Short communication

Association between the findings on MRI screening for syringomyelia in asymptomatic Cavalier King Charles spaniels and observation of clinical signs consistent with syringomyelia in later life

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Abstract

This questionnaire-based study investigated the association between the findings on MRI screening for syringomyelia (SM) in 79 asymptomatic Cavalier King Charles spaniels (CKCS) and the subsequent development of clinical signs consistent with SM in later life. Owners reported clinical signs consistent with SM in 16% of all dogs at the time of questionnaire. A significantly greater proportion of CKCS with a syrinx visible on MRI screening were reported to show clinical signs in later life (36%) when compared to dogs without a visible syrinx (7%) (P = 0.006, OR 6.9). Whether the findings of MRI screening can be used to indicate the likelihood of an asymptomatic CKCS developing clinical signs consistent with SM in later life warrants further prospective study in a larger cohort of dogs.

Keywords: Chiari-like malformation; Dog; Neuropathic pain

Syringomyelia (SM) is the term used to describe a fluid-filled cavity within the spinal cord parenchyma (Rusbridge et al., 2000). Screening for SM using magnetic resonance imaging (MRI) is commonly performed for breeding selection in the Cavalier King Charles spaniel (CKCS) because of its high prevalence in the breed. The aim of this study was to investigate whether the findings of MRI screening in asymptomatic CKCS are associated with the development of clinical signs consistent with SM in later life.

The MRI database at the authors' institution was searched for all CKCS without reported clinical signs consistent with SM (such as phantom scratching, spontaneous vocalisation, other behavioural signs of pain) for which elective screening for SM had been performed between 2006 and 2009. Complete neurological examination was not performed prior to MRI screening. The owners of these dogs were contacted in May 2013 and asked to complete a telephone questionnaire (ethical committee reference CR106). Owners were not made aware of the purpose of the study nor the focus on SM at the time of questionnaire. The questionnaire focused on the general medical history of each dog, the observation of clinical signs defined by the authors as consistent with SM since the time of screening, and if so, at what frequency (Appendix A). Clinical signs defined as consistent with SM included phantom scratching and signs of discomfort or spontaneous vocalisation. Observation of ataxia, paresis, scoliosis or behavioural changes (such as quietness, decreased interest in play) were only defined as consistent with SM if discomfort and scratching or facial rubbing were also reported. Dogs were excluded from the study if there was a known history of other medical conditions that could have mimicked SM by causing clinical signs similar to those listed above. These conditions included epilepsy, heart failure, skin or ear disease, orthopaedic disease, intervertebral disc disease, 'episodic falling syndrome' or 'fly catching'.

All imaging was performed under sedation using 0.3 mg/kg butorphanol (Torbugesic, Zoetis) and 10 μg/kg medetomidine (Sedator, Dechra) administered by IM injection. A 0.2 Tesla permanent magnet (Esaote VetMR spa) was used before October 2008 and a 0.25 Tesla permanent magnet (Esaote VetMR Grande) after this date. T1- and T2-weighted sagittal (2006-2009) and T1-weighted transverse images (2007-2009) were obtained extending from the thalamic adhesion to the level of the C4 vertebra, as for the acquisition of images under the current British Veterinary Association/Kennel Club SM scheme. Scans were randomised and read in a blinded manner by a board-certified neurologist (European College of Veterinary Neurology). A syrinx was defined in this study as a fluid-filled cavity within the spinal cord parenchyma > 1mm in size, isointense to cerebrospinal fluid and visible on all imaging sequences (Houang et al., 1988). The presence of Chiari-like malformation (defined as caudal herniation of part of the cerebellum into or through the foramen magnum) and effusion in the tympanic bullae was also recorded for each case. Dogs were excluded if concurrent spinal diseases, such as atlanto-occipital overlapping or intervertebral disc disease, were observed.

Questionnaire results were combined with MRI data to generate 2 groups: those with a syrinx at the time of imaging and those without. A multivariable binary logistic regression was performed to investigate association between syrinx presence at MRI screening, sex, age at the time of MRI, time interval between imaging and questionnaire, tympanic bulla effusion and the subsequent development of owner-perceived clinical signs consistent with SM. All statistical tests were performed using SPSS v.21 (IBM) with a P value < 0.05 considered statistically significant. Data are expressed as median and interquartile range (IQR).

Seventy-nine questionnaires met the inclusion criteria (53% response rate) consisting of 75 breeder-owned and four privately-owned dogs (25 male, 54 female). Dogs were scanned at a median age of 2.6 years (IQR 2.2 - 3.5 years), with a median time interval between imaging and time of questionnaire or death of 4.5 years (IQR 3.8 - 6.0 years). The prevalence of Chiari-like malformation was 99%.

Twenty-five dogs (32%) had a syrinx identified on MRI and 54 dogs (68%) had no syrinx at the time of imaging (Fig. 1). Thirteen of all 79 dogs (16%) were subsequently reported to display clinical signs consistent with SM, with a median age at onset of 5 years (IQR 4 - 7 years). Only four of the 54 dogs (7%) without a syrinx at MRI screening displayed clinical signs in later life (Fig. 2). Three of these four dogs had a second MRI scan performed 2-4 years after the first scan to exclude an alternative diagnosis for the clinical signs observed, at which time all dogs had a visible syrinx. Nine of the 25 dogs (36%) with a syrinx observed on MRI developed clinical signs consistent with SM later in life (Figs. 3a and 3b).

The presence of a syrinx at screening was the only parameter in the logistic regression to have a significant association with the development of perceived clinical signs of SM in later life ($P = 0.006$), with an odds ratio of 6.9 (95% CI 1.8 - 27.4). Sex ($P = 0.472$), age at the time of imaging ($P = 0.529$), time interval between imaging and questionnaire ($P = 0.911$), and tympanic bulla effusion ($P = 0.610$) were not found to be associated with the development of clinical signs in later life.

The clinical progression in both dogs and humans showing clinical signs of SM is relatively well studied (Driver et al., 2012; Plessas et al., 2012). However, there are few

articles reporting the clinical progression in asymptomatic human patients (Singhal et al., 2011; Strahle et al., 2011) and none in dogs without clinical signs. It has been previously reported that SM is a progressive disease in CKCS, in terms of both syrinx size on MRI and the severity of clinical signs observed in affected dogs (Driver et al., 2012; Plessas et al., 2012). The severity of clinical signs and clinical progression also appear to correlate with syrinx size in both humans and dogs (Bogdanov et al., 2002; Rusbridge et al., 2007). In line with these findings, this study is the first to report that asymptomatic CKCS with a syrinx observed at routine MRI screening appear to be at increased risk of developing clinical signs consistent with SM in later life compared to dogs without a syrinx, at the time of writing. The fact that over 75% of the dogs that were subsequently perceived to show clinical signs did so at least daily, supports the suggestion that this is a disease with a high morbidity in affected animals.

As for other retrospective and questionnaire-based studies, there are limitations which include inaccuracies in owner perception and recollection, and a lack of follow-up imaging in dogs with reported clinical signs to exclude other diseases that may have mimicked or exacerbated signs of SM, such as otitis media or intervertebral disc disease. It must also be considered that Chiari-like malformation alone may have contributed to some of the clinical signs reported by owners of dogs in this study. The owners of dogs with a syrinx observed at screening may also have been more likely to interpret the future behaviour of their dogs as consistent with SM compared to owners of dogs with a clear scan. Seven of the 25 dogs with a syrinx identified on MRI in this study had an intra-parenchymal fluid-filled cavity < 2mm in diameter (1.3 - 1.8mm). The inclusion of dogs with a cavity < 2mm in size (often termed ‘central canal dilation’) may have underestimated the association between observation of a syrinx at MRI screening and the reporting of clinical SM in later life. The small number of

dogs that were subsequently reported to display clinical signs of SM in this study limited the power of multivariate analysis to definitively exclude an association between variables other than syrinx presence on MRI and the development of clinical signs in later life. Whether an asymptomatic CKCS with a syrinx observed on MRI is more likely to display clinical signs consistent with SM in later life compared to dogs without a visible syrinx remains to be confirmed by both clinical and MRI follow-up of a larger cohort of asymptomatic CKCS.

Conflict of interest statement

None of the authors has any financial or personal relationships that could inappropriately influence or bias the content of the paper.

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Appendix A: Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi: …

References

Bogdanov, E.I., Mendelevich, E.G., 2002. Syrinx size and duration of symptoms predict the pace of progressive myelopathy: retrospective analysis of 103 unoperated cases with craniocervical junction malformations and syringomyelia. Clinical Neurology and Neurosurgery 104, 90-97.

Driver, C.J., De Risio, L., Hamilton, S., Rusbridge, C., Dennis, R., McGonnell, I.M., Volk, H.A., 2012. Changes over time in craniocerebral morphology and syringomyelia in cavalier King Charles spaniels with Chiari-like malformation. BMC Veterinary Research 8, 215.

Houang, M.T., Stern, M., Brew, B., Pell, M., Darveniza, P., 1988. Magnetic resonance imaging (MRI) appearances of syringohydromyelia. Australasian Radiology 32, 172-177.

Plessas, I.N., Rusbridge, C., Driver, C.J., Chandler, K.E., Craig, A., McGonnell, I.M., Brodbelt, D.C., Volk, H.A., 2012. Long-term outcome of Cavalier King Charles spaniel dogs with clinical signs associated with Chiari-like malformation and syringomyelia. Veterinary Record 171, 501.

Rusbridge, C., MacSweeny, J.E., Davies, J.V., Chandler, K., Fitzmaurice, S.N., Dennis, R., Cappello, R., Wheeler, S.J., 2000. Syringohydromyelia in Cavalier King Charles spaniels. Journal of the American Animal Hospital Association 36, 34-41.

Rusbridge, C., Carruthers, H., Dube, M.P., Holmes, M., Jeffery, N.D., 2007. Syringomyelia in cavalier King Charles spaniels: the relationship between syrinx dimensions and pain. Journal of Small Animal Practice 48, 432-436.

Singhal, A., Bowen-Roberts, T., Steinbok, P., Cochrane, D., Byrne, A.T., Kerr, J.M., 2011. Natural history of untreated syringomyelia in pediatric patients. Neurosurgical Focus 31, E13.

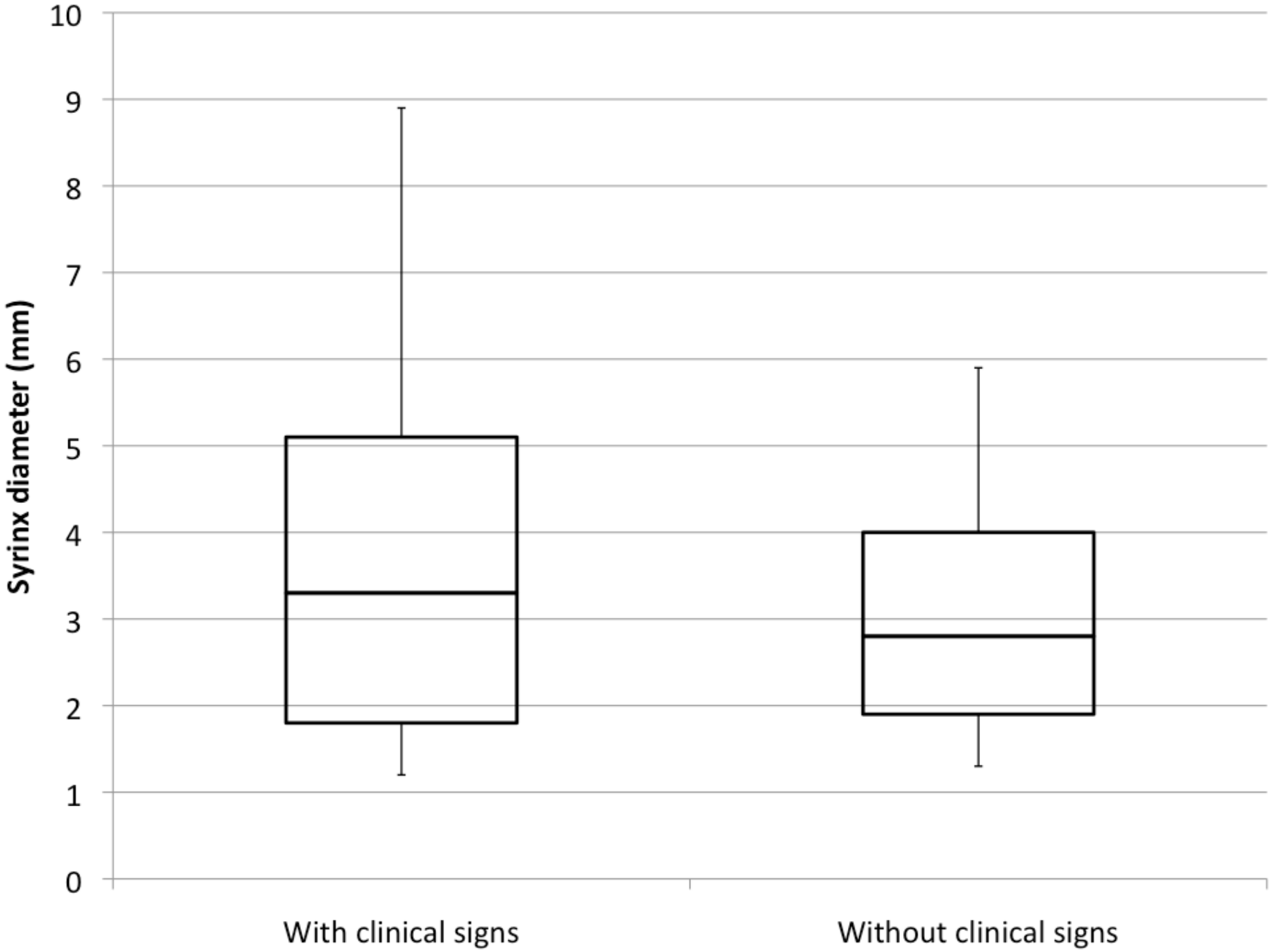
Strahle, J., Muraszko, K.M., Kapurch, J., Bapuraj, J.R., Garton, H.J., Maher, C.O., 2011. Natural history of Chiari malformation Type I following decision for conservative treatment. Journal of Neurosurgery: Pediatrics 8, 214-221.

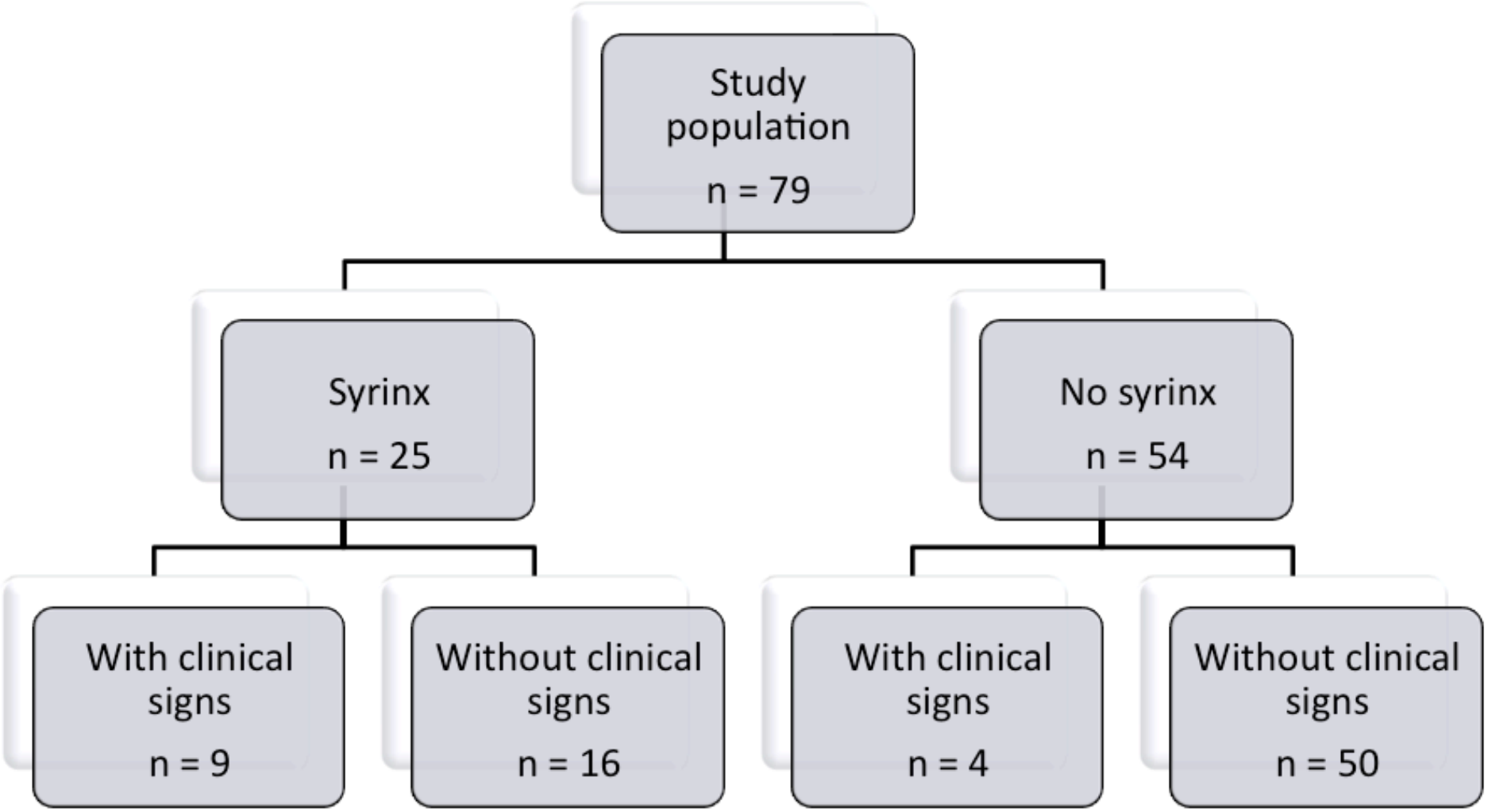
Figure legends

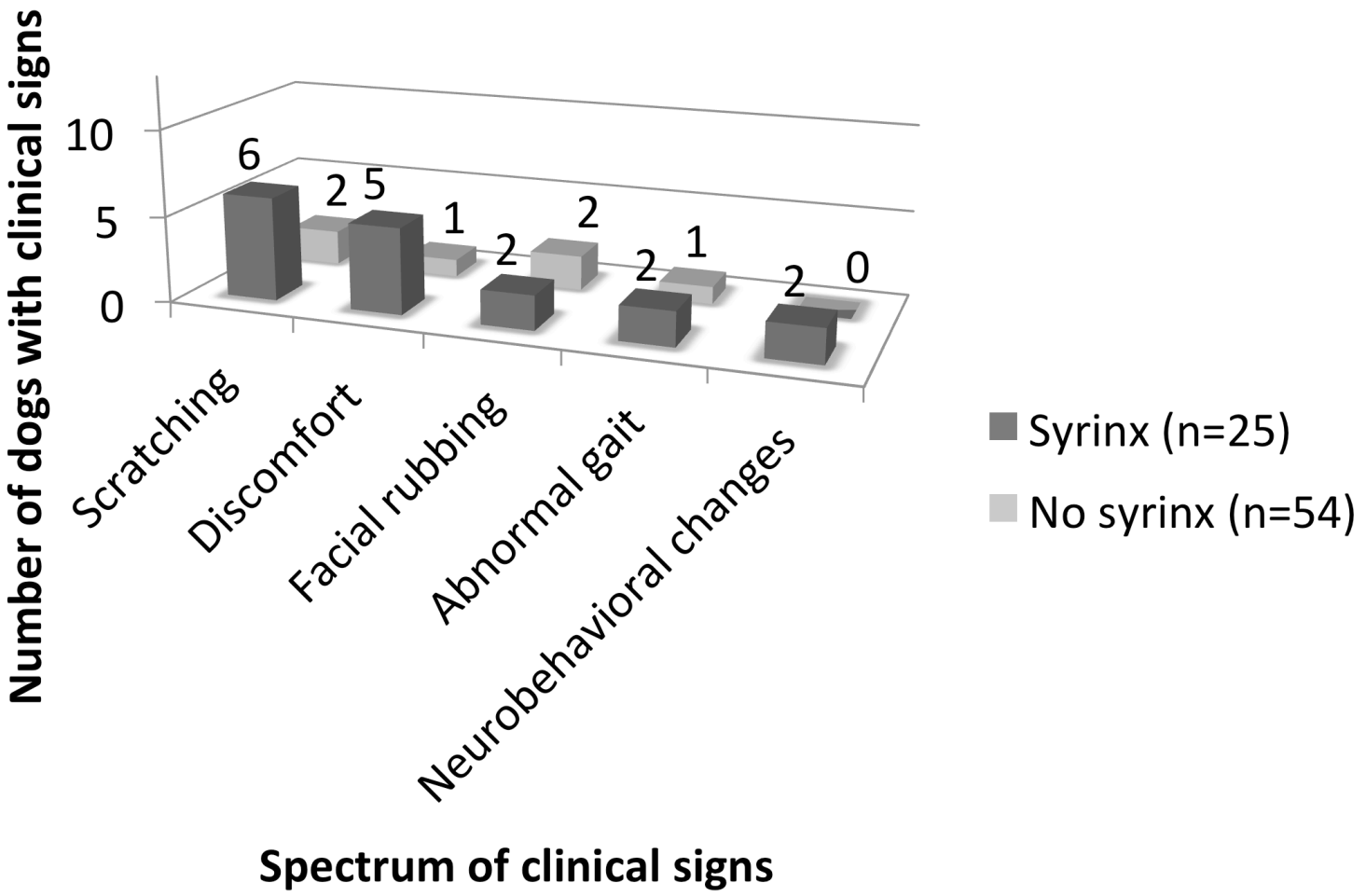
Fig.1. Box-and-whisker plots depicting the maximum syrinx diameter for dogs that were reported to show clinical signs of SM in later life and those that remained without clinical signs.

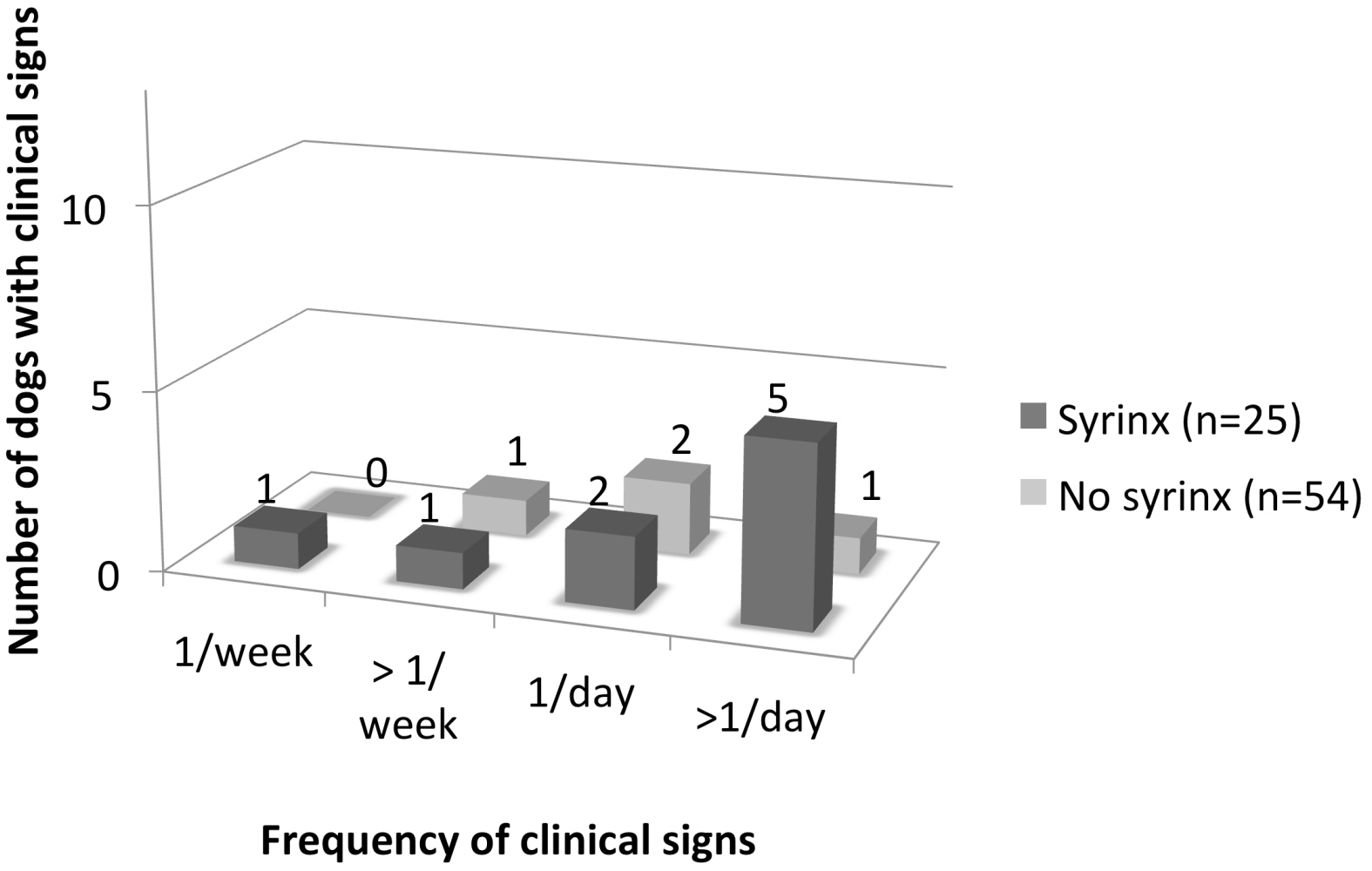
Fig. 2. Flow chart demonstrating the number of dogs in the study population divided into 2 groups dependent on presence or absence of a syrinx at the time of MRI screening. The distribution of CKCS showing clinical signs at the time of questionnaire and those without clinical signs is shown for each group.

241 Fig. 3a. The spectrum of clinical signs consistent with SM reported for CKCS with and
242 without a syrinx at the time of MRI screening.
243
244 Fig. 3b. The frequency of different clinical signs reported for CKCS with and without a
245 syrinx at the time of MRI screening.


10
9
8
7
6
5
4
3
2
1
0
Syrinx diameter (mm)
With clinical signs
Without clinical signs


Study population
n = 79
Syrinx
n = 25
No syrinx
n = 54
With clinical signs
n = 9
Without clinical signs
n = 16
With clinical signs
n = 4
Without clinical signs
n = 50


Number of dogs with clinical signs
10
5
0
6
2
5
1
2
2
2
1
2
0
Scratching
Discomfort
Facial rubbing
Abnormal gait
Neurobehavioral changes
Spectrum of clinical signs
Syrinx (n=25)
No syrinx (n=54)


Number of dogs with clinical signs
10
5
0
1
0
1
1
2
2
5
1
1/week
> 1/ week
1/day
>1/day
Frequency of clinical signs
Syrinx (n=25)
No syrinx (n=54)

APPENDIX - QUESTIONNAIRE

Section 1: GENERAL

Questionnaire Number (for office use only) ☐

Pedigree Name : _____.

Kennel Cub Registration Number: _____.

Sex (***please tick*** √): Male ☐ Male neutered ☐ Female ☐ Female neutered ☐

Age at which dog was first MRI screened for syringomyelia (in years and months e.g. 2 years 6 months) _____.

Did your dog have any of the following medical problems either before or after first MRI screening? *Please tick* √ Yes or No

	BEFORE MRI	**AFTER MRI**
Heart disease	Yes ☐ No ☐	Yes ☐ No ☐
Skin/ear disease	Yes ☐ No ☐	Yes ☐ No ☐
Bone/joint/disc disease (lameness, back pain)	Yes ☐ No ☐	Yes ☐ No ☐
Epilepsy	Yes ☐ No ☐	Yes ☐ No ☐
Collapse/cramp during exercise	Yes ☐ No ☐	Yes ☐ No ☐
Fly-catching	Yes ☐ No ☐	Yes ☐ No ☐

Any other medical problems that may have caused signs of pain (please specify here)_____.

Section 2: CLINICAL SIGNS

(Note: If your dog has died, please indicate answers according to clinical signs observed prior to his/her death):

Since his/her first syringomyelia MRI screening scan, has your dog ever shown any of the clinical signs described in sections 2a to 2d?

Please indicate the **age of onset** (age first noticed) and **most appropriate frequency** where applicable:

Never - Never observed ***N/A not applicable***

>1/d – observed more than once per day

=1/d – observed once per day ***=1/wk – observed once per week***

>1/wk – observed more than once per week ***<1/wk – observed less than once per week***

2a.

Have you ever noticed SCRATCHING:	**Age of onset**	**Frequency** ***(please tick √ as appropriate)***						
		Never	**>1/d**	**=1/d**	**>1/wk**	**=1/wk**	**<1/wk**	**N/A**
Of the shoulder / neck region								
Elsewhere (please specify location here)								

If shoulder/neck scratching was observed, did the foot make contact with skin of the shoulder/neck? Yes ☐ No ☐

If scratching has been observed was it/is it worse when dog exercised/excited? Yes ☐ No ☐

2b.

Have you ever noticed DISCOMFORT/VOCALISATION:	**Age of onset**	**Frequency *(please tick √ as appropriate)***						
		Never	**>1/d**	**=1/d**	**>1/wk**	**=1/wk**	**<1/wk**	**N/A**
When dog is excited								
When dog is touched								
When dog is picked up								
When dog changes head position								
When dog jumps up/down								
When dog passes faeces								
For no obvious reason								
Signs of neck pain (low head carriage, stiff neck)								
Mouth/ear rubbing								

2c.

Have you ever noticed any of the following CHANGES IN GAIT AND POSTURE?	**Age of onset**	**Frequency *(please tick √ as appropriate)***						
		Never	**>1/d**	**=1/d**	**>1/wk**	**=1/wk**	**<1/wk**	**N/A**
Incoordinated gait								

Weakness when walking – If possible please indicate if front or hind limbs or both:								
Twisted neck (scoliosis)								

2d.

Have you ever noticed any of the following BEHAVIOURAL CHANGES?	**Age of onset**	**Frequency *(please tick √ as appropriate)***						
		Never	**>1/d**	**=1/d**	**>1/wk**	**=1/wk**	**<1/wk**	**N/A**
Quietness, decreased interest in play/activity/food								