Evaluation of Hydrocephalic Ventricular Alterations in Maltese Dogs Using Low Field MRI

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ABSTRACT

The purpose of this work to evaluate quantitatively ventricular alterations of hydrocephalic Maltese dogs using low-tesla MRI. The height, area, and volume of the ventricles and brain were measured in 40 Maltese (20 normal and 21 hydrocephalic dogs) on MR images (at 0.2T MRI). All of the relative ventricle sizes were defined as the percent size of the ventricle/size of the brain. The ventricle sizes of hydrocephalic dogs were significantly larger than the normal dogs, as were the relative ventricle-brain sizes. Five symptoms were observed in the hydrocephalic group: circling, head tilt, seizure, ataxia, and strabismus. The ventricle/brain with height (1D) was linear relative to the area (2D) and volume (3D). Its correlations with area and volume were as good as the ventricle/brain height ratio in case of hydrocephalic dog. Therefore, one-dimensional, two-dimensional, and three-dimensional quantitative methods may be complementary. We expect that the stage of hydrocephalic symptoms can be classified if statistical significance for ventricular size among symptoms is determined with the analysis of a large number of hydrocephalic cases.

INTRODUCTION

Hydrocephalus is affected by blockage of cerebrospinal fluid (CSF) outflow in the ventricles or in the subarachnoid space over the brain. Alternatively, the condition may result from an overproduction of CSF fluid, from a congenital malformation blocking normal drainage of the fluid, or from complications of head injuries or infections.[1-3] This condition also could be termed a hydrodynamic disorder of CSF. Acute hydrocephalus occurs over days, subacute hydrocephalus over weeks, and chronic hydrocephalus over months or years.

There are three classes in hydrocephalus. First, normal pressure hydrocephalus (NPH) describes a condition that rarely occurs in comparatively young patients. Enlarged ventricles and normal CSF pressure at lumbar puncture (LP) in the absence of papilledema led to the term NPH.[4]

Secondly, benign external hydrocephalus is a self-limiting absorption deficiency of infancy and early childhood with raised intracranial pressure (ICP) and enlarged subarachnoid spaces. The ventricles usually are not enlarged significantly, and resolution within 1 year is the rule.[5]

The third, communicating hydrocephalus occurs, when full communication occurs between the ventricles and subarachnoid space. It is caused by overproduction of CSF, defective absorption of CSF, or venous drainage insufficiency.[6]

Forth, noncommunicating hydrocephalus occurs when CSF flow is obstructed within the ventricular system or in its outlets to the arachnoid space, resulting in impairment of the CSF from the ventricular to the subarachnoid space.[7]

Lastly, congenital hydrocephalus applies to the ventriculomegaly that develops in the fetal and infancy periods, often associated with macrocephaly. The most common causes of congenital hydrocephalus are obstruction of the cerebral aqueduct flow, Arnold-Chiari malformation, or Dandy–Walker malformation.[8, 9]

Magnetic resonance (MR) imaging is commonly used to evaluate companion animals for suspected central nervous system (CNS) disease. Many studies in the autism literature have utilized MRI as a method for studying volumetric differences in the brains of autistic subjects vs those of typically developing children. Reports from such studies include an increase in total brain volume[10] and cerebellar and parietal lobe abnormalities.[11] MRI has also proved to be a sensitive tool for assessing white matter changes and cerebral atrophy both in living subjects [12, 13] as well as in the post-mortem brain[14] in disorders such as Alzheimer's disease. In addition, MRI have used to evaluate quantitatively in the veterinary diagnosis and many animal studies.[15-17]

Various studies for the measurement of the hydrocephalic ventricle in canine breeds have been attempted using CT/MRI and sonography.[18-20] The imaging modalities have been generally processed by analysis of only the morphology such as the ventricle size and volume. It has been reported that the ratio of the ventricle height to brain height was 80% (reference range, 0–14%) and the ratio of the ventricle area to the hemisphere brain was 7.1% (normal range, 3.0–7.6%).[15, 16]

In humans, the correlation between ventricular height and volume is as good as the ventricle/brain ratio, which has previously been shown to be the best non-volumetric correlate of ventricular volume.[21-23] However, in canines, an evaluation and comparison of the analysis methods have not yet been reported. Therefore, we hypothesized that the analyzed result by the area/volume of brain and ventricle could discriminate as accurate as by their heights between normal and hydrocephalic canine. The final purpose of present study was to evaluate quantitatively ventricular alterations of hydrocephalic Maltese dogs using low-tesla MRI.

MATERIALS AND METHODS

AnimalsForty one Maltese dogs (0–5 years; 21 dogs with hydrocephalic symptoms and 20 healthy dogs) were used in the study without sex discrimination. All of

the symptoms of each hydrocephalic dog were recorded, and the age-matched dogs without any symptoms were involved for the comparison study between normal and hydrocephalic dogs. This study was approved by the Institutional Animal Care and Use Committee at the College of Veterinary Medicine, Konkuk University (IACUC No.: KU09047). All of the dogs without symptoms were considered normal following a physical and hemodiagnostic (complete blood count) examination and determination of blood chemistry. Diagnosis of the dogs was performed at the Doctor's Pet Hospital in Seoul, Korea, over a 5-year period (from 2004 to 2009). Although blood physical/chemical examinations--complete blood count (CBC), total protein (TP), aspartate aminotrasferase (AST), alanine aminotrasferase (ALT), blood urea nitrogen (BUN) and creatinine (CREA)--were performed. All values indicated healthy condition, and the difference between dogs with and without symptoms was also not significant.

TREATMENT AND DATA ACQUISITION

The MR scan of the clinical patient was performed under general anaesthesia. Following prermedication with butorphanol at a dose rate of 0.2 mg/kg body weight, the animal received propofol at a dose of 5 mg/kg body weight. Then it was intubated and connected to a closed-system anaesthetic unit to provide the animal with oxygen, while the propofol dose was doubled. Rocuronium at a dose of 0.6 mg/kg body weight was applied as a muscle relaxant.

MR experiments were conducted using open magnet MRI at 0.2T (E-scan, Esaote, Genoa, Italy) with human knee coils. Dogs were placed in sternal recumbency on the scanning table. Transverse and dorsal T1-weighted MR images were acquired using a repetition time (TR) of 650 ms and an echo delay time (TE) of 25 ms. The slice thickness was 4–6 mm, with no gap.The total thickness of images was 4 cm. A total of 6–8 MR image slices were used, with a volume of interest (VOI) that covered from the frontal robe to the cerebellum. As the brain sizes of the canines were different, the VOI covered changing slice thicknesses and number of slices. Figure 1 shows representative T1-weighted axial images of normal and hydrocephalic Maltese dogs at the level of the interthalamic adhesion.

Data Analysis

T1-weighted MR images were analyzed across a series of regions of interest (ROI) as illustrated in Figure 2. Figure 2A shows that the height (mm) of the brain and height of the right and left ventricles was measured. In order to measure the areas, (Figure 2B) and volumes (Figure 2C) of the whole brain and left and right ventricles, each section was extracted on all T1-weighted MR images. These results present the height as "mm," the area as "mm^2" and the volume as "$mm.^3$" The height and areas of the brain and both ventricles were measured at the level of the interthalamic adhesion. The transverse image at the level of the interthalamic adhesion was used to identify the onset of ventricular expansion. Although in some puppies the rostral horns dilated first, ventricular expansion by cerebrospinal fluid (CSF) was most apparent at this level first. The onset of ventricular expansion was defined as the day that expansion by CSF was first visible in unilateral or bilateral lateral ventricles on the above transverse image. The pattern of onset of ventricular expansion was also evaluated by inspection on the transverse image at the level of the intraventricular foramen.

As a next step, the ventricle to brain height ratio (VBHR, ventricle height/brain height × 100), the ventricle to brain area ratio (VBAR, ventricle area/brain area × 100) and the ventricle to brain volume ratio (VBVR, ventricle volume/brain volume × 100) were calculated. Last, the comparison between VBHR and VBVR as well as the difference between normal dogs and dogs with hydrocephalus were investigated.

Statistical analysis

All of the data was analyzed using ImageJ (National Institutes of Health, Bethesda, MD USA) and SPSS (Windows Version 13.0; SPSS, Chicago, IL USA). All of the data

***Figure 1**. Transverse T1-weighted images of hydrocephalic dogs at the level of the interthalamic adhesion are shown: (A) normal and (B) hydrocephalic dog brain. The ventricle size of a hydrocephalic dog was larger as compared to a normal dog.*

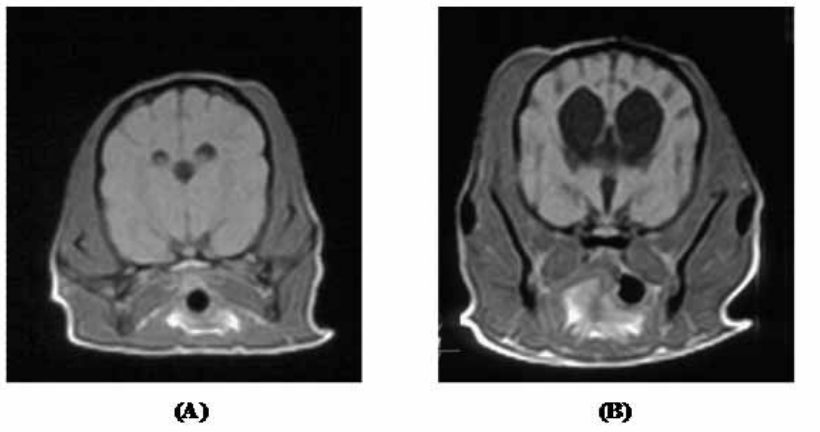
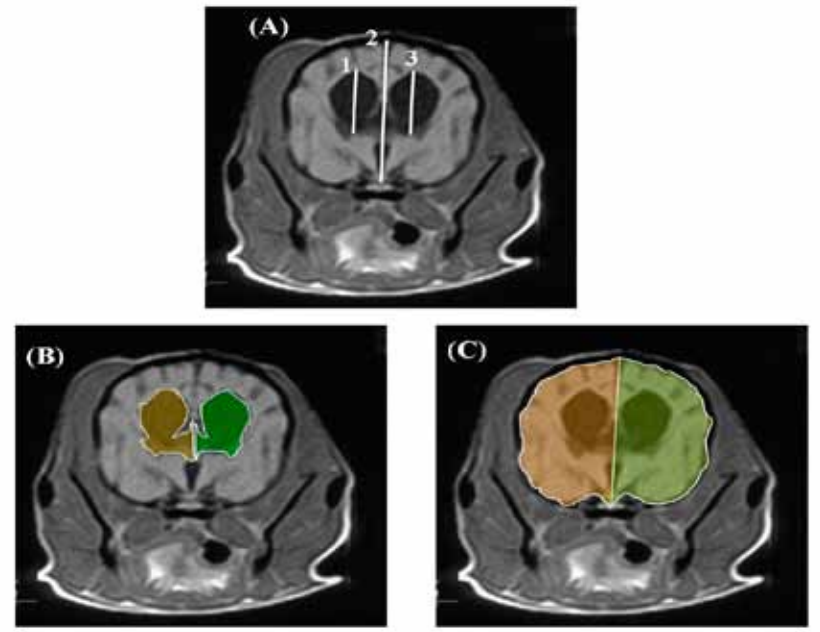


***Figure 2.** (A) Heights of the right and left ventricles and brain were gauged at the interthalamic adhesion level. (B, C) Areas of right/left ventricles and brain at the level of the interthalamic adhesion were automatically calculated. Volumes were measured by summation after multiplying the slice thickness by calculated area of each image slice The lateral right and left ventricles and the corresponding whole brain were outlined manually.*



was analyzed with the Student's two-tailed t test, in order to compare significant differences among the three determined ratios. P-values less than 0.05 were considered as statistically significant.

RESULTS

Table 1 shows the heights, areas and volumes for hydrocephalus cases in both dog breeds. Comparing normal dogs, the brain size of hydrocephalic group was not significantly different from normal dogs'.

The VBHR, VBAR and VBVR values of each Maltese dog are listed in Table 2 and 3. Figure 3 shows that three values (VBHR, VBAR and VBVR) were in linear proportion to each other. The statistical results of the right and left VBHR, VBAR and VBVR for both normal and hydrocephalic group were measured as shown in Table 4 and Figure 4. Although the difference between right and left side in same group was not significant ($P>0.1$), all values VBVR, VBAR and VBHR were also significantly different between dogs with and without hydrocephalus ($P < 0.01$). Hydrocephalic symptoms included circling, head tilt, seizure, ataxia and strabismus. Particularly, all hydrocephalic canines had a circling action except in one dog.

DISCUSSION

MR imaging is possible to assess more exactly ventricle size and shape in vivo than another diagnostic method such as CT and ultrasound [15, 24]. Due to the varying anatomy between canine breeds, comparative size analysis was limited. In our work, the relative ventricle sizes which are a height, area and volume allow compensation for variation in brain size and three parameters (VBHR, VBAR and VBVR) were used to evaluate hydrocephalic brains. Statistically significant differences in brain size among different dog breeds have been reported [16]. MR images allow the classification of the shape of the brain, which has to be kept in mind looking at ventricle size. A literature research on the classification of various dogs according their head's shape revealed some discrepancies [25]. Clinically symptomatic hydrocephalus may also occur in particular lines of beagles as a developmental anomaly and in beagle-type mongrels, but clinically symptomatic hydrocephalus is typically not seen in the general beagle population. It has recently been reported that the size, symmetry and volume of the lateral ventricles in healthy dogs is variable [15, 26].

In this work, we were establish three factors which are VBHR, VBAR and VBVR in order to quantitatively evaluate hydrocephalic ventricular alterations in 1-D (heights of brain and ventricles), 2-D (areas) and 3-D (volumes). VBAR and VBVR were in proportion to VBHR. As well as it was confirmed that the correlation of VBAR and VBVR for the evaluation of a hydrocephalic brain was as good as VBHR.

Table 1. *Height, area and volume of brain, right and left ventricles in Maltese dogs: mean values (standard deviation: SD) of dogs with and without hydrocephalus.*

			Normal (n=20)	Hydrocephalus (n=21)
Height (mm)	Brain		38.88±3.00	40.28 ± 4.32
	Ventricle	Right	5.49±1.57	12.34 ± 4.58
		Left	5.41±2.15	12.71 ± 5.11
Area (mm2)	Brain		1387.22±138.88	1469.54 ± 299.43
	Ventricle	Right	42.38±29.93	142.20 ± 144.09
		Left	43.50±29.45	151.82 ± 160.14
Volume (mm3)	Brain		47244.22±7820.14	50655.39 ± 17288.62
	Ventricle	Right	1037.04±647.13	4610.19 ± 1153.04
			1084.47±716.73	4840.85 ± 1107.55

***Table 2**. Data for all of Maltese dogs (normal)*

Canine#		VBHR		VBAR		VBVR	
		right	left	right	left	right	left
Normal	MN01	19.80	19.15	8.46	8.20	5.84	6.65
	MN02	22.80	17.03	11.74	6.34	8.97	6.29
	MN03	11.29	10.98	4.00	4.34	2.39	3.01
	MN04	10.58	8.56	2.78	2.91	1.13	1.35
	MN05	13.57	18.20	4.54	5.88	4.16	4.75
	MN06	7.96	9.69	2.16	3.13	1.94	3.17
	MN07	16.37	12.35	5.97	3.79	3.33	1.74
	MN08	15.92	16.60	5.41	5.11	4.37	3.82
	MN09	10.89	16.35	12.27	14.05	5.45	7.80
	MN10	19.91	22.10	9.94	10.00	8.95	8.79
	MN11	13.82	8.29	2.84	1.58	1.41	0.44
	MN12	10.65	0.00	3.56	0.00	4.99	2.15
	MN13	8.78	11.80	1.50	4.93	1.23	1.70
	MN14	18.10	20.69	7.89	9.23	8.67	9.90
	MN15	15.93	23.45	5.21	11.28	5.83	10.96
	MN16	19.04	17.57	18.46	15.92	8.81	7.63
	MN17	14.74	16.27	6.25	6.96	5.02	4.99
	MN18	10.07	8.47	2.28	3.02	1.14	1.79
	MN19	12.61	12.60	3.62	4.63	2.44	2.94
	MN20	11.26	11.14	4.25	5.02	5.07	6.37

***Table 3.** Data for all of Maltese dogs (hydrocephalus)*

Canine#		VBHR		VBAR		VBVR	
		right	left	right	left	right	left
Hydrocephalus	MH01	27.80	20.49	6.77	5.04	7.06	5.96
	MH02	48.64	59.44	26.92	33.01	23.45	27.70
	MH03	41.27	45.83	9.44	10.37	10.75	10.68
	MH04	25.04	27.85	5.42	6.08	6.45	7.10
	MH05	26.72	31.22	7.64	8.29	7.51	7.87
	MH06	30.43	27.84	12.43	8.27	10.93	8.71
	MH07	29.78	32.60	7.12	9.89	7.33	10.02
	MH08	38.09	36.56	10.69	12.31	9.97	11.46
	MH09	53.37	53.71	26.26	27.33	21.76	20.44
	MH10	30.65	23.58	6.96	3.82	6.31	4.62
	MH11	32.42	30.13	7.54	8.29	7.35	9.13
	MH12	33.84	45.06	9.06	14.46	8.08	10.88
	MH13	31.79	32.56	5.66	5.72	5.76	5.27
	MH14	20.72	22.55	4.87	7.55	4.03	6.24
	MH15	21.08	25.17	6.82	6.85	7.06	7.99
	MH16	21.76	19.69	4.75	4.46	4.34	4.79
	MH17	26.57	28.64	5.67	6.29	7.64	7.67
	MH18	23.68	23.18	5.25	5.20	4.77	4.89
	MH19	24.16	23.60	5.92	6.33	4.27	4.66
	MH20	21.43	27.62	3.74	6.24	2.28	5.17
	MH21	28.73	21.85	9.24	4.19	6.48	3.52

Figure 3. *The relationship among VBAR, VBVR and VBHR in right side (A, B) and left side (C, D) of Maltese dogs: VBHR was in proportion to VBAR and VBVR regardless of normal/hydrocephalus.*

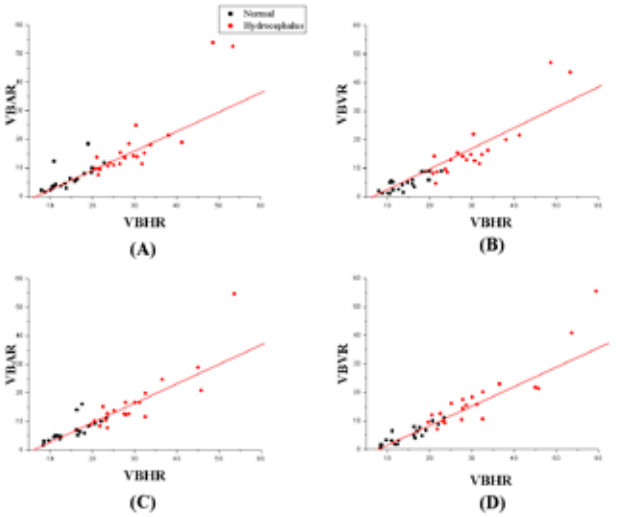


Figure 4. *VBHR, VBAR and VBVR between normal and hydrocephalic group. This is the graph of Table 4.*

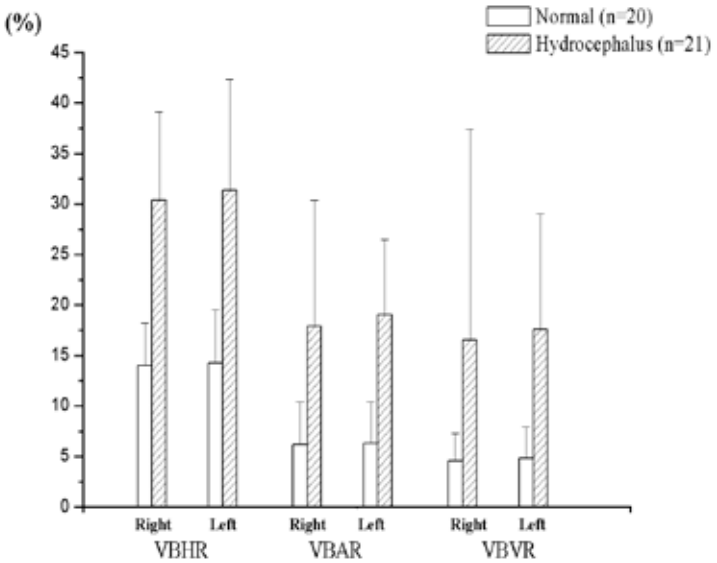


***Table 4**. VBHR, VBAR and VBVR between normal and hydrocephalic group in two dog breeds: mean percentage (standard deviation: SD)*

			Normal	Hydrocephalus	P-value
Maltese	VBHR	Right	14.20 (4.17) %	30.37 (8.78) %	4.84E-9
		Left	14.21 (5.34) %	31.39 (10.98) %	1.88E-7
	VBAR	Right	6.15 (4.25) %	17.92 (6.34) %	2.71E-4
		Left	6.32 (4.08) %	19.05 (7.42) %	6.84E-4
	VBVR	Right	4.56 (2.72) %	16.53 (10.47) %	1.45E-5
		Left	4.81 (3.09) %	17.60 (11.39) %	2.02E-5

In case of Maltese, normal group had VBHR < 15%, VBAR < 7% and VBVR < 5% while hydrocephalic group had VBHR > 30%, VBAR > 17% and VBVR > 16%. These values may enable standards for a hydrocephalic diagnosis to be estimated. However, these values cannot be absolute standards, as several variables will affect the results such as hydrocephalic grade, breed, age, sex and ventricular symmetry.

Several studies that have quantitatively measured ventricular alterations of hydrocephalic dogs using height, area and volume of the brain and ventricle have been reported [16-19]. This study was to confirm that the three measurement methods had statistical significance in Maltese. Also, the P-values of VBHR, VBAR and VBVR were less than 0.01. However, for higher order dimensional analysis, more data, time and processing stages were required. One of findings in this work was that the use of 1-D quantitative analysis was also available for an exact diagnosis of hydrocephalus and could save time and effort. Nevertheless, veterinarians depend on fast processing of three methods (1D, 2D and 3D analysis) for accurate diagnoses. Because the size of brain and ventricle can be different as well as VBHR, VBAR and VBVR is different case by case. For example, in case of human pediatric hydrocephalus, the 1D analysis (Evan's ratio) was not accurate rather than 3D (volumetric) analysis [22, 27].

According to the dog breed, symptoms and anatomical change of a neuro-disease may be different [28, 29]. Therefore, hydrocephalic alteration of each breed deserves to be investigated. In this work, the difference between with and without hydrocephalus in the only Maltese dog breed was statistically significant. If hydrocephalus in another canine breed such as bulldog, German shepherd dog and Chihuahua was investigated, a different pattern of results (correlation between symptom and anatomical change) may be observed. Thus, valuable and helpful information can be provided if the hydrocephalic study is conducted after the stage of the hydrocephalic symptoms is classified [30-32]. Although the body weight of hydrocephalic dogs was smaller than that of normal dogs in this study, the decrease in the body weight should be considered as a minor symptom for the diagnosis of canine hydrocephalus because a decrease of body weight can be due to multiple causes. Therefore, we denoted five symptoms found in hydrocephalic canines in this study: circling, head tilt, seizure, ataxia and strabismus. We were not able to determine a correlation between symptoms and ventricular size of a canine in this study. However, the stage of the hydrocephalic symptoms can be classified if statistical significance of ventricular size among the symptoms is found from an analysis of a sufficient number of hydrocephalic cases.

In human infants and children, asymmetric lateral ventricles and unilateral hydrocephalus due to many causes such as intrauterine or postnatal compression, compression, intrauterine, intracranial or intraventricular hemorrhage, and congenital

or acquired atresia of the intraventricular foramen have been reported [33-36]. In addition, some abnormal signs appeared in patients with atresia of the intraventricular foramen and intracranial or intraventricular hemorrhage were found by ultrasound. Lateral ventricular asymmetry has been found in the human neonate and this could occur by intrauterine or postnatal compression. Although the bilateral hydrocephalus cases in two canine breeds were evaluated with the 1D, 2D and 3D analytic method on MR images, three analytic methods will be able to apply to unilateral hydrocephalus.

MR imaging allows exact assessment of ventricle size and shape in vivo. Furthermore, advanced MR imaging techniques such as MR spectroscopy, diffusion weighted/tensor and perfusion imaging can identify metabolism, preoperative hemodynamic and diffusion coefficient changes. Although several articles [3, 37-39] have already published the application for human hydrocephalus using diffusion and perfusion MR techniques, studies of canine hydrocephalus have not been performed. Advanced MR techniques will be able to allow innovation in veterinary diagnosis included in canine study. In addition, the stage of hydrocephalic symptoms can be classified if statistical significance for ventricular size among symptoms is determined with the analysis of a large number of hydrocephalic cases.

CONCLUSION

In summary, this work aimed to evaluate ventricular alterations due to hydrocephalus in Maltese dogs using low-field MR imaging. We demonstrated that 1D, 2D and 3D quantitative ratios for the evaluation of hydrocephalic ventricular alteration were significantly higher as compared to normal animals. As well as the correlation with ventricular area or volume was as excellent as the ventricle/brain height ratio. Finally, we expect that our trials and results can be helpful to analyze hydrocephalic dogs. A further study is needed to investigate different dog breeds and the classification of canine hydrocephalus symptom stage.

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