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The morphometric measurement of the brain stem in Turkish healthy subjects according to age and sex

Running Title: The brain stem morphometry according to age and sex

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Abstract

Background: This paper was determined the morphometric measurements of the brainstem including mesencephalon, pons and medulla using MRI in Turkish healthy population.

Materials and methods: Two hundred sixty three (263; 158 females and 105 males) subjects ranging from 18 up to 65 years were included in this study. The measurements were taken from subjects having brain MRI in the Radiology Department. Statistical analysis were done by SPSS 21.00 package programme. ANOVA Test and Chi-Square Test were used to determine the relation between measurements and age and sex groups. The $p < 0.05$ value was considered as significant.

Results: The overall means and standard deviations of the measurements were: Pons anteroposterior diameter, 15.41 ± 1.27 mm; pons vertical diameter, 22.02 ± 2.07 mm; mesencephalon anteroposterior diameter 9.39 ± 1.00 mm; Mesencephalon vertical diameter, 15.20 ± 1.53 mm; distance between the interpeduncular fissure and aqueduct, 11.72 ± 1.58 mm; distance from cerebral peduncles to aqueduct, 13.64 ± 1.66 mm; anterior surface of the pons midway between the mesencephalon and medulla to the fourth ventricular floor, 21.62 ± 1.64 mm; the shortest anteroposterior diameter of the medulla at the pontomedullary junction, 13.46 ± 1.28 mm, and the shortest anteroposterior diameter of the medulla at the

medullospinal junction, 10.24 ± 1.43 mm in females, respectively, whereas the corresponding values were 15.58 ± 1.53 mm; 22.64 ± 2.35 mm; 9.37 ± 1.66 mm; 15.64 ± 1.52 mm; 11.14 ± 1.31 mm; 13.01 ± 1.30 mm; 21.97 ± 1.65 mm; 13.47 ± 1.19 mm; 9.91 ± 1.35 mm in males, respectively. There were found significant difference in some parameters such as pons vertical diameter, mesencephalon vertical diameter, distance between the interpeduncular fissure and aqueduct, and distance between cerebral peduncles to aqueduct between sex.

Conclusions: The brainstem dimensions of healthy population provides important and useful knowledge in terms of comparison of abnormalities clinically and data may be valuable for the representatives of clinical disciplines.

Key words: brainstem morphometry, age and sex changes, Turkish population

Introduction

The brainstem which is divided in three parts; mesencephalon, pons and medulla, is one of the critical small anatomic pattern and it includes many important cranial nerve nuclei, tracts and fibers [1-3]. The brainstem directs vital functions including breathing, blood pressure, heart rate, swallowing, movement ability, sensation of face, mouth, tongue, extremities [4]. Moreover, it is surrounded by the clivus anteriorly; by the temporal bone petrosus part laterally; by the cerebellum posteriorly; by the diencephalon superiorly [2,3]. Furthermore, the brainstem structures play an important role, because brain functions including motor, sensory, sympathetic, and parasympathetic are integrated and pass through the medulla, pons and mesencephalon [3]. There can be difficulty in surgery because of brainstem complex structure [3,4]. Additionally, surgical procedures of the brainstem lesions make difficulties due to morbidity and mortality risk. Moreover, brainstem gliomas usually are settled into pons, sometimes they originates from mesencephalon or medulla [5]. So, it requires the detailed functional and topographical anatomy knowledge and microsurgical information [1,4,6]. Imaging techniques such as computed tomography (CT) and Magnetic resonance imaging (MRI) provide an assessment opportunity of intracranial structures [7,8]. It has been reported CT were insufficient in revealing atrophic changes in the brainstem region [9]. Therefore, the MRI using was more suitable for examination and it has become possible to achieve reliable and accurate neuroanatomical views [9,10]. In this respect, the MRI of brain stem regions gives critical detailed knowledge about brain related with normal aging or in neuromuscular diseases [11-15], and normal brain growth and atrophy [16]. Also, MRI

determines shrinkage in the brainstem and proves to be a strong predictor of disease progression [8]. On the other hand, the studies of MRI have associated with mesencephalon morphology in many neurologic disorders like Parkinson disease (PD) and Wilson disease (WD). Therefore, the morphometric data performed using MRI, may explain the underlying neurochemical or pathologic situations [16]. Previous studies investigate age and sex related changes in the brainstem [11-13,17-19]. In that studies results of age related differences and sex in brainstem may give different results in general [11-13,18,19]. However, the results of age-dependent brainstem measurement in studies are still controversial. Besides, the brainstem linear measurements with MRI were rare in Turkish healthy population in the literature [8,10,16]. The linear measurements can be performed more quickly, practical and suitable for work and do not require additional hard and software [9]. On the other hand, the interpeduncular fissure and cerebral peduncles's localization surface could be difficult. Because of the volume between brain and surrounding cerebrospinal fluid (CSF), these measurements were difficult for identification the interpeduncular fissure [20]. This is the first study considering the morphometric measurements and ratios of the brainstem using MRI in detailed to investigate age and sex differences in the brainstem region in Turkish healthy population. In order to understand the pathologies of brainstem structures and the effects of neurodegenerative diseases on brain stem, measurements of age and sex differences in normal healthy individuals should be well known. Therefore, in this study, it was aimed to determine the age and sex differences of brainstem structures in healthy Turkish individuals using MRI.

Materials and methods

This study was carried out from the 263 healthy adult subjects (158 females; 105 males) aged 18-65 years over a period of 2 years between January 2017 and 2019. All the test procedures were approved by ethics committee. Cranial MRI findings were evaluated by radiologists and anatomists. Moreover, inclusion criteria for adult subjects selected by criteria of optimal health were no history of receiving a diagnosis of cancer, hemiplegia, intracranial tumoral mass, any neurologic disease (such as multiple sclerosis, amyotrophic lateral sclerosis or dementia, Parkinson's disease), having surgical operation related brain and psychiatric illness.

MRI was performed using a 1.5 T MRI system (Siemens; Essenza, Erlangen, Germany). Brain MRI protocol including axial T2-weighted turbo spin echo (TR:3600, TE:87 ms; slice thickness 5 mm; gap 1.5 mm) and sagittal T2-weighted spin echo (TR:3600, TE: 87 ms; slice thickness 5 mm; gap 1.5 mm) was used. The measurements were performed from

digital MRI images on a hospital using caliper function with x2 magnification. Using the midsagittal T2-weighted spin echo image, the following parameters of brainstem dimensions were evaluated [1,12,20,21].

(DIPFA) The distance between the interpeduncular fissure and the aqueduct.

(DCPA) The distance from the anterior surface of the cerebral peduncles to the aqueduct

(DPMM) The distance between the anterior surface of the pons midway between the mesencephalon and medulla to the fourth ventricular floor.

(MOPMJ) The shortest anteroposterior diameter of the medulla at the pontomedullary junction.

(MOMSJ) The shortest anteroposterior diameter of the medulla at the medullospinal junction.

(PAP) Pons anteroposterior diameter as the distance between two points perpendicular to the midline along the tangent lateral to the pons.

(PVD) Pons vertical diameter was measured mid- point between its upper and lower borders and perpendicular to its long axis to the fourth ventricle.

(MBAPD) Mesencephalon anteroposterior diameter at a midline level on a sagittal section.

(MBVD) Mesencephalon vertical diameter was measured across the mesencephalon to the tectum.

The ratio values of the DPMM/MOPMJ, DPMM/MOMSJ, DPMM/DIPFA, DPMM/DCPA and, midbrain/pons calculated.

The data were divided into two groups: healthy adult female and male subjects. Furthermore the data were divided also into five groups according to age; subjects aged between 18-30 years for Group 1; 31-40 years for Group 2; 41-50 years for Group 3; 51-60 years for Group 4; and 61-68 years for Group 5 (Table 2). The measurements were made on the computer screen with an electronic caliper and estimations were expressed as millimeters. The SPSS 21.0 program was used for statistical analysis of the measurement results. From these measurements, means, standard deviations (SD), minimum (min.) and maximum (max.) values were calculated. In all statistical analyses; p value under 0.05 was considered statistically significant.

Results

The values of minimum, maximum, mean and standard deviation of diameters of the mesencephalon [(distance between the interpeduncular fissure and aqueduct) (DIPFA) and (distance from cerebral peduncles to aqueduct) (DCPA)], pons [(anterior surface of the pons midway between the mesencephalon and medulla to the fourth ventricular floor) (DPMM)], and medulla [(the shortest anteroposterior diameter of the medulla at the pontomedullary junction) (MOPMJ), and (the shortest anteroposterior diameter of the medulla at the medullospinal junction) (MOMSJ)], and brain stem ratio measured in 263 healthy subjects (158 females and 105 males) were shown in Table 1-6. There are significant difference in some measurements such as pons vertical diameter (PVD); mesencephalon vertical diameter (MVD); distance between the interpeduncular fissure and aqueduct (DIPFA); and distance from cerebral peduncles to aqueduct (DCPA), DPMM/MOMSJ, DPMM/DIPFA, and DPMM/DCPA between sex ($p < 0.05$), (Table 1-2). The means of the brain stem ratio measurements (except midbrain/pons ratio) were further in males than females (Table 2). Also, there were no significant difference in all measurement ($p > 0.05$) (except “DIPFA, and DCPA measurements), whereas significant difference were found in DPMM/MOMSJ, DPMM/DIPFA, and DPMM/DCPA measurements according to age groups of healthy females and males ($p < 0.05$) (Table 3-4). The distribution of the brainstem diameters according to age groups of females was shown in Table 5. In females, statistically significant difference were found some measurements values such as DIPFA ($p = 0.009$), DCPA ($p = 0.003$), MOMSJ ($p = 0.035$), DPMM/MOMSJ ($p = 0.034$), DPMM/DIPFA ($p = 0.012$) and, DPMM/DCPA ($p = 0.009$). Also, DIPFA values were decreased with increased age. The lowest value was seen in seventh decade (Group 5). The mesencephalon AP diameter value showed the reduction until age of the 61 years and after the age of 60 years this value increased. DPMM/DIPFA and DPMM/DCPA measurements increased until age of the 60 years, while after the age of the 61 this value showed decrease (Table 5). In males, there were no statistically significant difference in all measurements. The highest value of PAP was seen in the age of the 31-40 years, while the lowest value was in the age of 61 years and after (Table 6).

Discussion

Brainstem which is a small area have vital importance and have many functionally primary nuclei, fibers, neurons and nerve tracts [1]. The brainstem consists of mesencephalon, pons and medulla oblongata [3], and it controls many functions such as breathing, blood pressure, heart rate control, swallowing and make sounds [4]. Moreover, this part constitutes

the crossing for descending and ascending tracts which links medulla spinalis to the top of the nervous system. These tracts may be obstructed due to demyelinating diseases, neoplasm or vascular disorder. Furthermore, nuclei of the glossopharyngeal, the vagal, the accessory and the hypoglossal nerves emerge between inferior cerebellar peduncle and olivary nucleus in medulla oblongata [22]. The pons lies in the posterior cranial fossa and forms superior part of the 4th ventricle. Additionally, descending and ascending tracts which are the most critical structures, pass from the pons. Also, the childhood astrocytomas are the most common tumor seen in brainstem [22,23]. The mesencephalon is the shortest, rostral and superior part of the brainstem and lies at the junction of the middle and posterior cranial fossae. The cerebral aqueduct which is the cavity of the mesencephalon. It is one of the narrower structures of the ventricular system and CSF passes by the cerebral aqueduct between 3rd ventricle to the 4th ventricle and reaches subarachnoid space by foraminae. Also, the oculomotor and trochlear nerve arise from mesencephalon and there are two important nuclei which are the name of substantia nigra and red nucleus [22-24]. Additionally, the brainstem external anatomy knowledge helps in surgical planning due to relation between the external and internal structures, and the anatomical reference points on the brainstem [10]. Also, the DPMM to MOPMJ ratio, and DPMM to MOMSJ ratio were declared that these were found abnormally small in subjects having tumors including pons and medulla. The DPMM/DIPFA, and DPMM/DCPA values were reported as abnormally small in the tumor of pons and mesencephalon. Additionally, brainstem measurements helps in diagnosing of tumors or atrophy of this part of brain. The brain stem normal values play an important role in evaluation of neurochemical and or pathologic changes in subjects with neurodegenerative disorders [9, 12, 13, 20]. Especially, midbrain morphometric data provides the early detection of the disorders [13]. Koehler et al measured the distance between the interpeduncular fissure and the aqueduct (DIPFA), the distance from the anterior surface of the cerebral peduncles to the aqueduct (DCPA), the distance between the anterior surface of the pons midway between the mesencephalon and medulla to the fourth ventricular floor (DPMM), the shortest anteroposterior diameter of the medulla at the pontomedullary junction (MOPMJ), and the shortest anteroposterior diameter of the medulla at the medullospinal junction (MOMSJ), DPMM to MOPMJ ratio, and DPMM to MOMSJ ratio, DPMM to DIPFA ratio and DPMM to DCPA ratio in healthy subjects, subjects having glioma and having brain atrophy (Table 7). All measurements except DPMM/MOPMJ, DPMM/DIPFA and DPMM/DCPA values were higher in subjects having glioma than healthy subjects (20). Subjects with brain atrophy have smaller diameters than healthy subjects. Also, in the same study, normal value of the DPMM

was stated, it ranged from 26.0 mm to 38.0 mm [20]. The DPMM/DIPFA, and DPMM/DCPA values were lower in Koehler et al's findings of subjects having glioma than our findings of the healthy population. The measurements of MOMSJ and the ratio of DPMM to DCPA were higher in our study than Koehler et al's findings of healthy population whereas DPMM/MOPMJ, and DPMM to MOMSJ ratios were higher subjects having glioma than our findings. The mesencephalon, pons and medulla measurements of our study were lower than Chinese population performed with Xiaochun et al [25].

In the literature, some studies on medulla, pons and mesencephalon are shown in Table 8. In Sudanese healthy subjects aged between 21-30 years, the mesencephalon and medulla diameters were decreased with increased age from age of the 31-40 years to over the age of 60 years and beyond. However, the pons diameter were decreased over the age of 50 years. Additionally, there were no found significant difference in brainstem measurements between sex [12]. In Finland, Raininko et al declared mesencephalon diameter decreased over the age of 60 years, whereas the pons diameter did not decrease with age. Also, sagittal diameter of medulla decreased over the age of 50 years, while in coronal diameter such decrease was not seen [9]. There were no found significant differences in changes related sex [9]. In all values of our study except medulla, there was a decrease over the age of 50 years similar to Sudanese and Finns, and there were no significant differences between sex similar to above studies [9,12]. The reason of the age related changes of brainstem was shown as mesencephalon and especially, this decline might be due to loss of superior cerebellar fiber bundles such as brachium conjunctivum, fasciculus cerebello thalamicus. Also, these measurements related brainstem of normal subjects might be important for indicate the differences between patients having neurological disorders such as PD, Alzheimer's disease (AD) or Schizophrenia [12]. These parameters were lower in our study than the studies performed with Sudanese and Japanese, and Massey et al [12,21,26]. In Massey et al's study, pons AP diameter of subjects with Multiple System Atrophy (MSA) were lower than healthy subjects, patients with Parkinson's disease and progressive supranuclear palsy (PSP). Also, the lowest value of mesencephalon AP diameter was obtained in subjects having PSP. Additionally, mesencephalon to pons ratio was used as a clinical biomarker of PSP in some studies [26, 27]. So, the mesencephalon to pons ratio might be lower in PSP. In this study, this ratio was 0.613 ± 0.074 and 0.606 ± 0.087 in females and males, respectively. On the other hand, in researches of age related changes, the lowest value of mesencephalon to pons ratio was obtained in the sixth decades in females (Group 4), whereas, the highest value was seen in the same decade in males. Also, there were no found significant difference between age

groups both two sexes. Consistently, our ratio was similar to findings of healthy subjects of Massey et al's study [26].

In previous studies, age and sex-related changes in the brain stem were investigated [11-13,17-19,21]. Knowledge of the brainstem of healthy subjects provides to compare with data of subjects who suffer from neurologic disorders such as PD, AD and Huntington disease and determine the aberrations or differences between healthy and patient groups. In the brainstem, age related differences are unclear yet [12]. Doraiswamy et al reported that mesencephalon volume and anteroposterior diameter was significantly lower in subjects above the age of 50 than younger subjects. The researchers have suggested that the underlying cause may be age-related decline in nigra neurons, degenerations in the neuronal system such as serotonergic or cranial nervous system, or loss of neuromotor functions. Moreover, the other reason of the age related reduction in mesencephalon might be neuronal death or degeneration of nuclei and tracts [13,16]. It is widely accepted that the mesencephalon measurements may be an important marker in determination of the neurologic disorders [13]. In another study performed in healthy Koreans by Lee et al, mesencephalon and medulla volumes decreased with increasing age in both sexes. Pons volume was lower in old females than young females, whereas pons volume of males had a reverse situation. On the other hand, males had larger pons and medulla than females [11]. Consistently, in a study done in USA, pons were larger in males than females [17]. Oguro et al in their study of Japanese population reported that the values of mesencephalon tegmentum (MT), mesencephalon pretectum (MP), base of pons (PB), and pontine tegmentum (PT) showed a decrease with aging between the ages of 60 years and 80 years in males, whereas there were no found proportional changes in females. Also, decrease in measurements of MT, MP, and PB were significant. Furthermore, in females PT value was higher than males during period after the age of the 50 years. Additionally, in the ages of 80 years females had greater values in measurements of MT, MP, PB and PT than males with the same age group [19]. In a study reported by Shah et al, there was significant age related decrease in the mesencephalon cross sectional area and neuronal death and nuclei degeneration was responsible for age related decrease in midbrain [28]. In the literature, there are few studies on brain stem in healthy Turkish population. In a study of Murshed et al, there were no significant difference between males and females aged 13-50 years in whole brainstem volume measurements. But, the significant differences were found in the age of 51-77 years between sex. Whole brainstem area was larger in males than females whereas, there were no significant differences of whole brainstem dimension all age groups [16]. The reason of the reduction in brainstem age and sex related changes were shown as intrinsic and

extrinsic factors including sex hormones, or hypertension and habits such as smoke and alcohol [11, 16,19]. Moreover, environmental factors including acquired diseases, toxin exposure, trauma can lead to developmental aberrations and loss of brain tissue [16, 29]. This process might be affected by genetic factors [28]. Also, the brain volume may be affected from racial differences [11]. In the Antar et al's study, the effects of the age on the brainstem volume based upon the some factors such as regional factors, genetics or several demographical features were documented. In addition, the authors were noted that the slice thickness, size, subject's form, and the mean age of the study samples may affect MRI measurement results [10]. In 42 fresh cadavers having mean age of 45 years, the mean lengths of brainstem, medulla oblongata, and pons were found as 54.37 mm, 16.43 mm and 29.6 mm, respectively. Also, there were no significant differences between sex and the brain structures [10]. In the present study, the dimensions of pons vertical diameter, mesencephalon vertical diameter, the distance between the interpeduncular fissure and the aqueduct (DIPFA), and the distance from the anterior surface of the cerebral peduncles to the aqueduct (DCPA) were significantly different in both sexes ($p < 0.05$). However, pons dimensions, mesencephalon vertical diameter, the distance between the anterior surface of the pons midway between the mesencephalon and medulla to the fourth ventricular floor (DPMM), the shortest anteroposterior diameter of the medulla at the pontomedullary junction (MOPMJ), and the shortest anteroposterior diameter of the medulla at the medullospinal junction (MOMSJ) measurements, and the ratio of mesencephalon to pons were larger in males than females. In addition, the data regarding distance between the interpeduncular fissure and the aqueduct (DIPFA), and the distance from the anterior surface of the cerebral peduncles to the aqueduct (DCPA) were decreased with increasing age (from 18 to 70). Pons anteroposterior diameter (PAP) and vertical diameter (PVD) were lowest in the age of the 41-50 years, whereas PAP value was highest in 31-40 years old. PVA value was the highest in the age of 60-70 years. The shortest anteroposterior diameter of the medulla at the pontomedullary junction (MOPMJ) were increased in the age of 51-60 years. This increasing remains unchanged between in the age of 51-60 years and 61-70 years. The shortest anteroposterior diameter of the medulla at the medullospinal junction (MOMSJ) were decreased with age, while the highest value was seen in the age of 61-70 years. The dimensions of mesencephalon were decreased both between in the fourth and fifth decades, and in the sixth and seventh decades. In evaluation of measurements, some of brainstem measurements remain speculative. It was arised from the features of the study groups such as genetic factors, mean age, race, or method features including slice thickness and size. Especially, the significant difference seen in values

of DIPFA, DCPA, DPMM/MOMSJ, DPMM/DIPFA, DPMM/DCPA arised from results of females. It is speculated that the reason of this situation might be various sex hormones and differences of aging process in both sexes.

Conclusions

In conclusion, this is the first study considering the morphometric measurements and ratios of the brainstem in a Turkish healthy population using MRI in detailed. Our study give important knowledge and normative data related brainstem measurements and it sorts out the studies like age related changes or sex differences in Turkish population. These presented findings will provide an evaluation opportunity to data regarding age and sex related brainstem studies and will shed light on patients with neurologic disorders. The age and sex related normal dimension changes of the brain stem are necessary in evaluation of mesencephalon, pons and medulla in neurological disorders and aging process.

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Legends of Tables

Table 1. The distribution of Brainstem diameters according to sex.

Table 2. The sex related changes of Brainstem ratio measurement.

Table 3. The distribution of the Brainstem diameters according to age groups of healthy females and males.

Table 4. The brainstem ratio measurements according to age groups of healthy females and males.

Table 5. The distribution of the Brainstem diameters and brainstem ratios according to age groups in females.

Table 6. The distribution of the Brainstem diameters and brainstem ratios according to age groups in males.

Table 7. The comparison of the different studies' data.

Table 8. The comparison of the different population' data.

Table 1. The distribution of Brainstem diameters according to sex

Parameters	Females (158)	Males (105)	P value
Pons anteroposterior diameter (PAP)	15.41 ± 1.27 (12.30-22.60)	15.58 ± 1.53 (12.20-19.30)	0.326
Total	15.47 ± 1.38 (12.20-22.60)		
Pons vertical diameter (PVD)	22.02 ± 2.07 (13.80-29.00)	22.64 ± 2.35 (13.70-27.60)	0.025
Total	22.27 ± 2.20 (13.70-29.00)		
Mesencephalon anteroposterior diameter (MBAPD)	9.39 ± 1.00 (6.50-12.30)	9.37 ± 1.66 (7.30-13.10)	0.854
Total	9.38 ± 1.07 (6.50-13.10)		
Mesencephalon vertical diameter (MBVD)	15.20 ± 1.53 (11.70-19.40)	15.64 ± 1.52 (11.70-19.10)	0.022
Total	15.38 ± 1.54 (11.70-19.40)		
Distance between the interpeduncular fissure and aqueduct (DIPFA)	11.72 ± 1.58 (8.00-16.90)	11.14 ± 1.31 (8.80-14.70)	0.002
Total	11.49 ± 1.51 (8.00-16.90)		
Distance from cerebral peduncles to aqueduct (DCPA)	13.64 ± 1.66 (9.30-18.50)	13.01 ± 1.30 (9.30-17.10)	0.001
Total	13.39 ± 1.55 (9.30-18.50)		
Anterior surface of the pons midway between the mesencephalon and medulla to the fourth ventricular floor (DPMM)	21.62 ± 1.64 (17.50-28.60)	21.97 ± 1.65 (18.10-29.90)	0.100
Total	21.76 ± 1.65 (17.50-29.90)		
The shortest anteroposterior diameter of the medulla at the pontomedullary junction (MOPMJ)	13.46 ± 1.28 (10.00-18.00)	13.47 ± 1.19 (10.90-18.10)	0.917
Total	13.46 ± 1.24 (10.00-18.10)		
The shortest anteroposterior diameter of the medulla at the medullospinal junction (MOMSJ)	10.24 ± 1.43 (7.20-15.10)	9.91 ± 1.35 (7.30-13.40)	0.064
Total	10.11 ± 1.40 (7.20-15.10)		

Table 2. The sex related changes of Brainstem ratio measurements

Groups	Females (158)	Males (105)	Total	P
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DPMM/MOPMJ	1.617±0.156 (1.15-2.04)	1.639±0.148 (1.23-2.14)	1.626 (1.15-2.14)	0.261
DPMM/MOMSJ	2.146±0.289 (1.46-3.01)	2.253±0.330 (1.76-3.78)	1.626 (1.15-2.14)	0.006
DPMM/ DIPFA	1.870±0.228 (1.34-2.89)	1.993±0.225 (1.45-2.56)	1.626 (1.15-2.14)	<0.001
DPMM/DCPA	1.602±0.184 (1.26-2.14)	1.700±0.170 (1.34-2.23)	1.626 (1.15-2.14)	<0.001
Midbrain/Pons	0.613±0.074 (0.44-0.94)	0.606±0.087 (0.40-0.84)	0.610 0.40-0.94	0.505

Table 3. The distribution of the Brainstem diameters according to age groups of healthy females and males

Groups	Group 1 (91)	Group 2 (99)	Group 3 (42)	Group 4 (23)	Group 5 (8)
Pons anteroposterior diameter (PAP)	15.38±1.31 (12.60- 18.70)	15.67±1.46 (12.30- 22.60)	15.24±1.41 (13.10- 18.10)	15.47±1.18 (12.20- 17.10)	15.35±1.48 (13.20- 17.30)
P=0.440					
Pons vertical diameter (PVD)	22.51±1.98 (14.30- 27.60)	22.03±2.24 (13.80- 27.20)	22.00±2.33 (13.70- 24.60)	22.60±2.56 (15.10- 29.00)	22.80±2.34 (19.80- 27.40)
P=0.410					
Mesencephalon anteroposterior diameter (MBAPD)	9.63±1.08 (7.30-13.10)	9.34±1.05 (6.50- 12.90)	9.11±1.08 (7.00- 12.00)	9.19±0.97 (7.40-11.40)	9.09±0.92 (7.40-10.00)
P=0.052					
Mesencephalon vertical diameter (MBVD)	15.43±1.52 (11.70- 18.80)	15.52±1.48 (11.70- 19.40)	15.05±1.52 (11.80- 18.90)	15.43±1.78 (13.00- 18.40)	14.61±1.73 (11.90- 17.20)
P=0.297					
Distance between the interpeduncular fissure and aqueduct. (DIPFA)	11.89±1.48 (8.80-15.70)	11.41±1.56 (8.70-16.90)	11.18±1.50 (8.00-14.80)	11.09±1.15 (9.20-13.00)	10.58±1.05 (9.10-12.00)

P=0.010					
Distance from cerebral peduncles to aqueduct (DCPA)	13.85±1.60 (9.30-18.50)	13.25±1.61 (9.30-18.00)	13.11±1.44 (10.50-17.00)	12.96±0.98 (10.70-14.30)	12.56±1.01 (11.30-14.30)
P=0.006					
Anterior surface of the pons midway between the mesencephalon and medulla to the fourth ventricular floor (DPMM)	21.64±1.46 (18.00-25.90)	21.90±1.66 (17.50-29.90)	21.95±2.11 (17.50-28.60)	21.71±1.21 (19.60-23.60)	20.60±1.73 (18.20-22.80)
P=0.220					
The shortest anteroposterior diameter of the medulla at the pontomedullary junction (MOPMJ)	13.38±1.13 (10.90-16.90)	13.56±1.13 (10.20-18.20)	13.60±1.59 (10.00-18.00)	13.20±1.33 (10.80-15.30)	13.20±1.64 (10.70-15.20)
P=0.570					
The shortest anteroposterior diameter of the medulla at the medullospinal junction (MOMSJ)	10.40±1.54 7.20-15.10	9.98±1.30 (7.30-13.40)	9.90±1.41 (7.60-12.60)	9.69±1.07 (7.70-12.10)	10.66±1.20 (9.40-12.70)
P=0.059					

Table 4. The brainstem ratio measurements according to age groups of healthy females and males

Groups	Group 1 (91)	Group 2 (99)	Group 3 (42)	Group 4 (23)	Group 5 (8)
DPMM/MOPMJ	1.625±0.138 (1.24-1.96)	1.623±0.151 (1.23-2.14)	1.628±0.180 (1.15-2.01)	1.658±0.167 (1.40-2.00)	1.574±0.161 (1.34-1.74)
P=0.736					
DPMM/MOMSJ	2.119±0.297	2.227±0.311	2.255±0.343	2.264±0.248	1.942±0.163

	(1.46-2.82)	(1.63-3.78)	(1.62-3.03)	(1.79-2.70)	(1.73-2.22)
P=0.005					
DPMM/ DIPFA	1.840±0.203 (1.34-2.30)	1.946±0.249 (1.36-2.56)	1.986±0.247 (1.58-2.89)	1.976±0.201 (1.58-2.39)	1.960±0.205 (1.68-2.20)
P=0.002					
DPMM/DCPA	1.577±0.163 (1.26-1.98)	1.671±0.203 (1.28-2.23)	1.685±0.170 (1.36-2.10)	1.686±0.166 (1.42-2.14)	1.645±0.140 (1.46-1.83)
P=0.002					
Midbrain/Pons	0.630±0.078 (0.44-0.83)	0.599±0.077 (0.46-0.94)	0.601±0.076 (0.40-0.78)	0.599±0.096 (0.46-0.84)	0.594±0.794 (0.40-0.94)
P=0.070					

Table 5. The distribution of the Brainstem diameters and brainstem ratios according to age groups in females

Parameters	Females (n=158)				
	Group I	Group II	Group III	Group IV	Group V
Pons anteroposterior diameter (PAP)	15.37±1.16 (12.90-17.50)	15.43±1.54 (12.30-22.60)	15.14±1.21 (13.20-17.20)	15.66±0.92 (13.60-17.10)	15.82±0.56 (15.00-16.30)
p=0.705					
Pons vertical diameter (PVD)	22.31±1.96 (14.30-24.90)	21.35±2.15 (13.80-26.90)	22.57±1.29 (19.90-24.60)	22.20±2.63 (15.10-29.00)	22.26±1.85 (19.80-24.20)
p=0.079					
Mesencephalon anteroposterior diameter (MBAPD)	9.65±0.93 (7.30-11.60)	9.29±1.04 (6.50-12.30)	9.19±1.15 (7.00-12.00)	9.08±0.87 (7.40-10.50)	9.30±0.76 (8.40-10.00)
p=0.117					
Mesencephalon vertical diameter (MBVD)	15.39±1.51 (11.70-18.80)	15.28±1.52 (11.80-19.40)	14.40±1.47 (11.80-17.60)	15.27±1.57 (13.20-17.50)	15.22±1.42 (13.30-17.20)
p=0.136					
Distance between the interpeduncular fissure and aqueduct. (DIPFA)	12.23±1.45 (9.50-15.70)	11.54±1.70 (8.70-16.90)	11.50±1.69 (8.00-14.80)	11.03±1.22 (9.20-13.00)	10.66±0.96 (9.50-12.00)
p=0.009					
Distance from cerebral peduncles to aqueduct (DCPA)	14.24±1.51 (11.30-18.50)	13.35±1.81 (9.30-18.00)	13.47±1.70 (10.50-17.00)	12.92±1.05 (10.70-14.30)	12.58±1.08 (11.40-14.30)
p=0.003					
Anterior surface of the pons midway between the	21.73±1.21 (18.00-25.50)	21.50±1.64 (17.50-25.60)	22.00±2.69 (17.50-28.60)	21.64±1.18 (19.60-23.10)	19.98±1.70 (18.20-22.30)
p=0.157					

mesencephalon and medulla to the fourth ventricular floor (DPMM)					
The shortest anteroposterior diameter of the medulla at the pontomedullary junction (MOPMJ)	13.44±1.16 (10.90-16.90)	13.43±1.07 (10.20-16.30)	13.90±1.87 (10.00-18.00)	13.24±1.38 (10.80-15.30)	12.80±1.49 (10.00-18.00)
	p=0.363				
The shortest anteroposterior diameter of the medulla at the medullospinal junction (MOMSJ)	10.62±1.55 (7.20-15.10)	9.97±1.31 (7.50-12.60)	10.30±1.40 (8.10-12.60)	9.57±1.10 (7.70-12.10)	10.38±1.13 (9.40-12.20)
	p=0.035				
DPMM/MOPMJ	1.625±0.133 (1.24-1.96)	1.608±0.148 (1.39-2.04)	1.599±0.211 (1.15-2.01)	1.649±0.178 (1.40-2.00)	1.574±0.189 (1.34-1.74)
	p=0.783				
DPMM/MOMSJ	2.087±0.301 (1.46-2.82)	2.185±0.069 (1.63-3.01)	2.160±0.318 (1.62-3.01)	2.283±0.233 (1.89-2.70)	1.935±0.189 (1.73-2.22)
	p=0.034				
DPMM/ DIPFA	1.798±0.210 (1.34-2.30)	1.890±0.218 (1.36-2.32)	1.937±0.283 (1.63-2.89)	1.978±0.193 (1.67-2.39)	1.884±0.208 (1.68-2.11)
	p=0.012				
DPMM/DCPA	1.540±0.162 (1.26-1.98)	1.632±0.201 (1.28-2.13)	1.634±0.179 (1.36-2.10)	1.686±0.170 (1.42-2.14)	1.594±0.184 (1.26-2.14)
	p=0.009				
Midbrain/Pons	0.631±0.076 (0.44-0.83)	0.606±0.079 (0.46-0.94)	0.607±0.063 (0.51-0.74)	0.582±0.066 (0.46-0.76)	0.588±0.046 (0.53-0.65)
	p=0.090				

Table 6. The distribution of the Brainstem diameters and brainstem ratios according to age groups in males

Parameters	Females				
	Group I	Group II	Group III	Group IV	Group V
Pons anteroposterior diameter (PAP)	15.39±1.59 (12.60-18.70)	15.95±1.34 (12.60-19.30)	15.34±1.60 (13.10-18.10)	14.82±1.85 (12.20-16.60)	14.57±2.37 (13.20-17.30)
	P=0.182				

Pons vertical diameter (PVD)	22.94±1.98 (15.80-27.60)	22.77±2.13 (15.30-27.20)	21.43±2.97 (13.70-24.30)	24.06±1.85 (21.60-26.10)	23.70±3.22 (21.50-27.40)
	P=0.068				
Mesencephalon anteroposterior diameter (MBAPD)	9.60±1.37 (7.40-13.10)	9.40±1.07 (7.40-12.90)	9.03±1.02 (7.30-10.90)	9.58±1.29 (8.00-11.40)	8.73±1.22 (7.40-9.80)
	P=0.413				
Mesencephalon vertical diameter (MBVD)	15.53±1.57 (11.90-18.80)	15.78±1.40 (11.70-19.10)	15.70±1.29 (13.00-18.90)	16.02±2.52 (13.00-18.40)	13.60±2.00 (11.90-15.80)
	P=0.175				
Distance between the interpeduncular fissure and aqueduct. (DIPFA)	12.17±1.27 (8.80-13.50)	11.27±1.40 (8.90-14.70)	10.87±1.25 (9.30-13.50)	11.28±0.99 (9.90-12.60)	10.43±1.41 (9.10-11.90)
	P=0.682				
Distance from cerebral peduncles to aqueduct (DCPA)	13.01±1.50 (9.30-17.10)	13.15±1.35 (10.90-16.20)	12.76±1.06 (10.90-14.90)	13.10±0.77 (11.90-14.00)	12.53±1.10 (11.30-13.40)
	P=0.797				
Anterior surface of the pons midway between the mesencephalon and medulla to the fourth ventricular floor (DPMM)	21.44±1.91 (18.10-25.90)	22.33±1.59 (19.90-29.90)	21.91±1.38 (19.20-24.70)	21.98±1.43 (19.90-23.60)	21.63±1.46 (20.00-22.80)
	P=0.249				
The shortest anteroposterior diameter of the medulla at the pontomedullary junction (MOPMJ)	13.24±1.05 (10.90-15.60)	13.71±1.18 (11.30-18.10)	13.31±1.24 (11.40-16.70)	13.06±1.27 (11.40-14.90)	13.87±1.97 (11.60-15.20)
	P=0.366				
The shortest anteroposterior diameter of the medulla at the medullospinal junction (MOMSJ)	9.94±1.44 (7.80-12.90)	9.98±1.31 (7.30-13.40)	9.49±1.33 (7.60-12.50)	10.12±0.95 (9.00-11.10)	11.13±1.38 (10.10-12.70)
	P=0.309				
DPMM/MOPMJ	1.625±0.150 (1.41-1.96)	1.638±0.155 (1.23-2.14)	1.657±0.141 (1.28-1.88)	1.690±0.130 (1.58-1.89)	1.573±0.138 (1.45-1.72)
	P=0.788				
DPMM/MOMSJ	2.189±0.282 (1.78-2.68)	2.274±0.349 (1.76-3.78)	2.351±0.348 (1.82-3.03)	2.195±0.319 (1.79-2.62)	1.954±0.147 (1.80-2.08)
	P=0.219				
DPMM/ DIPFA	1.931±0.152 (1.65-2.28)	2.001±0.268 (1.45-2.56)	2.04±0.201 (1.58-2.33)	1.965±0.254 (1.58-2.20)	2.087±0.150 (1.92-2.20)
	P=0.442				

DPMM/DCPA	1.658±0.137 (1.46-1.95)	1.715±0.198 (1.34-2.23)	1.726±0.154 (1.52-1.94)	1.685±0.169 (1.42-1.83)	1.728±0.037 (1.70-1.77)
	P=0.603				
Midbrain/Pons	0.627±0.084 (0.49-0.80)	0.593±0.077 (0.47-0.84)	0.595±0.089 (0.40-0.78)	0.662±0.163 (0.48-0.84)	0.603±0.068 (0.56-0.68)
	0.268				

Table 7. The comparison of the different studies' data

Comparison of studies (mm)		Parameters								
		DIPFA mean (min.-max.)	DCPA mean (min.-max.)	DPMM mean (min.-max.)	MOPMJ mean (min.-max.)	MOMSJ mean (min.-max.)	DPMM/ MOPMJ mean (min.-max.)	DPMM/ MOMSJ mean (min.-max.)	DPMM/ DIPFA	DPMM/ DCPA
Koehler et al. ²⁰	Healthy subjects	13.2 (11.1-15.3)	18.1 (15.0-21.2)	26.6 (24.5-28.7)	15.3 (14.0-16.6)	9.4 (8.1-10.7)	1.7 (1.7-1.8)	2.8 (2.6-3.0)	2.0 (1.9-2.2)	1.5 (1.4-1.6)
	Subjects having glioma	22.1 (20.2-24.0)	22.95 (20.9-25.1)	29.5 (26.5-32.2)	17.58 (15.3-22.0)	11.55 (6.9-19.4)	1.7 (1.2-1.9)	2.9 (1.4-4.3)	1.25 (1.1-1.4)	1.3 (1.2-1.6)
	Subjects having brain athropy	12.83 (11.5-13.8)	17.77 (17.0-18.2)	19.67 (16.0-21.5)	11.67 (10.6-12.8)	8.6 (7.4-10.0)	1.73 (1.3-1.9)	2.33 (2.2-2.6)	1.53 (1.4-1.6)	1.1 (0.9-1.2)
Xiaochun et al. ²⁵	Healthy subjects	13.10	-	23.20	14.70	12.50	-	-	-	-
Present Study	Females	11.72 (8.00-16.90)	13.64 (9.30-18.50)	21.62 (17.5-28.6)	13.46 (10.0-18.0)	10.24 (7.20-15.10)	1.617 (1.15-2.04)	2.146 (1.46-3.01)	1.870 (1.34-2.89)	1.602 (1.26-2.14)
	Males	11.14 (8.80-14.70)	13.01 (9.30-17.10)	21.97 (18.10-29.9)	13.47 (10.9-18.10)	9.91 (7.30-13.40)	1.639 (1.23-2.14)	2.253 (1.76-3.78)	1.993 (1.45-2.56)	1.700 (1.34-2.23)
	Total	11.49 8.00-16.90	13.39 (9.30-18.50)	21.76 (17.50-29.90)	13.46 (10.00-18.10)	10.11 (7.20-15.10)	1.626 (1.15-2.14)	2.189 (1.46-3.78)	1.919 (1.34-2.89)	1.641 (1.26-2.23)

Table 8. The comparison of the different populations' data

Studies	Groups	Parameters (mm)				
		Pons AP diameter (PAP)	Pons vertical diameter (PVD)	Mesencephalon AP Diameter (MBAPD)	Mesencephalon vertical diameter (MBVD)	Midbrain to pons ratio
Elhussein et al. ¹²	Healthy subjects	-	22.40	-	15.40	-
Hara et al. ²¹	Healthy subjects	22.77	28.40	15.10	-	-
Massey et al. ²⁶	Healthy subjects	17.8	-	11.1	-	0.62
	Progressive supranuclear palsy	17.1	-	7.55	-	0.44
	Parkinson's disease	18.3	-	11.4	-	0.63
	Multiple system atrophy	14.8	-	10.8	-	0.77
Present Study	Healthy females	15.41	22.02	9.39	15.20	0.613 0.44-0.94
	Healthy males	15.58	22.64	9.37	15.64	0.606 0.40-0.84
	Total	15.47	22.27	9.38	15.38	0.610 0.40-0.94