ARTIKEL PENELITIAN

Hyperhomocysteinemia : an Independent Risk Factor for Acute Ischemic Stroke in Immanuel Hospital Bandung

Slamet Santosa, Widhongjudana Linggajaya**
*Dedeh Supantini**, Nancy Suhendra***
**Dept. of Biochemistry, Faculty of Medicine, Maranatha Christian University*
***Dept. of Neurology, Faculty of Medicine, Maranatha Christian University*

Abstrak

Stroke merupakan suatu penyakit dengan morbiditas dan mortalitas yang tinggi, baik di Indonesia maupun negara-negara lain. Hiperhomosisteinemia merupakan salah satu faktor risiko penyakit pembuluh darah, antara lain stroke iskemik. Penelitian ini bertujuan untuk mengevaluasi apakah hiperhomosisteinemia merupakan suatu faktor risiko independen pada kejadian stroke iskemik di Rumah Sakit Immnuel Bandung.

Pada penelitian yang bersifat observasional deskriptif ini, dicari data berbagai faktor risiko penderita stroke iskemik akuta (SIA). Data diperoleh dari rekam medik RS Immanuel periode Juli 2003 sampai dengan Agustus 2004. Kemudian data dianalisis secara statistik untuk mencari nilai rerata, standar deviasi, dan proporsi dari setiap faktor risiko yang menimbulkan SIA pada selang kepercayaan 95%.

Dari 37 orang penderita SIA (23 pria, 14 wanita, usia rata-rata 58,35 tahun) yang memenuhi kriteria penelitian, didapatkan hasil kadar plasma homosistein total (tHcy) 12,08µmol/L , SD 6,57µmol/L , proporsi 43,2% (95%CI:27,2-59,2). Sedangkan kadar plasma kolesterol total, trigliserida, LDL kolesterol, HDL kolesterol berturut turut adalah 188 mg/dl , SD 33,3 mg/dl , proporsi 35,1% (95%CI:16,1-36,9) ; 141 mg/dl , SD 45,1 mg/dl , proporsi 24,1% (95%CI:10,2-26,1) ; 120,5 mg/dl , SD 30,1 mg/dl , proporsi 37,8% (95%CI:18,2-39,5) ; 43,7 mg/dl , SD 10,4 mg/dl , proporsi 27,1% (95%CI:11,8-40,8). Faktor risiko lain seperti hipertensi, diabetes mellitus, dan merokok merupakan kriteria eksklusi. Dari 37 orang sehat yang menjadi kontrol (serupa dalam usia dan gender) didapatkan hasil kadar tHcy 8.48µmol/L, SD 2.48µmol/L, proporsi 10.8% (95%CI : 2.78-13.2), p<0.005. Odds rasio hiperhomosisteinemia sebagai faktor risiko SIA adalah 6.28.

Dapat disimpulkan bahwa hiperhomosisteinemia nampaknya merupakan suatu faktor risiko independen terhadap penderita stroke iskemik akuta di Rumah Sakit Immanuel Bandung.

Kata kunci *: hiperhomosisteinemia, stroke iskemik, faktor risiko independen*

Introduction

Homocysteine, a normal breakdown product of the essential amino acid methionine, is believed to exert several toxic effects. Increased homocysteine levels may also be a risk factor for the development of many other conditions,

including stroke, thromboembolism (blood clots that can dislodge and cause stroke, heart atttack, and other complications), osteoporosis, inflammatory bowel disease (Chron's disease and ulcerative colitis), Alzheimer's disease, death from diabetes, miscarriage, and other complications of pregnancy and hypothyroidism (Boushey, 1995). Scientists have yet to prove that elevated homocysteine levels cause any of these diseases. However, most doctors believe that high homocysteine increases the risk of at least heart disease. Fortunately, homocysteine levels can easily be reduced with safe and inexpensive B vitamin supplementation.

Hyperhomocysteinemia can cause adverse vascular effects, involving oxidative damage to vascular endothelial cells and increasing proliferation of vascular smooth muscle cells after metabolism of homocysteine to homocysteine thiolactone. Oxidative modification of low-density lipoprotein (LDL) promotes the formation of foam cells, which in turn yields another source of reactive oxygen species (ROS). Endothelial dysfunction, prolifera-tion of vascular smooth muscle cells, lipid peroxidation, and oxidation of LDL caused by ROS can induce atherothrombosis (Gouaille, 1999). The reference for normal tHcy level in human adults is variable, but in the range of 5 to 15 μmol/L. In this study, we take a plasma tHcy level exceeding 11.35 μmol/L to characterize hyper-homocysteinemia (Widjajakusuma, 2001).

Stroke is the third leading cause of death and a significant cause of disability in the United States. Of the roughly 600,000 new and recurrent cases of stroke each year, 160,000 are fatal. Currently, there are 4 million stroke survivors, many of whom have significant disabilities, and more than $50 billion is spent on stroke care each year (Ingall, 2001). The main focus of primary stroke prevention is modification of risk factors for stroke. Old age, male sex, race (eg, African American), and heredity are clearly documented stroke risk factors and are nonmodifiable. The modifiable risk factors that have been identified include hyper-tension, diabetes mellitus, smoking, and various cardiac conditions (table 1).

Table 1. Stroke Risk Factors (Ingall,2001)

Nonmodifiable	**Cardiac**
Older age	Atrial fibrillation
Male sex	Coronary artery disease
Race	Congestive heart failure
Genetic factors	Left ventricular dysfunction with mural thrombus
Modifiable	Mitral stenosis
Hypertension	Left ventricular hypertrophy
Cigarette smoking	Patent foramen ovale
Carotid artery stenosis	Atrial septal aneurysm
Physical inactivity	Mitral annular calcification
Diabetes mellitus	Mitral valve strands
Hyperlipidemia	Aortic arch atheroma
Transient ischemic attack	Aortic stenosis
	Mitral valve prolaps

Regular exercise has been shown to reduce premature mortality from cardiovascular diseases. Until recently, however, the effect of physical activity on risk of stroke was unclear. Data from the Northern Manhattan Stroke Study showed that leisure-time physical activity significantly reduced the risk of stroke among men and women; young and old; and whites, blacks, and Hispanics (overall adjusted odds ratio [OR], 0.37; 95% CI, 0.25 to 0.55). A dose-response relationship was seen with both intensity of physical activity (light-moderate activity OR, 0.39; heavy activity OR, 0.23) and duration of activity (<2 hr/wk OR, 0.42; 2 to 5 hr/wk OR, 0.31). The Center for Disease Control and Prevention recommends that all persons engage in at least 30 minutes of moderately intense physical activity on most, and preferably all, days of the week (Ingall, 2002).

Diabetes mellitus is a well-recognized independent risk factor for stroke. After adjustment for the confounding effects of other risk factors, the relative risk of stroke associated with diabetes has been estimated to be 1.5 to 3. Whether hyperlipidemia is a risk factor for stroke is still uncertain. Many studies have shown that it is a modifiable risk factor for coronary heart disease, but epidemiologic evaluation has not established a conclusive link between hyperlipidemia and stroke. Although a direct correlation between hyperlipidemia and clinical outcome of stroke has yet to be clearly established, recent evidence has shown that lowering elevated lipid levels with statin medications is associated with a reduction in the occurrence of first stroke, especially

in patients with coexisting coronary heart disease.

The purpose of this study is to evaluate hyperhomocysteinemia as an independent risk factor for acute ischemic stroke in Immanuel Hospital patients.

Material and Method

This research was a descriptive-observational retrospective study and performed by identification total plasma homocysteine (tHcy) levels and other risk factors such as lipid profile among acute ischemic stroke (AIS) patients and healthy-control populations based on the research criteria. The data were collected from Immanuel Hospital's medical records from July, 2003 to August, 2004.

Inclusion criteria :

- Ischemic stroke patients, diagnosed by clinical and laboratory examination and brain CT-scan
- Within 2 weeks after the first clinical manifestations
- 40 to 80 years old male or female

Exclusion criteria :

- Malnutrition, Alcoholics, Smokers,
- Renal disease, Diabetes mellitus, Hypertension, Neoplasia, Hypothyroidism
- Ongoing therapeutic drugs such as cholestyramine, fibrate, metformin, methotrexate, anticonvulsant, penicillinamine, acetylcysteine, and theophylline

Results

Based on the research criteria, there were 37 acute ischemic stroke (AIS) patients and 37 healthy-control subjects matched in age and gender (23 male and 14 female, with the mean age being 58.35 years old). The mean value and standard deviation from the baseline characteristics of the AIS patients and control group can be seen in table 2.

In tables 3 and 4, we can see the proportion of each risk factor (homocysteine and the lipid profile) for becoming an acute ischemic stroke. We have already excluded the other risk factors (diabetes mellitus, hypertension, and smoking). Based on table 3, we calculated the odds ratio of hyperhomocysteinemia and its value was 6.28.

Table 2. Baseline characteristics of the subjects (AIS and Control)

	AIS Group (n=37)	Control Group (n = 37)	p
1. Gender : - male	23	23	
- female	14	14	
2. Age (years)	58.35 (7.18)	58.35 (7.18)	
3. Biochemical markers (plasma):			
-Total homocysteine (µmol/L)	12.08 (6.57)	8.48 (2.48)	<0.005
-Total cholesterol (mg/dl)	188 (33.3)		
-LDL cholesterol (mg/dl)	120.4 (30.1)		
-HDL cholesterol (mg/dl)	43.7 (10.4)		
-Triglyseride (mg/dl)	141 (45.1)		
-Glucose fasting (mg/dl)	96.6 (20.5)		
-2 hr post prandial (mg/dl)	110.4 (29.4)		
-Creatinine (mg/dl)	0.97 (0.24)		
-Natrium (meq/L)	135.4 (7.30)		
-Potassium (meq/L)	4.32 (0.97)		

AIS : acute ischemic stroke; p : significancy (Student t-Test, 95%CI)

Table 3. The distribution of hyperhomocysteinemia in AIS and Control

	AIS (n)	Control (n)	Proportion (% ; 95%CI)
(+)	16	4	
Hyperhomocysteinemia			AIS : 43.2% (95%CI:27.2-59.2)
(> 11.35µmol/L) (–)	21	33	
			Control : 10.8% (95%CI:2.7-13.2)
	37	37	

AIS : acute ischemic stroke

Table 4. The distribution of lipid profile in AIS patients

		AIS (n)	Proportion (% ; 95%CI)
Hyper-Total Cholesterolemia (> 200 mg/dl)	(+)	13	35.1% (95%CI:16.6-36.9)
	(–)	24	
		37	
Hyper-Triglyceridemia (> 150 mg/dl)	(+)	9	24.1% (95%CI:10.2-26.1)
	(–)	28	
		37	
Hyper-LDL cholesterolemia (> 130 mg/dl)	(+)	14	37.8% (95%CI:18.2-39.5)
	(–)	23	
		37	
Hypo-HDL cholesterolemia (< 40 mg/dl)	(+)	10	27.1% (95%CI:11.8-40.7)
	(–)	27	
		37	

AIS : acute ischemic stroke ; CI : confidence interval

Discussion

The mean concentration of total plasma homocysteine (tHcy) in acute ischemic stroke patients in Immanuel Hospital is 12.08 µmol/L, and this value is significantly different from the one in healthy-control subjects (8.48 µmol/L), with $p < 0.005$ (Santosa, 2005). This condition is the same as the other researches, that there is an increase of total plasma homocysteine (tHcy) levels in acute ischemic stroke patients. However, the tHcy level in acute ischemic stroke patients in Immanuel Hospital (12.08 µmol/L) was different from the others (Eikelboom : 12.7 µmol/L ; Tan : 13.4 µmol/L ; Adunsky : 13.8 µmol/L ; Tanne : 17.4 µmol/L ; Pratama : 17.72 µmol/L). The differences might be caused by nonmodifiable and modifiable predisposition factors such as age, race, ethnicity, genetic, daily diet, smoking, blood lipid levels, and the preparation of the blood samples. Anyhow, these various

tHcy levels in AIS patients are still significant compared to the normal populations. (Eikelboom : 10.5 µmol/L, p=0.004 ; Tan : 10.5 µmol/L, p<0.001 ; Adunsky : 9.8 µmol/L, p<0.001 ; Pratama : 15.11 µmol/L, p=0.021 ; Santosa : 8.48 µmol/L, p<0.005).

In this study, all subjects in acute ischemic stroke (AIS) group has normal value limits for the other risk factors such as blood total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and blood glucose. Together with normal blood pressure levels and non-smoking habit of the subjects, these conditions indicate that there is no influence by the other risk factors for becoming an acute ischemic stroke in our subjects. Furthermore, hyperhomocysteinemia is indicated as a risk factor for ischemic stroke (odds ratio 6.28), and this feature is similar to the others. Tanne reports that hyperhomocysteinemia has 3.3 fold increase to become ischemic stroke, while in Pratama study it is 3.22 times greater and Tan report that the risk factor for stroke is 2.53 times greater in hyperhomocysteinemia patients. These relative risk differences might be due to the differences in age, race, ethnic, gender, and genetic factors.

The prevalence of hyperhomocysteinemia in acute ischemic stroke patients in this study (43.2%) is different from the others (Lumenta : 33.3% ; Tan : 53% ; Pratama : 72.5%). The differences might be caused by the various normal value limits of the plasma tHcy level (Tan : 12.0 µmol/L ; Pratama : 15.0 µmol/L ; Widjajakusuma : 11.35 µmol/L). Considering with the prevalence of lipid profiles in this study, we can seen that hyperhomocysteinemia had a greater prevalence than lipid profiles for becoming a risk factor for AIS. Unfortunately, we do not have data about lipid profiles of the control subjects and the other modifiable and non-modifiable risk factors for ischemic stroke.

Conclusions

1. There is an indication that hyperhomocysteinemia is an independent risk factor for vascular diseases such as acute ischemic stroke.
2. The concentration of total plasma homocysteine (tHcy) in acute ischemic stroke patients in Immanuel Hospital is greater than that in healthy populations.
3. The prevalence of hyperhomocysteinemia in acute ischemic stroke patients in Immanuel Hospital is greater than that in healthy populations.

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