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Volumetric calculation of cerebellum in Akkaraman sheep and Hair goat using Cavalieri's principle

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ABSTRACT

The aim of this study is to calculate the cerebellum volume in Akkaraman sheep and Hair goat using the Cavalieri's principle. Cerebellum of 12 healthy 1-2 year old male animals (6 sheep and 6 goats) were used in the study. The weight of the cerebellum separated from the rhombencephalon was calculated with a sensitive electronic balance, and its volume was calculated with Archimedes' principle. In the volume measurement to be made with Cavalieri's principle, the cerebellum was blocked with 8% agar to prevent tissue loss during slicing. The stained sections were scanned with a horizontal scanner at 600 dpi resolution. Gray matter and white matter volume were calculated separately by dropping the point counting grid on cross sections in ImageJ software. Cerebellum weight was calculated as 11.6 gr in sheep and 12.55 gr in goats. The ratio of cerebellum weight to total brain weight was calculated as 0.10 in both species. It was observed that the cerebellum weighs an average of 9.8% of the total brain weight in sheep. In the goat, it was observed that the cerebellum constituted 10.11% of the brain. Gray matter and white matter volumes were calculated as 6.75 ml and 3.36 ml in sheep, respectively. In the goat, the gray matter and white matter volumes were measured as 6.80 ml and 3.82 ml, respectively. Total cerebellum volume was found to be 10.14 ml and 10.65 ml in sheep and goats, respectively. In sheep, 65.55% of the cerebellum volume consisted of gray matter and 33.08% of white matter. In goats, 63.88% of the cerebellum consisted of gray matter and 35.85% of white matter. No statistical difference was observed in the volume measurement results obtained in both species ($p>0.05$). In recent years, there has been an increase in neurodegenerative disease models in farm animals. These diseases can cause changes in the volume of the cerebellum. In this context, it is thought that the volume values obtained from healthy sheep and goat cerebellum in the current study will be important for future studies

Akkaraman koyunu ve Kıl keçisinde Cavalieri prensibi kullanılarak cerebellum hacminin hesaplanması

ÖZET

Bu çalışmanın amacı, Akkaraman koyunu ve Kıl keçisinde cerebellum hacmini Cavalieri prensibi kullanarak hesaplamaktır. Çalışmada sağlıklı 1-2 yaşlarında 12 adet erkek hayvana ait (6 koyun ve 6 keçi) cerebellum kullanıldı. Rhombencephalon'dan ayrılan cerebellum'un hassas terazi ile ağırlığı, Archimedes' principle ile hacmi hesaplandı. Cavalieri prensibi ile hacim ölçümü esnasında doku kaybının önüne geçmek için cerebellum'lar 8%'lik agar ile bloklandı. Gri madde ve ak madde ayrımının net yapılabilmesi için, gri madde Berlin blue makroskobik boyama metodu ile boyandı. Boyanan kesitler 600 dpi çözünürlükte tarandı. Taranan bu kesitlere ImageJ programında noktalı alan ölçüm cetveli atılarak gri madde ve ak madde hacmi ayrı ayrı hesaplandı. Yapılan ölçüm sonuçlarına cerebellum ağırlığı koyunda 11.6 gr, keçide 12.55gr hesaplandı. Cerebellum ağırlığının toplam beyin ağırlığına oranı her iki türde de 0.10 olarak ölçüldü. Koyunda cerebellum beynin ağırlığının 9.8% 'ini, keçide ise 10.11%'unun oluşturmaktadır. Gri madde ve ak madde hacmi koyunda sırasıyla 6.75 ml ve 3.36 ml hesaplandı. Keçide ise gri madde ve ak madde hacmi sırasıyla 6.80 ml ve 3.82 ml olarak ölçüldü. Toplam cerebellum hacminin koyun ve keçide sırasıyla 10.14 ml ve 10.65 ml olduğu görüldü. Koyunda cerebellum hacminin 65.55%'ini gri madde, 33.08%'ini ise ak maddenin oluşturmaktaydı. Keçide ise cerebellum'un 63.88%'i gri madde, 35.85%'ini ise ak maddeden oluşmaktaydı. Elde edilen hacim ölçümü sonuçlarında her iki türde de istatistiki fark gözlenmemiştir ($p>0.05$). Çiflik hayvanlarında son yıllarda nörodejeneratif hastalık modellerinde bir artış görülmektedir. Bu hastalıklar cerebellum hacminde değişikliğe neden olabilmektedir. Bu açıdan mevcut çalışmada sağlıklı koyun ve keçi cerebellum'undan elde edile hacim değerlerinin, gelecekteki çalışmalar için faydalı olacağı düşünülmektedir.

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1. Introduction

The cerebellum is the largest part of the rhombencephalon (hindbrain) and is located above the pons and medulla oblongata. It is connected to the brain stem on both sides by three peduncles (pedunculus cerebellaris). It is roughly globular and has much-fissured on it (1, 2). It is separated from the hemispherium cerebri by the tentorium cerebelli membranaceum located inside the fissura transversa cerebri (1, 3). The cerebellum consists of two large hemispherium cerebelli and a narrow ridge named vermis between them (1). In the cerebellum, the gray matter forms the cortex cerebelli and the white matter forms the corpus medullare (3, 4). In the median section of the cerebellum, the cortex cerebelli and corpus medullare are easily distinguished (3).

The cerebellum is involved in the control of balance, postural, locomotor activities, and coordination of skeletal muscles. The center of balance is located in the lobus flocculonodularis, while the lobus caudalis controls motor functions (1, 4). Cerebellar ataxia, manifested by loss of coordination and balance, occurs when there are deficits of function in the cerebellum (4). In addition, volumetric losses are observed in the cerebellum in neurodegenerative diseases. It is known that there is a significant decrease in the volume of the cerebellum, especially in Alzheimer's disease (5-7). This change causes seriously affecting one's ability to carry out daily activities (8). In addition to volumetric changes, Purkinje cells are also damaged in diseases such as epilepsy, Huntington's disease, and Alzheimer's disease (9). It is known that the cerebellum volume decreases with age, which is due to the loss of white matter. It has been shown that diabetes, higher serum glucose and lower cholesterol levels are associated with cerebellum volume. In addition, it has been shown that the factors determining the volume of the hemispherium cerebri do not entirely overlap with the volume of the cerebellum (10). This situation reveals that the cerebellum volume should be handled separately, mainly in itself.

In recent years, farm animals have been frequently preferred as model animals in neuroscience research due to the similarity of the neuroanatomical structures of the brain in farm animals, especially sheep, to the human brain compared to laboratory animals (11-13). The neuroanatomical structures of the brain in farm animals and the fact that the cortex cerebri consists of prominent lobes, such as in humans and primates, make these animals advantageous against laboratory animals with lissencephalic brains (12, 14, 15). The primary reasons for preference are that farm animals are easily available, docile animals, their breeding is widespread, and does not include ethical problems encountered in carnivores and primates in research (11, 16).

Cavalieri's principle is the preferred method for calculating the volume of biological structures in an unbiased manner. This method is primarily preferred in calculating the volume of irregular shapes in the discipline of stereology (17). Cavalieri's principle is to use a two-dimensional cross-section or projection of a three-dimensional structure (18-20). The area of these surfaces is calculated with a point counting grid. Then, the volume of the irregularly shaped biological structure is calculated by an unbiased method by multiplying the surface area of each section by the section thickness (17, 18, 20).

Morphometric studies in the cerebellum, which has a very important role in the balance control and coordination of the body, have been carried out in many different species with different methods. In the study conducted on primates, it was observed that the pongid and hylobatid apes cerebellum volume was larger than the average cerebellum volume of monkeys. Accordingly, it was concluded that not all primate brains are organized similarly (21). Morphometric studies have been carried out on the cerebellum of domestic mammals such as sheep (22-25), cattle (26, 27), dogs (7, 28) and cats (29, 30). In addition to these studies using different methods, morphometric studies were also carried out in the cerebellum using stereological methods. Laboratory animals are generally used, calculations were made on rats (31-33), mice (34), guinea pig (29) and rabbit (35, 36) cerebellum. In addition, the volume of gray and white matter in the cerebellum and the number of Purkinje cells were examined using stereological methods in pigs (37) and cats (38) from domestic mammals. In addition, calculations were made in the cerebellum, which has a higher volumetric ratio in the brain due to its function with this method in the chicks (39).

The motivation of the study is that the measurement studies performed in the cerebellum of farm animals using Cavalieri's principle are limited. The change in cerebellum volume in neurodegenerative diseases is an important factor in understanding the effects of these diseases on the nervous system. It is especially important to observe the total volume of the cerebellum and the changing in gray matter and white matter. In recent years, there has been an increase in models of these neurodegenerative diseases in farm animals. In this context, the aim of the study is to calculate gray matter, white matter and total volume in healthy sheep and goat cerebellum using Cavalieri's principle.

2. Material and Methods

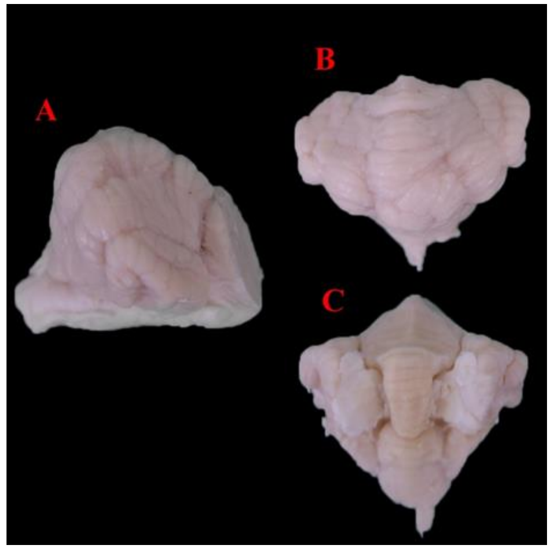
Animals

Six healthy male sheep and goat heads (1-2 years old) (sheep/goats body weights: 48±3,74 kg/ 33±4,46 kg) were used in the study. The heads were obtained from an agricultural enterprise (a state agricultural enterprise in Konya), where there was constantly monitored under mandatory official veterinary medical care. The slaughtering process was carried out under the control of a veterinarian. The Ethics Committee of Selçuk University Faculty of Veterinary Medicine approved the study procedure in the session held on 30/03/2023 (Decision number 2023/26). It was fixed by injecting 10% formaldehyde from the arteria carotis communis into the heads of sheep and goats. For the fixation to be homogeneous in every part of the brain, the heads were kept in containers containing 10% formaldehyde solution for 15 days. Thus, the brain and cerebellum were ensured to maintain their shape within the skull. Using the dorsal approach, the brains were removed from the cavum cranii with the dura mater encephali preserved (Figure1).

Şekil 1: Dura mater ensefali ile ensefalon
***Figure 1:** Encephalon with dura mater encephali*

Preparation of specimens

Meninges were removed from the brain tissue, respectively. At the level of the sulcus pontocruralis, the rhombencephalon was separated from the other parts of the encephalon. Then, the cerebellum was carefully separated from the pedunculus cerebellaris, which consists of three peduncles and connects the cerebellum with the pons, medulla oblongata and crus cerebri (Figure 2).



Şekil 2: Rhombensefalon, ensefalonun diğer kısımlarından ayrılmıştır. A. Rhombencephalon; B. Serebellumun dorsal yüzü; C. Serebellumun ventral yüzü

Figure 2: *Rhombencephalon was separated from the other parts of the encephalon. A. Rhombencephalon; B. Dorsal aspect of the cerebellum; C. Ventral aspect of the cerebellum*

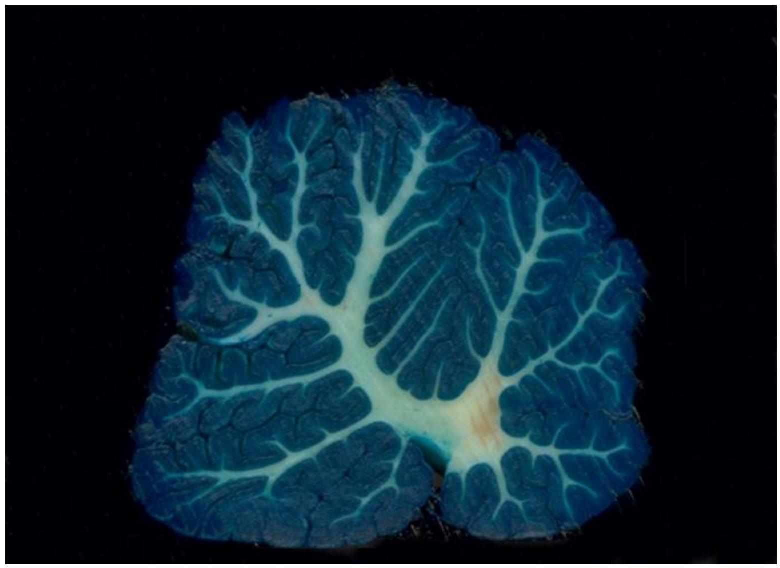
The weights of the cerebellum were measured with a sensitive electronic balance (OHAUS CS200) and their volumes were measured with Archimedes' principle. The cerebellum was kept under running tap water overnight before sectioning for volume calculation. The cerebellum was blocked with 8% agar (Blood Agar Base LABM-LAB028) to prevent tissue loss during slicing (Figure 3) (40, 41). After the blocks were kept at room temperature (24 hours), sagittal sections were taken with an electric meat slicer (SINBO SMS-5601). Sections (thickness of 2.48 mm) were taken starting from the flocculus of one side to the flocculus of the other side.

Şekil 3: Kanlı agar ile bloke edilmiş cerebellum

Figure 3*: Cerebellum was blocked with blood agar*

Staining of sections

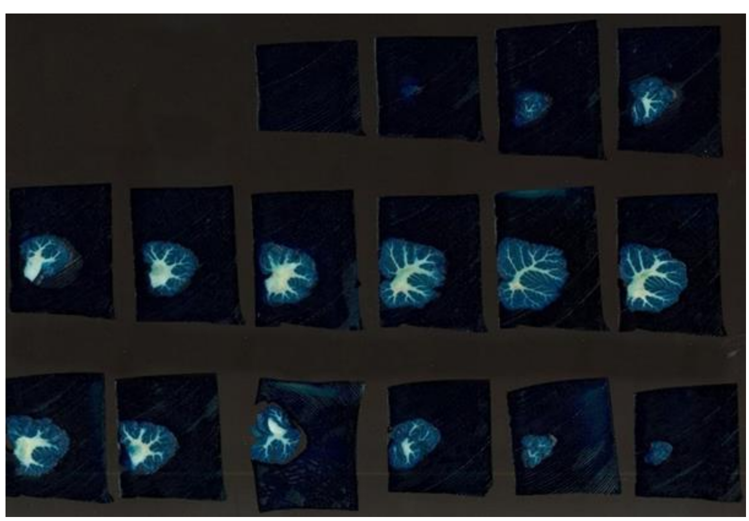
In the sections obtained from the cerebellum, the gray matter was stained with Berlin Blue in order to make a clear distinction between gray matter and white matter in the cortex cerebelli and corpus medullare during volume measurement. Mulligan, iron chloride and potassium ferricyanide solutions were used in the staining process. The sections were kept in solutions according to the staining procedure, and the gray matter was stained with Berlin Blue (42, 43). In the encephalon, the body of neurons is located in gray matter. The neuron density in different mammalian species is higher in the cerebellum than in other parts of the encephalon (44, 45). Therefore, staining of gray matter with Berlin Blue has been more successful with this method compared to staining performed in other parts of the brain (Figure 4).



Şekil 4: Berlin mavisi ile boyanmış serebellum kesiti

***Figure 4**: Cross section of cerebellum stained with Berlin blue*

The same surface of the sections stained with Berlin Blue was scanned using a horizontal scanner (hp Scanjet G4010) at 600 dpi resolution in JPG (Joint Photographic Expert Group) file format (Figure 5).

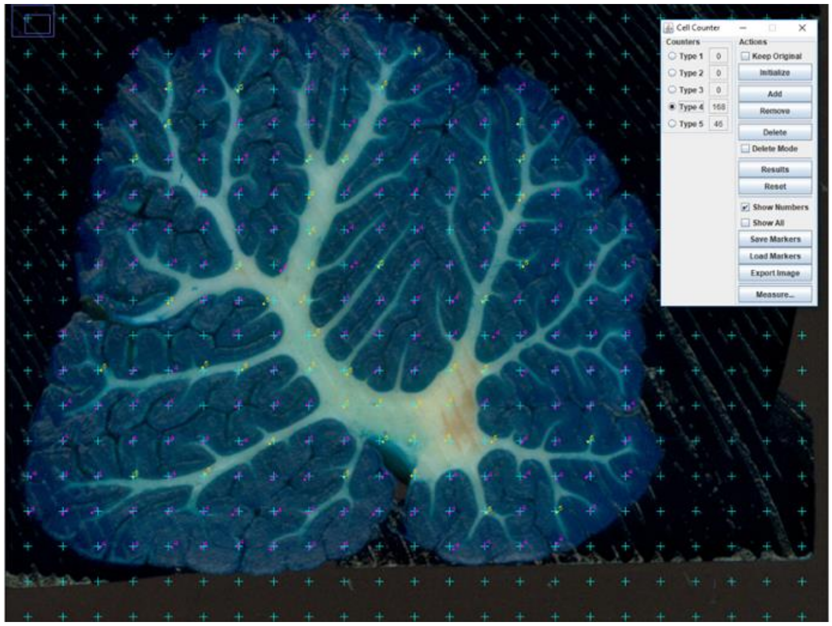


Şekil 5: Tarayıcı ile taranan kesitler

***Figure 5:** Sections scanned with a horizontal scanner*

Calculation of volume using Cavalieri's principle

Cavalieri's principle was used to calculate the volume of gray matter and white matter in sections whose gray matter was stained and scanned with Berlin Blue. The gray matter and white matter area were calculated in the section surface area in ImageJ (Image Processing and Analysis in Java) software. The point counting grid on cross section surface was placed using ImageJ software (Figure 6). Then, the surface areas were calculated by counting the points dropping into the gray matter and white matter separately. This procedure was repeated three times, and the averages of the counted points were obtained.



Şekil 6: Kesit yüzeyindeki noktalı alan ölçüm cetveli

Figure 6: *The point counting grid on cross section surface*

After point counting for all sections, the volume of each section was calculated with the help of the following equation used in volume measurement in Cavalieri's principle.

$$V= t \times \Sigma P \times a(p)$$

V= volume; t = section thickness; ΣP= total number of points hitting the cross sections surface area; a(p)= known area per point placed at random over on the cross sections surface area (point counting grid). After calculating each section's volume, the cerebellum's total volume was calculated with the help of the equation below (18, 46-48).

$$V_{Top}=V1+V2\ldots\ldots Vn$$

Statistical analyses were performed using SPSS 25.0 ((IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). The normality of variables was tested using the Shapiro-Wilk test and the homogeneity of variances was checked Levene's test. The difference between the two species' cerebellum was performed using Student's t-test for parametric variables.

Nomina Anatomica Veterinaria was used for the anatomical terms (49)

3. Results

Demographic data of the study population was presented in Table 3.1. Cerebellum weight, cerebellum volume (Archimedes' principle), cerebellum/total brain(TB) volume ratio and percentage, number of slices and average cross-section thickness are summarized in Table 1.

Tablo 1: Akkaraman koyunu ve Kıl keçilerinden elde edilen demografik veriler (n=6).

Table 1: *Demographic data was obtained from Akkaraman sheep and Hair goats (n=6).*

Parameter	**Sheep Mean ±SD**	**Median**	**Goat Mean ±SD**	**Median**
Cerebellum weight (g)	11.6 ± 1.2	11.95	12.55 ± 1.2	11.95
Cerebellum volume (mL)	12.92 ± 1.2	13.25	13.83 ± 1.33	13.00
Cerebellum: TB weight ratio	0.10 ± 0.008	0.10	0.10 ± 0.010	0.10
Cerebellum: TB volume ratio (mL per mL)	0.11 ± 0.009	0.11	0.11 ± 0.011	0.11
Cerebellum percentage within TB (%)	9.8 ± 0.77	10.00	10.11 ± 0.91	9.93
Number of slices	13.8 ± 2.04	15.00	12.67 ± 0.82	12.50
Average of cross-section thickness (mm)	2.40 ± 0.2	2.30	2.58 ± 0.33	2.45

SD, standard deviation; TB, total brain

In the cerebellum weight measurements, it was observed that the cerebellum was heavier in goats. Similarly, the volume result obtained with Archimedes' principle was found to be greater in goats. The ratio of cerebellum weight to total brain weight was found to be close to each other in both species. Similar results were found for the volume ratio. It was observed that 9.8% of the brain weight in sheep and 10.11% in goats was made up of the cerebellum. In the sections obtained for Cavalieri principles, it was seen that the average section thickness and the number of sections were close to each other in both species.

The volume of gray matter and white matter forming the cortex cerebelli and corpus medullare in the cerebellum were calculated separately. Using the Cavalieri principles were obtained volume of the gray matter, white matter and indices/ratio were summarized in Table 2.

According to the results of the volume measurement using the Cavalieri principle in sheep and goat cerebellum, it was observed that the gray matter volume was very close to each other in both species. Similarly, the white matter values were found to be close to each other. It was observed that the total volume of the cerebellum was slightly higher in goats, but this difference was not statistically significant. It was determined that the GM: WM and GM: Cerebellum ratio was higher in sheep, while the ratio of WM: Cerebellum was higher in goats. The volumetric values and ratios obtained showed no statistical difference between sheep and goats. It was determined that 65.55% of the cerebellum volume in sheep was composed of gray matter and 33.08% of white matter. In goats, 63.88% of the total volume was gray matter and 35.85% was white matter. Considering this ratio, it was seen that the white matter volume in the cerebellum was higher in percent in goats. Fresh cadavers could not be used in the study due to rapid autolysis of the brain tissue after euthanasia. The shrinking effect of formaldehyde in the brains used was ignored (50,51).

Tablo 2: Akkaraman koyunu ve Kıl keçisi beyinciklerinde gri madde, beyaz madde, oran ve CE değerlerinin ortalamaları.

Table 2: *The means of values gray matter, white matter, ratio, and CE in Akkaraman sheep and Hair goats cerebellum (n=6).*

Parameter	Sheep Mean ±SD Median	Minimum Maximum	Goat Mean ±SD Median	Minimum Maximum	p
GM (mL)	6.75 ± 1.04 6.38	5.99 8.68	6.80 ± 0.63 6.73	6.04 7.87	0.92^{t}
WM (mL)	3.36 ± 0.49 3.32	2.65 4.01	3.82 ± 0.70 3.65	3.16 5.00	0.21^{t}
Total Cerebellum volume (mL)	10.14 ± 1.49 9.74	8.65 12.7	10.65 ± 1.2 10.24	9.20 12.19	0.53^{t}
GM:WM ratio (mL per mL)	2.02 ± 0.16 1.95	1.88 2.26	1.81 ± 0.22 1.86	1.41 2.08	0.09^{t}
GM:Cerebellum ratio (mL per mL)	0.67 ± 0.019 0.66	0.65 0.69	0.64 ± 0.03 0.65	0.59 0.68	0.12^{t}
WM:Cerebellum ratio (mL per mL)	0.33 ± 0.016 0.34	0.31 0.34	0.36 ± 0.031 0.35	0.32 0.41	0.09^{t}

**p<0.05; t Student's t test; SD, standart deviation; CE, coefficient of error GM, gray matter; WM, white matter*

4. Discussion and Conclusion

In the current study, gray matter and white matter volume were calculated using Cavalieri's principle in sheep and goat cerebellum. It has been shown in many studies that the cerebellum effects from a volumetric deficiency in neurodegenerative diseases. In Alzheimer's disease, there may be volumetric losses in the cerebellum at a level that will cause negative effects on the performance of daily activities (5-8). In cases such as diabetes and lower cholesterol levels, the change in hemispherium cerebri and cerebellum does not overlap (10). This shows that the change in cerebellum volume should be examined separately.

Neuroanatomical structures of brain are more similar to humans in farm animals compared to laboratory animals. This situation has brought these animals to the forefront of neuroscience in recent years. Some neurodegenerative disease models are established in these animals (12-14). It is very important to observe the gray and white matter changes in the substructures of the brain in these disease models. This change in the cerebellum is also very important in terms of the disease's diagnosis. In this respect, the gray matter and white matter values obtained from healthy animals in the current study are very important for studies to be carried out on these diseases.

The ratio of cerebellum volume to total brain volume was compared in primates. The volume ratio of pongid and hylobatid apes cerebellum was found to be much larger than that of other monkeys (21). It was observed that the ratio of sheep and goat cerebellum in the total brain was close to the average value of monkeys, except for the two breeds mentioned. It was observed that the cerebellum occupies a larger percentage of the total brain volume in goats. where locomotor activity coordination is more important than in sheep.

Brain weight, encephalization and cerebellar quotients were determined in the study conducted in dairy cattle, beef cattle and crossbred from domestic mammals. The study determined that the cerebellum weight constitutes 9.9% of the total brain weight (26). This ratio was calculated as 9.8% in sheep and 10.11% in goats in the current study. It has been observed that this value obtained from cattle is very close to sheep and slightly lower than goats. In another study, the cerebellum morphology of cattle, sheep, and goats was examined. Cerebellum weight in sheep was measured greater than the value obtained in the current study. The ratio of cerebellum to total brain weight was calculated lower than the value obtained in the current study. It is thought that the reason why the cerebellum weight value is higher and its ratio to brain weight is lower is due to the use of merino sheep and sheep over three years old in the study. Sheep between 1-2 years of age were used in the present study. Similarly, in the same study, cerebellum weight was higher, and the ratio of the cerebellum to total brain weight was lower in goats. The age of the goats used in the study was not specified. In addition, the use of different breeds of goats in the study is thought to cause this difference. The current study used only one goat breed (Hair goat). The cerebellum ratio obtained from cattle to total brain weight was calculated close to the value obtained from sheep and goats in the current study (25).

In dogs, the volume of the cerebellum was calculated using medical images. Dogs with normal and cerebellar degenerative diseases were used in the study to determine the ratio of the cerebellum to other parts of the brain. The percentage of cerebellum volume in the brain did not change with age in dogs aged 1 to 5 years. In the study using different dog breeds, the cerebellum percentage was between 8.84% and 9.86% (7). It is seen that the cerebellum volume in dogs is lower than the volume values obtained from sheep and goats. It is seen that the cerebellum percentage values obtained from dogs are also lower than the weight percentage of the cerebellum in sheep and goats.

Gray matter and white matter volume in the cerebellum was calculated using Cavalieri's principle in New Zealand rabbits. According to the results, it was observed that the percentage of white matter in the cerebellum of females was higher than that of males (36). The gray matter and white matter percentages in males were found to be very close to the percentages obtained from sheep in the current study using male animals. It was determined that the percentage of white matter in goats was higher than in rabbits. In another study, in which Cavalieri's principle was used, the cerebellum volume was calculated in male cats (38). It is seen that the percentage of gray matter in the cerebellum of cats is much higher than that of sheep and goats, and the percentage of white matter is lower.

The cerebellum volume of sheep and goats was calculated in the study, in which Cavalieri's principle was used to calculate the most realistic volume in biological structures. Using Cavalieri's principle, the volume of gray matter and white matter forming the cerebellum were calculated separately. In the cerebellum, gray matter and white matter volume and their ratios show a decrease or change in some neurodegenerative diseases. There has been an increase in these disease models in farm animals in recent years. It is thought that these values obtained from the cerebellum of healthy animals will be important data for future neurodegenerative disease studies on these animals.

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Conflict of Interest

The authors do not have any conflict of interest

Authors' Contributions

Bu bölümde makalenin yazar/yazarlarının çalışmaya katkıları aşağıdaki başlıklar yardımıyla yazar(lar)ın isim-soyisimleri kullanılarak belirtilmelidir.

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Veri analizi ve yorum: Ali KOÇYİĞİT
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Etik Onay

The Ethics Committee of Selçuk University Faculty of Veterinary Medicine approved the study procedure in the session held on 30/03/2023 (Decision number 2023/26).

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