



Ventriculomegaly in Cavalier King Charles Spaniels with Chiari-like malformation: relationship with clinical and imaging findings

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ABSTRACT. The objective of this study was to calculate lateral ventricles dimension in Cavalier King Charles Spaniel dogs with Chiari-like malformation and investigate the association between ventriculomegaly and signalment, clinical signs, ventricular asymmetry, grade of Chiari-like malformation, syringomyelia and index of medullary kinking. Retrospectively, 43 client-owned Cavalier King Charles Spaniels, older than 1 year of age, with magnetic resonance imaging diagnosis of Chiari-like malformation were enrolled. Initial and follow-up (up to 36 months) clinical status was graded. Images were reviewed to quantify the enlargement of lateral ventricles, evaluate ventricular symmetry, grade of Chiari-like malformation, grade of syringomyelia and medullary kinking index. Cases presenting epileptic seizures during the evaluation period were also recorded. The most common initial clinical signs were scratching and neck pain. Ventriculomegaly was identified in 70% of dogs, Chiari-like malformation grade 2 was observed in 77% of cases, ventricular asymmetry and syringomyelia were identified in 54% and 80% of dogs, respectively; the median medullary kinking index was 37.77%. Moreover, 28% of dogs presented epileptic seizures. No significant association was identified between dimension of lateral ventricles and signalment, clinical signs, and imaging findings; no significant association was identified between ventriculomegaly and epilepsy ($P \geq 0.05$). In conclusion, the prevalence of ventriculomegaly in Cavalier King Charles Spaniels is high but this finding does not seem related to the severity of clinical signs, presence of Chiari-like malformation, syringomyelia and craniocervical junction abnormalities such as medullary kinking.

KEYWORDS: cavalier king charles spaniels, Chiari-like, dog, syringomyelia, ventriculomegaly

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Chiari-like malformation (CM) in dogs is a developmental disease due to malformation of the skull and craniocervical junction resulting in decreased volume of the caudal fossa and subsequent herniation of cerebellum and brainstem through the foramen magnum [10, 21, 22]. This condition is frequently described in brachycephalic, small and toy breed dogs [10, 21]; in Cavalier King Charles Spaniels (CKCS) in particular, its incidence is reported to be as high as 100% [10].

Diagnosis of CM is based on evaluation of magnetic resonance imaging (MRI) studies of the head and the cervical vertebral column [23]; the British Veterinary Association and the Kennel club (BVA/KC) created a CM grading system (CM 0–2) to assess cerebellar morphology [2].

The foramen magnum obstruction induced by CM causes cerebrospinal fluid (CSF) space reduction, abnormal CSF circulation at the level of craniocervical junction and its accumulation above the craniocervical junction. These phenomena can result in syringomyelia (SM) and/or ventriculomegaly [8, 10, 13, 24].

SM, defined as a fluid-filled cavity within the spinal cord [24, 25], has been associated to CM, with a reported incidence of 50–70% in CM-affected dogs [2, 10].

Enlargement of ventricular system in CKCS with CM has also been identified in various reports, and one study documented hydrocephalus in 65% of dogs with CM [15, 21, 25]. Moreover, a correlation between the severity of ventriculomegaly and SM has

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been reported [8].

Furthermore, concurrent anomalies of the craniocervical junction are reported in dogs with CM/SM [3, 4, 10]. In particular, medullary kinking is one of these and is defined as an elevation of the caudal medulla oblongata at the craniocervical junction with possible compression of the subarachnoid space [3, 16]. This abnormality can be quantified (medullary kinking index) on T2-weighted (T2-W) sagittal MRI [16].

Clinical signs described in dogs with CM or SM are vocalization, scratching, reduced activity, spinal pain, scoliosis, abnormal gait with thoracic and pelvic limb ataxia or paresis [10, 20, 26]. However, these clinical signs are not specific of CM and can be similar to other conditions such as intervertebral disc extrusion or otitis media with effusion (OME) [26]. The latter in particular, is frequently described in CKCS and clinical signs are represented by spontaneous vocalization, head and neck pain, scratching of the cervical region [6].

Moreover, epileptic seizures are frequently reported in dogs with CM, prevalently in CKCS [21].

A possible association between ventricular dilation and SM with seizures has been proposed in CKCS [8, 24]. However, the clinical relevance of ventriculomegaly is unclear [8] and results of previous studies are not concordant [7].

The main aims of this study were to quantify ventricular dilation in CKCS with CM, evaluate the relationship of ventriculomegaly with signalment, clinical signs and follow-up, CM grade, SM and medullary kinking index.

Another objective was to record if there were patients with epileptic seizures to investigate possible correlation between epilepsy and grade of ventricular dilation.

MATERIALS AND METHODS

This retrospective study was conducted at the Clinica Neurologica Veterinaria NVA in Milan, Italy collecting data from June 2013 to April 2019. All procedures were performed after obtaining the owners' written consent.

Medical records of client-owned CKCS dogs, older than 1 year of age, that underwent MRI of the head and cervical column and with a final MRI diagnosis of CM were retrieved from the digital database and included in the study. The search terms used were "Cavalier King Charles Spaniel", "Chiari-like malformation", "CKCS". Information about signalment, clinical history, initial physical and neurological findings, complete blood count and serum biochemistry results, MRI findings, treatment, and outcomes was collected and each dog was assigned a study number so that investigators could be blinded. Dogs were excluded if their breed was different from CKCS, if they were younger than 1 year, if they were affected by relevant hematologic abnormalities or other concurrent diseases (such as orthopedic or dermatological problems) that could influence CM-related clinical signs, if information on initial examination was not accessible or if their therapy for CM and SM included surgical procedures. In addition, dogs were not included if the MRI study did not involve the head and cervical column, if it was not evaluable due to imaging artifacts, or if it identified encephalic space-occupying lesions or other concurrent central nervous diseases able to cause a similar clinical presentation to CM.

Gender, body weight and age at the time of first visit were recorded for each dog included in the study and clinical data were reviewed for any history of scratching or rubbing of the neck, head, and shoulder with attention to the frequencies of episodes, decreased interaction, episodes of spontaneous vocalization or pain during cervical column manipulation and abnormal gait. Based on history and examination findings, a grading system (from 0 to 5) was applied to classify neurological status [5].

During data collection, information on the presence of epileptic seizures (yes/no) was also recorded. Epileptic seizures were defined according to the definition of the international veterinary task force consensus report [1]; dogs that presented fly-catching syndrome [36] were not considered in the group of epileptic patients.

MRI was performed with a 0.3 Tesla scanner (Hitachi Airis II, Hitachi Medical Systems, Milan, Italy) and a human knee coil was used. MRI was carried out following the protocol advised by BVA/KC CM and SM scheme [2]; each dog was anesthetized and positioned in sternal recumbency, with head and neck in extension and with the skull base aligned with the floor of the vertebral canal of C1 and C2 vertebral body. Sequences obtained for the brain scan included sagittal and transverse spin echo (SE) T1-weighted (T1-W) and fast spin echo (FSE) T2-W images, and transverse fluid attenuated inversion recovery (FLAIR) images; SE T1-W and FSE T2-W dorsal images, and T1-W images after contrast administration (gadobenate dimeglumine 0.1 mmol/kg [MultiHance, Bracco Imaging SpA, Milan, Italy]) were performed if considered necessary by the radiologist or clinician (Table 1). Sequences obtained for the spinal cord included sagittal and transverse SE T1-W and FSE T2-W images (Table 1). All MRI studies were evaluated with OsiriX MD V.9.0.2, Pixmeo Sarl, Bernex, Switzerland. T1-W and T2-W sagittal MRI images were reviewed independently by two readers, a senior ECVN resident (F.T.) and a final year veterinary student (S.C.) trained by a board-certified neurologist (R.L.) and a senior ECVN Resident (F.T.), to obtain a consensus on the diagnosis of CM. The following variables were determined: dimension and symmetry of lateral ventricles, grade of CM and of SM, medullary kinking index, and the occurrence of unilateral or bilateral OME. Dimension of lateral ventricles was calculated on T1-W transverse images measuring the height of the left and right lateral ventricles (VHL and VHR) and the height of the brain (BH) at the level of the interthalamic adhesion [17] (Fig. 1). Based on these measurements, lateral ventricles were categorized as normal sized ($VH/BH \times 100$: 0–14%), moderately enlarged ($VH/BH \times 100$: 15–25%), or severely enlarged ($VH/BH \times 100$: >25%) [11] and each of these MRI measurements was independently repeated three times by the two readers (F.T. and S.C.) and mean values were obtained. Moreover, to evaluate the reproducibility and repeatability of the measurements inter and intra-rater agreement was calculated. In addition, an attempt to identify dogs with internal hydrocephalus was made following the criteria proposed by Laubner *et al.* (2015) [14] and cases with ventriculomegaly were further classified as hydrocephalic if ventricular/brain index was ≥ 0.6 , if there was an elevation of the corpus callosum, a dorsoventral flattening of the interthalamic adhesion, periventricular edema, dilation of olfactory recesses, thinning of cortical sulci and disruption of the internal

Table 1. Magnetic resonance imaging parameters used for the study of the brain and spinal cord of Cavalier King Charles Spaniels with Chiari-like malformation

MRI plain and sequence	Anatomical region	TR (msec)	TE (msec)	Flip angle (°)	Slice thickness (mm)
Sagittal T1-WI	Brain	638–681	15–18	90	4
Sagittal T2-WI	Brain	2,734–3,390	100	90	4
Transverse T1-WI	Brain	627–696	15–18	90	4
Transverse T2-WI	Brain	2,634–3,842	100	90	4
Transverse FLAIR	Brain	8,800–10,000	100	90	4
Dorsal T1-WI	Brain	590	18	90	4
Dorsal T2-WI	Brain	2,712–3,390	100	90	4
Sagittal T1-WI	Spinal cord	459–638	15–18	90	4
Sagittal T2-WI	Spinal cord	2,734–3,842	100	90	4
Transverse T1-WI	Spinal cord	481–696	18	90	4
Transverse T2-WI	Spinal cord	3,163–3,842	100	90	4

MRI, magnetic resonance imaging; TR, time of repetition; TE, time of echo; WI, weighted images; FLAIR, fluid attenuated inversion recovery.

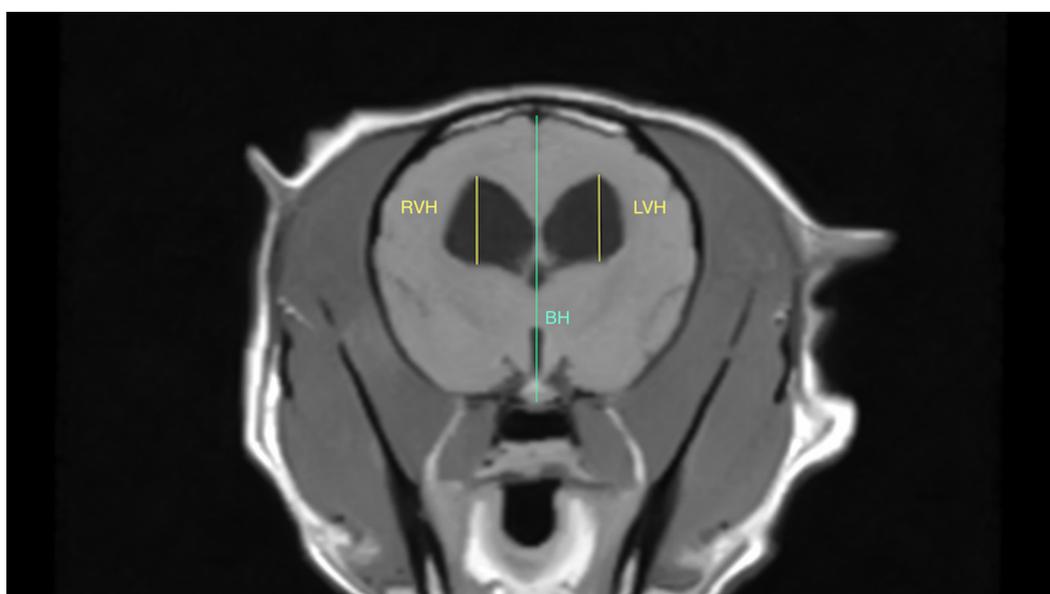


Fig. 1. Transverse T1-weighted magnetic resonance image of a Cavalier King Charles Spaniel affected by severe ventriculomegaly. The image shows the measurement of the right and left lateral ventricle height (RVH and LVH, yellow lines) and of the brain height (BH, green line) at the level of the interthalamic adhesion.

capsule [14].

Presence of ventricular asymmetry was also independently investigated by the two readers on transverse T1-W images [19]. Ventricles were classified as symmetric if the asymmetry of lateral ventricles was judged absent, mildly asymmetric if the asymmetry was evident in several but not all the images in transverse plane, moderately asymmetric if the asymmetry was detectable in all the images in transverse plane, or severely asymmetric if the size of one lateral ventricle was twice the size of the contralateral ventricle [19]. Agreement between the two readers on ventricular symmetry classification was also evaluated.

CM was graded according to the CM scheme proposed by the BVA/KC as CM grade 1 (CM1), cerebellum indented (not round), or CM grade 2 (CM2), cerebellum impacted or herniated through the foramen magnum [2]. SM was graded according to the SM scheme proposed by the BVA/KC: in SM grade 0 (SM0), normal spinal cord; SM grade 1 (SM1), central canal dilation <2 mm; SM grade 2 (SM2), central canal dilation >2 mm, separate syrinx or pre-syrinx with or without central canal dilation [2]. In cases classified as SM2, the maximum width of the syrinx was measured by one reader (F.T.) on transverse T1-W images [23] and on transverse T2-W images [8, 27].

Medullary kinking index was calculated by measuring the distance from the ventral subarachnoid to the point of greatest neural compression at the level of craniocervical junction, dividing this value for the diameter of the adjacent normal portion of cervical spinal cord and multiplying by 100 [16].

MRI measurements of SM2 maximum width and medullary kinking index were repeated three times by one reader (F.T.) and mean values were obtained. Moreover, to evaluate the repeatability of these measurements intra-rater agreement was calculated.

Additionally, the content of the tympanic bulla was evaluated and the occurrence of unilateral or bilateral OME was recorded in case of evidence of material that appeared isointense on T1-W images and hyperintense on T2-W images [18, 33].

Information relative to medical treatment and follow-up data based on clinical re-evaluation and/or telephone interviews with the owners at 1–2 weeks, 1–3 months, 4–8 months and 12–36 months were collected. The same information obtained during the initial examinations was used for follow-up evaluation and applying the same grading system as initial neurological examination (grade 0–5) [5].

Statistical analysis was performed using MedCalc version 19.3.1 (MedCalc Software; Ostend, Belgium; and SAS version 9.4, SAS Institute; Cary, NC; USA). Normality of continuous data was assessed using Shapiro-Wilk test and normally distributed data variables were reported as mean and standard deviation (SD), whereas non-normally distributed data as median and range. The intra-rater and inter-rater intra-class coefficients (ICCs) with 95% confidence intervals (CI) were calculated for VHL, VHR, BH, VHL/BH, VHR/BH. The ICC score ranged from 0 (no agreement) to 1 (perfect agreement) [29]. A poor agreement was defined when $ICC < 0.8$; good if $0.8 < ICC < 0.9$ and excellent if $ICC > 0.9$. The final classification of subjects into the three classes of ventriculomegaly (absent ventriculomegaly 0–14%, moderate ventriculomegaly 15–25%, severe ventriculomegaly >25%) provided by the two readers and the classification of ventricular symmetry were assessed by the kappa inter-rater agreement index. After evaluating the repeatability and reproducibility of the measurements, the measures calculated by one reader (F.T.) were used for statistical analysis. Moreover, the ICCs with 95% CI were calculated for measurements of maximal width of syrinx on T1-W and T2-W images and for medullary kinking index.

The association between ventriculomegaly (scored in the three classes: 0–14%, 15–25%, >25%) and other variables (signalment, initial and follow-up neurological grade, ventricular symmetry, CM and SM grade, severity of central canal dilation, medullary kinking index, presence/absence of epileptic seizures) was assessed.

For normally distributed data, a One-way ANOVA test was applied to evaluate if ventricular enlargement scores showed significant differences for the dependent variables, whereas Kruskal-Wallis test was used for non-normally distributed ones and χ^2 test (or Fisher exact test) for counting data. The Spearman rank correlation test was also calculated to evaluate the association between ventricular dimension and clinical score (at different time points), ventricular asymmetry score, CM and SM grade.

A *post hoc* analysis was performed to estimate the sample size necessary to detect a significant association between class of ventriculomegaly and other variables. The sample size calculation was based on a previous publication where 10 dogs per group enabled power calculation of 80% and a type I error rate (α) of 5% [5]. A *P*-value <0.05 was considered statistically significant.

RESULTS

The medical records of 111 CKCS with CM were reviewed and 43 dogs met inclusion criteria; 68 dogs were excluded for various causes (in 36 dogs an MRI including both the head and cervical column was not performed, 9 had concurrent central nervous system diseases along with CM and in 23 dogs information relative to clinical history and initial physical and neurological findings was not available).

Twenty-eight (65%) dogs were male and 15 (35%) were female (Table 2). The percentage of male dogs was significantly higher ($P=0.01$) than females. The mean \pm SD body weight at first presentation was 9.3 ± 2.3 kg and mean \pm SD age was 4.8 ± 3.1 years (Table 2).

Seven (16%) dogs presented an initial neurological grade of 0, 4 (9%) had an initial neurological grade of 1, 7 (16%) had an initial neurological grade of 2, 23 (53%) had an initial neurological grade of 3 and 2 (5%) had an initial neurological grade of 5.

Table 2. Data of signalment, initial and follow-up neurological scores, number of epileptic dogs related to each class of ventriculomegaly

	Class of ventriculomegaly (%)			Total	<i>P</i> -value
	0–14	15–25	>25		
N. of Animals	13	22	8	43	
Sex Male/Female	8/5	15/7	5/3	28/15	0.91 [†]
Body weight kg (mean \pm SD)	9.7 ± 2.2	9.4 ± 2.3	8.3 ± 2.4	9.3 ± 2.3	0.37 ^{††}
Age Years (mean \pm SD)	4.5 ± 3.0	4.5 ± 3.0	6.1 ± 3.1	4.8 ± 3.1	0.43 ^{††}
Initial NS median score (observed range)	3 (0–5)	3 (0–5)	3 (0–3)	3 (0–5)	0.88 ^{†††}
Follow-up NS median score (observed range)					
- 1–2 weeks	1 (0–3)	2 (0–5)	2 (0–4)	2 (0–5)	0.15 ^{†††}
- 1–3 months	1 (0–3)	2 (0–5)	2 (0–4)	2 (0.5)	0.05 ^{†††}
- 4–8 months	0.5 (0–3)	2 (0–5)	1 (0–4)	2 (0–5)	0.23 ^{†††}
- 12–36 months	1.5 (0–3)	2 (0–5)	2 (0–5)	2 (0–5)	0.37 ^{†††}
N. of dogs with epilepsy (% respect the class of ventriculomegaly)	3 (23%)	7 (32%)	2 (25%)	12 (28%)	0.84 [†]

N, number; NS neurological score. Symbols: [†] χ^2 test; ^{††}One-way ANOVA; ^{†††}Kruskal-Wallis non parametric test.

Short term follow-up (1–2 weeks after initial evaluation) was available for 40 patients; 8 (20%) dogs had a neurological grade of 0, 8 (20%) had a neurological grade of 1, 13 (33%) had a neurological grade of 2, 9 (23%) had a neurological grade of 3, 1 (3%) had a neurological grade of 4 and 1 (3%) had a neurological grade of 5. A second follow-up (1–3 months after initial evaluation) was accessible for 40 patients; 10 (25%) dogs had a neurological grade of 0, 9 (23%) had a neurological grade of 1, 11 (28%) had a neurological grade of 2, 8 (20%) had a neurological grade of 3, 1 (3%) had a neurological grade of 4 and 1 (3%) had a neurological grade of 5. Medium term follow-up (4–8 months after initial evaluation) was available for 39 dogs; 13 (33%) dogs had a neurological grade of 0, 6 (15%) had a neurological grade of 1, 12 (31%) had a neurological grade of 2, 5 (13%) had a neurological grade of 3, 2 (5%) had a neurological grade of 4 and 1 (3%) had a neurological grade of 5. Long term follow-up (12–36 months after initial evaluation) was available for 34 patients; 8 (24%) dogs had a neurological grade of 0, 7 (21%) had a neurological grade of 1, 10 (29%) had a neurological grade of 2, 6 (18%) had a neurological grade of 3 and 3 (9%) had a neurological grade of 5. To summarize, among initially symptomatic (36/43) dogs, 8/36 (22%) dogs remained stable, 4/36 (11%) neurologically progressed and 18/36 (50%) improved at the end of the evaluation period (12–36 months). Among initially asymptomatic (7/43) dogs, 3/7 (43%) dogs did not develop clinical signs, 1/7 (14%) neurologically progressed and 3/7 (43%) died for unrelated problem at the end of the evaluation period (12–36 months).

Medical treatment adopted for symptomatic dogs included: non-steroidal anti-inflammatory drugs (carprofen 2 mg/kg PO every 12 hr [Rimadyl, Pfizer Srl, Rome, Italy]), corticosteroids (prednisolone 0.5 mg/kg PO every 24 or 12 hr [Vetsolone, Bayer SpA, Milan, Italy]), antiepileptics (gabapentin 10 mg/kg PO every 8 or 12 hr [Gabapentin ABC, ABC Pharmaceuticals SpA, Turin, Italy] and pregabalin 4 mg/kg PO every 12 hr [Lyrica, Pfizer Srl, Rome, Italy]), opioids (tramadol 2–3 mg/kg PO every 12 hr [Altadol, Formevet SpA, Milan, Italy]), diuretics (furosemide 1 mg/kg PO every 24 hr [Diuren, Teknofarma SpA, Turin, Italy]) and proton pump inhibitors (omeprazole 1 mg/kg PO every 24 hr [Omeprazolo Teva, Teva Srl, Milan, Italy]).

Epileptic seizures were identified in 12/43 (28%) patients (Table 2).

Ventriculomegaly was considered absent (0–14%) in 13/43 (30%) dogs, moderate (15–25%) in 22/43 (51%) dogs and severe (>25%) in 8/43 (19%) dogs (Table 2). Hydrocephalus was identified in 3/43 (7%) animals. The intra-rater agreement relative to triplicate measurements of VHL, VHR and BH was excellent for both the observers (F.T. ICC: 0.99 for all measurements; S.C. ICC: 0.99 for VHL and VHR and 0.96 for BH). The inter-rater agreement was excellent (ICC: 0.99) for the triplicate measurements of VHL, VHR, VHL/BH and VHR/BH, while it was good (ICC: 0.88) for the triplicate measurements of BH. The agreement between the two readers for final classification of subjects into the three classes of ventriculomegaly was good (k inter-rater agreement index: 0.88).

Ventricular asymmetry was identified in 23/43 (54%) patients and was considered mild in 14 cases, moderate in 5, and severe in 4. Inter-rater agreement for the evaluation of ventricular symmetry was excellent (k inter-rater agreement index: 1).

CM1 was observed in 10/43 dogs (23%), while 33/43 (77%) patients were affected by CM2 (Table 3).

Sagittal and transverse MRI to assess the presence/absence of SM were available in 39 dogs. SM was identified in 31 (80%) dogs; 5 (12%) had SM1 and the remaining 26 (60%) dogs had SM2. SM0 was detected in 8 (19%) cases (Table 3). The mean \pm SD maximal width of the SM2 syrinx measured on T1-W and T2-W transverse images was 4.49 mm \pm 1.91 mm and 4.97 mm \pm 1.92 mm, respectively (Table 3). Intra-rater agreement relative to the triplicate measurement of maximal width of syrinx was excellent for both T1-W (ICC: 0.99) and T2-W images (ICC: 0.99).

The medullary kinking index was calculated in all dogs and median value was 37.77% (range 0–51.12%) (Table 3). The intra-rater agreement relative to the triplicate calculation of this index was excellent (ICC: 0.96).

OME was identified in 6/43 dogs unilaterally and in 11/43 bilaterally.

In our sample of CKCS with CM, no significant association was found between ventriculomegaly and gender ($P=0.91$), body

Table 3. Grades of Chiari-like malformation and syringomyelia, maximal widths of syringomyelia grade 2 measured on T1-weighted and T2-weighted images, medullary kinking indexes related to each class of ventriculomegaly

	Class of ventriculomegaly (%)			Total	P-value
	0–14	15–25	>25		
Grading of CM (N. dogs (% respect the class of ventriculomegaly))					
CM1	3 (23%)	6 (27%)	1 (12%)	10 (23%)	0.89 [†]
CM2	10 (77%)	16 (73%)	7 (87%)	33 (77%)	
Grading of SM (N. dogs (% respect the class of ventriculomegaly))					
SM0	4 (31%)	4 (18%)	0	8 (19%)	0.52 [†]
SM1	2 (15%)	3 (14%)	0	5 (12%)	
SM2	7 (54%)	13 (59%)	6 (75%)	26 (60%)	
Missing	0	2	2	4	
Maximal width of SM2 on T1-WI (mean \pm SD)	4.45 \pm 2.76	4.36 \pm 1.79	4.81 \pm 1.16	4.49 \pm 1.91	0.90 ^{††}
Maximal width of SM2 on T2-WI (mean \pm SD)	5.12 \pm 2.75	4.84 \pm 1.84	5.08 \pm 1.10	4.97 \pm 1.92	0.94 ^{††}
MKI median % (range)	37.50 (0–51.12)	38.37 (0–45.76)	31.94 (0–46.56)	37.77 (0–51.12)	0.83 ^{†††}

CM, Chiari-like malformation; N, number; CM1, Chiari-like malformation grade 1; CM2, Chiari-like malformation grade 2; SM, syringomyelia; SM0, no syringomyelia; SM1, syringomyelia grade 1; SM2, syringomyelia grade 2; WI, weighted images; MKI, medullary kinking index. [†]Fisher exact test; ^{††}One-way ANOVA; ^{†††}Kruskal-Wallis non parametric test.

weight ($P=0.37$), or age ($P=0.43$) (Table 2).

No significant association was found between the presence of ventriculomegaly and the possibility to have neurological signs at initial evaluation ($P=0.73$) or to develop clinical signs during long-term follow-up ($P=0.31$). Moreover, a significant association was not identified between class of ventriculomegaly and neurological scores at initial presentation ($P=0.88$) or at follow-up ($P\geq 0.05$ at all times) (Table 2). Additionally, ventriculomegaly was not significantly associated with the presence of epileptic seizures ($P=0.84$) (Table 2).

OME was not significantly associated ($P=0.81$) with evidence of clinical signs during initial evaluation.

Ventricular asymmetry was not significantly associated ($P=0.09$) with ventriculomegaly in our CM cohort.

In all classes of ventriculomegaly, the majority of dogs had CM2, but the class of severe ventriculomegaly had a higher percentage of dogs with CM2 compared with other classes (87% of dogs with CM2 in the class of severe ventriculomegaly vs. 74% with CM2 in the classes of absent and moderate ventriculomegaly) (Fig. 2). However, this association was not significant ($P=0.89$) (Table 3).

No significant association was identified between grade of SM and class of ventriculomegaly ($P=0.52$) (Table 3). In the group of SM2, dogs with severe (>25%) ventriculomegaly frequently had higher values of maximal width of the syrinx (4.81 ± 1.16 mm and 5.08 ± 1.1 mm on T1-W and T2-W images, respectively) compared with dogs that had an absent (0–14%) or moderate (15–25%) ventriculomegaly (4.40 ± 2.10 mm and 4.90 ± 2.13 mm on T1-W and T2-W images, respectively) (Figs. 3 and 4). However, the differences were not significant ($P=0.90$; $P=0.94$) (Table 3).

Finally, no significant association was found between medullary kinking index and class of ventriculomegaly ($P=0.83$) in our population of dogs (Table 3).

DISCUSSION

Lateral ventricle dimension, size and symmetry vary among different breeds of healthy dogs [11, 28, 32, 35]. In fact, the incidence of ventriculomegaly reported in Beagle is 47.6% and 8% in Labrador Retriever [11]. Another study conducted on Griffon Bruxellois documented moderate or severe ventriculomegaly in 75% of dogs [22].

Ventriculomegaly and hydrocephalus have been documented in CKCS with CM/SM [15, 25]. Ventricular dilation can occur secondary to obstruction and disturbance of CSF flow at the craniocervical junction [10, 22]. However, the clinical relevance of ventriculomegaly and its correlation with other imaging findings in CKCS with CM is unclear and not fully investigated [8, 15].

The objective of our study was that of evaluating the dimension of lateral ventricles and relationship between ventriculomegaly and other variables of CM in this breed.

Moderate (15–25%) to severe (>25%) ventriculomegaly was documented in 70% of CKCS with CM.

The majority of dogs were male, mean body weight was 9.3 kg and mean age was 4.8 years. A significant association between class of ventriculomegaly and gender, body weight and age were not identified. These results are in line with previous studies in dogs where no relationship between signalment and possibility of developing CM-SM related clinical signs was encountered [5, 12, 34].

Interestingly, in humans with Chiari type I malformation there is a positive association between body mass index and SM; in fact,

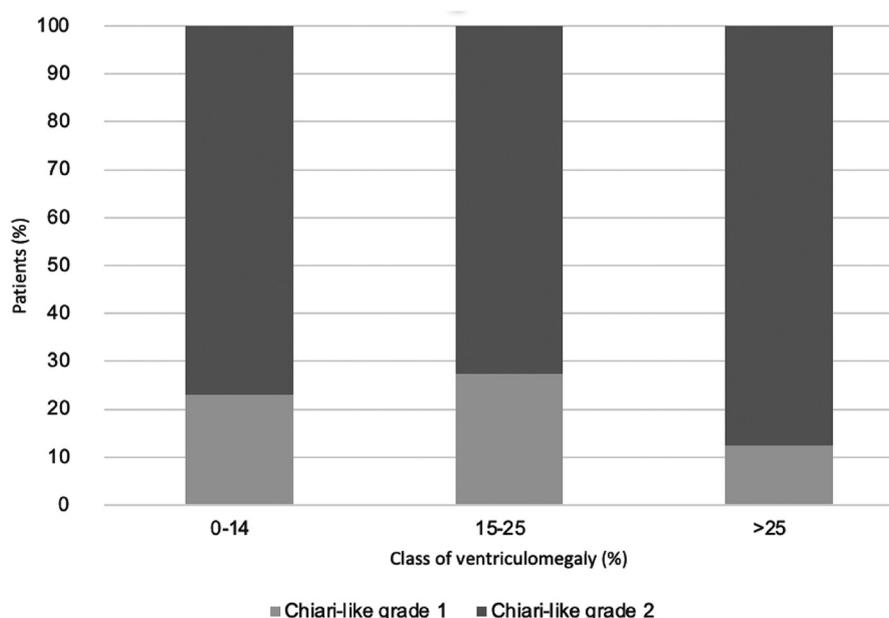


Fig. 2. Percentage of patients affected by Chiari-like malformation grade 1 or Chiari-like malformation grade 2 related to each class of ventriculomegaly (0–14%=absent ventriculomegaly; 15–25%=moderate ventriculomegaly; >25%=severe ventriculomegaly).

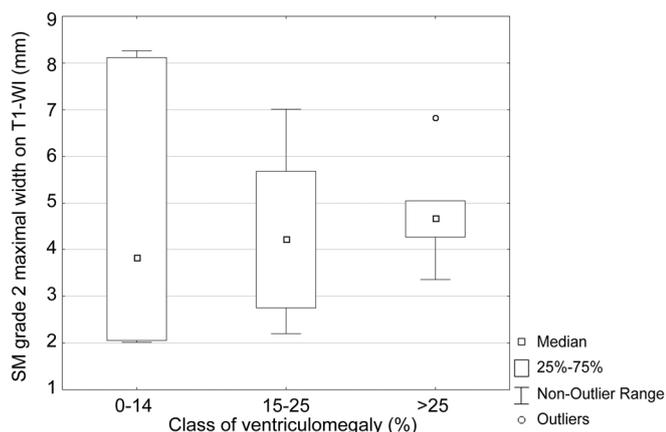


Fig. 3. Distribution of maximal width measurements of syringomyelia (SM) grade 2 in each class of ventriculomegaly (0–14%=absent ventriculomegaly; 15–25%=moderate ventriculomegaly; >25%=severe ventriculomegaly); magnetic resonance imaging measurements on T1-weighted images (T1-WI).

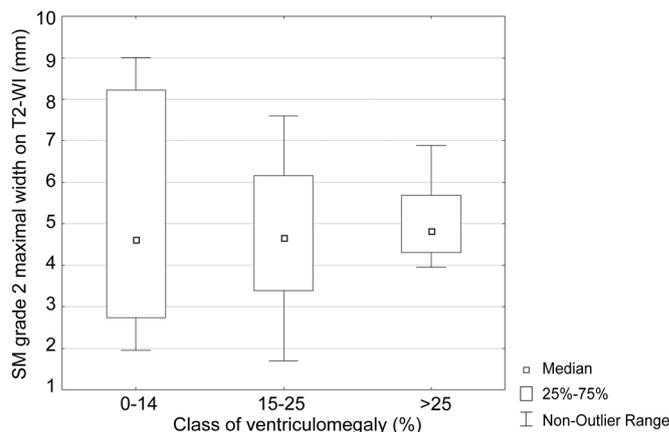


Fig. 4. Distribution of maximal width measurements of syringomyelia (SM) grade 2 in each class of ventriculomegaly (0–14%=absent ventriculomegaly; 15–25%=moderate ventriculomegaly; >25%=severe ventriculomegaly); magnetic resonance imaging measurements on T2-weighted images (T2-WI).

body weight reduction is recommended in obese patients affected by the disease [21]. It is possible that the use of body condition score in our cases may have allowed a more objective evaluation of the obesity of the patients. However, due to the retrospective nature of our study it was impossible to obtain these data.

The most common clinical signs identified during initial clinical exam were scratching and neck pain. These findings are comparable with results of previous researches where vocalizations, spinal pain, exercise intolerance, scratching and rubbing of the head and facial regions were some of the most frequent clinical signs reported in dogs with CM associated with pain with or without SM [5, 26].

At the end of the evaluation period, the majority of symptomatic dogs improved their neurological score and only a minority of dogs had progression of clinical signs. These results are concordant with the study of Lu *et al.* (2003) [15] where 51% of symptomatic CKCS improved and only 15% deteriorated during the evaluation period. However, other reports documented a progression of clinical signs in 25–75% of symptomatic CKCS during an evaluation period of 38 to 71 months [4, 20, 31]. In our study, follow-up information was obtained by reviewing telephone interviews with owners for a maximum follow-up period of 36 months. It is possible that the absence of clinical re-evaluation and the relatively short period of follow-up might have influenced our results.

No association between clinical signs and class of ventriculomegaly was identified. Previous studies that evaluated the dimension of lateral ventricles in dogs did not find any significant association between presence of clinical signs and ventricular size [9, 30]. Moreover, in symptomatic CKCS, no association has been identified between ventricular size, other morphometric variables such as volume of the caudal cranial fossa, cerebellar herniation, craniocervical junction abnormalities and presence or deterioration of clinical signs [4, 15, 20].

Primary secretory otitis media is frequently described in CKCS and the reported clinical signs may be similar to those described in dogs with CM [6]. Interestingly, no relationship between OME and clinical signs was found in our population. These results are concordant with previous literature and it is possible that otitis media is a consequence of the brachycephalic conformation of CKCS, but the clinical significance of the disease is unclear [12, 15, 26, 34].

In our population, 28% of dogs developed epileptic seizures during the evaluation period; no significant association was identified between presence of epileptic seizures and severity of ventriculomegaly; moreover, none of the 3 hydrocephalic dogs presented epilepsy in our study. These results confirm that CKCS with CM have an elevated incidence of epileptic seizures [21] and support the previous theory that ventriculomegaly does not seem to have a role in the pathogenesis of epilepsy in this breed [7].

Considering morphological differences and the subsequent clinical impact between the ventriculomegaly and hydrocephalus, an attempt to differentiate the two entities was made following the schemes proposed by Laubner *et al.* (2015) [14]. Hydrocephalus was observed in 3/43 dogs. All of the 3 dogs were younger than 7 years old, were affected by severe (>25%) ventriculomegaly and had a SM2; 2 of the 3 dogs were symptomatic during the initial neurological examination and 1 was asymptomatic; neither of these dogs presented epileptic seizures during the evaluation period. The reduced number of patients with hydrocephalus did not allow statistical analysis.

Asymmetry of lateral ventricles is frequently reported during evaluation of MRI studies of canine breeds and its prevalence is different among breeds. For example, the prevalence of ventricular asymmetry reported in normal Beagles is 47.6%; in Labrador retriever is 31% and in German Shepherd and Yorkshire Terrier is 70% [11, 19]. In our report, the prevalence of lateral ventricular asymmetry in CKCS was 54% and no significant association was found between presence of ventricular asymmetry and ventriculomegaly. This result might support the previous theory that ventricular asymmetry may be an incidental anatomical variant [19].

Dogs with severe (>25%) ventriculomegaly were more likely to have CM2 than CM1. However, CM2 was the most frequently

grade reported in all classes of ventriculomegaly and a significant association was not identified between class of ventriculomegaly and CM grade. To authors' knowledge, there are no other studies evaluating the correlation between these variables, and based on our results no correlation exists between severity of ventriculomegaly and severity of CM.

With regards to the presence of SM, previous studies identified SM in 50–70% of dogs with CM [10] and Driver *et al.* (2010) [8] identified an association between ventricle and syrinx dimensions.

In our study, SM was identified in 80% of dogs, but a significant association between dimensions of lateral ventricles and dimensions of syrinx was not identified. Driver *et al.* (2010) [8] used a different method to calculate ventricular dimensions and did not grade SM according to severity. The different modalities adopted between studies hinders the possibility to draw any conclusions about this topic. However, in our study the number of dogs in the group of severe ventriculomegaly was lower than that of the other 2 groups of ventriculomegaly, and this might have negatively influenced the results.

Medullary kinking index is one of the craniocervical junction anomalies frequently described in association with CM [3, 16]. In human medicine, medullary kinking is reported in patients with Chiari type II malformation with an overall prevalence of 70%; the clinical signs associated with the condition are neuropathic pain and signs related to cervicomedullary disease [3]. In veterinary medicine, the reported prevalence of medullary kinking index in CKCS is of 66–100%; previous studies conducted in CKCS with CM revealed that high values of medullary kinking index were associated with presence of neurological signs, but a significant association between the index and severity or worsening of clinical signs, or with the development of SM, was not identified [3, 4]. In our study, medullary kinking was identified in 93% of dogs and an association between ventricular dimension and medullary kinking index was not identified. To our knowledge, no previous studies have analyzed this correlation in dogs.

Limitations of the current study include its retrospective nature and the impossibility to obtain some important data. The number of patients in the group of severe (>25%) ventriculomegaly was smaller (8 patients) than expected (10 patients) and might have influenced the statistical analysis. The study population was smaller than expected because some dogs initially enrolled in the study did not meet inclusion criteria for various reasons.

Information relative to telephone interviews with the owner was reviewed to obtain follow-up data and clinical re-exam to verify the impression of the owner was not always performed, which might represent a bias in collecting the data. Nevertheless, a grading scheme with specific points was used to collect data and if the information requested was not reported in the database it was considered missing.

The use of low field MRI could represent a limitation, especially for evaluation of the syrinx dimension. However, presence and syrinx dimension were always evaluated considering T1-W and T2-W images based on the concept that T1-W images are preferred in a low-field machine to evaluate syrinx dimension, while T2-W images are more sensitive to evaluate the presence of edema, pre-syrinx of the spinal cord [23]. Finally, among multiple craniocervical junction abnormalities only the role of medullary kinking index was investigated herein and it could be interesting to extend the analysis to the other anomalous conditions that can occur in conjunction with CM/SM.

Overall, our results suggest that the incidence of ventriculomegaly in CKCS with CM is common. However, the presence of ventriculomegaly does not appear to be related to the development of clinical signs, grade of CM and SM, or index of medullary kinking. Moreover, although the incidence of epilepsy is high in CKCS with CM, no association was seen between ventricular size and epileptic seizures.

Further prospective studies with larger number of patients are warranted to investigate the relationship between ventriculomegaly and CM in CKCS.

CONFLICT OF INTEREST. The authors declare that there were no conflicts of interest.

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