

## MRI-based morphometric analysis in relation to Chiari-like malformation in brachycephalic canine breeds

*MRI-gebaseerde morfometrische analyse gerelateerd aan chiari-achtige malformatie bij brachycefale hondenrassen*

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### ABSTRACT

The aim of this study was to investigate potential differences and correlations between brain and skull morphology and the clinical signs of brachycephalic dogs with and without Chiari-like malformation (CLM). Various measurements were derived from magnetic resonance images of the brain and craniocervical junction of thirty brachycephalic dogs in a flexed-neck position. Each dog was assigned a clinical grade. The distance from the planum of the foramen magnum to the pons was significantly reduced, providing evidence of craniocephalic disproportion similar to human patients with Chiari malformation type I. Cerebral length relative to cranial length was significantly increased in dogs with CLM compared with control dogs, supporting the hypothesis that CLM is governed by a global overcrowding of the brain, dissimilar to the human condition. Significant correlations were identified between these measurements and the extent of cerebellar herniation. No significant differences or correlations were identified with clinical grade. This is the first described morphometric analysis to use a strictly brachycephalic study population inclusive of a control group free from CLM.

### SAMENVATTING

Het doel van deze studie was om de potentiële verschillen en correlaties te onderzoeken tussen de hersen- en schedelmorfologie en de klinische klachten van brachycefale hondenrassen met en zonder chiari-achtige malformaties (CLM). Van MRI-afbeeldingen van de hersenen en de craniocervicale overgang van dertig brachycefale honden met de nek in flexie werden verscheidene metingen afgeleid. Aan elke hond werd een klinische score toegewezen. Er was sprake van een significant kleinere afstand tussen het planum van het foramen magnum en de pons, wat bewijs leverde voor craniocefalie-disproportie vergelijkbaar met de chiari-malformatie type I bij de mens. De cerebrale lengte in relatie tot de craniale lengte bij de honden met CLM was significant groter dan die van de honden in de controlegroep zonder CLM. Dit ondersteunde de hypothese dat er bij CLM sprake is van een globale overpopulatie van de hersenen; dit in tegenstelling tot bij de mens. Er was sprake van een significante correlatie tussen deze metingen en de mate van cerebellaire herniatie. Er werden echter geen significante verschillen tussen, noch correlaties met de klinische score aangetoond. Dit is de eerste beschrijving van een morfometrische analyse van een uitsluitend brachiocefale populatie bij zowel een studiegroep met CLM als een controlegroep zonder CLM.

### INTRODUCTION

Chiari-like malformation (CLM) has been recognized in several brachycephalic canine breeds including the cavalier King Charles spaniel, griffon Bruxellois, French bulldog, Chihuahua, Pomeranian, Maltese terrier, Pug, Boston terrier, miniature poodle, shih-tzu, Beagle, Affenpinscher, Miniature dachs-

hund, Tibetan spaniel and Yorkshire terrier (Dewey et al., 2005; Marino et al., 2012). It has been reported as a canine analogue of the human condition Chiari malformation type I (Marino et al., 2013). In the cavalier King Charles spaniel (CKCS), the prevalence of CLM approaches 95% (Dewey and Rusbridge, 2008). It is regarded as a heritable condition and is characterized by caudal displacement of the cerebellum into

or through the foramen magnum (Rusbridge, 1997; Rusbridge and Knowler, 2004) and by overcrowding of the caudal cranial fossa (Cross et al., 2009; Rusbridge, 2013).

An important consequence of CLM is syringomyelia (SM), a condition whereby fluid-filled cavities develop within the parenchyma of the spinal cord. SM is presumed to result from alteration of cerebrospinal fluid (CSF) flow patterns secondary to constriction at the cervicomedullary junction (Rusbridge et al., 2006). SM has been found to be late in onset and progressive in nature, with a prevalence of up to 70% in dogs with CLM (Parker et al., 2011).

There is considerable variation in clinical signs associated with the CLM-SM complex. The most consistent clinical signs in dogs include neck pain, back pain, lameness, scoliosis, ataxia, and apparent pruritus of the head, neck and shoulder regions referred to as phantom scratching (Dewey et al., 2005; Dewey and Rusbridge, 2008; Rusbridge et al., 2000; Dewey et al., 2004). In humans, it is recognized that Chiari malformation alone can cause significant morbidity and reduced quality of life (Panigrahi et al., 2004). Clinical signs of CLM-SM are most often progressive (Plessas et al., 2012) and can be highly debilitating and distressing for both dogs and their owners. Surgical and medical treatment options are available but have variable and often limited success (Dewey et al., 2007; Rusbridge et al., 2007; Motta and Skerritt, 2012).

Magnetic resonance imaging (MRI) is considered the gold standard for the diagnosis of CLM in humans and dogs (Lu et al., 2003). Consistent findings include a change in shape of the caudoventral aspect of the cerebellum, referred to as coning of the vermis, directed caudally through the foramen magnum, attenuation of the subarachnoidal space dorsally, indentation of the cerebellum by the squamous part of the occipital bone, and elevation of the medulla at the corticomedullary junction (Marino et al., 2012; Rusbridge et al., 2000; Dewey et al., 2004; Carrera et al., 2009; Cerda-Gonzalez et al., 2010). A flexed neck position increases the extent of cerebellar herniation and is useful in assessing the full extent of this feature (Upchurch et al., 2011). Other craniovertebral junction abnormalities associated with Chiari-like malformation include atlanto-occipital overlap, occipital dysplasia, atlantoaxial subluxation and dorsal angulation of the dens (Marino et al., 2012; Stalin et al., 2008; Cerda-Gonzalez et al., 2009).

Despite extensive previous research, an irrefutable risk morphology for the CLM-SM complex has not been established. This may be, in part, due to the lack of understanding of its pathogenesis and a lack of suitable controls for comparisons. Previous morphometric studies have produced conflicting results (Cross et al., 2009; Carrera et al., 2009; Cerda-Gonzalez et al., 2009; Driver et al., 2010; Shaw et al., 2012). This is likely, in part, due to the lack of consistent control groups. The high prevalence of CLM in the CKCS

prohibits a comparison with CLM free dogs within this breed alone. In this study, a strictly brachycephalic study population was utilized for morphometric comparisons between dogs with and without CLM. This inclusion criteria was applied due to the fact that CLM has only been reported in these breeds (Marino et al., 2012; Dewey et al., 2004). In many studies, mesocephalic dogs have been used as control groups (Cross et al., 2009; Carrera et al., 2009; Shaw et al., 2012; Shaw et al., 2013). Comparisons between dogs of radically different skull shapes is likely to skew the results of a morphometric analysis due to overall geometric discrepancies. In light of this, other studies have used clinically normal CKCS or CKCS with CLM but without SM (Cerda-Gonzalez et al., 2009; Driver et al., 2010; Carruthers et al., 2009; Couturier et al., 2008; Fenn et al., 2013; Mitchell et al., 2014). Because of the late-onset, progressive nature of SM and the lack of consistent correlation with clinical signs, these control groups may not be entirely representative of disease free individuals. Furthermore, the conclusions of these studies have been challenged by more recent studies suggesting that some of the features identified, such as indentation and impaction of the cerebellar vermis, have a high prevalence in normal dogs, and therefore may be unsuitable for the diagnosis of CLM (Harcourt-Brown et al., 2014). The authors of the current study hypothesized that comparisons amongst brachycephalic dog breeds, including CKCS, may uncover morphometric differences potentially accountable for the development of CLM/SM. Such features could be used to update the current British Veterinary Association and Kennel Club breeding recommendations, adapted from Capello and Rusbridge (2007). Employing a CLM free, brachycephalic control group allows for more reliable comparisons, and is, to the authors' knowledge, the first time it has been employed in the investigation of this condition. In addition, this is the first study to report measurements of the hindbrain of non-CKCS brachycephalic dogs in a flexed neck position.

The aim of this study was to identify risk factors via investigation of potential differences and correlations between brain and skull morphology and clinical signs of brachycephalic dogs with and without CLM.

## MATERIALS AND METHODS

### Case selection

Approval for this study was granted by the institution's Veterinary Ethical Review Committee. A prospective cross-sectional study was performed. The study population consisted of brachycephalic dogs of any age, gender and bodyweight, which underwent MRI of the brain and cranial cervical spinal cord at the Hospital for Small Animals, University of Edinburgh between November 2013 and December 2015 for the investigation of neurological disease. Dogs

with intracranial disease, which could have affected brain morphology and increased intracranial pressure, were excluded from the study.

### MRI examination

All dogs were imaged under general anesthesia using the same 1.5 Tesla MRI unit (Philips Intera, 1.5T system, Philips Medical Systems, the Netherlands). Each dog was placed into dorsal recumbency with the neck flexed at approximately 110-130° to mimic the posture of a normal standing dog consistent with previous studies (Upchurch et al., 2011; Cerda-Gonzalez et al., 2009). A 45°-foam wedge was placed behind the head and held in place by sandbags, a technique previously described (Upchurch et al., 2011). T2-weighted, spin-echo transverse and 'flexed-neck' sagittal sequences of the head and cranial cervical region were obtained. T2-weighted sequences were chosen because hyperintense cerebrospinal fluid (CSF) provides contrast between the brain parenchyma and the skull bone. Flexed-neck sequences were obtained for the purposes of maximizing safety of a CSF tap from the cisterna cerebellomedullaris, and to standardize the position of the craniocervical joint. Gaining this sequence allows visualization of the distance between the spinal cord and the skin surface, and determined whether or not the cerebellar vermis was at risk of puncture prior to a cisternal CSF tap. Flexing the neck also maximizes the extent of cerebellar herniation (Upchurch et al., 2011). The dogs were divided into two groups: those with CLM and a control group without CLM. CLM was assigned in the presence of

all three of the following imaging criteria: herniation of the cerebellum through the foramen magnum, attenuation of the subarachnoid space dorsally and medullary elevation.

### Morphometric measurements

Images were uploaded into a DICOM viewer (OsiriX<sup>R</sup> DICOM workstation). Thirteen measurements were made by a diagnostic imaging resident blinded to the signalment, history and clinical findings of the patient in order to reduce bias and standardize the error. Using the mid-sagittal T2-weighted image, a line was drawn from the dorsal to the ventral rim of the foramen magnum. The distances to several neural structures were measured perpendicular to this plane, including the tectum mesencephali, fastigium and pons, which in humans have been proven to be reliable indicators of the presence of craniocervical disproportion (Urbizu et al., 2014) (Figure 1A). If the cerebellum was herniated through the foramen magnum, the distance to the caudal tip of the vermis was measured at a right angle from the planum of the foramen magnum, a technique that has been widely utilized (Cerda-Gonzalez et al., 2009; Couturier et al., 2008; Driver et al., 2012; Freeman et al., 2014) (Figure 1B). The cerebellar surface area was estimated via free-hand using the closed polygon measurement tool (Carrera et al., 2009; Lu et al., 2003) (Figure 1C). The cerebral length was measured as a straight line across the longest dimension of the cerebrum, from the maximal convexity of the internal surface of the occipital bone to the rostral margin of

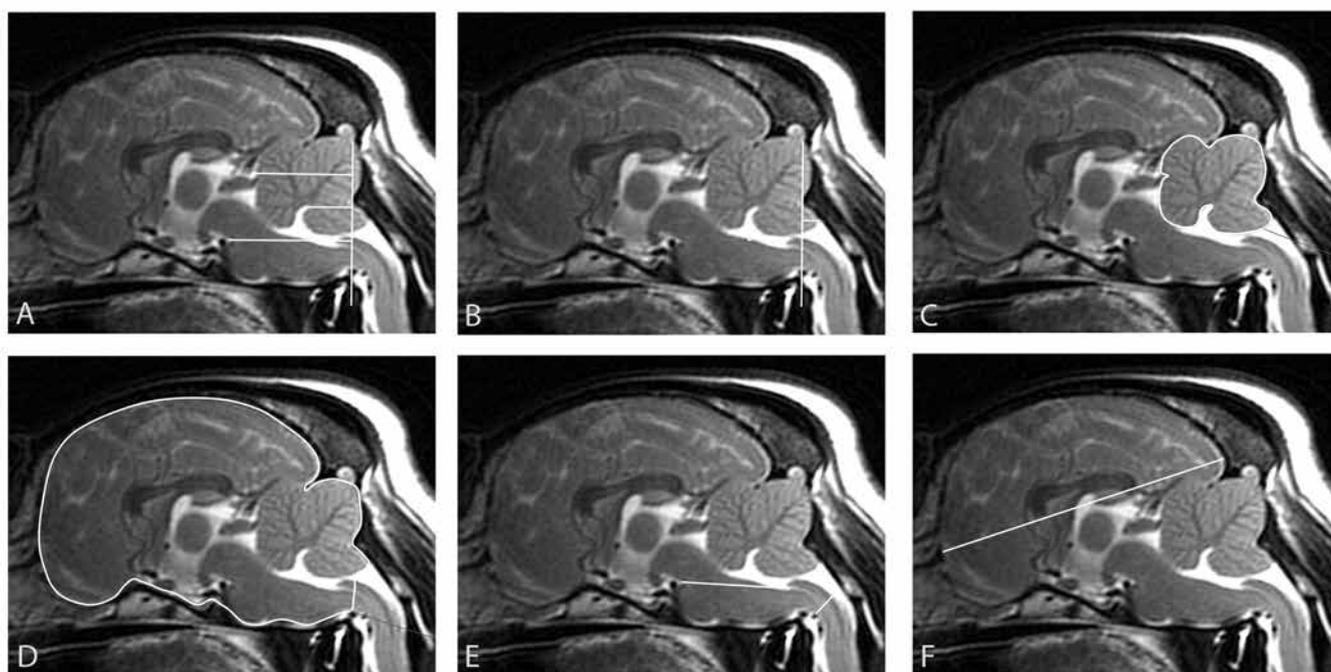


Figure 1. Morphometric measurements included A. the distance of the pons, fastigium and tectum mesencephali from the planum of the foramen magnum, B. length of herniated cerebellum, C. surface area of the cerebellum, D. surface area of the entire brain, E. distance between the obex and pons and the spinal cord diameter, and F. cerebral length.

**Table 1. Clinical grading scheme.**

| Grade | Clinical Signs   |
|-------|--|
| 0     | Normal   |
| 1     | Occasional phantom scratching of the shoulder, neck or flank, or facial/ear rubbing  |
| 2     | Phantom scratching of the shoulder, neck or flank, or facial/ear rubbing multiple times per week, and signs of neck or back pain |
| 3     | Phantom scratching of the shoulder, neck or flank, or facial/ear rubbing multiple times per day, and signs of neck or back pain  |

the olfactory bulbs on a mid-sagittal image (Figure 1F). The cranial length was measured from the nasion at the nasofrontal suture to the inion, the central surface point on the external occipital protuberance. The cranial width was measured as a line drawn across the widest part of the braincase (euryon to euryon) from a transverse T2-weighted sequence (Schmidt et al., 2011). The distance between the pons and the obex was measured, and the spinal cord diameter was measured across its greatest dorsoventral width at the pivot of flexion (Figure 1E). It was hypothesized by the authors that the diameter of the spinal cord at the pivot of flexion might be relevant in the disruption of CSF flow dynamics.

Due to the anatomic variation in skull conformation and the size of brachycephalic dogs, all measurement values were normalized in order to achieve more accurate comparisons. The measurements were normalized by calculating ratios with nearby measurements. Distances from the planum of the foramen magnum to the tectum mesencephali, fastigium and pons were divided by the length from the planum to the rostral border of the cerebrum along those same lines. The cerebellar herniation length was divided by the distance to the caudal margin of the fourth ventricle along the same line. The cerebellar area was divided by the total mid-sagittal surface area of the brain, similar to previous studies (Carrera et al., 2009; Lu et al., 2003) (Figure 1D). The cerebral length was expressed as a proportion of cranial length. The cranial index was calculated by dividing cranial length by cranial width. Measurements were separately normalized by body weight. Once all measurements were completed, the signalment of each dog was recorded.

### Clinical Grading

A neurological examination was performed on each dog by a board-certified veterinary neurologist. All dogs were graded for clinical signs, which have been associated with CLM-SM. Grading was based on a review of the clinical history and the results of the neurological examination, and was scored on a scale of 0-3 by another veterinarian, blinded to the

MRI-based morphometric measurements as depicted by Table 1.

### Statistical analysis

All quantitative and qualitative data was entered into Minitab® 17 Statistical Software. The normality of distribution of each variable within the control and CLM groups were evaluated via a Normal Probability Plot.

A two-sample t-test was performed for each morphometric measurement comparing dogs with CLM and dogs without CLM to determine whether the means of the two independent groups was statistically significantly different.

A Spearman rank-order correlation coefficient was calculated to measure the strength and direction of association between each of the morphometric measurements, the extent of cerebellar herniation and the clinical grade. The Spearman correlation between cranial measurements and body weight was also investigated.

Lastly, the potential influence of the variation in the degree of neck flexion was investigated via testing for correlation with cerebellar herniation. Statistical significance was set to  $p < 0.05$  throughout.

## RESULTS

A total of thirty dogs were included in the study, of which five were neutered males, seven intact males, twelve neutered females and six intact females. The breeds represented included the CKCS (16), French bulldog (5), Pug (3), Chihuahua (2), Boxer (2), Staffordshire bull terrier (1) and the Papillon (1). Twenty dogs constituted the CLM group including CKCS (15), Chihuahuas (2), a Papillon (1), Staffordshire bull terrier (1) and a Pug (1). Ten dogs without evidence of CLM on MR imaging were classified as the control group including French bulldogs (5), Boxers (2), a Chihuahua (1), Pug (1) and a CKCS (1).

The dogs of the CLM group had a mean age of 5.4 years with a range of 7 months to 9.3 years. The dogs of the control group had a mean age of 4.7 years with a range of 1 year to 9.5 years. Within the CLM group,

four dogs were assigned a clinical grade of 0, none a clinical grade of 1, six a clinical grade of 2 and ten a clinical grade of 3. Within the control group, two dogs were assigned a clinical grade of 0, none a clinical grade of 1, five a clinical grade of 2 and three a clinical grade of 3.

The flexed-neck sequence allowed an accurate depiction of the extent of cerebellar herniation and thereby the risk involved with cisternal CSF puncture. Normal probability plots confirmed a normal distribution of each morphometric measurement in the control and CLM groups.

The dogs with CLM had a significantly reduced distance from the planum of the foramen magnum to the pons in comparison to the control group (normalized median 3.89 versus 4.24) ( $p = 0.002$ ) (Figure 2A). There was no significant correlation between this distance and the bodyweight. There were no statistically significant differences in distances from the planum of the foramen magnum to the tectum mesencephali and fastigium. The cerebellar surface area relative to the entire brain surface area was not significantly different between the two groups.

The dogs with CLM had a significantly increased cerebral length relative to cranial length in comparison to the control group (normalized median 0.812 versus 0.709) ( $p < 0.001$ ) (Figure 2B). There were no statistically significant differences between the ratio of pons to obex distance and spinal diameter ( $p = 0.928$ ), nor between the cranial index ( $p = 0.146$ ) of dogs with and without CLM. A negative, statistically significant correlation was identified between the distance from the planum of the foramen magnum to the pons and the extent of cerebellar herniation ( $p = -0.459$ ,  $p = 0.011$ ). A positive, statistically significant correlation was identified between the cerebral length relative to cranial length ratio and the extent of cerebellar herniation ( $p = 0.709$ ,  $p < 0.001$ ) (Figure 3).

No further statistically significant correlations were identified between the various morphometric measurements and the degree of cerebellar herniation or the clinical grading scheme ( $p < 0.226$ ,  $p > 0.247$ ).

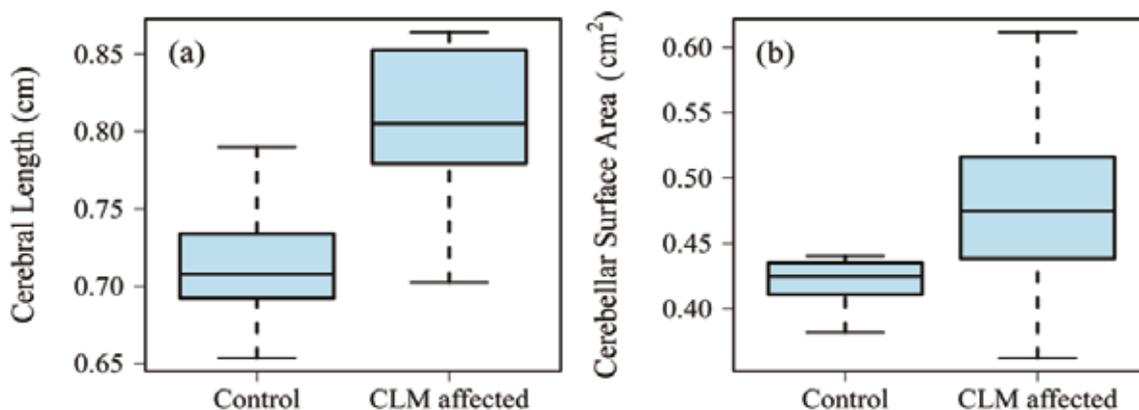
Lastly, there was no correlation between the angle of neck flexion and cerebellar herniation ( $p = 0.178$ ,  $p = 0.345$ ).

## DISCUSSION

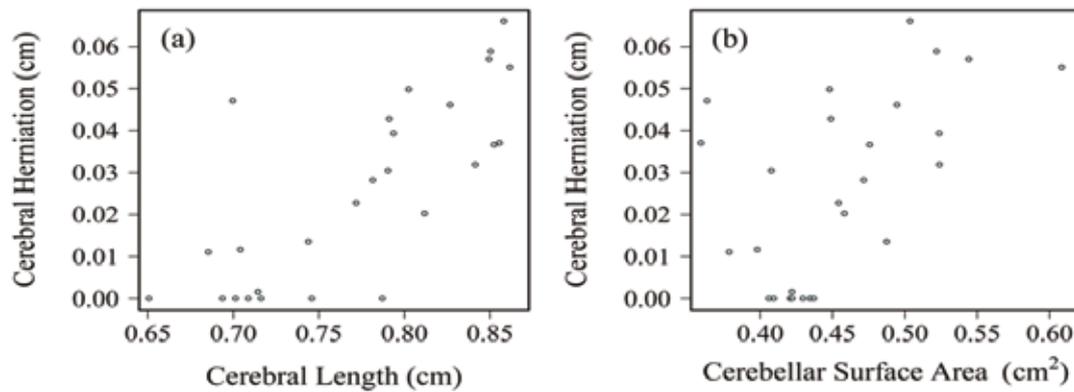
The aim of this study was partially met with the discovery of two important differences between brachycephalic dogs with and without CLM, as well as a significant correlation between these findings and the extent of cerebellar herniation. Due to the lack of correlation with the clinical signs however, the term risk factor cannot confidently be applied.

The distances from the planum of the foramen magnum to the tectum mesencephali, fastigium and pons have been proven to be reliable indicators of the presence of a cranioccephalic disproportion in humans (Urbizu et al., 2014). Despite the differences in posture between the two species, the results of the study suggest that these measurements could also be used in dogs to assess the presence of cranioccephalic disproportion. The dogs with CLM had a significantly reduced distance from the foramen magnum to the pons compared to the control group. In addition, there was a significant negative correlation between this distance and the degree of cerebellar herniation. This has some resemblance with the results of human studies, although likely for different reasons. In human patients with Chiari malformation type I, the distances between the pons, fastigium and corpus callosum from the planum of the foramen magnum are all reduced reflecting decreased depth of the posterior cranial fossa (Urbizu et al., 2014). Impaired occipital bone development and resultant posterior cranial fossa volume reduction is implicated and widely accepted as the cause of cerebellar herniation in human patients with Chiari malformation type I (Milhorat et al., 1999).

The results of the current study are difficult to compare with others due to the use of differing control groups. Two-dimensional measurements in CKCS



**Figure 2.** Boxplots of A. distance from the planum of the foramen magnum to the pons in dogs with CLM and control dogs and B. cerebral length relative to cranial length in dogs with CLM and control dogs. The box represents the interquartile range, the whiskers represent the upper and lower 25% of the distribution, and the horizontal line is the median.



**Figure 3. Scatterplots of A. cerebellar herniation versus distance from planum of foramen magnum to the pons and B. cerebellar herniation versus cerebral length relative to cranial length.**

and mesocephalic dogs have been compared (Carrera et al., 2009). The radically different skull morphology, however, hinders interpretation. Volumetric measurements in affected and non-affected CKCS (Cerdeira-Gonzalez et al., 2009), CKCS and small breed dogs (Cross et al., 2009), and CKCS with and without SM (Driver et al., 2010) have led to conflicting results. The reduction of the foramen magnum to pons distance in the current study could reflect regional shortening of the caudal fossa, or could reflect caudal displacement of the pons by, for example, an overcrowded forebrain. The correlation between this measurement and the degree of cerebellar herniation is interesting as it has not previously been identified and adds further value to this parameter and its association with CLM in dogs. These measurements will need to be tested on a larger number of dogs in order to validate their use in assessing craniocervical disproportion and possibly, the risk of development of SM. These are simple linear measurements, which do not require specialized software as in the case of volumetric measurements, making them valuable for implementation on a large scale in breeding schemes.

The dogs with CLM in this study had a statistically significantly increased cerebral length relative to cranial length in comparison to the control dogs, suggestive of global brain overcrowding. The moderately strong positive relationship between cerebral length over cranial length and the degree of herniation has not previously been reported and suggests that more severe CLM may be associated with forebrain crowding. Supratentorial involvement in CLM has been suggested in previous studies. A volumetric study, which demonstrated that CKCS have a higher percentage of parenchyma within the rostral cranial fossa than labradors and small breed dogs (Cross et al., 2009). Another study found that syringomyelia is significantly associated with a smaller frontal sinus size (Scrivani et al., 2007). The findings of the current study suggest that this implication could be extended to the brachycephalic subgroup, and that a simple, linear measurement could potentially be used to assess

global crowding proven by volumetric studies, which required more specialized software. Overcrowding in the supratentorial portion of the cranium could potentially displace the entire cerebellum and brainstem caudally against the occipital bone contributing to the development of cerebellar herniation and resultant alterations in CSF. By this theory, forebrain overcrowding could be responsible for the caudal displacement of the pons, thereby explaining the reduction in distance between the pons and the foramen magnum as identified in this study. Crowding within the rostral cranial fossa may also account for the variable success rates reported with surgical treatment, which focuses on decompression of the foramen magnum and reconstruction of the caudal cranial fossa (Dewey et al., 2007; Rusbridge et al., 2007).

A flexed neck position was used in this study because it has been shown to maximize the extent of cerebellar herniation (Upchurch et al., 2011), which was used as a criterion for CLM. Flexing the neck stretches the dorsal atlanto-occipital membrane, which, in an extended neck position, lays dorsocaudally on the cerebellum and could be mistaken for part of the occipital bone affecting measurements of the foramen. Moreover, in a recent study, it has been demonstrated that neck extension increases the odds of indentation and impaction of the cerebellar vermis into the foramen magnum (Harcourt Brown et al., 2014). For this reason, it has been proposed that the position of the head in relation to the neck should be standardized to compare the morphology of the cerebellum amongst dogs. The authors of the current study propose that a thorough MRI investigation of CLM in canine patients should include a sagittal sequence in this flexed-neck position in order to fully express the degree of cerebellar herniation and to assess the suitability of at-risk patients for a cisternal CSF puncture. The spinal cord was measured at its hinge point to assess whether the cord of CLM-affected dogs was excessively stretched during flexion of the neck. Excessive stretching of the cord could potentially cause collapse of the central canal. Obstruction of the subarachnoid space at this

point could, based on the Venturi effect or suction effect, cause formation of syringomyelia caudal to this site (Rusbridge et al., 2006). Because no significant differences were identified between affected and non-affected dogs, this theory remains unfounded. It has been proposed that CLM may be associated with a higher grade of brachycephaly, as defined by the cranial index of the braincase (Schmidt et al., 2011). In the current study, there was no statistically significant difference between the cranial indices of dogs with and without CLM, nor a statistically significant correlation between cranial index and extent of cerebellar herniation. In fact, the dogs with the lowest cranial indices were two pugs (1.25 and 1.25), both free of CLM. A Staffordshire bull terrier with the second highest cranial index (1.76) had CLM. This is the first report of CLM in a Staffordshire bull terrier, a breed, which has been previously described to have occipital dysplasia (Janeczek et al., 2011). These findings oppose the theory that a higher degree of brachycephaly alone predisposes to CLM; however, the small sample size employed in this study must be considered. Cranial index does not take cranial height into account. Griffon Bruxellois dogs with CLM have been demonstrated to have a shortened basicranium compensated for by an increase in height of the cranial cavity in comparison to normal Griffon Bruxellois dogs (Rusbridge et al., 2009). In another study, a greater amount of cranium distributed caudally was found to be protective against syrinx development in CKCS. In the same study, a risk phenotype of brachycephaly with rostrocaudal doming that is more rostrally distributed, was proposed (Mitchell et al., 2014). It is most likely that cranial base shortening on its own does not result in CLM, and more likely, that other factors, such as rostrally distributed doming, are involved.

CLM in dogs has previously been attributed to a volume mismatch between the caudal fossa and the parenchyma contained within it, resulting in overcrowding of the hindbrain and herniation through the foramen magnum (Rusbridge et al., 2000; Cerda-Gonzalez et al., 2009; Levine, 2004). Whether such a degree of caudal fossa overcrowding by itself is sufficient to cause herniation of the hindbrain is uncertain. In this study, there was no significant difference in mid cerebellar surface area relative to mid total brain surface area between brachycephalic dogs with and without CLM. This result supports those of previous studies, which used control groups consisting of CKCS (Lu et al., 2003) and mesaticephalic dogs (Carrera et al., 2009). In the current study, these findings are extended to the subgroup of brachycephalic dogs with and without CLM. Conversely, in one study, it was found that CKCS less than two years of age with CM/SM had a larger cerebellar volume relative to total brain volume compared with CKCS older than five years with CLM only (Shaw et al., 2012). SM is a late-onset disease; therefore, despite the age criteria, this control group may erroneously include dogs, which will develop SM in the future. A dynamic component

has been proposed to cranial cavity volumetry, with increasing caudal fossa volumes over time secondary to bone resorption at the foramen magnum (Driver et al., 2012). The sum of previous results and that of the current study is certainly suggestive of an undersized caudal fossa in CLM. A volumetric analysis utilizing a CLM free brachycephalic control group is warranted to investigate cerebellar oversize as a source of volume mismatch.

No statistically significant correlations were identified between the clinical grade of the patient and any of the various measurements. A few dogs in the control group, with no evidence of cerebellar herniation, exhibited signs of severe neuropathic pain whilst other dogs with extensive cerebellar herniation were clinically normal. This supports previous research where, similarly, no statistically significant correlations were identified between the extent of cerebellar herniation and the type of neurological signs exhibited nor with the presence of syringomyelia (Upchurch et al., 2011; Couturier et al., 2008; Lu et al., 2003). A recent longitudinal study also found no association between the morphology of the craniocervical junction and the appearance and progression of clinical signs in CKCS (Cerda-Gonzalez et al., 2016). Potential reasons for the lack of correlation in the current study may relate to a true lack of association between clinical signs and the selected morphological features, the small sample size, or to inadequacy of the designed grading scheme to accurately and specifically categorize clinical subgroups. Correlation has been identified between syrinx width and pain, scratching behavior and scoliosis in veterinary patients (Rusbridge et al., 2007). In contrast, a more recent study did not find a significant relationship between syringomyelia and both the development and worsening of clinical signs (Cerda-Gonzalez et al., 2016). Syrinx formation and clinical signs are often late in onset. Therefore, it is possible that the grading system of the current study has failed to capture the true severity of disease especially in the younger, potentially pre- or subclinical dogs in this study.

No statistically significant associations nor correlations were identified between the ratio of the distance from the obex to the pons and the spinal cord diameter. This ratio was calculated to assess whether a larger spinal cord diameter was associated with CLM. Obstruction to the flow of cerebrospinal fluid at the foramen magnum has been demonstrated in CKCS with CLM (Cerda-Gonzalez et al., 2009). It has been hypothesized that the diameter of the spinal cord at the pivot of flexion may be relevant in this disruption of CSF flow dynamics. The lack of statistically significant differences in the current study may reflect the true lack of a relationship or may be due to the small sample size and resultant deficiency in statistical power.

Limitations of the current study include the small number of dogs within the sample, most notably reflected in the control group and the potential popula-

tion bias of dogs presenting with neurological disease at an advanced stage. Additional research with a larger population of brachycephalic dogs with and without CLM and perhaps with the omission of younger dogs to limit the risk of including pre- or subclinical individuals, is necessary to corroborate the present findings. A larger study population would allow the use of a multivariate analysis and increase the power. Age-matching would also be appropriate given that the length of cerebellar herniation and syrinx width increase over time (Driver et al., 2012; Cerda-Gonzalez et al., 2016). The clinical grading system used was not entirely specific for dogs affected by the CLM-SM complex. Some dogs had evidence of otitis media, commonly identified in CKCS (Lu et al., 2003; Owen et al., 2004), which may have erroneously impacted the grade.

The linear measurements used in this study have neglected the transverse axis and may therefore not correlate accurately with the true overall dimensions of the brain and the brain case. Two-dimensional measurements were used for simplicity and for the potential of a measurement or ratio becoming useful in a clinical setting. Future studies using three-dimensional volumetric measurements in conjunction with the described brachycephalic control group may have superior accuracy.

The classification of CLM based only on three imaging-based criteria may be a misrepresentation. Ideally, syringomyelia would have been added to the inclusion criteria for the dogs in the experimental group. Due to the prospective nature of this study, it was deemed unethical to acquire further MR sequences to assess the entire spinal cord, which would unnecessarily prolong the duration of general anesthesia. CLM predisposes dogs to SM. However, not all dogs with CLM develop SM suggesting that there may be factors that predispose to the development of SM in the presence of CLM. Recent research has discovered a number of other imaging features associated with the CLM-SM complex including increased cerebellar pulsation (Driver et al., 2013), dorsally compressive atlantoaxial bands and obex position (Cerda-Gonzalez et al., 2015), and a shortened distance across the craniocervical junction (Knowler et al., 2016). Further research could consider the inclusion of these additional imaging features in the diagnostic criteria for further accuracy.

## CONCLUSIONS

The existing data in this study supports the use of a simple, two-dimensional measurement to potentially differentiate brachycephalic dogs with craniocervical disproportion, as demonstrated in human patients with Chiari malformation type 1. This measurement will need to be tested on a larger number of dogs to validate its use in assessing craniocervical disproportion, and possibly, the development of SM. The cur-

rent study also supports the hypothesis that CLM in dogs is a disease process governed by a global overcrowding of the brain. It is likely that rostral and caudal cranial fossa overcrowding work in concert with other factors, which share common phenotypical presentations to induce the CLM-SM complex. This theory has been concluded by other studies, but with more complex and expensive methodology. The fact that these simple linear measurements do not require specialized software, as in the case of volumetric measurements, make them valuable for implementation on a large scale in breeding schemes. A brachycephalic study population is most suitable for further investigation of this disease as many breeds display features of CLM and controls are readily available.

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## Persbericht

### Boehringer AH bundelt haar krachten met partners over heel de wereld om hondsdolheid uit te roeien



**Brussel, 6 oktober 2017** – Boehringer Ingelheim, de wereldleider op het vlak van veterinaire vaccins tegen hondsdolheid, bundelt haar krachten wereldwijd met dierenartsen, huisdierigenaars, NGO's en overheidsinstanties. Het bedrijf wil bekendheid geven aan het belang van maatregelen voor de preventie van hondsdolheid en de aandacht vestigen op de ernstige bedreiging die hondsdolheid vormt voor dieren en mensen in grote delen van de wereld.

In meer dan 150 landen en regio's<sup>1</sup>, vooral in Azië en Afrika, is hondsdolheid nog steeds endemisch. Wereldwijd sterven elke dag zo'n 160 mensen aan hondsdolheid en 40% daarvan zijn kinderen<sup>1</sup>. Mits een goede vaccinatiestrategie en investeringen is hondsdolheid een goed te voorkomen ziekte<sup>1</sup> die echter bijna altijd fataal afloopt van zodra de symptomen van de infectie opduiken. Niet-gevaccineerde honden vormen de belangrijkste bron van infectie met het rabiësvirus. Volgens de Wereldgezondheidsorganisatie zouden menselijke sterfgevallen door hondsdolheid kunnen worden geëlimineerd door wereldwijd minstens 70% van de hondenpopulatie te vaccineren.<sup>1</sup>

Boehringer Ingelheim heeft zich ertoe verbonden een bijdrage te leveren aan de mondiale inspanningen voor het uitroeien van hondsdolheid. Het maakt hierbij gebruik van een holistische aanpak die voorlichting van het publiek combineert met de vaccinatie van huisdieren, wilde dieren en vee om deze dodelijke ziekte te voorkomen en zo levens te redden.

### Referenties

1. World Health Organization, 2017. Rabies Home. (<http://www.who.int/rabies/en/>)