# CRANIOFACIAL ANTHROPOMETRY, SKULL BONE THICKNESS AND INTRACRANIAL VOLUME CHANGES IN EPILEPTIC PATIENTS

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# CRANIOFACIAL ANTHROPOMETRY, SKULL BONE THICKNESS AND INTRACRANIAL VOLUME CHANGES IN EPILEPTIC PATIENTS

**by**

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## LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| mm | ---------- | millimeter |
| ILAE | ---------- | International League against Epilepsy |
| CNS | ---------- | Central nervous system |
| WHO | ---------- | World Health Organization |
| SUDEP | ---------- | Sudden unexpected death in Epilepsy |
| IGE | ---------- | Idiopathic generalized Epilepsies |
| EEG | ---------- | Electroencephalography |
| AED | ---------- | Anti-Epileptic drug |
| ADHD | ---------- | Attention deficit hyperactivity disorder |
| TLE | ---------- | Temporal lobe Epilepsy |
| FLE | ---------- | Frontal lobe Epilepsy |
| MTS | ---------- | Mesial Temporal Sclerosis |
| CT | ---------- | Computed Tomography |
| 3D CT | ---------- | Three dimensional computed tomography |
| 2D CT | ---------- | Two-dimensional computed tomography |
| MRI | ---------- | Magnetic Resonance Imaging |

| | | |
|---|---|---|
| CBCT | ---------- | Cone beam computerized tomography |
| USG | ---------- | Ultrasonography |
| SPET | ---------- | Single-photon emission computed tomography |
| VNS | ---------- | Vagal nerve stimulation |
| NAW | ---------- | North American White |
| SBT | ---------- | Skullbone thickness |
| ICV | ---------- | Intracranial brain volume |
| MCD | ---------- | Malformations of cortical development |
| 3DFM | ---------- | 3D facial morphometry |
| TACT | ---------- | Tuned-Aperture Computed Tomography |
| MIMICS | ---------- | Mimics 17.02 Materialise |
| MITK 3M3 | ---------- | Medical Imaging Interaction Toolkit |
| WWW | ---------- | Woman with epilepsy |
| BMI | ---------- | Basal Metabolic Index |
| ICD | ---------- | Inner canthal distances |
| HC | ---------- | Head circumferences |
| OSA | ---------- | Obstructive sleep apnea |
| HUSM | ---------- | Hospital University Sains Malaysia |
| USM | ---------- | University Sains Malaysia |

| | | |
|---|---|---|
| DIACOM | ---------- | Digital Imaging and Communications in Medicine |
| SPSS | ---------- | Statistical Package for the Social Sciences |
| SF | ---------- | Sudanese female |
| AA | ---------- | African-American |
| UFH | ---------- | Upper facial height |
| LFH | ---------- | Lower facial height |
| PFH | ---------- | Posterior facial height |
| GCC | ---------- | Gulf Cooperation Council |
| HFI | ---------- | Hyperostosis Frontalis Interna |
| TBI | ---------- | Traumatic brain injury |
| AD | ---------- | Alzheimer’s disease |
| IQR | ---------- | Interquartile range |

## LIST OF APPENDICES

**ANTROPOMETRI KRANIOFASIAL KETEBALAN TULANG TENGKORAK DAN PERUBAHAN ISIPADU INTRAKRANIAL DALAM PESAKIT EPILEPSI**


**ABSTRAK**

Epilepsi adalah sejenis penyakit yang disebabkan oleh kecelaruan genetik dan saraf. Penggunaan ubat anti-epilepsi yang berpanjangan boleh mengakibatkan perubahan wajah atipikal, kekasaran pada ciri-ciri wajah dan hipertrofi gusi. Banyak kajian yang telah dijalankan keatas dimensi kraniofasial, ketebalan tulang tengkorak (SBT), dan isipadu otak didalam kranium (ICV) keatas populasi penduduk normal dipelbagai negara dan bangsa. Namun, kajian sedemikian amat jarang dibuat keatas pesakit yang mempunyai ganguan epilepsi dan data yang ditemui sangat terhad. Oleh itu, kajian ini bertujuan untuk mengkaji antropometri kraniofasial, SBT dan ICV ke atas pesakit epilepsi lelaki dan perempuan di Malaysia. Kajian yang dijalankan ini dapat menyumbang kepada strategi pengurusan perubatan yang lebih berkesan untuk mereka. Satu kajian retrospektif telah dijalankan menggunakan data daripada pesakit epilepsi bermula dari tahun 2010 sehingga 2017 yang telah menerima rawatan selama lima tahun dan dibandingkan dengan data subjek kawalan yang dipilih berdasarkan keputusan imbasan tomografi computer (CT) di Jabatan Radiologi, Hospital Universiti Sains Malaysia (HUSM). Sejumlah 200 data imbasan CT telah dikumpulkan daripada arkib dan kelulusan daripada pihak berkuasa telah dipinta untuk memastikan kelangsungan kajian ini. Berdasarkan kriteria inklusi, kajian ini dibahagikan kepada kumpulan epilepsi dan kawalan bagi kedua-dua jantina didalam anggaran dimensi antropometri (lelaki n=14, perempuan n=15), SBT (lelaki n=17, perempuan n=15), dan ICV (lelaki n=17, perempuan n=15). Data imbasan CT yang lain telah diketepikan berdasarkan kriteria eksklusi. Analisa data telah dijalankan di Pusat Pengajian Sains Pergigian, USM. Imbasan CT secara tiga dimensi (3D) telah

digunakan untuk mengukur kedua-dua parameter kraniofasial dan SBT melalui perisian MIMICS; manakala MITK 3M3 bagi mengukur ICV. Sebanyak dua puluh parameter telah digunakan bagi pengukuran antropometri kraniofasial. Ukuran SBT telah dilakukan di tiga lapisan; iaitu di glabela, di bregma, dan diantara keduanya. Tahap ukuran konsistensi telah ditentukan oleh tiga penilai bagi kedua-dua parameter kraniofasial dan SBT, dan dua penilai bagi ukuran ICV. Data daripada ukuran kraniofasial pesakit epilepsi lelaki menunjukkan bacaan tambahan ukuran yang ketara di nasion_bregma dan bacaan yang kurang pada ukuran lengkuk zigoma tengah kepada lengkuk zigoma tengah, nasion kepada alveoli, lebar nasal atasan kanan ke kiri, lebar zigoma atasan kanan ke kiri, lebar zigoma bawah kanan ke kiri, berbanding dengan kumpulan kawalan. Manakala, dikalangan pesakit epilepsi perempuan, ukuran rabung orbit depan-atasan kanan ke kiri adalah lebih tinggi dan lebar; zigoma atasan kanan ke kiri lebih rendah berbanding kumpulan kawalan. Oleh itu, kajian ini dapat menyimpulkan bahawa epilepsi mungkin memberi kesan terhadap perubahan pada tulang muka dan cranium. Bagi SBT pula, kumpulan lelaki tidak menunjukkan perubahan yang ketara; namun kumpulan pesakit epilepsi perempuan telah menunjukkan pertambahan ukuran ketara pada glabella_bregma. Data ukuran ICV pual tidak menunjukkan sebarang perbezaan di antara kedua-dua jantina. Sebagai konklusi, keputusan hasil kajian ini keatas kumpulan epilepsi adalah mungkin di sebabkan oleh pengaruh kesan ubatan anti-epilepsi di kalangan pesakit epilepsi. Data daripada kajian ini akan memberi manfaat kepada para pengkaji di bidang kraniofasial dan juga para pengamal perubatan yang terlibat secara langsung di dalam memberikan rawatan kepada pesakit epilepsi.

**Key words:** Epilepsi, Ketebalan tulang tengkorak, Kraniofasial, Isipadu otak intrakranial, Komputasi Tomografi, MITK 3M3

# CRANIOFACIAL ANTHROPOMETRY, SKULL BONE THICKNESS AND INTRACRANIAL VOLUME CHANGES IN EPILEPTIC PATIENT


## ABSTRACT

Epilepsy is a genetic and neurological disorder. Prolonged use of anti-epileptic drugs causes atypical facial shape, facial coarsening, gingival hyperplasia, gum hypertrophy. Many studies were done on craniofacial dimensions, skull bone thickness (SBT), and intracranial brain volume (ICV) in normal populations of different countries and races and different disorders, but very few references were found on epilepsy patients. The present study examined craniofacial anthropometry, SBT, and ICV in male and female epilepsy patients in Malaysia, it could aid with a better care approach for them. A retrospective study was done using data from epileptic patients from 2010-2017 who were under medication for five years as well as data from control subjects were selected who had their computed tomography (CT) scan at the Radiology Department, Hospital Universiti Sains Malaysia (HUSM). A total of 200 CT data of 18-60 years of age of both gender were collected from the archive 2010-2017 duration with permission for this study. Based on the inclusion criteria, subjects involved in this study were divided into epilepsy and control groups of both genders in anthropometric dimensions (male n= 14, female n= 15), SBT (male n= 17, female n= 15), and ICV (male n= 17, female n= 15) estimation. Other CT data were excluded based on exclusion criteria. Data measurements were carried out in the School of Dental Science, USM. A 3D CT scan was used for the measurement of both craniofacial and SBT by using MIMICS software and MITK 3M3 software was used for ICV measurement. Twenty parameters were used for craniofacial anthropometry measurements. SBT was

measured at three levels; at glabella, at bregma, and in between the two. The internal consistency level was determined by three raters for craniofacial and SBT, and two raters for ICV measurements. In the craniofacial measurement, epileptic males showed significantly higher measurements in nasion_bregma (n_br) and lower measurements in the mid zygomatic arch to mid zygomatic arch (zy_zy)), nasion to alveoli (na_al), superior nasal width right to left (snmr.r-snmr.l), superior zygomatic width right to left (zt.r_zt.l), inferior zygomatic width right to left (zti.r_zti.l) compared to the control group. Anterior-superior orbital ridge right to left (sor.r_sor.l) was significantly higher and superior zygomatic width right to left (zt.r_zt.l) was significantly lower measurements in epileptic female than the control. Regarding craniofacial anthropometry, the study can conclude epilepsy might have effects on some facial and cranial bones but not on all areas in both genders. For SBT, the male group did not show any significant difference but epileptic females showed significantly higher measurements in glabella_bregma. It can determine that epilepsy may not have an effect on male skull bone but can produce an effect on female skull bone.ICV did not reveal any significant differences between epileptic and control groups and epilepsy might not have any effect on ICV of both genders. The current findings in the epileptic group could be attributed to the effects of anti-epileptic medicines particularly in the treatment of epileptic populations. Furthermore, this reference data will be a valuable resource for craniofacial researchers as well as medical experts in the future for the betterment of their lives.

**Keywords:** Epilepsy, Skullbone thickness, Craniofacial, Intracranial brain volume, Computed Tomography, MITK 3M3

# CHAPTER 1

# INTRODUCTION

## 1.1 INTRODUCTION OF EPILEPSY

Epilepsy is the third most common neurological disorder, succeeding stroke and Alzheimer's disease. The highest frequency of newly identified cases occurs among children and adults. About 50 million people globally have epilepsy and nearly 80% of epilepsy occurs in developing countries including Malaysia (Arulsamy et al., 2015). 1st task force of the International League Against Epilepsy, (2005) (ILAE) mentioned the conceptual or theoretical definition of epilepsy as a disease characterized by a stable predisposition to generate epileptic seizures as well as the neurobiological, cognitive, psychological, and social consequences of this condition. One important note to mention is that seizures and epilepsy are not the same. Seizure is an event and epilepsy is the disease (Shakirullah et al., 2014). ILAE (2005) also mentioned that "A seizure (epileptic) is a spasmodic event due to abnormal, excessive, hypersynchronous discharges from a cumulation of neuron of the central nervous system (CNS)". Abnormal CNS activity has various manifestations, which depend on the distribution of discharges. However, in some individual cases, the conceptual definition of epilepsy was not clear. So practical (operational) definition of epilepsy was designed for both doctors and patients. Fisher et al defined as "Epilepsy is the disease which has at least two unprovoked or reflex seizures happening more than 24 hours at a distance" (Fisher et al., 2014) The operational definition reflects the clinicians' thinking about epilepsy, though this definition is

also not perfect. This definition will be improved when more information is collected about seizures for the better treatment of epileptic patients (Fisher et al., 2014).

There are several important causes of epilepsy was found such as genetic factors, head injury, birth trauma, cerebrovascular disease, and intracranial infections (Shakirullah et al, 2014)

Conferring to World Health Organization, (WHO) epileptic disorder is an abnormal brain activity that causes episodic disturbances in movement, consciousness, or feeling when there is a sudden intense electrical impulse occurs (Arulsamy et al., 2015). Nowadays, epilepsy is defined as a "disease", not a "disorder". International League Against Epilepsy (ILAE) redefined the definition of epilepsy**.** The new definition and classification facilitate the investigation, drug applications or surgical treatments, responses, and typical clinical courses for different types of seizures and epilepsy (Jessica J et al., 2018).

### 1.1.1 Classifications of Epilepsy:

#### 1.1.1 (a) Focal seizures

Focal seizures are confined within cerebral hemispheres. They are classified into simple and complex seizures. Complex partial seizures are related to loss of consciousness whereas simple partial seizures are not, and it is less harmful unless related to loss of consciousness. The epileptic process of simple partial seizures is involved with the neocortical structures, the limbic system, and the brain stem.

Partial seizures can convert into generalized seizures and change into secondarily generalized seizures.

### 1.1.1 (b) Primary generalized seizure

This type of seizure can occur at an early age which is associated with the family history. It produces concurrently from both cerebral hemispheres and clinically involves both sides of the body. Various causes of the epileptic disorder are related to structural brain loss tumors, infection, infraction, developmental anomaly, vascular malformation, specific brain pathology, etc. Different groups of seizures provide the knowledge regarding the types of neurological imaging like computed tomography scan which is appropriate for proper diagnosis with its superior soft-tissue contrast, multiplanar imaging capability, and lack of beam hardening artifacts, nearly all the substrates of epilepsy are seen with greater sensitivity than the accuracy of MR imaging.

### 1.1.1(c) Frontal lobe epilepsy (FLE)

Frontal lobe epilepsy is classified as either a focal or secondary generalised seizure or a combination of the two. Frontal lobe epilepsy is the most prevalent type of focal seizure. It covers 20% to 30% of all partial epilepsies and it is the largest subgroup of the extratemporal lobe epilepsies common in children. The patients who had 18% frontal lobe locus underwent surgery (Hosking PG, 2003).

### 1.1.1(d)Temporal lobe epilepsy (TLE)

Partial-onset epilepsies account for about 60% of all adult epilepsies, while temporal lobe epilepsy (TLE) is the most common one. It needs advanced neuroimaging, positive EEG, and appropriate clinical semiology for proper diagnosis (Jose and Lizbeth, 2012).

## 1.2 INTRODUCTION ON PARAMETERS

### 1.2.1 Introduction & History of Craniofacial Anthropometry

Anthropometry is an art and science broadly used for measuring soft and hard tissue proportions (Chandra et al, 2012). Geography, ethnicity, nutritional status, and lifestyle have a significant impact on body dimensions. Anthropometric study shows variations in craniofacial appearance and body characteristics among the different races [Farkas et al, (2005); Farkas et al (1994)]. Variations were observed in the anatomy of the head and neck area by direct measurements from radiography or in situ cephalometry [Farkas et al, (2005); Enlow et al, (1982); Harris et al, (1977)]. An anatomist named Johann Sigismund Elsholtz from Germany was the first to develop anthropometrical techniques in 1654 [Jayaratne and Zwahlen, (2014); Kolar and Salter,(1997)]. Before developing the practical scientific field, the term anthropometry had generally been used to discuss the human soul. However, further development of the anthropometry process took place during the last two centuries. During this period of development, many techniques had been applied to enrich the process of anthropometry. Elsholtz's technique is an important one that was widely

used throughout both the 18th and 19th centuries for human growth and quantitative morphological studies on population classifications. Many of the researches were focused on the cephalic index which is a ratio between the width and length of the cranium. Furthermore, comprehensive measurements of the body were conceivable after developing several instruments for anthropometry such as spreading and sliding calipers. For the first time in 1870 anthropometry examines the whole human body or measures, the proportions of its parts were used by Quetelet from Belgium. Nevertheless, anthropometry was first designated by Alphonse Bertillon in 1879. Farkas and Kerel Hajnis, renowned anthropologists together developed a system of facial measurement of congenital anomalies and traumatic deformities in patients, but Farkas also worked on creating the largest database of North American White (NAW) adults and Children norms [Jayaratne and Zwahlen, (2014); Anderson and Habal, (2009)].

Anthropometric studies on the living body are termed somatometry. The branch of somatometry that deals with the measurement of the head are called cephalometry. The measurements of the skull are called craniometry. Facial proportion differs among the different ethnic groups and today, most of the available studies are done on the western population **(**Taskinalp and Erdem, 2009).

The head part of the human body shows the least change. The skull part contains higher bony tissue, so its growth is much slower from birth. Also, due to its structure, it contains lots of fixed points. These points are called surface landmarks or anthropological points. The head defines the majority of the anthropological points in

the human body. Because this feature makes the studies is easier and more reliable. [Yıldırım and Mesut (1995); Mesut and Yıldırım, (1989)].

The facial image helps to estimate the age of a person. Age estimation in this study is defined as the age of a person based on his or her biometric features, precisely because of two-dimensional facial images (Petra GRD, 2013). Many research projects were done on the craniofacial morphology of individuals from different aspects. Anthropometric measurements of the face are significant in facial reconstructive surgery and in determining optimal face proportions (Taskinalp and Erdem, 2009). The information on these variations is of great value in case of reconstruction of craniofacial abnormality or for medico-legal purposes. The knowledge of normal craniofacial patterns of subjects belonging to various ethnic and age groups is important for clinical and research purposes (Alcalde et al, 1998). The different factors motivated many researchers to measure the normal characteristic values of different races and ethnic groups in the world (Alam M.K et al, 2013). The principle of the analysis is to compare the data of the patient with a normal reference group so that it makes the difference between the patient's actual dentofacial relationship and those expected for his/her racial and ethnic group are revealed. Most cephalometric studies have proven that the 'norms' should be based on ethnicity, sex, and age differences [Alam et al, (2013); Purmal et al, (2013); Wu et al, (2007); Ajayi OE, (2005); Yeong and Huggare, (2004); Cooke and Wei, (1988)].

Anthropometry is not only used by medical clinicians and maxilla-facial surgeons but also by other professional groups of people such as anthropologists, clinician dentists, forensic specialists to law enforcement officials who are concerned

about this inter-ethnic or racial facial variation, but scientifically proven studies on this issue are significantly rare. The craniofacial study will be helpful in the field of plastic and reconstructive surgery, head-neck surgery, oral and maxillofacial surgery, orthodontics, and forensic investigations. Computer-based stereophotogrammetry and dense surface models were effective in detecting subtle relevant face shape abnormalities or dysmorphisms in patients with epilepsy and pathogenic structural genomic variants (Chinthapalli et al, 2013).

### 1.2.2 Introduction on skull bone thickness (SBT) with general anatomy

The bones of the skull are classified as the cranium and facial bones. The vault is the upper half of the cranium, whereas the base of the skull is the lower part (Standring S, 2020). The skull is the head's bony skeleton. It protects the brain, specific sense organs, and cranial sections of the respiratory and digestive systems, as well as provides attachments for many of the head and neck muscles. It includes 22 bones, out of these 8 cranial bones that form the neurocranium are connected by synarthrodial joints. The cranium consists of the following bones, two of which are paired Frontal bone: 1, Parietal bones: 2, Occipital bone: 1, Temporal bones: 2, Sphenoid bone: 1, Ethmoid bone: 1. The facial bones consist of the following, two of which are single: Zygomatic bones: 2, Maxillae: 2, Nasal bones: 2, Lacrimal bones: 2, Vomer: 1, Palatine bones: 2, Inferior conchae: 2, Mandible: 1 (Snell R., 2011).

Most of these cranial bones are considered flat bones and can be identified by a layered bone structure where a cancellous bone layer, called diploe makes a sandwich between two layers of dense cortical bone. These cortical layers are

represented as the inner and outer tables of the skull (Saladin., 2007). The inner table is more fragile and thinner than the outward table. The periosteum covers the outer and interior surfaces of the bones. Previous studies have utilized cadavers and primates to evaluate the mechanical properties of the skull [McElhaney et al, (1970); Hubbard et al, (1971); Jaslow CR., (1990); Peterson and Dechow., (2003)].

The skull is a valuable source of information for establishing biological and personal identification. The diagnosis of sex from a young skull is particularly unpredictable. While sex differences in measures of the mandible, orbits, tooth size, and pattern of the dental eruption have been found, they do not reach a degree of discrimination that will allow consistent and efficient assessment. In general, the male skull is more sturdy and the female skull is more slender, though there are obvious genetic, and thus ethnic, differences that must be considered when determining sex from a skull. The female forehead is often taller, more vertical, and more rounded than the male, and there is noticeable retention of the frontal eminences in the female (Snell R, 2011).

Facial reconstruction is important for forensic investigation. Identify in general, there are two ways of facial reconstruction: (1) Computer reconstruction — a laser 3-D scanner is used to scan the skull, and an 'average' virtual face is wrapped around the skeletal structure. This method is mainly automated and involves little training and skill. It is quick and cheap to implement, but it requires a big data set to ensure that the 'average' face used is appropriate. (2) Modeled reconstruction - the skull is typically cast, and pegs are put into the cast at the required tissue depth. In the 'American' method, a clay skin is subsequently formed over the pegs to imitate

the face. Facial superimposition is important once a possible name has been determined, the skull may need to be compared to images of the suspect. In some cases, an image of the skull is placed on a picture of the missing person's face (Standring S, 2020).

### 1.2.3 Introduction on intracranial volume (ICV)

Evaluation of brain development and atrophy of the brain by the measurement of brain volume is a valuable indicator. Diagnosis and follow-up of neurological diseases provide a useful contribution. Length measurement of the ventricular size and the subarachnoid space has been performed by a two-dimensional method using single CT scan slices. However, this method does not present an accurate estimation of the ventricular or other intracranial volumes. Nowadays, the development of modern imaging techniques like magnetic resonance imaging (MRI) and CT images have made possible accurate measurements of ICV [Ambarki et al., (2012); Ambarki et al., (2011); Anderson et al., (2007); Bradley et al., (2004); Buckner et al, (2004); Embong et al, (2013); Rajion AZ,(2006); Sahin et al, (2008)] where possible assessable information from slices were taken through different parts of the living brain. Recently measurements of intracranial volume have been assumed by three-dimensional measurement using CT scan slices of the brain and cranium (Hamano et al, 1990).

Intracranial volume (ICV) is well-defined as the volume within the cranial cavities including the brain, meninges, and cerebrospinal fluid (Whitwell et al., 2001). The volume rises from birth throughout childhood. The maximum growth is

completed in the first five years (Sgouros et al., 1999). The ICV reaches its final size at the age of 16-20 years and it was supposed that it does not change its size thereafter (Wolf et al., 2003). At about 20 years of age, the brain volume begins to decrease, however it is assumed that ICV remains constant even after the brain atrophies, as it is replaced with cerebrospinal fluid (Rushton and Ankney.,1996). Neurodegenerative disease and premature brain size ICV measurements may also provide reliable indicators [Jenkins et al., (2000); Mazonakis et al., (2004); Pengas et al., (2009)]. During the last decades, many studies have focused on the assessment of ICV [(Anderson et al., (2007); Sahin, (2012); Tate et al., (2011); Ueda et al., (2010)].

ICV gives us a more constant and accurate normalization factor for estimating volumetric changes at the onset of a disease (Eritaia et al, 2000). Numerous procedures have been proposed for the assessment of ICV such as anthropometry, cephalometry, point-counting, and planimetry techniques (Sahin et al 2007). The packing method is the most accurate in vitro method for the measurement of ICV. The others are the linear measurement and cephalometry methods predicting the ICV using measuring the length, width, and height of the skull directly over the bony structure or lateral and anteroposterior roentgenograms (Manjunath YK, 2002).

## 1.3 PROBLEM STATEMENT

Studies of general craniofacial morphometry have been done in different parts of the world such as Europe (Toma et al, 2011), Africa (Manyama et al, 2014), some Asian nations (Ngew and Aljunid, 2009), and the United States (Goodwin et al, 2014). Only a few studies on quantitative craniofacial features have been performed

on normal subjects [Abdullah et al, (2006); Yusof A, (2007); Hussien et al, (2009); Al-Khatib A, (2010)]. Based on the literature review, few references of craniofacial anthropometric data for epileptic subjects were found.

Seizures have a major impact on the development of cerebral damage. Early post-traumatic seizure (EPTS) enhances morbidity and mortality after traumatic brain injury (TBI). Post-traumatic seizures (PTS) and post-traumatic epilepsy (PTE) are common and severe consequences of traumatic brain injury. The anthropometric parameters of the skull have an important relation to traumatic brain injury especially associated with craniotomy or craniosurgery (Pingue et al, 2021). Data regarding three-dimensional CT scan in skull bone thickness and intracranial brain volume of epileptic patients in Malaysia have not yet been examined. Detailed quantitative analysis of the characteristics features of the craniofacial anthropometry, skull bone thickness, and intracranial brain volume in epilepsy patients using 3D technology would be useful for clinicians for better and improved management to maintain their quality of life in the future.

## 1.4 JUSTIFICATION

The measurement of skull bone thickness and intracranial brain volume by 3D CT scans are noble in epileptic patients in Malaysia. The imaging studies regarding the craniofacial anthropometry, skull bone thickness, and intracranial brain volume measurement using CT scan should be contributed as essential clinical and valuable research data of the epileptic patient in Malaysia. The current study evaluates the variation of intracranial volume as well as skull bone thickness that

affect the shape of the face in epileptic patients as compared to control the population.

In a study suggested by Chintapalli K., (2012), anti-epileptic medications influence facial appearances on the face, such as gingival hyperplasia, acne, facial coarsening, or weight gain after long-term usage (Chintapalli K, 2012),. Anthropometric craniofacial pattern profiles are used to define atypical facial proportions in a certain syndrome, especially in genetic disorders. This study will determine the dimensional accuracy of the craniofacial measurements of the face which will help maxillofacial surgeons to get an idea during reconstructive operation. In this study, 3D-CT will be applied as the exploration device to produce craniofacial information. This is because of the capacity of observing and performing estimations from a few survey points with spontaneous and quick repositioning of the 3D pictures (Katsumata et al, 2005). Additionally, 3D CT A digitization strategy will have turned out to be enormously exact and delicate to acquire the information, and it can be utilized as a part of both clinical practice and research grounds. This study uses an open-source framework that reduces costs for the benefit of the patients.

CT data of many craniofacial anomalies is necessary for treatment and research purposes. 3D CT scan may help to expand and improve treatment planning, provide comprehensive morphological study and clinical information. In advanced years, 3D CT imaging is the more extended and widely used normal data. 3DCT should be easily established and attained from the patient without disease process (Rajion AZ, 2004). The normal data can be used for a long time for clinical evaluation of patients and applied planning craniofacial surgical interventions. In this

study, the target is to evaluate the craniofacial anthropometry, frontal bone thickness, and intracranial brain volume changes in epilepsy by 3D CT scans, and such type of study was not conducted in Malaysia before. So, in this perspective this study is novel. Moreover, very few similar types of studies were carried out abroad as well. The present imaging study regarding the craniofacial anthropometry, skull bone thickness, and intracranial brain volume measurement using CT scan will contribute to essential clinical and valuable research data of the epileptic patients in Malaysia, which might be beneficial for the management of epileptic patients, to maintain their quality of life and volume interpretation images using craniometric measurements also concerning the craniofacial application.

## 1.5 RESEARCH HYPOTHESIS

### 1.5.1 Null Hypothesis

1. There are no significant differences in the craniofacial anthropometry measurements in the male epileptic group compared with the male control group as well epileptic females compared to control females.
2. There are no significant differences in the skull bone thickness (SBT) measurements in epileptic males related with the control male in addition in a female epileptic group compared with the female control group.
3. There are no significant differences in the intracranial volume (ICV) measurements in epileptic males compared with the control males and in a female epileptic group compared with the female control group.

### 1.5.2 Alternate Hypothesis

1. There are significant differences in the craniofacial anthropometry measurements in the male epileptic group compared with the male control group as well epileptic females compared to control females.

2. There are significant differences in the skull bone thickness (SBT) measurements in epileptic males related with the control males in addition in a female epileptic group compared with the female control group.

3. There are significant differences in the intracranial volume (ICV) measurements in epileptic males compared with control males and in the female epileptic group compared with the female control group.

## 1.6 OBJECTIVES

### 1.6.1 General objective

To compare the craniofacial anthropometry, skull bone thickness (SBT), and intracranial volume (ICV) measurements between normal and epileptic subjects using 3D imaging.

### 1.6.2 Specific objectives

1. To determine and compare the craniofacial anthropometric measurement in male control and male epileptic groups.
2. To determine and compare the craniofacial anthropometric measurement in female control and female epileptic groups.

3. To evaluate and compare the skull bone thickness (SBT) between male control and male epileptic groups.
4. To evaluate and compare the skull bone thickness (SBT) between female control and female epileptic groups.
5. To determine and compare intracranial volume (ICV) measurement between male control and male epileptic groups.
6. To determine and compare intracranial volume (ICV) measurement between female control and female epileptic groups.

## 1.7 SIGNIFICANCE OF THE STUDY

The assessment of craniofacial anthropometry, skull bone thickness, and intracranial volume in epilepsy patients is of prime importance in medical fields. Information and results of analyses derived from this study may also benefit individuals in other fields. In addition, these reference data will provide an important resource for craniofacial researchers as well as medical researchers in the future. This study only used the diagnosed epilepsy patients who were using antiepileptic drugs [Sato et al (2001); Sheth et al., (2002)]. So there would be changes present in frontal lobe epilepsy after using antiepileptic drugs for a long time to detect whether any changes occur in the facial and frontal cranial bones. However, it is difficult to evaluate the causes of the bony changes as those changes are due to epileptic disorder itself or chronic use of antiepileptic drugs; antiepileptic drugs are used as early as epilepsy is diagnosed (Sato et al, 2001).

Hence, we intended to measure the changes in craniofacial anthropometry, skull bones thickness (SBT), and intracranial volume (ICV) by 3D CT images using Mimics V17.0 and MITK 3M3 image analysis framework respectively in male and female epileptic patients and comparing with the control subjects in Hospital Universiti Sains Malaysia (HUSM).

## 1.8 SUMMARY OF CHAPTER 1

This chapter summarized the definition, epidemiology, causes, and epileptic group classifications of epilepsy. Besides, this study stated the problem statement, justification, research hypothesis, general and specific objectives, and significance of the study.

# CHAPTER 2

# LITERATURE REVIEW

## 2. LITERATURE REVIEW ON EPILEPSY:

### 2.1 Epidemiology of epilepsy

However epilepsy is common worldwide, it is understudied in most regions of the world. Epilepsy is related to different provocative causes and affects almost all generations, ethnicity, and ages population. The global prevalence rate of epilepsy varies among countries. On the other hand, epilepsy is comparatively higher in females than males in New York, Bolivia, Honduras, and Argentina. In Asian nations such as China, India, Turkey, and Saudi Arabia, the prevalence rate is higher in males and more common in females in Pakistan which is similar to European countries. The prevalence rate of epilepsy in males and females is also variable in African nations. Generalized epilepsy is common in America, Asia, Europe, and Africa when compared to the other types of epilepsies (Shakirullah et al., 2014).

The incidence rate of epilepsy is higher in developing countries than the industrialized states. This could be due to a lack of resources to treat epilepsy, as well as being more vulnerable to epilepsy's hazards, such as infections (Arulsamy et al., 2015). Similarly, the incidence is also higher in males than in females (Miskov S, 2009). Kapoor et al., (1998) concluded that the incidence of intracranial structural

lesions associated with epilepsy is relatively higher in younger than older children (Moifo et al., 2014).

## 2.2 Classification of epilepsy

The updated classifications of seizures and epilepsies, which were newly published by the International League Against Epilepsy (ILAE), are given in figure 1.1. These new classifications permit for the inclusion of some previously unclassifiable seizure types and utilize more instinctive terminology (Walter et al., 2018). The diagnosis of epilepsy is well-known if (1) two or more unprovoked seizures occur, or (2) one seizure occurs in a person whose risk of recurrence is at least 60%, or (3) one or more seizures occur in the context of a known epilepsy syndrome (Wiebe et al., 2001).

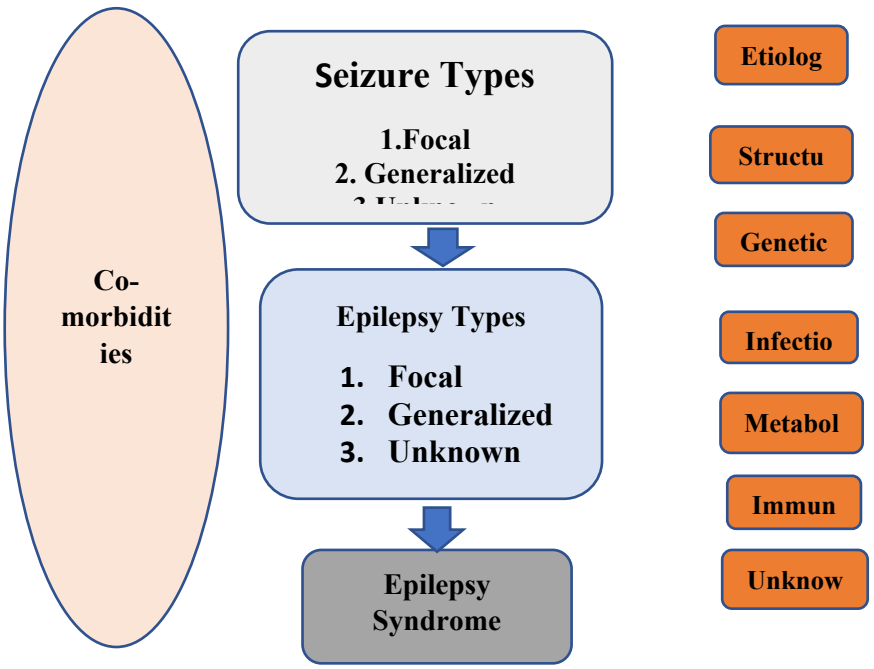


Figure 2.1: Classification of the epilepsies [International League Against Epilepsy (ILAE 2017)] Walter et al., (2018)

Intractable mesial temporal lobe epilepsy (MTLE) with hippocampal sclerosis (HS) patients who had long term video-EEG registered seizures included a study, it revealed generalized tonic-clonic seizures and symptomatic localised reacted epilepsy are more common in the 30-59-year-old male population, whereas females in 15-50 year age group have more idiopathic or genetic and cryptogenic or unknown generalised seizures. Men are more susceptible to seizures associated with structural brain damage [Janszky et al, (2004); Miscov S, (2014)]. Febrile seizures (FS), head trauma, positive family history, developmental delay, and genetic disorder are the contributing factors to the pediatric epilepsy population (Gadgil and Udani, 2011). A few studies suggested a single epileptic occurrence does not require any antiepileptic drug. Nevertheless, recurrence of two unprovoked seizures with abnormal electroencephalography with brain imaging, nocturnal seizures, or an epileptic syndrome associated with seizures should be started with monotherapy in adults. The proper AEDs drug is determined by the type of seizure. Antiepileptic medicines have a significant risk of antagonistic effects, which may include cognitive and behavioral impairments. When the patient has recovered from epilepsy for 2-5 years then discontinuation of antiepileptic drugs may be indicated **(**Liu et al, 2017)**.** Alternative treatments, such as surgical resection of the seizure focus, ketogenic diets, vagus nerve stimulators, and implantable brain neurostimulators, will be considered for seizure patients who are uncontrolled with these medications.(Copeland L et al, 2017). A study conducted in Nigeria showed anti-epileptic medicine hurt antioxidants (Iwuozo E, 2016). A study of women with epilepsy (WWE) with unfavorable pregnancy outcomes, normal pregnancy outcomes, and healthy controls on the Kerala Registry of Epilepsy and Pregnancy in South India revealed that usage of AED is linked to fetal malformations and teratogenesis (Damayanthi et al, 2012).

It has recently been established that pregnant women with epilepsy (WWE) who use anti-epileptic medicines (AEDs) such as Valproic acid and its monotherapy application is responsible for the development of congenital malformations (Cynthia and Nitin, 2008).

### 2.2.1 Frontal lobe epilepsy (FLE)

Based on location, a focal seizure can be classified as focal, temporal, occipital, and parietal. Frontal lobe epilepsy affects various areas of the brain, including the dorsolateral, frontolateral, orbitofrontal, cingulate gyrus, and motor regions. It is caused by a variety of medical disorders, including head injury, trauma, tumor, infection, and genetic disorder. It also affects both sexes equally, but men are more affected than women. When compared, the onset of left frontal lobe seizures affects those around the age of 11, while the right frontal lobe epilepsy usually begins earlier at 9 years of age **(**McGonigal and Chauvel, 2004). In frontal lobe epilepsy, the patients who do not respond to anticonvulsant medications are treated with surgery, and for those who are not eligible for surgery, electrical brain surgery is used as an alternative method (Kellinghaus and Luders, 2004).. Seventeen FLE children (10 female and 7 male) showed that there was frontal and extra frontal cortical thinning present in both right and left FLE patients (Widjaja et al, 2011).

### 2.2.2 Temporal lobe epilepsy (TLE)

An author said primary temporal lobe epilepsy is managed by antiepileptic drugs but patients resistant to drugs should be assessed by surgical resection (Ojemann and George, 1997). The effective and safe surgical way of temporal lobe epilepsy is anterior temporal lobe resection (Copeland et al., 2017).

## 2.3 Genetic basis of craniofacial abnormalities about epilepsy

Genetics is one of the potential causes of epilepsy, which is a typical heterogeneous disorder. Several mechanisms which cause epilepsy have been identified during the last 20 years, and it is assumed that 40-70 percent of all episodes of epilepsy are caused by hereditary factors (Zubkov and Kuzniecky, 2015). .Recurrent seizures are more common and are linked to structural brain damage. Nonetheless, repeated unprovoked seizures or idiopathic seizures have no definitive reason but neurological abnormalities are thought to be hereditary (Steinlein KO, 2008). Most of the genes expressed in the brain and convert subunits of ion channels, play an important role in neuronal propagation. Interruption of genes persuades brain hyperexcitability and initiates seizures. Genes like LIS1, DCX, ARX, FLNA, GPR56, and MECP2 are related to syndrome and cerebral cortical malformations are highly associated with epilepsy. Recently, focal onset epilepsy associated with intellectual disability has been identified in mutations in TBC1D24. Currently, the ASPM gene is the major microcephaly gene, while the PNKP gene is linked to microcephaly with seizures and early-onset epilepsy with developmental delay. Mutations in the TUBA1A gene have been linked to both lissencephaly and

polymicrogyria, both of which have been linked to epilepsy (Zubkov and Kuzniecky, 2015). Chromosomal deletions and duplications have been found in patients with epilepsy of Trisomy 21, ring chromosome 20, fragile X syndrome. In recent years, copy number variants (CNVs) like microdeletions and microduplications have emerged as a potential pathogenic factor in a variety of neurological and psychiatric diseases (Vadlamudi et al., 2018). Recurrent microdeletions have been found in up to 3% of individuals with idiopathic generalised epilepsy in genome-wide scans of focal and generalised epilepsy (Poduri and Lowenstein, 2011). More pathogenic gene mutations, non-coding DNA variants, and copy number variations will be identified in the current day to elucidate the many pathways that can lead genes to seizures. (Steinlein KO, 2008).

The face develops very early in pregnancy, and it is strongly related to the cranial neural crest cells. Disruption in early embryological development can have a wide range of impacts, ranging from modest neurologic and facial traits, such as asymmetry, to a severe impact on facial shape as indicated by a CL/P (Cleft lip palate) or anomalies identified in craniofacial abnormalities. Heritability studies have shed light on the genetic and environmental factors that influence facial shape (Richmond et al., 2018).

### 2.4 Prevalence and effects of epilepsy in male

Epilepsy affects men, women, and children of all races, religions, ethnic backgrounds, and social classes. Individuals from certain groups of male populations have higher risk factors. Several important causes of epilepsy like genetic factors,

head injury, birth trauma, cerebrovascular disease, and intracranial infections are more prevalent in males than females **(**Shakirullah et al, 2014). The prevalence rate is higher in males in North, Central, and South America. Several studies showed a higher prevalence rate in males. [Melcon et al., (2006); Reggio et al (1996); Rocca et al, (2001)]. The prevalence is also higher in males in Asian countries such as China, India, Turkey, and Saudi Arabia. The prevalence of epilepsy in males and females in the sub-continent of Africa is inconstant. On the contrary, the prevalence rate in males is higher compared to females in Ethiopia, Tunisia, Kenya, and Zambia [Tekle-Haimanot et al, (1990); Reggio et al., (1996), Kaiser et al (1996); Attia-Romdhane et al, (1993)]. Dent et al (2005) showed in their study that the prevalence becomes higher in males as compared to females [Rwiza et al. (1992), Snow et al.,(1993)]. Compared with race and ethnicity, males also possess a higher incidence rate of status epilepticus, sudden unexpected death in epilepsy (SUDEP), prognosis, and mortality. These differences between males and females may be due to the influence of sex hormones on seizures and epilepsies, as well as changes in the endocrine system and levels of sex hormones by epileptiform activities. Nevertheless, the absolute difference in gender-specific prevalence is minimal. The study conducted in India showed that the prevalence of males (5.1 per 1000) is significantly higher than females (2.2 per 100) (Bharucha et al, 1988)**.** Regarding the effects of epilepsy, males had a higher rate of generalized and idiopathic tonic-clonic seizures, specific epileptic syndromes juvenile myoclonic epilepsy (JME), and temporal lobe epilepsy (TLE) also typical risk factors like brain injury (Kishk et al, 2019 & Yin Hu et al, 2021). A study also noted that men suffering from epilepsy have been discovered to be predisposed to erectile dysfunction 57 percent is the maximum (Hellmis E, 2007).

## 2.5 Prevalence and effects of epilepsy on females

Idiopathic generalized epilepsies (IGEs), which may represent 15-20% of all epilepsies are more common among females [McHugh and Dalanty, (2008); Kishk et al., (2019)]. The percentage differs from country to country in Europe such as in Italy where the prevalence is higher in females than males. A study suggested that the ratio become changes due to previous condition and the prevalence become higher in females than in males [Cruz et al, (1985); Lavados et al, (1992); Forsgren et al, (1992); Placencia et al, (1992); Nicoletti A., et al., (1999); Al Rajeh et al, (2001); Osuntokun et al, (1982); Osuntokun et al, (1987); Longe and Osuntokun, (1989)]. Compared to Asia, the prevalence is higher in females in Pakistan [Aziz H, (1997); Radhakrishnan et al, (2000); MacDonald et al, (2000); Onal et al., (2002); Li et al., (1985); Koul et al, (1988)]. Syndromes have been linked to such anomalies associated with certain AEDs, such as 'fetal hydantoin syndrome', Dysmorphic features, including epicanthal folds, long philtrum, flat nasal bridge, digital hypoplasia, and hypertelorism (Crawford et al, 1999). A study mentioned that the AEDs (Phenytoin, Valproate, Barbiturates, Benzodiazepines, Lamotrigine have adverse effects like facial clefts, craniofacial, Orofacial clefts as well non-syndromic facial cleft (Bangar et al, 2016).

## 2.6 Neuropsychiatric disorder in children and adolescents

Attention deficit hyperactivity disorder (ADHD) is common in children and adolescents. Children with epilepsy have an increased prevalence of mental health