MR VOLUMETRY OF TOTAL VENTRICULAR VOLUME AND TOTAL BRAIN VOLUME IN NORMAL ADULT POPULATION IN KELANTAN

BY:

DR NUR FARAHWAHIDA BT MUHAMMAD AZMI

Dissertation Submitted in Partial Fulfillment of the Requirement for the Degree of Master of Medicine (RADIOLOGY)

2014

MR Volumetry of Total Ventricular Volume and Total Brain Volume in Normal Kelantan Adult Population.

M.A. Farahwahida[1], H. Juhara[1], WM Salmah[1]
Department of Radiology, Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan

Abstract:

Background: This study documented the normal value of total ventricular volume in adult Malay Kelantan population, the normal ventricular brain ratio and the differences in between genders.

Methodology: 58 healthy subjects aged 40years and above were included whom undergone MRI brain examinations in HUSM. Axial and sagittal T1-weighted images retrieved from PACS were analysed. The brain and ventricular outlines were delineated using OSIRIX software. The sum of the ventricular area multiplied by 0.7 were calculated as the total ventricular volume in each patient. The ventricular brain ratio obtained by dividing the total ventricular volume with the brain volume and multiplied by 100. The volumes of ventricle and brain were analyzed using paired t-test. Independent t-test was used to analyze ventricular of both male and female. P value of less than 0.05 ($p<0.05$) was taken as significant. Results were expressed as mean ±standard deviation (SD).

Result: The mean total ventricular volume was 21.67cm^3 (12.82), while that for male and female was 28.14cm^3 (15.61) and 16.02cm^3 (5.50) respectively. Mean total ventricular to brain ratio (in percentage) for all subjects was 1.71 (0.89). Mean VBR for male subjects was 2.09 (1.11) and 1.37 (0.44) for female. There was significant difference of the mean total ventricular volume and VBR between male and female subjects (p value <0.05).

Conclusion: This study has obtained the normal mean value for the total ventricular volume and ventricular brain ratio in adult Kelantan population, which are statistically significant difference between difference genders.

Introduction:

Recent advancement in CT scan and MRI has enabled the morphometric measurement and volume analysis of the cerebral structures. Both MRI and CT scan offers realiable method in assessment and evaluation of the brain however MRI is the imaging of choice in soft tissue differentiation without radiation effect to the patient. The first MRI-based volumetric computation of the entire normal brain is reported by Filipek et al (1989), and subsequently many related studies of the intracranial structures and normative data in a population were established.

Ventricular enlargement is a nonspecific finding. Apart from ageing process the enlargement of brain ventricles have been proven to be associated with some disorders including white matter loss in patients with vascular problems, Alzheimer's disease, traumatic brain injury, gray matter loss in schizophrenics and in cases of normal pressure hydrocephalus. In the literature, the process of ventricular enlargement is either due to brain parenchymal atrophy or from neuronal loss. However, the ventricular brain ratio (VBR) must be calculated to determine the correlation between the parenchymal atrophy and the degree of the ventricular enlargement.

Ventricular brain ratio (in percentage) is the product of total ventricular volume divided by the total brain volume multiplied with 100. The mean ratio was found to be 2.0 in normal subject according to a recent study published by Akdogan et al. In contrast, racial and sexual differences in the ventricular-brain ratio (VBR) related to differences in intracranial area. Higher VBR is corresponding with the pathological or abnormal cases for example atrophy or hydrocephalus.

The normal intracerebral ventricular volumes in the literature vary markedly among population. Different age group exhibit different values. In general the total ventricular volume (TVV) have wide range (range 7–70 cm^3). The measured cerebral volume is 16.2 cm^3 and 24.9 cm^3 in second and fourth decade of Korean people respectively (Chung *et al.*, 2006). Ventricle volumes among healthy adult Turkeish population were found to range from 6.3cm^3 to

87.9cm^3 however in this study not much gender related difference is found, with mean of TVV was 30.62 ± 18.17 in male and 22.08 ± 12.94 in female (Akdogan *et al.*, 2010).

The brain volume and ventricular measurements provide stable and accurate data in studying and estimating the volumetric changes that occur either in ageing process or due to pathological process. There are many methods of assesing the ventricular volume as well as total brain volume either by CT imaging or MRI which may produce reliable measurements of structures and ventricles in the brain.

To this date, studies reporting the total ventricular volume and ventricular brain ratio are limited especially in the context of our population. In Malaysia, currently there is no reference value of normal TVV and VBR. Thus efforts are made to provide such a database. The general objective for this study is to determine the total ventricular volume and ventricular-brain volume ratio in normal healthy adult Malay in Kelantan aged 40 and above. This data can be used later in predicting degenerative changes in patients with Alzheimer's disease or patients with psychiatric illnesses such as schizophrenia and bipolar disorder.

Literature review:

The evaluation of cerebral ventricles in the humans has great importance similar to the rest of the brain compartments. Accurate measurements of the ventricles are necessary to aid in diagnosis and for further management plan of the patients. Different methods are applicable in measuring the total ventricular volume either by means of CT scan, MRI or radioisotope ventriculography. The easiest, simple and direct method is by manually by multiplying the summation of the ventricular areas in all slices with the slice thickness. Many studies have measured the lateral ventricles, third and fourth ventricles separately and made correlation with gender and age group. The normal total ventricular volume in the literature varies markedly, ranging from 7-70cm^3 (Cramer *et al.*, 1990; Akdogan *et al.*, 2010). However in general, researchers do not find any specific gender related difference in total ventricular volume.

Lateral ventricular volume is one of the most common measurements in volumetric assessment of the brain. Enlargement of the ventricular system is nonspecific and generally regarded as an indirect measure of white matter loss, because much of the ventricular systems surrounded by white matter structures (Coffey *et al.*, 1993; Blatter *et al.*, 1995). The lateral ventricles volumes are known to increase with age. The left ventricle was shown to be larger on the average than the right in either sex (Last and Tompsett, 1953), while both lateral ventricles were larger in the male. The mean value of third and fourth ventricles volume in many studies revealed $0.5cm^3$-$1.0cm^3$ and $0.9cm^3$-$1.6cm^3$ respectively (Cramer *et al.*, 1990; Aziz *et al.*, 2004). Researchers have found that individuals with schizophrenia had enlarged ventricles compared to the healthy subjects (Weinberger *et al.*, 1979; Rabins *et al.*, 1987; Kemali *et al.*, 1989). The enlarged ventricles are also found in various other types of organic dementia(Jacobs *et al.*, 1978). In bipolar disorder, mild ventricular enlargement and the presence of white matter hyper-intensities are among the most consistently reported abnormalities (McDonald *et al.*, 2004).

The ventricular-brain ratio (VBR) was introduced by Synek et al(1976) shortly after the advent of computed tomography (CT) in measuring ventricular size. The formula in calculating the VBR in previous study was as below (Synek and Reuben, 1976):

$$VBR\% = \frac{\text{Ventricular cross-sectional area}}{\text{Brain cross-sectional area}} \times 100\%$$

The normal VBR in previous studies is approximately 5 in normal, 7 in borderline cases and greater than 10 in abnormal conditions (Barron *et al.*, 1976). It reflects the association between the ventricle and the brain size. Female has lower VBR than male (Williams *et al.*, 1985). In term of age, VBR has slight increase after 49 years old and at age 59 there was sharp increase in the VBR in both sexes (Zauhair A. Jaumah* MbchB, 2009). The VBR is not increased in panic disorder (Uhde and Kellner, 1987) however there was a significant association between VBR and duration of benzodiazepine use. In this study, the ventricular size of panic disorder patients falls well within the normal range compared with reported values of mean VBR in normal control groups in the literature (Weinberger *et al.*, 1979).

Objectives:

General objective is to determine the total ventricular volume and total brain volume in normal Kelantan adult aged 40 and above. The specific objectives are as follows:

1. To determine the mean of total ventricular volume (TVV) and total brain volume (TBV) in normal Kelantan adult population.
2. To compare the mean of the total ventricular volume (TVV) and total brain volume (TBV) between male and female in normal Kelantan adult population.
3. To determine the mean ventricular brain ratio (VBR) in normal Kelantan adult population.
4. To compare the mean of ventricular brain ratio (VBR) between male and female in normal Kelantan adult population.

Research Hypotheses:

1. There is significant mean difference of TVV between male and female in normal Kelantan adult population.
2. There is significant mean difference of TBV between male and female in normal Kelantan adult population.
3. There is significant mean difference of VBR in between male and female in normal Kelantan adult population.

Research methodology:

This was a comparative cross sectional retrospective study of 58 subjects of Malay population and had undergone MR brain imaging in Department of Radiology, Hospital Universiti Sains Malaysia from May 2008 until November 2009 whereby they had normal MR brain findings. Data were collected from archive MRI images of patients stored in PACS who were involved in previous study entitled Magnetic Resonance Measurement of Total Intracranial Volume among Normal Malay Population: Accuracy of Alternative Measurement Method.

We included 58 patients; 31 men and 27 women aged 41 to 77 years old.

Inclusion criteria were those with age 40 and above of Malay ethnic living in Kelantan with normal MRI brain findings or age related changes (e.g. atrophy and/or lacunar infarct). Exclusion criteria were those with focal neurological deficit, history of psychological/psychiatric illness, history of dementia, history of epilepsy history of significant head trauma (documented intracranial hemorrhage), abnormal MRI brain finding [e.g. tumors] and patients with history of alcohol abuse.

All brain MRI examinations of the participants were performed using a 1.0 Tesla Signa Horizon LX from the GE Company. Scout sequences were obtained to ensure proper positioning of the patient's head. The MRI sequence parameters are as tabulated (Table 1). The sagittal scanning were performed from right to left giving result of first slice as on right side and last slice was on the left side of the subject's cranium.

Axial T1 and sagittal T1 with 5mm slice thickness and 2mm gap were analyzed in the measurement of the total ventricular volume and total brain volume.

Table 1: Parameters of MRI Sequences

Sequences	TE	TR	Field of view	NEX
T1 weighted	11	420	20x20	2.0
T2weighted	79.3	4020	20x20	2.0
FLAIR	147	9002	20x20	2.0

All subjects' data collection were taken from archive images retrieved from PACS system. These images were transferred into the OsiriX system 3.2.1 version in an Apple MAC PRO PC with 2.66 GHz Dual Core Intel Xeon processor as the diagnostic viewing workstation. The monitor used for this workstation was Apple Cinema HD Display (23" Flat Panel) with optimum resolution of 1920 x 1200.

Volumetric analysis was performed using the OsiriX software by a single observer (writer) who undergone a validation test by a well-trained intra-observer Radiologist.

Axial T1-weighted images were used for ventricular area analysis. Measurements were done manually by tracing the entire outline to get the ventricular area. For lateral ventricle volumes, measurement started in the most superior slice showing one or both lateral ventricles and ended in the most inferior slice on which the temporal horn was still visible in one or both hemispheres. Arbitrary lines are made whenever the choroid plexus obscuring the lateral ventricular outline. Similar principle applied to both third and fourth ventricles. Corresponding sagittal images are used to ensure the boundaries of superior and inferior limit of the 3rd and 4th ventricles.

Measurements were made in three times for each slice in order to get an average measurement. A difference of 0.05cm^2 between three times measurements was allowed. The average measurement for each slice will be summed together to get the total area in centimeter square. Volumes of all ventricles will be calculated by multiplying the total area of ventricles, in the unit of square centimeters (cm^2) with 0.7 cm (corresponding to the sum of the gap between the slices and the slice thickness). By using this method, the TVV was then obtained, in the unit of centimeters cubic (cm^3). Figure 1.1-1.3 show the contours of all the ventricles at different level.

In order to calculate for ventricular brain ratio (VBR), the brain volume is measured. For total brain volume measurement, manual tracing performed by delineating the brain surface from the dura. The measurements were done on alternate slice of the sagittal T1 images starting from first slice (slice 1, 3, 5, 7...19) based on previous study done by Busro (2010). Figure 2 shows the contours of the brain surface in alternate sagittal slices.

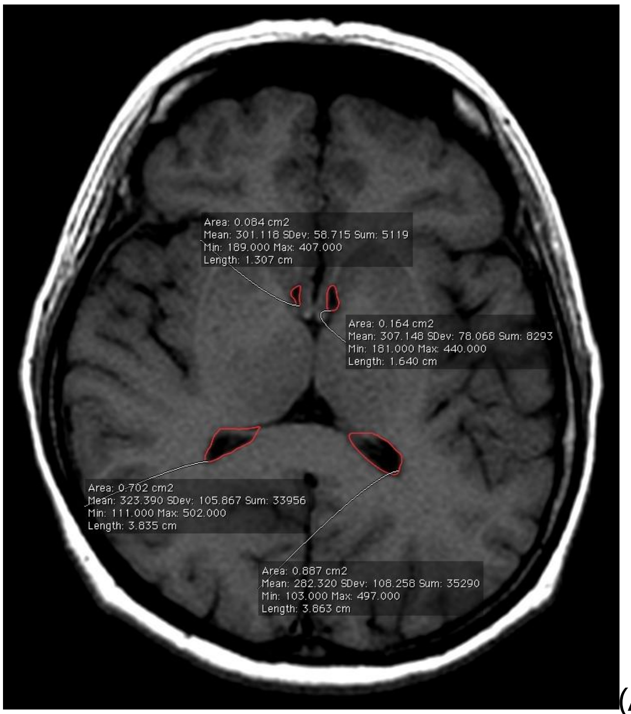
Similar to TVV, measurements were made in three times to get the average measurement with a difference of 5.0cm^2 between three times measurements was allowed. The average measurement for each slice will be summed together to get the total area in centimeter square. Total brain volume is measured by total surface areas of these odd number of slices (ΣA2) multiply by 1.4cm (2 x SL).

VBR was calculated by dividing the total ventricular volume by the total brain volume and multiplied by 100 to get the percentage VBR, modified from previous study (Synek and Reuben, 1976).

(A)

(B)

Figure 1.1: Anatomical outline of lateral ventricles on T1-Weighted image. (A) Highest level of lateral ventricle. (B) Widest level of lateral ventricles (including the choroid plexus)

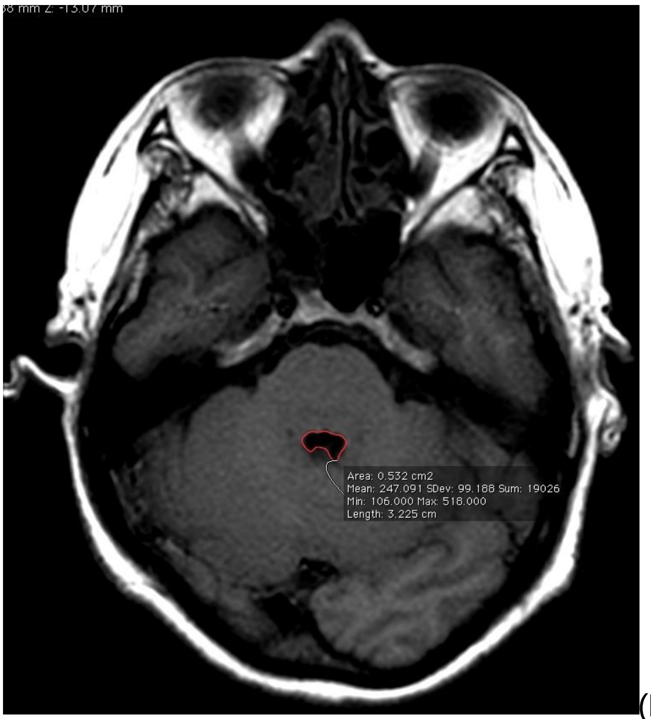


(A)

(B)

Figure 1.2: Anatomical outline of frontal horn, third ventricle and occipital horn on T1-Weighted Image. (A) Frontal horn (superior part), third ventricle (middle) and occipital horn (inferior part). (B) Widest level of third ventricle. (note that occipital horn also visible bilaterally)

(A)

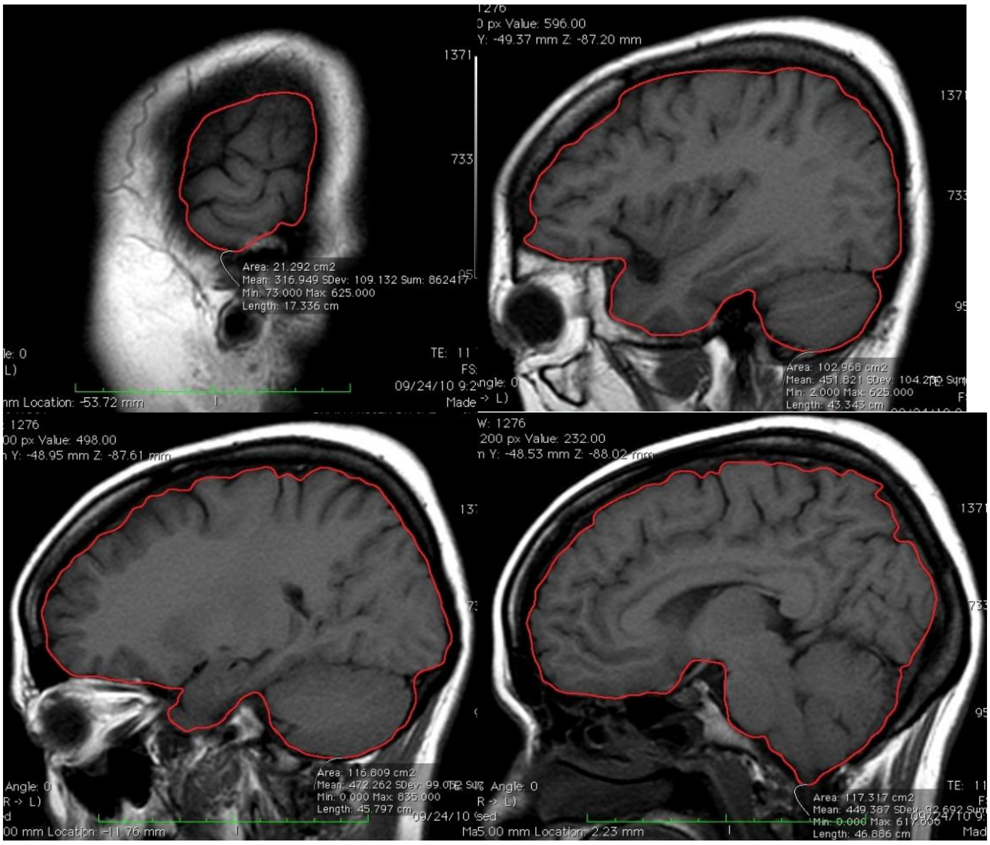


(B)

Figure 1.3: Anatomical outline of fourth ventricle on T1-Weighted image. (A) Superior part of fourth ventricle (almost aqueduct of Sylvius). (B) Widest fourth ventricle level

(C)

Figure 1.3: Anatomical outline of fourth ventricle on T1-Weighted image. (C) Inferior-most part of fourth ventricle.



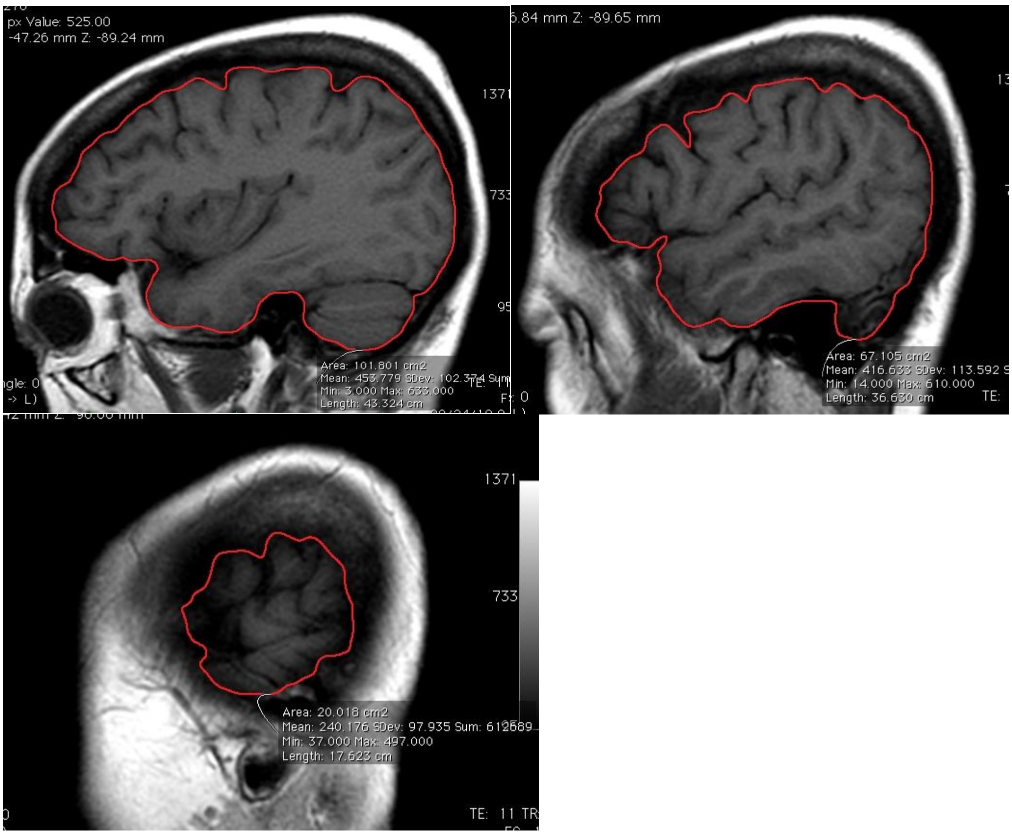


Figure 2: Sagittal T1 Images Showing Alternate Slices of Brain.

From total 58 subjects, 6 samples (10% of total) were randomly selected and analyzed by the radiologist and the researcher. Interrater reliability was then calculated using Intraclass correlation which were validated based on Intraclass Correlation[b] was 0.995[a] with 95% Confidence Interval was 0.902- 0.999.

The volumes of ventricle and brain were analyzed using paired t-test. Independent t-test was used to analyze ventricular of both male and female. P value of less than 0.05 ($p<0.05$) was taken as significant. Results were expressed as mean ±standard deviation (SD).

Results:

All the participants included are 40 years old and above (up to 77 years old) with mean age (SD) of 56.40 (8.28) years (Figure 3). 27 participants are males and 31 are females. The sample was almost equally distributed between sex groups.

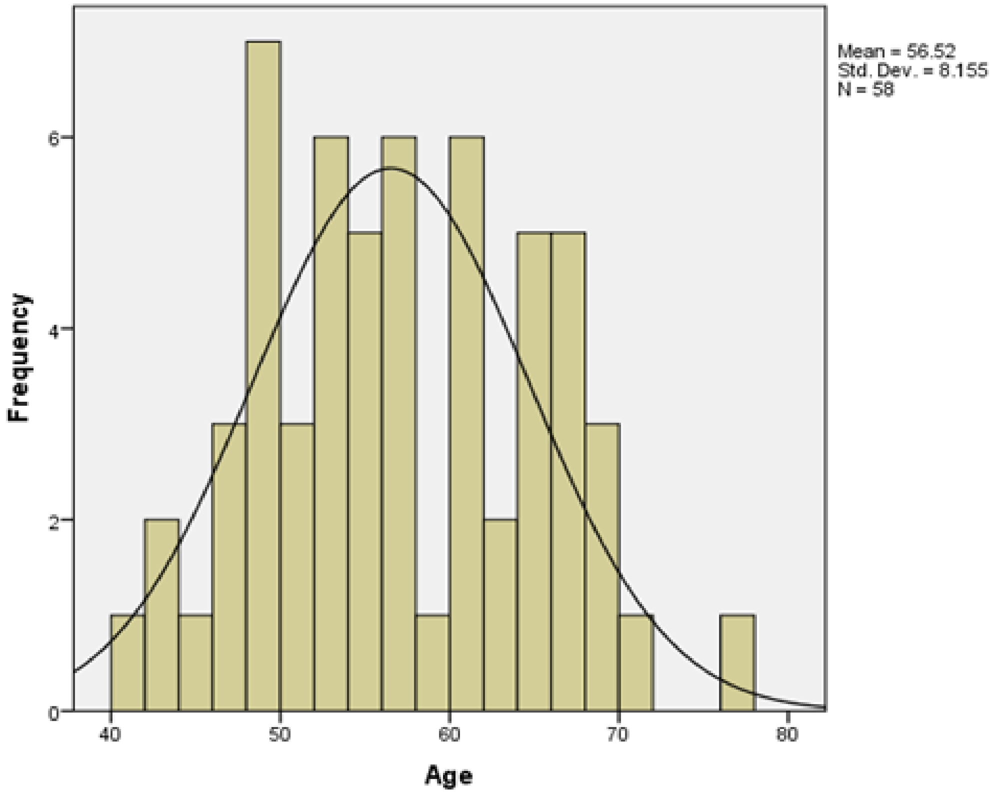


Figure 3: Age distribution of study participants.

Mean total ventricular volume (TVV) for all subjects was 21.67cm^3 (12.82cm^3). The mean TVV was ranging from 4.70cm^3 to 74.95cm^3. The mean TVV was 28.14cm^3 (15.61) and 16.02cm^3 (5.50) for male and females, respectively. There is significant difference of mean TVV between the gender (*p* value <0.001). (Table 2)

Table 2: Comparison of mean TVV (cm^3) between male and female subjects

GENDER	Mean	Std. Deviation	Mean difference (95% CI) Min, max	*t* statistic(df)	*p* value*
Male	28.15	15.61	(12.13)5.6	3.84	
Female	16.02	5.50	8,	(31.60)	0.001
Total	21.67	12.82	18.57		

*Independent Sample *t*-Test

Total ventricular volume to total brain volume ratio was calculated in order to get the ventricular brain ratio (VBR). The mean total ventricular to brain ratio (in percentage) for all subjects was 1.71 (0.89). Maximum VBR was 5.66 while the minimum VBR was 0.39. Mean VBR for male subjects was 2.09 (1.11) and 1.37 (0.44) for female. There is significant difference of mean VBR between the male and female subjects (*p* value <0.05). (Table 3)

Table 3: Comparison of Mean VBR between Male and Female Subjects

GENDER	Mean	Std. Deviation	Mean difference (95% CI) Min, max	*t* statistic (df)	*p* value*
Male	2.09	1.11	0.716 (0.282,1.151)	3.301(56)	.002
Female	1.37	0.44			
Total	1.71	0.89			

*Independent Sample *t*-Test

Discussion:

The target sample size was 70 subjects for this study. However because of this study was done based on pre-existing samples collected previously, only 58 patients were included as the age was 40 years and above. The sample was almost equally distributed between the sex groups; they were 27 males and 31 females. Studied population composed of all Malay ethnic, thus it does not representative for the Malaysian per say as Malaysia has multiracial population. This is merely because the study was done in Kelantan where the main ethnic population in this state was Malay (accounts approximately 95% of the population), based on the Survey done in 2009.

The total number of subjects for this study was smaller compared to previous similar studies. The sample for our study also had narrow range of age as we only focused on adult of 40 years and above. The largest sample size was used by Kruggel F (2006) to establish normative value of head compartments based on MRI in which 502 healthy subjects were enrolled between 16 and 70 years, including 254 males and 248 females. Quantitative Volumetric Analysis of Brain MR: Normative Database study by Blatter *et al.*

(1995) has obtained the normal TVV and TBV value, involving 194 normal subjects with age ranging from 16 to 65 years. Zauhair *et al.* (2009) had large sample size for their study of the normal measurement of the lateral ventricles, third ventricles and VBR in apparently normal Iraqi population using CT scan. The sample included 112 healthy normal subjects (66 males and 46 females) with the age ranging between 10 to 69 years. Recent studies among 300 adult Black Zimbabweans ranging from 10 to 80 years were involved in evaluation of the cerebral ventricles by Zilundu (2013).

In this study, the mean total ventricular volume was 21.67cm^3 (12.82), representing the value for Malay population. Our results are almost similar to most of the studies either by using or ventricular casts, CT scan or MRI. The closest study to our study was a study done by Blatter *et al.* (1995) which summing the lateral ventricles, third and fourth ventricles based on multispectral segmentation of brain MRI on axial images. Their study revealed total ventricular volume of 21.12cm^3 (8.85) by using standard spin echo images which has no significant differences compared to fast spin echo images that was 20.76cm^3 (8.99). In our study, the ventricular volumes were found to range from 4.70cm^3 to 74.95cm^3 which are similar to their study (6.3cm^3 to 87.9cm^3). The mean TVV yield in our study is also similar compared to the value found by Matsumae *et al.* (1996) (mean TVV 25cm^3) and Kohn *et al.* (1991) (mean TVV 21cm^3) in which they used segmentation technique for volume estimation.

Mean TVV in our study is smaller than a CT study done by N. Acer *et al.* (2009) which revealed mean TVV based on point-counting method and planimetric method of 15.5cm3 (3.5) and 15.3cm3 (3.4). Their study included only 14 young Turkish volunteers. Similarly, Cramer *et al.* (1990) found mean TVV of 17.4cm^3 in small sample size of 38 normal subjects, with was smaller compared to our result. This variation could be attributed by small sample size and younger age.

Another study in Korean population, Chung *et al.* (2006) has found TVV of 16.2cm^3 and 24.9cm^3, in second and fourth decades respectively. However our study did not correlate the TVV according to age group because we focused on adult of 40 years and above. Thus we can only make assumption that our result is similar to fourth decade Korean population as our subjects mean age was 56.40 years (8.28). Table 4 shows the TVV values in certain studies.

Table 4: Total ventricular volume (TVV) [cm^3] in adults (20 years and above):

	Method	TVV
Bruck	Casts	17.8
Last and Tompsett (1953)	Casts	16.8
Brassow and Baumann (1978)	CT	30.9
Reid *et al.* (1981)	CT	12.7
Rosenbloom *et al.* (1984)	CT	13.8
Cramer *et al.* (1990)	MRI	17.4
Matsumae *et al.* (1996)	MRI	25.0
Our study	MRI	21.7

In this study, we found that the male subjects have larger total ventricular volume than the female, and the difference was statistically significant (p <0.001). Our results are contradicting most of the recent studies that stated no significant difference between male and female total ventricular volume. However significant sex-related differences in measurements of the ventricular system using small sample size in preliminary CT study were reported by Gyldensted *et al.* (1976). In general, the values obtained in this study are still not much difference compared to those studies.

Blatter *et al.* (1995) reported there were statistically significant differences for the third ventricle and total ventricular volume in the male of 46 to 55 years of age after normalization for total intracranial volume were done. Their TVV for this age group in male was 19.88 cm^3 (5.34) and in female was 16.72 cm^3 (3.57). In older age group (56-65 years old) which almost similar to mean age of our study subjects, the TVV for male was 26.11cm^3 (10.50) and 26.50cm^3 (13.63) for female.

A study by Akdogan *et al.* (2010) revealed no significant gender related difference in the mean of TVV, 30.62cm^3 (18.17) in male and 22.08cm^3 (12.94) in female. However the methodology was different compared to ours as they measured the ventricles based on CT stereological method. In another MRI stereological study by N. Acer *et al.* (2010), there was smaller total ventricular volume in female subjects however the differences did not reach statistical significance (p > 0.05). Their TVV was 17.2cm^3 (2.5) and 13.9cm^3 (3.7) for males and females using the point-counting technique and by using the planimetric method, 16.9cm^3 (2.4) and 13.8cm^3 (3.7) for males and females. Their study was almost similar to Cramer *et al.* (1990) which stated that the TVV was 18.0cm^3 and 16.3cm^3 in males and females respectively. The differences could be due to the different methodology used by N. Acer *et al.* (2010) and smaller sample size for both N. Acer *et al.* (2010) (14 subjects) and Cramer *et al.* (1990) (38 subjects).

We have obtained the mean total ventricular to brain ratio (VBR) for all subjects, which was consistent with the rest of the studies. The normal VBR in previous studies was approximately 5 in normal, 7 in borderline cases and greater than 10 in abnormal conditions (Takeda and Matsuzawa, 1985). In term of age, VBR has slight increase after 49 years old and at age 59 there was sharp increase in the VBR in both sexes (Zauhair A. Jaumah* MbchB, 2009). However as we did not correlate the VBR with the age group, we were not able to confirm this finding.

The method used in our study was different from the original method explained by Synek *et al.* (1976). In the previous study, the VBR was calculated based on the slice on which the lateral ventricle has the widest diameter. The ventricular area then divided with the brain area multiplied with 100. The VBR in our study was derived from the total ventricular volume divided with the total brain volume (both in cm3) and the product was multiplied by 100. However no significant changes compared with the rest of the studies using the original method.

In this study, we found that the male subjects have higher VBR than the female, and the difference was statistically significance (p value <0.05). The mean VBR for male and female were 2.09 (1.11) and 1.37 (0.44) respectively. This result was consistent with previous study by Parks *et al.* (1988) stated that the female has lower VBR value than male. In a study by Blatter *et al.* (1995), VBR according to age group was 1.27 (0.28) and 2.08 (1.11) in females of 46-

55 and 56 -65 years old. As for male, the VBR was 1.52 (0.43) and 2.07 (0.88) in 46-55 and 56 -65 years age group respectively. Thus their study also proven that male has higher VBR than female, similar in our study.

However in Iranian population, a study done by Zauhair *et al.* (2009) based on CT scan involving 112 healthy subjects stated that there was no significant difference in between male and female which were contradicts to the previous report stated that female has lower VBR than male. They reported the mean VBR of 4.53 (1.2) in male and 4.16 (1.2) in female. The differences could be due to larger sample size and the calculation using original method of VBR as described by Synek *et al.* (1976).

Conclusion:

This study has obtained the normal mean value for the total ventricular volume and ventricular brain ratio in adult Kelantan populations. This study also has revealed statistically significant difference of the mean total ventricular volume and mean ventricular brain ratio seen between male and female.

References:

Acer, N., Uğurlu, N., Uysal, D., Unur, E., Turgut, M. & Çamurdanoğlu, M. (2010). Comparison of two volumetric techniques for estimating volume of intracerebral ventricles using magnetic resonance imaging: a stereological study. *Anatomical science international,* 85(3), 131-139.

Akdogan, I., Kiroglu, Y., Onur, S. & Karabulut, N. (2010). The volume fraction of brain ventricles to total brain volume: a computed tomography stereological study. *Folia Morphol,* 69(4), 193-200.

Alberstone, C. D. (2009). Anatomic basis of neurologic diagnosis. Thieme.

Arnone, D., Cavanagh, J., Gerber, D., Lawrie, S., Ebmeier, K. & McIntosh, A. (2009). Magnetic resonance imaging studies in bipolar disorder and schizophrenia: meta-analysis. *The British journal of psychiatry,* 195(3), 194-201.

Augustine, J. R. (2008). Human Neuroanatomy. Academic Press.

Aziz, A., Hu, Q. & Nowinski, W. L. (2004) In *Proc. of SPIE Vol*, Vol. 5369, pp. 575.

Barron, S. A., Jacobs, L. & Kinkel, W. R. (1976). Changes in size of normal lateral ventricles during aging determined by computerized tomography. *Neurology,* 26(11), 1011-1011.

Bayer, S. A. & Altman, J. (2007). The human brain during the early first trimester. CRC press.

Beyer, J. L. & Krishnan, K. R. R. (2002). Volumetric brain imaging findings in mood disorders. *Bipolar Disorders,* 4(2), 89-104.

Blatter, D. D., Bigler, E. D., Gale, S. D., Johnson, S. C., Anderson, C. V., Burnett, B. M., Parker, N., Kurth, S. & Horn, S. D. (1995). Quantitative volumetric analysis of brain MR: normative database spanning 5 decades of life. *American journal of Neuroradiology,* 16(2), 241-251.

Buchsbaum, M. S., Yang, S., Hazlett, E., Siegel, B. V., Jr., Germans, M., Haznedar, M., O'Flaithbheartaigh, S., Wei, T., Silverman, J. & Siever, L. J. (1997). Ventricular volume and asymmetry in schizotypal personality disorder and schizophrenia assessed with magnetic resonance imaging. *Schizophr Res,* 27(1), 45-53.

Caviness, V. S., Jr., Filipek, P. A. & Kennedy, D. N. (1992). Quantitative magnetic resonance imaging and studies of degenerative diseases of the developing human brain. *Brain Dev,* 14 Suppl, S80-5.

Chung, S. C., Tack, G. R., Yi, J. H., Lee, B., Choi, M. H., Lee, B. Y. & Lee, S. Y. (2006). Effects of gender, age, and body parameters on the ventricular volume of Korean people. *Neurosci Lett,* 395(2), 155-8.

Coffey, C. E., Wilkinson, W. E., Weiner, R. D., Djang, W. T., Webb, M. C., Figiel, G. S. & Spritzer, C. E. (1993). Quantitative cerebral anatomy in depression: a controlled magnetic resonance imaging study. *Archives of General Psychiatry,* 50(1), 7.

Condon, B., Wyper, D., Grant, R., Patterson, J., Hadley, D., Teasdale, G. & Rowan, J. (1986). Use of magnetic resonance imaging to measure intracranial cerebrospinal fluid volume. *The Lancet,* 327(8494), 1355-1357.

Cramer, G., Allen, D., DiDio, L., Potvin, W. & Brinker, R. (1990). Evaluation of encephalic ventricular volume from the magnetic resonance imaging scans of thirty-eight human subjects. *Surgical and Radiologic Anatomy,* 12(4), 287-290.

Cruz-Orive, L. M. (1997). Stereology of single objects. *Journal of Microscopy,* 186(2), 93-107.

Elfaki, A., Osman, T., Elsheikh, A., Hamdoun, A. & Şahin, B. (2011). Evaluation of the intra-rater variation for the estimation of volume of cerebral structures using the cavalieri principle on magnetic resonance images. *Journal of Experimental and Clinical Medicine,* 28(1).

Fernicola, P. J. (2011). Concussion: When the skull just isn't protection enough. [Online] Available [Accessed 12 November 2013].

Filipek, P. A., Richelme, C., Kennedy, D. N. & Caviness, V. S., Jr. (1994). The young adult human brain: an MRI-based morphometric analysis. *Cereb Cortex,* 4(4), 344-60.

Flanagan, B. J. (2009). The biology of the Brain. [Online] Available [Accessed 9 November 2013].

Glastonbury, C. M., Osborn, A. G. & Salzman, K. L. (2011). Masses and Malformations of the Third Ventricle: Normal Anatomic Relationships and Differential Diagnoses. *RadioGraphics,* 31(7), 1889-1905.

Gomori, J., Steiner, I., Melamed, E. & Cooper, G. (1984). The assessment of changes in brain volume using combined linear measurements. *Neuroradiology,* 26(1), 21-24.

Gray, H. (1918). Anatomy of the Human Body [Online] Available [Accessed 12 November 2013].

Greenstein, B. & Greenstein, A. (2000). Color atlas of neuroscience: Neuroanatomy and neurophysiology. Thieme.

Gyldensted, C. (1977). Measurements of the normal ventricular system and hemispheric sulci of 100 adults with computed tomography. *Neuroradiology,* 14(4), 183-192.

Huang, H., Xue, R., Zhang, J., Ren, T., Richards, L. J., Yarowsky, P., Miller, M. I. & Mori, S. (2009). Anatomical characterization of human fetal brain development with diffusion tensor magnetic resonance imaging. *J Neurosci,* 29(13), 4263-73.

Jacobs, L., Kinkel, W. R., Painter, F., Murawski, J. & Heffner Jr, R. R. (1978). Computerized tomography in dementia with special reference to changes in size of normal ventricles during aging and normal pressure hydrocephalus. *Alzheimer's Disease: Senile Dementia and Related Disorders. Raven Press, New York, Aging,* 7, 241-259.

Jacoby, R. J. & Levy, R. (1980). Computed tomography in the elderly. 3. Affective disorder. *The British journal of psychiatry,* 136(3), 270-275.

Kemali, D., Maj, M., Galderisi, S., Milici, N. & Salvati, A. (1989). Ventricle-to-brain ratio in schizophrenia: a controlled follow-up study. *Biological psychiatry,* 26(7), 756-759.

Kempton, M. J., Geddes, J. R., Ettinger, U., Williams, S. C. & Grasby, P. M. (2008). Meta-analysis, database, and meta-regression of 98 structural imaging studies in bipolar disorder. *Archives of General Psychiatry,* 65(9), 1017.

Kennedy, D. N., Haselgrove, C. & McInerney, S. (2003). MRI-based morphometric analysis of typical and atypical brain development. *Mental retardation and developmental disabilities research reviews,* 9(3), 155-160.

Kruggel, F. (2006). MRI-based volumetry of head compartments: normative values of healthy adults. *Neuroimage,* 30(1), 1-11.

Last, R. & Tompsett, D. (1953). Casts of the cerebral ventricles. *British Journal of Surgery,* 40(164), 525-543.

Levine, D. & Barnes, P. D. (1999). Cortical maturation in normal and abnormal fetuses as assessed with prenatal MR imaging. *Radiology,* 210(3), 751-758.

Madden, M. E. (2001). Introduction to sectional anatomy. Lippincott Williams & Wilkins.

Mancall, E. L. & Brock, D. G. (2011). Gray's Clinical Neuroanatomy. Elsevier Health Sciences.

Marcus, D. S., Wang, T. H., Parker, J., Csernansky, J. G., Morris, J. C. & Buckner, R. L. (2007). Open Access Series of Imaging Studies (OASIS): Cross-sectional MRI Data in Young, Middle Aged, Nondemented, and Demented Older Adults. *J Cogn Neurosci,* 19(9), 1498-1507.

McDonald, C., Zanelli, J., Rabe-Hesketh, S., Ellison-Wright, I., Sham, P., Kalidindi, S., Murray, R. M. & Kennedy, N. (2004). Meta-analysis of magnetic resonance imaging brain morphometry studies in bipolar disorder. *Biological psychiatry,* 56(6), 411-417.

Musa, B. (2010). Magnetic Resonance Measurement of Total Intracranial Volume among Normal Malay Population: Accuration of Alternative Measurement Method, University Sains Malaysia, Kelantan, Malaysia.

N.M., S. (2009). I. Nervous System. [Online] Available [Accessed 12 November 2013].

O'Rahilly, R. R. & Müller, F. (2006). The embryonic human brain: an atlas of developmental stages. John Wiley & Sons.

Osaka, K., Handa, H., Matsumoto, S. & Yasuda, M. (1980). Development of the cerebrospinal fluid pathway in the normal and abnormal human embryos. *Pediatric Neurosurgery,* 6(1), 26-38.

Ott, B. R., Cohen, R. A., Gongvatana, A., Okonkwo, O. C., Johanson, C. E., Stopa, E. G., Donahue, J. E., Silverberg, G. D. & Alzheimer's Disease Neuroimaging, I. (2010). Brain ventricular volume and cerebrospinal fluid biomarkers of Alzheimer's disease. *J Alzheimers Dis,* 20(2), 647-57.

Pearlson, G. D., Kim, W. S., Kubos, K. L., Moberg, P. J., Jayaram, G., Bascom, M. J., Chase, G. A., Goldfinger, A. D. & Tune, L. E. (1989). Ventricle-brain ratio, computed tomographic density, and brain area in 50 schizophrenics. *Archives of General Psychiatry,* 46(8), 690.

Penn, R. D., Belanger, M. G. & Yasnoff, W. A. (1978). Ventricular volume in man computed from CAT scans. *Ann Neurol,* 3(3), 216-223.

Rabins, P., Pearlson, G., Jayaram, G., Steele, C. & Tune, L. (1987). Increased ventricle-to-brain ratio in late-onset schizophrenia. *Am J Psychiatry,* 144(9), 1216-1218.

Raof, H. W. R. W. A. (2010) (Ed, MALAYSIA, D. O. S.) DEPARTMENT OF STATISTIC MALAYSIA, PUTRAJAYA.

Razvanski, B. (2012). The Brain
[Online] Available [Accessed 12 November 2013].

Reite, M., Reite, E., Collins, D., Teale, P., Rojas, D. & Sandberg, E. (2010). Brain size and brain/intracranial volume ratio in major mental illness. *BMC psychiatry,* 10(1), 79.

Roberts, N., CRUZ-ORIVE, L., Reid, N., Brodie, D., Bourne, M. & Edwards, R. (1993). Unbiased estimation of human body composition by the Cavalieri method using magnetic resonance imaging. *Journal of Microscopy,* 171(3), 239-253.

Singh, I. (2006). Textbook of human neuroanatomy. JAYPEE BROTHERS PUBLISHERS.

Standring, S., Ellis, H., Healy, J., Johnson, D., Williams, A., Collins, P. & Wigley, C. (2005). Gray's anatomy: the anatomical basis of clinical practice. *American Journal of Neuroradiology,* 26(10), 2703.

Starr, C., Taggart, R., Evers, C. & Starr, L. (2012). Volume 5-Animal Structure & Function. Cengage Learning.

Synek, V. & Reuben, J. (1976). The ventricular-brain ratio using planimetric measurement of EMI scans. *British Journal of Radiology,* 49(579), 233-237.

Takeda, S. & Matsuzawa, T. (1985). Age-related brain atrophy: a study with computed tomography. *Journal of gerontology,* 40(2), 159-163.

Uhde, T. W. & Kellner, C. H. (1987). Cerebral ventricular size in panic disorder. *Journal of affective disorders,* 12(2), 175-178.

Weed, L. H. (1935). Certain anatomical and physiological aspects of the meninges and cerebrospinal fluid. *Brain,* 58(3), 383-397.

Weinberger, D. R., Torrey, E. F., Neophytides, A. N. & Wyatt, R. J. (1979). Lateral cerebral ventricular enlargement in chronic schizophrenia. *Archives of General Psychiatry,* 36(7), 735.

Williams, A., Reveley, M., Kolakowska, T., Ardern, M. & Mandelbrote, B. (1985). Schizophrenia with good and poor outcome. II: Cerebral ventricular size and its clinical significance. *The British journal of psychiatry,* 146(3), 239-246.

Woods, B. T., Douglass, A. & Gescuk, B. (1991). Is the VBR still a useful measure of changes in the cerebral ventricles? *Psychiatry Research: Neuroimaging,* 40(1), 1-10.

Wright, I. C., Rabe-Hesketh, S., Woodruff, P. W., David, A. S., Murray, R. M. & Bullmore, E. T. (2000). Meta-analysis of regional brain volumes in schizophrenia. *American Journal of Psychiatry,* 157(1), 16-25.

Wyper, D. J., Pickard, J. D. & Matheson, M. (1979). Accuracy of ventricular volume estimation. *Journal of Neurology, Neurosurgery & Psychiatry,* 42(4), 345-350.

Yoshii, F., Barker, W. W., Chang, J. Y., Loewenstein, D., Apicella, A., Smith, D., Boothe, T., Ginsberg, M. D., Pascal, S. & Duara, R. (1988). Sensitivity of cerebral glucose metabolism to age, gender, brain volume, brain atrophy, and cerebrovascular risk factors. *Journal of Cerebral Blood Flow & Metabolism,* 8(5), 654-661.

Young, P. (1999). CHAPTER 2. TOPOGRAPHY OF THE CENTRAL NERVOUS SYSTEM. [Online] Available [Accessed 12 November 2013].

Zatz, L. M. & Jernigan, T. L. (1983). The ventricular-brain ratio on computed tomography scans: validity and proper use. *Psychiatry Res,* 8(3), 207-214.

Zauhair A. Jaumah* MbchB, M. د. ز. ع. ج. (2009). C.T Scan Measurements of the Lateral and Third Ventricles in Apparently Normal Iraqi Subjects. *Journal of the Faculty of Medicine □□□□ □□□□□ □□□□,* 51(3), 320-322.

1 INTRODUCTION

In this modern era of advanced radiological imaging, there have been a lot of studies done in evaluating the brain and intracerebral structures. Recent advancement in CT scan and MRI has enabled the morphometric measurement and volume analysis of the cerebral structures. Both MRI and CT scan offers realiable method in assessment and evaluation of the brain however MRI is the imaging of choice in soft tissue differentiation with the advantage of no radiation effect to the patient. The first MRI-based volumetric computation of the entire normal brain was reported by Filipek *et al* (1989), and subsequently many related studies of the intracranial structures and normative data in a population were established.

Ventricular enlargement is a non-specific finding. Apart from ageing process the enlargement of brain ventricles have been proven to be associated with some disorders including white matter loss in patients with vascular problems, Alzheimer's disease and traumatic brain injury; gray matter loss in schizophrenics and in cases of normal pressure hydrocephalus. In the literature, the process of ventricular enlargement is either due to brain parenchymal atrophy or from neuronal loss. Therefore, the ventricular brain ratio (VBR) must be calculated to determine the correlation between the parenchymal atrophy and the degree of the ventricular enlargement.

Ventricular brain ratio (in percentage) is the product of total ventricular volume divided by the total brain volume multiplied by 100. The mean ratio was found to be 2.0 in normal subject according to a recent study published by Akdogan *et al*. In contrast, racial and sexual differences in the ventricular-brain ratio (VBR) related to differences in intracranial area. Higher VBR is corresponding with the pathological or abnormal cases, for example atrophy or hydrocephalus.

The normal intracerebral ventricular volumes vary markedly among population. Different age group exhibit different values. In general the total ventricular volume (TVV) have a wide range (range 7–70cm^3). The measured cerebral volume is 16.2cm^3 and 24.9cm^3 in 100 subjects involving second and fourth decade of Korean people respectively (Chung *et al.*, 2006). Ventricle volumes among healthy Turkeish adult population were found to range from 6.3cm^3 to 87.9cm^3 however in this study not much gender related difference is found. In a recent study involving 80 normal subjects, the mean TVV was 30.62 ± 18.17 in male and 22.08 ± 12.94 in female (Akdogan *et al.*, 2010).

Overall, there is not much different between adult brain volume in people of differing ages and sexes. It is well known that males have larger brain volume compared to females. In aging process, men subsequently show greater volume loss in whole brain volume and in the frontal lobes and temporal lobes, whereas in women there is increased volume loss in the hippocampi and parietal lobes. However most studies are done mainly in the developed country and limited studies done in Asian population.

The brain and ventricular volume measurements provide stable and accurate data in studying and estimating the volumetric changes that occur either in ageing process or due to pathological process. There are many methods of assesing the ventricular volume as well as total brain volume either by CT imaging or MRI which may produce reliable measurements of structures and ventricles in the brain.

To this date, studies reporting the total ventricular volume, total brain volume and ventricular brain ratio are limited especially in the context of our population. In Malaysia, currently there is no reference value of normal TVV, TBV and VBR. Thus efforts are made to provide such a database. This study is designed mainly to document the total ventricular volume and total brain volume in the normal healthy patients specifically the 40 year old and above population as well as to provide normative data about ventricular-brain volume ratio. This data can be used later in predicting degenerative changes in patients with Alzheimer's disease or patients with psychiatric illnesses such as schizophrenia and bipolar disorder.

2 LITERATURE REVIEW

2.1 OVERVIEW

Brain size, volume and the ratio of brain size to total intracranial volume has been a topic of interest since the advent of newly emerging and highly technical facilities to study the brain. Similarly the study on cerebral ventricular volume, its relation with the brain volume as well as the ventricular brain ratio is of interest mainly in the psychiatric and neuromedical field.

Ventricular brain ratio (VBR) is an important variable in the investigation of several neurological and neuropsychiatric disorders. In order to understand further this study, a brief anatomy on brain and ventricles will be emphasized. Function of the brain ventricle and cerebrospinal fluid as well as the clinical significance will also be discussed further.

2.2 ANATOMY OF BRAIN AND ITS COVERING

2.2.1 Brain

The brain is the most complex organ in a vertebrate's body (O'Rahilly and Müller, 2006). The brain consists of three divisions i.e. the forebrain, midbrain and hindbrain (Table 2.1). This consists of two cerebral hemispheres. Each hemisphere contains a cavity known as the lateral ventricle.

Table 2.1 Brain divisions.

Adapted from (Young, 1999)

Primary Division	Secondary Division	Parts	Cavity
PROSENCEPHALON (forebrain)	Telencephalon (end brain)	Cerebral Hemisphere Cortex Medullary Part Telencephalic Nuclei	Lateral Ventricle
	Diencephalon (thru brain)	Thalamus Epithalamus Hypothalamus Subthalamus	Third Ventricle
MESENCEPHALON (midbrain)	Mesencephalon	Midbrain	Cerebral Aqueduct
RHOMBENCEPHALON (hindbrain)	Metencephalon	Pons Cerebellum	Fourth Ventricle
	Myelencephalon	Medulla Oblongata	

Cerebral hemispheres are partly separated from each other by the longitudinal interhemispheric fissure, which is occupied by a fold of dura mater; the falx cerebri. Each hemisphere has a superolateral, medial and inferior surface. The corpus callosum (the largest bundle of nerve fibers in the entire nervous system) is connecting bilateral hemispheres (Greenstein and Greenstein, 2000) (Figure 2.1). It forms the roof of the frontal horn of the lateral ventricle of each side and curved sagitally.

Each cerebral hemisphere has frontal, occipital and temporal poles which are located in the anterior, posterior, and middle cranial fossa respectively.

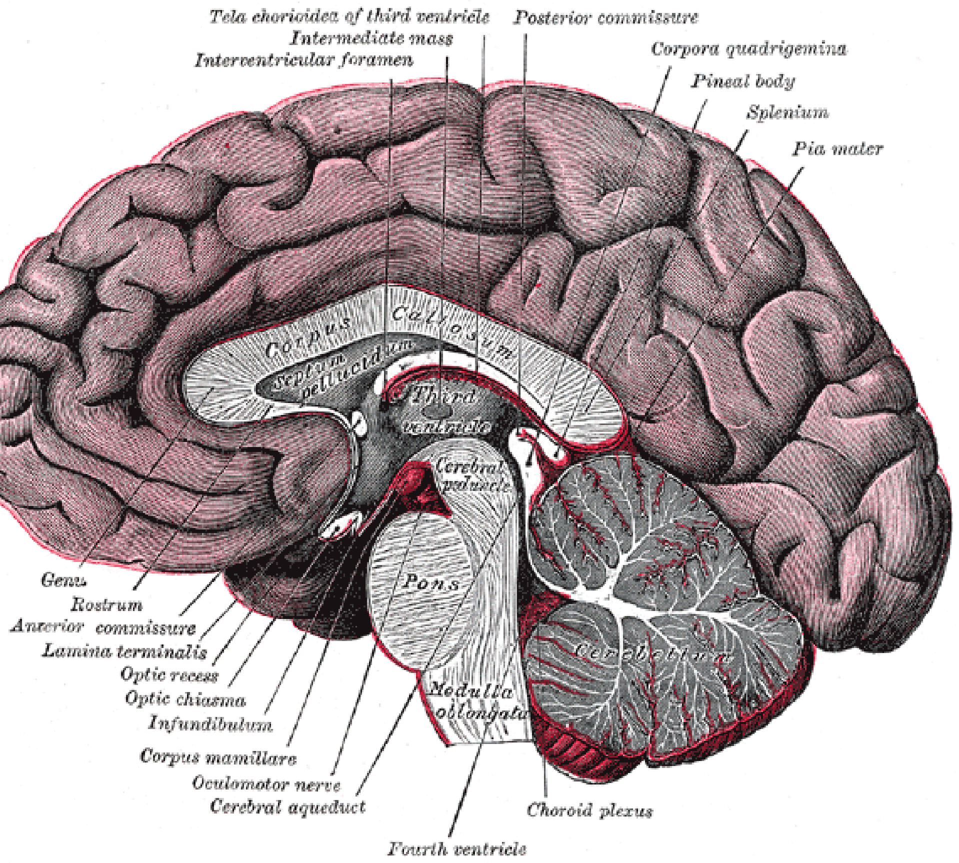


Figure 2.1: Parts of the brain

Adapted from (Standring *et al.*, 2005)

The cerebral cortex in a normal human which is estimated to contain 15–33 billion neurons (Elfaki *et al.*, 2011). The cerebral cortex is the gray matter of the hemisphere's surface, which are folded or convoluted into gyri, and are separated from each other by sulci (Figure 2.2). The complex pattern of folding allows an increased cortical surface to occupy a smaller cranial volume. The pattern of folding that forms the sulcal and gyral patterns remains highly preserved across humans and related to higher intellectual function compared to other mammal (Beyer and Krishnan, 2002). However there are certain gyri and sulci that are relatively consistent and provide landmarks that can identify structural and functional subdivisions of the brain.

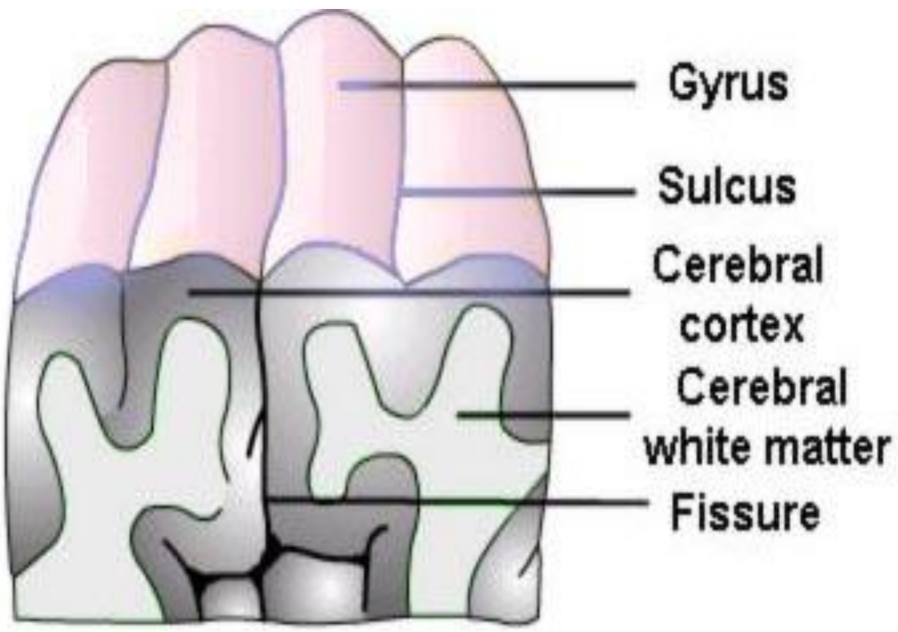


Figure 2.2: Gyri and sulci

Adapted from (N.M., 2009)

The lateral fissure or also known as Sylvian fissure begins on the inferior surface of the brain and extends laterally toward the superolateral surface of the hemisphere. From here it proceeds posteriorly between the frontal and parietal lobes on its superior side and the temporal lobe on the inferior side. The insula is buried deep to the lateral fissure (Greenstein and Greenstein, 2000).

The central sulcus begins on the medial surface of the hemisphere and, upon reaching the superolateral surface it descends between the frontal and parietal lobes (Figure 2.3). The precentral gyrus which is located immediately anterior to the central sulcus is known as the motor area. This area concerned with muscular activity, mostly in the opposite half of the body. The post-central gyrus, located immediately posterior to the central sulcus. This area is an important primary receptive area for somatic sensation. The various sensory pathways reach this region by means of relays in the thalamus (Greenstein and Greenstein, 2000).

Each cerebral hemisphere is arbitrarily divided into frontal, parietal, occipital, and temporal lobes.

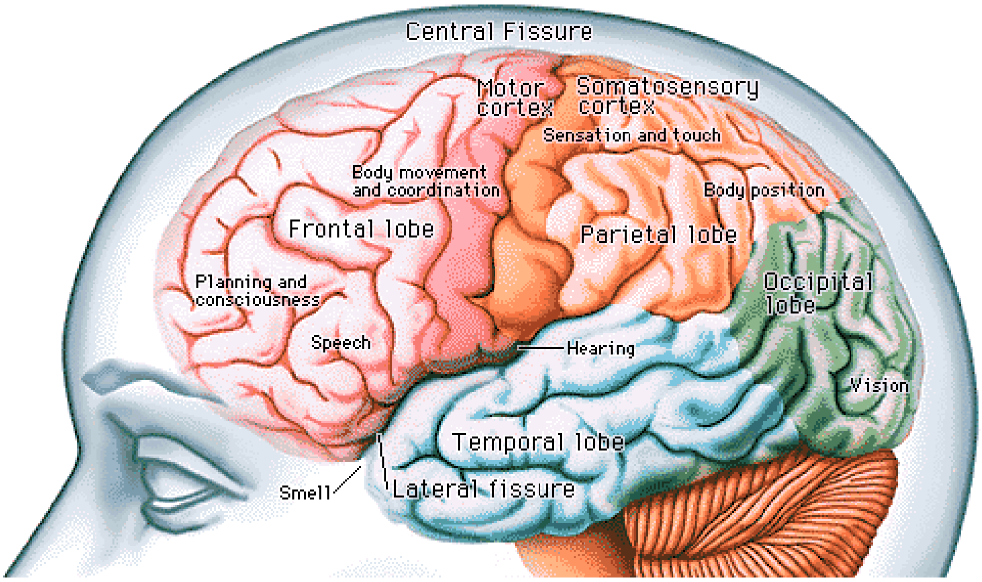


Figure 2.3: Brain lobes and its function.

Adapted from (Flanagan, 2009).

2.2.2 Brain's covering

The brain and spinal cord is covered by the meninges which consist of 3 tissue layers, namely the pia, arachnoid, and dura mater (Weed, 1935) (Figure 2.4). The pia, together with the arachnoid are referred to as the leptomeninges, whereas the dura is known as the pachymeninges.

The innermost of the 3 layers is the pia mater, which tightly covers the brain conforming to its grooves and folds (Greenstein and Greenstein, 2000). There are plenty of blood vessels within this layer that descend into the brain. Second layer which is outside the pia mater is the arachnoid mater, which tightly contours the brain. The arachnoid mater is a thin web-like layer. The space in between these two layers is the subarachnoid space, which contains cerebrospinal fluid (CSF) and major blood arteries supplying the brain. The dura mater is the outermost meningeal layer, which lines the interior skull. This layer composed of 2 individual layers, which are the meningeal dura and the periosteal dura. Venous sinuses are located in between these layers. The dura mater fold that separates the cerebellum from the cerebrum tentorium is termed tentorium cerebelli whereas the falx cerebri is a fold that separates the left and right cerebral hemispheres (Weed, 1935).

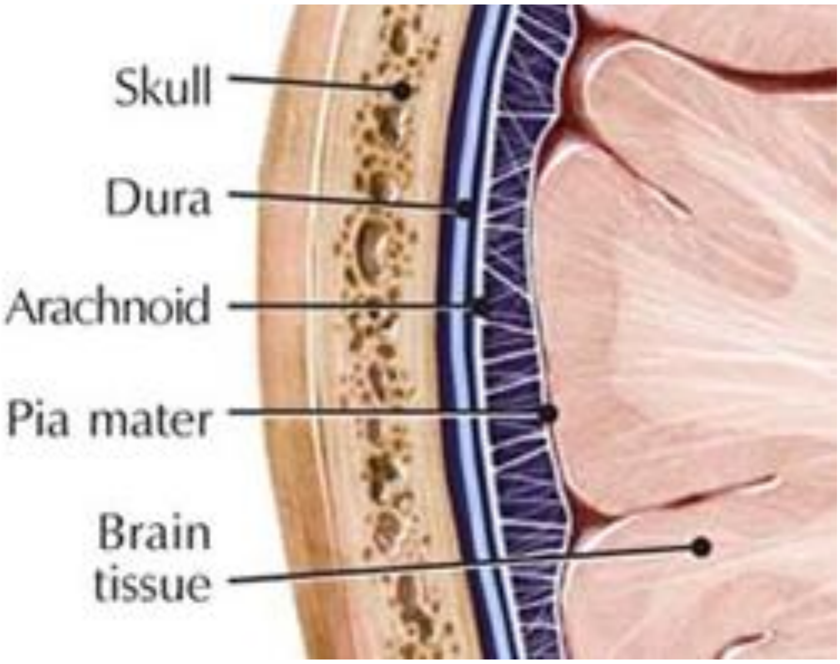


Figure 2.4: Layers of the meninges.

Adapted from (Fernicola, 2011)

2.3 ANATOMY OF VENTRICULAR SYSTEM

The cerebral ventricles is a highly conserved system of cavities within the brain and consists of a series of interconnecting spaces and channels in the brain which contain cerebrospinal fluid (CSF) (Bayer and Altman, 2007). This system was first described by the ancient Greek physician Herophilus (335-280 BC) (Yoshii *et al.*, 1988).

The two lateral ventricles communicate with the third ventricle by an interventricular foramen of Monroe on each side. The third ventricle communicates with the fourth ventricle through the aqueduct of Sylvius (Figure 2.5). The fourth ventricle becomes continuous with the central canal of the medulla and spinal cord and opens into the subarachnoid space by means of 3 apertures located just inferior to the cerebellum. These 3 apertures are a midline opening (foramen of Magendi) and two lateral openings, foramen of Luschka (Standring *et al.*, 2005).

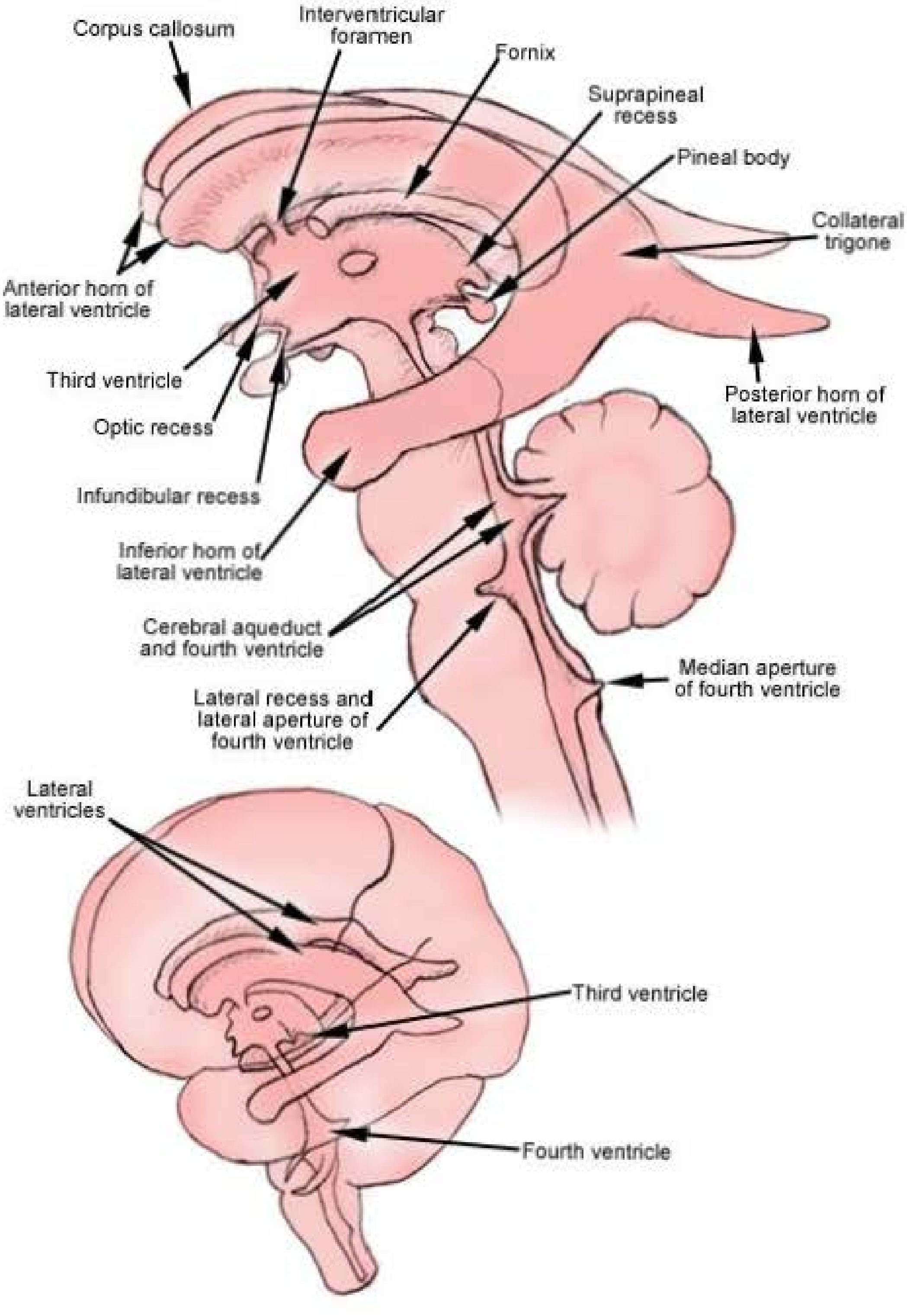


Figure 2.5: Ventricular system

Adapted from (Standring *et al*., 2005)

The ependyma is a type of neuroglia that lines the ventricles of the brain and the central canal of the spinal cord (Starr *et al.*, 2012). In the ventricles, vascular fringes of pia mater (also known as tela choroidea) invaginates their covering of modified ependyma and projects into the ventricular cavities. This combination of vascular tela and cuboidal ependyma is termed as the choroid plexus (Figure 2.6). The choroidal plexuses invaginated into the cavities of the lateral, third, and fourth ventricles and they are the site of production of cerebrospinal fluid (Osaka *et al.*, 1980).

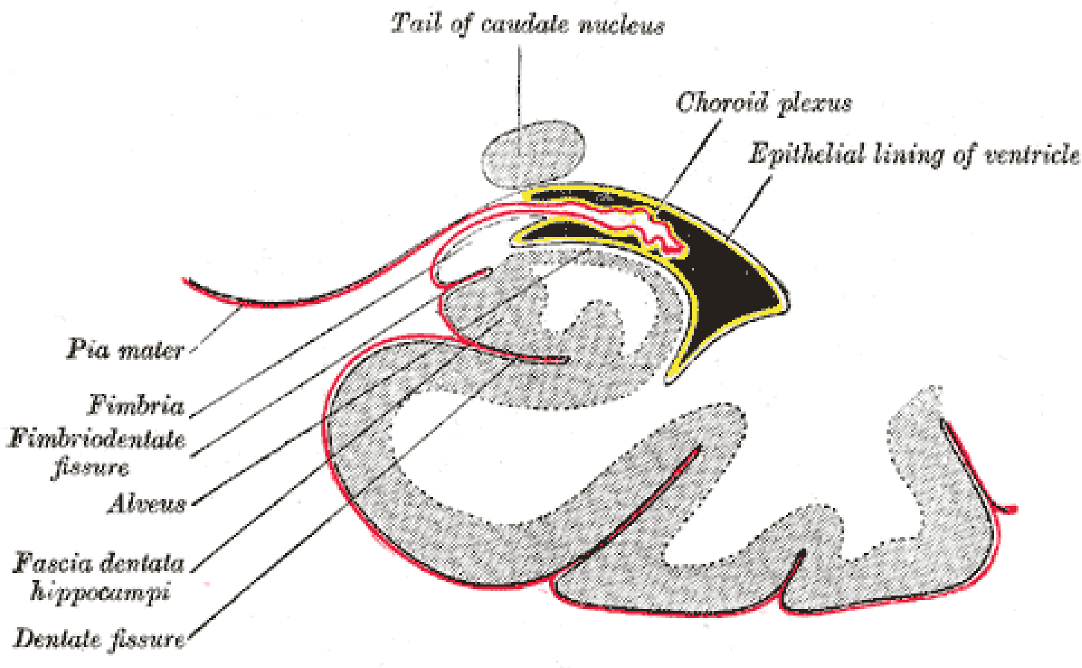


Figure 2.6: Choroid plexus.

Adapted from (Gray, 1918)

2.3.1 Lateral ventricles and its anatomical boundaries.

Each lateral ventricle is a cavity in the interior of a cerebral hemisphere and each communicates with the third ventricle by an interventricular foramen (Figure 2.5). The portion of the lateral ventricle anterior to the foramen is termed frontal or anterior horn. Posteriorly, the central part of the ventricle divides into occipital or posterior and temporal or inferior horns which extend into corresponding lobes of the cerebral hemisphere (Alberstone, 2009).

The frontal horn of the lateral ventricle is limited inferiorly by the rostrum, anteriorly by the genu, and superiorly by the body of the corpus callosum. Laterally, it is confined by the bulging head of the caudate nucleus. Medially, a thin vertical partition separates the right and left lateral ventricle which is termed septum pellucidum (Singh, 2006).

The central part of the lateral ventricle lies superior to the thalamus and the body of the caudate nucleus, and inferior to the trunk of the corpus callosum. Medially, the two lateral ventricles are separated from each other by the posterior portion of the septum pellucidum and the fornix. In the angle between the diverging occipital and temporal horns, the floor of the cavity presents a triangular elevation (the collateral trigone) associated with an underlying groove (Madden, 2001).

The variable occipital horn tapers posteriorly into the occipital lobe of the hemisphere. Each posterior horn is bounded by a sheet of fibers (tapetum) derived from the body and the splenium of the corpus callosum on the superolateral side. Two elevations may project laterally into the occipital horn on the medial side. The bulb of the occipital horn is the superior elevation, produced by fibers, that is forceps major which is derived from the splenium. The inferior part of the occipital horn is associated with a groove (calcarine sulcus) on the exterior of the hemisphere. Nevertheless, a third, as yet unreported elevation may be present at the junction of the medial wall and the floor of the occipital horn reported (Roberts *et al.*, 1993).

The temporal horn extends inferoanteriorly as it continues posterior to the thalamus to enter the temporal lobe of the hemisphere. Laterally, it is bounded by the tapetum which is derived from the corpus callosum (Singh, 2006). The hippocampus lies inferiorly and superiorly, the tail of the caudate nucleus runs forward to reach the amygdaloid body, which is at the rostral extent of the temporal horn of the ventricle.

2.3.2 Third ventricle and its anatomical boundaries.

The third ventricle is a narrow cleft between the two thalami (Glastonbury *et al.*, 2011). Over a variable area the thalami are frequently adherents to each other, giving rise to the interthalamic adhesion (Mancall and Brock, 2011). The floor of the ventricle is formed by the hypothalamus. The anteroinferior extent of the floor of this ventricle is crossed by the optic chiasm. The anterior wall is formed by the lamina terminalis, a delicate sheet that connects the optic chiasma to the corpus callosum. The thin roof of the ventricle consists of ependyma covered by two layers of pia (known as the velum interpositum) (Osaka *et al.*, 1980).

The third ventricle communicates with the lateral ventricles by means of the interventricular foramina (Figure 2.5). Each interventricular foramen is situated at the superoanterior portion of the third ventricle, at the anterior limit of the thalamus. This represents the site of outgrowth of the cerebral hemisphere in the embryo. From this foramen, a shallow groove, the hypothalamic sulcus, may be traced posteriorward to the cerebral aqueduct (Singh, 2006). The sulcus marks the boundary between the thalamus (superior) and the hypothalamus (inferior).

There are two protrusions on the anterior aspect of the third ventricle which are supra-optic recess (above the optic chiasma) and infundibular recess (above the pituitary stalk) (Augustine, 2008). Another there are two protrusions on the posterior aspect, above the cerebral aqueduct which are the suprapineal recess (above the pineal gland) and the pineal recess (protruding into the stalk of the pineal gland).

The aqueduct is the narrow channel in the midbrain that connects the third and fourth ventricles (Mancall and Brock, 2011).

2.3.3 Fourth ventricle and its anatomical boundaries.

The fourth ventricle is a rhomboid-shaped cavity (Figure 2.5) dorsal to the pons and medulla and separating these portions of the brain stem from the cerebellum (Glastonbury *et al.*, 2011). Rostrally, it narrows to become continuous with the cerebral aqueduct of the midbrain. Caudally, it narrows and leads into the central canal of the medulla and becomes continuous with the central canal of the spinal cord (Madden, 2001). Laterally, the widest portion of the ventricle is prolonged on each side as the lateral recess. The superior and inferior cerebellar peduncles form the lateral boundaries of the ventricle.

The ventral aspect or floor of the fourth ventricle (the rhomboid fossa) is formed by the pons rostrally and by the medulla caudally (Greenstein and Greenstein, 2000). It is related directly or indirectly to the nuclei of origin of the last eight cranial nerves. A median groove divides the floor into right and left halves. Each half is divided by a longitudinal groove which is called the sulcus limitans, into medial or basal and lateral or alar portions. The medial portion, known as the medial eminence, overlies certain motor nuclei and the area lateral to the sulcus limitans overlies certain sensory nuclei (Greenstein and Greenstein, 2000).

The caudal most portion of the floor of the fourth ventricle is shaped like the point of a pen and contains the important respiratory, cardiac, vasomotor, and deglutition centers (Mancall and Brock, 2011).

The posterior boundary or roof of the fourth ventricle is extremely thin and concealed by the cerebellum. It consists of sheets of white matter (superior and inferior medullary vela), which are lined by ependyma and stretch between the two superior and the two inferior cerebellar peduncles. The median and lateral apertures are the only means by which cerebrospinal fluid formed in the ventricles enters the subarachnoid space (Osaka *et al.*, 1980).

2.4 CEREBROSPINAL FLUID AND THE CSF FLOW

The cerebrospinal fluid (CSF) is a clear, watery fluid that fills the ventricles of the brain and the subarachnoid spaces around the brain and spinal cord (Cruz-Orive, 1997). CSF is produced primarily by the choroid plexus of the ventricles (up to 70% of the volume), with most of it being formed by the choroid plexus of the lateral ventricles. The rest of the CSF production is the result of trans-ependymal flow from the brain to the ventricles.

CSF flows from the lateral ventricles, through the interventricular foramens, and into the third ventricle, cerebral aqueduct, and the fourth ventricle (Osaka *et al.*, 1980). Only a very small amount enters the central canal of the spinal cord. CSF flow is the result of a combination of factors, which include the hydrostatic pressure generated during CSF production, arterial pulsations of the large arteries, and directional beating of the ependymal cilia. The flow of CSF is illustrated in the Figure 2.7.

The ventricles constitute the internal part of a communicating system containing CSF (Weed, 1935). The external part of the system is formed by the subarachnoid space and cisterns. The CSF is absorbed from the subarachnoid space into the venous blood by the small arachnoid villi and the larger arachnoid granulations.

The total CSF volume contained within the communicating system in adults is approximately 150 mL, with approximately 25% within the ventricular system (Osaka *et al.*, 1980). Production rate of CSF is approximately 20mL per hour, and an estimated 400-500mL of CSF is produced and absorbed daily (Acer *et al.*, 2010). The normal absorption capacity of CSF is approximately 2-4 times the rate of production. The normal CSF pressure is ranged between 65-195mm H_2O in adults while for children younger than 6 years, normal CSF pressure ranges between 10-100 mmH_2O.

Brain ventricles and the CSF have numerous functions. It includes supporting the brain growth during evolution, protecting against external trauma, controlling homeostatic pressure, hormonal as well as signaling mechanisms that involved in the brain function (Cramer *et al.*, 1990).

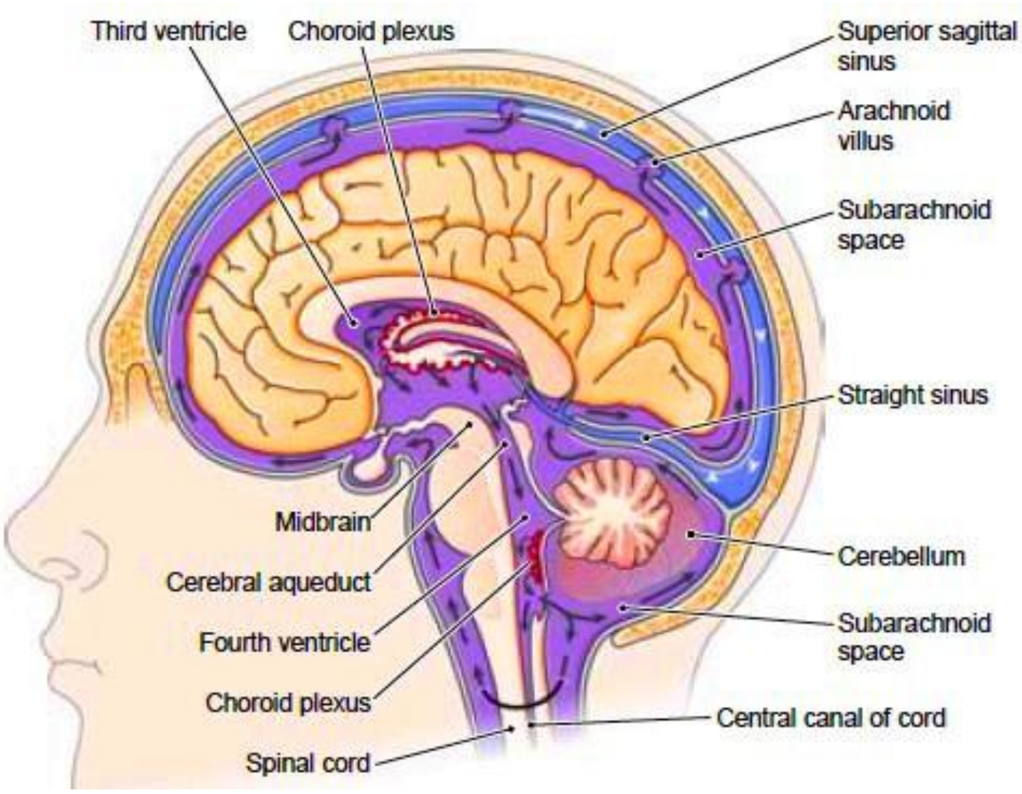


Figure 2.7: CSF flow

Adapted from (Razvanski, 2012)

2.5 DEVELOPMENT OF BRAIN AND THE VENTRICLE

The embryonic human brain originates from a neural plate forms within few weeks of gestational age which undergone neurulation by fourth week of intrauterine life. The neural tube will be divided into anterior and posterior which will form into brain and spinal cord respectively. This anterior part comprises of three brain vesicles (also called as primary embryonic brain vesicles) i.e. prosencephalon, mesencephalon and rhombencephalon (Last and Tompsett, 1953).

The brain has smooth surfaces initially, however by 16 weeks most of the sulci started to develop. This formation of the sulci indicates cortical maturation and is the most important indicator (Levine and Barnes, 1999). Towards end of the normal gestation, the brain growth and gyration proceed rapidly, along with the myelination.

The embryonic brain ventricles lie within the brain vesicles. The neural canal dilates within the prosencephalon, leading to the formation of the lateral ventricles and third ventricle. The cavity of the mesencephalon forms the cerebral aqueduct. The dilation of the neural canal within the rhombencephalon forms the fourth ventricle. During early development, the septum pellucidum is formed by the thinned walls of the two cerebral hemispheres and contains a fluid-filled cavity, which may persist as normal variant (O'Rahilly and Müller, 2006).

Tufts of capillaries invaginate the roofs of prosencephalon and rhombencephalon, forming the choroid plexuses of the ventricles. CSF flows out of the fourth ventricle through the three apertures formed at the roof of the fourth ventricle by week 12 of gestation (Augustine, 2008).

As the brain developing, the ventricles are also expanding massively, with the rate of ventricular volume expansion is faster than the brain growth (Bayer and Altman, 2007) and reach maximum ventricle-to-tissue ratio.

Eventually the ventricle will assume the adult size and configuration around 24 weeks of gestation (Figure 2.8).

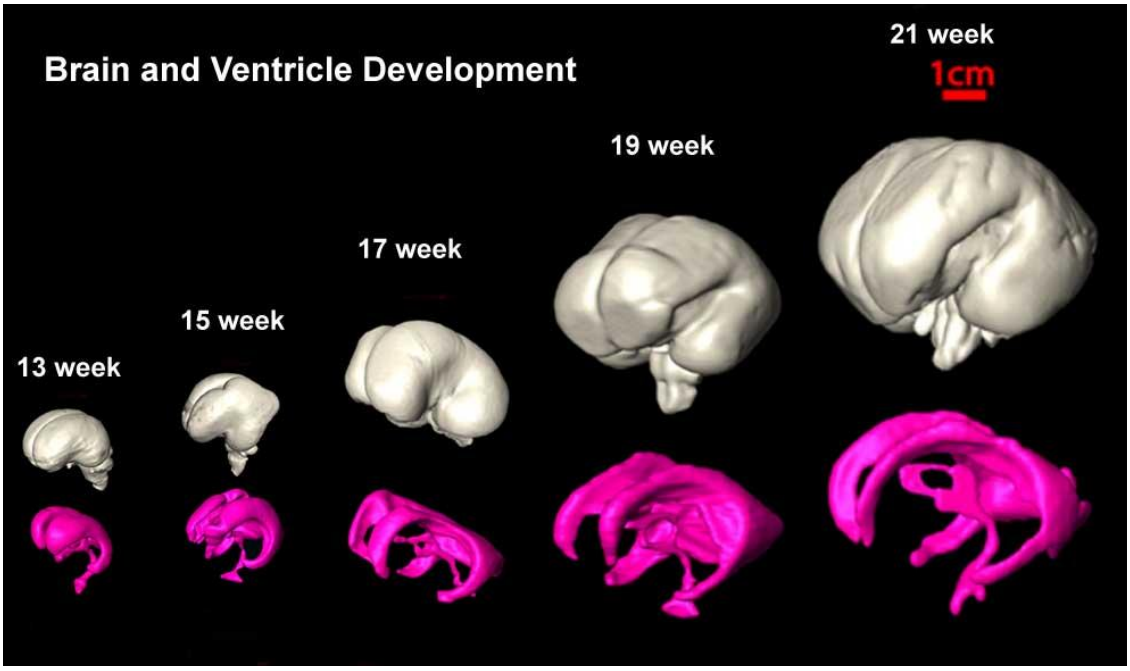


Figure 2.8: Brain and Ventricle Development

Adapted from (Huang *et al.*, 2009)

Relatively rapid brain growth is within the first 2 years of life, by which time it has achieved 80% of its adult weight. By 9 years of age, the brain volume is approximately about 95% of the adult brain volume with the brain of the female child is 93% of the volume of male child (Blatter *et al.*, 1995). Whole brain and intracranial space grew by 25%–27% between early childhood (mean age, 26 months) and adolescence (mean age, 14 years) (Last and Tompsett, 1953). Progressive decline in brain weight begins at about 45 to 50 years of age and reaches its lowest values after age 86 years, by which time the mean brain weight has decreased by about 11% relative to the maximum brain weight attained in young adults (Penn *et al.*, 1978).

2.6 VOLUMETRIC ASSESSMENT OF BRAIN AND VENTRICLES

Multiple studies have been made in the past to establish a relationship between the cerebral ventricles and brain size in normal subjects which were done in certain population. There are multiple methods of brain compartments measurement either by post-mortem study which were done more than 100 years ago and regarded as a gold standard in the past (Woods *et al.*, 1991) or by radiological imaging methods.

The development of computerized axial tomography has enabled us to properly visualize and measure the outlines of the brain and ventricular system as well as identifying any structural abnormalities (Gyldensted, 1977). However there are limitations to do CT studies in normal subjects due to the bone artifacts. Thus the subsequent development of magnetic resonance imaging (MRI) offers great advantages in term of safer human study without radiation exposure and extra benefit of functional study (Reite *et al.*, 2010).

MRI is also more sensitive than CT for better soft tissue contrast with additional multiplanar imaging capabilities. Not surprisingly due to extensive studies done on human brain, few websites are developed solely to archive this volumetric data for example "Internet Brain Volume Database" (Kennedy *et al.*, 2003), MRI-based Volumetry of Head compartments: Normative Values of Healthy Adults (Wyper *et al.*, 1979) and "Open Access Series of Imaging Studies (OASIS): Cross-sectional MRI data in young, middle aged, non-demented, and demented older adults" (Marcus *et al.*, 2007).

Recent studies using MRI as the tool not only focusing on normal cerebral development, as well as ageing process in normal subjects, but also in studying pathological changes that took place in psychiatric and neuromedical disorders, and correlations are made with age and gender (Caviness *et al.*, 1992; Buchsbaum *et al.*, 1997; Ott *et al.*, 2010).

2.7 TOTAL VENTRICULAR VOLUME IN NORMAL POPULATION

The evaluation of cerebral ventricles in the humans has great importance similar to the rest of the brain compartments, especially in pediatrics group and neurological pathology. Accurate measurements of the ventricles are necessary to aid in diagnosis and for further management plan of the patients. There are multiple modalities can be done in assessment of the ventricles, for example by the usage of pneumoencephalogram in the good old days and either CT scan or MRI in the recent studies.

Different methods are applicable in measuring the total ventricular volume either by means of CT scan, MRI or radioisotope ventriculography. The easiest, simple and direct method is by manually by multiplying the summation of the ventricular areas in all slices with the slice thickness. Another method is by intraventricular injection of radioisotope which offers a potentially more accurate volume determination because of his higher signal-to-noise ratio however requires intraventricular catheterization (Wyper *et al.*, 1979).

Recent studies have demonstrated that the volume of organs or structures can be obtained using Cavalieri principle of stereological approaches (Roberts *et al.*, 1993; Cruz-Orive, 1997). In the Cavalieri principle the sum of the sectional surface area of the slices is multiplied by the section thickness and the volume is estimated. The sectional surface area of the slabs could be assessed either by point counting and planimetry method (Elfaki *et al.*, 2011). Of these two, planimetry is the most commonly used technique for estimation of volume, which involves manually tracing the boundaries of objects of interest on images of sections. This method was proven to be accurate however time consuming compared to point counting (Acer *et al.*, 2010).

A lot of studies have measured the lateral ventricles, third and fourth ventricles separately and made correlation with gender and age group (Gyldensted, 1977; Yoshii *et al.*, 1988; Cramer *et al.*, 1990; Chung *et al.*, 2006; Zauhair A. Jaumah* MbchB, 2009). The normal total ventricular volume in the literature varies markedly, ranging from 7-70cm^3 (Cramer *et al.*, 1990; Akdogan *et al.*, 2010). Earlier studies using ventricular casts revealed the total ventricular volume ranging of 16.8cm^3 to 17.8cm^3 (Last and Tompsett, 1953). In Korean population, the ventricular volumes in second and fourth decades are 16.2cm^3 and 24.9cm^3 respectively. However in general, these studies do not find any specific gender related difference in total ventricular volume.

The volume of the lateral ventricles is known to increase with age. The left ventricle was shown to be larger on the average than the right in either sex (Last and Tompsett, 1953), while both lateral ventricles were larger in the male. The mean value of third and fourth ventricles volume in many studies revealed 0.5cm^3 - 1.0cm^3 and 0.9cm^3 - 1.6cm^3 respectively (Cramer *et al.*, 1990; Aziz *et al.*, 2004).

2.8 TOTAL BRAIN VOLUME IN NORMAL POPULATION

Many studies had been performed overseas which provide normative data of total brain volume for the population (Filipek *et al.*, 1994; Blatter *et al.*, 1995; Kruggel, 2006; Marcus *et al.*, 2007). Several studies have investigated age-associated changes in different gender. Establishment of quantitative normative data of the normal ageing process is a prerequisite for any understanding of reduction, either diffuse or focal, in brain tissue. Recent study has demonstrated that decreasing brain volume with age is rather a diffuse phenomenon affecting different brain regions (Gomori *et al.*, 1984). For example a CT study done by Takeda and Matsuzawa reported both CSF and a "brain atrophy index" are increased with age in normal male and female subjects (Takeda and Matsuzawa, 1985).

MRI has been widely used for volumetric measurements of brain volume and its substructures. In general, total brain volume is estimated averaging 1100-1200ml in Western population, however another study done in Florida estimates mean total brain volume was 2032cm^3 (± 216) for men and 1813cm^3 (± 204) for women in total of 58 subjects aged 21-81 (Yoshii *et al.*, 1988) which is higher than the rest. By using MRI, the mean brain volume in 49 healthy yield in Boston's participants was 1227cm^3 (± 135) and was significantly larger in men (1302 ± 112 cm^3) than in women (1143 ± 106 cm^3) (Kruggel, 2006). This value is not much different compared to the recent study published that the total brain volume of female is 1365cm^3 (± 102) and 1464cm^3 (± 94) in male (Blatter *et al.*, 1995).

Based on population, several studies have been done to ascertain the normal total brain volume by using MRI or CT scan which are well correlated with the previous autopsy studies. For example a study done among Manhattan residence revealed that Hispanic and African American participants had 2.8% and 1.6% larger relative brain volumes than the white subjects, respectively (Takeda and Matsuzawa, 1985). However to this date, no study ever been done in assessing the normal value of total brain volume in Asian.

2.9 VENTRICULAR BRAIN RATIO

The ventricular brain ratio (VBR) is introduced by Synek *et al*. (1976) shortly after the advent of computed tomography (CT) which would replace the linear measurements in use with pneumoencephalography in measuring the ventricular size (Synek and Reuben, 1976). Originally the VBR used the planimetrically measured area of the lateral ventricles on the axial slice where they are largest as the numerator of the ratio, and the area of the whole brain on the same slice as the denominator. The latter measurement was used to correct for systematic variations in ventricular size due to variations in the brain size.

The value of the VBR seemed established later on after subsequent studies done and reported that the VBRs of a series of patients with enlarged ventricles correlated much more highly with an independently derived volume measurement than did previously described linear measurements (Penn *et al.*, 1978). Subsequently, the majority of CT studies of ventricular size in psychiatric and neurological disorders have used the VBR (Woods *et al.*, 1991).

The formula in calculating the VBR is as below (Synek and Reuben, 1976):

$$VBR\% = \frac{\text{Ventricular cross-sectional area}}{\text{Brain cross-sectional area}} \times 100\%$$

VBR is commonly calculated in quantitative neuroimaging studies by several techniques either planimetric or automated and by a number of investigators (Table 3) (Zatz and Jernigan, 1983). The VBR value, brain and ventricular volumes are well related and are significant as demonstrated in the previous studies.

The normal VBR in previous studies is approximately 5 in normal, 7 in borderline cases and greater than 10 in abnormal conditions (Barron *et al.*, 1976). It reflects the association between the ventricle and the brain size. In Iranian population, there is no significant difference in between male and female (Zauhair A. Jaumah* MbchB, 2009) which are contradicts to the previous report stated that female has lower VBR than male (Williams *et al.*, 1985).

In term of age, VBR value remains relatively stable until 60 years old whereby afterwards it increased in age-dependent manner (Pearlson *et al.*, 1989). In a recent study in Iraqian population, VBR is slightly increased after 49 years old and at age 59 there was sharp increase in the VBR in both sexes (Zauhair A. Jaumah* MbchB, 2009).

2.10 CLINICAL SIGNIFICANCE OF TOTAL VENTRICULAR VOLUME, TOTAL BRAIN VOLUME AND VENTRICULAR BRAIN RATIO

2.10.1 Overview

In normal aging process, studies have found that multiple physiological processes occurring in the brain compartment. It is well established that the brain's volume decreases with age (Coffey *et al.*, 1993). Brain atrophy as a normal degenerative process starts after the age of 40 years and start early in deep structures of the brain before cortex. Aging was associated with more pronounced sulcal atrophy.

In the magnetic resonance imaging study, age-related volume loss was significantly greater in men than women in whole brain and frontal and temporal lobes, whereas it was greater in women than men in hippocampus and parietal lobes. These gender differences suggest that female sex hormones may protect the brain from atrophy associated with aging (Condon *et al.*, 1986).

Lateral ventricular volume is one of the most common measurements in volumetric assessment of the brain. Enlargement of the ventricular system is nonspecific and generally regarded as an indirect measure of white matter loss, because much of the ventricular systems surrounded by white matter structures (Coffey *et al.*, 1993; Blatter *et al.*, 1995).

Scientific study of CT scans of the ventricles in the late 1970s has revolutionized the study of mental disorder. Researchers have found that individuals with schizophrenia had enlarged ventricles compared to the healthy subjects (Weinberger *et al.*, 1979; Rabins *et al.*, 1987; Kemali *et al.*, 1989).

There are still debates whether the enlargement of the ventricles is a cause or a result of schizophrenia, till now it has not yet been ascertained. The enlarged ventricles are also found in various other types of organic dementia (Jacobs *et al.*, 1978). In fact, ventricle volumes have been found to be mainly explained by environmental factors and to be extremely diverse between individuals.

2.10.2 Schizophrenia

In schizophrenia, large numbers of researchers has agreed on the finding that there are global brain volume differences in schizophrenia. Meta-analysis study stated that cerebral volume was lower (98%) and total ventricular volume was higher (126%) in patients with schizophrenia than in comparison subjects (Wright *et al.*, 2000). They have found that absolute volumes of all ventricular subdivisions were also greater in patients with schizophrenia.

Absolute whole brain volume was lower in the schizophrenia patients than the comparison subjects (98%). Relative volumes of whole brain gray matter and white matter were approximately in line with the global difference: 98% for gray matter and 99% for white matter. Relative to the global reduction of cerebral volume, there were no hemispheric differences (left 100%, right 100%). The frontal lobes were relatively small (left 98%, right 98%), but the temporal lobe volume differences were in line with the whole brain differences (left 100%, right 100%). Medial temporal lobe structures were relatively small however relative volumes of basal ganglia structures were higher in the subjects with schizophrenia.

For the majority of structures, there was little evidence for a major gender effect modulating the volume differences in schizophrenia.

2.10.3 Bipolar disorders

Despite 25 years of structural neuroimaging of patients with bipolar disorder there remains considerable debate over the sensitivity and specificity of structural brain changes in bipolar disorder. In bipolar disorder, mild ventricular enlargement and the presence of white matter hyper-intensities are among the most consistently reported abnormalities (McDonald *et al.*, 2004). Bipolar disorder is associated with global and prefrontal volumetric brain reductions, enlarged lateral ventricles and an enlarged globus pallidus (Kempton *et al.*, 2008). However compared with individuals with schizophrenia, people with bipolar disorder has a reduced right amygdala volume and comparatively smaller lateral ventricles (Arnone *et al.*, 2009).

2.10.4 Panic disorders

The VBR is not increased in panic disorder (Uhde and Kellner, 1987) however there was a significant association between VBR and duration of benzodiazepine use. In this study, the ventricular size of panic disorder patients falls well within the normal range compared with reported values of mean VBR in normal control groups in the literature (Weinberger *et al.*, 1979).

2.10.5 Depression

In a study done by Uhde *et al* (1987), there was association between ventricular size and degree of cognitive impairment in affectively ill patients (Uhde and Kellner, 1987) and strong correlation between VBR and the age of patients. However in other studies, no consistent positive correlation between age and VBR in normal control populations (Weinberger *et al.*, 1979; Jacoby and Levy, 1980), despite the fact that it is generally agreed that ventricular size increases with age group (Gyldensted, 1977).

3 OBJECTIVES

3.1 GENERAL OBJECTIVE

To determine the total ventricular volume and total brain volume in normal Kelantan adult aged 40 and above.

3.2 SPECIFIC OBJECTIVES

1. To determine the mean of total ventricular volume (TVV) and total brain volume (TBV) in normal Kelantan adult population.
2. To compare the mean of the total ventricular volume (TVV) and total brain volume (TBV) between male and female in normal Kelantan adult population.
3. To determine the mean ventricular brain ratio (VBR) in normal Kelantan adult population.
4. To compare the mean of ventricular brain ratio (VBR) between male and female in normal Kelantan adult population.

3.3 RESEARCH HYPOTHESES

1. There is significant mean difference of TVV between male and female in normal Kelantan adult population.
2. There is significant mean difference of TBV between male and female in normal Kelantan adult population.

3. There is significant mean difference of VBR in between male and female in normal Kelantan adult population.

4 METHODOLOGY

4.1 STUDY DESIGN

This was a cross-sectional study of 58 subjects in Kelantan population with normal MR brain done in Department of Radiology, Hospital Universiti Sains Malaysia from May 2008 till November 2009. The ethical approval for this study was obtained on 26th September 2013 with Reference number: USM/JEPeM/2013(143).

4.2 POPULATION AND SAMPLE

4.2.1 Reference Population

All adults in Kelantan whom had undergone MRI in Hospital Universiti Sains Malaysia.

4.2.2 Source of Population

All adults in Kelantan whom had undergone MRI brain in Hospital Universiti Sains Malaysia with images stored in PACS.

4.2.3 Inclusion Criteria

1. Age 40 years old and above.
2. Normal MRI brain findings or patient with age related changes who has no significant clinical presentation.

4.2.4 Exclusion Criteria

1. Focal neurological deficit
2. History of psychological/psychiatric illness
3. History of dementia
4. History of epilepsy
5. History of significant head trauma (documented intracranial hemorrhage)
6. History of alcohol abuse

4.2.5 Sampling Method

Convenient sampling is used in this study.

4.2.6 SAMPLE SIZE CALCULATION

For objective 1

The sample size was calculated based on previous study by Akdogan et al (2010). Sample size calculation was done using single mean formula.

a) To determine the total ventricular volume (TVV) in normal Kelantan adult population**.**

N = sample size

σ = 13 [standard deviation of TVV].

z = 1.96 [the percentile of the normal distribution corresponding to the 95% confidence interval]

Δ = 4.0 cm^3 [the estimated difference from population mean]

$$N = \left\{\frac{z \times \sigma}{\Delta}\right\}^2$$

$$= \left\{\frac{1.96 \times 13}{4}\right\}^2$$

$$= 41$$

The total sample size was 45 patients (taking the non-response rate of 10%).

b) To determine the total brain volume (TBV) in normal Kelantan adult population.

N = sample size

σ = 185 [standard deviation of TVV].

z = 1.96 [the percentile of the normal distribution corresponding to the 95% confidence interval]

Δ = 50 cm^3 [the estimated difference from population mean]

$$N = \left\{ \frac{z \times \sigma}{\Delta} \right\}^2$$

$$= \left\{ \frac{1.96 \times 185}{50} \right\}^2$$

$$= 53$$

The total sample size was 58 patients (taking the non-response rate of 10%)

For objective 2

The sample size was calculated based on previous study by Blatter et al (1995). Sample size calculation was done using two means formula.

a) To compare the mean of the total ventricular volume (TVV) between male and female in normal Kelantan adult population.

The mean of total ventricular volume was 16.95cm^3 and standard deviation; σ was 2.38cm^3 for female. The mean and standard deviation for male were 13.76cm^3 and 3.74cm^3 respectively (Blatter *et al.*, 1995).

Z_α = 1.96 for α = 0.05

$Z_{1-\beta}$ = 0.8 for 80% power

Expected detectable difference between male and female, Δ **=** 3cm^3

$$\text{Sample Size, } N = \frac{2\sigma^2 (Z_\alpha + Z_\beta)^2}{\Delta^2}$$

$$= \frac{2\,(37.4)^2\,(1.96 + 0.8)^2}{(30)^2}$$

$$= 23$$

Resulting in 23 patients in each group, total sample is 46.

With expected a 10% non-response rate, sample size was 46 + (46 x 0.1) = 51 patients.

b) To compare the mean of the total brain volume (TBV) between male and female in normal Kelantan adult population.

The mean of total brain volume was 1177.55cm^3 and standard deviation; σ was 184.95cm^3 for female. The mean and standard deviation for male were 1343.01cm^3 and 179.62cm^3 respectively.

$Z_{\alpha} = 1.96$ for $\alpha = 0.05$

$Z_{1-\beta} = 0.8$ for 80% power

Expected detectable difference between male and female, $\Delta = 160cm^3$

$$\text{Sample Size,} \quad N = \frac{2\sigma^2 (Z_{\alpha} + Z_{\beta})^2}{\Delta^2}$$

$$= \frac{2\,(184.95)^2\,(1.96 + 0.8)^2}{(160)^2}$$

$$= 22$$

Resulting in 22 patients in each group, total sample is 44.

With expected a 10% non-response rate, sample size was 44 + (44 x 0.1) = 48 patients.

For objective 3

To determine the mean of ventricular brain ratio (VBR) in normal Kelantan adult population, single mean formula was used. With σ of 0.88, z = 1.96 and Δ = 0.25 [the estimated difference from population mean] (Blatter *et al.*, 1995), calculated sample size is 48.

With expected a 10% non-response rate, sample size was 53 patients.

For objective 4

To compare the mean of ventricular brain ratio (VBR) between male and female in normal Kelantan adult population, two means formula was used. The mean of ventricular brain ratio was 1.27 and standard deviation; σ was 0.28 for female. The mean and standard deviation for male were 1.52 and 0.43 respectively (Blatter *et al.*, 1995).

$Z_{\alpha} = 1.96$ for $\alpha = 0.05$

$Z_{1-\beta} = 0.8$ for 80% power

Expected detectable difference between male and female, $\Delta = 0.3$

$$\text{Sample Size,} \quad N = \frac{2\sigma^2 (Z_{\alpha} + Z_{\beta})^2}{\Delta^2}$$

$$= \frac{2(0.43)^2 (1.96 + 0.8)^2}{(0.3)^2}$$

$$= 32$$

Resulting in 32 patients in each group, total sample is 64.

With expected a 10% non-response rate, sample size was 64 + (64 x 0.1) = 70, which is the largest sample size calculated for every objectives.

4.3 RESEARCH TOOLS

4.3.1 MRI Image Acquisition

All brain MRI examinations of the participants were performed using a 1.0 Tesla Signa Horizon LX supplied by General Electric Company. Scout sequences were obtained to ensure proper positioning of the patient's head. The MR brain protocol series were performed in Sagittal T1 5mm thickness, 2mm gap and Axial T1, T2 and FLAIR 5mm thickness, 2mm gap with tilt.

As for the MRI sequence parameters are as tabulated (Table 4.1). The sagittal scanning were performed from right to left giving result of first slice as on right side and last slice was on the left side of the subject's cranium.

Table 4.1: Parameters of MRI Sequences

Sequences	TE	TR	Field of view	NEX
T1 weighted	11	420	20x20	2.0
T2 weighted	79.3	4020	20x20	2.0
FLAIR	147	9002	20x20	2.0

All patients' data collection was taken from archive images retrieved from Picture Archiving and Communications System (PACS). These images were transferred into the OsiriX system 3.2.1 version in an Apple Mac Pro Personal Computer (PC) with 2.66 GHz Dual Core Intel Xeon processor as the diagnostic viewing workstation. The monitor used for this workstation was Apple Cinema

High Definition (HD) Display (23” Flat Panel) with optimum resolution of 1920 x 1200.

OsiriX is an image processing application dedicated to Digital Imaging and Communication in Medicine (DICOM) images produced for medical equipment (MRI, CT, PET, PET-CT etc.). OsiriX is complementary to existing viewers. It is a multidimensional image navigation and display software was designed for display and interpretation of large sets of multidimensional and multimodality images. OsiriX is able to receive images transferred by DICOM communication protocol from any PACS or medical imaging modality. The processing and image rendering tools of the software are based on the open-source libraries Insight Segmentation and Registration Toolkit (ITK) and Visualization Toolkit (VTK). This ensures that all new developments in image processing that could emerge from other academic institutions using these libraries can be directly ported to the OsiriX program.

OsiriX is provided free of charge under the GNU’s Not Unix! Operating System (GNU) open-source licensing agreement. The usage of software for diagnostic or therapeutic purposes is regulated by authorities. The OsiriX has certified version available which is labeled as Medical Device class II United States Food and Drug Administration (FDA, USA) and class IIb "*Communauté Européenne*" mark (CE-Label, Europe) for clinical use.

4.4 SETTING

4.4.1 MR Volumetry measurement of Total Ventricular Volume

All measurements were performed using OsiriX software that available in Apple computer in Department of Radiology, HUSM. Volumetric analysis is performed by a single observer undergone validation test by a well-trained intra-observer Radiologist.

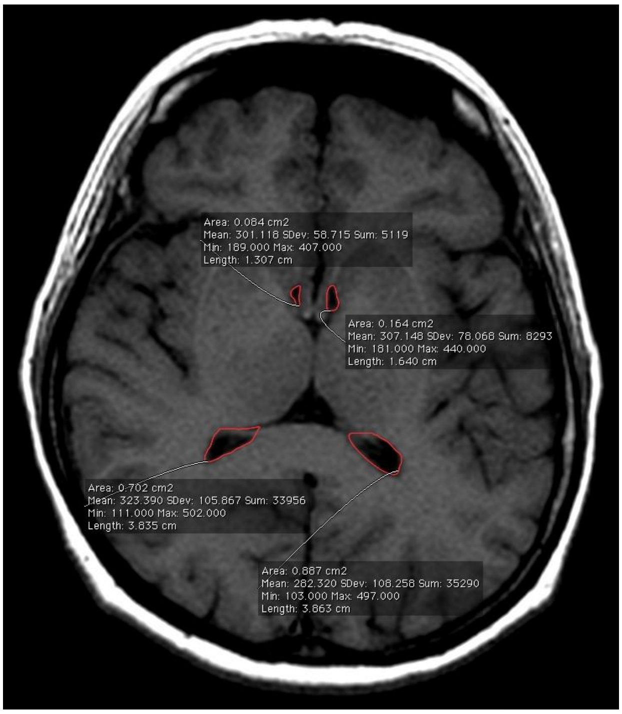
In all subjects, axial slices in T1 weighted images were used for analysis. All the ventricles' outline were manually traced and measured. The brightness of the image was adjusted to improve the visual clarity of the boundary of the ventricles. For lateral ventricle volumes, measurement was started in the most superior slice showing one or both lateral ventricles and ended in the most inferior slice on which the temporal horn was still visible in one or both hemispheres. An arbitrary line was made whenever the choroid plexus obscuring the lateral ventricular outline. Similar principle applied to both third and fourth ventricles. Corresponding sagittal images were used to ensure the boundaries of superior and inferior limit of the 3^{rd} and 4^{th} ventricles.

Measurements were made three times for each slice in order to get an average measurement. A difference of $0.05cm^2$ between three times measurements was allowed. The average measurement for each slice will be summed together to get the total area in centimeter square. Volumes of all ventricles will be calculated by multiplying the total area of ventricles, in the unit of square centimeters (cm^2) with 0.7 cm (corresponding to the sum of the gap between the slices and the slice thickness). By using this method, the TVV was then obtained, in the unit of centimeters cubic (cm^3). Contours of all the ventricles were shown in Figure 4.1-4.3.

(A)

(B)

Figure 4.1: Anatomical outline of lateral ventricles on T1-Weighted image. (A) Highest level of lateral ventricle. (B) Widest level of lateral ventricles (including the choroid plexus)

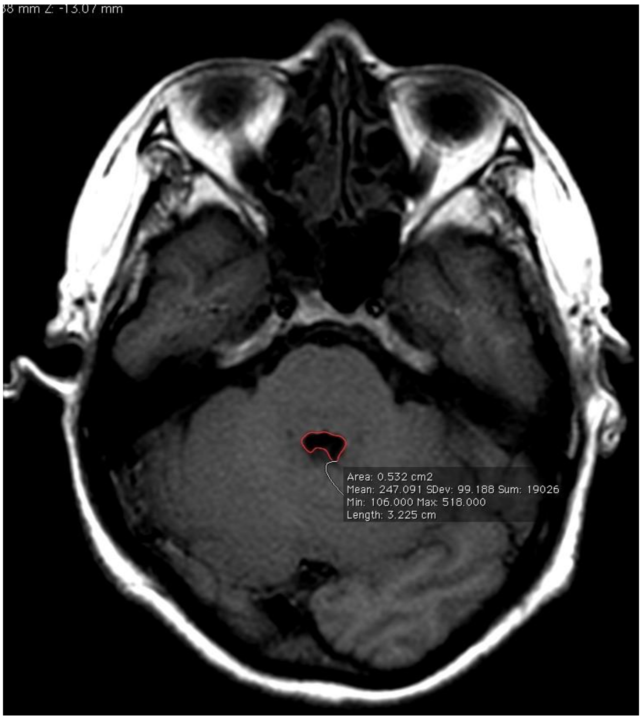


(A)

(B)

Figure 4.2: Anatomical outline of frontal horn, third ventricle and occipital horn on T1-Weighted Image. (A) Frontal horn (superior part), third ventricle (middle) and occipital horn (inferior part). (B) Widest level of third ventricle. (note that occipital horn also visible bilaterally)

(A)



(B)

Figure 4.3: Anatomical outline of fourth ventricle on T1-Weighted image. (A) Superior part of fourth ventricle (almost aqueduct of Sylvius). (B) Widest fourth ventricle level

(C)

Figure 4.3: Anatomical outline of fourth ventricle on T1-Weighted image. (C) Inferior-most part of fourth ventricle.

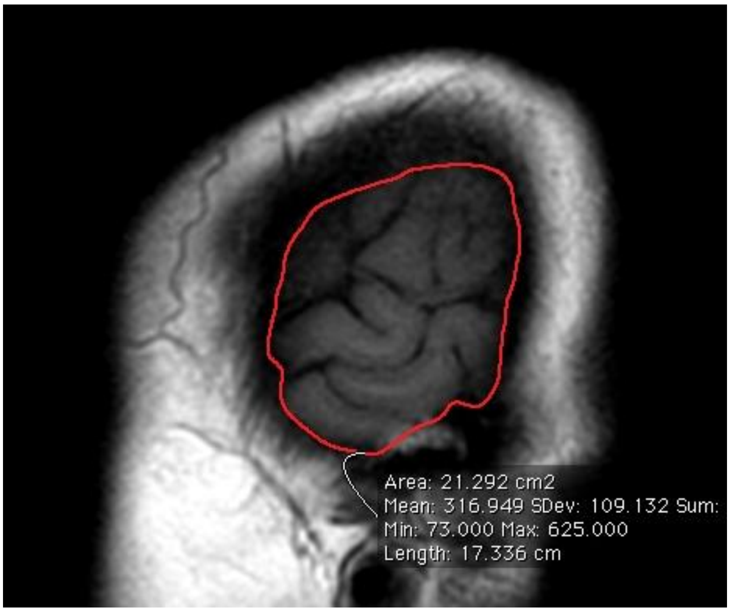
4.4.2 MR Volumetry measurement of Total Brain Volume

For total brain volume measurement, manual tracing performed by delineating the brain surface from the dura. The brightness of the image was adjusted to improve the visual clarity of the boundary of the brain.The measurements were done on alternate slice of the sagittal T1 images starting from first slice (slice 1, 3, 5, 7...19) based on previous study (Musa, 2010). In this study, it was proven that the alternate slice volumetric measurement method in which data were measured in alternate slices are equivalent to the standard volumetric measurement method in which data for each slice were calculated. Figure 4.4 shows the contours of the brain surface in alternate sagittal slices.

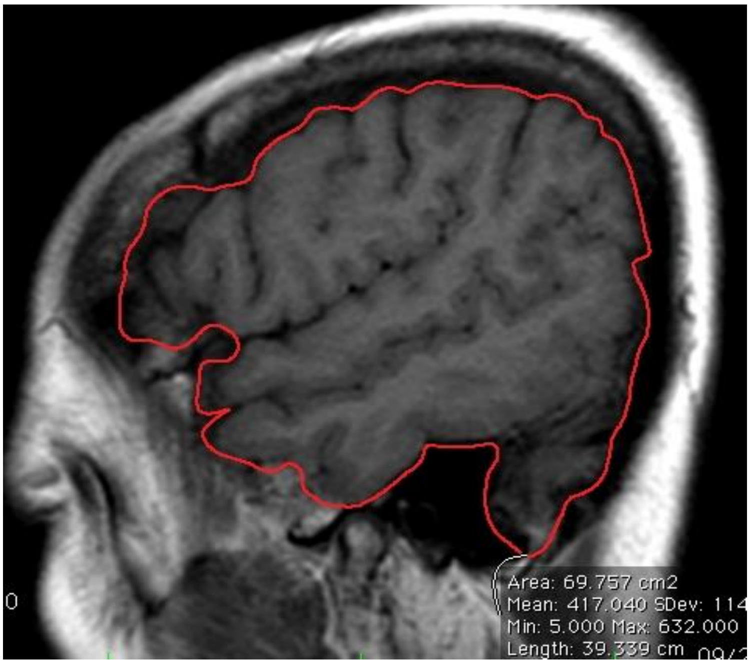
Measurements were made in three times for each measured slice in order to get an average measurement. A difference of 5.0cm^2 between three times measurements was allowed. The average measurement for each slice will be summed together to get the total area in centimeter square. Total brain volume is measured by total surface areas of these odd numbers of slices (in cm^2) multiply by 1.4cm (2 x slice thickness). Formula use is as below:

$$TBV = \text{Total slice area} \times 1.4\text{cm}$$

VBR was calculated by dividing the total ventricular volume by the total brain volume and multiplied by 100 to get the percentage VBR (Synek and Reuben, 1976).

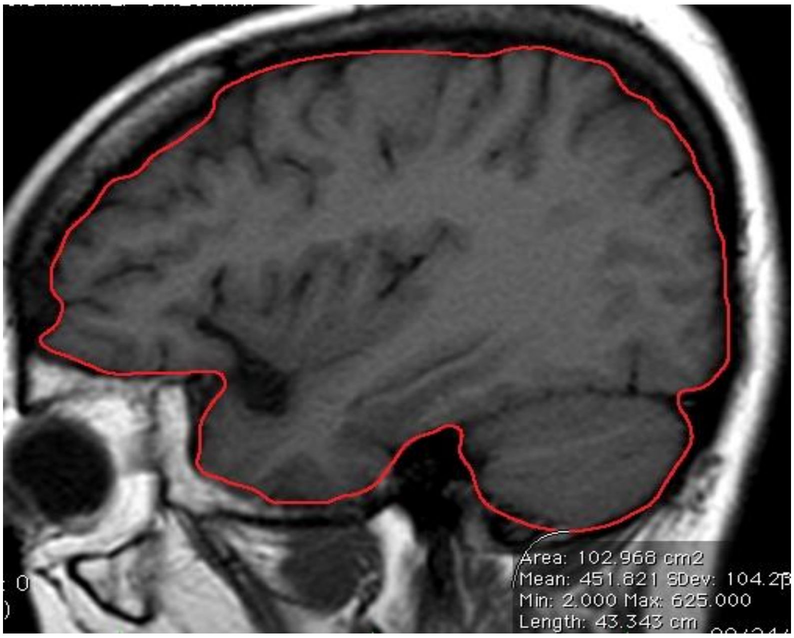


(A) Slice 1

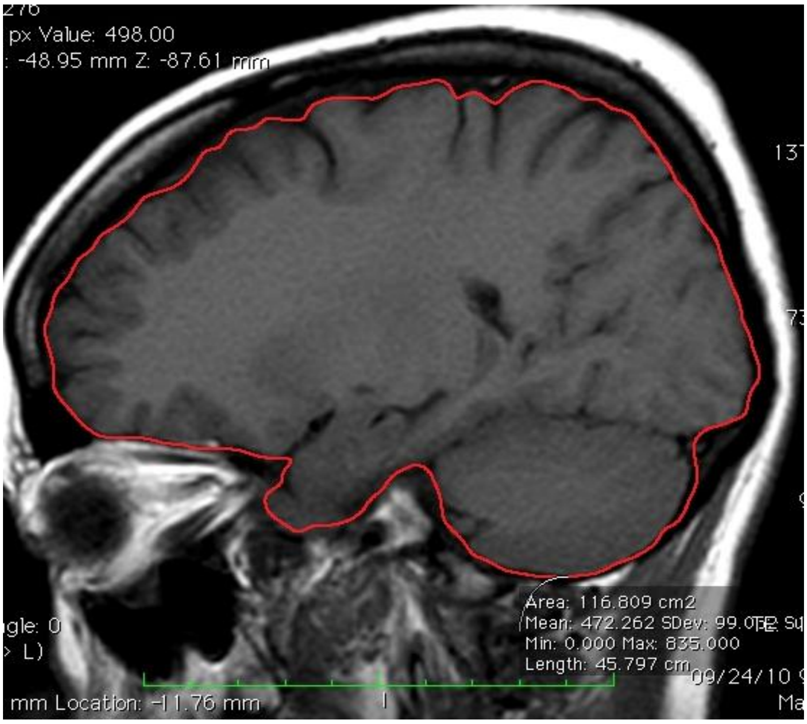


(B) Slice 3

Figure 4.4: Sagittal T1-Weighted images showing alternate slices of brain.

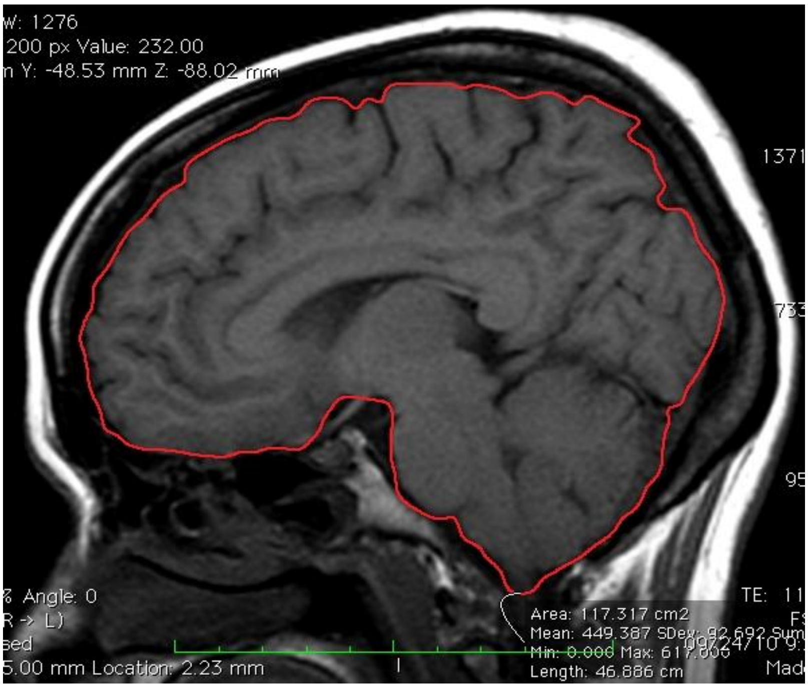


(C) Slice 5

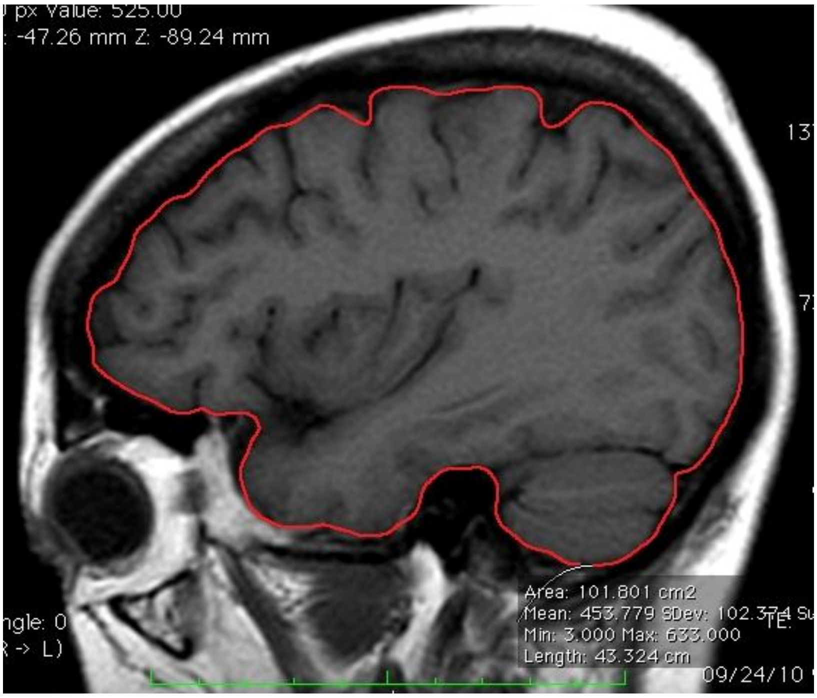


(D) Slice 7

Figure 4.4 continued: Sagittal T1-Weighted images showing alternate slices of brain.

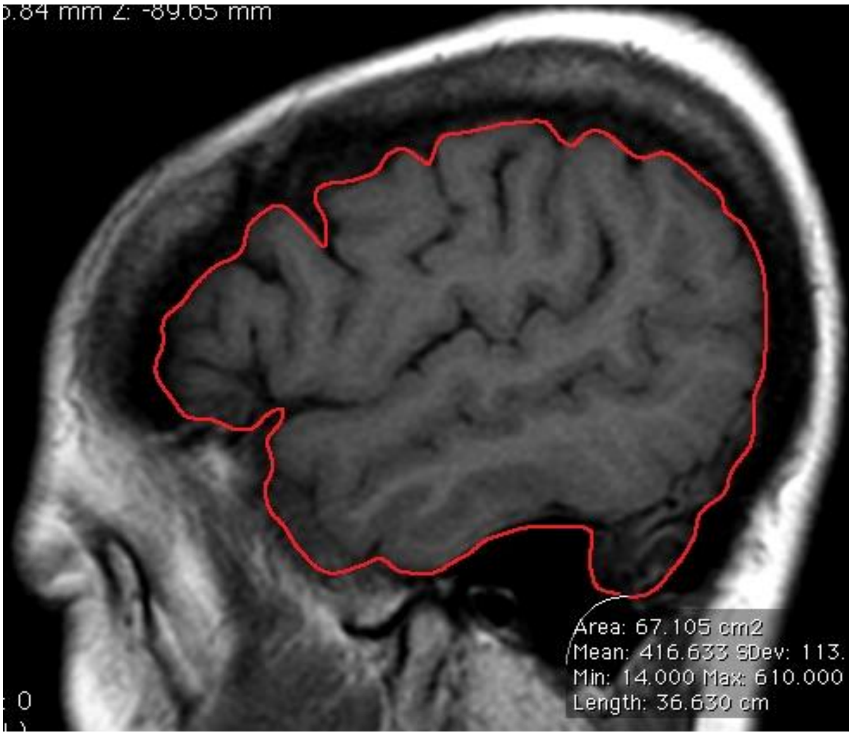


(E) Slice 9



(F) Slice 11

Figure 4.4 continued: Sagittal T1-Weighted images showing alternate slices of brain.



(G) Slice 13

(H) Slice 15

Figure 4.4 continued: Sagittal T1-Weighted images showing alternate slices of brain.

4.5 VALIDATION OF TECHNIQUE

Validation test was performed with the radiologist. From total 58 subjects, 6 samples (10% of total) were randomly selected and analyzed by the radiologist and the researcher. Interrater reliability was then calculated using Intraclass correlation (Table 4.2). Both raters were blinded to the subject age and gender.

Table 4.2: Interrater reliability (Intraclass coefficients)

	Intraclass Correlation[b] (single measure)	95% Confidence Interval	
Total ventricular volume	0.995[a]	0.902,	0.999
Total brain volume	0.983[a]	0.886,	0.998

Interrater correlation was obtained from 10% of total sample size analyzed independently by two different raters.

Two-way mixed effects model where people effect are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.
b. Type A intraclass correlation coefficients using an absolute agreement definition.
c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

**A result of 0.8 and more validate rater's measurement.*

4.6 DATA COLLECTION

All data were entered in patient's data sheet.

Variables recorded were includes:

i) Demographic data; age, gender

ii) Lateral ventricle, third and fourth ventricle volume,

iii) Total ventricular volume

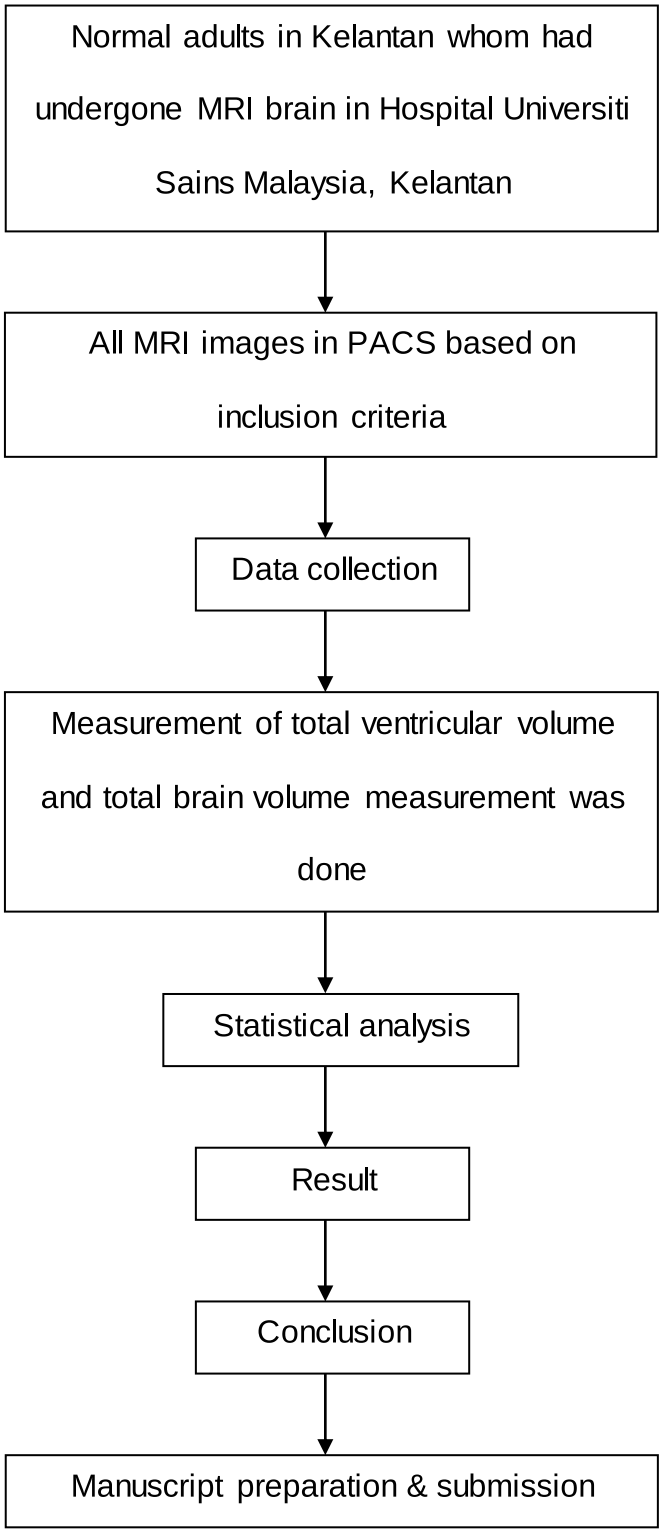
iv) Brain volume

4.7 STATISTICAL ANALYSIS

Data entry and analysis were performed using Statistical Package for Social Sciences (SPSS version 20) software program. Socio-demographic data was analyzed using descriptive analysis where tabulation and graphical analysis were performed.

The volumes of ventricle and brain were analyzed using paired t-test. Independent t-test was used to analyze ventricular volume and brain volume of both male and female. P value of less than 0.05 ($p<0.05$) was taken as significant. Results were expressed as mean ± standard deviation (SD).

4.8 FLOW CHART OF RESEARCH DESIGN



5 RESULTS

5.1 DEMOGRAPHIC CHARACTERISTIC

A total of 58 healthy adult Malays were included in this study with response rate of 83.0% due to pre-existing sample size limitation of adult more than 40 years of age.

All the participants included are 40 years old and above (up to 77 years old) with mean age (SD) of 56.40 (± 8.28) years. The sample was almost equally distributed between sex groups. (Table 5.1 and Figure 5.1)

Table 5.1: Demographic characteristic of study participants

Gender	Frequency	Percentage
Male	27	46.6
Female	31	53.4
Total	58	100.0

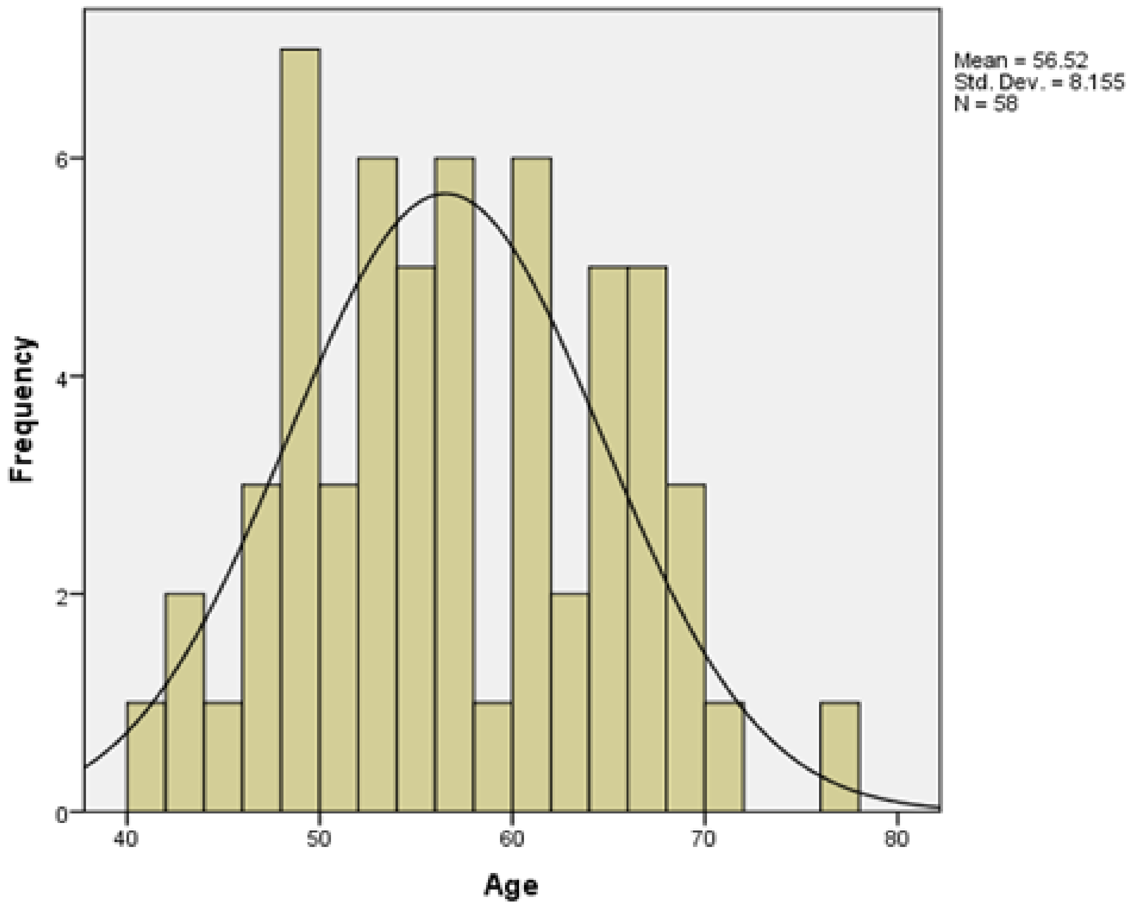


Figure 5.1: Age distribution of study participants.

5.2 MEAN TOTAL VENTRICULAR VOLUME

Mean total ventricular volume (TVV) for all participants was 21.67cm^3 (±12.82cm^3) (Table 5.2 and Figure 5.2). The mean TVV was ranging from 4.70cm^3 to 74.95cm^3. The mean TVV was 28.14cm^3 (± 15.61) and 16.02cm^3 (± 5.50) for male and females, respectively. There is significant difference of mean TVV between the gender (*p* value <0.001) (Table 5.3).

5.3 MEAN TOTAL BRAIN VOLUME

Mean total brain volume for all participants was 1245.29cm^3 (± 125.34) (Table 5.4). The minimum total brain volume obtained was 986.38cm^3 while the maximum total brain volume was 1594.99cm^3. The mean total brain volume was 1338.05cm^3 (± 91.96) for male and 1164.49cm^3 (± 89.61) for female. There is no significant difference of mean TBV between male and female subjects (*p* value >0.05) (Table 5.5).

5.4 VENTRICULAR BRAIN RATIO (VBR)

Total ventricular volume to total brain volume ratio was calculated. Mean total ventricular to brain ratio (in percentage) for all subjects was 1.71 (± 0.89) (Table 5.6). Maximum VBR was 5.66 while the minimum VBR was 0.39. Mean VBR for male subjects was 2.09 (± 1.11) and 1.37 (± 0.44) for female. There is significant difference of mean VBR between the male and female subjects (*p* value <0.05) (Table 5.7).

Table 5.2: Mean total ventricular volume in all subjects

Gender	Mean	Std. Deviation	Minimum	Maximum	95% CI
Male	28.15	15.61	8.11	74.95	21.97,34.32
Female	16.02	5.50	4.70	30.47	14.00,18.04
Total	21.67	12.82	4.70	74.95	

*t-test for two independent sample

Table 5.3: Comparison of mean TVV between male and female subjects

Variable	Mean (SD)	Mean difference (95% CI) Min, max	*t* statistic (df)	*p* value*
TVV (cm^3)	28.15	(12.13)	3.84	0.001
Male	(15.61)	5.68, 18.57	(31.60)	
TVV (cm^3)	16.02			
Female	(5.50)			

*t-test for two independent sample

Table 5.4: Mean total brain volume in all subjects

Gender	Mean	Std. Deviation	Minimum	Maximum	95% CI
Male	1338.12	91.97	1132.42	1594.99	1301.74, 1374.51
Female	1164.49	89.61	986.38	1344.49	1131.62, 1197.37
Total	1245.29	125.34	986.38	1594.99	

**t*-test for two independent sample

Table 5.5: Comparison of mean TBV between male and female subjects

Variable	Mean (SD)	Mean difference (95% CI) Min, max	*t* statistic (df)	*p* value*
Male TBV (cm^3)	1338.12 (91.97)	(173.63) 125.79, 221.47	7.27 (56.0)	0.712
Female TBV (cm^3)	1164.49 (89.61)			

**t*-test for two independent sample

Table 5.6: Mean ventricle brain ratio (VBR) in all subjects

Gender	Mean	Std. Deviation	Minimum	Maximum	95% CI
Male	2.09	1.11	0.72	5.66	1.65, 2.53
Female	1.37	0.44	0.39	2.68	1.21, 1.54
Total	1.71	0.89	0.39	5.66	

**t*-test for two independent sample

Table 5.7: Comparison of mean VBR between male and female subjects

Variable	Male Mean (SD)	Female Mean (SD)	Mean difference (95% CI) Min, max	*t* statistic (df)	*p* value*
VBR (%)	2.09 (1.11)	1.37 (0.44)	0.716 (0.282,1.151)	3.301 (56)	0.002

**t*-test for two independent sample

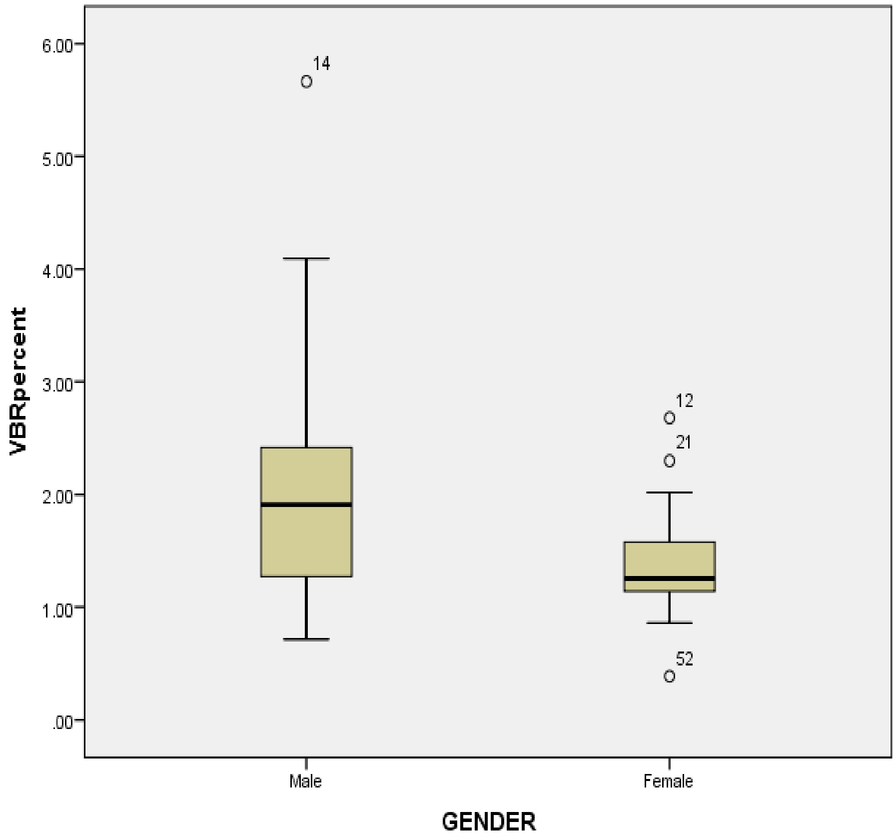


Figure 5.2: Ventricle brain ratio for male and female

6 DISCUSSION

6.1 DEMOGRAPHIC CHARACTERISTICS

The target sample size was 70 subjects for this study. However because study was done based on pre-existing samples collected previously, only 58 patients were included as the age was 40 years and above. The sample was almost equally distributed between the sex groups; they were 27 males and 31 females. Studied population composed of all Malay ethnic, thus it could not represent Malaysian population in general as Malaysia is multiracial. This is merely because the study was done in Kelantan where the main ethnic population in this state was Malay that accounts approximately 95% of the population (Raof, 2010).

The total number of subjects for this study was smaller compared to previous similar studies. The sample for our study also had narrow range of age as we only focused on adult of 40 years and above due to limitation as this study was based on preexisting study subjects. The largest sample size was used by Kruggel F (2006) to establish normative value of head compartments based on MRI in which 502 healthy subjects were enrolled between 16 and 70 years, including 254 males and 248 females.

Quantitative Volumetric Analysis of Brain MR: Normative Database study by Blatter *et al.* (1995) has obtained the normal TVV and TBV value, involving 194 normal subjects with age ranging from 16 to 65 years. Zauhair *et al.* (2009) had large sample size for their study of the normal measurement of the lateral ventricles, third ventricles and VBR in apparently normal Iraqi population using CT scan. The sample included 112 healthy normal subjects

(66 males and 46 females) with the age ranging between 10 to 69 years. Recent studies among 300 adult Black Zimbabweans ranging from 10 to 80 years were involved in evaluation of the cerebral ventricles by Zilundu (2013).

6.2 MEAN TOTAL VENTRICULAR VOLUME

In this study, the mean total ventricular volume was 21.67cm^3 (± 12.82), representing the value for Kelantan population. Our results are almost similar to most of the studies either by using or ventricular casts, CT scan or MRI. The closest study to our study was a study done by Blatter *et al.* (1995) which summing the lateral ventricles, third and fourth ventricles based on multispectral segmentation of brain MRI on axial images. Their study revealed total ventricular volume of 21.12cm^3 (± 8.85) by using standard spin echo images which has no significant differences compared to fast spin echo images that was 20.76cm^3 (± 8.99).

In our study, the ventricular volumes were found to range from 4.70cm^3 to 74.95cm^3 which are similar to their study (6.3cm^3 to 87.9cm^3). The mean TVV yield in our study is also similar compared to the value found by Matsumae *et al.* (1996) (mean TVV 25cm^3) and Kohn *et al.* (1991) (mean TVV 21cm^3) in which they used segmentation technique for volume estimation.

Mean TVV in our study is smaller than a CT study done by N. Acer *et al.* (2009) which revealed mean TVV based on point-counting method and planimetric method of 15.5cm^3 (± 3.5) and 15.3cm^3 (± 3.4). Their study included only 14 young Turkish volunteers. Similarly, Cramer *et al.* (1990) found mean TVV of 17.4cm^3 in small sample size of 38 normal subjects, with was smaller compared to our result. This variation could be attributed by small sample size and younger age.

Another study in Korean population, Chung *et al.* (2006) has found TVV of 16.2cm^3 and 24.9cm^3, in second and fourth decades respectively. However our study did not correlate the TVV according to age group because we focused on adult of 40 years and above. Thus we can only make assumption that our result is similar to fourth decade Korean population as our subjects mean age was 56.40 years (± 8.28). Summary of the previous studies are as in table 6.1.

Table 6.1: Total ventricular volume (TVV) in adults measured in previous studies

Researcher	**Method**	**TVV** (cm^3)
Bruck	Casts	17.8
Last and Tompsett (1953)	Casts	16.8
Brassow and Baumann (1978)	CT	30.9
Reid *et al.* (1981)	CT	12.7
Rosenbloom*et al.* (1984)	CT	13.8
Cramer *et al.* (1990)	MRI	17.4
Matsumae*et al.* (1996)	MRI	25.0
Our study	MRI	21.7

6.3 COMPARISON OF THE MEAN TVV BETWEEN MALE AND FEMALE

In this study, we found that the male subjects have larger total ventricular volume than the female, and the difference was statistically significant (p<0.001). The mean volume of TVV for male and female were 28.14cm^3 (± 15.61) and 16.02cm^3 (± 5.50) respectively. Our results contradict most of the recent studies that stated no significant difference between male and female total ventricular volume. However significant sex-related differences in measurements of the ventricular system using small sample size in preliminary CT study were reported by Gyldensted *et al.* (1976). In general, the values obtained in this study are still not much difference compared to those studies.

Blatter *et al.* (1995) reported there were statistically significant differences for the third ventricle and total ventricular volume in the male of 46 to 55 years of age after normalization for total intracranial volume were done. Their TVV for this age group in male was 19.88cm^3 (± 5.34) and in female was 16.72cm^3 (± 3.57). In older age group (56-65 years old) which almost similar to mean age of our study subjects, the TVV for male was 26.11cm^3 (± 10.50) and 26.50cm^3 (± 13.63) for female.

A study by Akdogan *et al.* (2010) revealed no significant gender related difference in the mean of TVV, 30.62cm^3 (± 18.17) in male and 22.08cm^3 (± 12.94) in female. However the methodology was different compared to ours as they measured the ventricles based on CT stereological method. In another MRI stereological study by N. Acer *et al.* (2010), there was smaller total ventricular volume in female subjects however the differences did not reach statistical significance ($p > 0.05$). Their TVV was 17.2cm^3 (± 2.5) and 13.9cm^3 (± 3.7) for males and females using the point-counting technique and by using the planimetric method, 16.9cm^3 (± 2.4) and 13.8cm^3 (± 3.7) for males and females. Their study was almost similar to Cramer *et al.* (1990) which stated that the TVV was 18.0cm^3 and 16.3cm^3 in males and females respectively. The differences could be due to the different methodology used by N. Acer *et al.* (2010) and smaller sample size for both N. Acer *et al.* (2010) (14 subjects) and Cramer *et al.* (1990) (38 subjects).

6.4 MEAN TOTAL BRAIN VOLUME

In this study, the mean total brain volume (TBV) was 1245.29cm^3 (± 125.34) for all subjects. Our results are consistent with previous studies either by using CT scan or MRI. An MRI study done by Blatter *et al.* (1995) revealed total brain volume of 1273.25cm^3 (± 155.62) by using standard spin echo images which has no significant differences compared to fast spin echo images that was 1285.40cm^3 (± 147.78).

It is well known that the brain volume is decreasing with advancing age. However our study could only demonstrate the changes in the fourth decade till seventh decade group even though we did not correlate specifically the TBV with the age group. Akdogan *et al.* (2010) has found the mean TBV of 1359.38cm^3 (± 253.84), 1281.75cm^3 (± 184.48) and 1240.22cm^3 (± 142.86) in fourth, fifth and sixth decade respectively.

In our study, the mean TBV is larger than a study by Gur *et al.* (1991) whereby they found that the mean TBV was 1090.91cm^3 (± 114.3) in 69 healthy subjects ranging from 18 to 80 years old. The estimated volume of the MRI brain by Matsumae *et al.* (1996) was 1025cm^3 which also consistent with the literature for example, study by Blinkov & Glezer, 1968; Henery & Mayhew, 1989 and Regeur & Pakkenberg, 1989.

6.5 COMPARISON OF THE MEAN TBV BETWEEN MALE AND FEMALE

In this study, we found that there was no significant difference between the male and female total brain volume. The mean volume of TBV for male and female were 1338.05cm^3 (± 91.96) and 1164.49cm^3 (± 89.61) respectively. There is significant gender difference in brain size of 8% as established in the literature (Jacobs *et al.*, 1978; Wyper *et al.*, 1979; Filipek *et al.*, 1994). Our results are statistically not significant as our study revealed 12% gender difference, which could be attributed by small sample size study.

Condon *et al.* (1988) did in-vivo MRI study in 40 normal subjects and they found that there was significant decrease in the normalized brain volume between the ages of 20 and 60 years in males by 1.6% per decade. In females the decrease was less (0.5%) however this was not statistically significant.

A study by Yoshii *et al.* (1988) in 58 adults by using MRI revealed higher TBV than the rest of studies. They found that the mean TBV for male was 2032cm^3 (± 216) and 1813cm^3 (± 204) for female. In this study there was no decline in TBV in male in increasing age. We could not demonstrate this finding as we did not correlate the TBV with the age group. The summary of the TBV in previous studies are as listed in Table 6.2.

Table 6.2: Total brain volume in adults measured in previous studies

Author	Age range	Female (cm^3) (SD)	n	Male (cm^3) (SD)	n
Yoshii *et al.*(1988)	21-81	1813(204)	29	2032 (216)	29
Blatter *et al.*(1995)	36-45	1365(102)	44	1464 (94)	43
Filipek *et al.* (1994)	Not known	1325 (85)	10	1435 (116)	10
Matsumae *et al.*(1996)	24-80	1143 (106)	23	1302 (112)	26
Kruggel F (2006)	16-70	1304 (88)	248	1417 (86)	254
Narr *et al.* (2003)	33-35	1168 (81)	13	1273 (129)	15
Reite *et al.* (2010)	18-55	1216 (106)	47	1354 (111)	42
Tanskannen *et al.* (2009)	33-35	1215 (88)	40	1351 (101)	60
Arango *et al.* (2008)	33-35	1220 (91)	32	1424 (137)	34
Gur *et al.* (1991)	18-80	1046 (110)	35	1138 (101)	34
Our study	41-77	1164 (90)	31	1338 (92)	27

Multiple studies were done in assessing the TBV in three major Axis I mental disorders. A long term study by Reite *et al.* (2010) over 13 years period measuring the intracranial volume (ICV), TBV, TVV, VBR and TBV/ICV ratio in 224 subjects of schizophrenia, schizoaffective disorder and bipolar disorder. However the TBV found in control subjects compared to the mental disorder groups were statistically no difference. In general the schizophrenia patients have relatively smaller TBV and higher VBR. No significant changes of the TBV in the schizoaffective and bipolar disorder patients. The summary for the previous studies measuring TBV in schizophrenia patients are as in Table 6.3.

Table 6.3: Comparison TBV in schizophrenia patients in previous study

Author	**Age range**	**Male TBV** (cm^3) (SD)	**Female TBV** (cm^3) (SD)
Reite *et al.* (2010)	18-55	1316 (118)	1137 (134)
Tanskannen *et al.* (2009)	33-35	1328 (110)	1182 (73)
Narr *et al.* (2003)	33-35	1268 (110)	1152 (97)
Arango *et al.* (2008)	33-35	1365 (142)	1209 (115)

6.6 MEAN VENTRICULAR BRAIN RATIO

The mean total ventricular to brain ratio (VBR) for all subjects was 1.70 (± 0.89). The maximum VBR was 5.66 and the minimum VBR was 0.39. This result was consistent with the rest of the studies. The normal VBR in previous studies was approximately 5 in normal, 7 in borderline cases and greater than 10 in abnormal conditions (Zauhair A. Jaumah* MbchB, 2009). In term of age, VBR has slight increase after 49 years old and at 59 there was sharp increase in the VBR in both sexes (Barron *et al.*, 1976). However as we did not correlate the VBR with the age group, we were not able to confirm this finding.

The method used in our study was different from the original method explained by Synek *et al.* (1976). In that study, the VBR was calculated based on the slice on which the lateral ventricle has the widest diameter. The ventricular area was then divided with the brain area multiplied by 100. The VBR in our study was derived from the total ventricular volume divided by the total brain volume (both in cm^3) and the product was multiplied by 100. However no significant changes compared with the rest of the studies using the original method. The summary of the previous study measuring VBR are as in table 6.4.

6.7 COMPARISON OF THE MEAN VBR BETWEEN MALE AND FEMALE

In this study, we found that the male subjects have higher VBR than the females, and the difference was statistically significance (p value <0.05). The mean VBR for male and female were 2.09 (± 1.11) and 1.37 (± 0.44) respectively. This result is consistent with previous study by Parks *et al.* (1988) stated that the female has lower VBR value than male. In a study by Blatter *et al.* (1995), VBR according to age group was 1.27 (± 0.28) and 2.08 (± 1.11) in females of 46-55 and 56-65 years old. As for males, the VBR was 1.52 (± 0.43) and 2.07 (± 0.88) in 46-55 and 56-65 years age group respectively. Thus their study also proven that male has higher VBR than female.

However in Iranian population, a study done by Zauhair *et al.* (2009) based on CT scan involving 112 healthy subjects stated that there was no statistically difference in between male and female's VBR which were contradicts to the previous report stated that statistically female has lower VBR than male. They reported the mean VBR of 4.53 (± 1.2) in male and 4.16 (± 1.2) in female, which showed slight difference between genders. This could be due to larger sample size and the calculation using original method of VBR as described by Synek *et al.* (1976).

Table 6.4: Ventricular brain ratio in adults measured in previous studies. *Adapted from* (Zatz and Jernigan, 1983)

<table>
<tr><th>Studies</th><th>Age Group
No. of Subjects</th><th>0-9</th><th>10-19</th><th>20-29</th><th>30-39</th><th>40-49</th><th>50-59</th><th>60-69</th><th>70-79</th><th>80-89</th></tr>
<tr><td>Barron et al, 1976
(± SD)</td><td>135</td><td>1.8
(1.5)</td><td>3.3
(2.7)</td><td>3.1
(2.3)</td><td>4.2
(3.1)</td><td>4.4
(3.1)</td><td>5.2
(2.3)</td><td>6.4
(3.1)</td><td>11.5
(4.6)</td><td>14.1
(5.4)</td></tr>
<tr><td>Jacobs et al, 1976
(± SD)</td><td>146</td><td>2.9
(1.1)</td><td>3.7
(1.4)</td><td>4.2
(1.4)</td><td>4.2
(1.4)</td><td>4.4
(1.6)</td><td>6.7
(2.3)</td><td>7.2
(2.3)</td><td>11.0
(2.7)</td><td>13.0
(3.6)</td></tr>
<tr><td>Weinberger et al, 1979
(± SD)</td><td>56</td><td></td><td></td><td>3.1
(2.2)</td><td>4.1
(2.6)</td><td>3.8
(2.0)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Earnest et al, 1979
(± SD)</td><td>100</td><td></td><td></td><td></td><td></td><td></td><td></td><td>10.5
(2.9)</td><td>10.9
(4.4)</td><td>12.7
(3.8)</td></tr>
<tr><td>Jacoby et al, 1980
(± SD)</td><td>50</td><td></td><td></td><td></td><td></td><td></td><td></td><td>13.5
(2.9)</td><td>14.0
(4.3)</td><td>17.0
(2.0)</td></tr>
<tr><td>Zatz and Jernigan, 1983
(± SD)</td><td>47</td><td colspan="6">4.3
(2.3)</td><td></td><td></td><td></td></tr>
<tr><td>Andreasen, 1982
(± SD)</td><td>30</td><td></td><td>3.4
(1.4)</td><td>5.2
(3.5)</td><td>3.4
(1.1)</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td colspan="3">“Normal” patients</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Pearlson et al, 1981
(± SD)</td><td>35</td><td colspan="6">3.6
(2.6)</td><td></td><td></td><td></td></tr>
<tr><td>Andreasen et al, 1982
(± SD)</td><td>44</td><td></td><td>5.4
(3.1)</td><td>4.0
(3.0)</td><td>5.1
(3.2)</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Weinberger et al, 1982
(±SD)</td><td>26</td><td colspan="6">2.9
(2.9)</td><td></td><td></td><td></td></tr>
</table>

7 CONCLUSION

This study has established the normal mean value for the total ventricular volume, total brain volume as well as well as ventricular brain ratio in adult Kelantan population of 40 year old and above. This study has also revealed statistically significant difference of the mean total ventricular volume and mean ventricular brain ratio between male and female. However there was no significant difference of the mean total brain volume between the male and female in Kelantan population.

8 LIMITATIONS

There were few limitations in this study. Firstly, this is a cross-sectional study whereby the sample was taken from the same pool done by previous researchers from same institution. They have included 168 participants with age ranging from 7 to 77 years however not all images available both in proper sagittal and axial images, thus only small participants with majority of age 40 years and above included in this study. Therefore this study had smaller number of population as compared to previous normative data studies for example by Kruggel *et al* (2006). The sample population however was almost equally distributed between both sexes in different age group.

Secondly because of narrow age range (40-77 years old), we were not able to correlate between all the parameters measured (TVV, TBV, VBR) with the age group as what many other studies have done.

Thirdly, this normative data could only be applied to the Kelantan population and do not represent a true multiracial Malaysian population.

Fourthly, the MRI brain study for all participants were done using 1.0T MRI machine in which the quality of images are less compared with higher magnetic strength. This may influence the accuracy of anatomical boundary outline for volumetric measurement of the ventricles especially smaller ventricular parts for example the fourth and third ventricle on axial images.

9 RECOMMENDATIONS

In future, it is an advantage for future researchers to do the study with larger sample population involving multiracial population in Malaysia, which could represent the Malaysian as a whole. Longitudinal study of aging effect to the ventricle is better and to include the younger age group, thus correlation between the TVV, TBV and VBR with age can be made.

It is also better for the future researchers to do the MRI volumetric study on brain and its compartments using higher Tesla MRI machine for better image visualization.

Acer, N., Uğurlu, N., Uysal, D., Unur, E., Turgut, M. & Çamurdanoğlu, M. (2010). Comparison of two volumetric techniques for estimating volume of intracerebral ventricles using magnetic resonance imaging: a stereological study. *Anatomical science international,* **85(3),** 131-139.

Akdogan, I., Kiroglu, Y., Onur, S. & Karabulut, N. (2010). The volume fraction of brain ventricles to total brain volume: a computed tomography stereological study. *Folia Morphol,* **69(4),** 193-200.

Alberstone, C. D. (2009). Anatomic basis of neurologic diagnosis*.* Thieme.

Arnone, D., Cavanagh, J., Gerber, D., Lawrie, S., Ebmeier, K. & McIntosh, A. (2009). Magnetic resonance imaging studies in bipolar disorder and schizophrenia: meta-analysis. *The British journal of psychiatry,* **195(3),** 194-201.

Augustine, J. R. (2008). Human Neuroanatomy*.* Academic Press.

Aziz, A., Hu, Q. & Nowinski, W. L. (2004) In *Proc. of SPIE Vol*, Vol. 5369, pp. 575.

Barron, S. A., Jacobs, L. & Kinkel, W. R. (1976). Changes in size of normal lateral ventricles during aging determined by computerized tomography. *Neurology,* **26(11),** 1011-1011.

Bayer, S. A. & Altman, J. (2007). The human brain during the early first trimester*.* CRC press.

Beyer, J. L. & Krishnan, K. R. R. (2002). Volumetric brain imaging findings in mood disorders. *Bipolar Disorders,* **4(2),** 89-104.

Blatter, D. D., Bigler, E. D., Gale, S. D., Johnson, S. C., Anderson, C. V., Burnett, B. M., Parker, N., Kurth, S. & Horn, S. D. (1995). Quantitative volumetric analysis of brain MR: normative database spanning 5 decades of life. *American journal of Neuroradiology,* **16(2),** 241-251.

Buchsbaum, M. S., Yang, S., Hazlett, E., Siegel, B. V., Jr., Germans, M., Haznedar, M., O'Flaithbheartaigh, S., Wei, T., Silverman, J. & Siever, L. J. (1997). Ventricular volume and asymmetry in schizotypal personality disorder and schizophrenia assessed with magnetic resonance imaging. *Schizophr Res,* **27(1),** 45-53.

Caviness, V. S., Jr., Filipek, P. A. & Kennedy, D. N. (1992). Quantitative magnetic resonance imaging and studies of degenerative diseases of the developing human brain. *Brain Dev,* **14 Suppl,** S80-5.

Chung, S. C., Tack, G. R., Yi, J. H., Lee, B., Choi, M. H., Lee, B. Y. & Lee, S. Y. (2006). Effects of gender, age, and body parameters on the ventricular volume of Korean people. *Neurosci Lett,* **395(2),** 155-8.

Coffey, C. E., Wilkinson, W. E., Weiner, R. D., Djang, W. T., Webb, M. C., Figiel, G. S. & Spritzer, C. E. (1993). Quantitative cerebral anatomy in depression: a controlled magnetic resonance imaging study. *Archives of General Psychiatry,* **50(1),** 7.

Condon, B., Wyper, D., Grant, R., Patterson, J., Hadley, D., Teasdale, G. & Rowan, J. (1986). Use of magnetic resonance imaging to measure intracranial cerebrospinal fluid volume. *The Lancet,* **327(8494),** 1355-1357.

Cramer, G., Allen, D., DiDio, L., Potvin, W. & Brinker, R. (1990). Evaluation of encephalic ventricular volume from the magnetic resonance imaging scans of thirty-eight human subjects. *Surgical and Radiologic Anatomy,* **12(4),** 287-290.

Cruz-Orive, L. M. (1997). Stereology of single objects. *Journal of Microscopy,* **186(2),** 93-107.

Elfaki, A., Osman, T., Elsheikh, A., Hamdoun, A. & Şahin, B. (2011). Evaluation of the intra-rater variation for the estimation of volume of cerebral structures using the cavalieri principle on magnetic resonance images. *Journal of Experimental and Clinical Medicine,* **28(1)**.

Fernicola, P. J. (2011). Concussion: When the skull just isn't protection enough. [Online] Available [Accessed 12 November 2013].

Filipek, P. A., Richelme, C., Kennedy, D. N. & Caviness, V. S., Jr. (1994). The young adult human brain: an MRI-based morphometric analysis. *Cereb Cortex,* **4(4),** 344-60.

Flanagan, B. J. (2009). The biology of the Brain. [Online] Available [Accessed 9 November 2013].

Glastonbury, C. M., Osborn, A. G. & Salzman, K. L. (2011). Masses and Malformations of the Third Ventricle: Normal Anatomic Relationships and Differential Diagnoses. *RadioGraphics,* **31(7),** 1889-1905.

Gomori, J., Steiner, I., Melamed, E. & Cooper, G. (1984). The assessment of changes in brain volume using combined linear measurements. *Neuroradiology,* **26(1),** 21-24.

Gray, H. (1918). Anatomy of the Human Body [Online] Available [Accessed 12 November 2013].

Greenstein, B. & Greenstein, A. (2000). Color atlas of neuroscience: Neuroanatomy and neurophysiology. Thieme.

Gyldensted, C. (1977). Measurements of the normal ventricular system and hemispheric sulci of 100 adults with computed tomography. *Neuroradiology,* **14(4),** 183-192.

Huang, H., Xue, R., Zhang, J., Ren, T., Richards, L. J., Yarowsky, P., Miller, M. I. & Mori, S. (2009). Anatomical characterization of human fetal brain development with diffusion tensor magnetic resonance imaging. *J Neurosci,* **29(13),** 4263-73.

Jacobs, L., Kinkel, W. R., Painter, F., Murawski, J. & Heffner Jr, R. R. (1978). Computerized tomography in dementia with special reference to changes in size of normal ventricles during aging and normal pressure hydrocephalus. *Alzheimer's Disease: Senile Dementia and Related Disorders. Raven Press, New York, Aging,* **7,** 241-259.

Jacoby, R. J. & Levy, R. (1980). Computed tomography in the elderly. 3. Affective disorder. *The British journal of psychiatry,* **136(3),** 270-275.

Kemali, D., Maj, M., Galderisi, S., Milici, N. & Salvati, A. (1989). Ventricle-to-brain ratio in schizophrenia: a controlled follow-up study. *Biological psychiatry,* **26(7),** 756-759.

Kempton, M. J., Geddes, J. R., Ettinger, U., Williams, S. C. & Grasby, P. M. (2008). Meta-analysis, database, and meta-regression of 98 structural imaging studies in bipolar disorder. *Archives of General Psychiatry,* **65(9),** 1017.

Kennedy, D. N., Haselgrove, C. & McInerney, S. (2003). MRI-based morphometric analysis of typical and atypical brain development. *Mental retardation and developmental disabilities research reviews,* **9(3),** 155-160.

Kruggel, F. (2006). MRI-based volumetry of head compartments: normative values of healthy adults. *Neuroimage,* **30(1),** 1-11.

Last, R. & Tompsett, D. (1953). Casts of the cerebral ventricles. *British Journal of Surgery,* **40(164),** 525-543.

Levine, D. & Barnes, P. D. (1999). Cortical maturation in normal and abnormal fetuses as assessed with prenatal MR imaging. *Radiology,* **210(3),** 751-758.

Madden, M. E. (2001). Introduction to sectional anatomy. Lippincott Williams & Wilkins.

Mancall, E. L. & Brock, D. G. (2011). Gray's Clinical Neuroanatomy. Elsevier Health Sciences.

Marcus, D. S., Wang, T. H., Parker, J., Csernansky, J. G., Morris, J. C. & Buckner, R. L. (2007). Open Access Series of Imaging Studies (OASIS): Cross-sectional MRI Data in Young, Middle Aged, Nondemented, and Demented Older Adults. *J Cogn Neurosci,* **19(9),** 1498-1507.

McDonald, C., Zanelli, J., Rabe-Hesketh, S., Ellison-Wright, I., Sham, P., Kalidindi, S., Murray, R. M. & Kennedy, N. (2004). Meta-analysis of magnetic resonance imaging brain morphometry studies in bipolar disorder. *Biological psychiatry,* **56(6),** 411-417.

Musa, B. (2010). Magnetic Resonance Measurement of Total Intracranial Volume among Normal Malay Population: Accuration of Alternative Measurement Method, University Sains Malaysia, Kelantan, Malaysia.

N.M., S. (2009). I. Nervous System. [Online] Available [Accessed 12 November 2013].

O'Rahilly, R. R. & Müller, F. (2006). The embryonic human brain: an atlas of developmental stages. John Wiley & Sons.

Osaka, K., Handa, H., Matsumoto, S. & Yasuda, M. (1980). Development of the cerebrospinal fluid pathway in the normal and abnormal human embryos. *Pediatric Neurosurgery,* **6(1),** 26-38.

Ott, B. R., Cohen, R. A., Gongvatana, A., Okonkwo, O. C., Johanson, C. E., Stopa, E. G., Donahue, J. E., Silverberg, G. D. & Alzheimer's Disease Neuroimaging, I. (2010). Brain ventricular volume and cerebrospinal fluid biomarkers of Alzheimer's disease. *J Alzheimers Dis,* **20(2),** 647-57.

Pearlson, G. D., Kim, W. S., Kubos, K. L., Moberg, P. J., Jayaram, G., Bascom, M. J., Chase, G. A., Goldfinger, A. D. & Tune, L. E. (1989). Ventricle-brain ratio, computed tomographic density, and brain area in 50 schizophrenics. *Archives of General Psychiatry,* **46(8),** 690.

Penn, R. D., Belanger, M. G. & Yasnoff, W. A. (1978). Ventricular volume in man computed from CAT scans. *Ann Neurol,* **3(3),** 216-223.

Rabins, P., Pearlson, G., Jayaram, G., Steele, C. & Tune, L. (1987). Increased ventricle-to-brain ratio in late-onset schizophrenia. *Am J Psychiatry,* **144(9),** 1216-1218.

Raof, H. W. R. W. A. (2010) (Ed, MALAYSIA, D. O. S.) DEPARTMENT OF STATISTIC MALAYSIA, PUTRAJAYA.

Razvanski, B. (2012). The Brain
[Online] Available [Accessed 12 November 2013].

Reite, M., Reite, E., Collins, D., Teale, P., Rojas, D. & Sandberg, E. (2010). Brain size and brain/intracranial volume ratio in major mental illness. *BMC psychiatry,* **10(1),** 79.

Roberts, N., CRUZ-ORIVE, L., Reid, N., Brodie, D., Bourne, M. & Edwards, R. (1993). Unbiased estimation of human body composition by the Cavalieri method using magnetic resonance imaging. *Journal of Microscopy,* **171(3),** 239-253.

Singh, I. (2006). Textbook of human neuroanatomy*.* JAYPEE BROTHERS PUBLISHERS.

Standring, S., Ellis, H., Healy, J., Johnson, D., Williams, A., Collins, P. & Wigley, C. (2005). Gray's anatomy: the anatomical basis of clinical practice. *American Journal of Neuroradiology,* **26(10),** 2703.

Starr, C., Taggart, R., Evers, C. & Starr, L. (2012). Volume 5-Animal Structure & Function*.* Cengage Learning.

Synek, V. & Reuben, J. (1976). The ventricular-brain ratio using planimetric measurement of EMI scans. *British Journal of Radiology,* **49(579),** 233-237.

Takeda, S. & Matsuzawa, T. (1985). Age-related brain atrophy: a study with computed tomography. *Journal of gerontology,* **40(2),** 159-163.

Uhde, T. W. & Kellner, C. H. (1987). Cerebral ventricular size in panic disorder. *Journal of affective disorders,* **12(2),** 175-178.

Weed, L. H. (1935). Certain anatomical and physiological aspects of the meninges and cerebrospinal fluid. *Brain,* **58(3),** 383-397.

Weinberger, D. R., Torrey, E. F., Neophytides, A. N. & Wyatt, R. J. (1979). Lateral cerebral ventricular enlargement in chronic schizophrenia. *Archives of General Psychiatry,* **36(7),** 735.

Williams, A., Reveley, M., Kolakowska, T., Ardern, M. & Mandelbrote, B. (1985). Schizophrenia with good and poor outcome. II: Cerebral ventricular size and its clinical significance. *The British journal of psychiatry,* **146(3),** 239-246.

Woods, B. T., Douglass, A. & Gescuk, B. (1991). Is the VBR still a useful measure of changes in the cerebral ventricles? *Psychiatry Research: Neuroimaging,* **40(1),** 1-10.

Wright, I. C., Rabe-Hesketh, S., Woodruff, P. W., David, A. S., Murray, R. M. & Bullmore, E. T. (2000). Meta-analysis of regional brain volumes in schizophrenia. *American Journal of Psychiatry,* **157(1),** 16-25.

Wyper, D. J., Pickard, J. D. & Matheson, M. (1979). Accuracy of ventricular volume estimation. *Journal of Neurology, Neurosurgery & Psychiatry,* **42(4),** 345-350.

Yoshii, F., Barker, W. W., Chang, J. Y., Loewenstein, D., Apicella, A., Smith, D., Boothe, T., Ginsberg, M. D., Pascal, S. & Duara, R. (1988). Sensitivity of cerebral glucose metabolism to age, gender, brain volume, brain atrophy, and cerebrovascular risk factors. *Journal of Cerebral Blood Flow & Metabolism,* **8(5),** 654-661.

Young, P. (1999). CHAPTER 2. TOPOGRAPHY OF THE CENTRAL NERVOUS SYSTEM. [Online] Available [Accessed 12 November 2013].

Zatz, L. M. & Jernigan, T. L. (1983). The ventricular-brain ratio on computed tomography scans: validity and proper use. *Psychiatry Res,* **8(3),** 207-214.

Zauhair A. Jaumah* MbchB, M. د. ز. ع. ج. (2009). C.T Scan Measurements of the Lateral and Third Ventricles in Apparently Normal Iraqi Subjects. *Journal of the Faculty of Medicine □□□□ □□□□ □□□□,* **51(3),** 320-322.

Appendix A

<u>PATIENT'S DATA SHEET 1: Magnetic Resonance Imaging (MRI)</u>

Age: Sex:
RN:

TOTAL VENTRICULAR VOLUME MEASUREMENT:

SLICE	VENTRICLE				MEASUREMENT			
	3RD	4TH	LAT V		**Measure 1**	**Measure 2**	**Measure 3**	**Average**
			Rt	Lt				
TOTAL VOLUME								

TOTAL VENTRICULAR VOLUME (TVV) = TOTAL ALL SLICES X 0.7cm

Appendix B

PATIENT'S DATA SHEET 2: Magnetic Resonance Imaging (MRI)

Age: Sex:
RN:

TOTAL BRAIN VOLUME MEASUREMENT:

	MEASUREMENT			
	Measure 1	**Measure 2**	**Measure 3**	**Average**
SLICE 1				
SLICE 3				
SLICE 5				
SLICE 7				
SLICE 9				
SLICE 11				
SLICE 13				
SLICE 15				
SLICE 17				
SLICE 19				
TOTAL VOLUME				

TOTAL BRAIN VOLUME (TBV) = TOTAL ALTERNATE SLICE X 1.4cm

Appendix C

DATA SHEET:

MR VOLUMETRY OF TOTAL VENTRICULAR VOLUME AND TOTAL BRAIN VOLUME IN NORMAL KELANTAN ADULT POPULATION.

NO	RN	AGE	SEX	NO	RN	AGE	SEX
1				31			
2				32			
3				33			
4				34			
5				35			
6				36			
7				37			
8				38			
9				39			
10				40			
11				41			
12				42			
13				43			
14				44			
15				45			
16				46			
17				47			
18				48			
19				49			
20				50			
21				51			
22				52			
23				53			
24				54			
25				55			
26				56			
27				57			
28				58			
29				59			
30				60			

MR VOLUMETRY OF TOTAL VENTRICULAR VOLUME AND TOTAL BRAIN VOLUME IN NORMAL ADULT POPULATION IN KELANTAN.

Dr Nur Farahwahida Muhammad Azmi

MMed Radiology

Department of Radiology

School of Medical Sciences, Universiti Sains Malaysia

Health Campus, 16150 Kelantan, Malaysia

Introduction: There are many neurological and neuropsychiatric disorders which can cause changes in ventricular volume and brain volumes; namely schizophrenia, bipolar disorder, depression and Alzheimer's disease other than aging process. Thus, to diagnose these conditions and to monitor the progression of the illnesses, the normal value of the total ventricular volume, total brain volume and ventricular brain ratio should be established. Currently there is no normative data of MR Volumetry of total ventricular volume and total brain volume as well as ventricular brain ratio available for Kelantan population. From this study, it is hoped that the normative data can be established.

Objectives: The general objective of this study is to determine the total ventricular volume and total brain volume in normal healthy adult aged 40 and above in Kelantan and to calculate the ventricular brain ratio.

Methods and materials: This was a cross sectional study of 58 subjects of Kelantan population and had undergone MR brain imaging in Department of Radiology, Hospital Universiti Sains Malaysia from May 2008 till November 2009 whereby they had normal MR brain findings. Fifty eight patients who fulfilled the inclusion criteria were included in the study.

MRI of brain was performed using a Signa Horizon LX 1.0 Tesla from the GE Company. Axial T1 and sagittal T1 with 5mm slice thickness and 2mm gap were analyzed in the measurement of the total ventricular volume and total brain volume. Ventricular boundaries were manually traced on each MRI axial slices. For the brain volume, manual tracing of the brain outline was done using alternate slice method. Image display and manual tracing of the ventricles and brain areas were performed using Osirix software ver.3.7.1. Data was compiled and analyzed using PASW Statistic ver.20 (SPSS, Chicago IL).

Results: The mean total ventricular volume for normal adult was 21.67cm^3 (± 12.82), while that for male and female was 28.14cm^3 (± 15.61) and 16.02cm^3 (± 5.50) respectively. The mean total brain volume for normal adult was 1245.29cm^3 (± 125.34), while that for male and female was 1338.05cm^3 (± 91.96) and 1164.49cm^3 (± 89.61) respectively. The mean ventricular brain ratio for normal adult was 1.70 (± 0.89), while that for male and female was 2.09 (± 1.11) and 1.37 (± 0.44) respectively. There was significant difference of the total ventricular volume and ventricular brain ratio between male and female (p value <0.05).

Conclusion: This study provided the normal mean value for the total ventricular volume, total brain volume as well as well as ventricular brain ratio in normal Kelantan adult population aged 40 year and above. This study showed statistically significant difference of the mean total ventricular volume and mean ventricular brain ratio seen between genders.

Dr Juhara Haron: Supervisor

Dr Win Mar @ Salmah Jalaludin: Co-Supervisor

ACKNOWLEDGEMENT

Alhamdulillah, all the praises are for Allah SWT as with His blessing I was able to complete this dissertation. I would like to express my deep gratitude to my supervisor, Dr Juhara Haron and my co-supervisor Dr Win Mar @ Salmah Jalaludin, for their patient guidance, enthusiastic encouragement and useful critiques of this research work. I would also like to thank Prof. Dr Syed Hatim and Dr. Aniza Bt Abdul Aziz, for their advice and assistance in statistical input. My grateful thanks are also extended to all the lecturers and all staffs in the Department of Radiology, School of Medical Sciences, Universiti Sains Malaysia, whom without their cooperation and assistance this study would not be completed, as well as the ethical committee for giving ethical approval.

Finally, and most importantly, I would like to thank my husband, Engku Ariff Tuan Lonik and my beloved children, Engku Akiff Farhan and Engku Akiffa Farhani. Their support, encouragement, quiet patience and unwavering love were undeniably the main reason for me to get through this master programme. I thank my parents, Muhammad Azmi Haji Abu Bakar and Wan Jaharah Wan Sulong, for their support and my mother in law, Tuan Som Tuan Mud, for her caringness. Thank you for your understanding.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABBREVIATION

CE	*Communauté Européenne*
CI	Confidence Interval
CSF	Cerebrospinal Fluid
CT	Computed Tomography
DICOM	Digital Imaging and Communication in Medicine
FDA	United States Food and Drug Administration
FLAIR	Fluid-attenuated Inversion Recovery
GNU	GNU's Not Unix! Operating System
HD	High Definition
IBM	International Business Machines Corporation
ICV	Intracranial Volume
IR	Inversion Recovery
ITK	Insight Segmentation and Registration Toolkit
mmH_2O	Milimeter Water
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
OASIS	Open Access Series of Imaging Studies
PACS	Picture Archiving and Communications System
PC	Personal Computer
PET	Positron Emission Tomography
PET-CT	Positron Emission Tomography- Computed Tomography

RU	Research University
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences
T1WI	T1-Weighted image(s)
T2WI	T2-Weighted image(s)
TBV	Total Brain Volume
TVV	Total Ventricular Volume
VBR	Ventricular Brain Ratio
VTK	Visualization Toolkit

ABSTRAK

Tajuk:

Pengukuran Jumlah Isipadu Ventrikel dan Otak Menggunakan Pengimejan MR di Kalangan Penduduk Dewasa Normal di Kelantan.

Pengenalan:

Terdapat banyak penyakit saraf dan jiwa yang berupaya merubah isipadu ventrikel dan otak, terutama penyakit skizofrenia, gangguan bipolar, kemurungan dan nyanyuk Alzheimer, selain daripada proses penuaan. Oleh itu, untuk mendiagnosis dan memantau kemajuan penyakit tersebut, nilai isipadu ventrikel, isipadu otak dan nisbah ventrikel kepada otak yang normal hendaklah diketahui. Buat masa ini tidak terdapat nilai normal berkaitan pengukuran isipadu ventrikel dan otak menggunakan pengimejan MR untuk populasi melayu. Daripada kajian ini, adalah diharapkan bahawa data normatif boleh ditubuhkan.

Objektif:

Objektif kajian ini adalah untuk menentukan jumlah isipadu ventricular dan jumlah isipadu otak pada orang Kelantan dewasa yang sihat berumur 40 tahun ke atas serta untuk mendapatkan nisbah ventrikel kepada otak.

Tatacara:

Ini merupakan kajian irisan lintang bagi mengukur isipadu ventrikel dan otak di kalangan sukarelawan normal berumur 40 tahun dan ke atas yang telah menjalani pengimejan MR melalui kajian terdahulu yang dijalankan di Jabatan Radiologi Hospital Universiti Sains Malaysia dari bulan Mei 2008 hingga November 2009 dimana keputusan MRI mereka adalah normal. Lima puluh lapan pesakit yang memenuhi kriteria kemasukan telah dimasukkan ke dalam kajian ini.

Siri pengimejan MR otak dan ventrikel ini dilakukan menggunakan mesin MR Signa Horizon LX 1.0 Tesla daripada syarikat GE. Imej yang digunakan dalam kajian ini adalah di dalam siri T1 axial dan sagittal dengan ketebalan lebaran sebanyak 5 mm dan sengkangan sebanyak 2mm. Sempadan ventrikel dikesan secara manual untuk setiap keratan imej MRI. Untuk isipadu otak, sempadan otak dikesan secara manual menggunakan kaedah selang. Paparan imej dan pengukuran ventrikel serta otak ini dilakukan melalui stesen kerja Osirix versi 3.7.1. Kemasukan data dan analisis dilakukan dengan menggunakan program perisian Statistical Package for Social Sciences (SPSS versi 20).

Keputusan

Min isipadu untuk semua ventrikel bagi orang dewasa adalah 21.67cm^3 (± 12.82), yakni 28.14cm^3 (± 15.61) untuk lelaki dan 16.02cm^3 (± 5.50) untuk perempuan. Min isipadu untuk otak bagi orang dewasa adalah 1245.29cm^3 (± 125.34), yakni 1338.05cm^3 (± 91.96) untuk lelaki dan 1164.49cm^3 (± 89.61)

untuk perempuan. Min nisbah ventrikel kepada otak bagi orang dewasa adalah 1.70 (± 0.89), yakni 2.09 (± 1.11) untuk lelaki dan 1.37 (± 0.44) untuk perempuan. Ada perbezaan ketara min semua ventrikel dan min nisbah ventrikel kepada otak di antara lelaki dan perempuan (*p* value <0.05).

Kesimpulan:

Kajian ini telah berjaya memperolehi nilai isipadu normal untuk ventrikel, otak dan juga nisbah ventrikel kepada otak dalam populasi dewasa berumur 40 tahun dan lebih di Kelantan. Kajian ini juga membuktikan perbezaan ketara min isipadu ventrikel dan min nisbah ventrikel kepada otak di antara lelaki dan perempuan.

ABSTRACT

Topic:

MR Volumetry of Total Ventricular and Brain Volume in Normal Adult Population in Kelantan.

Introduction:

There are many neurological and neuropsychiatric disorders which can cause changes in ventricular volume and brain volumes; namely schizophrenia, bipolar disorder, depression and Alzheimer's disease other than aging process. Thus, to diagnose these conditions and to monitor the progression of the illnesses, the normal value of the total ventricular volume, total brain volume and ventricular brain ratio should be established. Currently there is no normative data of MR Volumetry of total ventricular volume and total brain volume as well as ventricular brain ratio available for Kelantan population. From this study, it is hoped that the normative data can be established.

Objectives:

The general objective of this study is to determine the total ventricular volume and total brain volume in normal healthy adult Malay aged 40 and above and to calculate the ventricular brain ratio.

Methods and materials:

This was a cross sectional study of 58 subjects of Malay population and had undergone MR brain imaging in Department of Radiology, Hospital Universiti Sains Malaysia from May 2008 till November 2009 whereby they had normal MR brain findings. Fifty eight patients who fulfilled the inclusion criteria were included in the study.

MRI of brain was performed using a Signa Horizon LX 1.0 Tesla from the GE Company. Axial T1 and sagittal T1 with 5mm slice thickness and 2mm gap were analyzed in the measurement of the total ventricular volume and total brain volume. Ventricular boundaries were manually traced on each MRI axial slices. For the brain volume, manual tracing of the brain outline was done using alternate slice method. Image display and manual tracing of the ventricles and brain areas were performed using Osirix software ver.3.7.1. Data was compiled and analyzed using PASW Statistic ver.20 (SPSS, Chicago IL).

Results:

The mean total ventricular volume for normal adult was 21.67cm^3 (± 12.82), while that for male and female was 28.14cm^3 (± 15.61) and 16.02cm^3 (± 5.50) respectively. The mean total brain volume for normal adult was 1245.29cm^3 (± 125.34), while that for male and female was 1338.05cm^3 (± 91.96) and 1164.49cm^3 (± 89.61) respectively. The mean ventricular brain ratio for normal adult was 1.70 (± 0.89), while that for male and female was 2.09 (± 1.11) and 1.37 (± 0.44) respectively. There was significant difference of the total ventricular volume and ventricular brain ratio between male and female (p value <0.05).

Conclusion:

This study provided the normal mean value for the total ventricular volume, total brain volume as well as well as ventricular brain ratio in normal Kelantan adult population aged 40 year and above. This study showed statistically significant difference of the mean total ventricular volume and mean ventricular brain ratio seen between genders.