

The Effects of Antiepileptic Drugs Use Duration on IQ in Focal Cortical Dysplasia Patients

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ABSTRACT

Background: Focal Cortical Dysplasia (FCD) is an important pathologic condition in epilepsy, however, due to inadequate diagnostic examination, it is often underdiagnosed. Patients may take antiepileptic drugs before definitive diagnosis of FCD, and it has been associated to impairment of cognitive function including Intelligence Quotient (IQ).

Aim: To investigate the effects of the duration of antiepileptic drugs use on IQ of FCD patients or suspected FCD.

Method: This study was an observational retrospective cohort study by reviewing medical records of epilepsy patients with suspect of FCD (n=42) from 2017 to 2018. The study was conducted in one general hospital in Semarang, Indonesia. Data of antiepileptic drugs use duration and Wechsler Adult Intelligence Scale (WAIS) or Wechsler Intelligent Scale for Children Revised (WISC-R) IQ prior epilepsy surgery were collected. The data were then analyzed using Spearman and regression test.

Results: Sixteen patients (38.1%) had used antiepileptic drugs up to 10 years and twenty six patients (61.9%) had used for more than 10 years. WAIS IQ score ≤ 90 were found on 19 patients (45.23%). There was a significant correlation between anti epileptic drug use duration with WAIS IQ score ($P < 0.05$) with medium grade correlation ($CC = -0.45$). Regression test showed a significant effect between anti epilepsy drug use duration and WAIS IQ score ($P < 0.05$, RR 2.23 95% CI (1.15-4.34)).

Conclusion: Antiepileptic drug use duration had significantly decreased the WAIS IQ score in epilepsy patient with FCD.

Keywords: FCD, IQ, duration of anti epileptic drug use

INTRODUCTION

Epilepsy is one of the most common neurological disorders in society, especially in developing countries. The exact number of people with epilepsy in Indonesia is still unknown due to the poor record system in this country and also the lack of awareness of epilepsy patients to seek treatment. Based on its etiology, epilepsy is divided into structural, genetic, infection, metabolic, and immune systems. Epilepsy with structural abnormalities causes most of epilepsy that are resistant to the drug.¹ In such cases, an MRI scan is required to determine the imaging of the structural abnormalities present in the patient's brain. More than 30% of patients are called epilepsy or drug-resistant epilepsy, because it cannot be controlled by anti-epilepsy drugs (AED). Focal Cortical Dysplasia (FCD) tends to cause refractory epilepsy. FCD is a malformation and impairment of neuron migration, which is usually found in the early decade of life.² The long-term use of anti-epilepsy drugs will affect the cognitive function of FCD patients.³

When patients have seizure within a few minutes, there is weakness until the death of brain neuron cells. If the seizure continues, it will result in more dead brain cells, intellectual disturbances, mental retardation, and even intellectually severe patients. IQ test is one of neuropsychological examinations that is always done before epilepsy surgery.⁴ The IQ test method used in the Dr Kariadi General Hospital is Wechsler Adult Intelligence Quotient (WAIS) IQ test and Wechsler Intelligent Scale for Children Revised (WISC-R). Both pediatric and adult

patients are always worried if the decrease of IQ will affect their career and future life. Until now, there is still a question whether the duration of anti-epilepsy drugs use have effects on IQ of FCD patient.

The neurosurgery department of Dr Kariadi General Hospital Semarang has done a lot of research on epilepsy. In this study, more emphasis was given to the influence of the duration of anti-epilepsy drugs use to Intelligent Quotient of patients with focal cortical dysplasia suspect. The expected goal of this study was to determine the effect of the duration of anti-epilepsy drug use on Intelligent Quotient of suspects to be focal cortical dysplasia patients.

METHOD

Forty two epilepsy patients with radiological focal cortical dysplasia had chosen based on the inclusion and exclusion criteria. The inclusion criteria included having complete pre surgical assessment and routine AED consumption; such as valproate, carbamazepine, phenytoin, and phenobarbital. Patients with microencephaly, brain trauma history, and history of brain surgery were excluded from this study. This study used analytic observational type of research and the design was retrospective cohort. Samples were taken from medical records of epilepsy surgery patients in Dr. Kariadi General Hospital Semarang from 2017-2018 by a consecutive method. The independent variable in this study was the duration of anti epileptic drug use while the dependent variable was IQ of suspected FCD patients measured by WAIS or WISC-R method depending their age.

This study obtained the ethical clearance and permission from Dr. Kariadi General Hospital Semarang prior to the data collection. This study took complete medical records of epilepsy patients and then grouped them into radiological FCD and non-FCD patients, patients were suspected for FCD if there was an abnormality in their imaging of the cortex. After that, the duration of AED used and WAIS/ WISC-R total IQ patient before surgery were recorded in suspected FCD patients. The data analysis used Spearman Rank and Linear Regression.

RESULTS

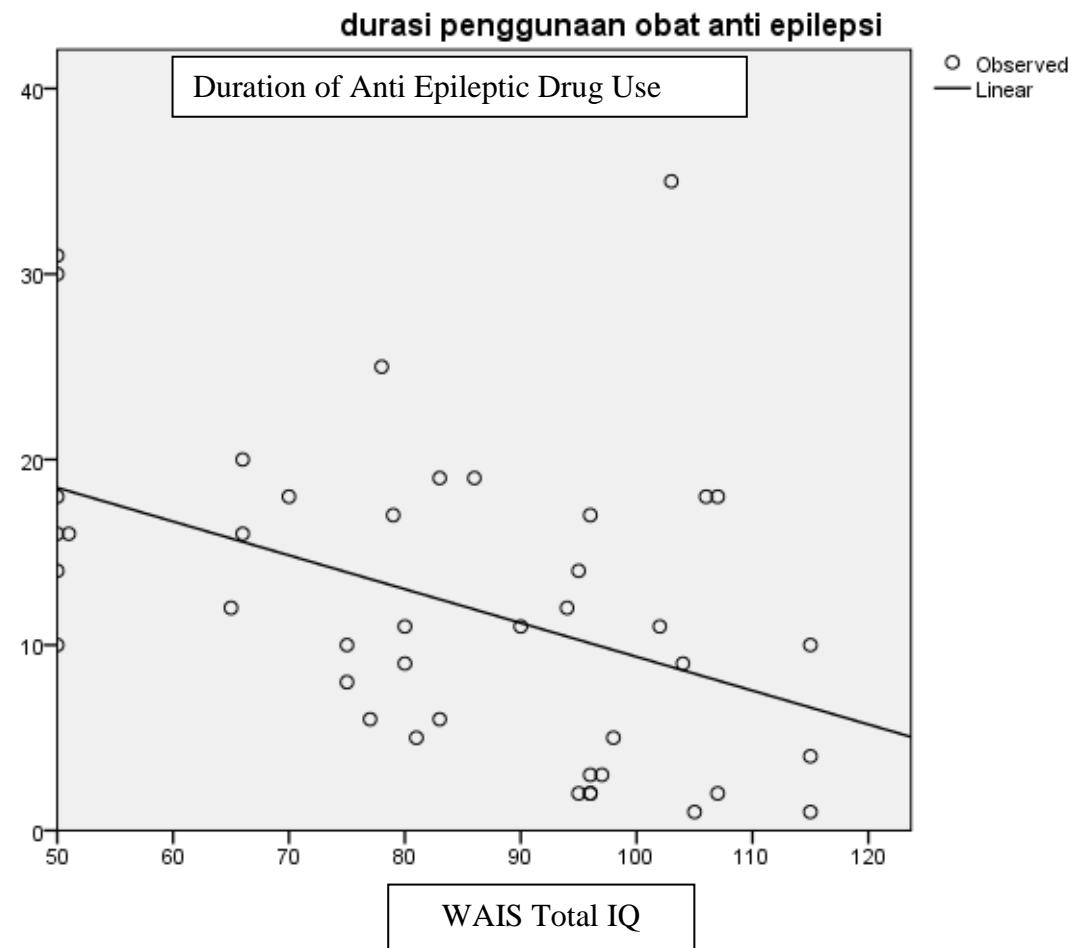
Table 1 showed the patient's characteristics. There were 42 samples in this research consisting of 28 (66.7%) males and 14 (33.4%) females. Patients started to use anti-epilepsy drugs at the average age of 11.2 years. From the data analysis, the youngest age of patients started using AED was at the age of 5 months and the oldest age started using AED was at age of 33 years old. Patient performed surgery and the duration of AED use were at the average of 22 years old and of 10.8 years respectively. The youngest patient performed surgery was at the age of 5 years, while the oldest patient performed surgery at the age of 49 years.

As many as 24 samples (57.10%) experienced seizures more than 4 times a month, while 18 samples (42.9%) were having seizures less than 4 times a month. There was a significant difference of patient's WAIS total IQ between the group of patient that used AED for less than 10 years and more than 10 years ($p < 0.05$).

As can be seen from table 2, sixteen patients had used AED for less than 10 years and 26 patients had used AED for more than 10 years. Patients with a WAIS total IQ up to 90 were 19 patients (45.23%) while 23 patients (54.76%) had a WAIS total IQ more than 90. RR in this study showed the results of 2.23 which can be interpreted that the duration of the anti-epileptic drugs use over 10 years was a risk factor decreasing WAIS total IQ under 90 because RR more than 1.

Linear regression analysis showed that the duration of AED use influenced the patient's IQ with significance p value of 0.003 (Figure 1). Spearman correlation analysis also showed that the results of the study correlated significantly ($p = 0.003$). The correlation coefficient in this study was -0.45 which meant that the duration of AED use had a medium correlation to the decrease in WAIS total IQ of FCD patient.

Figure 1: Linear Regression



{P*;P**(CC)}
{0.003*;0.003**(-0.45)}

*Linear Regression Test
 *Spearman Correlation Test

Table 1: Characteristics of the patients

Patient data	Descriptive variable {f;%;mean±SD;(min-max)}	WAIS Total IQ {mean±SD}	p*
Onset <18 >18	{35;83.33;8±1.2;(3-13)} {7;16.7;25±2.03;(18-33)}	{84±19.5} {84±26}	0.95
Age of surgery <18 >18	{19;45;12.7±4;(5-18)} {23;55;29±8;(19-49)}	{82.3±22.7} {85.3±19.6}	0.96
Gender Male Female	{28;66.7} {14;33.3}	{83.3±21.1} {86.5±17.6}	0.60
Frequency of Seizure >4 times/ month >4 times/ month	{18;42.9} {24;57.1}	{90±14.5} {78.8±14.5}	0.08
Duration of AED use <10 years >10 years	{16;38.1;4.25±0.68(1-9)} {26;61.9;17.23±1.3(10-35)}	{95±3.2} {77.2±3.2}	0.004

*Independent T-Test

Table 2: Duration of AED use and WAIS total IQ

Duration of AED use	Wais Total IQ		Total
	≤90	>90	
≤10	11	5	16
>10	8	18	26
Total	19	23	42

DISCUSSION

The age of initial use of anti-epileptic drugs in this study was in the range of 5 months to 33 year old. The initial onset of using anti-epilepsy drugs used in this study was possible equal to the onset of early epilepsy because when patients knew that they had epilepsy they went to the doctor and were given anti-epileptic drugs by doctors. The average of initial AED use was 11.2 year old, which was still included in the category of children. The results were consistent with previous research conducted by Fauser⁵ in 2006 which stated that 92.5% of the samples used in the study were in the category of children. The presence of epilepsy in children has a fatal consequence of stunted brain development. The younger the patient suffers epilepsy, the worse it will be due to its cognitive function.

A total of 28 samples (66.70%) were male, while 14 samples (33.33%) were female. The results are in accordance with research conducted by Xilma⁶ which states that Focal Cortical Dysplasia can be found in patients of male sex than women. Xilma's study showed that 72% of the study sample was male.⁶ A research from Chung also shows the result that FCD are more dominant in men.² The phenomenon occurs because some malformations of the brain are X-linked and therefore inherited only in men.⁷

As many as 24 patients (57.1%) experienced a seizure attack more than 4 times a month and the 18 remaining patients (42.9%) experienced less than 4 attacks in a month. The data were grouped by the researchers to control confounding variables because researchers found references from previous studies that the number of seizures affected IQ in epilepsy patients of any etiology. This is because many neuron cells are weakened and die

every seizure attack. Such persistent seizures also affect patients' mental growth and development.⁸⁻¹⁰

The seizures occur due to the role of mammalian target of rapamycin (mTOR) pathway. The active of mTOR pathway results in increased activity of cell division and proliferation resulting in anatomic lesions of the brain. mTOR pathway also results in increased expression of neurotransmitters and ion channels resulting in hyperactivity of neuron cells. The morphological and functional changes of the nerve cells result in more seizure symptoms in FCD patients.¹¹ Because of this pathogenesis, the most appropriate treatment of patients with FCD is surgery to remove anatomical lesion that present in the patient brain. Patients who consume AED continuously do not get a significant improvement in the seizures and will even cause some new problems like intelligence disorders.

The results of data analysis showed that the duration of AED use had an effect and was significantly related to WAIS total IQ of Focal Cortical Dysplasia patients. Regression analysis performed showed p value of 0.003, while spearman correlation analysis showed significance of 0.003. The correlation coefficient obtained from the results of data processing was -0.45 meaning that the duration of AED use had a medium relationship with the FCD patient's IQ and the nature of the relationship was negative. Thus, the longer the patient using anti-epileptic drugs, the lower the WAIS total IQ patients. The results in this study were in accordance with the hypothesis made before the study conducted.

This phenomenon corresponds to the pathogenesis and epileptogenesis of focal cortical dysplasia, namely cell maturation failure which results in the development of the cortex being inhibited, the cortical developmental resistance causing lesions of the FCD. The failure of cortical development results in abnormalities of GABAergic or GABA receptor cells, as we know that GABA has inhibitory function in the pyramidal nervous system and controls the excitability of the cortex. FCD type II causes faster cortical development than FCD type I.¹²

The medium level of the relationship was due to the fact that there were still some other variables that had a larger relationship such as the frequency of seizures, the

initial onset, the length of epilepsy, and the age of the patient. The exercise factor was closely related to the patient's IQ because although the patients have epilepsy with good cognitive function, they will have higher IQ test results than patients who have never trained their cognitive function. The side effects of some drugs also affect the result of WAIS total IQ of FCD patients. The longer the drug is being used, the greater the side effects on the cognitive system of FCD patients. In the majority of pediatric patients, long-term use of AED will affect brain development by causing apoptosis, affecting neurogenesis, synaptogenesis, proliferation, and migration of neuronal cells. If the use of AED in the patient is discontinued, there will be a significant increase in the patient's cognitive abilities.¹³

These are some previous studies on anti-epilepsy drugs with the cognitive and intelligence systems of patients. The use of phenytoin causes degradation of memory, concentration, visomotor, and mental speed that depends on the dose used.¹⁴⁻¹⁷ At the time of treatment discontinuation there is no significant effect on memory, intelligence, and visuomotor compared to the time of administration.¹⁸ This is in accordance with the results of this study which shows the effect of prolonged use of anti-epilepsy drugs on WAIS total IQ result of patient taken before the patient's surgery.

Carbamazepine use will cause adverse effects of deterioration in information processing, attention, memory, and arithmetic.¹⁹⁻²² The side effects of Valproate and carbamazepine are almost identical except in the attention and memory aspect. Phenobarbital has an adverse effect of reducing the patient's IQ test after 2 years of use and most patients experiencing it are pediatric patients.²³ The use of phenobarbital results in a worsening of cognitive function that is worse than carbamazepine and valproate. Studies on clobazam showed no difference in cognitive side effects when compared with carbamazepine. The results in each study show different effects on the child because there is a period of development and maturation of the brain still occurs in the child.

The relationship of this study had medium correlation coefficient because of the genetic and environmental factors affect IQ in patients. The genetic factors possessed have a large influence on patients IQ because the genetic codes that are inherited, will affect brain growth and development.^{24,25} Although genetic factors have a great influence to personal IQ but it is still found differences in intelligence among family members. Environmental factors that influence the Intelligence Quotient (IQ) are stimulation given by parents, the quality of education in the early life, and physical activity that people done. Children who are given enough stimulation to stimulate their intelligence will have better intelligence than children who are not given stimulation to stimulate intelligence.²⁶⁻³⁰ The quality of education in kindergartens and play groups has a role in the formation of people intelligence because at that time synaptogenesis and pruning happen in the human brain.³¹ Adequate physical activity in children will make it easier for the child to create and consolidate memory, whereas in adults sufficient physical activity will maintain executive functions such as planning and scheduling for the future.³²⁻³⁴ Socio-economic condition of the family is also considered

to be related to the development of individual IQ at that family.³⁵

However, the provision of AED in the long term certainly has adverse side effects for patients both small and large. Several previous studies were consistent with the results of this study that the longer the AED given to the patient will result in side effects in the form of decreased WAIS total IQ results below normal.

The weakness of this study was the limitations of researchers in paying attention to patient compliance in taking anti-epilepsy drugs, patients who regularly took AED and who did not routinely take AED then it had differences of WAIS total IQ results. The dose of drug was not controlled in this study. Different doses would cause side effects in different stage of intelligence. Researchers did not have patient IQ data when they had not been exposed to epilepsy to differentiate which patients who had a low IQ from the beginning and which patients who have low IQ because of long term AED use.

CONCLUSION

The findings concluded that the duration of anti-epileptic drugs use had an effect and significantly related to the WAIS total IQ of suspected FCD patients. The longer duration of anti-epileptic drug use, the lower total WAIS of IQ from suspected FCD patients.

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