MAGNETIC RESONANCE MEASUREMENT OF TOTAL INTRACRANIAL VOLUME AMONG MALAY POPULATION: ACCURACY OF ALTERNATIVE MEASUREMENT METHODS

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My beloved wife, Nur Suriyani Zakaria and daughters, Nurin Irdiena and Nur Aina Insyirah.

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ABSTRAK

Bahasa Melayu

Tajuk:

Pengukuran Jumlah Isipadu Kranium Menggunakan Kaedah Magnetik Resonan Di Kalangan Populasi Melayu: Ketepatan Pengukuran Menggunakan Kaedah-kaedah Alternatif

Pendahuluan:

Jumlah isipadu kranium didefinisikan sebagai isipadu di dalam ruangan tengkorak (kranium) yang merangkumi otak beserta selaput dan cecair di sekelilingnya, dan juga cecair di dalam sistem ventrikel otak. Ia memberikan satu faktor pengukuran yang stabil dan paling sesuai sebagai perbandingan normalisasi bagi pengukuran perubahan isipadu di bahagian-bahagian otak lain dalam kajian berkaitan proses penuaan, pelbagai penyakit neurologi dan psikiatri kerana ianya adalah konstan dan tidak berubah dengan peningkatan usia dan jarang dipengaruhi oleh perubahan-perubahan patologi. Kemajuan teknologi magnetic resonan (MR) telah membolehkan kita mengukur isipadu otak dan bahagian-bahagiannya dengan lebih tepat. Pelbagai kaedah pengukuran jumlah isipadu kranium menggunakan magnetic resonan telah dijalankan dan didapati bahawa pengukuran menggunakan kaedah manual adalah yang terbaik. Pengukuran manual menggunakan kaedah MR yang paling tepat adalah dengan mengukur setiap kepingan imej MR yang merangkumi keseluruhan bahagian otak. Walaubagaimanapun, penggunaan kaedah ini memerlukan masa yang lama. Oleh yang demikian, kaedah-

kaedah pengukuran alternatif bagi mengukur jumlah isipadu kranium yang boleh mengurangkan penggunaan masa tanpa mengurangkan ketepatan and kejituan bacaan perlu dihasilkan. Kajian ini telah mengukur jumlah isipadu kranium menggunakan kaedah-kaedah pengukuran alternatif dan kaedah pengukuran piawai. Seterusnya, perbandingan mengenai ketepatan kaedah-kaedah pengukuran alternatif berbanding dengan kaedah pengukuran piawai dalam menggunakan teknik MR telah dilakukan.

Objektif:

Untuk membandingkan ketepatan kaedah-kaedah pengukuran alternatif dengan kaedah pengukuran piawai menggunakan imej MR dalam pengiraan jumlah isipadu kranium.

Tatacara:

Ini adalah kajian ke atas data retrospektif yang membandingkan jumlah isipadu kranium menggunakan kaedah-kaedah pengukuran alternatif dan kaedah pengukuran piawai di kalangan populasi orang Melayu. Kajian ini melibatkan penggunaan data-data daripada 59 subjek (32 orang perempuan dan 27 orang lelaki) yang mana data-data mereka telah diambil daripada sistem PACS. Empat teknik pengukuran jumlah isipadu kranium telah dijalankan iaitu tiga teknik alternatif; Kaedah Pengukuran Separuh Bahagian Kranium di sebelah kanan dan kiri serta Kaedah Pengukuran Selang-seli Antara Kepingan Imej dan satu Kaedah Pengukuran Piawai. Kesemua kaedah pengukuran dilakukan penggunakan OsiriX versi 3.2.1. Min dan sisihan piawai jumlah isipadu

kranium yang telah diukur kemudiannya dikira, dianalisis dan dibandingkan. Jumlah min untuk jumlah isipadu kranium antara jantina juga telah dikira.

Keputusan:

Jumlah min dan sisihan piawai jumlah isipadu kranium bagi kesemua subjek ialah 1375.67 (148.61) cm^3. Jumlah min bagi jumlah isipadu kranium bagi subjek-subjek lelaki dan perempuan masing-masing ialah 1439.14 (142.49) cm^3 dan 1322.12 (133.12) cm^3. Terdapat perbandingan yang signifikasi bagi jumlah min bagi jumlah isipadu kranium antara subjek-subjek lelaki dan perempuan ($p = 0.002$). Terdapat hubungkait yang bagus di antara jumlah isipadu kranium yang diperolehi menggunakan kaedah-kaedah pengukuran alternatif berbanding dengan yang diperolehi daripada kaedah pengukuran piawai [ICC (0.977 to 0.981) and Cronbach's Alpha (0.991)].

Kesimpulan:

Kajian ini telah menunjukkan bahawa kaedah-kaedah pengukuran alternatif adalah setanding dengan kaedah pengukuran piawai bagi pengiraan jumlah isipadu cranium. Kaedah-kaedah pengukuran yang tersebut adalah bersesuaian dan boleh diguna-pakai untuk mengukur jumlah isipadu kranium tanpa berlakunya kehilangan dari segi ketepatan dan kejituan.

ABSTRACT

English

Topic:

Magnetic Resonance Measurement of Total Intracranial Volume Among Malay Population: Accuracy of Alternative Measurement Methods.

Introduction:

Total intracranial volume (TIV) is defined as the volume within the cranium, including the brain, meninges and cerebrospinal fluid. It provides a stable and accurate normalization factor for estimating volumetric changes of brain structures in studies of ageing process, various neurological and neuropsychiatric diseases as it is constant and did not changed with increasing age and less vulnerable to pathological changes. With the advance of the technology, magnetic resonance (MR) imaging has made possible accurate measurements of the brain and its substructures. Various methods of MR volumetric measurement of TIV had been established and manual method is the best. The best manual MR volumetry is obtained by measuring each MR slices that cover the brain. However, obtaining TIV via the standard manual method is time consuming. Therefore alternative volumetric measurement methods which reduced the time consumption in measuring TIV without alteration of their accuracy and reliability should be established. This study had calculated the estimation of TIV using alternative measurement and standard methods. Thus, comparison of the accuracy of measuring TIV using alternative measurement methods with the standard measurement method can be evaluated.

Objectives:

To compare the accuracy of MR volumetry of TIV using alternative measurement methods with the standard measurement method.

Methodology:

This was a cross sectional comparative study of TIV measured using alternative measurement methods and standard measurement method among normal Malay population. The study involved the data from total of 59 subjects (32 females and 27 males) with the age ranging from 15 to 50 years old. All the patients' data were taken from archive images from PACS system. TIV measurement was performed manually using OsiriX version 3.2.1 using three methods namely Half Cranial Measurement Method on right and left side as well as Alternate Slice Measurement Method and a Standard Measurement Method by two observers. The rater was initially undergone reliability. The mean and standard deviation (SD) of TIV measured using the alternative and standard methods were calculated, analyzed and compared. Mean difference of TIV between genders were also calculated.

Results:

Mean total intracranial volume of all subjects was 1375.67 (148.61) cm^3. Mean total intracranial volume for male and female were 1439.14 (142.49) cm^3 and 1322.12 (133.12) cm^3 respectively. There were significant differences in the total intracranial volume between male and female subjects ($p = 0.002$).

There were good correlation between the TIV obtained from the alternative measurement methods and that from the standard method [ICCs (0.977 to 0.981) and Cronbach's Alpha (0.991)].

Conclusions:

The study had shown comparable alternative measurement methods for total intracranial volume without significant loss of the accuracy and reliability of these methods as compared to the standard measurement method. This study also revealed that the male subjects had significantly larger total intracranial volume as compared to female subjects.

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ABBREVIATION

AVSIS	Automated Volumetric Segmented Brain System
CSF	Cerebrospinal fluid
C1	Atlas
DICOM	Digital Imaging and Communication In Medicine
FDA	Food and Drug Administration Agency
FLAIR	fluid-attenuated inversion recovery
GNU	General Public Licence
HUSM	Hospital University Sains Malaysia
HIT	Himeji Institute Technology System
ITK	Insight Segmentation and Registration Toolkit
LTIV	TIV obtained from Half Cranial Measurement Method on the left side of cranium
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
PACS	Picture Archiving and Communication System
PET	Positron Emission Tomography
PET-CT	Positron Emisson Tomography – Computed Tomography
RTIV	TIV obtained from Half Cranial Measurement Method on the right side of cranium
SD	Standard deviation
STORE SCU	Service Class Provider (SCP) for the Storage Service Class
TIV	Total Intracranial Volume
TIVAlt	TIV obtained from Alternate Slice Measurement Method on the left side of cranium
TIVS	TIV obtained from Standard Measurement Method
T1WI	T1 Weighted Image
T2WI	T2 Weighted Image
VTK	Visualization Toolkit

1. INTRODUCTION

Total intracranial volume (TIV) is defined as the volume within the cranium, including the brain, meninges, and cerebrospinal fluid (CSF). Real volumes and weights are measured, data from autopsy studies may be considered as the ‘‘gold standard’’ to measure total intracranial volume (Peters et al., 2000). However, inherent technical and logistical problems affect the measurements including type of illness, intervals between death and brain removal, weighing in the fresh or fixed condition which may affect the results. Nowadays, with the advancement of the imaging technology, magnetic resonance imaging (MRI) has made possible accurate measurements of the brain and its substructures. It also provides non-invasive method in investigating brain morphology. A common problem of many previous volumetric studies is as a result of inadequate methods employed to accurately correct volumes for non-pathological, inter-patient differences which are mainly due to both genetic and environmental factors such as age, sex, body and head size (Rushton and Aukney, 1996). Genetic or environment factors may lead to abnormal brain growth and TIV as overall that very early in the course of subject’s development (Wood et al., 2005). It is important that for volumetric analysis of any brain structures for confounding effects of other dependent variables to be normalized with a control factor to avoid bias from the results of interindividual variation.

TIV provides more stable and accurate normalization factor for estimating volumetric changes at the onset of various neurological and neuropsychiatric diseases as

it is less vulnerable to pathological changes. Although TIV may be affected in neurodevelopmental disorders such as schizophrenia (Andreasen et al., 1990 and Pearlson et al., 1989), Huntington's disease (Nopoulos et al., 2011) and bipolar disorder (Vita et al., 20009), TIV is still superior over cerebral volume in the measures of rates of atrophy of the brain substructures. TIV can be used for estimation of premorbid brain volume from serial MR images which have been proposed as diagnostic markers and, it can also be used as surrogate markers of disease progression for therapeutic trial in disease such as Alzheimer's disease (Killiany RJ et al., 2000; Jenkins et al., 2000). TIV can be measured and data were used in normalization with brain and its substructures volume (Kruggel F., 2006).

Magnetic resonance (MR) images can be obtained via various planes of MRI studies – for example, coronal, sagittal and axial planes. A study by (Eritaia et al., 2000) evaluated various sampling strategies to measure TIV from sagittal T1-weighted MR images and concluded that the TIV can be confidently traced by using a 1-in-10 section strategy without significant loss of accuracy. TIV can also be calculated by summation and linear interpolation of the segmented axial slices. No significant differences between TIV result measured on T1-weighted MR images and T2-weighted MR images (Whitwell et al., 2001). TIV is generally measured manually from T1-weighted MR images as automated and semi-automated MR-volumetric segmentations are difficult to be performed from standard T1-weighted MR images since there is little contrast between brain and CSF. However, gold standard method of measuring TIV by using MR images are time consuming as all slices need to be evaluated and analyzed. Therefore, this study

will provide alternative MR volumetric measurement methods that evaluate and analyze lesser number of slices by using alternate slice and half cranial measurement methods.

Many studies had been performed overseas which provide normative data of total intracranial volume for the population. A study by Kruggel F. (2004) in California, USA found that TIV for male was 1616.3 + 91.1 cm^3 and female was 1494.6 + 96.3 cm^3, ; Whitwell et al. (2000), UK in which mean TIV 1382 + 144 cm^3 (male more than female of 179 cm^3). Blatter et al. (1993) did study population at Utah, USA which indicate TIV for male is 1558 $\pm$ 97 cm^3 and female was 1352 $\pm$ 115 cm^3 whereas Jenskin et al. (2000) from London, UK indicates TIV for male was 1512.5 ± 128.2 cm^3 and female was 1316.8 ± 97.6 cm^3. Ishii et al. (2005) at Japan did similar study among Japanese population which they found that TIV was 1387$\pm$ 106 cm^3 (manual); 1341 $\pm$ 102 cm^3(AVSIS); 1421 $\pm$ 109 cm^3 (HIT). Majority of these studies are using axial and/or coronal sequences of T1-W MR images. Several investigators have defined normal age-specific value for total intracranial volume in neurologically normal subject, but, to our knowledge, no one has reported value for healthy subject in our country.

The aim of this study is to compare the accuracy of alternative measurement methods of the total intracranial volume in normal Malay population in general by using sagittal T1-Weighted MRI sequences. Thus it will provide the simple and less time consuming methods of MR measurement as compared to standard method. The study will also establish a normative value for the total intracranial volumes on sagittal MRI for future reference.

2. LITERATURE REVIEW

2.1 OVERVIEW

The shape, size and intracranial volume of skull have been of interest to radiologists since the very beginning of the field, as well as to biologist and anthropologists, who have used these measures to estimate brain volume (Davis et al., 1977; Beal et al., 1984; Pagel et al., 1988; Eisenberg et al., 1992; Lieberman et al., 2000). Quantification of total intracranial volume (TIV) can be computed straightforward fashion by using magnetic resonance imaging (MRI). The validity and accuracy of findings from the volumetric studies is highly dependent on the reliability of the methodology applied. TIV is an important variable in the investigation of several neurological and neuropsychiatric disorders. Total intracranial volume is commonly calculated in quantitative neuroimaging studies but often not reported (Sanfilipo et al., 2000); it is rarely the major objective or variable under investigation.

TIV can be defined as the volume within the cranium, including the brain, meninges and cerebrospinal fluid (CSF). It is less vulnerable to pathological changes made it is more superior over cerebral volume as correction factor for head size. TIV did not change with age, although the normalized brain volume of both men and women began to decrease after the age of 40 years (Matsumae et al., 1996). In neurodegenerative disorders such as Alzheimer disease, TIV offers an index of premorbid brain size (Jenskin et al., 2000).

2.2 ANATOMY OF INTRACRANIAL CAVITY

Both genetic and environment factors including the gender, race, body, head size and early nutritional status may influenced the development of the brain and its substructures. The brain growth is also limited by the skull. The cranial cavity contains the brain, and its surrounding meninges, portion of cranial nerves, arteries, veins and venous sinuses. Therefore one needs to really understand about the boundaries of the intracranial cavity.

2.2.1 Skull Vault

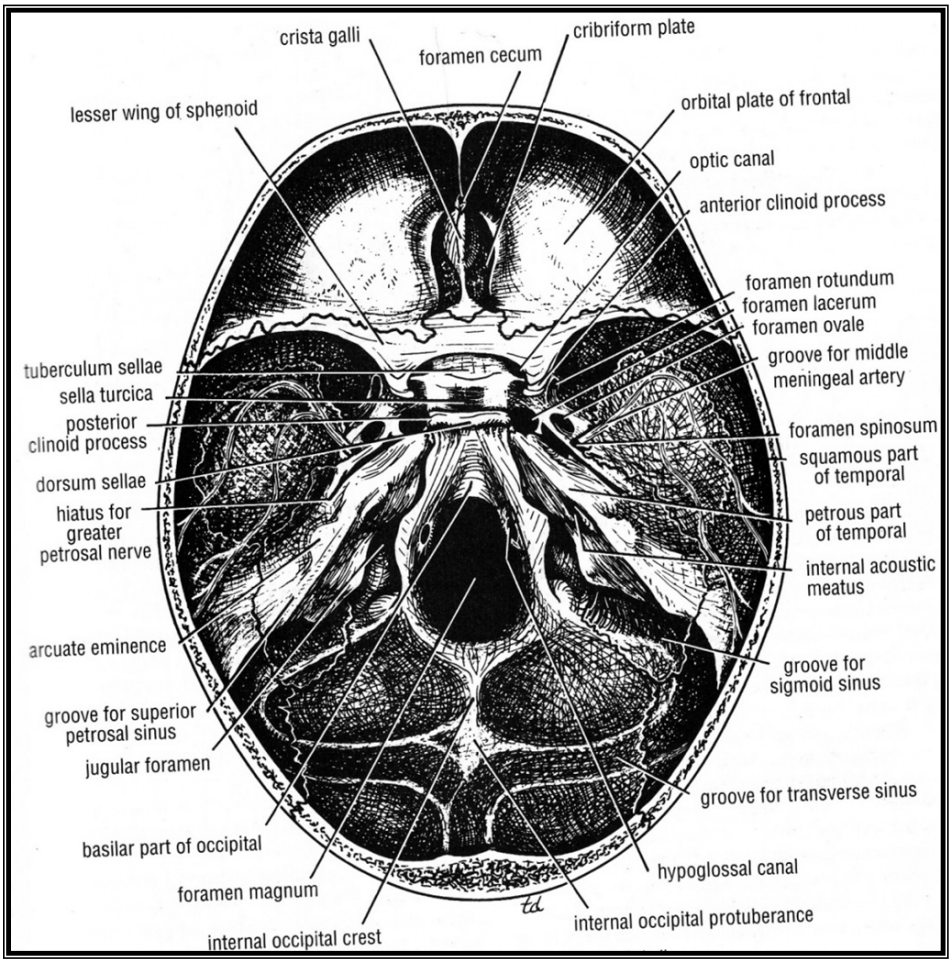
The skull vault is formed by the two parietal and temporal bones as well as frontal and occipital bones. These bones are connected by the coronal, sagittal, and lambdoid sutures.

2.2.2 Base of Skull

Interior of the base of the skull is best described into three cranial fossae:

a. Anterior cranial fossa
b. Middle cranial fossa, and
c. Posterior cranial fossa.

Figure 2-1 Inner surface of base of skull *[modified from Snell RS (2008)]*



a. Anterior Cranial Fossa

This lodges the frontal lobes of the cerebral hemispheres. It is bounded by the inner surface of the frontal bone and in the midline there is a crest for attachment of falx cerebri. Its posterior boundary is the lesser wing of the sphenoid which articulates laterally with the frontal bone and meets the anterior inferior angle of the parietal bone, or pterion. Median part of the anterior cranial fossa is limited posteriorly by groove for optic

chiasma. The floor of the fossa is formed by the ridged of orbital plate of the frontal bone laterally and by the cribiform plate of the ethmoid medially.

b. Middle Cranial Fossa

It consists of a small median part and expanded lateral parts. The median raised part is formed by the body of the sphenoid, and the expanded lateral parts form concavities on either side, which lodge the temporal lobes of cerebral hemispheres. The boundaries of the medial cranial fossa are the lesser wing of the sphenoid anteriorly and superior borders of the petrous parts of temporal bones posteriorly. Laterally, the fossa is bounded by squamous parts of the temporal bones, the greater wing of the sphenoid and the parietal bones. The floor of each lateral part of the fossa is formed by the greater wing of the sphenoid and the squamous and petrous parts of the temporal bone. Median part of the fossa is formed by the body of sphenoid.

c. Posterior Cranial Fossa

This is very deep and lodges the parts of hindbrain, namely, the cerebellum, pons and medulla oblongata. Anterior and posterior boundaries of the fossa are the superior border of the petrous part of the temporal bone and internal surface of the squamous part of the occipital bone respectively. Tentorium cerebelli formed the roof of the posterior cranial fossa. Foramen magnum occupies the central area of the floor which tranmits the medulla oblongata and its surrounding meninges, the ascending spinal parts of the accessory nerves, and the two vertebral arteries.

2.2.3 Meninges

Underneath the inner table of the skull, here lie the dura of the meninges (Figure 2-2 and Figure 2-3). The meninges invest the brain and spinal cord. It consists of three parts that are the outer layer of fibrous dura mater, the arachnoid mater and the inner, the pia mater. The outer dura mater and arachnoid mater are applied closely with a potential space in between known as subdural space. The arachnoid space is situated between the arachnoid and the pia mater, contains cerebrospinal fluid, which surrounds the cerebral arteries and veins. The cranial dura has two separate layers to enclose the dural venous sinuses which is the outer layerknown as the periosteum of inner table of the skull whereas the inner layer covers the brain and gives rise to falx and tentorium. Dura is hyperdense on CT and relatively hypointense on MRI. Recognition of the dura mater is important in order to accurately measure the intracranial volume (Eritaia et al., 2000).

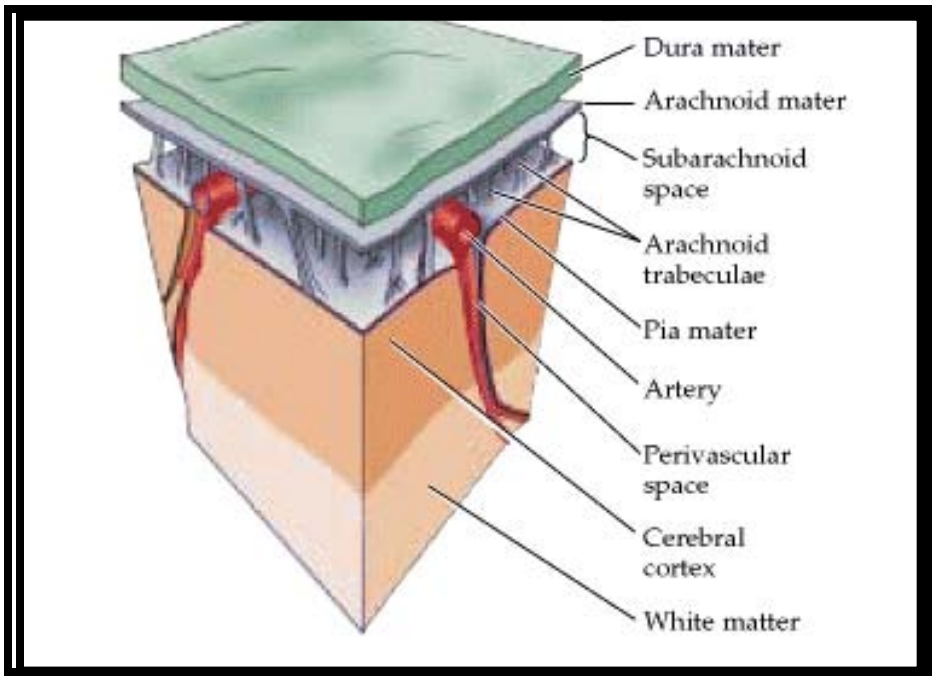


Figure 2-.2 The meninges layers *[modified from Snell RS (2009)]*

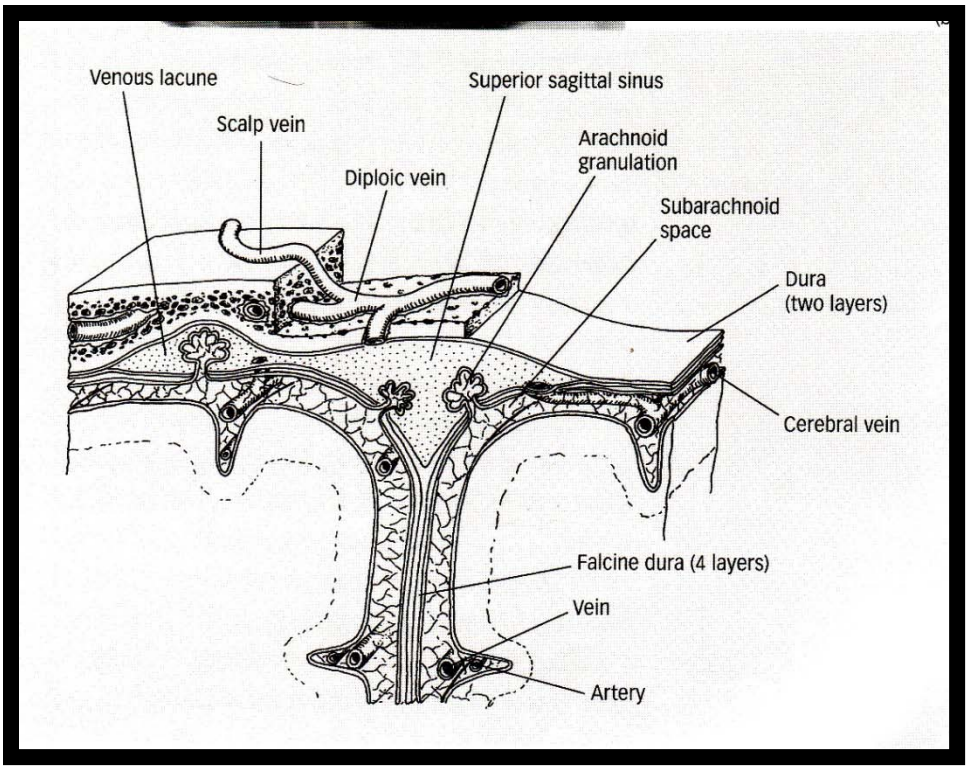


Figure 2-3 Diagram of venous lacunes and arachnoid granulation *[modified from Butler et al. (2005)]*

2.2.4 Brain

Brain is that part of the central nervous system that lies inside the cranial cavity. It is continuous with the spinal cord through the foramen magnum. The main parts of the brain are as described in table 2-1.

Table 2-1 Parts of Brain

Major Parts of the Brain		**Cavities of the Brain**
Forebrain	Cerebrum	Right and lateral ventricles
	Diencephalon	Third ventricle
Midbrain		Cerebral Aqueduct
Hindbrain	Pons	Fourth ventricle
	Medulla Oblongata	and central canal
	Cerebellum	

2.2.4.1 Cerebrum

The largest part of the brain and consist of two cerebral hemispheres, connected by a mass of white matter called corpus callosum (Figure 2-4). Each hemisphere extends from the frontal to the occipital bones, above the anterior and middle cranial fossae, and posteriorly, above the tentorium cerebelli. The hemispheres are separated by a deep cleft, the longituidinal fissure, into which projects the falx cerebri

The surface layer of each hemisphere is called the cortex and is composed of grey matter. Cerebral cortex is thrown into folds, or gyri, separated by fissures, or sulci. A number of large sulci conveniently subdivide the surface of each cerebral hemisphere into lobes. The lobes are named of the cranium under which they lie. They are all 4 lobes in

each cerebral hemisphere. The frontal lobe is situated anterior to the central sulcus and above the lateral sulcus whereas the parietal lobe located posterior to the central sulcus and above the lateral sulcus. The occipital lobe is lies below the parieto-occipital sulcus. The temporal lobe is located inferior to the lateral sulcus.

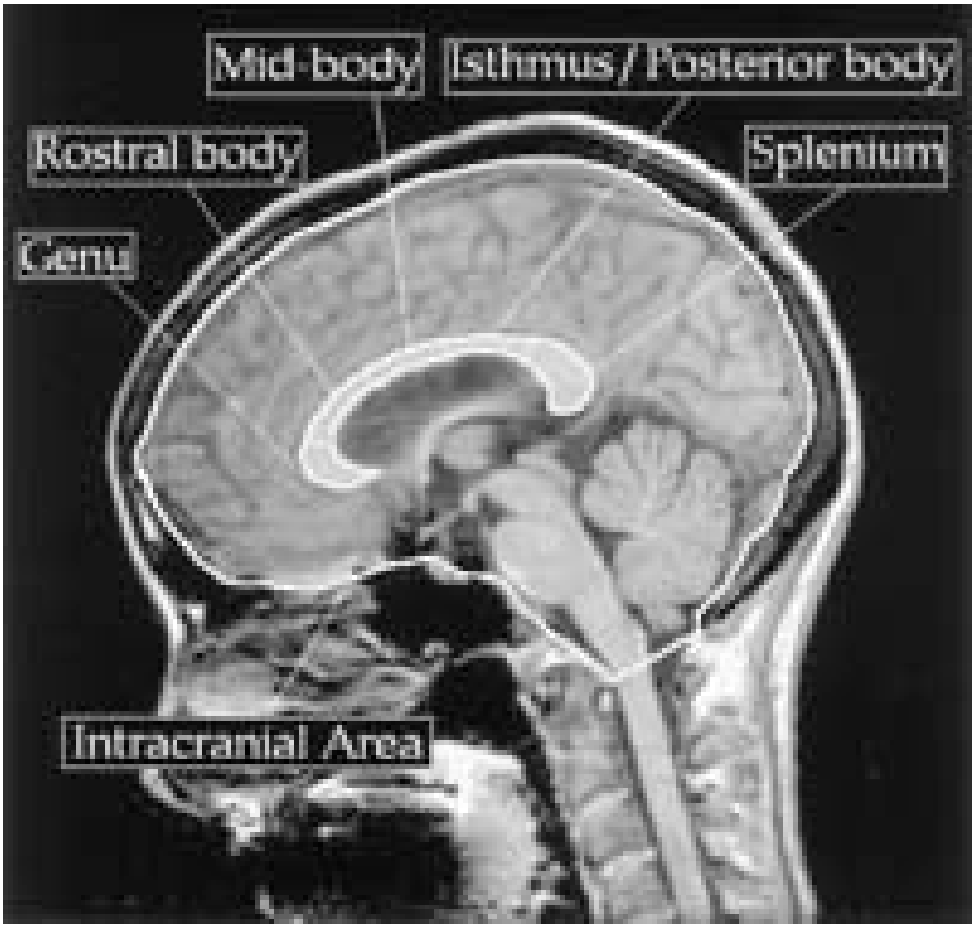


Figure 2-4: TIWI of Mid Sagittal Brain *[Ilustrated from Mostofsky et al. (1999)]*

2.2.4.2 Diencephalon

The diencephalon is almost completely hidden from the surface of the brain. It consists of a dorsal thalamus, and a ventral hypothalamus. The thalamus is a large grey matter mass lies on either side of the third ventricle. Hypothalamus forms the inferior part of the lateral wall and floor of the third ventricle. The following structures are located in the floor of the third ventricles which are the optic chiasma, the tuber cinereum and the infundibulum, the mammilary bodies and the posterior perforated substances.

2.2.4.3 Midbrain

This is the narrow part of the brain that passes through the tentorial notch and connects the forebrain to the hindbrain. The midbrain comprises of two lateral halves, called cerebral peduncles which is devided into an crus cerebri and tegmentum by substantia nigra. Narrow cavity of the midbrain is cerebral aqueduct which connects the third and fourth ventricles. Tectum is part of the midbrain that lies posterior to cerebral aqueduct which consists of two superior and two inferior colliculi which are deeply placed in between the cerebellum and the cerebral hemisphere. Pineal gland is a glandular structure that lies between the superior colliculi. It is attached by a stalk to the region of posterior wall of the third ventricle. Figure 2-5 show gross anatomy of the midbrain.

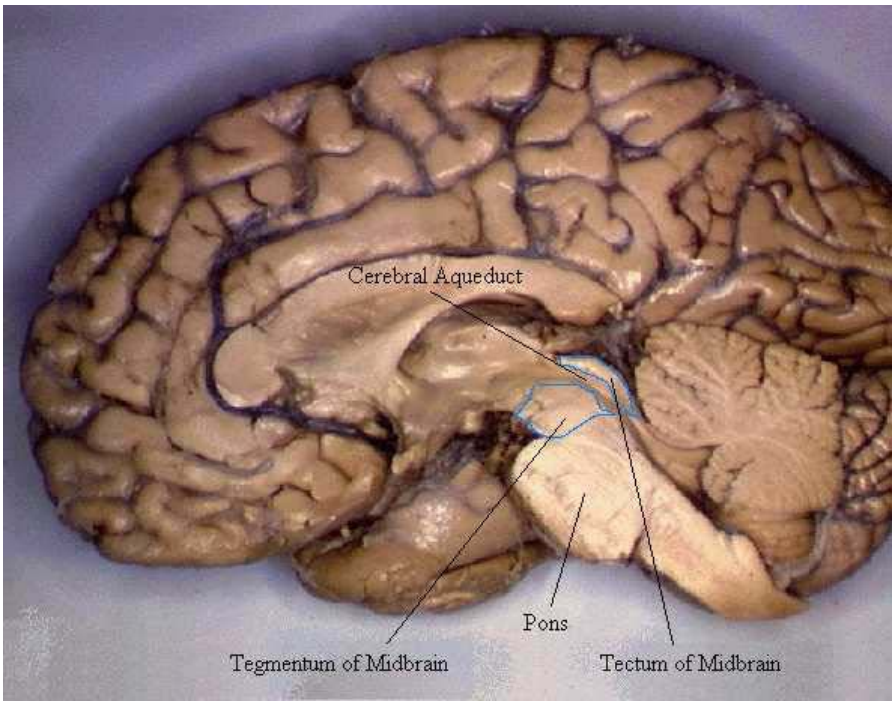


Figure 2-5: Gross specimen of brain showing midbrain anatomy *[illustration from Gray's Anatomy (2008)]*

2.2.4.4 Hindbrain

This consists of the pons and medulla oblongata as well as the cerebellum. Pons is anterior to the cerebellum surface and above the medulla oblongata. The medulla oblongata is a conical in shape and connects the above pons to the spinal cord inferiorly. Pyramid are seen on either side of anterior surface of the medulla which devided by median fissure. The cerebellum lies within the posterior cranial fossa beneath the tentorium cerebelli. It consists of two hemispheres connected by medial portion called the vermis. The cerebellum is connected to the midbrain by superior cerebellar peduncles, to the pons by middle cerebellar peduncles and to the medulla oblongata by inferior cerebellar peduncles.

2.2.4.5 Ventricular system

The ventricular system consists of two lateral ventricles, the third ventricle, and the fourth ventricle (Figure 2-6). The lateral ventricles are in communication with the third ventricle via the Foramen of Monroe. The third ventricle and fourth ventricle is connected by cerebral aqueduct.

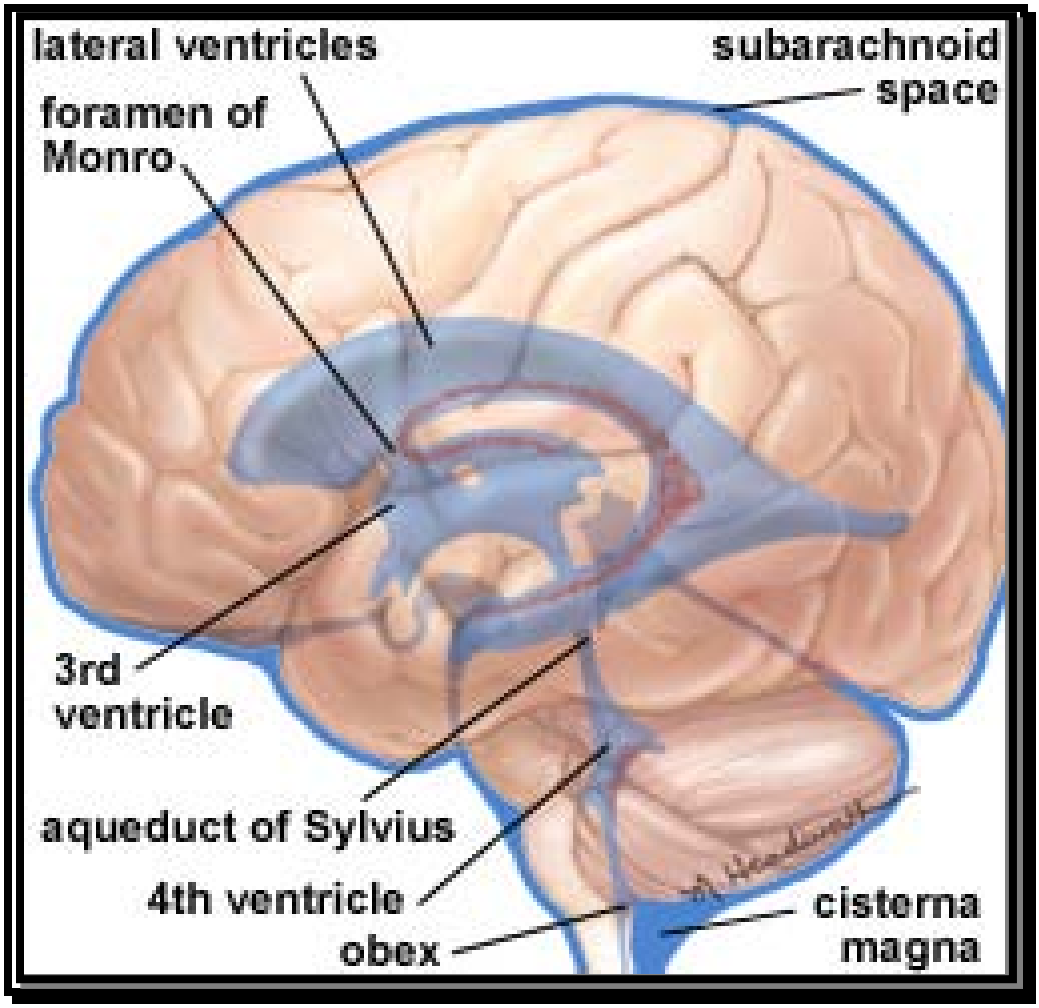


Figure 2-6: Anatomy of ventricular system and CSF flow *[Modified from Gray's Anatomy (2008)]*

2.3 DEVELOPMENT OF BRAIN AND INTRACRANIAL CAVITY

The brain starts to develop during the fourth week of intrauterine life where the neural tube expands to form the three vesicles of forebrain, midbrain and hindbrain. The brain has smooth surfaces up to 18 weeks. However, approximately 15 weeks the surface of the growing brain begins to fold into sulci and gyri (Levine and Barnes, 1999) with formation of major sulci, except for the occipital lobe, are in place by 28 weeks of gestation. Cerebral ventricles may develop around 24 weeks of gestation. Towards end of the normal gestation, the brain growth and gyration proceed rapidly, along with the myelination.

Relatively rapid brain growth is demonstrated in the first 2 years of life, by which time it has achieved 80% of its adult weight. By age 5 years brain size is approximately 90% of adult size (Dekaban and Sadowsky, 1978). A study by Spiros et al. (1999) had shown that the growth pattern of the brain is somehow almost similar to the growth of total intracranial volume with a rapid linear growth during the first 5 years of life. Similar study showed that in subsequent years, TIV growth continues but at a much slower rate, with a mild spurt starting at approximately 10 years and lasting for an additional 5 years and reaching more than 90% of adult size at age of 15 years. The intracranial volume in the first few months of life is on average 900 cm^3 in males and 600 cm^3 in females. By the age of 15 years, it increases up to 1500 cm^3 in males and 1300 cm^3 in females, increased by factors of 1.6 and 2.1, respectively. By the time the child reaches 2 years of age, intracranial volume has reached 77% (1150 cm^3 in males and 1000 cm^3 in females)

and, by 5 years, 90% (1350 cm^3 in males and 1200 cm^3 in females) of the volume observed at age 15 years. Skull growth occurs along the suture lines and is determined by brain expansion takes place during normal growth of the brain.

After age of 15 years, TIV reach its maximum size. Total intracranial volume does not change with age. Studies have shown that insult, nutritional factors, prematurity, and birth or delivery complications may all be risk factors for smaller brain and head size. Thus, in response to normal development, adverse environmental effects, or both, once brain growth stabilizes early in life, it sets the parameters for stable intracranial volume for the remainder of life, and TIV can be used as an indicator of optimal brain volume at maturity or before disease onset or acquired injury.

2.4 MR IMAGING OF BRAIN AND TOTAL INTRACRANIAL VOLUME ESTIMATION

Computed tomography (CT) and magnetic resonance imaging (MRI) are the most commonly performed imaging investigation for the intracranial structures especially for the brain. MRI is superior in displaying the anatomical detail of intracranial structures compared to CT because the contrast sensitivity of MRI is superior to that of CT. MRI can also provide images in multiple planes without need to alter the patient's position in the scanner. The content of middle and posterior fossae structures are better visualized using MRI because it does not suffer from the streak artefacts arising from the bone as in CT which may mask soft tissue detail.

MRI has been widely used for volumetric measurements of brain volume and its substructures. It is an important research tool where brain of neuropsychiatric patients can be investigated in vivo. It is a noninvasive method for investigating brain morphology. This also permits the direct comparison of postmortem calculations of intracranial capacity with MR-based quantification, because the 1977 study by Davis and Wright reported the actual intracranial and brain volume at autopsy. Table 2-2 below shows the relationship between previous studies based on autopsy and MR imaging studies of brain volume. From the table 2-2, previous studies had shown that the result of the brain volume in the MRI-based study (Blatter et al., 1995; Flatter et al., 1994; Kruggel F., 2006) is well in line with the autopsy data (Chrzanowska and Sadowsky, 1978; Filipek et al., 1994).

Table 2.2 Brain volume [ml] in young adults (20–30 years): comparison with published data *[Kruggel (2006)]*

	Method	Female	N	Male	n
Chrzanowska and Beben (1973)	Autopsy	1286 ± –	–	1434 ± –	–
Debakan and Sadowsky (1978)	Autopsy	1283 ±30	76	1420 ± 20	151
Blatter et al. (1995)	MRI	1365 ± 102	44	1464 ± 94	43
Filipek et al. (1994)	MRI	1325 ± 85	10	1435 ± 116	10
Kruggel F (2006)	MRI	1304 ± 88	145	1417 ± 86	145

Brain weights from autopsy studies were converted into volumes using a specific density of 1.02 g/ml (Miller et al., 1980).

There was no universally accepted method for estimating head size by using MR imaging. In some studies, the cerebral volume was commonly used as a correction factor in volumetric studies which may due to easier and faster method of measuring cerebral volume than TIV. However, adopting cerebral volume as a normalizing factor may prove misleading if the whole brain itself is already atrophic due to the effect of the disorder. Assuming that most neurological disorders do not affect the cranial size before it has completed its growth. TIV has been recognized as a suitable constant for normalizing the size of individual brain structures (Free et al., 1995; Eritaia et al., 2000). Unfortunately, automated measurement of TIV is difficult from standard T1-weighted images due to

little contrast between bone and CSF. Therefore laborious and time consuming manual tracing of intracranial cavity is a drawback.

In previous studies, the estimation of TIV can be obtained in different MR acquisition techniques such as proton density (PD) sequences (Hartley et al., 2000; Palm et al., 2006), TI Fast Echo spin (FSE) sequence (Whitwell et al., 2000) and T2 FSE sequence (Jenkins et al., 2005). As MRI ability to do multiplanar tasking, estimation of TIV which have been derived from MRI sequences can be performed in sagittal (Jack et al., 1989; Fujioka et al., 2000), axial and coronal planes (Free et al., 1995, Laakso et al., 1997). The number of slices used to estimate head size has also varied significantly, and the definition of TIV has been inconsistent across studies (Lye et al., 2006). Linear interpolation of areas was used to obtain an estimate of TIV from segmented section.

A study by Eritaia et al. (2000) evaluated various sampling strategies to measure a total TIV from sagittal, coronal and axial T1-weighted images and concluded that the TIV can be confidently traced by using a 1-in-10 section strategy without significant loss of accuracy. Total intracranial volume can also be calculated by summation and linear interpolation of the segmented axial slices. No significant differences between total intracranial volumes measured on T1 Weighted images and T2 Weighted images (Whitwell et al., 2001). Pengas et al. (2008) studied that the TIV can also be estimated by just measuring half of the cranium. In the study, there was high correlation between full cranial and mid cranial measurements within different MR images.

Many semi-automated and automatic volumetric measurement of segmented brain structures including the TIV on MRI have been established. MR data analysis was performed using the software BRAINS (Andreasen *et al*., 1992, 1993). Measures in BRAINS, generated by automatic segmentation, have been carefully validated against manual tracings considered to be the gold standard (Harris *et al*., 1999). The TIV is also can be automatically delineated in each segmented MR volume using artificial neural networks (Magnotta *et al*., 1999). A fully automated volumetric segmented brain system (AVSIS) (Ishii K. et al., 2006) can also measured TIV based on MR imaging with good results when compared to manual and semiautomated [Himeji Institute Technology (HIT)] method. Unfortunately, automated and semi-automated segmentation of TIV is difficult from standard T1W MR images, since there is little contrast between bones and CSF. An additional acquisition is required, which tends to have poor gray/white matter contrast. While this is feasible, it extends the amount of time spent in scanner by the participant or patient, which increases costs and may result in motion artifact. As a result, TIV has generally measured manually from the T1W MR images.

In past studies, TIV has been measured by summing the measured areas on a specified number of slices (not the whole dataset) multiplied by the distance between slices (Free S et al., 1995; Briellman et al., 1998; Hashimoto et al. 1998). However, the accuracy and efficiency of protocols to measure TIV has not been formally analyzed. The most accurate method for measuring TIV is to assess all slices. Eritaia et al. (2000) studied of total 30 normal controls selected from normative population data set at the Mental Health Research Institute if Victoria in 2000, found a positive relationship

between the numbers of slices used to estimate TIV and the accuracy of that measurement. TIV was measured manually tracing the intracranial cavity on a slice by slice protocol from MR sagittal images in this study. As a number of slices sampled decreased, the Intraclasss Correlation Coefficient (ICC) between estimated TIV and the actual TIV also decreased. However, the rate at which these two measures of accuracy decreased was small, implying that it is possible to adopt a less time intensive sampling strategy when measuring TIV.

2.5 TOTAL INTRACRANIAL VOLUME IN NORMAL POPULATION

MR imaging has made it is possible to attempt accurate, in vivo volumetric measurement of the total intracranial cavity as well as whole brain and its substructures. The quantitative estimation of the volume of brain structures become an important part of diagnostic procedure, especially when disease causes poorly noticeable macroscopic changes (Jack, Twomey *et al.* 1989). As a reliable procedure for volumetric analysis of brain structures must control for confounding effects of other dependent variables that may bias the results, total intracranial volume provide the best available control of premorbid brain volume especially in those with generalized cerebral atrophy. The intracranial cavity is rapidly increasing in size during the first 5 years, then slowing growing and reached almost its maximum dimension after the age of 15 years (Spiros et al., 1999). The intracranial cavity did not changed with age and therefore, the total intracranial volume will provide a reference for normalization with other brain structures.

Many studies had been performed overseas which provide normative data of total intracranial volume for the population. A study by Kruggel F of total 502 population normal healthy subjects in 2006 at California, USA found that TIV for male was 1616.3 $\pm$ 91.1 cm^3 and female was 1494.6 $\pm$ 96.3 cm^3. Whitwell et al. (2000) studied in London, United Kingdom showed the mean TIV 1382 $\pm$ 144 cm^3 (male more than female of 179 cm^3). Blatter et al. (1995) did study of normal population in Utah, USA which indicate TIV for male is 1558 $\pm$ 97 cm^3 and female was 1352 $\pm$ 115 cm^3 whereas study by Jenkins et al. (2001) from London, UK had shown TIV for male was 1512.5 ± 128.2 cm^3 and female was 1316.8 ± 97.6 cm^3. A study by Ishii K. et al. (2006) in Japan noted that TIV was 1387$\pm$ 106 cm^3 (manual); 1341 $\pm$ 102 cm^3 [automated measurement of segmented image system (AVSIS)]; 1421 $\pm$ 109 cm^3 [Himeji Institute for Technology method (HIT)] of normal 15 control subjects. In majority of these studies, they show significant mean difference between male and female TIV.

2.6 IMPORTANCE OF TOTAL INTRACRANIAL VOLUME

Measuring total intracranial volume allows whole-brain and regional volumetric measures to be normalized for head size. Normalization of brain structures with TIV is also used to estimate the premorbid brain degeneration diseases (Drachman, 2002; Edland et al., 2002; Jenskin et al., 2000; Wolf et al., 2003) or brain degeneration due to diffuse or focal brain damage. TIV is a good control as it is constant and did not changed with increasing age or by neurodegenerative disease processes. Studies of normalization of brain substructures' volume (i.e. cerebrum, hippocampus, temporal lobe) with TIV in many disease processes such as neurodegenerative disease can reduced individual variation which may have important implication in progression studies.

Total intracranial volume may be affected in neurodevelopmental disorders such as schizophrenia (Pearlson et al., 1989 and Andreasen et al., 1999). As shown in the study described above, TIV is also linearly associated with hippocampal volume, thus making it a useful normalizing factor for subcortical and limbic structures. It is believed that from both studies, the reduction in TIV as compared to control population is due to the disease process had been started before the brain reach its maximum size. TIV is not affected by increasing age (Fotenos et al, 2005) and other neurodegenerative diseases such as Alzheimer disease, multiple sclerosis and epilepsy (Blatter et al., 1995; Matsumae et al., 1996; Jenkins et al. 2000; Killiany et al., 2000; Dalton et al., 2004; Lye et al., 2006). Thus it is an important constant for normalization in volumetric measures of brain and its substructures.

3. OBJECTIVES

3.1 GENERAL OBJECTIVE

To compare the accuracy of MR volumetry of total intracranial volume (TIV) using alternative measurement methods with the standard measurement method.

3.2 SPECIFIC OBJECTIVES

1. To determine TIV of normal Malay population.
2. To compare TIV using Half Cranial Measurement Method with Standard Measurement Method.
3. To compare TIV using Alternate Slice Measurement Method with Standard Measurement Method.
4. To determine the mean differences between male and female TIV among normal Malay population.

3.3 NULL HYPOTHESIS

1. No significant difference between TIV when measuring all slices of T1-Weigthed sagittal MR images (standard measurement method) with alternate slices and half-cranial measurement methods (alternative measurement methods).
2. No significant difference of TIV between male and female population.