

Relationship between APO-A, APO-B, and C-reactive Protein with Depression in Epileptic Patients

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ABSTRACT

Background: Epilepsy is one of the oldest neurological disease requiring long-term treatment. Long-term use of certain anti-epileptic drugs (AED) will strongly induce cytochrome-P450 (CYP) enzyme resulting increase of homocysteine associated with risk of cerebrovascular disease and depression. The purpose of this study was to determine relationship between serum level of ApoA, ApoB, and C-Reactive Protein (CRP) with depression in epileptic patients receiving AED therapy.

Subjects and Method: Respondents of this cross-sectional study were epileptic outpatients in neurology clinic Dr. Moewardi Hospital, Surakarta receiving AED therapy and met inclusion and exclusion criteria. Depression condition was evaluated by Hamilton Depression Rating Scale (HDRS). Serum level of ApoA, ApoB, and CRP of each respondent were measured from vein blood. Data were analyzed by a multiple linear regression.

Results: There were 51 epileptic patients with proportional ratio between men and women

(1.2:1) with age range from 18 to 59 years old. The average length of AED 92.67 months (Mean= 92.67; SD= 91.58). Average of HDRS score was 8.49. Meanwhile, average of ApoA level was 86.14 mg/dL, average of ApoB level was 47.57 mg/dL, and average of CRP level was 0.18 mg/dL. Serum level of ApoA, ApoB, and CRP increased depression (HDRS score) in epileptic patients.

Conclusion: There was a statistically significant relationship between serum level of ApoA, ApoB, and CRP with depressive condition of epileptic patients receiving long-term AED treatment.

Keywords: ApoA, ApoB, C-Reactive Protein, depression, epilepsy

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BACKGROUND

Epilepsy is one of the oldest neurological diseases found at all ages and can cause hives and mortality. It is estimated that there are about fifty million people with epilepsy in the world. The population of active epilepsy (those with uncontrolled seizures or those requiring treatment) in developing countries is estimated to be between 6 and 10 per 1000 population.

Based on the results of research on the incidence of epilepsy from the epilepsy study group of the Indonesian neurologists association at 18 hospitals in 15 cities in 2013 for 6 months, there were 2,288 patients consisting of 487 new cases and 1801 old cases. The average age of new cases was 25.06 years old (Mean= 25.06; SD= 16.9), while the mean age in old cases was 29.2 years old (Mean= 29.2; SD= 16.5) (Octa-

viana and Khosama, 2014). One of the criteria for reclassified epilepsy based on the International League Against Epilepsy (ILAE) in 2014 is that patients have been seizure-free for more than 10 years and not using drugs for the last 5 years (Fisher et al., 2014), so that epilepsy requires long-term treatment.

Provision of long-term OAE therapy will cause various side effects, which include metabolic disorders, endocrine disorders, behavioral disorders and cognitive problems, as well as side effects of the drug itself (Brodie and Mintzer, 2013). The side effects of OAE vary from person to person. This is related to genetic polymorphism, age, gender, body weight, the presence of liver disease, the presence of kidney disease, nutritional status, smoking habits, and compliance with OAE use. Therefore, it is not easy to predict the side effects and efficacy of OAE in each individual (Saruwatari et al., 2010).

Old OAE groups such as carbamazepine, phenytoin, and phenobarbital can trigger atherosclerosis. This is because these drugs can induce cytochrome P450 (CYP) enzymes in the liver which are involved in cholesterol synthesis and metabolism. This is associated with an increased rate of atherosclerosis, which is marked by an increase in markers as a marker of vascular risk which includes: homocysteine, folate, lipoproteins, C-reactive protein (CRP), apolipoprotein B (apoB), and apolipoprotein A1 (apoA1) (Chuang and Chuang, 2012).

The levels of apoB and apoA1 describe the total number of atherogenic particles, especially the number of low-density lipoprotein (LDL) particles in the plasma. The role of apolipoproteins is very important in atherosclerosis because it can bind to LDL receptors in the endothelium and cause LDL to be stuck in the walls of blood

vessels. LDL will be oxidized to oxidized-LDL (ox-LDL) which in turn will trigger atherosclerosis (Waldius and Jungner, 2006). In the process of atherosclerosis formation, endothelial activity will occur which causes an increase in CRP levels, an increase in pro-inflammatory factors such as cytokines, TNF- α , IL-6, abnormal conditions of the hypothalamus-pituitary axis, and changes in the homeostasis of the sympathetic and parasympathetic nervous systems (Alvarez et al., 2013). Increased activity of inflammatory mediators characterized by the release of inflammatory cytokines will result in an increase in serotonin metabolism and will have an impact on decreasing the number of neurotransmitters characterized by hypothalamic-pituitary-adrenal hyperactivity (Philippe, 2016).

Long-term use of OAE will also strongly induce CYP so that there is an increase in homocysteine due to a decrease in cofactors used for homocysteine metabolism such as folic acid and vitamin B12 (Kim and Lee, 2013). Increased homocysteine levels will be associated with the risk of cerebrovascular disease and depression (Papakostas and Petersen, 2004). The mechanism of homocysteine activity on the central nervous system (CNS) and depressive conditions is not clear, but it is known that homocysteic acid and cysteine sulphonic acid will have a toxic impact on the CNS receptors of N-methyl-D-aspartate and these changes will lead to depressive conditions (Ebesunun et al., 2012).

A study by Terao et al. (2000) shows that the serum levels of high-density lipoprotein (HDL) and apoA1 were lower while the serum levels of LDL and apoB were higher in patients with depression. From this study, it was found that the severity of depression was associated with an increase in serum apoB levels and a decrease in

serum apoA1 levels (Terao et al., 2000). Other studies have also reported an association between depression and serum apolipoproteins. Several molecular biology hypotheses can explain this condition. The first hypothesis is that depression related to genetic factors may contribute to changes in serum lipid levels. The second hypothesis is that an increase in the lipid profile will have an impact on metabolic disorders, resulting in a condition of segmental cerebral hypoxia and will have an impact on depression. In addition, increasing the lipid profile will also result in damage to the serotonergic system which will lead to depression (Oh-Young and Sung-Pa, 2014).

Based on the above assumptions, the researcher wanted to discover the effect of ApoA, ApoB, and CRP levels on the clinical condition of depression in people with epilepsy who received OAE therapy at Dr. Moewardi Hospital Surakarta because there has been no research on this matter at this Hospital.

This study is conducted to determine the relationship between levels of ApoA, ApoB, and CRP with the clinical condition of depression in people with epilepsy who received OAE therapy at Dr. Moewardi, Surakarta. This study is expected to be useful for all parties involved in the management of epilepsy so that they can conduct early detection of depressive disorders in people with epilepsy who receive OAE therapy through these three markers, so that they can determine the right and effective therapy and improve the quality of life of people with epilepsy.

SUBJECTS AND METHOD

1. Study Design

This study was an analytic observational study with a cross-sectional study design. The study was conducted in the outpatient installation of Dr. Moewardi Hospital Surakarta

from November 2017 to January 2018.

2. Population and Sample

The subjects used in this study were 51 outpatients who received OAE therapy in the neurological polyclinic of Dr. Moewardi Hospital, Surakarta. To facilitate the determination of the sample, inclusion criteria were used which included: primary epilepsy patients who underwent single treatment or combination drugs carbamazepine (CBZ), phenytoin (PHT), phenobarbital (PB), or valproic acid (VPA) more than 1 year old, aged more than 18 years old, and willing to take part in research. Meanwhile, the exclusion criteria used included: obesity (body mass index of men >27 and women >27), hypertension (systolic blood pressure ≥ 140 mmHg and diastolic ≥ 90 mmHg), consumption of anti-hyperlipidemia drugs, cardiovascular disease, history of liver dysfunction, history of impaired kidney function, history of diabetes mellitus, history of inflammatory disease, being in a state of infection at the time of examination, pregnant, users of hormonal contraceptives, alcohol drinkers, recipients of steroid therapy for more than 3 months, and people with psychiatric disorders.

3. Study Variables

The dependent variable was the degree of depression. The independent variables were the levels of Apo-A, Apo-B, and CRP.

4. Operational Definition of Variables

In this study, the levels of ApoA, ApoB, and CRP were the values obtained from the examination of the patient's cubital venous blood serum which was carried out on the day the patient visited the neurological polyclinic of Dr. Moewardi Hospital, Surakarta. The researchers used Advira 1800 series reagent with spectroscopic methods in this study. Meanwhile, depressive disorders include grief, guilt, suicidal thoughts, insomnia, work and activity dis-

orders, retardation, agitation, anxiety, psychological and somatic disorders, hypochondriasis symptoms, weight loss, depersonalization and derealization, paranoia, obsessive compulsive disorder, helplessness, hopelessness, and feelings of worthlessness which measured using the Hamilton Depression Rating Scale (HDRS) instrument. Respondents with an HDRS score ≤ 7 were included in the normal category, 8-13 included in the mild depression category, 14-18 included in the moderate depression category, 19-22 included in the category of major depression, and ≥ 23 included in the category of very severe depression (Todorova and Velikova, 2012).

5. Data Analysis

The data from the study results were tested with a single correlation test and multiple correlation tests according to the normality of the data distribution to determine the relationship between levels of ApoA, ApoB, and CRP with depressive conditions in persons with epilepsy. The relationship is statistically significant if the value is $p < 0.05$.

6. Research Ethics

Research ethical issues including informed consent, anonymity, and confidentiality, were addressed carefully during the study process. The research ethical clearance approval letter was obtained from the Health Research Ethics Committee of Dr. Moewardi Hospital, Surakarta, Indonesia, No. 871/X/HREC/2016.

RESULTS

1. Sample Characteristics

Study has been carried out on 51 people with epilepsy in the neurological polyclinic

Dr. Moewardi, from November 2017 to January 2018, who fulfilled the inclusion and exclusion criteria, consisted of 28 (54.90%) men and 23 (45.09%) women. The characteristics of the study subjects can be seen in table 1.

The average age of the subjects of this study was 32 years old (Mean= 32.77; SD= 11.42) with an age range of 18-59 years old. The average length of use of OAE from respondents in this study was 92 months (Mean= 92.67; SD= 91.58) with a range of 15-402 months. The study subjects' last seizure was 190 days (Mean= 190.20; SD= 445.82) with a range of 1-2190 days.

The results of blood laboratory tests showed that the average ApoA level was 86.14 mg/dL (Mean= 86.14; SD= 25.68), the average of 15-91 ApoB level was 47.57 mg/Dl (Mean= 47.57; SD= 17.25), the average of CRP level was 0.18 mg/dL (Mean= 0.18; SD= 0.26). The average of HDRS score was 8.49 (Mean=8.49; SD= 6.40).

2. Bivariate Analysis

The Kolmogorov-Smirnov test was used to assess the normality of the distribution of the research data because the number of data was more than 30. The normality test is useful for determining the statistical test used in this study. The results of the Kolmogorov-Smirnov test showed that the CRP data were not normally distributed, therefore, the researchers used the Spearman correlation test and multiple correlation test in the data analysis of this study. The results of the correlation test can be seen in Table 2.

Table 1. The Characteristics of Study Subject

Subject Characteristics	N	%
Age (years old)		
- 18-28	22	43.13
- 29-39	13	25.49
- 40-50	12	23.52
- 51-60	4	7.84
Educational level		
- Primary school	11	21.56
- Junior high school	7	13.72
- Senior high school	24	47.05
- College	9	17.64
Duration of OAE consumption (months)		
- 1-60	30	58.82
- 61-121	8	15.68
- 122-182	7	13.72
- 183-243	2	3.92
- 244-304	2	3.92
- 305-365	1	1.96
- 366-426	1	1.96
The last seizure		
- ≤ 2 day	11	21.56
- ≥ 2 day	40	78.43
Type of OAE		
- Carbamazepine (CBZ)	4	7.84
- Phenytoin (PHT)	25	49.01
- Phenobarbital (PB)	-	0.00
- Valproic Acid (VPA)	12	23.52
- The combination of phenytoin and valproic acid	7	13.72
- Combination of carbamazepine and valproic acid	1	1.96
- Combination of carbamazepine and phenobarbital	2	3.92
Type of seizure		
- General tonic clonic	39	76.47
- General tonic	4	7.84
- General Flax	8	15.68
Level of depression		
- Normal	21	41.18
- Mild	19	37.25
- Moderate	4	7.84
- Severe	7	13.73

Table 2. The Results of Spearman Correlation Test

Variables	r	p
ApoA →level of depression	-0.11	0.438
ApoB →level of depression	-0.18	0.220
CRP →level of depression	-0.14	0.327
ApoA+ApoB+CRP →level of depression	0.21	0.531

3. Multivariate Analysis

Multiple linear regression test is used to assess the strength of the relationship between each independent variable and the

dependent variable in this study. Multiple linear regression tests were performed with the addition of the interaction terminology 'degree of depression' × 'duration of treat-

ment', with a backward elimination procedure. After adjusting the covariate duration

of treatment, a statistically significant data were found as shown in Table 3.

Table 3. The Results of Multiple Linear Regression Test of the effect of ApoA, ApoB, CRP on depression

Independent Variable	b	p
ApoA	-0.22	0.024
ApoB	-0.20	0.018
CRP	-0.66	0.010
ApoA+ApoB+CRP	0.64	0.038

DISCUSSION

The results of this study showed that the highest incidence of epilepsy was in the age range of 18-28 years old with a percentage of 43.13% or 22 patients. This is consistent with previous research which states that the incidence and prevalence of epilepsy generally appears at age (Mean = 25.06; SD= 16.90) years old for new cases and at age (Mean = 29.2; SD = 16.5) years old for old cases (Octaviana and Khosama, 2014).

Based on gender, the highest incidence of epilepsy in this study was found in the male, which was 28 patients (54.90%), while in female was 23 patients (45.09%). This is in accordance with previous studies which showed that the incidence of epilepsy in men (5.1 per 1000) was higher than in women (2.2 per 1000) (Poonam et al., 2010).

The most recent education level of the patients in this study was the Senior High School (HS) which were 24 patients (47.05%) followed by Primary School (PS) which were 11 patients (21.56%). In this study, the level of education had no effect on depressive conditions. Depressive conditions are associated with increased side effects of OAE use in epileptic patients (Kanner et al., 2012).

From the results of this study, it was found that the most common types of OAE used by people with epilepsy were phenytoin which was used by 25 people (49.01%) and valproic acid which was used by 12 people (23.52%). This distribution which

supported this study found no significant relationship between depressive conditions and levels of ApoA and ApoB. Previous studies have suggested that phenytoin, valproic acid, lamotrigine, and oxcarbazepine are used as mood-stabilizing agents. Meanwhile, depressive disorders and affective disorders were more commonly found in the administration of carbamazepine, levetiracetam, topiramate and vigabatrin (Lee et al., 2011).

The average ApoA level in this study was 86.14 mg/dL and the mean ApoB level was 47.57 mg/dL. This shows that both the ApoA value and the ApoB value in this study are below the normal value (the normal value of ApoA in men is ≥ 120 mg/dL and in women is ≥ 140 mg/dL, while the normal value of ApoB in men is 104-202 mg/dL and in women it is 108-225 mg/dL). ApoA and ApoB are structural components in very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and LDL which play a role in the process of atherosclerosis. High levels of ApoA and ApoB will increase the risk of LDL sticking to blood vessel walls. ApoA and ApoB levels can be influenced by gender, race, lifestyle, stress conditions, exercise habits, personality type, alcohol, drug use, obesity, and genetic diseases such as sickle cell anemia. ApoA and ApoB levels increase with age and the levels are higher in elderly men than women. ApoA and ApoB levels will decrease in conditions of

low fat and cholesterol diet, estrogen replacement therapy in postmenopausal women, and in patients who are given vitamin B₃ (niacin) or lovastatin. In the research conducted, it was found that all respondents received vitamin B complex supplementation. Vitamin B₃ is needed by the body to form the co-enzyme nicotinamide adenine nucleotide (NAD), which degrades carbohydrates, fats, proteins, and alcohol into energy. Vitamin B₃ also plays a role in stimulating the formation of prostaglandin I₂, a hormone that helps prevent the accumulation of platelet aggreration (John, 2009). NAD also plays a role in preventing the formation of oxidized LDL by increasing LDL receptor activity, producing less monocyte adhesion, reducing foam cell formation, preventing platelet formation, reduce chemical damage, and reduce vascular toxicity. LDL that is captured by the LDL receptor can be converted into HDL (Guyton and Hall, 2011).

In this study, it was found that the average CRP level was 0.18 mg/dL. The normal value of CRP is ≤ 0.3 mg/dL, so that the average patient in this study has normal CRP levels. This could be related to the patient's last seizure condition. In line with this theory, the last seizure condition of more than 2 days in this study was found in 45 patients (88.24%), while the last seizure which was less than two days was only found in 6 patients (11.76%). This condition is in accordance with the theory about CRP. CRP is a biomarker of chemical reactions that occur in the acute phase of inflammation, which will increase in levels 24-48 hours after the onset of inflammation including after a seizure in epilepsy (Fordjour et al., 2015).

HDRS is an instrument that can be used to diagnose depression. Previous research concluded that HDRS was used as a measure of depression symptoms in

epilepsy patients (Fordjour et al., 2015). The average value of HDRS in this study was 8.49. This condition indicated that the average patient in this study was experiencing moderate depression. This condition is in accordance with previous research that states that the condition of major depression in epilepsy patients is quite difficult to diagnose. This is due to the effects of the basic disease on impaired feelings, cognitive, and memory function as well as the side effects of OAE which can cause unclear depressive symptoms (Getz, 2002).

From this study, it was found that the levels of ApoA, ApoB, and CRP together have a correlation coefficient of correlation to HDRS of 0.213 and a value of $p > 0.05$ ($p = 0.531$), which mean that there was no significant relationship between levels of ApoA, ApoB, and CRP on the value. HDRS. The insignificance of these results might arised due to the uneven distribution of OAE types in this study as seen from the dominant use of phenytoin in the subjects involved (49.01%). This insignificance is also confused with the vigilance in excluding the type of OAE used by sufferers. After the researchers tried to get the normal data distribution by doing an outlier based on the length of use of OAE by using multiple linear regression analysis with the backward elimination method, a statistically significant relationship was found between ApoA, ApoB, CRP, and ApoA, ApoB, and CRP on the HDRS score as seen in table 3. The results showed a moderate relationship between ApoA, ApoB, and CRP with the HDRS score with a correlation coefficient (R) of 0.637. The coefficient of determination (R²) of 0.791 mean that the percentage of the effect of ApoA, ApoB and CRP levels on the HDRS score is 79.1% and the remaining 20.9% was influenced by other factors.

The limitation of this study was the uneven distribution of data so that abnormal data were obtained and the time of sampling was short. In addition, the insignificance of the statistical results in this study before the outlier can also be influenced by genetic factors and the provision of vitamins that are not restricted in this study. Finally, after the outlier was carried out there was a statistically significant relationship between the levels of ApoA, ApoB, and CRP on the depressive condition of people with epilepsy who consumed long-term OAE.

AUTHOR CONTRIBUTION

Diah Kurnia Mirawati, Nella Lusti Widhiarningsih, Titian Rakhma, Subandi, Rivan Danuaji, Pepi Budianto, Hanindya Riani Prabaningtyas, and Stefanus Erdana Putra collected the data, measured ApoA, ApoB, and CRP level, held history taking, did data analysis, and wrote the manuscript.

CONFLICT OF INTEREST

The authors declare that the study was conducted with no commercial or financial relationships that could be considered as a potential conflict of interest.

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