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The volume fraction of brain ventricles to total brain volume: a computed tomography stereological study*

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This study has been designed to estimate the volume fraction of the brain ventricles volume to total brain volume and to correlate them with gender and age in normal subjects. Cranial computed tomography (CT) images of 80 normally evaluated subjects (five female and five male for each decade) were selected from 1,073 CT examinations. The volumes of total brain, cerebral aqueduct, fourth, third, and lateral ventricles and their ratios were estimated using the Cavalieri method and volume fraction-stereological methods. The ratio of total brain ventricle volume to total brain volume was comparable between the two genders ($p > 0.05$, independent t test). Mean volume fraction of total ventricle volume to total brain volume was found to be 1.21% in the first and 3.37% in the last decades. Mean volume fraction was found to increase significantly with age ($p < 0.01$, $r = 0.630$, Pearson). In conclusion, the mean percentage of total ventricle volume within the total brain volume was found to be 2%. We demonstrated the volume fraction of total ventricle to total brain in normal subjects. Total ventricle volume to total brain volume fractions can be important tools in determining ventricle volumes, which denote variability in some diseases (Alzheimer, schizophrenia, neurodegenerative disorders, etc.) and can be estimated by stereological methods. (Folia Morphol 2010; 69, 4: 193–200)

Key words: brain ventricles, brain volume, Cavalieri method, volume fraction, stereology

INTRODUCTION

The brain ventricular system consists of a series of interconnecting spaces and channels in the brain. The lateral ventricle (LV) within each cerebral hemisphere lies in a large C-shaped configuration. The LVs communicate with the third ventricle (TdV) through the interventricular foramen (foramen of Monro), which is a slit like a midline cavity lying between the right and left halves of the diencephalon. The TdV continues with the cerebral aqueduct (CA) caudally as a narrow tube that passes the length of the midbrain, and turns with the fourth ventricle (FV), a wide tent shaped cavity lying between the brain stem (BS) and cerebellum (CBL) [28].

Brain ventricle volumes denote variability in some diseases such as hydrocephalus [6], schizophrenia [25], Alzheimer's [19], and a group of neurodegenerative disorders [30], but some of

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these diseases also represent parenchymal atrophy leading to ventricle/brain ratio changes [26, 30]. Some previous studies [15, 21, 31] reported variable results concerning the measurements of ventricle volumes in different age groups. Coffey et al. [8] reported different results about the relation between brain ventricle volume and gender. Consequently, the gender and age related volume fraction of the ventricle to brain changes is still obscure.

Cavalieri is a modern stereological method that can be applied on either microscopic [1] or radiological images [9]. This method allows an estimation to be made of the volumes of irregular objects in an efficient and unbiased manner [11]. The volumetric estimations according to Cavalieri principles can be achieved on computed tomography (CT) and magnetic resonance (MR) images [24]. Volume fraction is a stereological approach denoting the ratio of body components to each other independently of the body size of the individuals [9]. The volume and volume fraction approach of stereological methods provides information about volumetric relations of the components of structures [2]. A requirement for the application of this method is an entire set of 2D slices through the object, provided they are parallel, separated by a known distance, and begin randomly within the object — criteria that are met by standard MR imaging and CT scanning techniques [9, 24].

This study set out to determine the total ventricle and individual ventricle-total brain or brain sites of volume fraction related to different gender and age groups in normal subjects.

MATERIAL AND METHODS

Cavalieri method and volume estimation

By using the Cavalieri principle, an unbiased estimate of the volume of an object of arbitrary shape and size may be obtained efficiently and with known precision [23]. The Cavalieri method provides quantitative data on 3D structures using 2D images [24]. A transparent grid point scale [9, 23] was superimposed on CT images to count the number of points visible in the brain. Counting was repeated three times for each image, and the mean point number (Q) was calculated. The total volume of an object of arbitrary shape and size was estimated using the following formula [11, 23].

$$V = (Q) \times (a) \times (t)$$

V — volume; Q — the total counted number of points hitting of the object; a — the unit area represented by each grid point; t — the distance between the two sections.

The formula could be rewritten for the radiological studies as described previously using the formula given below [9, 14, 24]:

$$V = (\Sigma Q) \times [(SU) \times d / SL]^2 \times (t)$$

V — volume (of the brain structure or ventricle); ΣQ — the total counted number of points hitting of the brain structure or ventricle; SU — the scale unit; d — the distance between two points in the point grid; SL — the length of the scale; t — the section thickness (including interval) of consecutive sections.

SU and SL are used to include the linear magnification in the final estimate. All calculations and other related data were obtained as a spreadsheet using Microsoft Excel. After initial setup and preparation of the formulas, the point counts, formulas, and other data were entered for each subject and the final data were obtained automatically. The coefficient of error (CE) was also estimated in this study, as described in the literature [11].

The method requires sectioning of the structure in a series of parallel planes. To avoid bias, the first section must be placed at a uniform and random position in a constant interval of length, and the series of sections must encompass the object entirely. Thus, an unbiased estimate of volume can be obtained by multiplying the total area of the section-cut surfaces by the mean section thickness [9].

Volume fraction

The volume fraction of a component within a reference volume is a simple and very widely used parameter in biomedical science [13]. Consequently, it is used to express the proportion of a phase or component within the whole structure. The volume fraction of a phase *Y* within a reference volume is simply expressed as follows [13]:

$$Vv = \text{Volume of phase } Y \text{ in reference space} / \text{Volume of reference space}$$

where the Vv (*Y*, ref) indicates volume fraction of *Y* phase within the reference volume. Using this approach, Vv (alveoli, lung) and Vv (tumour, liver) can be estimated. Volume fraction ranges from 0 to 1 and is often expressed as a percentage. The volume fraction of a phase can be estimated by means of the Cavalieri principle on radiological images using the point counting approach [9]. The volume frac-

tion formula in combination with the Cavalieri principle can be written as follows [9]:

$$Vv\,(Y, \text{ref}) = [V\,Y = (\Sigma Q) \times [(SU) \times d / SL]^2 \times (t)] / / [V\,\text{ref} = (\Sigma Q) \times [(SU) \times d / SL]^2 \times (t)]$$

Since the same images are used for the volume fraction estimation of any subject, the number of the points counted (i.e. ΣQ) is the only value of the volume fraction formula, which changes. Thus, the formula can be simply changed to [5, 13]:

$$Vv\,(Y, \text{ref}) = \Sigma Q\,Y / \Sigma Q\,\text{ref}$$

where, "ΣQ *Y*" indicates the number of points hitting the *Y* phase and "ΣQ ref" the number of points hitting the reference space. Usually, the phase within the reference space is smaller in size.

A combined point-counting grid (CPCG) was used in this study. A CPCG is composed of two sets of points of different densities on the same grid. We can describe this grid as a CPCG with 1/16 area fraction. The volume fraction of a component within the organ can be estimated by placing the CPCG over the section series, counting the number of coarse points that hit the reference space including the phase, and counting the number of all points hitting only the phase. As the ratio of fine to coarse points is 1/16, a slightly modified version of the above equality can be used to estimate the volume fraction of a component within the subject.

$$Vv\,(Y, \text{ref}) = (\Sigma Q\,Y) / 16 \times (\Sigma Q\,\text{ref})$$

In the new formula, none of the parameters in the volume estimation equation is required except the number of points hitting the phase and the reference space. This new approach is not affected by the reduction/magnification ratio of the images for each group [9].

The total brain volume (TBV) and the components of other structures, i.e. cerebrum (CBR), CBL, BS, and ventricle volumes, were also estimated using the Cavalieri principle using the stereological methods as described in previous studies [20, 23].

Subjects

This study was approved by the Pamukkale University Medical Ethics Committee (No. 400-3/95). The study group was drawn from 1,073 patients referred for head CT examination for various indications in one year. Patients with space-occupying lesions, intracranial bleeding, recent infarction, trauma, postoperative scanning, and incomplete clinical information were excluded on the basis of CT findings. Patients who had no pathologic evidence (free of any neurological signs) and had normal head CT took part in the study. All subjects were admitted to the Department of Radiology in Pamukkale University, Faculty of Medicine (Turkey). Five male and five female normal subjects were chosen for each decade. Thus, we carried out the present study on 80 subjects consisting of 40 females and 40 males. The mean ± SD age of the male group was 40.9 ± 3.7 years, while the mean age in the female group was 41.4 ± 3.6 years. No neuropsychological assessment/test of cognitive function was performed because of subjects who were in different age groups. The whole brain volume was estimated from each image using the point-counting technique. All measurements were performed blinded to subject details and the results of any other measurements.

Computed tomography study

All subjects had axial transverse scanning of the brain, performed on a Phillips multislice CT scanner (Phillips, Holland). The scans were obtained on a plane at an angle of 15° to the infraorbitomeatal line with the following parameters: scan time 3.0 s, 120 kV, 100 mA, and slice thickness 5 mm with no inter-slice gap. Subjects received unenhanced CT scans consisting of 24–28 slices, and 12–14 slices with random sampling scheme [17] were used for evaluation. The first image in the series to be analysed was chosen randomly from the first two images. Therefore, slice thickness (t) = 10 mm. Slice thickness of 20 mm (*d*) was used for the evaluation of total brain, CBR, and CBL whereas 5 mm (*d*) in CPCG was used for all ventricle evaluations (Fig. 1).

Statistical analysis

SPSS for Windows was used for statistical analysis. Values are expressed in terms of mean and standard deviation (mean ± SD). The volumes of cerebellum, brain, and ventricles were compared between the genders using the independent t test. The Pearson correlation test was also applied to see the relation between the results of volume estimates. A p value lower than 0.05 was accepted as being statistically different.

RESULTS

Five male and five female (in total 10) normal subjects for each decade were evaluated. The total subject number was 80 with a mean age of 41.2 ± ± 23.5 (mean ± SD) (Table 1).

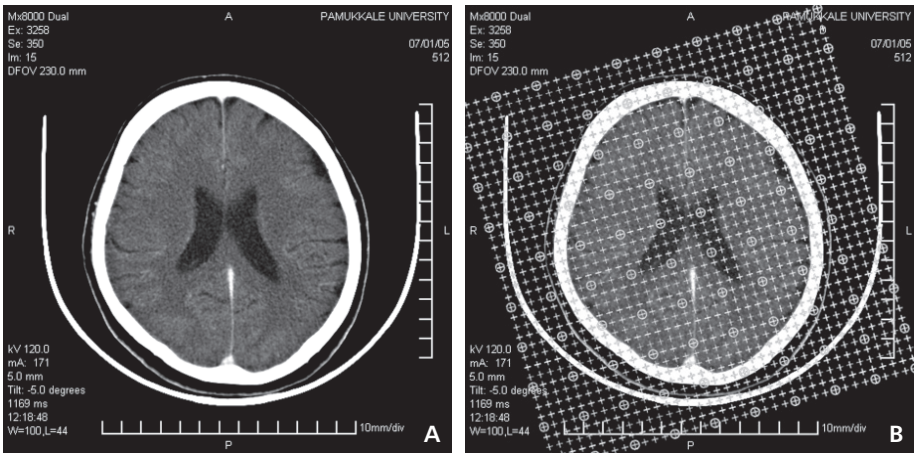

Figure 1. A. A transverse computed tomography (CT) image of the brain; **B.** Same CT image with a combined point-counting grid superimposed on it for the estimation of volume and volume fraction of the ventricles and brain sites.

Table 1. Gender and mean age of the subjects

Gender	N (no. of subjects)	Age (mean ± SD)
Female	40	41.4 ± 23.6
Male	40	41.0 ± 23.7
Mean	80	41.2 ± 23.5

The mean (± SD) total ventricle volumes (TVVs) were 22.08 ± 12.94 cm^3 and 30.62 ± 18.17 cm^3 in females and males, respectively (Table 2). The total brain and, separately, CBR and BS, CBL, and the TVVs and their estimated CE values are summarised in Table 3. Additionally, volumes of the LV, TdV, and FV for each decade are summarised in Table 4.

The volume fraction of the TVV to total brain volume (TBV) was 1.81 ± 0.98% in females and 2.18 ± 1.30% in males. There was no statistical difference between volume fraction and gender ($p > 0.05$, independent t test) (Table 5). However, mean volume fraction (MVF) increased significantly with age ($p < 0.01$, $r = 0.630$, Pearson) (Table 6). The MVF of the TVV to TBV was 1.21% in the first decade and 3.37% for the last decade. Only the results of the second and third decades were close to each other, but in general the volume fraction represented a correlation with age ($r = 0.630$, Pearson) (Table 6, Fig. 2).

The estimated volume fractions for each decade are summarised in Table 6. No statistical relation was found between the volume fraction of CA and fourth ventricle volume (FVV)/CBR and BS and the volume fraction of CA and FVV/CBL. On the other hand, statistically significant relations were found between the values of each decade and the volume fractions of TVV/TBV, the lateral ventricle volume (LVV)/TBV, TVV/CBR and BS, LVV/CBR and BS, and the third ventricle volume (TdVV)/CBR and BS (Table 6). The obtained volume fractions related with gender are summarised in Table 5 although no significant relation was found between these variables ($p > 0.05$).

Table 2. The mean volumes of the brain sites and genders (cm^3 ± SD)

Gender	N	TBV	CBR and BS volume	CBL volume	TVV	LVV	TdVV	CA and FVV
Female	40	1,177.55 ± ± 184.95	1,068.38 ± ± 168.61	112.51 ± ± 26.69	22.08 ± ± 12.94	18.44 ± ± 12.07	1.83 ± ± 0.88	1.80 ± ± 0.82
Male	40	1,343.01 ± ± 179.62	1,211.26 ± ± 159.75	133.18 ± ± 29.92	30.62 ± ± 18.17	26.32 ± ± 17.28	2.24 ± ± 1.09	2.04 ± ± 0.85

TBV — total brain volume; CBR — cerebrum and brain stem volume; BS — brain stem; CBL — cerebellum volume; TVV — total ventricle volume; LVV — lateral ventricle volume; TdVV — third ventricle volume; CA — cerebral aqueduct; FVV — fourth ventricle volume

Table 3. Decades of the subjects, volumes of the brain sites, and estimated mean coefficient errors

Decades (age groups)	TBV	CE (for total brain)	CBR and BS volume	CE (for CBR and BS)	CBL volume	CE (for CBL)	TVV	CE (for total ventricle)
1–10	978.44 ± 253.84	0.01	909.19 ± 235.73	0.02	74.88 ± 23.88	0.09	11.45 ± 4.44	0.08
11–20	1,221.42 ± 131.17	0.01	1,107.02 ± 111.15	0.02	110.00 ± 27.59	0.08	16.62 ± 5.79	0.12
21–30	1,345.18 ± 134.40	0.01	1,217.70 ± 126.89	0.02	128.26 ± 23.81	0.10	20.09 ± 6.45	0.10
31–40	1,328.21 ± 178.28	0.01	1,187.43 ± 160.06	0.02	142.18 ± 21.70	0.06	20.01 ± 12.47	0.11
41–50	1,359.58 ± 193.10	0.01	1,223.84 ± 182.71	0.02	134.96 ± 16.21	0.06	25.19 ± 11.63	0.09
51–60	1,281.75 ± 184.48	0.01	1,155.05 ± 163.47	0.02	125.99 ± 27.25	0.06	29.52 ± 13.05	0.10
61–70	1,240.22 ± 142.86	0.01	1,114.93 ± 144.14	0.02	138.66 ± 28.36	0.06	37.61 ± 23.13	0.10
> 70	1,309.99 ± 90.44	0.01	1,187.87 ± 86.97	0.02	124.46 ± 14.4	0.06	43.82 ± 13.58	0.09
Mean		0.01		0.02		0.07		0.10

TBV — total brain volume; CE — coefficient of error; CBR — cerebrum and brain stem volume; BS — brain stem; CBL — cerebellum volume; TVV — total ventricle volume

Table 4. Decades and volumes of all ventricles (cm^3 ± SD)

Decades (age groups)	LVV	TdVV	CA and FVV	TVV
1–10	8.70 ± 4.09	1.37 ± 0.53	1.40 ± 0.63	11.45 ± 4.44
11–20	13.47 ± 4.79	1.32 ± 0.65	1.82 ± 1.00	16.62 ± 5.79
21–30	16.37 ± 6.32	1.90 ± 0.88	1.80 ± 0.55	20.09 ± 6.45
31–40	16.41 ± 11.72	1.71 ± 0.70	1.89 ± 0.99	20.01 ± 12.47
41–50	20.82 ± 10.86	2.18 ± 1.15	2.13 ± 0.83	25.19 ± 11.63
51–60	24.98 ± 12.02	2.42 ± 0.80	2.11 ± 0.89	29.52 ± 13.05
61–70	32.90 ± 22.00	2.37 ± 1.08	2.33 ± 0.99	37.61 ± 23.13
> 70	39.25 ± 13.04	2.72 ± 1.21	1.84 ± 0.71	43.82 ± 13.58

LVV — lateral ventricle volume; TdVV — third ventricle volume; CA — cerebral aqueduct; FVV — fourth ventricle volume; TVV — total ventricle volume

Table 5. Volume fraction (% ± SD) in both genders

Gender	N	Volume fraction						
		(TVV/TBV)*	(LVV/TBV)*	(TVV/CBR and BS)*	(LVV/CBR and BS)*	(TdVV/CBR and BS)*	(CA and FVV/ /CBR and BS)*	(CA and FVV/CBL)*
Female	40	1.81 ± 0.98	1.51 ± 0.92	2.00 ± 1.07	1.66 ± 1.01	0.16 ± 0.07	0.30 ± 0.08	1.65 ± 0.80
Male	40	2.18 ± 1.30	1.90 ± 1.21	2.45 ± 1.41	2.12 ± 1.33	0.17 ± 0.08	0.32 ± 0.09	1.55 ± 0.59
Mean	80	2.00 ± 1.16	1.70 ± 1.09	2.23 ± 1.26	1.89 ± 1.19	0.17 ± 0.08	0.31 ± 0.13	1.60 ± 0.70

*$p > 0.05$; TVV — total ventricle volume; TBV — total brain volume; LVV — lateral ventricle volume; CBR — cerebrum and brain stem volume; TdVV — third ventricle volume; BS — brain stem; CA — cerebral aqueduct; FVV — fourth ventricle volume; CBL — cerebellum volume

DISCUSSION

We found a significant correlation between the volume fraction of TVV to TBV and age ($p < 0.05$), but no relation was found with gender and the volume fraction of TVV to TBV ($p > 0.05$). The mean ratio was found to be 2.00% overall in normal subjects whereas it was 1.21% in the first decade and 3.37% in the age group above 70 years old. Development of brain atrophy and ventricular enlargement in the older-age population was reported in previous studies [15, 21]. However, the ventricular system also represents an enlargement during the childhood

Table 6. Volume fractions in each decade

Decades (age group)	N	Volume fraction						
		(TVV/TBV)*	(LVV/TBV)*	(TVV/CBR and BS)*	(LVV/CBR and BS)*	(TdVV/CBR and BS)**	(CA and FVV/ /CBR and BS)**	(CA and FVV/CBL)**
1–10	10	1.21 ± 0.48	0.92 ± 0.46	1.30 ± 0.50	0.99 ± 0.48	0.14 ± 0.04	0.15 ± 0.05	1.91 ± 0.73
11–20	10	1.32 ± 0.31	1.06 ± 0.27	1.45 ± 0.36	1.22 ± 0.34	0.10 ± 0.04	0.15 ± 0.07	1.58 ± 0.45
21–30	10	1.50 ± 0.39	1.23 ± 0.41	1.66 ± 0.43	1.35 ± 0.45	0.15 ± 0.06	1.33 ± 0.03	1.42 ± 0.46
31–40	10	1.44 ± 0.72	1.19 ± 0.70	1.61 ± 0.81	1.31 ± 0.76	0.14 ± 0.06	0.15 ± 0.07	1.25 ± 0.67
41–50	10	1.68 ± 0.86	1.48 ± 0.67	1.99 ± 0.75	1.69 ± 0.71	0.16 ± 0.07	0.18 ± 0.08	1.68 ± 0.74
51–60	10	2.32 ± 1.11	1.95 ± 1.00	2.56 ± 1.19	2.16 ± 1.07	0.20 ± 0.08	0.18 ± 0.09	1.79 ± 1.12
61–70	10	2.89 ± 1.45	2.52 ± 1.39	3.21 ± 1.55	2.79 ± 1.49	0.21 ± 0.09	0.20 ± 0.07	1.70 ± 0.71
> 70	10	3.37± 1.15	3.02 ± 1.10	3.73 ± 1.32	3.34 ± 1.26	0.22 ± 0.10	0.15 ± 0.06	1.49 ± 0.58
Mean	80	2.00 ± 1.16	1.70 ± 1.09	2.23 ± 1.26	1.89 ± 1.19	0.17 ± 0.08	0.31 ± 0.13	1.60± 0.70

*p < 0.01; **p > 0.05; TVV — total ventricle volume; TBV — total brain volume; LVV — lateral ventricle volume; CBR — cerebrum and brain stem volume; TdVV — third ventricle volume; BS — brain stem; CA — cerebral aqueduct; FVV — fourth ventricle volume; CBL — cerebellum volume

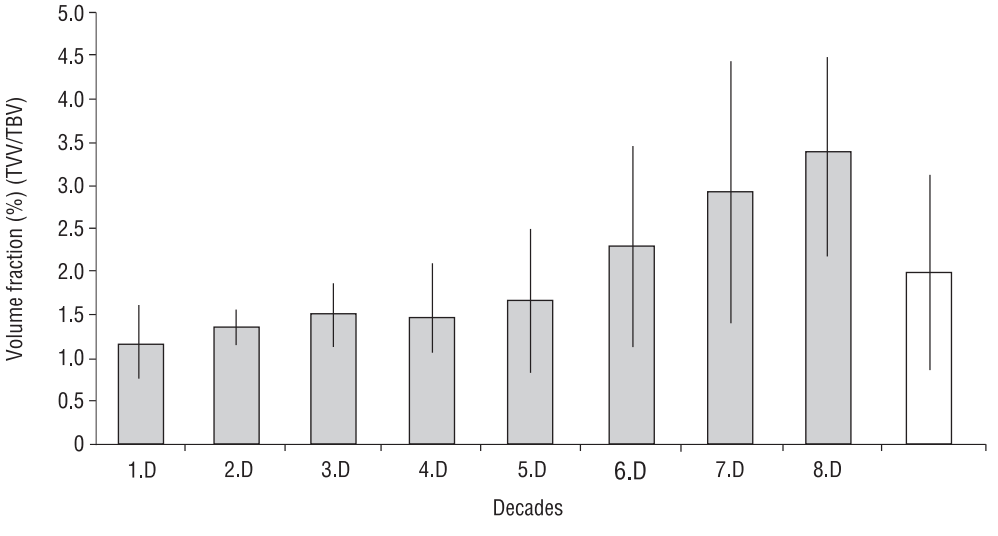

Figure 2. The volume fraction of total ventricle volume (TVV) to total brain volume (TBV) in decades (D: decade, ± SD, last white bar indicates MVF in all subjects).

period but not in a linear manner [31]. Nonetheless, there is no study denoting the brain ventricle volume fraction in childhood and old-age groups. Herein, we are reporting how the brain ventricle volume fraction changes related to eight decades.

The volume fraction of a component within a reference volume is a simple and very widely used parameter in biomedical applications [13]. It is independent of the body size of the subject and examines the volumetric relation between the components of structures [9]. Therefore, we determined the total brain, CBR and BS, CBL, and ventricle volume, and the fraction values independently from the body mass index and cranial volumes.

CT imaging may produce reliable measurements of structures and ventricles in the brain. The Cavalieri method provides quantitative data on 3D structures using 2D images [22]. Volumetric measurements can be achieved objectively and effectively on CT and MR images based on the Cavalieri principles [24]. The CE or relative standard error represents the precision of the volume estimate obtained using the Cavalieri principle [23]. A CE must be determined for each subject to make a correct sampling and estimation [16]. A CE value lower than

10% is within the acceptable range [11, 20, 23]. In our study, CE values were calculated separately for the total brain, total ventricles, CBL, CBR, and BS volumes estimated (Table 3). These values were 0.01, 0.10, 0.07, and 0.02, respectively. All estimated CE values were found to be equal or below 10%.

The enlargement of brain ventricles associated with some disorders such as Alzheimer's [19], Schizophrenia [10, 18, 25], hydrocephaly [12], and aging [29] has been demonstrated in previous studies. This enlargement process is usually attributed to brain parenchymal atrophy [4, 21]. Ventricular dilatation also resulted from the neuronal loss [26]. However, the brain ventricle ratio must be known in order to determine the correlation between the parenchymal atrophy and the degree of the ventricular enlargement. Studies reporting the brain ventricle ratio in these diseases are limited [3, 10]. Furthermore, different volume measurement or estimation methods were used in these studies. In this study we presented the basic reference values for these kinds of cerebral disorders with the obtained preliminary results.

Normal brain ventricular volumes in the literature vary markedly. Ventricle volume values with a wide range have been reported in literature (range 7–70 cm^3). Chung et al. [7] found 16.2 cm^3 and 24.9 cm^3 ventricle volumes in second and fourth decade Korean people, respectively. Ventricle volumes in our study were found to range from 6.3 cm^3 to 87.9 cm^3. The mean of the total ventricle volume was 22.08 ± 12.94 in female and 30.62 ± 18.17 in male subjects. However, we did not find any gender related difference between the TVV and TBV because of the mean value of the brain volume estimation ($p > 0.05$).

Brain atrophy usually affects all brain sites, but in some disease it is seen as a partial pattern [10, 30]; then the ratio of LVV to CBR or TdV to CBR becomes important. We demonstrated the volume fraction of LVV to CBR and BS and TdVV to CBR and BS volume in each decade.

The cerebral aqueduct (CA) is anatomically related with the midbrain whereas the fourth ventricle (FV) is BS and CBL. However, there is an embryogenetic developmental difference between the lateral and third ventricle or CA and FV. Lateral and third ventricles originate from the forebrain in embryogenetic development while CA originates from the midbrain and FV from the rhombencephalon [28]. The CA extends throughout the dorsal quarter of the midbrain in the midline. The CA continues with the FV inferiorly [28]. The FV is a cavity situated anterior to the CBL and posterior to the Pons and medulla oblongata [27]. These structures were evaluated with the ventricles because of their anatomically close relationship whereas there was no relation between the age and volume fraction of CA and FV to CBR and BS ($p > 0.05$) and volume fraction of CA and FV to CBL ($p > 0.05$).

CONCLUSIONS

In conclusion, TVV to TBV volume fractions can be important tools in determining some diseases such as hydrocephalus, schizophrenia, Alzheimer's, a group of neurodegenerative disorders, and aging and can be estimated by stereological methods. The TVV was found to be 2% of the TBV, while there was no difference with gender, whereas a strong correlation with age was found in each decade ($p < 0.01$). Consequently, we conclude that the values of the volume fraction TVV to TBV = = 2.00 ± 1.16%, LVV to TBV = 1.70 ± 1.09%, TVV to CBR and BS = 2.23 ± 1.26%, LVV to CBR and BS = 1.89 ± 1.19%, TdVV to CBR and BS = 0.17 ± ± 0.08%, CA and FVV to CBR and BS = 0.31 ± 0.13%, and CA and FVV to CBL = 1.60 ± 0.70% in the normal healthy population of each decade must be considered in studies regarding with aging and neurodegenerative pathologies. Our future direction is to evaluate this stereological method with estimations of the volume fractions of TVV to TBV in clinical approach aging and neurodegenerative disorders.

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