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MRI of the optic nerve sheath and globe in cats with and without presumed intracranial hypertension

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Abstract

Objectives The study aimed to: (1) test MRI repeatability of measurements of optic nerve sheath diameter (ONSD), optic nerve diameter (OND) and eye globe transverse diameter (ETD); (2) investigate the associations between the OND, ONSD and ETD; (3) assess whether these measurements are affected by age or body weight; and (4) test the association between ONSD, OND, ETD and ONSD: ETD ratio with presumed intracranial pressure (ICP) status.

Methods This was a retrospective and blinded study where patients were allocated to presumed normal or intracranial hypertension groups based on MRI findings. The ONSD and ETD were measured and recorded. Interclass correlation coefficient (ICC) was calculated to investigate interobserver agreement. Data were analysed using the Pearson correlation coefficient, two-sample *t*-test and general linear model ANOVA.

Results: Seventy-seven cats were included, 62 with presumed normal ICP and 15 with presumed intracranial hypertension. The ICC showed moderate-to-good reliability for all measurements. Positive correlations were identified for: (1) ETD and weight; (2) ONSD and age; (3) OND and age; (4) ONSD and ETD; (5) ONSD: ETD ratio and presumed ICP status; and (6) ONSD and presumed ICP status. No difference was detected between the presumed normal and intracranial hypertension groups and ONSD, as well as ONSD: ETD ratio and presumed ICP status when patient age was considered.

Conclusions and relevance The measurement of the ONSD and the ONSD: ETD ratio on T2-weighted MRI might not be reliable as non-invasive tests for diagnosing intracranial hypertension in cats.

Keywords: Brain; cranial nerve II; Cushing's reflex; intracranial hypertension; neurology; magnetic resonance imaging

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Introduction

Intracranial pressure (ICP) is described as the pressure exerted by the brain and its surrounding structures against a non-elastic cranium. Increased ICP causes a reduction of cerebral blood flow and contributes to cerebral ischaemia.[1] It is associated with poor prognosis, and can cause non-reversible neurological deficits, brain herniation and death.[1]

The gold standard methods for intracranial hypertension estimation are invasive and include intraventricular catheterisation and intraparenchymal probes.[2] These techniques are complex, expensive and are associated with a high risk of complications, and numerous contraindications have been described.[2–4] Therefore, these procedures are uncommonly used in daily practice, which has led to the investigation and development of non-invasive methods of ICP assessment.[5,6]

In humans and dogs advanced diagnostic imaging modalities are commonly used to identify findings suggestive of elevated ICP.[7–9] In humans, the most common MRI characteristics described are compression and shifting of the brain parenchyma, narrowing of the venous sinuses, increased optic nerve sheath diameter (ONSD), elongation of the optic nerve (ON), flattening of the

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posterior sclera, protrusion of the optic papilla, reduction of the pituitary gland size or an empty sella.[7,10,11]

In dogs, MRI findings showing the strongest association with increased ICP are mass effect, caudal transtentorial or subfalcine herniation, perilesional oedema, displacement of the lamina quadrigemina, effacement of the cerebral sulci and compression of the suprapineal recess, third or fourth ventricle.[9,12]

Additionally, the enlargement of the ONSD measured by ultrasonography (US) or MRI has been proven to be a reliable indirect method of intracranial hypertension detection in humans[13–15] and dogs.[8,16,17] Recent prospective studies in healthy human volunteers have also shown a correlation between the ONSD and the eye globe transverse diameter (ETD) measured with US[18] and MRI,[19] and the ONSD: ETD ratio measured on US might be used as a non-invasive test of increased ICP.[20] No association was found between the ONSD and clinical variables, including sex, height, weight, body mass index and head circumference.[18,19] In dogs, no correlation was found between ONSD and age, but a moderate positive correlation was seen between ONSD and body weight.[8]

In feline medicine, only one recent ultrasonographic study investigating the ONSD and increased ICP is available, and found a positive correlation between the two.[21]

The aims of this study were multi-fold. We aimed to test the repeatability of MRI measurements for ONSD, optic nerve diameter (OND) and ETD, which has not been previously tested in cats; to study the association between the OND and the ETD; to assess if these measurements were affected by age or body weight; and, finally, to test the association between ONSD, OND, ETD and ONSD: ETD ratio with ICP status.

We hypothesised that detecting enlargement of the ONSD could be used as a non-invasive test for diagnosing intracranial hypertension in cats and that there would be a positive correlation between the ONSD and ETD.

Materials and methods

Patient population

The hospital's database was searched to identify cats whose medical records contained details of physical and neurological examination, and in which an MRI examination of the brain was performed between January 2009 and December 2019. The medical records of each patient were reviewed by JL and age, sex, breed, body weight, clinical suspicion of increased ICP and presumptive or final diagnosis were recorded. The availability of MRI images of the brain in the following sequences was required: transverse and dorsal plane T2-weighted (T2W), transverse plane T1-weighted (T1W) and T1W after administration of intravenous gadoteridol contrast medium (0.1 mmol/kg dose [Prohance; Bracco Diagnostics]). Patients were excluded if the MRI examination did not include diagnostic scans of the entire brain or if there was evidence of intraocular pathology on clinical examination. Ethical approval was obtained from the veterinary ethical review committee of the University of Edinburgh (VERC . 155.19).

MRI review and measurements

All images were stored in a commercially available picture archiving communication system. The studies were acquired using two MRI systems (1.5 Tesla Philips and 1.5 Tesla Siemens Magnetom Avanto). Image analysis was undertaken on a dedicated reporting station with calibrated LCD monitors (iMac; Apple) using commercially available DICOM viewing software (HOROS; Nimble).

The MRI examinations were blindly and independently reviewed by three observers (board-certified neurologist, radiologist and radiology resident [AS, EM, JL]). First, T2W transverse and T2W dorsal scans focused on the rostral area of the brain were reviewed to obtain ONSD and ETD. Measurement of the maximum ONSD was made by identifying the scans between the eye and optic canal that best displayed the ON. Measurements were made perpendicular to the long axis of the nerve using callipers included in the viewing software (Figure 1). The left eye

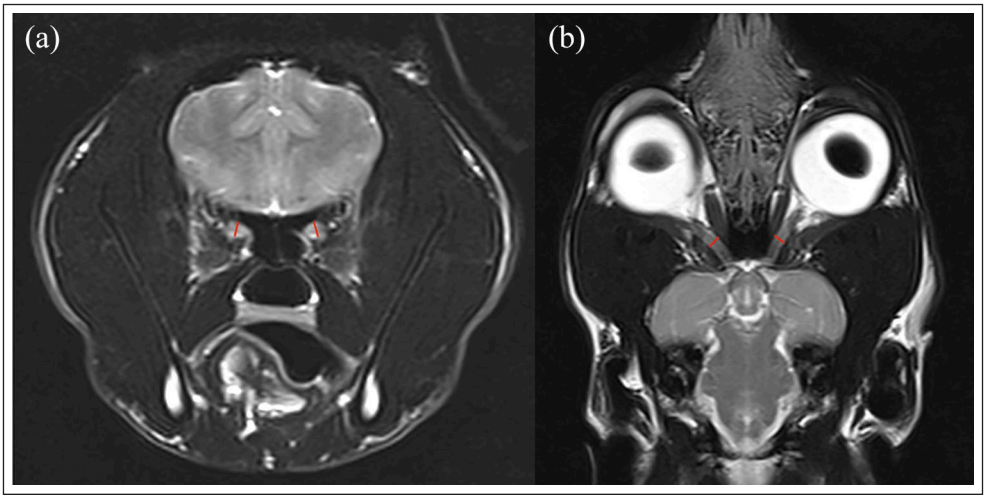

Figure 1 T2-weighted MRI images of a feline brain in (a) transverse and (b) dorsal planes. Red lines perpendicular to the long axis of the nerve indicate how the measurements of the optic nerve sheath diameter were taken

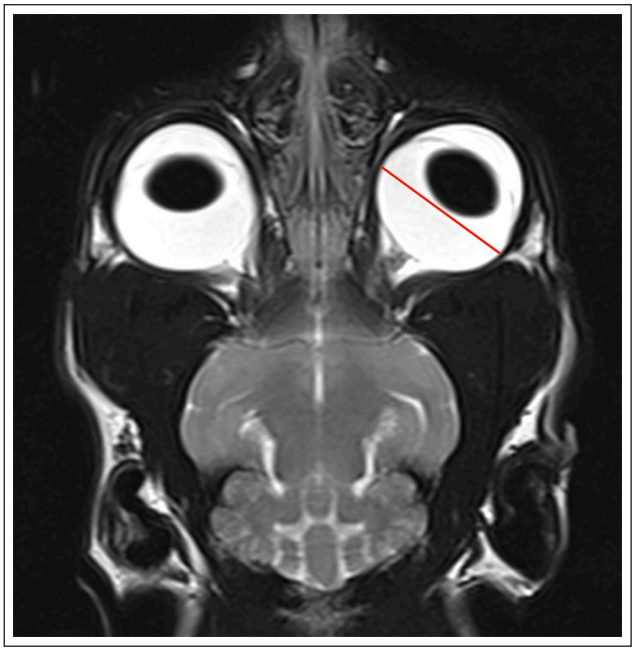

Figure 2 T2-weighted MRI images of a feline brain in dorsal plane. Red line indicates the maximal globe transverse diameter measured parallel to the equator of the lens and immediately caudal to its posterior margin

(OS) and right eye (OD) for any one cat were measured at the same time, but the measurements could have been made on different slices at the reader's discretion. Maximal ETD was also measured in the T2W dorsal image. This was measured parallel to the equator of the lens and immediately caudal to its posterior margin (Figure 2). To determine intra-observer variability, JL performed repeated measurements on the patients, 3 months apart and also measured and recorded the OND in transverse planes. The ONSD: ETD ratios were calculated for the left and right eye. Additionally, sheath sizes were calculated by subtracting the OND size from the ONSD.

Two months after the first examinations, the entire MRI examination was reviewed by JL and presence or absence of MRI characteristics of presumed intracranial hypertension was recorded. The MRI characteristics previously described in dogs with intracranial hypertension[9] were used, including mass effect, oedema, effacement of sulci, midline shift and collapse of the ventricles or cisterns. The patients were assigned to the 'presumed intracranial hypertension' group when at least two of these MRI characteristics were detected, and were classified as 'presumed normal' if one or none of the above were identified, as reported in dogs.[9]

Lastly, the medical records, imaging diagnosis and final or presumptive diagnosis were recorded.

Statistical analysis

Descriptive statistics were performed and distributions of numerical data were assessed for normality using the Anderson–Darling test. Interclass correlation coefficients (ICCs) and their 95% confidence intervals were calculated to investigate inter-observer agreement using R (v4.0.0 C). The remaining statistical analyses were performed with Minitab (Minitab 17 Statistical Software 2010).

A mean of all three observervations for ONSD and ETD were calculated and used for further statistical analysis.

Pearson correlation coefficients were used to test the correlations between the OND, ONSD, ETD, and weight and age, as well as to investigate the correlation between the calculated sheath size and age in both groups. The same test was used to test the correlations between the ETD with age and weight in both groups. The correlation between the ONSD and ETD was also investigated for the first time in veterinary literature. Therefore, this parameter was only studied in cats in the presumed normal group. Differences in the ONSD and ETD in the two groups, as well as ONSD: ETD ratio with the presumed ICP status, were tested using two-sample *t*-tests. Univariate analyses were performed first to explore potential relationships between these variables. Then, a further general linear model ANOVA was performed to assess the effect of cofounding variables in factors showing significance on univariate analysis. Hence, we investigated the relationship of presumed ICP status with ONSD and age, ETD and weight, and ONSD: ETD ratio and weight. Statistical significance was defined as $P < 0.05$.

Results

A total of 104 cats were identified. Seventy-seven met the inclusion criteria. Twenty-seven patients were excluded either owing to lack of complete MRI sequences (n = 8/27), or when the ONS was not optimally visualised in the scan plane (n = 19/27). Of the included patients, there were 36 females (three entire, 33 spayed) and 41 males (one intact, 40 castrated). Median age was 109 months (mean 104.7 months; range 4–295 months). Median body weight was 5.4 kg (mean 4.59 kg; range 1.4–9.1 kg); however, body weight was not recorded for one patient. Represented breeds included domestic shorthair (n = 50), domestic longhair (n = 5), Maine Coon (n = 4), British Shorthair (n = 4), Bengal (n = 2), Birman (n = 2), Burmese (n = 2), Ragdoll (n = 2) and one patient of each of Burmilla, Chinchilla, Oriental, Russian Blue, Siamese and Siberian.

The most common presumed or final diagnoses were idiopathic epilepsy (n = 20), neoplasia (n = 17) and otitis (n = 10), followed by metabolic disorders (n = 7), infectious diseases (n = 5), feline hyperesthesia syndrome (n = 4), vestibular syndrome (n = 3), vascular events (n = 3), hyperadrenocorticism (n = 1), Chiari-like malformation (n = 1), feline hippocampal necrosis (n = 1) and meningoencephalocoele (n = 1). The cause of the clinical signs was unknown in four cases.

Two groups were identified. The presumed normal group consisted of 62 patients. These patients did not show any MRI criteria for increased ICP.[9] There were 29 females (three intact, 26 spayed) and 33 males (one intact, 32 castrated). Median age was 102.5 months (mean 100.6 months; range 4–295 months). Median body weight was 4.3 kg (mean 4.58 kg; range 1.4–9.1 kg).

The presumed intracranial hypertension group included 15 patients. All patients showed at least 3/5 MRI criteria for increased ICP.[9] There was one patient with 4/5 criteria present, four patients with 3/5 criteria present and nine patients with all five criteria consistent with increased ICP. There were eight females (all spayed) and seven males (all neutered). Median age was 130 months (mean 121.5 months; range 12–214 months). Median body weight was 4.7 kg (mean 4.6 kg; range 2.9–7.6 kg); however, body weight was not recorded for one patient.

All recorded measurements for the whole study population and presumed normal and presumed intracranial hypertension groups are summarised in Table 1. Normal data distribution was accepted for both groups.

The ICCs showed moderate-to-good reliability for all the measurements. The ICC for the ONSD in transverse plane was 0.66 and 0.71 for OD and OS, respectively. In the dorsal plane, it was 0.57 and 0.66 for OD and OS, respectively. The highest reliability was found for the ETD with ICC of 0.87 for both eyes.

Results of univariate analysis are found in Table 2. Owing to concerns over the completeness and impact of maturity on the measurements taken, the analysis was performed repeatedly, first excluding the patient for

Table 1 Measurements obtained for the whole study population

		Whole study population		Presumed normal		Presumed intracranial hypertension	
		Mean	Range	Mean	Range	Mean	Range
ONSD (mm)	OD transverse	2.5	1.95– 3.13	2.5	1.95–3.13	2.63	2.40–2.90
	OD dorsal	2.42	1.8–2.8	2.4	1.80–2.80	2.5	2.20–2.68
	OS transverse	2.54	1.9–3.18	2.5	1.90–3.18	2.65	2.35–2.88
	OS dorsal	2.42	1.73–2.95	2.4	1.73–2.95	2.5	2.23–2.80
OND (mm)	OD	1.24	0.6–1.6	1.23	0.6–1.6	1.29	1.0–1.5
	OS	1.28	0.8–1.5	1.3	0.8–1.8	1.27	0.9–1.6
Sheath (mm)	OD	1.3	0.8–1.9	1.3	0.8–1.9	1.34	1.1–1.7
	OS	1.25	0.5–2	1.2	0.5–2	1.36	1.0–1.9
ETD (mm)	OD	21.06	17.73–22.78	21.0	17.73–22.78	21.22	20.33–21.78
	OS	21.0	17.73–22.43	21.07	17.73–22.43	21.2	20.38–21.65
ONSD: ETD	OD	0.12	0.10–0.15	0.12	0.10–0.15	0.12	0.11– 0.14
	OS	0.12	0.10–0.15	0.12	0.10–0.15	0.12	0.11–0.13

ONSD = optic nerve sheath diameter; OND = optic nerve diameter; sheath = nerve sheath size; ETD = eye globe transverse diameter; OD = right eye; OS = left eye; transverse = transverse plane; dorsal = dorsal plane

Table 2 Results of the univariate analyses

	OD transverse	OS transverse	OD dorsal	OS dorsal
ONSD/weight				
r	0.173	0.116	0.186	0.222
P value	0.135	0.318	0.108	0.054
ETD/weight				
r	–	–	0.407	0.348
P value	–	–	<0.05	0.002
ONSD/age				
r	0.343	0.303	0.338	0.331
P value	0.002	0.007	0.003	0.006
OND/age				
r	0.098	–0.053	–	–
P value	0.395	0.644	–	–
ETD/age	–	–		
r	–	–	0.131	0.168
P value	–	–	0.256	0.144
ONSD/ETD				
r	0.299	0.263	0.438	0.484
P value	0.018	0.039	<0.05	<0.05
ONSD/ICP status				
95% CI	–0.2261 to –0.0360	–0.2469 to –0.0200	–0.1873 to 0.0020	–0.2297 to 0.0007
P value	0.008	0.023	0.055	0.051
ETD/ICP status				
95% CI	–	–	–0.513 to 0.127	–0.403 to 0.141
P value	–	–	0.228	0.338

Pearson correlation coefficients and results of the two sample *t*-tests obtained for the whole study population
OD = right eye; transverse = transverse plane; OS = left eye; dorsal = dorsal plane; ONSD = optic nerve sheath diameter; ETD = eye globe transverse diameter; OND = optic nerve diameter; ICP = intracranial pressure; CI = confidence interval

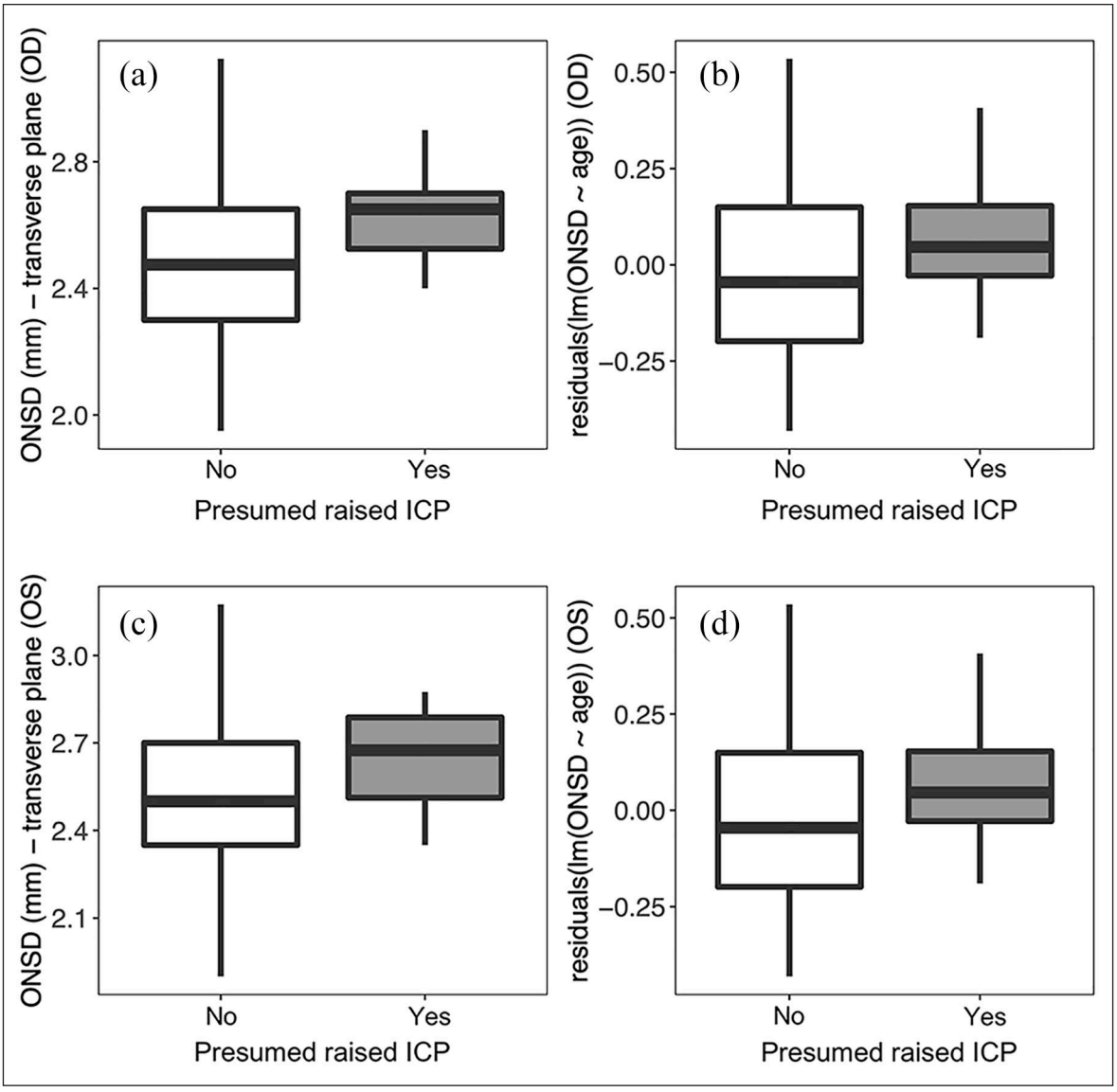

Figure 3 Box plots of (a,c) optic nerve sheath diameter (ONSD) and intracranial pressure (ICP) status, and (b,d) ONSD, age and ICP status for the (a,b) right (OD) and (c,d) left eye (OS). Note that a significant difference is only present in panels (a) and (c). This difference is no longer significant when patient age is considered (b,d). No = presumed normal group; Yes = presumed intracranial hypertension group

which the weight was not recorded, and second the two patients younger than 12 months of age. There was no qualitative change in results with regard to statistical significance in either of those analyses.

Owing to the apparent positive correlations for ONSD and age, and ETD and weight, further general linear model ANOVA tests were performed. No significant differences were observed when ONSD, age and ICP status were studied together neither in transverse (for OD, $P = 0.105$; for OS, $P = 0.135$) nor dorsal plane (for OD, $P = 0.164$; for OS, $P = 0.147$) (Figure 3). No significant differences were found for ETD, weight and presumed ICP status (for OD, $P = 0.650$; for OS $P = 0.873$). No significant differences were found for ONSD: ETD ratio, age and ICP status when studied together either (for OD, $P = 0.183$; for OS, $P = 0.177$).

Discussion

This is the first study to describe the MRI measurements of the ONSD, OND and ETD in cats with and without presumed intracranial hypertension. We found moderate-to-good inter-observer agreement in the measurements performed. Slight differences were observed between the transverse and dorsal planes. Therefore, we suggest that both planes could be used for assessment of the structures described.

Our results showed that there is a significant difference in the ONSD between the two groups but only when patient age is not considered. Hence, the ONSD was associated with age rather than ICP status in this population. This association was weak; however, this finding led to further analysis in the measurement of the OND and sheath size, to understand which of these structures increased with age. We therefore measured the OND of all patients and calculated the sheath size by subtracting the OND from the ONSD value. When the associations of both variables were studied, they showed that the OND increased with age, and the sheath size remained unchanged. These findings were unexpected, as in people and dogs a significant positive association between the ONSD and increased ICP exists.[8,15]

In the human and veterinary literature, the positive correlation of ONSD/OND with age and ICP status is ambiguous. The ONSD measured by US or MRI has been proven to be a reliable indirect method of intracranial hypertension detection in humans[13–15] and dogs.[8,16,17] No association of ONSD and any clinical variable including age has ever been identified.[8,18,19] However, the three variables together (ICP status, ONSD, age) have not been investigated.

In cats, only one US study assessing the ONSD and its relationship with ICP is available, and suggested that increased ONSD is positively correlated with increased ICP. The relationship between ONSD and weight/age was assessed as a simple correlation, and the three variables together (ONSD, age, ICP status) were not investigated.[21] This report also suggested that ONSD decreased in size with age, which differs from our findings. Interestingly, there is a large difference in the measurements of ONSD from the mentioned study and our sample, and the US measurements were smaller than the MRI ones.[21] These variations may result from the difference in spatial resolution of the two imaging modalities and the signalment differences in the populations studied.

In contrast, our results agree with a previous study on CT measurements of ocular structures in healthy cats,[22] where the OND was noted to increase in size with age. Similar findings have also been reported in rats[23] and children.[24]

The reason why OND appears to increase with age in cats is unknown and an extensive description of changes within the ON with age is only available in human literature.[25] In people, the ON at birth is small and becomes myelinated during the first years. The maximum size is reached between 12 and 15 years of age, after which the nerve size remains relatively static. With time (suggested after 60 years of age), the meninges and fibrous septa become wider and occupy more of the cross-sectional area. The axons are also thought to progressively decrease in size, which is likely caused by loss of ganglion cells.[25] We hypothesise that, with age,[25] the axons become more loosely structured, making an apparently wider OND, despite loss of ganglion cell. This would explain the increase of the OND in our study population. Further studies on ageing of the feline ON are needed to verify this hypothesis.

It has also been shown that the subarachnoid space of the human ON is not homogeneous.[26] Closest to the globe the arrangement of the trabeculae is denser than in its distal portion. It is therefore possible that the feline ONSD measurements differ depending on how close to the globe the measurement is taken.

Herein, we also identified associations between the ONSD and ETD in healthy group. This has not been described in the veterinary literature before and is in concordance with human studies where ONSD is correlated with ETD.[18,27] In human medicine the ONSD: ETD ratio measured on US has also been described as a potential non-invasive indicator of increased ICP.[20] However, in our population, the ONSD: ETD ratios were significantly associated with ICP status only when age was not considered.

We also found positive correlations between the ETD and weight. Differently to what has been published about dogs,[8] feline ONSD was independent of weight. Perhaps this is due to the much larger size variation of the canine population. Cats are generally more uniform in size and variation in breeds with regard to size is less pronounced. Also, similarly to human literature,[18] we did not identify a correlation between feline ETD and age.

This study has some limitations. First, its retrospective nature resulted in a limited number of patients and unequal number of subjects in the two groups. A larger number of cats would have allowed a more accurate description of the findings and determination of whether correlations other than the ones described existed. The exact location of the measurement was not standardised for the OND and ONSD, which may have potentially affected the results, including the inter-observer agreement. In a clinical setting, it is challenging to standardise the ON measurement as the patients included in the study presented for a brain, rather than ON, MRI. When assessing the brain on MRI the nerve will routinely be imaged obliquely. Hence, we selected the best slice and could not standardise the measurement site. Therefore, our results should be considered with caution as mainly moderate ICCs were found. Finally, there was no reference standard measure of direct ICP in our study population and the presumed diagnosis of intracranial hypertension was undertaken based on MRI findings.

Conclusions

This study contributes valuable data to the existing literature. Our findings showed that OND, ONSD, ETD and ONSD: ETD ratio are associated with age while being independent of weight and presumed ICP status. Therefore, the results of this study suggest that

measurement of the ONSD and ONSD/ETD on T2W MRI might not be reliable as non-invasive tests for diagnosing intracranial hypertension in cats.

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Ethical approval This work involved the use of non-experimental animals only (including owned or unowned animals and data from prospective or retrospective studies). Established internationally recognised high standards ('best practice') of individual veterinary clinical patient care were followed. Ethical approval from a committee, while not specifically required for publication in *JFMS*, was nonetheless obtained, as stated in the manuscript.

Informed consent Informed consent (either verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (either experimental or non-experimental animals) for the procedure(s) undertaken (either prospective or retrospective studies). No animals or humans are identifiable within this publication, and therefore additional informed consent for publication was not required.

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