A STUDY OF HIPPOCAMPAL T2 RELAXOMETRY VALUE IN TEMPORAL LOBE EPILEPSY PATIENT

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AED	Antiepileptic drug
AH	Amygdalohippocampectomy
ATL	Anterior temporal lobe lobectomy
CSF	Cerebrospinal fluid
EEG	Electroencephalogram
HS	Hippocampal sclerosis
ILAE	International League Against Epilepsy
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance spectroscopy
MTS	Mesial Temporal sclerosis
MTLE	Mesial Temporal Lobe Epilepsy
PACS	Picture Archiving and Communication System
RIS	Radiology Information System
ROI	Region of Interest
T	Tesla
TLE	Temporal Lobe Epilepsy
TE	Time to Echo
USM	Universiti Sains Malaysia
VNS	Vagal Nerve Stimulation
WHO	World Health Organization

ABSTRAK

Latar belakang: Pada masa sekarang, terdapat banyak teknik kuantitatif bagi pengimejan resonans magnetic (MRI) yang boleh mengesan perubahan pada lobar temporal bagi pesakit yang menghidap sawan lobar temporal otak. Salah satu dari teknik kuantitatif yang telah lama diketahui ialah bacaan T2 relaxometry. Secara keseluruhan, ianya mempunyai ketepatan yang lebih baik untuk pengesanan perubahan tidak normal pada lobar temporal otak berbanding dengan teknik kualitatif.

Metod: Ini adalah kajian keratan rentas perbandingan yang telah dijalankan di Hospital Universiti Sains Malaysia, Kubang Kerian. Seramai 51 orang peserta yang terdiri daripada 19 orang pesakit sawan lobar temporal otak dan 32 orang kontrol telah mengambil bahagian di dalam kajian ini. Kajian telah berjalan selama satu tahun lima bulan daripada Ogos 2021 hingga Januari 2023. Bacaan hippocampus T2 relaxometry bagi pesakit sawan lobar temporal otak dan juga kontrol telah dikira, dan perbandingan bagi purata bacaan untuk kedua- dua kumpulan dilakukan. Ini adalah bagi mengetahui bacaan T2 relaxometry hippocampus yang normal dan juga bagi mendapatkan bacaan tidak normal untuk pesakit sawan lobar temporal otak. Korelasi bagi bacaan T2 relaxometry terhadap umur, jangkamasa penyakit sawan dan juga kekerapan sawan telah dilakukan menggunakan korelasi Pearson.

Keputusan: Purata bacaan T2 relaxometry hippocampus untuk pesakit adalah lebih tinggi daripada bacaan kontrol. Manakala bacaan hippocampus kanan adalah lebih tinggi berbanding hippocampus kiri untuk golongan pesakit dan kontrol**.** Iaitu bagi pesakit bacaan hippocampus kanan dan kiri adalah 110.13 (10.51)ms dan 107.15 (9.43)ms masing- masing. Bagi kontrol pula bacaan hippocampus kanan dan kiri

adalah 99.54 (4.00)ms dan 97.00 (3.46)ms masing- masing. Bagi korelasi hanya jangkamasa penyakit sawan yang mempunyai korelasi sederhana positif dengan T2 relaxometry hippocampus kanan. Manakala korelasi lemah positif di antara T2 relaxometry hippocampus kanan dengan umur (**P**>0.01) dan juga korelasi lemah positif di antara kedua belah hippocampus dengan kekerapan sawan (**P**>0.01).

Kesimpulan: T2 relaxometry adalah merupakan teknik kuantitatif yang dapat membantu pengesanan perubahan tidak normal pada lobar temporal otak. Ianya telah dapat dibuktikan boleh mengesan perubahan pada lobar temporal seorang pesakit yang secara kualitatif dikatakan sebagai normal.

Kata Kunci: Sawan Lobar Temporal Otak, Mesial temporal sclerosis, T2 relaxometry, MRI protokol sawan

ABSTRACT

Background: In the advance of the current imaging technique for the detection of mesial temporal sclerosis for temporal lobe epilepsy patient, there are multiple quantitative techniques for Magnetic resonance imaging (MRI). One of the long known to be valuable technique is T2 relaxometry study where there is overall better accuracy for detection of mesial temporal sclerosis if compared with the qualitative assessment only.

Methods: This is a comparative cross-sectional study that was conducted at the Hospital Universiti Sains Malaysia, Kubang Kerian. A total of 51 participant were included in this study where 19 were temporal lobe epilepsy patients and 32 were control. Total duration of this study is one year and five months from August 2021 to January 2023. The hippocampal T2 relaxometry was calculated for control and temporal lobe epilepsy patient and the mean reading for these groups were compared. This is to get the normal value of hippocampal T2 relaxation time and abnormal value cut off point for epilepsy patient. The mean reading of T2 relaxometry for control and patient will be determine. Using Pearson correlation, the T2 relaxometry value correlation is made with age, duration of epilepsy and seizure frequency.

Results: The mean T2 relaxometry for epilepsy patient was higher than control. It is also noted to be higher in right hippocampus than left hippocampus in both patient and control. For temporal lobe epilepsy patient, the reading for right and left hippocampus were 110.13 (10.51)ms and 107.15 (9.43)ms respectively. Meanwhile for control the reading for right and left hippocampus were 99.54 (4.00)ms and 97.00 (3.46)ms

respectively. For correlation, moderate to good positive correlation was seen between the duration of epilepsy with T2 relaxometry of right hippocampus. Whereas poor positive correlation between the right hippocampus T2 relaxometry with age (***P***>0.01), as well poor positive correlation between both hippocampus T2 relaxometry with seizure frequency(***P***>0.01).

Conclusion: T2 relaxometry is a quantitate technique that can help in detection of subtle abnormality of hippocampus. In our study, one patient was reported to has normal hippocampus by qualitative assessment but had raised T2 relaxometry which follow the clinical diagnosis of epilepsy.

Keywords: Temporal lobe epilepsy, Mesial temporal sclerosis, T2 relaxometry, MRI epilepsy protocol

CHAPTER 1: BACKGROUND

1.1 Introduction

Epilepsy is a chronic non-communicable disease of the brain that affects around 50 million people worldwide. It is estimated that up to 70% of people living with epilepsy could live seizure free if properly diagnosed and treated (WHO, 2019).

The diagnosis of epilepsy normally requires the occurrence of at least 2 seizures more than 24 hours apart. Internationally acceptable classification of epilepsy types is based on the classification by International League Against Epilepsy (ILAE). Epilepsy types based on the revised ILAE classification 2017 are Focal Epilepsies, Generalized Epilepsy, Combined Generalized and Focal Epilepsies and Unknown type. (Scheffer *et al.*, 2017).

Focal epilepsies include unifocal and multifocal disorders as well as seizures involving one hemisphere. The interictal electroencephalogram (EEG) typically shows focal epileptiform discharges, however the diagnosis is made on clinical features and supported by EEG findings. Ideally, Magnetic resonance imaging (MRI) is the first neuroimaging investigation carried out to rule out the structural cause of epilepsy. The other five aetiologic groups are genetic, infectious, metabolic, immune and unknown group (Scheffer *et al.*, 2017).

Temporal lobe epilepsy (TLE) is known to be the commonest cause of focal epilepsy. About 70% of TLE is associated with hippocampal (mesial temporal) sclerosis; which histopathology evidence shows neuronal loss and gliosis (Sen and Sankaran, 2019). Hippocampus is a structure that is located at the medial temporal lobe which consist of head, body and tail. Anatomically, hippocampus is formed by

two distinctly interlocking C-shaped layers of neurons: the pyramidal layer (further designated as Cornu Ammonis; CA1, CA2, CA3, CA4) and dentate gyrus. Other major units of hippocampus are alveus, subiculum and fimbriae (Thomas *et al.*, 2008)**.** Classical hippocampal sclerosis (HS) is involving neuronal loss of CA1 subfields with preserved subiculum, relatively preserved CA2 and variable loss of CA3 with accompanying neuronal loss from the CA4 region. The non-classical HS include end-folium HS (neuronal loss restricted to CA4)**.** The other pathologic changes associated with HS include granule cell dispersion, mossy fiber sprouting, and alterations to interneurons. (Malmgren and Thom, 2012).

For qualitative MRI, visual assessment of hippocampal sclerosis (HS) are seen as volume loss, loss of internal architecture and T2/FLAIR signal hyperintensity. Hippocampal atrophy is usually associated with secondary signs such as lateral ventricle dilatation. Other secondary signs are atrophy of ipsilateral fornix, mamillary body and amygdala. HS is the most common pathology underlying refractory mesial temporal lobe epilepsy (MTLE) (Malmgren and Thom, 2012).

The term of refractory epilepsy or drug resistant epilepsy is failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drug (AED) schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom. Refractory epilepsy accounts for 30% of patient who do not respond to optimal treatment (Atrick *et al.*, 2000)(Murali and Raj, 2017)**.** For refractory seizure patient with maximum medical therapy, surgery is the next option to control the seizure. In a recent meta-analysis involving 16,253 participants, 10,518 (65%) achieved a good outcome of surgery (West *et al.*, 2015). A randomised controlled trial

study of adults with MTLE showed superiority of temporal lobe surgery when compared to continued AED therapy.

Based on USM experience, there are a total of 11 patients have undergone epilepsy surgery since 2004 until 2017. These surgeries include anterior temporal lobectomy (ATL) with amygdalohippocampectomy (AH) and vagal nerve stimulation (VNS). The post-surgery outcome of these patients based on ILAE scores are better in ATL with AH group compared to VNS with score of 1-3 and 4-5 respectively *(*Yee *et al., 2017)*

We aim to improve detection of mesial temporal lobe sclerosis by implementing the use of quantitative MR method in addition to the current qualitative method. This was important, aiming for the seizure free status in a surgically suitable patient.

1.2. Objective

1.2.1 General Objective

To assess hippocampal T2 relaxometry value in temporal lobe epilepsy patient.

1.2.2 Specific Objectives

1. To compare the mean T2 relaxometry value of hippocampus in temporal lobe epilepsy patient with control.

2. To correlate hippocampal T2 relaxometry value with age, duration of epilepsy and frequency of seizure.

1.3 Hypothesis

1. There is mean difference in hippocampal T2 relaxometry value between temporal lobe epilepsy patient with normal individual.

2. There is correlation between T2 relaxometry value with age, duration of epilepsy and seizure frequency.

1.4 Research Question

1. Is there any mean difference between the hippocampal T2 relaxometry value of temporal lobe epilepsy patient with normal individual.

2. Is there any correlation between the hippocampal T2 relaxometry value with patient's age, duration of epilepsy and seizure frequency.

CHAPTER 2: LITERATURE REVIEW

2.1. Quantitative methods for detecting hippocampal sclerosis

MR imaging can be divided into qualitative MR and quantitative MR. The example for qualitative (visual) MR assessments are T1W, coronal oblique T2W and coronal oblique FLAIR images of the hippocampus. Whereas for quantitative MR methods, the examples are volumetry study, Magnetic Resonance spectroscopy (MRS) and T2 relaxometry study. Quantitative MR provides a more sensitive and objective result in determination of related disease (Chen *et al.*, 2016) and can determine whether the abnormality is unilateral or bilateral (Bartlett *et al.*, 2007).

In temporal lobe epilepsy the qualitative changes for hippocampal sclerosis are seen as hyperintense hippocampus signal on T2W and FLAIR images, hippocampal atrophy and adjacent lateral ventricle dilatation as a secondary sign to hippocampal atrophy. Distinguishing mild or subtle hippocampal sclerosis from normal hippocampus is often not adequate with visual assessment (Murali and Raj, 2017). Approximately 15% of refractory epilepsy patient does not have MRI changes of hippocampal atrophy (Bernasconi *et al.*, 2000).

Types of quantitative MRI with overall accuracy for localisation of epileptogenic area:

1. Hippocampal volumetry - quantify hippocampal atrophy in relation with the individual subject head size. Overall lateralizing ability is 71% (Ercan *et al.*, 2016), Overall accuracy of 82.4% for localisation of epileptogenic area (Chen *et al.*, 2016).

2. Magnetic resonance spectroscopy (MRS) - Detecting biochemical changes before the visual changes by measuring NAA: (Cr/Cl). Overall lateralizing ability is 35% (Ercan *et al.*, 2016).

3. T2 relaxometry- Measuring T2 relaxation intrinsic to certain tissue. 94.1% overall accuracy for localisation of epileptogenic area (Chen *et al.*, 2016).

T2 relaxation value for grey matter is approximately 93 ms and for white matter is 97 ms (Carneiro et al., 2006). T2 relaxometry is one of MR quantitative technique type which measures T2 relaxation time intrinsic of certain tissue property (Winston et al., 2017). It is a quantitative MR method that uses multi spin echo sequence. The time to echo (TE) should be centered to T2 value of sample (Carneiro et al., 2006). There are also study which use fast dual- echo sequence for T2 measurement and it reveal to be reliable and showed good reproducibility (Okujava et al., 2002).

Study by Chen et al. have found that, among 17 patients who was diagnosed with refractory unilateral MTLE, all the abnormally high T2 values were correctly lateralised to the epileptogenic zone and 25 out of 27 of pathologically sclerotic region were detected by T2 relaxometry. There is one patient with negative MR findings has high T2 relaxometry and was confirmed on histopathology as subtle sclerosis.

Study by Bernasconi et al. have studied the value of T2 relaxometry on 11 patients with unilateral epilepsy but has no MR evidence of atrophy (labelled as normal MRI). They have found that T2 relaxometry is able to lateralise to the epileptogenic focus following history and video EEG in 9/11 patients. Seven of these patients operated, 5 sample have neuronal loss and 2 samples are not optimum. Six patients are seizure free post operation and one patient has rare occurrence of seizure.

Study by Sato et al. had shown that there are 4 patients with negative MR finding, which has T2 relaxometry that was concordance with the EEG findings. One patient is confirmed to have mesial temporal sclerosis, two patients have granular cell pathology and 1 patient has microdysgenesis. There was no post-surgical outcome stated for these patients. (*Sato et al*., 2016)

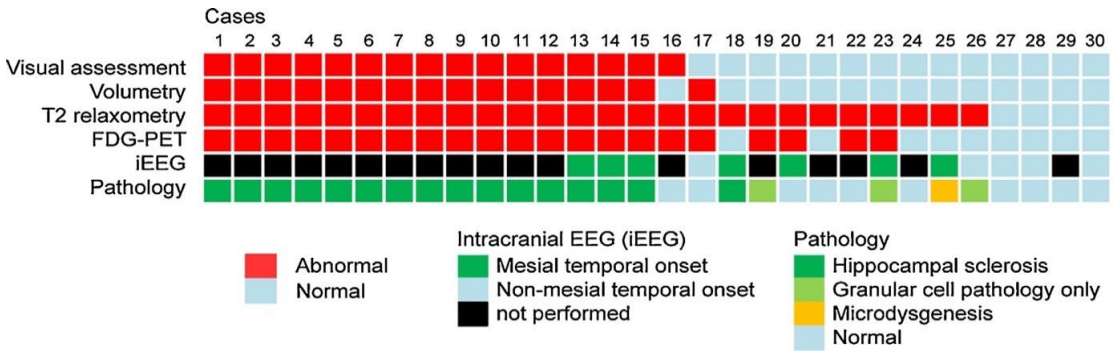


Figure 1: Summary result of study done by Sato et al. 2016

Although there are studies regarding T2 relaxometry done before, each of these studies were using different mean hippocampal T2 relaxometry which was derived from control population of these studies as tabulated in the Table 1.

Table 1: Comparison between previous studies regarding normal value cut off for T2 relaxometry.

Study	Control size (n)	Mean (SD) in millisecond (ms)		How measurement is taken	Scanner (T)
(Briellmann *et al.*, 2004) (Australia)	30	Right hippocampus 98 (2.7)	Left hippocampus 97 (3.5)	Circular ROI placed over hippocampal head	3.0
(Bartlett *et al.*, 2007) (UK)	15	Maximum 113 ms (1)		Drawn ROI over the hippocampus	3.0
(Chen *et al.*, 2016) (China)	14	Right hippocampus. 98.38 (3.96).	Left hippocampus 98.80 (3.91)	Drawn ROI over hippocampus and avoiding the CSF.	3.0
(Sato *et al.*, 2016) (Japan)	30	Right hippocampus 109.7(0.92)	Left hippocampus 109.88 (0.92)	Drawn ROI over the hippocampus, carefully avoiding CSF and hippocampus sulcus remnant.	3.0
(Winston *et al.*, 2017) (UK)	50	Right hippocampus 116.8 (3.60)	Left hippocampus 115.5 (4.11)	Automated segmentation with removal of voxel with >170 ms to minimise CSF contamination.	3.0
(Murali and Raj, 2017) (India)	20	Right hippocampus 101.57(6.87)	Left hippocampus 100.72(6.86)	Not stated	1.5

2.2 Temporal lobe epilepsy

Temporal lobe epilepsy (TLE) is known to be the commonest cause of focal epilepsy. Common features are memory impairment and aura. The diagnosis is made by clinical assessment with or without support evidence from EEG findings (Epilepsy management Malaysia, 2017). About 70% of TLE is associated with hippocampal (mesial temporal) sclerosis; which histopathology evidence shows neuronal loss and gliosis (Sen and Sankaran, 2019). In temporal lobe epilepsy the qualitative changes for

hippocampal sclerosis are seen as hyperintense hippocampus signal on T2W and FLAIR images, hippocampal atrophy and adjacent lateral ventricle dilatation as a secondary sign to hippocampal atrophy. Distinguishing mild or subtle hippocampal sclerosis from normal hippocampus is often not adequate with visual assessment (Murali and Raj, 2017). Approximately 15% of refractory epilepsy patient does not have MRI changes of hippocampal atrophy (Bernasconi *et al.*, 2000).

2.3 Electroencephalogram (EEG)

There are multiple types of EEG such as standard interictal scalp EEG and invasive EEG. It is used to detect the epileptiform discharges that support epilepsy diagnosis (Consensus Epilepsy, 2017). The characteristic EEG findings in the majority of temporal lobe epilepsy are spikes or sharp waves which phase reverse over anterior temporal regions(Nayak et al., 2020). However the interictal scalp EEG sensitivity is approximately 50% if done once and increased to 80% if repeated up to three times Consensus Epilepsy, 2017).

2.4 Intractable temporal lobe epilepsy or refractory epilepsy or drug resistant epilepsy

The term of refractory epilepsy or drug resistant epilepsy is failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drug (AED) schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom. Refractory epilepsy accounts for 30% of patient who do not respond to optimal treatment (Atrick et al., 2000)(Murali and Raj, 2017). For refractory seizure patient with maximum medical therapy, surgery is the next option to control the seizure. In a recent meta-analysis involving 16,253 participants, 10,518 (65%)

achieved a good outcome of surgery (West *et al.*, 2015). A randomised controlled trial study of adults with MTLE showed superiority of temporal lobe surgery when compared to continued AED therapy.

2.5 Conceptual Framework

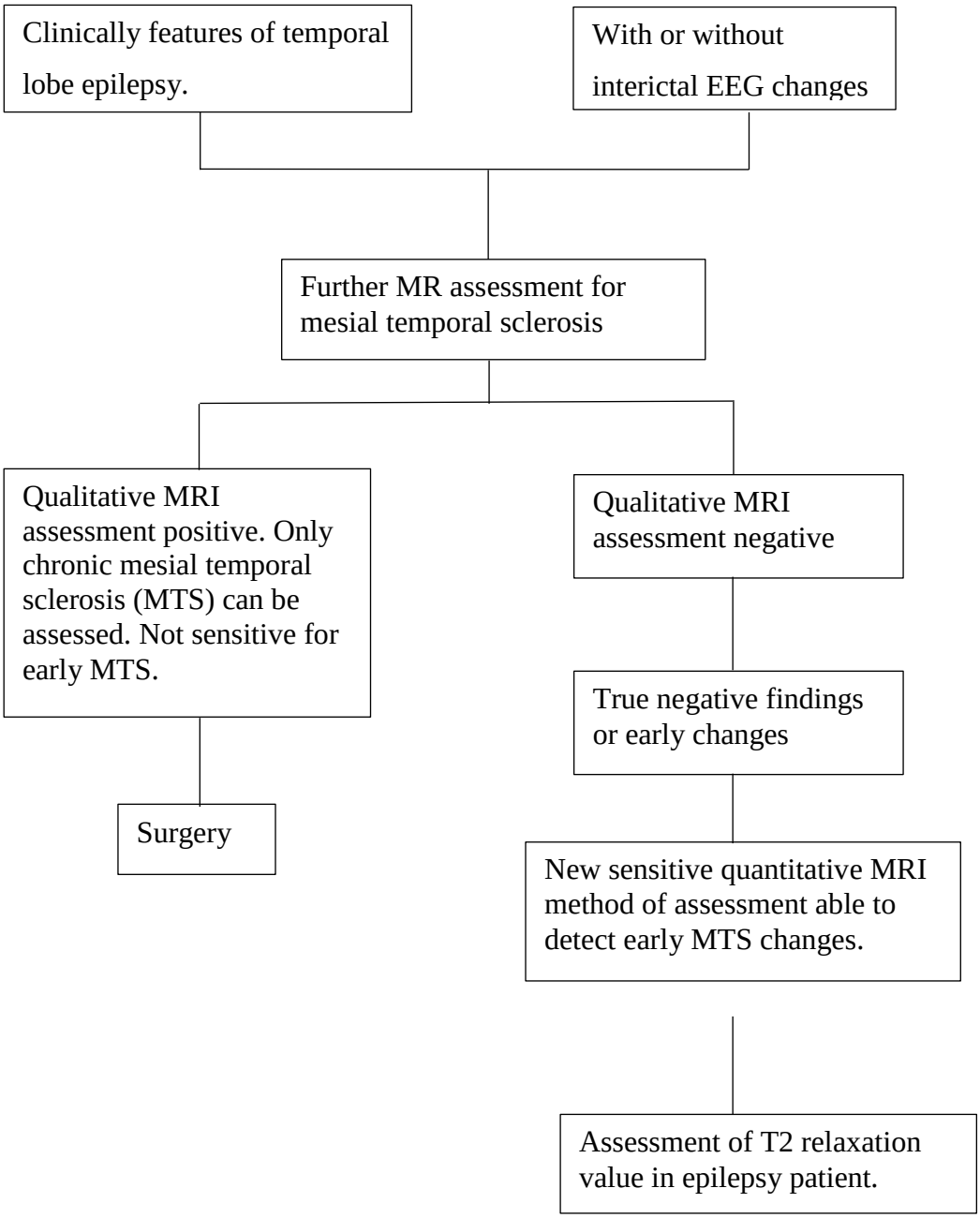


Figure 2: Conceptual framework

2.6 Rationale of Study

It has been proved from earlier studies that T2 relaxometry was able to detect hippocampal abnormalities and able to help for better prognostication on patient's outcome. However, the hippocampal T2 relaxometry normative value that was presented from few previous studies was different in each country although similar 3T machine was used. Hence no standardize value that was applicable worldwide. The difference may be attributable by the machine difference, population difference of technique difference.

To fill the gap, we aim to determine the mean T2 relaxometry normative in our center for future reference in diagnosing hippocampal abnormality in MRI. This is especially important to have a normative value to be able to be firm when deciding further treatment option for intractable epilepsy patient when their disease is not controlled despite of maximum antiepileptic drug (AED), however the MRI qualitative assessment is deemed normal.

CHAPTER 3: METHODOLOGY

3.1 Study Design

This is a comparative cross-sectional study which was conducted in MRI room, department of radiology, Hospital Universiti Sains Malaysia Kubang Kerian for one year and five months from August 2021 until January 2023. Data were collected from August 2021 until January 2023.

3.2 Sample Population

i. Reference Population/ Target population- Patient with confirmed case of temporal lobe epilepsy in Kota Bharu.

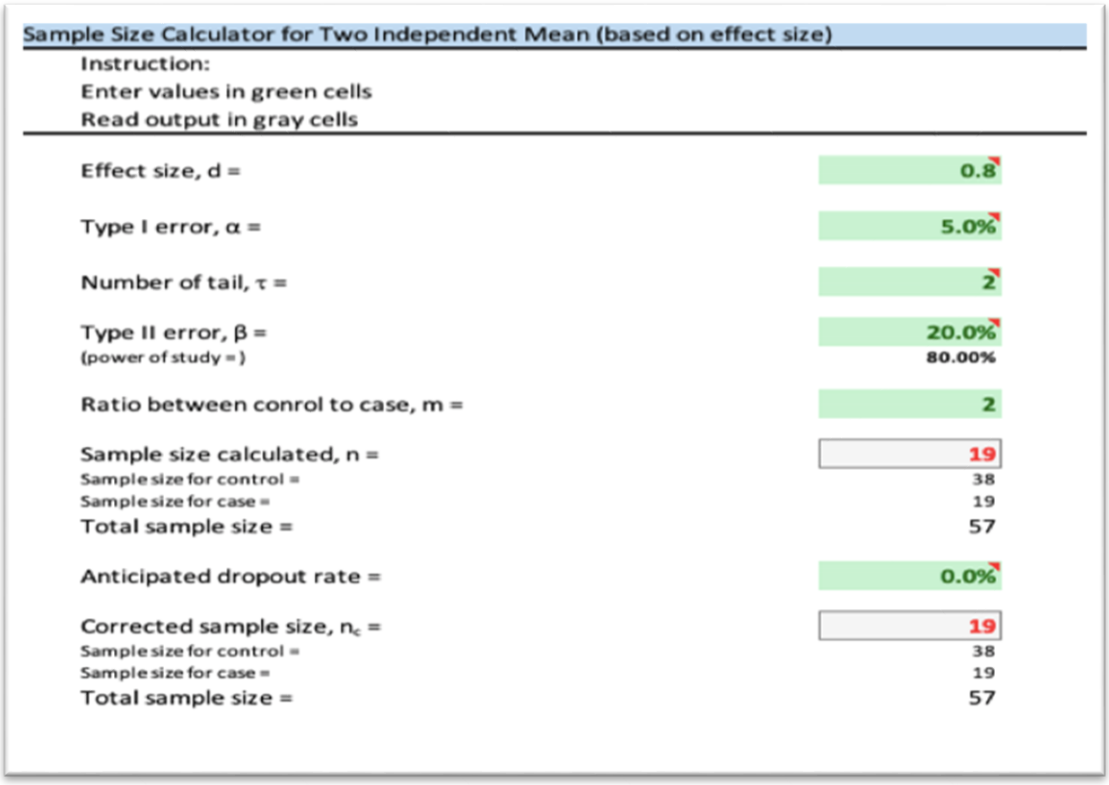
ii. Source Population- Temporal lobe epilepsy patient who get treatment in Universiti Sains Malaysia Hospital (HUSM).

iii. Study Population- Patient who is referred from neurology clinic for MR Brain examination.

iv. Sampling frame- Temporal lobe epilepsy patient who get treatment in Universiti Sains Malaysia Hospital (HUSM) based on inclusion and exclusion criteria.

3.3 Sample Size Calculation

1. For objective 1, the sample size is calculated using two independent mean from the effect size by using sample size calculator by Najib (2015). The effect size is set as 0.8, with alpha level at 5% and power at 80% and ratio between the control and patient is 2, estimated sample size for control is 38 and for patient is 19. Total sample size is 57. Reference is from Briellman *et al.*

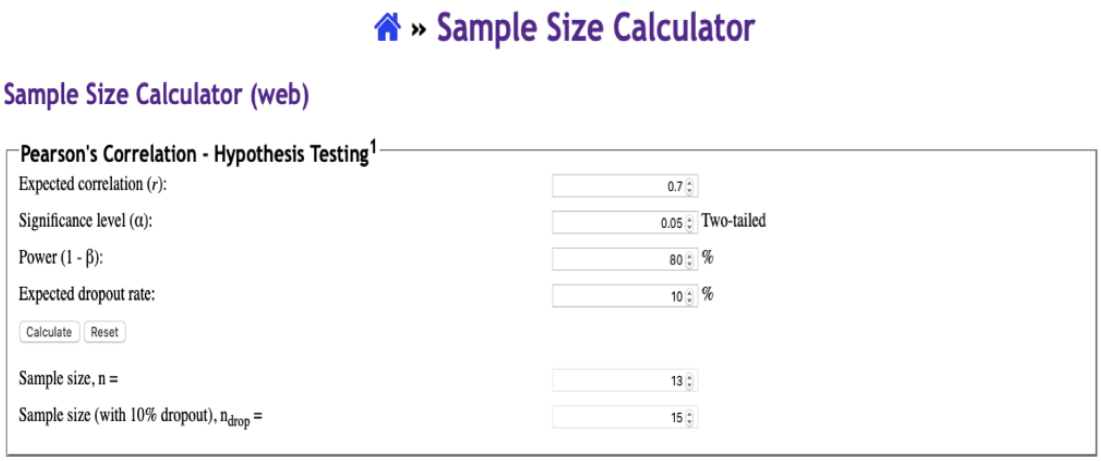


Sample Size Calculator for Two Independent Mean (based on effect size)

Instruction:
Enter values in green cells
Read output in gray cells

Effect size, d =	0.8
Type I error, α =	5.0%
Number of tail, τ =	2
Type II error, β =	20.0%
(power of study =)	80.00%
Ratio between conrol to case, m =	2
Sample size calculated, n =	19
Sample size for control =	38
Sample size for case =	19
Total sample size =	57
Anticipated dropout rate =	0.0%
Corrected sample size, n_c =	19
Sample size for control =	38
Sample size for case =	19
Total sample size =	57

2. For objective 2, which is to correlate hippocampal T2 relaxometry value based on age, duration of epilepsy and frequency of seizure. No previous study was done for correlation with T2 relaxometry. Using ample size calculator by Dr Arifin, W. N. (2021) is used. Using positive expected correlation with significance interval of 0.05 and power 80%, total estimated sample with expected dropout rate is 15.



From these two sample size, the sample size from objective 1 is taken as the study sample size where total sample size for temporal lobe epilepsy was 19 and total sample size for control is 38.

3.4 Sampling Method

Convenient sampling method- All temporal lobe epilepsy patients who fulfils inclusion and exclusion criteria will be included in the study. As for the control group, they are patients that has undergone MR brain for other reason such as chronic headache, tinnitus etc. Upon reviewing the MR images, they will be included in the study if the MR brain is normal, and they fulfil the inclusion criteria for control.

3.5 Inclusion Criteria

3.5.1 Inclusion Criteria for Patient

1. Age 15 years old and above.
2. Clinically diagnosed temporal lobe epilepsy
3. Seizure free within 72 hours before MRI is done.

3.5.2 Exclusion Criteria for Patient

1. Patient has other brain pathology (tumour, infarct etc).
2. Elderly patient with the age 65 years old and above with brain atrophy.
3. First trimester pregnancy.

3.5.3 Inclusion Criteria for Control

1. Age 15 years old and above.
2. Never has seizure before.
3. No psychiatric illness.
4. Normal MR brain findings.

3.5.4 Exclusion criteria for control

1. Has episode of seizure before
2. Underlying psychiatric illness
3. Abnormal MR brain findings
4. First trimester pregnancy.

3.6 Research Tools and Variables

1. Radiology Information System (RIS) – Picture Archiving and Communication System (PACS) version 6.0 and ViaRad for image acquisition and demographic/clinical data information.

2. Image Acquisition- MR imaging was performed by using Philips 3 Tesla (Achieve Mr scanner, Best, The Netherlands) with permitted automated shimming water suppression and data processing technique. A standard head coil will be used (SENSE-HEAD-32).

   MR sequences

   a) Brain sagittal T1W (TR 200/TE 15).

   b) Brain axial T1W (TR 200/ TE 33), T2W (TR 4300/TE 90).

   c) Temporal lobe series in coronal oblique perpendicular to long axis of hippocampus: in Coronal oblique T2W (TR 2185/ TE 100), Coronal Oblique FLAIR (TR 11000/TE 125).

   d) Coronal oblique T2_calc_MS sequence for the hippocampal region with multiple TE of 20/40/60/80/100 (T2 relaxometry sequence).

   The total duration for MR brain is 45 minutes to 1 hour. In this study, the additional T2 relaxometry sequence will take 5 minutes total duration to complete all the five different TE and is included in the total MR brain study duration of 45 minutes to 1 hour.

3. Philips Workstation – Using Philips IntelliSpace Portal 2015 software

4. IBM SPSS statistic version 28 will be used for data analysis.

3.7 Operational Definition

1. Temporal lobe epilepsy

Temporal lobe epilepsy was defined by the International League against Epilepsy (ILAE) a condition characterized by recurrent, unprovoked seizures originating from the medial or lateral temporal lobe. The seizures associated with this condition consist of simple partial seizures without loss of awareness and complex partial seizures (i.e. with loss of awareness). Common features are memory impairment and aura. The diagnosis is made by clinical assessment with or without support evidence from EEG findings (Epilepsy management Malaysia, 2017).

2. EEG findings

Electrophysiological examination was performed in the electrophysiological laboratories in Hospital Universiti Sains Malaysia, Neuroscience department. 25 lead EEG device with ECG. At least 2 separate EEG recordings were obtained from all patients and EEG records are evaluated and interpreted by a neurologist. The characteristic EEG findings in the majority of temporal lobe epilepsy are spikes or sharp waves which phase reverse over anterior temporal regions(Nayak *et al.,* 2020).

3. Seizure frequency

Adapted from American Academy of Neurology website. Each frequency type were given group numbers as follow:

7- Innumerable (i.e., ≥10 per day most days).

6- Multiple per day (i.e., 4 days per week with ≥ 2 seizures).

5- Daily (i.e., 4 or more days per week).

4- Weekly but not daily (i.e., 1–3 per week).

3- Monthly but not weekly (i.e., 1–3 per month).

2- At least once per year, but not every month (i.e., 10 or fewer in past 12 months).

1-Less than once per year.

0- Frequency not well defined.

4. Seizure duration

The seizure duration is taken as years in total where temporal lobe epilepsy patient had suffered the disease.

5. Refractory epilepsy.

Drug-resistant epilepsy as a failure of adequate trials of 2 tolerated and appropriately chosen and used anti-epileptic drug (AED) schedules.

6. Hippocampus anatomy on MRI.

The hippocampus is best visualised in the coronal oblique plane. The coronal oblique plane is angled perpendicular to the long axis of the hippocampal body. There are three parts of the hippocampus namely the head, body and tail. The MR landmarks are as follow:

a) Hippocampal head:

• basilar artery to interpeduncular cistern

• posterior most extent is the first slice where the uncal apex is clearly seen

b) Hippocampal body:

• interpeduncular cistern to superior colliculus.

c) Hippocampal tail:

• from superior colliculus

• from the point at which the fornix can be seen in full profile

7. T2 relaxometry.

This is an additional sequence which is called as T2_calc_MS for Philips machine. It is done in coronal oblique plane, perpendicular to the long axis of hippocampus. It is done with multiple TE 20/40/60/80/100. From these images of different TE, a T2 maps image is generated in the Philips workstation. This T2 map is an image in which each pixel intensity corresponded to the calculated T2 relaxation time. The calculation of the hippocampal T2 relaxation value is an automated calculation by drawing a region of interest (ROI) on the hippocampal head and body of hippocampus and taking the

maximum values as the mean value represented the T2 relaxation of that hippocampus.

3.8 Data Collection

1. Patients MR images will be interpreted by radiologist for qualitative assessment on the T2/FLAIR image looking for hyperintense signal and volume loss of the hippocampus. The secondary sign such as ipsilateral mamillary body, fornix and amygdala atrophy were also assessed. Later, this reading will be confirmed by senior radiologist independently. Findings will be listed in the report and presumptive diagnosis will be made by radiologists who reviewed the images. If there are any disagreement between radiologists, consensus must be reached, and collective decision made. The inter-rater reliability will be evaluated by using Cohen's kappa statistic.

2. The T2 maps images will be analyzed on the Philips IntelliSpace Portal 2015 workstation by the researcher without knowing the qualitative MR image result to prevent bias. The reading will be taken on the head and body of hippocampus. The highest reading will be the taken as T2 relaxometry value for that side of hippocampus. This is because previous studies have shown that in patient with unilateral hippocampal sclerosis, the anterior hippocampus was always affected (Woermann *et al.*, 1998). In control and patients, hippocampal T2 relaxation time was higher in the anterior than the posterior hippocampus (Woermann *et al.*, 1998).

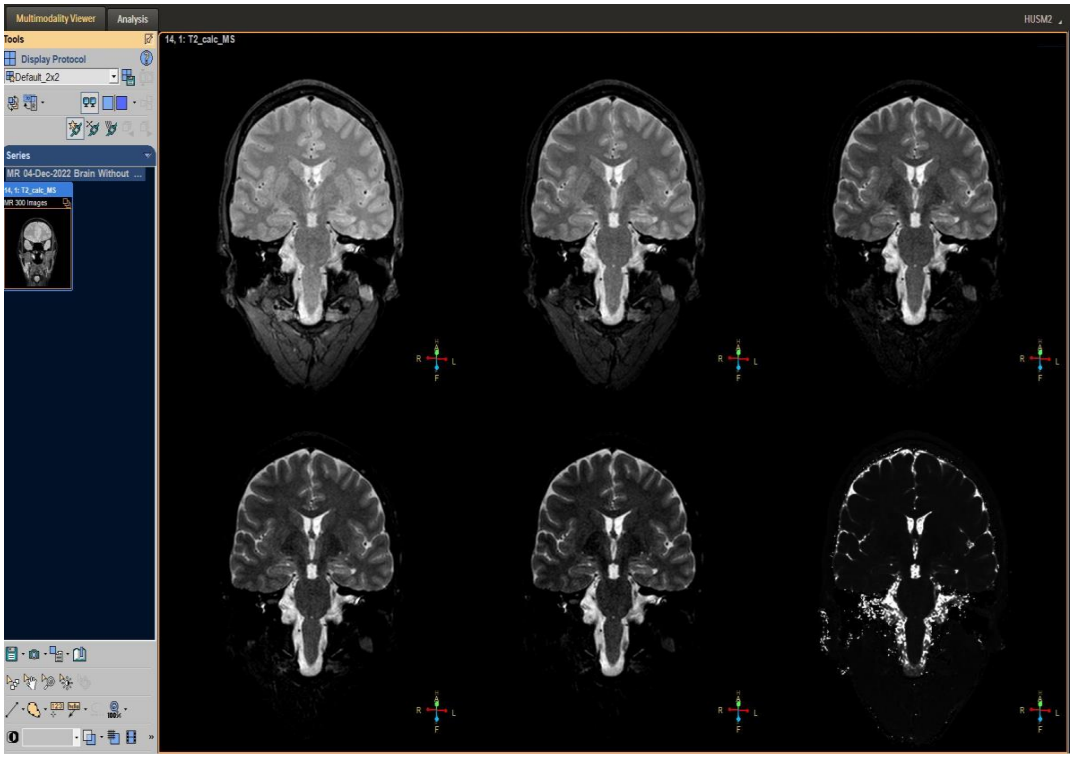


Figure 3: Above is MR Images with different TE. Upper images from the left to right TE 20/40/60 ms. For second row image from left to right TE are 80/100 ms. On the right lower most image is The T2 map image.

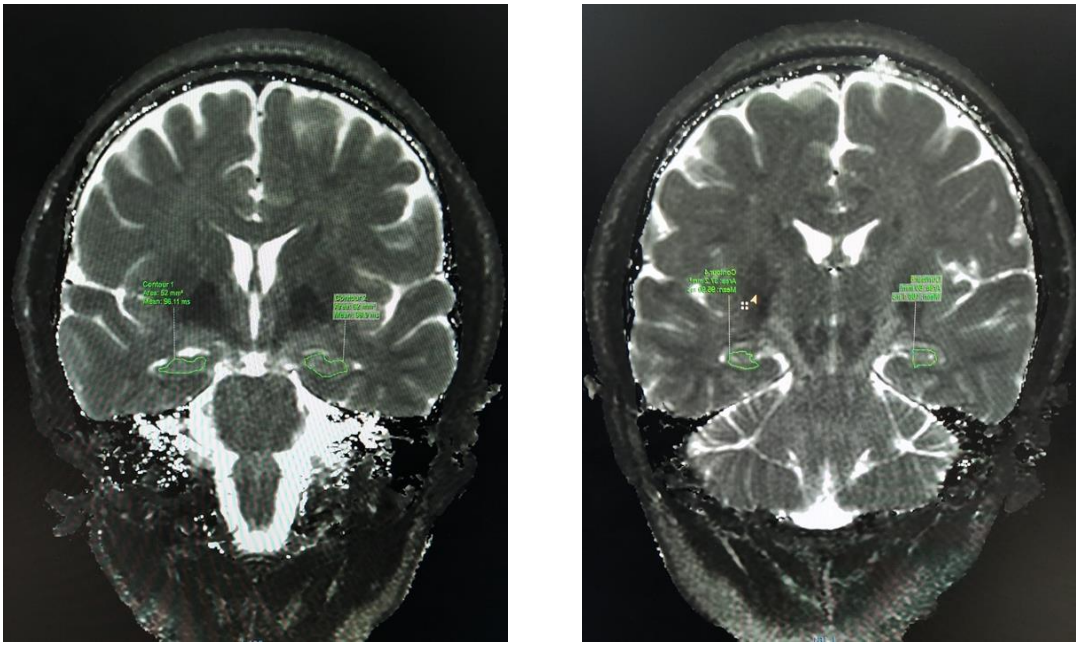


Figure 4: Above are images of T2 maps: ROI placement on the head of bilateral hippocampus will generate mean relaxation time of the hippocampus (Left is at the level of head hippocamps, right is at level of body).

3.9 Statistical analysis

All data were analysed using Statistical Product and Service Solutions (SPSS) for Mac – IBM Corp.© (Version 28). The descriptive statistics were used for discrete variables (sex and type of participants) was presented as n=frequency (%). Independent t-test was used to compare the mean of T2 relaxometry value between temporal lobe epilepsy patient and control. Pearson Correlation Coefficient was used to determine the correlation between T2 relaxometry value with the age, epilepsy duration and seizure frequency. Statistical analyses were presented in tables.

3.10 Confidentiality and Privacy

The subjects were identified using a unique serial number. No identifiable data was shared publicly. Upon completion of the study, all data was stored in CDs, and the database on the computer was erased. The data was retained by the researchers for knowledge purposes. The data will be kept as data Science/HUSM Brain Mapping Project Archive for Big Data Initiative only. Neither the name nor any identifying information was used in any publication or presentation resulting from this study.

3.11 Ethical consideration

This study was approved by Human Research Ethics Committee of Universiti Sains Malaysia (USM/JEPeM/21040319)