COGNITIVE DYSFUNCTION AMONG EPILEPSY PATIENTS

AND ITS ASSOCIATED FACTORS

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ABBREVIATION

AED   Anti epileptic drug

AE   Adverse effect

CAE   Cumulative adverse effect

FSIQ   Full scale of intelligence quotient

GTC   Generalized tonic clonic

ILAE   International League Against Epilepsy

IV   Independent variable

MLR   Multiple logistic regression

SE   Status epilepticus

SLR   Simple logistic regression

VFT   Verbal Fluency Test

TLE   Temporal Lobe Epilepsy

WASI   Wechsler Abbreviated Scale of Intelligence

WMS   Wechsler Memory Scale

ABSTRAK

Latarbelakang

Epilepsi dan fungsi kognitif mempunyai hubungan yang berkait rapat. Kesan sawan boleh menyebabkan gangguan dan kerosakan pada fungsi kognitif pesakit. Faktor-faktor yang mendorong kepada gangguan fungsi kognitif dalam epilepsi boleh dikategorikan kepada faktor sosiodemografik, faktor berkaitan sawan, faktor psikososial dan faktor rawatan. Kajian ini bertujuan menilai fungsi kognitif (intelektual (IQ), memori dan bahasa) dan faktor-faktor yang berkaitan dengan kelemahan fungsi kognitif dikalangan pesakit epilepsi dalam masyarakat setempat. Kajian ini diharapkan boleh membantu meningkatkan kualiti penjagaan pesakit dan rawatan penyakit epilepsi.

Metodologi

Ini merupakan kajian hirisan lintang yang mengambil masa setahun bermula dari bulan November 2015 hingga November 2016 di Hospital USM. Pesakit epilepsi berumur 16 sehingga 65 tahun yang menghadiri temujanji rawatan susulan di Klinik Neurologi,yang memenuhi syarat kemasukan serta bersetuju akan dipilih untuk terlibat di dalam kajian ini. Saiz sample terbesar yang diperlukan ialah 111 orang. Data demografi, faktor berkaitan sawan dan sejarah rawatan direkodkan. Pesakit kemudiannya menjalani satu set ujian neuropsikologi yang mana dijalankan oleh pegawai yang telah dilatih dalam bidang ujian neuropsikologi. Komponen yang dikaji adalah IQ, memori dan bahasa. Wechsler Abbreviated Scale of Intelligence (WASI) digunakan untuk mengkaji kadar IQ, manakala tahap memori dikaji menggunakan Wechsler Memory Scale (WMS) dan komponen bahasa dikaji menggunakan Verbal Fluency Test. Data-data ini dianalisa menggunakan 'correlation' dan 'logistik regression' untuk mengetahui faktor-faktor berkaitan kemerosotan fungsi kognitif dikalangan pesakit Epilepsi.

Keputusan

135 orang subjek dianalisa. Min umur subjek yang terlibat di dalam kajian ini adalah 30 ± 10.57 tahun. Min semasa diagnosis mula dikesan adalah 14+4.82 tahun. Min tempoh penyakit dihidapi adalah 15 ± 7.51 tahun, min bilangan serangan sawan 3 ± 1.41 kali sebulan dan min bilangan antiepileptic ialah 2 ± 0.85 ubat. Majoriti pesakit adalah berbangsa Melayu (71.9%). 70 orang daripada jumlah subjek adalah perempuan (51.9%) dan 65 orang adalah lelaki (48.1%). 58.2% menerima tahap pendidikan tinggi and 60.7% subjek adalah tidak bekerja atau masih belajar. 72.6% tidak mempunyai sejarah status epileptikus yang melebihi 30 minit. Ketiadaan sejarah keluarga epilepsi dikalangan 92.6% subjek dan 85.9% subjek tiada ko-morbiditi. Min kadar intelektual (FSIQ) adalah 85.18 ± 14.27, min kadar total memori 84.65 ± 12.91 dan min kadar kelancaran bahasa adalah 38.43 ± 8.57. Analisa 'multivariate' menunjukkan umur pesakit, tahap pendidikan, tabiat merokok, tempoh penyakit dihidapi, bilangan ubat antiepileptik dan sejarah status epileptikus berkait dengan kelemahan fungsi kognitif subjek yang dikaji.

Kesimpulan

Faktor-faktor sosiodemografi yang mempengaruhi kemerosotan fungsi kognitif pesakit epilepsi secara signifikan adalah faktor umur, tahap pendidikan dan tabiat merokok, manakala faktor-faktor berkaitan epilepsi termasuklah umur semasa diagnosis, tempoh penyakit yang dialami, kekerapan sawan, bilangan ubat anti-epileptik dan juga sejarah 'status epileptikus' yang melebihi 30 minit. Kami mencadangkan pengenalpastian awal profil kognitif pesakit melalui ujian saringan secara rutin dan juga ujian neuropsikologi ketika diagnosis epilepsi dibuat agar dapat dijadikan satu penilaian permulaan. Sebarang perubahan terhadap penilaian ini pada masa akan datang, sama ada disebabkan oleh faktor penyakit atau disebabkan kesan ubat anti-epileptik turut perlu dikenalpasti. Rawatan awal untuk mengawal sawan di samping rawatan rehabilitasi kognitif adalah penting untuk meningkatkan kualiti hidup pesakit.

ABSTRACT

Background

Epilepsy and cognition has an interchangeable relationship. The after-effect of seizure may cause disturbances or damages to one's cognitive function. Multiple factors may adversely affect cognition in epilepsy, which can be grouped into sociodemographic, seizure-related, psychosocial and treatment factors. The objective of this study is to evaluate cognitive function (intelligence (IQ), memory and language) and factors associated with poor cognition among epilepsy patients in local setting. The knowledge of cognitive profile in epileptic patient will assist in improving quality of care and treatment of epilepsy patients.

Methodology

This was a cross-sectional study from November 2015 to November 2016 in Hospital USM. Epilepsy patients aged 16 to 65 years old who attended follow up at Neurology clinic, willing to participate with informed consent and fulfilled the inclusion criteria were selected. The largest sample size required for analysis was 111 subjects. Demographic data, seizure-related history and treatment were recorded. Patients underwent a set of neuropsychological assessment conducted by a trained personnel. The components tested were IQ, verbal memory and language. Wechsler Abbreviated Scale of Intelligence (WASI) was used to measure IQ level, while verbal memory was assessed using the Wechsler Memory Scale (WMS) and Verbal Fluency Test was used for language assessment. Variables obtained were analyzed using multiple logistic regression to determine the factors associated with cognitive dysfunction among epilepsy patients.

Result

135 subjects were analyzed. The mean age of subject in this study was 30 ± 10.57 years old. The mean age of onset of epilepsy was 14 ± 4.82 years old. The mean duration of illness was 15 ± 7.51 years with mean attack of 3 ± 1.41 times per month and mean numbers of anti epileptic drug (AED) was 2 ± 0.85 drugs. Majority of subjects were Malay (71.9%). There were 70 female (51.9%) and 65 male (48.1%). 58.2% received higher education level and 60.7% were either not working or still studying. 72.6% had not experience status epilepticus (SE) of more than 30 minutes. No family history of epilepsy in 92.6% and absent of medical co morbidity in 85.9% of patients. The mean value of full scale of intelligence quotient (FSIQ) was 85.18 ± 14.27, total memory of 84.65 ± 12.91 and verbal fluency of 38.43 ± 8.57. Multivariate analysis revealed certain factors such as patient's age, educational level, smoking status, duration of illness, number of AED and history of SE of more than 30 minutes were associated with impaired cognitive function among subjects studied.

Conclusion

There was significant association between cognitive dysfunction and sociodemographic factors such as current age, level of education and smoking status. There was also significant association with epilepsy characteristics such as age of onset, duration of illness, seizure frequency, history of SE of more than 30 minutes and number of AED used. We recommend an early recognition of patient's cognitive profile via routine screening and neuropsychological assessment at the time of diagnosis. This would help to provide a baseline cognitive function. Any subsequent change in cognition among epilepsy patients either due to progression of the disease or the effect of treatment

should also be measured. Early seizure control combined with cognitive rehabilitation may help to improve quality of life of the patients.

CHAPTER ONE

INTRODUCTION

1.1 STUDY BACKGROUND AND RATIONALE

Cognitive function is defined as higher brain function, that is, the capacity of the brain to programme adaptive behaviour, solve problems, memorise information and focus attention. Epilepsy is a chronic neurological condition characterised by recurrent unprovoked seizures.

Cognitive dysfunction is one of the major contributors to the burden of epilepsy. Previous study (Normah et al, 2012) showed that cognitive and psychosocial profiles of non-institutionalized epilepsy patients were comparable to those in the normal population. Martin et al. (2002; 2005) reported that, in older adults with chronic epilepsy, cognitive deficits were similar as compared to healthy elderly in several areas of cognition such as verbal memory, expressive language, simple visual construction, conceptualization as well as their overall cognitive status.

Research has shown that many people with epilepsy have cognitive difficulties as a result of their seizures (Aldenkamp,2005). The type of cognitive difficulties experienced by the epileptic patients depends on the origin of seizure focus in the brain. Epilepsy patient may suffer impairment in the ability to briefly retain and process information in immediate (working) memory, impaired language ability, and impaired executive function ability (Kilgor & Irwin, 2001). This is also supported by Rijckevorsel (2006) who found that the most reported cognitive complaints in adults with epilepsy are mental slowness, memory impairment and attention deficits.

Multiple factors may adversely affect cognition in epilepsy, which can be grouped into sociodemographic, seizure-related, psychosocial and treatment factors (Dodrill, 1986; Dodrill, 2002; Meador, 2002). In Malaysia, research on the factors affecting cognitive or neuropsychological outcome in epilepsy is scarce. Normah et al. (2010) conducted a study on the predictors of verbal memory in 98 adults with epilepsy and found that significant sociodemographic predictors were age, races, level of education and occupation. Among seizure-related factors, the significant predictors of verbal memory were age of onset, illness duration, duration of sleep and temporal lobe epilepsy (TLE).

Available antiepileptic drugs (AEDs) have the potential to exert detrimental effects on cognitive function and therefore compromise patient wellbeing. On the other hand, some agents may serve to enhance cognitive function (Eddy et al, 2011).

While monotherapy is preferable for most patients with epilepsy, monotherapy is particularly desirable as epileptic patients with monotherapy scored better cognitive functions, than those with polytherapy (Suzette et al, 2013).

The aim of the study is to evaluate cognition (intelligence (IQ), memory and language) and factors associated with cognitive dysfunction among epilepsy patients in Hospital Universiti Sains Malaysia. Based on our literature search, we could not find any previous similar study in HUSM. We hope this study will provide additional knowledge in management of epilepsy among local patients as the neuropsychological assessments are most frequently used to aid diagnosis, evaluate the cognitive side effects of antiepileptic medications and monitor the cognitive decline in epilepsy patients.

1.2 OVERVIEW OF EPILEPSY

1.2.1 Definition

An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure.

1.2.2 Epidemiology

According to a 2012 survey done by the Center for Disease Control and Prevention (CDC) in USA, about 2.3 million adults were diagnosed with active epilepsy while an estimate of 1.7 million adults were having inactive epilepsy (diagnosed but no seizures for almost 12 months). The World Health Organization (WHO) on the other hand, believes that approximately 50 million people worldwide are suffering from epilepsy. They also believe that almost 80% of these reported cases originate from developing countries including Malaysia. Epileptic patients make up 1% of the overall Malaysian population.

1.2.3 Burden and impact of disease on economy and productivity

Patients with epilepsy have high unemployment rate in Malaysia despite a robust economy and minimal social security. Besides those who were unemployed, many were in part-time or low-income employment (Keang et al, 2013) Patients with epilepsy had significantly higher rates of health-related contacts and medication use and a higher socioeconomic cost, lower employment rates, and income compared with control subjects.

1.2.4 Classification of Epilepsy

The International League Against Epilepsy (ILAE), through the Commission for Classification and Terminology, has developed a working classification of seizures and epilepsy.
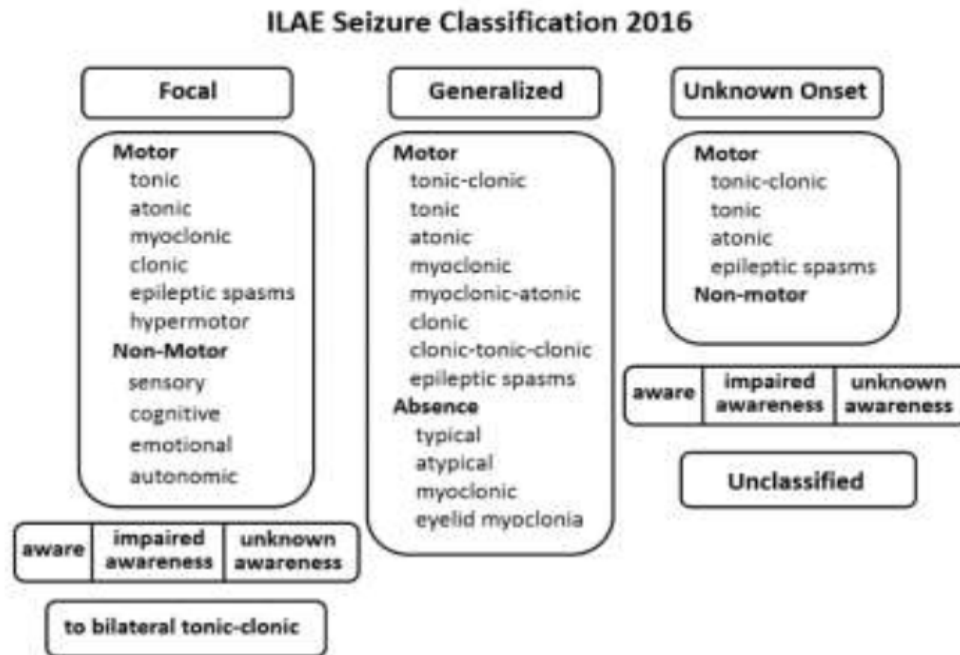
Figure 1: ILAE seizure classification 2016

1.2.5 Types of Epilepsy

In previous classifications, seizures were dichotomized into partial or generalized. This classification was inadequate for certain seizure types, such as spasms, which may appear generalized, despite being caused by a focal lesion. Generalized seizures are conceptualized as those that originate at some point within, and rapidly engage bilaterally distributed networks, which can be subcortical or cortical structures. A generalized presentation however can still arise from a focal lesion, and does not exclude the possibility of a surgical remedy.

The term focal has replaced partial to describe seizures that originate in networks limited to one hemisphere. Focal seizures may arise from either subcortical structures or neocortex.

In addition, the terms simple partial, complex partial, and secondarily generalized have been eliminated, since they were difficult to define pragmatically and were often used incorrectly.

Examples of preferred descriptors include:

- Without impairment of consciousness or awareness

- Involving subjective sensory or psychic phenomena

- With impairment of consciousness or awareness, or dyscognitive

- Evolving to a bilateral convulsive seizure

The term unknown mode of onset is used for seizure types where it remains unclear whether onset is focal, generalized, or perhaps either. A key example is epileptic spasms, concerning which there has traditionally been controversy, and current knowledge is inadequate to specify mode of onset as either focal or generalized.

1.2.6 Diagnosis

The diagnosis of epilepsy is made when:

1.At least two unprovoked (or reflex) seizures occurring >24 h apart

2.One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years

3.Diagnosis of an epilepsy syndrome

1.2.7 Management

The clinical diagnosis of Epilepsy can be confirmed by abnormalities on the interictal EEG. Video-EEG monitoring is the standard test for classifying the type of seizure or syndrome or to diagnose pseudoseizures (ie, to establish a definitive diagnosis of spells with impairment of consciousness). A CT scan is often obtained to exclude an obvious structural lesion, but an MRI is indicated if the patient continues to have seizures.

The goal of treatment in patients with epileptic seizures is to achieve a seizure-free status without adverse effects and monotherapy is desirable because it decreases the likelihood of adverse effects and avoids drug interactions.

1.2.8 Prognosis

The patient's prognosis for disability and for a recurrence of epileptic seizures depends on the type of epileptic seizure and the epileptic syndrome in question. Impairment of consciousness during a seizure may unpredictably result in morbidity or even mortality.

1.3 OVERVIEW OF COGNITION

1.3.1 Definition

Cognition can be defined as the capacity of the brain to process information accurately and to program adaptive behaviors. Cognition involves the ability to solve problems, to memorize information, or to focus attention. On a higher level, it involves dealing with complex situations creatively by transcending from the immediate circumstances to anticipate future acting

1.3.2 Definition of cognitive dysfunction

Cognitive dysfunction or brain fog is the loss of these intellectual abilities. This can affect a person's thoughts, memories, and reasoning capabilities, where it may manifest as trouble with recalling words, with the ability to do math problems, and with one's focus. Cognitive dysfunction can be seen in a variety of diseases or disorders. The issue of cognitive dysfunction in epilepsy is still challenging for clinicians. Patients with epilepsy frequently report some subjective impairment in cognitive functioning, with prevalence rates ranging from 44% for difficulties in learning and psychomotor retardation to 59% for sleepiness or tiredness (Meador KJ, 2006). In addition, 63% of patients perceive that antiepileptic drugs (AEDs) prevent them from achieving activities or goals (Trimbler, 2009).

1.3.2 Epidemiology

Mojs E et al (2007) reported there are about 30% people with cognitive dysfunctions connected to epilepsy. Primary emotional and cognitive dysfunctions might be caused by the same factor that cause epilepsy or develop due to the damage of the central nervous system in the course of epilepsy or are

related to the pharmacological treatment. Secondary emotional deficits are connected with negative social actions and negative social attitudes toward ill persons with epilepsy, mainly concerns on overprotective attitudes or social isolation. The prevalence of emotional disturbances is estimated at 5-50% in population of patients with epilepsy. The study shows the necessity of conducting psychotherapy and neuropsychological rehabilitation in the course of epilepsy as a part of schema of treatment.

1.3.3 Mechanism of cognitive dysfunction

Executive deficits including poor intelligence and difficult verbal fluency have been associated with damage to the most forward areas of the frontal lobes, as well as the cortical and subcortical structures that connect to the frontal lobes. The executive system involves the prefrontal cortex, basal ganglia and thalamus. The frontal lobes typically account for about 40% of the human brain. Frontal lobe functions, or more precisely executive functions, develop through adolescence. These facts together could explain that attention and executive function deficits are impaired whatever the syndrome, especially in younger patients.

The amygdala and hippocampal complex, two medial temporal lobe structures, are linked to two independent memory systems, each with unique characteristic functions.

The mechanism of cognitive impairment in epilepsy is complex. Negative effects on cognition may occur in the presence or absence of clinically manifest seizures, convulsive or nonconvulsive SE that occur during awakening or during sleep, and may occur due to focal or generalized EEG epileptic discharges

without epileptic symptomatology. Cognitive deficits associated with epilepsy and EEG epileptic discharges may be transient, persistent, or progressive.

1.3.4 Type of Epilepsy commonly associated with severe cognitive impairment

The frontal lobes support high-level cognition comprising executive skills and working memory that is vital for daily life functioning, thus frontal lobe epilepsy is associated with performance deficits in intelligence, language, and executive functions.

Memory problems are more marked in focal compared to generalized epilepsies, particularly short-term memory. The impairment is related to the laterality with a verbal learning deficit in the dominant lobe and a figural learning deficit in the non-dominant lobe. Impairment is more pronouced in dominant mesio-temporal lobe (MTL) epilepsy, with the severity of the deficit negatively correlated with the length of active epilepsy.

1.3.5 Factors associated with cognitive dysfunction

A number of factors influence the cognitive impact of epilepsy (Fig. 2). These include the aetiology of the disorder, in particular, whether there is underlying brain damage (Aldenkamp, 2005), epilepsy-related factors for example the nature of the epilepsy syndrome (Hommet 2006), duration of illness (Meador et al, 2001), location of the epileptogenic focus (Lezak 2004), age at onset (Anne et al, 2000) and seizure-related factors for example seizure type, seizure frequency, occurrence of status epilepticus (Alexandra et al, 2001) and treatment-related factors (Eddy CM et al, 2011) for example type and number of anti-epileptic drug, dosage and drug interactions.
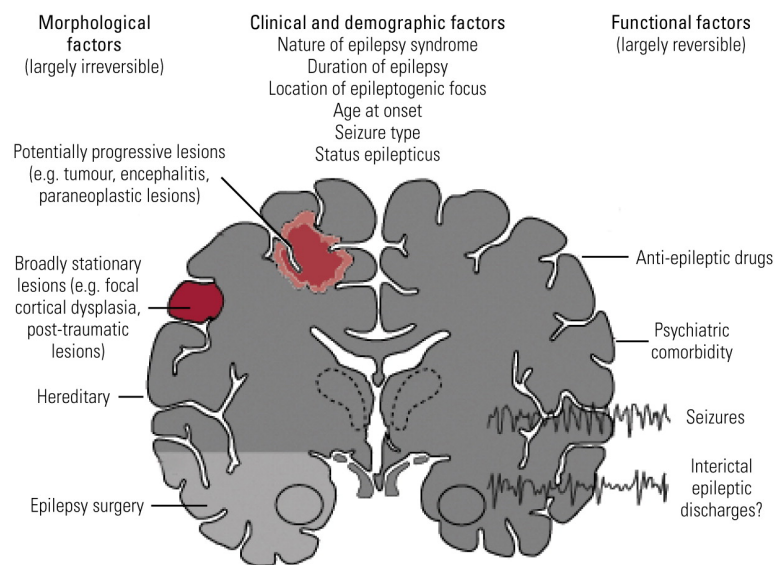
FIG 1 Factors affecting cognition in epilepsy (adapted from Elger et al 2004, with permission).

Figure 2: Factors influence the cognitive impact of epilepsy

1.3.6 Investigations of cognitive dysfunction

These include neuropsychology and neuroimaging assessment. A neuropsychological assessment in the routine care of people with epilepsy can provide a comprehensive and objective assessment of an individual's cognitive and psychological functioning. At times this role may be diagnostic, given that impairments in cognition or behavior can provide clues to the lateralization or localization of the seizure network, or the nature of the epilepsy syndrome. At other times the role may be prognostic, with assessments used to monitor and estimate the effect of ongoing seizures or a particular treatment on the future cognitive and behavioral functioning of an individual.

Neuroimaging studies includes functional MRI and volumetric allow the assessment of functional and structural damage related to epileptogenic lesions and foci, and are helpful to select surgical treatment, conduct intraoperative neuronavigation techniques, predict surgical deficits and evaluate patient recovery.

1.3.7 Treatment

Cognitive deficits in epilepsy are usually managed indirectly by aggressive seizure control (including earlier epilepsy surgery), selecting anti-epileptics with good cognitive profiles, and treating comorbid conditions such as depression. The beneficial effects of anti-epileptics in reducing seizures may offset their adverse cognitive effects. Direct therapy for cognitive deficits associated with epilepsy, such as vagal nerve stimulation, cholinergic replacement and stimulants have little evidence base, and are therefore not recommended in clinical practice. Memory rehabilitation strategies could be more helpful as a direct treatment for significant cognitive difficulties.

Where relevant, as a part of neurorehabilitation, psychological treatments such as cognitive behavior therapy or anxiety management can also be recommended to assist patient and family adjustment to epilepsy, complementing medical therapies.

1.3.8 Prognosis

Dementia resulting from progressive long-term cognitive impairment in pharmacoresistant epilepsy is a controversial concept. Helmstaedter & Elger (1999) have described it as a phantom. A plethora of evidence from cross-sectional and longitudinal studies shows that the progress of cognitive decline in chronic epilepsy is very slow and that, in adult epilepsies, successful treatment can stop or partly reverse it. In elderly people, any cognitive decline associated with epilepsy is usually due to early epilepsy-related deficit that then follows the course of physiological ageing (Elger, 2004).

1.3.9 Implication of cognitive dysfunction in management of epilepsy

Cognitive dysfunction in epilepsy represents an important factor that complicates clinical management and contributes to quality of life and outcome measures. A number of variables related to the individual patient, the underlying brain disorder and the AED treatment play a role. All of these factors need to be considered when discussing the cognitive problems of patients with epilepsy. Tailored treatment approaches addressing comorbidities and modifiable factors represent important strategies. Cognitive problems in epilepsy have represented and will continue to represent an important issue in patients with epilepsy. New AEDs and treatment strategies including cognitive rehabilitation and epilepsy surgery will have to take these aspects into consideration, possibly being as crucially as efficacy.

CHAPTER TWO

OBJECTIVES

2.1   RESEARCH QUESTIONS

Is there any association between the characteristic of epilepsy and cognitive dysfunction in epilepsy patients treated in HUSM?

2.2   RESEARCH HYPOTHESIS

1) The younger the age of onset of epilepsy, the lower their cognitive function

2) The longer the duration of epilepsy, the lower their cognitive function

3) The worst the seizure control, the lower their cognitive function

2.3   GENERAL OBJECTIVES

To evaluate the characteristic of epilepsy patients in HUSM and their cognitive function (intelligence (IQ), memory and language)

2.4   SPECIFIC OBJECTIVES

1) To determine the socio- demographic factors (age, sex, race, occupation and level of education) and characteristic of illness (age of onset, duration, severity) in epilepsy patients.

2) To evaluate the cognitive function among epilepsy patients

3) To determine association between age of onset and cognitive dysfunction among epilepsy patients

4) To determine association between duration of the epilepsy and cognitive dysfunction among epilepsy patients.

5) To determine association between seizure control and cognitive dysfunction.

CHAPTER THREE

METHODOLOGY

3.1 STUDY DESIGN

A cross sectional study

3.2 STUDY DURATION

The study duration was 1 year (from November 2015 to November 2016)

Patient's participation required one to two sessions of neuropsychology test

3.3 STUDY POPULATION

Epilepsy patients in Hospital Universiti Sains Malaysia

3.4 STUDY PARTICIPANTS

Epilepsy patients in Hospital Universiti Sains Malaysia who fulfilled inclusion & exclusion criteria

Inclusion criteria:

- Aged >16 year old to 65 years old

- Diagnosis of epilepsy was made by neurologist based on standard criteria

Exclusion criteria:

- Physical disability (i.e. blind or with hearing impairment)

- Unable to speak or read in English or Malay languages

- Presence of psychiatric comorbidities

- Underlying mental impairment or retardation

- Epilepsy syndrome associated with mental retardation

- Other neurological disorders known to cause mental disability (for example dementia, post trauma)

3.5 STUDY SETTING

Patients with Epilepsy who attended follow up at Epilepsy Clinic (Klinik Pakar Perubatan) in HUSM were identified. Patients who met the inclusions and exclusion criteria were invited to participate in the study. The patient's identification data was obtained from the patient. The information of treatment history was reviewed in the patient's folder. The data was collected using data collection form. The patient underwent a set of neuropsychological assessment conducted by a trained personnel in neuropsychology test. The components of the assessment were IQ, verbal memory and language. Wechsler Abbreviated Scale of Intelligence (WASI) was used to measure IQ level. Verbal memory was assessed using the Wechsler Memory Scale (WMS) and Verbal Fluency Test was used for language assessment

3.6 SAMPLING METHOD

- Simple random sampling was performed as a basic sampling technique where each epileptic patient was chosen entirely by chance and each member of the population has an equal chance of being included in the sample.

- Randomisation was done using random numbers.

- Epileptic patients who were followed up at Neurology Clinic, Hospital Universiti Sains Malaysia were identified during their clinic attendance.

3.7 DATA COLLECTION

- Ethical approval from local Ethics Committee was obtained prior to study

- List of epilepsy patients under follow up were screened.

- Subjects were screen for inclusion and exclusion criteria

- Informed consent was taken prior to the study.

- Patients who fulfilled inclusion and exclusion criteria and consented to participate in the study were given a date for neuropsychological assessment.

- Patient required 1 to 2 sessions to complete the full sets of assessment.

- Neuropsychology assessment was performed by a medical staff who was a neuropsychologist assistant and was trained in performing the neuropsychology test by the neuropsychologist.

- It was an interviewer guided test, and was carried out in either Bahasa Malaysia or English, according to patient's preference.

3.8 STUDY TOOLS

- A set of worldwide-validated neuropsychological assessment was administered to determine the IQ profiles, verbal memory and language.

- Wechsler Abbreviated Scale of Intelligence (WASI) is registered trademark of The Psychological Corporation - is administered to measure IQ level.
- Wechsler Memory Scale - Third Edition (WMS-III) Logical Memory, Verbal Paired Associates, and Visual Reproduction from the WMS-III (Wechsler, 1997) were administered to measure verbal and visual memory ability.

- Verbal Fluency Test: PAS - Test (Spreen & Benton, 1969, 1977), is a test of verbal fluency that consists of three trials. Each trial requires the participant to generate as many words as he or she can that begin with a specific letter (i.e., P, A, S) during a one- minute time period. This measure localizes to the left frontal lobe and was administered as an additional measure of executive functioning

3.9 VARIABLE DEFINITIONS

3.9.1 **Age of Onset**

Age of subject when he/she started to have his/her first seizure

3.9.2 **Higher educational level**

Secondary schooling and above (form 1 to college or university)

3.9.3 **Lower educational level**

Primary schooling and below (standard 6 and below, or not schooling)

3.9.4 **Smoking**

Smoking habit was divided into smoker and non-smoker. Smoker include patient who were still smoking for the past 3 months and non smokers were those who never smoke or already stopped for past 3 months

3.9.5 **Drinking alcohol**

Drinking habit was divided into alcoholic and non-alcoholic. The number of alcoholic drinks they had consumed in the last 7 days. This information was divided into "measures" of spirits, "glasses" of wine, and "pints" of beer. A standard measure of spirits and a glass of wine are considered to contain 8 g of

alcohol, while a pint of beer contains 16 g of alcohol. Participants were also asked to report the frequency of their drinking over the last 12 months by circling one of six specified options (twice a day or more, almost daily, once or twice a week, once or twice a month, special occasions only, none).

3.9.6   Status epilepticus (of more than 30 minutes)

History of single or recurrent convulsion that last for more than 30 minutes and are interrupted by only brief episode of partial recovery

3.9.7   Scoring system of intelligence and verbal fluency

SCORE	INTERPRETATION
>130	Very superior
120-129	Superior
110-119	High average
90-109	Average
80-89	Low average
70-79	Borderline
55-69	Mild retardation
40-54	Moderate retardation
25-39	Severe retardation
<24	Profound retardation

Table 3.1 Wechsler score classification of intelligence and memory (Wechsler, 1997)

SCORE	INTERPRETATION
>53	Superior
45-52	High average
31-44	Average
26-30	Low average
24-25	Borderline
17-23	Defective
<17	Very defective

Table 3.2 Verbal fluency test score (Spreen & Benton, 1969, 1977)

3.9.8 Normal cognitive function

Individuals with IQ and memory scores of more than 80 and verbal fluency score of more than 25

3.9.9 Cognitive dysfunction

Individuals with IQ and memory scores of less than 80 and verbal fluency score of less than 25

3.9.10 Seizure control

No focal or generalized seizure within past 1 year with AED

3.10 SAMPLE SIZE CALCULATION

For objective number 2, sample size is calculated by using single mean formula

$$n = \left(\frac{Z\sigma}{E}\right)^2$$

With:

n = sample size

Z = constant value of 1.96

σ = Population standard deviation

E = estimated difference from population mean (standard deviation * effect size)

Intelligence (IQ)	n = [(1.96)(13.43)/2.5] = 111	Normah et al, Science Direct 2010
Memory	n = {(1.96)(12.36)/2.5] = 94	Kenneth et al , Arch Neurol. 1995;52(10)
Verbal fluency/language	*no previous study	

For Objective no 3, 4, and 5, sample size calculated using correlation coefficient formula:

$$r = \frac{\sum z_X z_Y}{N}$$

Age of onset of epilepsy	r value of 0.42 to 0.83	Hermann et al, Epilepsia.
	making n = 43	2002
Duration of epilepsy	r value of 0.51 to 0.68	Richard et al, CrossMark,
	making n = 28	1980
Seizure control	No previous study	

Largest sample size calculated from Objective no.2 (111 subjects)

Hence, 111/(1-drop out rate) = 111/(1-0.2) = 111/0.8 = 138 subjects

Thus, 138 subjects needed with expected 20% dropout rate to achieve 80% power of study

3.11 STATISTICAL ANALYSES

All statistical analyses were performed using the Statistical Program for Social Sciences (SPSS version 20). The steps of statistical data analyses were as follow:

i) Descriptive Analysis

ii) Univariate Analysis

iii) Multivariate Analysis

Descriptive Analysis

For descriptive analysis, numerical variables were described as mean and standard deviation. Categorical data were presented in frequency and percentage units.

Univariate Analysis

For univariate analysis, simple logistic regression was used to determine the potential factors associated with impaired cognitive function among Epilepsy patients. Any factors with a p value less than 0.25 would be included in the multivariate analysis.

Multivariate Analysis

Multivariate analysis was used to look for factors associated with cognitive dysfunction among epilepsy patient. Stepwise methods, both forward and backward, with both logistic regression tests were used to obtain the preliminary model. The variables that remained significant after these methods were subsequently checked for interaction and multicollinearity. Clinical plausible interaction terms were created and entered into the model and an interaction was considered significant if the P value was < 0.05. To check the models's goodness

of fit, Hosmer-Lemeshow test and classification table Receiver Operating Characteristic (ROC) curves were computed.

3.12 FLOWCHART OF THE STUDY

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┌─────────────────────────────────────────────────┐
│ Epilepsy patients attended Neurology Clinic,     │
│ Klinik Pakar Perubatan HUSM from March 2016-     │
│ September 2016                                    │
│                                                   │
│                150 patients                       │
└─────────────────────────────────────────────────┘
                        │
                        │           ┌──────────────────────────────┐
                        │           │ 12 patients excluded:         │
                        │           │                               │
                        │           │ -4    with mental challenged  │
                        │           │                               │
                        │           │ -5    not consented           │
                        │           │                               │
                        │           │ -3    post trauma             │
                        ▼           └──────────────────────────────┘
┌─────────────────────────────────┐
│ 138 patients fulfilled study     │
│ criteria                         │
└─────────────────────────────────┘
                        │
                        │           ┌──────────────────────────────┐
                        │           │ 3 patients excluded           │
                        │           │                               │
                        │           │ -    not completed the full   │
                        │           │      set of assessment        │
                        ▼           └──────────────────────────────┘
┌─────────────────────────────────┐
│ 135 patients available for       │
│ analysis                         │
└─────────────────────────────────┘
                        ▼
┌─────────────────────────────────┐
│ Result and conclusion            │
└─────────────────────────────────┘
```