The Relationship Between Homocysteine Levels With The Degree of Severity In Patients With Acute Phase Ischemic Stroke At Haji Adam Malik General Hospital Medan

Rosa Zorayatamin Damanik*, Ratna Akbari Ganie**, Iskandar Nasution***

*Post Graduate of Clinical Pathology, Faculty of Medicine Universitas Sumatera Utara,Medan,Indonesia

** Departement of Clinical Pathology, Faculty of Medicine,Universitas Sumatera Utara,Medan,Indonesia

***Departement of Neurology, Faculty of medicine,Universitas Sumatera Utara,Medan,Indonesia

Abstract:

Background: Elevated homocysteine levels are an independent risk factor for ischemic stroke patients. Besides being an independent risk factor, homocysteine is also a factor that affects the prognosis of stroke, but the results are still controversial.

Objective: To Determine the relationship between homocysteine levels with the degree of severity in patients with acute phase ischemic stroke.

Methods: An analytical study with cross sectional design, involving 45 acute phase ischemic stroke patients who were hospitalized in the stroke corner room at Haji Adam Malik General Hospital, Medan. Homocysteine levels are grouped into 2 categories, namely high homocysteine levels (> 15 μmol / l) normal (≤ 15 μmol / l). The severity of acute phase ischemic stroke was examined using National Institute of Health Stroke Scale (NIHSS).

Results: Acute phase ischemic stroke patients have homocysteine levels of at least 4,4 μmol/l and maximum 24.1 μmol / l with average 11.5 μmol / l. 34 peoples (75,6%) suffers mild stroke and 11 people (24,4%) with moderate stroke. The logistic regression test results showed homocysteine levels were related to the severity of acute phase ischemic stroke. This means that acute phase ischemic stroke patients who have high homocysteine levels are estimated as predictors to increase the risk of acute phase ischemic stroke severity by 6,960 times compared to normal homocysteine levels ($p = 0,005$; $OR = 6,960$; 95% CI; 1,523-31,811).

Conclusions: Homocysteine levels show a strong relationship with the severity of acute phase ischemic stroke.

Index term- Homocysteine levels, acute phase ischemic stroke, NIHSS

I.   Introduction

Stroke is a clinical sign that develops rapidly due to focal (or global) brain disorders with symptoms that last for 24 hours or more and can cause death without any other obvious cause other than vascular.[1] Each year there are 795,000 peoples diagnosed with First or recurrent stroke. Approximately 610,000 of the population are patients with the first stroke and 185,000 are patients with recurrent stroke.[2]

Countries in the Asian, Russian and Eastern European regions experience the highest mortality rates and disabilities due to stroke.[3] In China, the incidence of stroke is expected to increase dramatically due to a combination of an aging population and high prevalence of smoking and hypertension.

Mortality rates in ASEAN countries are more varied. Data from the South East Asia Medical Information Center (SEAMIC) shows that stroke is the number four cause of death in ASEAN countries since 1992, number one is Indonesia, second are the Philippines and Singapore, third are Brunei, Malaysia and Thailand.

Data from Basic Health Research (Riskesdas) in 2007 showed that stroke is the leading cause of death at all ages with percentage of 15.4%. Every 7 people who died in Indonesia, 1 of them due to a stroke.[5] Riskesdas(2013) data reported the prevalence of stroke in Indonesia was 7.0 per 1,000 population. This number has increased from 2007 with a prevalence of 6 per 1,000 population.[6]

Patient who has stroke will experience a rapid decline in some functions of the brain because there is an interruption of blood supply to the brain.[7] In general, NSA (National Stroke Association) USA divides the stroke into ischemic stroke and Hemorrhagic stroke.[8] Ischemic stroke can be caused by three mechanisms, namely thrombosis, embolism, and reduction of overall systemic perfusion that causes hypoxia, where thrombosis and embolism are based on atherosclerotic plaque.[9,10]

there are several conventional risk factors due to abnormalities in the brain vessel wall, including: genetic, stress, hypertension, smoking, hyperlipidemia, and Diabetes Mellitus (DM).[12] In recent years there is independent risk factor that holds an important role in the occurrence of abnormalities of blood vessel walls, namely homocysteine. Homocysteine is an amino acid that has a sulfur group involved in the methionine cycle, namely in the remetilation pathway and the transulfuration pathway. The function of this cycle is to donate the required methyl groups to various body molecules and the synthesis of glutathione.[13,14]

Total Normal Homocysteine concentration (tHcy) ranges from 5-15 μmol / L in the fasting state. Hyperhomocysteinemia (HHcy) are classified as moderate (plasma tHcy concentration 15–30 μmol / L), intermediate (plasma tHcy concentration 31–100 μmol / L), and high (plasma tHcy concentration > 100 μmol / L). genetic factors can have an impact on plasma tHcy. Sex, aging, smoking, impaired kidney function, and some drugs such as corticosteroids and cyclosporine are some examples of acquired causes. C677T homozygous mutation of 5.10 Methylene Tetra Hydro Folate Reductase (MTHFR) is the main genetic factor.[16,17]

Several studies reported that high tHcy is a strong and independent risk factor for vascular disease including cerebral ischemic stroke in 109 young Asian adults (Chinese, Indian, and Malay) with ischemic stroke and had strong association between increased Hcy and ischemic stroke (OR = 5.17, 95% CI: 1.96–13.63, p = 0.001) .[18] Other studies of 120 Indian patients with acute ischemic stroke and reported that there was a significant relationship between HHcy and ischemic stroke (p = 0.001) .[19]

Research results in the Krishna District, Andhra Pradesh, India conclude that increased serum homocysteine is a strong and modifiable risk factor for cerebral ischemic stroke. Many studies show the importance of the development of complications such as cardiac vascular and cerebral ischemic stroke. The results of this study support the consideration of serum homocysteine as a marker of routine screening.[20] The results from research in Iran, conclude that high levels of Hcy is an independent risk factor for ischemic stroke patients living in the Iranian province of Fars. In addition, there is a significant relationship between increased levels of Hcy and the risk of death. [21]

Beside from being an independent risk factor, homocysteine is also investigated as a factor affecting the prognosis of stroke, but the results are still controversial and inconsistent.[22,23]

The aim of this study is to determine the relationship between homocysteine levels with the degree of severity in patients with acute phase ischemic stroke at Haji Adam Malik General Hospital, Medan.

II.   Method

This research is an analytic study with cross sectional design. The study was conducted from September to November 2018. The population were all patients suffering acute phase ischemic stroke who were hospitalized in the stroke corner room at the Haji Adam Malik General Hospital, Medan. The sample in this study is 45 people. Homocysteine serum were examined using Abbott Architect Plus C1 4100. The severity of ischemic stroke is examined using National Institute of Health Stroke Scale (NIHSS). Data were analyzed using logistic regression tests with confidence level 95% ($\alpha = 0.05$).

III.   Result

Table I. Patients Characteristic Distribution

Characteristic	Total	(%)	Mean
Age			
33-47 years	7	15,6	55,4
48-62 years	25	55,5	
63-77 years	13	28,9	
Sex			
Woman	17	37,8	
Man	28	62,2	
Homocysteine Level			
Normal ($\leq$ 15 mmol/l)	34	75.6	11.5
High (> 15 mmol/l)	11	24.4	
Stroke Severity			
Mild Stroke (Skor 1-4)	34	75.6	4.6
Moderate Stroke (Skor 5-15)	11	24.4	
Total	**45**	**100,0**	

Table 2. Relationship Between Homocysteine Level With The Degree Of Severity In Patients With Acute Phase Ischemic Stroke

Homocysteine Level	Stroke Severity				Total		p	OR	95% CI	
	Mild		Moderate						Lower	Upper
	N	%	N	%	N	%				
Normal	29	85,3	5	14,7	34	100,0	0,008	1,876	0,968	3,639
High	5	45,5	6	54,5	11	100,0				

IV.   Discusion

The results found that patients with acute phase ischemic stroke have a minimum age 33 years and a maximum 77 years with average age 55.4 years (± 11.2). The largest age group is 48-62 years, which is 25 people (55.5%) then followed by the 63-77 years age group, which is 13 people (28.9%) and 6 people (15.6%) 33-47 years age group. The results of this study are not much different from the research in the Neurosurgery Inpatient at Dr. Kariadi Hospital Semarang, who concluded that the mean age of patients after ischemic stroke was 52.97 (± 10.2) years.[24]

The National Stroke Association says that stroke can happen to anyone, the incidence of stroke has almost doubled after passing the age of 55.[25] This is due to the more oxidative stress and the wider process of atherosclerosis that occurs, thus weakening overall body functions mainly related to flexibility blood vessel. Entering the age of 50 years, the risk of stroke is doubled every age increases by 10 years.[26] However, stroke can also occur at a young age one of the causes is the existence of cardiac abnormalities that result in embolization.[27]

Incidence of Patients with acute phase ischemic stroke is higher in men than woman, as many as 28 people (62.2%) are men, the rest are women, as many as 17 people (37.8%). The results of this study are not much different from the research at Dr. Kariadi General Hosiptal, Semarang, who concluded that the incidence of stroke in men was higher than in women.[28]

Patients with acute phase ischemic stroke have minimum homocysteine level of 4.4 μmol / l and a maximum of 24.1 μmol / l with average homocysteine level 11.5 μmol / l and there are 34 people (75.6%) with normal homocysteine level. Homocysteine levels more than 15 μmol /l were defined as hyperhomocysteinemia.

The results of this study are not much different from studies in Iran concluding that the mean serum homocysteine level of all patients was less than (12.99 ± 5.6 μmol / L) and only 27.6% hyperhomocysteinemia. Whereas studies in India found as many as 60.6% of stroke patients with hyperhomocysteinemia.[23,30]

Acute phase ischemic stroke were assesed by NIHSS, there are 34 (75.6%) peoples who has mild ischemic stroke and 11 (24.4%) with moderate ischemic stroke. Minimum NIHSS score were 2 and maximum score were 8 with mean of NIHSS score were 4.6.

The results of this study are not much different from the research at Dr. Moewardi General hospital Surakarta concluded that as many as 30 people (76.7%) had NIHSS score ≤ 6 (mild stroke). While 7 people (23.3%) had NIHSS score > 6 (stroke) .[31]

Chi square test results obtained p value <0.05, this result shows that there is a relationship between homocysteine levels with the severity of acute phase ischemic stroke (OR = 1.8876; 95% CI = 0.968-3.639), this means that patients with high homocysteine levels (> 15 μmol / l) have estimated 1.88 times risk of suffering acute phase ischemic stroke. And logistic regression analysis found that acute phase ischemic stroke patients who have high homocysteine levels (> 15 μmol / l) increase the risk of stroke severity 6.960 times compared with normal homocysteine levels (p = 0.005; OR = 6.960; 95% CI 1.523 -31,811). OR =

6.960 shows a strong relationship between the levels of comocysteine and the severity of acute phase ischemic stroke.

The results of this study are not much different with the results of a study of 109 Asian adults (Chinese, Indian, and Malay) finding a strong relationship between increased homocysteine levels and ischemic stroke (OR = 5.17, 95% CI: 1.96–13.63, p = 0.001) .[18] meanwhile the results of studies in India with 120 patients with acute ischemic stroke showed that there was a significant relationship between levels of homocysteine and ischemic stroke (p = 0.001) .[19]

The limitation of this study is that the evaluation of homocysteine levels was not measured before the acute phase ischemic stroke occurs, so it cannot be compared with the acute phase ischemic homocysteine levels.

V.   Conclusion

Homocysteine levels have strong relationship with the severity of acute phase ischemic stroke. This means that acute phase ischemic stroke patients who have high homocysteine levels are estimated to increase the risk of the severity of acute phase ischemic stroke 6,960 times compared with normal homocysteine levels (p = 0.005; OR = 6.960; 95% CI; 1.523–31.811). OR value = 6.960 shows a strong relationship between the levels of comocysteine and the severity of acute phase ischemic stroke.

VI.   Reference

1. World Health Organization (WHO). WHO STEPS Stroke Manual: the WHO STEPwise approach to stroke surveillance. Geneva: World Health Organization; 2006. 4-6.
2. Benjamin, Emelia J., et al. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. Circulation, 2017, 135.10: e146-e603.
3. KIM, Anthony S.; Johnston, S. Claiborne. Global variation in the relative burden of stroke and ischemic heart disease. Circulation, 2011, 124.3: 314-323.
4. Moran, Andrew, et al. Future cardiovascular disease in China: Markov model and risk factor scenario projections from the coronary heart disease policy model–China. Circulation: Cardiovascular Quality and Outcomes, 2010, 3.3: 243-252.
5. Depkes RI. Riset Kesehatan Dasar (RISKESDAS) 2007. Lembaga Penerbitan Badan Litbangkes. Jakarta: Departemen Kesehatan Republik Indonesia, 2007
6. Kemenkes RI. Riset Kesehatan Dasar (RISKESDAS) 2013. Lembaga Penerbitan Badan Litbangkes. Jakarta, 2013
7. Khan, Muhammad Nazim, et al. Serum total and HDL-cholesterol in ischemic and hemorrhagic stroke. Ann. Pak. Inst. Med. Sci, 2014, 10.1: 22-6.
8. Soeharto, Iman. Serangan jantung dan stroke hubungannya dengan lemak & kolestrol. 2nd ed. Jakarta: PT Gramedia Pustaka Utama, 2004.
9. Sjahrir H. Stroke Iskemik. Yandira Agung, Medan, 2003, 1-3.
10. Aminoff MJ, Greenberg DA, Simon RP. Clinical neurology. 6th ed. New York/Toronto: Lange Medical Books, 2005; p. 285-319.
11. Bogousslavsky J, Lausanne P, Hennerici M.G,. Stroke prevention by the practitioner cerebrovascular disease. 2000: 9, 2-43.
12. Christina BG, Focus On Homocysateine, Springer Verlag Frence, 2001 : 11-79.
13. Clarke S, Banfield K.   S-Adenosylmethionine-dependent methyltransferases. In: Carmel R, Jacobsen DW, editors. Homocysteine in health and disease. Cambridge. Cambridge university press; 2001.p. 63-78.
14. Agarwal, Soumya, et al. Study of serum levels of Vitamin B12, folic acid, and homocysteine in vitiligo. Pigment International, 2015, 2.2: 76.
15. Kuller, L. H., et al. Multiple Risk Factor Intervention Trial Research G. Lipoprotein particles, insulin, adiponectin, C-reactive protein and risk of coronary heart disease among men with metabolic syndrome. Atherosclerosis, 2007, 195: 122-128.
16. Dierkes, Jutta; Westphal, Sabine. Effect of drugs on homocysteine concentrations. In: Seminars in vascular medicine. Copyright© 2005 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001 USA., 2005. p. 124-139..
17. Christopher, R., Nagaraja, D., Shankar, S.K.. Homocysteine and cerebral stroke in developing countries. Current Medicinal Chemistry. 2007; 14(22): 2393-2401 [Pubmed]
18. Tan, Nigel Choon-Kiat, et al. Hyperhomocyst (e) inemia and risk of ischemic stroke among young Asian adults. Stroke, 2002, 33.8: 1956-1962.
19. Biswas, Arijit, et al. Homocystine levels, polymorphisms and the risk of ischemic stroke in young Asian Indians. Journal of Stroke and Cerebrovascular Diseases, 2009, 18.2: 103-110.

20. Venkata Madhav, M., Anjaneya Prasad, V. and Pradeep Babu, K.V. Homocysteine as an Independent Risk Factor for Cerebral Ischemic Stroke in South Indian Population in Rural Tertiary Care Centre. IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) e-ISSN: 2279-0853, p-ISSN: 2279-0861. Volume 6, Issue 5 (May.- Jun. 2013), PP 49-53.
21. Ashjazadeh, Nahid; Fathi, Morteza; Shariat, Abdohamid. Evaluation of homocysteine level as a risk factor among patients with ischemic stroke and its subtypes. Iranian journal of medical sciences, 2013, 38.3: 233.
22. Okubadejo, Njideka U., et al. Exploratory study of plasma total homocysteine and its relationship to short-term outcome in acute ischaemic stroke in Nigerians. BMC neurology, 2008, 8.1: 26.
23. Saberi, Alia, et al. Serum homocysteine and the short-term outcome of ischemic stroke. Journal of Neurology Research, 2014, 4.1: 15-21.
24. Yudawijaya, Agus; Kustiowati, Endang; Pemayun, Tjokorda Gde Dalem. Homosistein plasma dan perubahan skor fungsi kognitif pada pasien pasca stroke iskemik. Media Medika Indonesiana, 2011, 45.1: 8-15.
25. ABD, Basim A. Mean platelet volume and its influence on the severity of acute ischemic stroke. Medical Journal of Babylon, 2014, 11.3: 500-506.
26. Lingga, Lanny. All About Stroke. Elex Media Komputindo, 2013.
27. Irfan, Muhammad. Fisioterapi bagi insan stroke. Yogyakarta: Graha Ilmu, 2010.
28. Widyayanto, Isnawan. Hubungan Antara Kadar Homosistein Serum Fase Akut dengan Kemandirian Fungsional Jangka Pendek Pasien Stroke Iskemik. Medica Hospitalia-Journal Of Clinical Medicine, 2017, 3.1.
29. Burhanuddin, Mutmainna, et al. Faktor risiko kejadian stroke pada dewasa awal (18-40 tahun) di kota Makassar tahun 2010-2012. 2013.
30. Kalita, Jayantee, et al. Relationship of homocysteine with other risk factors and outcome of ischemic stroke. Clinical neurology and neurosurgery, 2009, 111.4: 364-367.
31. Sudianto, Rut Pamela. Hubungan Kadar Hemoglobin dengan Prognosis pada Pasien Stroke Iskemik di RSUD Dr. Moewardi. 2015.
32. Markišić, Merdin; Pavlović, Aleksandra M.; Pavlović, Dragan M. The impact of homocysteine, vitamin B12, and vitamin D levels on functional outcome after first-ever Ischaemic stroke. BioMed research international, 2017, 2017.
33. Yaseen, Zainab, et al. "Prognostic Significance of Plasma Homocysteine and Malondialdehyde in Patients with Acute Ischemic Stroke." International Journal of Pharma Research and Health Sciences, 2015, 3. 727-736

Authors

First Author-Rosa Zorayatamin Damanik,Post Graduate of Clinical Pathology, Faculty of Medicine Universitas Sumatera Utara, drrosadamanik@gmail.com

Second Author-Ratna Akbari Ganie Departement of Clinical Pathology, Faculty of Medicine,Universitas Sumatera Utara

Third Author-Iskandar nasution,Departement of Neurology, Faculty of medicine,Universitas Sumatera Utara