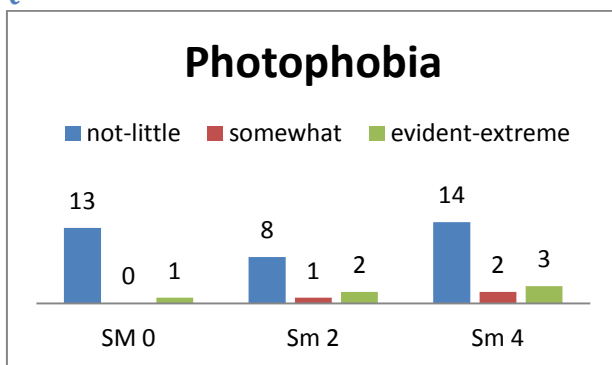
Chi-Square Test

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	2,904^a	4	,574
Likelihood Ratio	3,903	4	,419
Linear-by-Linear Association	1,773	1	,183
N of Valid Cases	45		

Photophobia

■ not-little ■ somewhat ■ evident-extreme

13 0 1 — 8 1 2 — 14 2 3

	SM 0	Sm 2	Sm 4

Because the P-value is >0,05 there is no significant relationship between the grade of SM and the extent of presence of the complaint.

Question 17

Chi-Square Test

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	5,475[a]	6	,484
Likelihood Ratio	5,584	6	,471
Linear-by-Linear Association	,008	1	,928
N of Valid Cases	45		

Because the P-value is >0,05 there is no significant relationship between the grade of SM and the extent of presence of the complaint
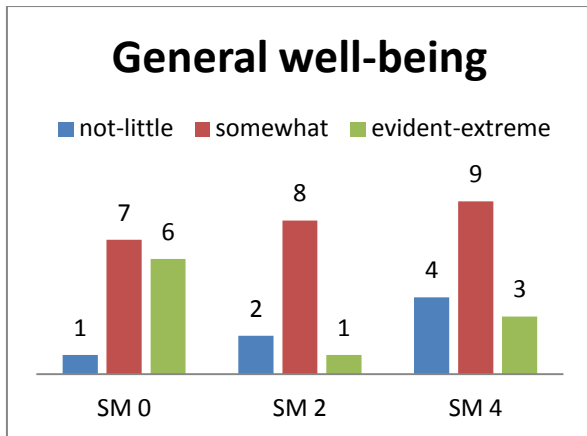
Question 17

Chi-Square Test

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	4,438[a]	4	,350
Likelihood Ratio	5,111	4	,276
Linear-by-Linear Association	,573	1	,449
N of Valid Cases	45		

Because the P-value is >0,05 there is no significant relationship between the grade of SM and the extent of presence of the complaint

In the survey the owners were also asked to describe how their dogs expressed pain. The next behavioral expressions were mentioned:

- Yelling while shaking out
- Yelling out of nothing
- Painful look in the eyes
- To nod
- Extremely calm/apathetic
- Blinking with the eyes
- Doesn't want to be stroked on the head
- Head shaking
- Wants to be in a cool and dark area
- Rubbing with the head
- To smack
- Keeping the eyes shut
- Can't handle noise
- Red eyes/tears
- Being dreamy
- To sigh
- Is always looking for a quit area
- Being cross

Used medication and their effiency according to the owners

	Yes	No	Partly
Carprofen/Rimadyl (NSAID)	6	1	2
Prednisolon (corticosteroide)	4	3	
Normast/PEA pure (palmitoylethanolamide)		6	3
Dolorex (analgeticum;butorfanol)		1	
Gabapentine (anti-epileptica;gaba agonist)	7		1
Pregabaline (anti-epileptica;gaba agonist)		1	
Cimetidine (H2-receptorantagonist)	1		
Fenobarbital/phenoral (barbituraat)	1		1
Tramatol (analgeticum/antitussivium)	1		1
Dexamethason(corticosteroide)	1		
Morfine (analgeticum)	1		
Trocoxil (NSAID)	1		
Meloxidyl (NSAID)	3	1	
Onsior (NSAID)	1		

About the prescribed drugs are two conclusions that can be drawn:

- NSAID's and gabapentin are most effective according to the CKCS owners
- Palmitoylethanolamide is not/partly effective according to the CKCS owners

Discussion

The aim of this study was to find a relationship between the clinical findings, MRI findings and the efficacy of the prescribed drugs in CKCS with CM/SM. Unfortunately only a few surveys were returned. A total of 45 surveys were completely filled in by owners from CKCS with complaints. Hence, the results are not sufficient enough to fully explore associations between clinical signs and the grade of SM (the MRI findings). Furthermore, as all dogs suffer from either CM 2 or 3, it is not possible to extrapolate for CM 0 to CM 3 and the clinical signs.

There are several reasons that might account for this. Similar to other retrospective, questionnaire-based studies, limitations of the present study include inaccuracies in owner perceptions and recollection. Owners may have difficulty in recognising that signs they see frequently could be problematic. In other words, such signs could become 'the norm', or they are subconsciously avoiding acknowledging suffering their pet. Furthermore there is the possibility that client-owned dogs are differently judged compared to the breeder-owned dog.

The questions in the survey that had be answered by the CKCS owners can roughly be divided into four groups. The first group of questions were about scratching, rubbing and oversensitivity and can be grouped under neuropathic pain signs. The second group of questions can be grouped under weather influences on neuropathic pain signs. The third group of questions were about general pain expression and the forth group of questions were about the general well-being of the dog.

Strictly we still do not have a good idea where the pain of dogs suffering from syringomyelia comes from but the type of behaviour exhibited by affected dogs is indicative of neuropathic pain. This is why the first group of questions is about neuropathic pain signs with the characteristics of allodynia, dysesthesia and hyperalgesia. For example, dogs seem to dislike touch to certain areas of skin and may be unable to tolerate grooming or a neck collar (11).

Generally, SM is associated with neuropathic pain, arising through damage and dysfunction of the CNS and then especially the dorsal horn of the spinal cord grey matter. The dorsal horn is a key centre for processing of sensory information for transmission to the brain (10). This dysfunction disrupts the dynamic balance between nociceptive input and descending regulatory control from the brainstem, leading to clinical signs including hyperalgesia, dyesthesia and allodynia (12). About the exact pathogenesis of this clinical signs several hypothesis exist. However a consistent finding is that pain appears to be associated with asymmetry of the syrinx (10). Incoming sensory information in the dorsal horn undergoes substantial processing within the various laminae and then is relayed via ascending pathways to the brain. Nociceptive information is transmitted by small non- myelinated C fibres which terminate predominantly in laminae 1 and 2 with some fibres penetrating deeper layers (11). Hu et al., 2012 (12) found that the dorsal horn structural asymmetry of symptomatic SM in CKCS is associated with profound alteration in laminar structure and expression of neuropeptides particularly SP (substance P). The finding of reduced levels of expression of pain-related neuropeptides is at first difficult to link with expression of pain related behaviour. One explanation comes from Yezierski et al., 2009 and is that the normal transport of SP from the site of manufacture in the dorsal root ganglia is disrupted by the lesion,

thus leading to increasing SP levels caudal tot the damaged region and increased pain-related behaviour in more caudal dermatomes(13). Another explanation is that the absolute levels of neuropeptides do not necessarily correlate with intensity of pain expression and, instead, there is a complex disturbance of the fine balance between pro-nociceptive and anti-nociceptive input to the dorsal horn and the patterns of neuropeptide expression merely illustrate the disruption of the grey matter structure and function.

Gorman et al., 2001 (14) found that after leaving an intraspinal injection of quisqualic acid (QUIS) they saw development of spontaneous excessive grooming behavior in rats. Earlier Yezierski et al., 1993 (15) found that rats injected with microinjections of quisqualic acid in the spinal cord expressed excessive grooming behavior 10-27 days post injection. They began with the removal of hair in the dermatome corresponding to the spinal segment injected, once initiated the grooming progressed and the skin of the groomed area showed heightened sensitivity i.e., allodynia, to mechanical stimuli applied to the 'groomed' area. This suggests that a disruption in the dorsal horn structure can benefit in the production of clinical signs in the CKCS. Hu et al., 2012 also found that the spinal cord dorsal horn in symptomatic CKCS is significantly more asymmetric than that of control animals, whereas the asymptomatic CKCS have changes that are midway between control and symptomatic CKCS. This suggests the possibility that progression from mild to severe asymmetry in CKCS is associated with development of clinical signs. (12)

In this study we only measured the diameter of the syrinxes while it probably would have been more useful to look at the grade of asymmetry of the syrinx because it appears that the asymmetry is the main factor that causes neurological pain. On the other hand, there were 20 dogs (almost half) with a syrinx grade 4, with a syrinx of 2 mm or greater you would expect signs of neuropathic pain according to the disrupting of the dorsal horn described above.

The second group of questions about weather influences on neurologic pain signs. According to Jun Sato., 2003 (16) low-pressure or low-temperature environment caused aggravating of mechanical allodynia, hyperalgesia and heat allodynia. The spontaneous pain related behaviour was also enhanced during both exposures in neuropathic or arthritic rats. Another research of Sato et al., 1991 showed that low pressure intensifies the abnormalities in pain related behaviours of neuropathic rats, and that sympathetic activity contributes to the low pressure effect (17). In this research there was no significant relationship between the different weather influences and the sensitivity of the CKCSs. This could be because owners are not really aware of the barometric pressure and they do not link the grade of the symptoms with the barometric pressure. The temperature influence is not easy to access because most of the dogs will live inside the house and the temperature will be rather constant. Then again the owners could have seen a aggravation of the phantom scratching while walking with the dog during winter. To really evaluate the effects of barometric pressure and temperature on neuropathic pain in CKCS it would be more reliable to do research in a climate controlled room and stimulate the dogs in different ways to observe if they react more painful during the different weather conditions.

The third group of questions about general pain expression (a.o. sudden vocalisation/pain expression or signs of headache according to the owner) is difficult to process. Signs from headache in a dog may be very different for each owner. There was a second question in the survey about what signs might be indicative for a headache according to the owner but this question was often not answered. Sudden vocalisation/pain expression is easier to recognize and a relationship with the diameter of the syrinx is to be expected. As mentioned previously the reason why there was no significant relationship could be that syrinx asymmetry is the most important factor in causing pain instead of the diameter.

The last group of questions is about general well-being aspects. Dogs with neuropathic pain are more likely to have disturbed sleep and problems with settling(18). They also tend to sleep with the head in unusual positions. Upchurch et al., 2011 (19) found in their research that cerebellar herniation and CSF space between cerebellum and brainstem were significantly increased in a flexed position. Other aspect of general well-being like appetite and liveliness are expected to reduce when an animal is suffering from chronic pain. The limitation of these questions is again the reliance on owner interpretation of liveliness and appetite, if the dog never had a good appetite the owner might not find it abnormal.

The last aspect of this study is the efficiency of the prescribed drugs. There are a few conclusions that can be drawn from the survey. Non Steroidal Anti Inflammatory Drugs (NSAID) and gabapentin (gaba agonist) are most effective. Palmitoylethanolamide had no effect, about the rest of the prescribed drugs nothing can be said because of a lack of information. The use of gabapentin modulate voltage-gated calcium channels resulting in a reduction of glutamate and substance P (20). As mentioned before substance P plays an important part in nociception and neuropathic pain because of the high density in the dorsal horn (11). NSAIDs are used because of their inhibitory effect on cyclooxygenase-1 and/or cyclooxygenase-2. They have direct spinal cord action by blocking hyperalgesia induced by the activation of spinal glutamate and substance P receptors(21).

The general limitation of this research is the reliance on owner perceptions and the measurement of the syrinx diameter instead of the asymmetry of the syrinx. A recommendation for further research is to use controlled settings to rule out other influences on clinical signs and ideally all interpretations of the extent of the clinical signs should be done by the same person.

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