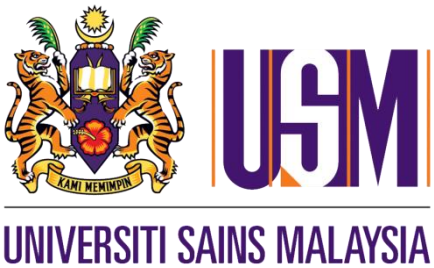
DIFFUSION TENSOR IMAGING AND APPARENT DIFFUSION COEFFICIENT VALUES OF HIPPOCAMPAL FORMATION IN MEDICALLY INTRACTABLE TEMPORAL LOBE EPILEPSY PATIENTS.

By:

DR FAROUK BIN HJ JALIL

Dissertation Submitted in Partial Fulfillment of the Requirements for Master of Medicine (Radiology)



UNIVERSITI SAINS MALAYSIA

2017

ACKNOWLEDGEMENT

The completion of this study would have not been possible without the participation, cooperation and assistance from so many people whose names may not all be enumerated. Their contributions are sincerely appreciated and gratefully acknowledged. However, I would like to express deep and utmost appreciation particularly to the following:

1. RUT grant (304/PPSP/61313116) as the main sponsor of this study.
2. Dr Win Mar @ Salmah Jalaluddin, lecturer at Radiology department who is also my supervisor and the principle investigator of the RUT grant.
3. Prof John Tarakan, who is co- supervisor of this dissertation.
4. Dr Ahmad Helmy Abdul Karim, ex-supervisor and ex-co-investigator of this study.
5. Neurology clinic, HUSM.
6. Prof Madya Dr Mohd Shafie Abdullah, Prof Madya Dr Mohd Ezane Aziz, Dr Juhara Haron, Dr Chandran, Dr Ahmad Tarmizi, Dr Wan Aireene, Dr Ahmad Hadif and Prof Madya Dr Wan Ahmad Kamil, lecturers/radiologists all of whom directly or indirectly contributed their ideas and comments to the success of this study.
7. Colleagues and all the staff in the Department of Radiology, HUSM.

TABLE OF CONTENT

LIST OF TABLES

LIST OF FIGURES

LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMNS

DTI	Diffusion tensor imaging
ADC	Apparent diffusion coefficient
DWI	Diffusion weighted imaging
FA	Fractional anisotropy
TLE	Temporal lobe epilepsy
MITLE	Medically intractable temporal lobe epilepsy
HS	Hippocampal sclerosis
EEG	Electroencephalogram
AED	Anti-epileptic drugs

ABSTRACT

Objective: The purpose of this study is to determine whether interictal DTI and apparent diffusion coefficients (ADC) provide a robust means for detecting hippocampal formation abnormalities in patients with medically intractable temporal lobe epilepsy (TLE).

Methodology: Fourteen patients and 14 controls were studied with hippocampal formation ADC maps, fractional anisotropy and Trace D values. MR images were evaluated for loss of volume and/or high signal intensity on T2-weighted images and compared with DTI and ADC maps. Mean and SDs were obtained for each measurement, and level of significance was determined ($P < .05$). The relationship between EEG lateralization and MR imaging and DTI/ADCs were studied.

Results : Ten patients had right-sided lateralization and 4 had left-sided lateralization on EEG. Patients demonstrated higher ADC within the diseased hippocampus (0.54 x 10^{-3} s/mm^2) in comparison with the contralateral side and that of controls (0.39 x10^{-3}s/mm^2 and 0.40 x 10^{-3}s/mm^2, respectively) ($P < .05$). Positive correlations were seen between hippocampal apparent diffusion coefficients and fractional anisotropy ($P < .05$)**.**

Conclusion : ADC and DTI have the capabilities to detect changes in the hippocampal formation and to lateralize the seizure focus in patients with TLE despite absence of morphological changes on conventional MRI sequence.

Keywords: *temporal lobe epilepsy (TLE); diffusion tensor imaging (DTI); Apparent diffusion coefficients (ADC), hippocampal sclerosis (HS)*

ABSTRAK

Objektif: Tujuan kajian ini adalah untuk menentukan sama ada DTI dan (ADC) menyediakan satu kaedah yang kukuh untuk mengesan keabnormalan hippocampus pada pesakit yang mempunyai epilepsi lobus temporal (TLE) yang sukar dikawal melaui perubatan.

Metodologi: Empat belas pesakit dan 14 subjek kawalan telah dikaji dengan peta ADC, pecahan anisotropi dan nilai Trace D hipocampus. Imej MR telah dinilai untuk atrofi dan / atau intensiti isyarat yang tinggi pada imej-imej T2 dan dibandingkan dengan DTI dan peta ADC. Min dan SD diperolehi bagi setiap pengukuran, dan tahap kepentingan telah ditentukan (P <0,05). Hubungan antara EEG lateralization dan pengimejan MR dan DTI / ADC telah dikaji.

Keputusan: Sepuluh pesakit mempunyai fokus epileptogenic di sebelah kanan manakala 4 pesakit di sebelah kiri pada EEG. Pesakit menunjukkan kadar ADC yang lebih tinggi dalam hippocampus ipsilateral (0.54 x 10^{-3} s/mm^2) jika dibandingkan dengan sebelah contralateral dan kawalan (0.39 x 10^{-3} s/mm^2dan 0.40 x 10^{-3} s/mm^2 masing-masing) (P <0,05). Korelasi positif dapat dilihat antara ADC map dan pecahan anisotropi hippocampus.(P <0,05).

Kesimpulan: ADC dan DTI mempunyai keupayaan untuk mengesan perubahan dalam pembentukan hippocampal dan lateralize fokus serangan sawan pada pesakit dengan TLE walaupun ketiadaan perubahan morfologi pada urutan MRI konvensional

Kata kunci: *temporal lobe epilepsy (TLE); diffusion tensor imaging (DTI); Apparent diffusion coefficients (ADC), hippocampal sclerosis (HS).*

CHAPTER 1 :

INTRODUCTION &

LITERATURE REVIEW

1. INTRODUCTION & LITERATURE REVIEW

The temporal lobe is the most epileptogenic region of the brain. In fact, 90% of patients with temporal interictal epileptiform abnormalities on their electroencephalograms (EEGs) have a history of seizures. Temporal lobe epilepsy was defined in 1985 by the International League Against Epilepsy (ILAE) as 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 (David Y Ko, 2014). Hippocampal sclerosis (HS) is considered the most frequent pathological finding in patients with mesial temporal lobe epilepsy. Hippocampal specimens of medically intractable TLE (MITLE) patients that underwent epilepsy surgery for seizure control reveal the characteristic pattern of segmental neuronal cell loss and concomitant astrogliosis (Cendes *et al.*, 2014). Definition for medical intractability or pharmacologically resistant MTLE may vary among centres, but it usually includes failure to achieve seizure control with two or more AEDs with adequate dosage and posology (Cendes *et al.*, 2014).

Hippocampal sclerosis or mesial temporal sclerosis refers to an entity of neuronal loss and atrophy with associated gliosis involving the hippocampus. It is a progressive disorder with evidence of premature accumulation of corpora amylacea in the hippocampus in medically refractory temporal lobe epilepsy with HS. Loss of volume and signal changes in the hippocampus are the two basic MRI features of HS. Because of anatomic orientation of hippocampus, MRI findings are best identified on coronal scans perpendicular to the long axis of hippocampus. Thin slices improve confidence in detecting asymmetry. The best conventional MR sequences to show alterations in the

normal architecture within hippocampus are inversion recovery and HR fast spin echo images. In inversion recovery sequence, the image is reconstructed in real rather than magnitude mode, provides exceptionally good gray-white contrast and is a good sequence for internal architecture. Hippocampal hyperintensity is best visualized in T2-weighted sequence. Increased signal is thought to reflect gliosis. Fast spin echo MR enables accurate definition of the extent of hippocampal sclerosis in patients with temporal lobe epilepsy. The signal changes in the hippocampus are highly sensitive for HS and occur in 84-100% patients with HS. The detection of multiple primary imaging criteria (loss of hippocampal volume, internal architecture, and signal change) and secondary imaging criteria (atrophy of ipsilateral mammillary body and fornix, atrophy of collateral white matter, atrophy of ipsilateral temporal lobe/hemisphere, and prominence of temporal horn) increases diagnostic confidence (Chinchure *et al.*, 2010).

In comparison with CT, MRI has higher sensitivity, exceptional soft tissue contrast, multiplanar imaging capability, and lack of ionizing radiation hence making it as the primary modality of choice in the evaluation of patients with epilepsy. The main purpose of neuroimaging in epilepsy is to identify the underlying structural changes and to assist in formulating a syndromic or etiologic diagnosis (Chinchure *et al.*, 2010).

Conventional magnetic resonance imaging (MRI) has been widely used for the diagnosis and detection of space occupying lesion in the brain that result in seizures. However, the major limitation of MRI is the fact that MRI studies can be completely normal in patients with MTLE. By contrast, diffusion tensor imaging(DTI) is sensitive to physiological changes that take place in the brain tissue ictally and interictally (Liacu *et al.*, 2012).

Diffusion MRI has many advantages over conventional imaging for detecting and characterizing structural abnormalities in seizures and epilepsies. In temporal lobe

epilepsy (TLE) patients, DTI has demonstrated that there are extensive, often bilateral white matter and extrahippocampal changes; significant white matter structural differences between right and left temporal lobe epilepsy; seizure propagation and white matter reorganization may be more widespread when seizures are generated in the dominant cerebral hemisphere due to greater pre-existing connectivity; and the extent of white matter and hippocampal diffusion changes can correlate with the duration or age of onset of seizures, supporting the hypothesis that seizures may damage the brain in a dose-dependent fashion (Shepherd and Hess, 2012).The use of DWI allows the recording of very early changes, usually before they can be detected by conventional T_1 WI or T_2 WI. In DWI, contrast is modulated by molecular water diffusion. The quantitative measure of DWI is the computed apparent diffusion coefficient (ADC) value. A change in ADC implies that water diffusion is altered as a result of biophysical changes (Nehlig, 2011).

Anisotropic water diffusion in neural fibres such as nerve, white matter in spinal cord, or white matter in brain forms the basis for the utilization of diffusion tensor imaging (DTI) to track fibre pathways. The fact that water diffusion is sensitive to the underlying tissue microstructure provides a unique method of assessing the orientation and integrity of these neural fibers, which may be useful in assessing a number of neurological disorders (Beaulieu, 2002).

However, the analysis and interpretation of the measured diffusion tensor is complex and should be performed with care. Many previous studies were primarily focusing on the diffusion anisotropy (usually the FA measure), which may not be sufficient to characterize the microstructural tissue changes. For instance, white matter abnormalities often causes the anisotropy to decrease, which may result from either increased radial (perpendicular) diffusivity and/or reduced axial (parallel) diffusivity.

Measurements of the trace D may help to better understand how the diffusion tensor is changing. Alternatively, more recent studies have started to examine measurements of either the eigenvalues or the radial and axial diffusivities directly to provide more specific information about the diffusion tensor (Alexander *et al.*, 2007).

The purpose of this study is to assess the utility of hippocampal DTI and ADC measurements in patients with known intractable temporal lobe epilepsy with comparison to the normal individuals.

REFERENCES

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system - A technical review. *NMR in Biomedicine*, **15(7-8)**,435-455. doi: 10.1002/nbm.782

Cendes, F., Sakamoto, A. C., Spreafico, R., Bingaman, W. & Becker, A. J. (2014). Epilepsies associated with hippocampal sclerosis. *Acta Neuropathologica*, **128(1)**,21-37. doi: http://dx.doi.org/10.1007/s00401-014-1292-0

David Y Ko, S. S.-S. (2014). *Temporal Lobe Epilepsy*. Retrieved from:http://emedicine.medscape.com/article/1184509-overview [Accessed].

Liacu, D., Idy-Peretti, I., Ducreux, D., Bouilleret, V. & de Marco, G. (2012). Diffusion tensor imaging tractography parameters of limbic system bundles in temporal lobe epilepsy patients. *J Magn Reson Imaging*, **36(3)**,561-568. doi: 10.1002/jmri.23678

Nehlig, A. (2011). Hippocampal MRI and other structural biomarkers: experimental approach to epileptogenesis. *Biomarkers in Medicine*, **5(5)**,585-597. doi: http://dx.doi.org/10.2217/bmm.11.65

Shepherd, T. M. & Hess, C. P. (2012). Epilepsy: Clinical Applications of Diffusion Tensor Imaging.In*:* Faro, H. S., Mohamed, B. F., Law, M. and Ulmer, T. J. (eds.), *Functional Neuroradiology: Principles and Clinical Applications*. Boston, MA: Springer US, pp 785-802.

CHAPTER 2 : STUDY PROTOCOL

2. STUDY PROTOCOL

Title:

Diffusion Tensor Imaging and Apparent Diffussion Coeffecient values of Hippocampal Formation in Medically Intractable Temporal Lobe Epilepsy patients.

General objective:

To determine DTI and ADC values of the Hippocampal Formation in medically intractable temporal lobe epilepsy patients.

Specific objectives:

1. To compare the mean DTI (Fractional anisotropy) values of the hippocampal formation in medically intractable temporal lobe epilepsy patients with normal individuals.
2. To compare the mean ADC values of the hippocampal formation in medically intractable temporal lobe epilepsy patients with normal individuals.
3. To compare the mean Trace D values of the hippocampal formation in medically intractable temporal lobe epilepsy patients with normal individuals.
4. To correlate fractional anisotropy (FA) value with ADC value in medically intractable temporal lobe epilepsy.

Study design:

This is a cross sectional study that was conducted in Radiology Department, Hospital USM, Kubang Kerian, Kelantan.

Population and Sample:

Patients who were diagnosed with medically intractable epilepsy.

Sampling technique:

Systematic random sampling.

Inclusion Criteria:

1. 18 years old and above.
2. Clinically diagnosed as intractable temporal lobe epilepsy.
3. Interictal epileptiform activity from either or both temporal lobe.
4. Patients are seizure-free for at least 24 hours.
5. MRI findings are either normal or presence of features of mesial temporal sclerosis (MTS).

Exclusion Criteria:

1. Abnormal findings apart from hippocampal sclerosis for patients.
2. Any abnormal findings on MRI on healthy subjects.
3. Recent seizures less than 24 hours.

Sample Size Calculation

Two means formula was used for sample size calculation. The difference of the mean between the normal and patients was 0.145 and of the standard deviation (σ) was 0.065.

By using the Power and Sample Size program, total sample size is 40 with 1:1 ratio between patients and control subjects.

Research Tools

1. MRI machine – Philips 3 Tesla Achieva MR Scanner, Best, The Netherlands.
2. MR sequences :
   (a) Brain sagittal T1W.
   (b) Brain axial T1W, T2W
   (c) Temporal lobe series: Oblique coronal IR, T2, FLAIR.
   (d) Diffusion tensor imaging
3. Workstation – Philips MR Extended Workspace 2.6.3.5.

Operational definition

1. Clinical diagnosis – Patients are diagnosed as temporal lobe epilepsy by neurophysician base on clinical history, physical examination and EEG.
2. Intractable epilepsy – range of epilepsy duration of more than 2 years, more than 2 drugs and more than 2 seizures per month.
3. Diffussion tensor imaging (DTI) values – DTI provides quantitative analysis of the magnitude and directionality of water molecules. The parameter measured is fractional anisotropy (FA) value which is is a scalar value between zero and one that describes the degree of anisotropy of a diffusion process. A value of zero means that diffusion is isotropic, i.e. it is unrestricted (or equally restricted) in all directions. A value of one means that diffusion occurs only along one axis and is fully restricted along all other directions. Mean diffusivity (trace D) is

also one of the parameter of the DTI which measures the magnitude of the water diffusivity.

4. Apparent diffusion coefficient (ADC) - ADC measures the magnitude of diffusion (of water molecules) within tissue but it depends on rotation variant. The measurement are recorded for a given region of interest (ROI) on the ADC map. An ADC of tissue is expressed in units of mm^2/sec. There is no unanimity regarding the boundaries of the range of normal diffusion, but ADC values less than 1.0 to 1.1 x 10^{-3} mm^2/sec are generally acknowledged in as indicating restriction.
5. Mesial temporal sclerosis - is characterized by hippocampal atrophy, increased T2 signal and loss of normal internal architecture.

Image acquisition of the subjects.

- Subject were screened against the inclusion/exclusion criteria. Subjects who agreed to participate will be asked to sign written informed consent forms.
- All subjects underwent MR imaging at MRI room in the Radiology department, HUSM using Philips 3 Tesla Achieva MR scanner, Best, The Netherlands**.**
- All subjects underwent the similar imaging protocol consisting of :
    1. Sagittal T1-weighted (Slice thickness – 5mm; Field of view – 230 x 183 x 143mm; TR/TE – 500/10ms; Reconstruction matrix – 512)
    2. Axial T1-weighted (Slice thickness – 5mm; Field of view – 230 x 183 x 154mm; TR/TE – 600/10ms; Reconstruction matrix – 512)
    3. Axial T2-weighted, (Slice thickness – 5mm; Field of view – 230 x 184 x 143mm; TR/TE – 3000/80ms; Reconstruction matrix – 512)

4. Oblique coronal T1 IR, (Slice thickness – 3mm; Field of view – 200 x 209 x 79mm; TR/TE – 600/100ms; Reconstruction matrix – 400)
5. Oblique coronal TSE-T2, (Slice thickness – 5mm; Field of view – 79 x 159 x 200mm; TR/TE – 1987/100ms; Reconstruction matrix – 512)
6. Oblique coronal FLAIR, (Slice thickness – 5mm; Field of view – 230 x 183 x 143mm; TR/TE – 600/100ms; Reconstruction matrix – 560)
7. DTI, (Slice thickness – 2mm; Field of view – 230 x 183 x 143mm; TR/TE – 8600/90ms; Reconstruction matrix – 512)

- A standard head coil was used (SENSE-HEAD-32).

Image analysis: DTI and ADC.

- All DTI image processing were performed using Philips MR Workspace 2.6.3.5 software.
- Fractional anisotropy (FA), Trace D and Apparent Diffussion Coefficient (ADC) values were obtained at the region of interest (right and left head of hippocampal formation). The oval shaped ROI of $0.4cm^2$ to $0.5cm^2$ were drawed on both hippocampal head using DTI sequence.
- Images were reviewed and analyzed by a neuroradiologist.

Statistical analysis

Analysis of mean ADC, Trace D and FA values were performed using PASW version 18. We used an independent t-test to investigate group differences in mean ADC, Trace D, and FA. Pearson correlation was used to examine relationships between mean FA and mean ADC.

CHAPTER 3 : MANUSCRIPT

3. MANUSCRIPT

3.1 INTRODUCTION

The temporal lobe is the most epileptogenic area of the brain. Majority of patients with temporal epileptiform abnormalities on their electroencephalograms (EEGs) have a history of seizures. Temporal lobe epilepsy was defined in 1985 by the International League Against Epilepsy (ILAE) as 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. (David Y Ko, 2014). Hippocampal sclerosis (HS) is considered the most frequent pathological finding in patients with mesial temporal lobe epilepsy (MTLE). Hippocampal specimens of medically intractable TLE patients that underwent epilepsy surgery for seizure control reveal the characteristic pattern of segmental neuronal cell loss and concomitant astrogliosis (Cendes *et al.*, 2014). Definition for medical intractable TLE may vary among centres, but it usually includes failure to achieve seizure control with two or more AEDs with adequate dosage and posology (Cendes *et al.*, 2014).

Conventional magnetic resonance imaging (MRI) has been widely used for the diagnosis and detection of space occupying lesion in the brain that result in seizures. However, in patients with MTLE, MRI studies can be completely normal as a limitation. Diffusion tensor imaging (DTI) is sensitive to physiological changes that take place in the brain tissue ictally and interictally (Liacu *et al.*, 2012).

Diffusion MRI has many potential advantages over conventional anatomic imaging for detecting and characterizing both acute seizures and epilepsy. Previous published data suggested that DTI has demonstrated extensive, bilateral white matter and extrahippocampal changes with significant white matter structural differences

between right and left temporal lobe epilepsy. In addition, the seizure propagation and white matter reorganization may be more widespread when seizures are generated in the dominant cerebral hemisphere due to greater pre-existing connectivity; and the extent of white matter and hippocampal diffusion changes can correlate with the duration or age of onset of seizures, supporting the hypothesis that seizures may damage the brain in a dose-dependent fashion (Shepherd and Hess, 2012).

The use of DWI allows the detection of very early changes, usually before they can be detected by conventional T1W or T2W. In DWI, contrast is modulated by molecular water diffusion. The quantitative measure of DWI is the computed apparent diffusion coefficient (ADC) value. A change in ADC implies that water diffusion is altered as a result of biophysical changes (Nehlig, 2011). Anisotropic water diffusion in neural fibers such as nerve, white matter in spinal cord, or white matter in brain forms the basis for the utilization of diffusion tensor imaging (DTI) to track fibre pathways. The fact that water diffusion is sensitive to the underlying tissue microstructure provides a unique method of assessing the orientation and integrity of these neural fibers, which may be useful in assessing a number of neurological disorders (Beaulieu, 2002).

The purpose of this study is to compare the DTI and ADC values of hippocampal formation in patients with medically intractable temporal lobe epilepsy with the normal individuals as well as to determine the correlation between FA and ADC values among the patients.

3.2 METHODOLOGY

Subjects

This study was approved by our ethical review board, and all participants were provided written informed consent before entering the study. Fourteen healthy volunteers without a history of neurological deficits or epilepsy and 14 patients with intractable temporal lobe epilepsy were examined prospectively with conventional MRI and diffusion imaging. No patient was in ictus or within 24 hours after ictus.

MRI and DTI Imaging

All MR imaging examinations were performed with a 3.0T unit (Philips Achieva MR scanner, Best, The Netherland). Conventional routine MR imaging included 2D T1-weighted sagittal spin-echo and T2-weighted axial fast spin-echo sequences with 5-mm thickness and fluid-attenuated inversion recovery (FLAIR) sequences with 2-mm thickness, epilepsy protocol sequences in oblique coronal plane perpendicular to the long axis of the hippocampus in T1W, T2W and FLAIR. Following conventional MRI sequences, DTI was performed with slice thickness – 2mm; field of view – 230 x 183 x 143mm; TR/TE – 8600/90ms; reconstruction matrix – 512 .

Image analysis

Patient's images were reviewed for the presence of hippocampal sclerosis based on the presence of hippocampal atrophy and high T2 signal intensity within it determined by an experienced neuroradiologist who was blinded to clinical information. For DTI and ADC analysis, images were evaluated quantitatively by placing the oval shaped ROI of $0.4cm^2$ to $0.5cm^2$ on both right and left hippocampal head in both groups (Figure 1).

Fractional anisotropy (FA), Trace D and Apparent Diffusion Coefficient (ADC) values were obtained. The mean ADC, FA and Trace D values in patients and normal subjects were compared. For patients, these values were taken from the affected side which may be either right or left [Right, n =10; Left, n= 4]. For the control group, the average values were taken from both sides. The results were compared with EEG to lateralize the epileptogenic focus.

Statistical analysis

Analysis of mean ADC, Trace D and FA values were performed using PASW version 18. We used an independent t-test to investigate group differences in mean ADC, Trace D, and FA. Pearson correlation was used to examine relationships between mean FA and mean ADC.

3.3 RESULTS

3.3.1 Demographic Data

Fourteen subjects were recruited for control and disease groups, respectively. Overall mean age of study subjects was 34 ±15 years old with minimum and maximum ages of 18 and 72 years old (Table 1). The genders comprised 16 (57%) female and 12 (43%) male. There were no significant difference ($p>0.05$) between mean age of control (35±13 year old) and disease (33±17 year old) groups. There was also no significant difference in gender distribution between the disease and control groups (Table 2).

3.3.2 MRI analysis

3.3.2.1 Hippocampal sclerosis evaluation

The vast majority (64.3%; n=9) of TLE patients in this study demonstrated no morphological changes in hippocampal formation to suggest mesial temporal sclerosis. Only four patients revealed mesial temporal sclerosis on the right and one patient on the left consistent with the EEG focus.

3.3.2.1 DTI analysis

The mean ADC, FA, and Trace D values of hippocampal formation in control group had no significant difference between the left and right sides (Table 3). There was significant difference of mean ADC, FA, and Trace D values of hippocampal formation between control and the ipsilateral sides of patients (Table 4). Mean ADC and Trace D values were significantly higher and mean FA values were significantly lower in MITLE patients. In patient's group, mean ADC, and Trace D values were higher and FA values were significantly lower in ipsilateral sides (Table 5). Using Pearson correlation analysis, there was significant moderate correlation ($r=-0.654$, $r^2 = 0.427$, $p<0.05$) between ADC and FA values of hippocampal formation in MITLE patients (Table 6). Scattergram with a regression line between ADC and FA of hippocampal formation in MITLE patients is shown in Figure 2.

3.4 DISCUSSION

The evolution of magnetic resonance imaging has allowed a better detection and characterization of hippocampal structural changes in temporal lobe epilepsy. In this study, diffusion abnormalities were detected in MITLE patients whether they were having normal conventional MRI findings or hippocampal sclerosis. For Mean ADC values in our study, ipsilateral epileptogenic focus had higher than contralateral side and also of normal subjects. This is consistent with findings of several previous studies

(Kantarci *et al.*, 2002; Lee *et al.*, 2004; Lui *et al.*, 2005; Yoo *et al.*, 2002., Assaf *et al.*, 2003a., Londono *et al.*, 2003). Extratemporal increased ADC values were also demonstrated in previous studies (Concha *et al.*, 2009; Keller *et al.*, 2012; Wang *et al.*, 2010).

The mean ADC values in this study is 0.54 x 10^{-3} s/mm^2 which is lower as compared to several previous published data. Studies by Yoo *et al*, (2002) and Londono *et al*, (2003) revealed higher ADC values in diseased hippocampi, measuring 1.05 x 10^{-3} s/mm^2 and 0.8 to 1.2 x 10^{-3} s/mm^2 respectively. The differences could be due to ROI placement in their studies. In Yoo *et al*, (2002), they analyzed the hippocampal formation on axial images displaying the entire hippocampal formation and placed a large single ROI on that particular slice. Londono *et al*., (2003) also obtained the similar axial slice. However, they placed three ROI in head, body and tail of the hippocampus.

In Londono *et al*., (2003) study, even though the whole hippocampal formation ADC result was higher than normal subjects, ADC value at the head region alone also yielded significant and similar result. In Assaf et al., (2003) study was conducted in similar fashion to our study placing the ROI only at the hippocampal head on oblique coronal slices obtaining the significant similar results. These two results indicate that taking DTI values on head region alone like in our study, give similar significant results as of taking the whole hippocampal formation.

Goncalves *et al.*, (2006) conducted a study on drug resistance TLE patients with ADC mapping of hippocampus and amygdala. Their results were higher (0.8 to 1.0 x 10^{-3} s/mm^2) even though they used to measure on oblique coronal images. This could be due to multiple ROI placement on head, body and tail. Our study also shows increased in mean Trace D values (1.51 x 10^{-3} s/mm^2) which is similar with study conducted by

Assaf *et al*, 2003. This is most likely due to the Trace D and ADC values are dependant each others.

The reason for higher ADC and Trace D values in TLE patients has not been yet established. It could be due to increase in interstitial water proton secondary neuronal cell loss or gliosis (Yoo *et al.*, 2002). Microstructural changes secondary to seizure propagation or to deafferentation might also underlie diffusion abnormalities (Thivard *et al.*, 2005). The disruption of microstructural environment, such as ischemic injury, gliosis, or cerebral dysgenesis will lead to less ordered arrangement of nerve and may lead to reduced cell density or expansion of extracellular space, resulting in increased mean diffusivity.

Our study also shows reduction in FA values in patients with or without conventional MRI findings of hippocampal sclerosis. This is consistent with previous studies (Assaf *et al.*, 2003b; Concha *et al.*, 2009; Govindan *et al.*, 2008; Liacu *et al.*, 2012; Rugg-Gunn *et al.*, 2001; Spitler *et al.*, 2014; Thivard *et al.*, 2005; Wang *et al.*, 2010; Widjaja *et al.*, 2011), which demonstrated reduced FA in ipsilateral hippocampus. FA loss according to Keller *et al.*, 2012 is the reflection of hippocampal sclerosis, changes in microstructural organization and extrahippocampal atrophy in patients with TLE with concomitant volume loss which is a proxy for neuronal atrophy.

The key explanation of the FA changes in MITLE patients is the concept of water diffusion. The axonal membranes and myelin pose barriers to water displacement, such that water preferentially diffuses along the direction of the axons (Beaulieu, 2002). As axons degenerate and break down with subsequent degradation of myelin, the barriers that normally hinder the diffusion of water across the axons disappear, allowing a more spatially uniform profile of water displacement (i.e., isotropic diffusion) (Liacu et al, 2012). However, Keller *et al*, 2012 concluded that FA

loss in patients with TLE is likely due to a degenerative effect of recurrent seizures or the chronic use of antiepileptic medication. The effects of having TLE were related to brain degeneration that was accelerated beyond the effects of normal aging (Keller *et al.*, 2012).

Our study corresponds well with previously mentioned published data on lateralizing capability by DTI and ADC mapping in temporal lobe epilepsy. Irrespective of presence or absence of hippocampal sclerosis, this study shows diffusion abnormalities in all patient with intractable temporal lobe epilepsy.

In conclusion, diffusion imaging is able to depict changes of the hippocampal architecture and lateralize the seizure focus in patients with MITLE despite absence of morphological changes on conventional MRI sequence with Trace D appears as the most significant parameter altered in the diseased hippocampi in our study.

3.5 REFERENCES

Alexander, A. L., Lee, J. E., Lazar, M. & Field, A. S. (2007). Diffusion Tensor Imaging of the Brain. *Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics,* **4(3)**,316-329. doi: 10.1016/j.nurt.2007.05.011

Assaf, B. A., Mohamed, F. B., Abou-Khaled, K. J., Williams, J. M., Yazeji, M. S., Haselgrove, J. & Faro, S. H. (2003a). Diffusion tensor imaging of the hippocampal formation in temporal lobe epilepsy. *AJNR Am J Neuroradiol,* **24(9)**,1857-1862.

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system - A technical review. *NMR in Biomedicine,* **15(7-8)**,435-455. doi: 10.1002/nbm.782

Cendes, F., Sakamoto, A. C., Spreafico, R., Bingaman, W. & Becker, A. J. (2014). Epilepsies associated with hippocampal sclerosis. *Acta Neuropathologica*, **128(1)**,21-37. doi: http://dx.doi.org/10.1007/s00401-014-1292-0

Chinchure, S., Kesavadas, C. & Thomas, B. (2010). Structural and functional neuroimaging in intractable epilepsy. *Neurology India,* **58(3)**,361-370. doi: http://dx.doi.org/10.4103/0028-3886.65569

Concha, L., Beaulieu, C., Collins, D. L. & Gross, D. W. (2009). White-matter diffusion abnormalities in temporal-lobe epilepsy with and without mesial temporal sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry,* **80(3)**,312. doi: http://dx.doi.org/10.1136/jnnp.2007.139287

David Y Ko, S. S.-S. (2014). *Temporal Lobe Epilepsy*. Retrieved from:http://emedicine.medscape.com/article/1184509-overview [Accessed].

Goncalves Pereira, P. M., Oliveira, E. & Rosado, P. (2006). Apparent diffusion coefficient mapping of the hippocampus and the amygdala in pharmaco-resistant temporal lobe epilepsy. *AJNR Am J Neuroradiol,* **27(3)**,671-683.

Govindan, R. M., Makki, M. I., Sundaram, S. K., Juhász, C. & Chugani, H. T. (2008). Diffusion tensor analysis of temporal and extra-temporal lobe tracts in temporal lobe epilepsy. *Epilepsy research,* **80(1)**,30-41. doi: 10.1016/j.eplepsyres.2008.03.011

Kantarci, K., Shin, C., Britton, J. W., So, E. L., Cascino, G. D. & Jack, C. R., Jr. (2002). Comparative diagnostic utility of 1H MRS and DWI in evaluation of temporal lobe epilepsy. *Neurology,* **58(12)**,1745-1753.

Keller, S. S., Schoene-Bake, J.-C., Gerdes, J. S., Weber, B. & Deppe, M. (2012). Concomitant Fractional Anisotropy and Volumetric Abnormalities in Temporal Lobe Epilepsy: Cross-Sectional Evidence for Progressive Neurologic Injury. *PLoS One,* **7(10)**. doi: 10.1371/journal.pone.0046791
http://dx.doi.org/10.1371/journal.pone.0046791

Lee, J. H., Chung, C. K., Song, I. C., Chang, K. H. & Kim, H. J. (2004). Limited utility of interictal apparent diffusion coefficient in the evaluation of hippocampal sclerosis. *Acta Neurol Scand,* **110(1)**,53-58. doi: 10.1111/j.1600-0404.2004.00261.x

Liacu, D., Idy-Peretti, I., Ducreux, D., Bouilleret, V. & de Marco, G. (2012). Diffusion tensor imaging tractography parameters of limbic system bundles in temporal lobe epilepsy patients. *J Magn Reson Imaging,* **36(3)**,561-568. doi: 10.1002/jmri.23678

Londono, A., Castillo, M., Lee, Y. Z. & Smith, J. K. (2003). Apparent diffusion coefficient measurements in the hippocampi in patients with temporal lobe seizures. *AJNR Am J Neuroradiol,* **24(8)**,1582-1586.

Lui, Y. W., Nusbaum, A. O., Barr, W. B., Johnson, G., Babb, J. S., Orbach, D., Kim, A., Laliotis, G. & Devinsky, O. (2005). Correlation of apparent diffusion coefficient with neuropsychological testing in temporal lobe epilepsy. *AJNR Am J Neuroradiol,* **26(7)**,1832-1839.

Nehlig, A. (2011). Hippocampal MRI and other structural biomarkers: experimental approach to epileptogenesis. *Biomarkers in Medicine,* **5(5)**,585-597. doi: http://dx.doi.org/10.2217/bmm.11.65

Rugg-Gunn, F. J., Eriksson, S. H., Symms, M. R., Barker, G. J. & Duncan, J. S. (2001). Diffusion tensor imaging of cryptogenic and acquired partial epilepsies. *Brain,* **124(3)**,627.

Shepherd, T. M. & Hess, C. P. (2012). Epilepsy: Clinical Applications of Diffusion Tensor Imaging.In*:* Faro, H. S., Mohamed, B. F., Law, M. and Ulmer, T. J. (eds.), *Functional Neuroradiology: Principles and Clinical Applications*. Boston, MA: Springer US, pp 785-802.

Spitler, K., Tirol, F., Fried, I., Engel Jr, J. & Salamon, N. (2014). Diffusion tensor imaging correlates of hippocampal sclerosis and anterior temporal lobe T2 signal changes in pharmacoresistant epilepsy. *International Journal of Epilepsy,* **1(1)**,1-7. doi: http://dx.doi.org/10.1016/j.ijep.2014.05.003

Thivard, L., Lehéricy, S., Krainik, A., Adam, C., Dormont, D., Chiras, J., Baulac, M. & Dupont, S. (2005). Diffusion tensor imaging in medial temporal lobe epilepsy with hippocampal sclerosis. *NeuroImage,* **28(3)**,682-690. doi: http://dx.doi.org/10.1016/j.neuroimage.2005.06.045

Wang, X.-q., Lang, S.-y., Hong, L., Lin, M., Yan-ling, M. A. O. & Yang, F. (2010). Changes in extratemporal integrity and cognition in temporal lobe epilepsy: A diffusion tensor imaging study. *Neurology India,* **58(6)**,891-899. doi: http://dx.doi.org/10.4103/0028-3886.73739

Widjaja, E., Geibprasert, S., Otsubo, H., Snead, O. C., 3rd & Mahmoodabadi, S. Z. (2011). Diffusion tensor imaging assessment of the epileptogenic zone in children with localization-related epilepsy. *AJNR Am J Neuroradiol,* **32(10)**,1789-1794. doi: 10.3174/ajnr.A2801

Yoo, S. Y., Chang, K. H., Song, I. C., Han, M. H., Kwon, B. J., Lee, S. H., Yu, I. K. & Chun, C. K. (2002). Apparent diffusion coefficient value of the hippocampus in patients with hippocampal sclerosis and in healthy volunteers. *AJNR Am J Neuroradiol,* **23(5)**,809-812.

3.6 TABLES AND FIGURES

3.6.1 TABLES

Table 1: Demographic data of patients.

Variable	
Age, year	
Mean	34
Standard Deviation	15
Minimum	18
Maximum	72
Gender, n (%)	
Female	16 (57)
Male	12 (43)

Table 2 : Demographic data of participant according to control and disease groups

Variable	**Study Group**		**P value**
	Normal	**MITLE**	
Age, year			
Mean	35	33	0.697
Standard Deviation	13	17	
Minimum	18	18	
Maximum	72	68	
Gender, n (%)			
Female	7 (50)	5 (35.7)	0.445
Male	7 (50)	9 (64.3)	

Table 3 : Comparison of between left and right mean ADC, FA, and TRACE D values in control patients.

Variable	Left (n=14)	Right (n=14)	P value
ADC	0.4036 (0.0268)	0.4212 (0.0398)	0.169
FA	0.3443 (0.0388)	0.3335 (0.0449)	0.486
Trace D	1.2393 (0.0835)	1.3082 (0.1976)	0.234

Note: independent t-test, statistically different at $p<0.05$

Table 4 : Comparison between ipsilateral* mean ADC, FA, and TRACE D values of MITLE patients and that of control subjects

Variable	Control (n=14) Mean (SD)	Ipsilateral* (n=14) Mean (SD)	P value
ADC	0.4043 (0.0292)	0.5400 (0.2687)	0.011*
FA	0.3432 (0.0429)	0.2864 (0.7919)	0.004*
Trace D	1.2404 (0.1330)	1.5107 (0.1974)	0.000*

Note: independent t-test, statistically different at $p<0.05$
*ipsilateral to epileptogenic focus

Table 5 : Comparison between ipsilateral* and contralateral** mean ADC, FA, and Trace D values in MITLE patients