Correlation between Magnetic Resonance (MR) Volumetry and Apparent Diffusion Coefficient (ADC) Value of Hippocampal Formation in Medically Intractable Temporal Lobe Epilepsy patients.

By:

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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
HA	Hippocampal atrophy
MTS	Mesial temporal sclerosis
MR	Magnetic resonance
MTLE	Mesial Temporal Lobe Epilepsy

ABSTRACT

Objective:

The purpose of this study is to determine volumetry values of the Hippocampal Formation in refractory Temporal Lobe Epilepsy patients comparing with volumetry values of normal individual, correlating the volumetry values with ADC (Apparent Diffusion Coefficient) values for detecting hippocampal formation abnormalities in patients with medically intractable temporal lobe epilepsy (MITLE). Other than that is to correlate MR volumetry values with duration of illness in refractory Temporal Lobe Epilepsy (TLE) patients.

Background: In this study, we compared the hippocampal volume of patients with underlying medically intractable temporal lobe epilepsy (MITLE) and normal subjects and to look for correlation between the hippocampal volume, ADC values and duration of illness.

Methodology: A total of 28 participants were recruited for the present study; there were 14 participants in control and TLE-positive group, respectively. MR images were evaluated for hippocampal volumetric calculation and was correlated with ADC maps and duration of illness. Mean and SDs were obtained for each measurement, and level of significance was determined.

Analysis of mean volumetry, ADC values were performed using PASW version 18. We used an independent t-test to investigate group differences in mean hippocampal volumetric value. Pearson correlation was used to examine relationships between mean hippocampal volumetric value and duration of illness, also as mean hippocampal volumetric value with ADC value.

Results:

There was no significant difference shown between the left and right hippocampal MR volumetric values in the control group. However, significant differences were shown in hippocampal MR volumetric values, were found between control and TLE-ipsilateral sites. There are also significant differences were shown in hippocampal volumetric values, were found between both sides of hippocampus in right and left TLE patients. The hippocampal MR volumetric values did not show significant correlation with the duration of illness. There was significant correlation between hippocampal volumetric value and ADC.

Conclusions:

Hippocampal volumetry have the capabilities to detect changes in the hippocampal formation and to lateralize the seizure focus in patients with TLE. There is no significant correlation between hippocampal volumetric values with duration of illness. There was significant correlation between hippocampal volumetric values with ADC.

Keywords: *temporal lobe epilepsy (TLE); hippocampal volumetry; Apparent diffusion coefficients (ADC), hippocampal sclerosis (HS), medically intractable temporal lobe epilepsy (MITLE)*

ABSTRAK

Objektif:

Tujuan kajian ini adalah untuk menentukan isipadu ‘hippocampus’ pada pesakit yang mempunyai epilepsi lobus temporal (TLE) dibandingkan dengan isipadu ‘hippocampus’ pada individu yang normal, menentukan signifikan antara isipadu ‘hippocampus’ dengan ADC untuk mengesan keabnormalan pembentukan ‘hippocampus’ pada pesakit yang mempunyai epilepsi lobus temporal (TLE) yang sukar dikawal melalui perubatan. Selain dari itu adalah untuk membandingkan isipadu hippocampus dengan jangkamasa penyakit epilepsi lobus temporal (TLE).

Latarbelakang:

Dalam kajian ini, kami membandingkan isipadu ‘hippocampus’ pada pesakit yang mempunyai epilepsi lobus temporal (TLE) yang sukar dikawal melalui perubatan dengan subjek yang normal untuk melihat perbandingan antara isipadu ‘hippocampus’ dengan ADC dan jangkamasa penyakit epilepsi lobus temporal (TLE). **Metadologi:** Terdapat sejumlah 28 orang peserta yang terlibat dalam kajian ini. Empat belas pesakit dan 14 subjek kawalan telah dikaji. Imej MR telah dinilai untuk kiraan isipadu hippocampus dan dibandingkan dengan peta ADC dan jangkamasa penyakit. Min dan SD diperolehi bagi setiap pengukuran, dan tahap signifikan telah ditentukan.

Analisis min isipadu ‘hippocampus’, nilai ADC menggunakan ‘PASW version 18’. Kami menggunakan ‘independent t-test’ untuk mengkaji signfikan min isipadu ‘hippocampus’ antara kumpulan yang dikaji. ‘Pearson correlation’ digunakan bagi mengkaji signifikan antara isipadu ‘hippocampus’ dengan jangkamasa penyakit, juga signifikan antara min isipadu ‘hippocampus’ dengan nilai ADC.

Keputusan:

Tiada signifikan perbezaan yang ditunjukkan antara kiri dan kanan isipadu 'hippocampus' di dalam kumpulan kawalan. Walaubagaimanapun, terdapat signifikan perbezaan pada nilai isipadu 'hippocampus' di antara kumpulan kawalan dan kumpulan pesakit epilepsi lobus temporal (TLE). Terdapat juga signifikan perbezaan pada nilai isipadu 'hippocampus' di antara kedua-dua belah 'hippocampus' pada pesakit yang mengalami epilepsi lobus temporal (TLE) di sebelah kanan dan kiri. Tiada hubungkait signifikan antara isipadu 'hippocampus' dengan jangkamasa penyakit epilepsi lobus temporal (TLE). Terdapat hubungkait signifikan antara isipadu hippocampus dengan ADC.

Kesimpulan:

Isipadu 'hippocampus' mempunyai keupayaan untuk mengesan perubahan dalam pembentukan 'hippocampus' dan 'lateralise' fokus serangan sawan pada pesakit dengan TLE. Tiada hubungkait signifikan antara isipadu hippocampus dengan jangkamasa penyakit epilepsi lobus temporal (TLE) . Terdapat hubungkait signifikan antara isipadu hippocampus dengan ADC .

Kata kunci: *temporal lobe epilepsy (TLE); hippocampal volumetry; apparent diffusion coefficients (ADC), hippocampal sclerosis (HS), medically intractable temporal lobe epilepsy (MITLE)*

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 characterised 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(1). Hippocampal sclerosis (HS) is considered the most frequent pathological finding in patients with mesial temporal lobe epilepsy (MTLE). Hippocampal specimens of pharmacologically resistant MTLE patients that underwent epilepsy surgery for seizure control reveal the characteristic pattern of segmental neuronal cell loss and concomitant astrogliosis (2). 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 (2).

HS or mesial temporal sclerosis (MTS) 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. Real-valued ("true") inversion recovery, the image is reconstructed in real

rather than magnitude mode, provides exceptionally good grey-white contrast and is a good sequence for internal architecture. Hippocampal hyperintensity is best visualized in HR fast spin echo images with T2-weighted scans. 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 3D spoiled GRE/FLASH sequence provides good information regarding hippocampal volume loss on the side of sclerosis. 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 (3).

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 (3).

Quantitative MR imaging can depict the presence and laterality of HA in TLE with accuracy rates that may exceed those achieved with visual inspection of clinical MR imaging studies. Thus, quantitative MR imaging may enhance standard visual analysis, providing a useful and viable means for translating volumetric analysis into clinical practice (4).

The combination of quantitative techniques (T1 volumetric with inversion-recovery and T2 relaxometry) and FLAIR optimize MTS diagnosis using MR (5).

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 (6).

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 (7).

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 (8).

Based on the scientific basis, there was a neurodevelopmental and neurodegeneration in patient who have temporal lobe epilepsy. It is a progressive disorder with evidence of premature accumulation of corpora amylacea and loss of volume in the hippocampus (9). Base on this, we are expecting more atrophy of the hippocampus overtime in TLE patient. There were no previous study, correlating the MR volumetry with the duration of illness in TLE patient. In our study we are quantitatively correlate the MR volumetry with the duration of illness.

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

CHAPTER 2: STUDY PROTOCOL

2. STUDY PROTOCOL

Title:

Correlation between Magnetic Resonance (MR) Volumetry and Apparent Diffusion Coefficient (ADC) value of Hippocampal Formation in Medically Intractable Temporal Lobe Epilepsy (MITLE) patients.

General objective:

To determine volumetry values of the Hippocampal Formation in refractory Temporal Lobe Epilepsy patients correlating with ADC value

Specific objectives:

1. To compare the mean MR volumetry values of the hippocampal formation in refractory Temporal Lobe Epilepsy patients with normal individuals.
2. To correlate MR volumetry values with ADC in refractory Temporal Lobe Epilepsy patients.
3. To correlate MR volumetry values with duration of illness in refractory Temporal Lobe Epilepsy patients.

Methodology:

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 temporal lobe epilepsy and under regular follow up at neurology clinic, Hospital USM, Kubang Kerian, Kelantan.

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:

1. For specific objective no. 1, (MRI volumetry) two means formula was used for sample size calculation. The difference of the mean between the normal and patients was 0.002 and of the standard deviation (σ) was 0.001. By using the Power and Sample Size Program, total sample size is 12.
2. For specific objective no.2, (ADC) two means formula was used for sample size calculation. For ADC value, 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. The largest sample size is 40 based on objective (2). With expected a 10% non response rate, sample size was 40 + (40 x 0.1) = 44.

Research Tools

1. MRI machine – Philips 3 Tesla Achieva MR Scanner, Best, The Netherlands.

2. MR sequences :

   - Brain sagittal T1W.
   - Brain axial T1W, T2W
   - Temporal lobe series: Oblique coronal IR, T2, FLAIR.
   - Diffusion tensor imaging

3. Workstation – Philips MR Extended Workspace 2.6.3.5.

4. Osirix ver 3.7.1 (Pixmeo Sarl)

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 permonth

3. Volumetric imaging- a specialized technique where all the MR signals are collected from the entire tissue sample and imaged as a whole entity.

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: Volumetry and Apparent Diffussion Coefficient (ADC)

- The MR imaging sequence used for volumetric analysis was oblique coronal T2 using Philips MR Workspace 2.6.3.5 software. Thresholds were selected for each structure to optimize grey-white contrast, and the same thresholds were used for all patients with epilepsy and controls. Volume calculation using Osirix Ver. 3.7.1 (Pixmeo Sarl).

- 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 volumetry, ADC values were performed using PASW version 18. We used an independent t-test to investigate group differences in mean hippocampal volumetric value. Pearson correlation was used to examine relationships between mean hippocampal volumetric value and duration of illness, also as mean hippocampal volumetric value with ADC value.

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