

ORIGINAL ARTICLE

Frequency of Elevated Homocysteine Levels in Patients with Ischemic Stroke

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ABSTRACT

Objective: To determine the frequency of elevated homocysteine levels in patients with ischemic stroke.

Study Design: Cross-sectional study.

Place and Duration of Study: Department of Medicine Unit II, Jinnah Hospital, Lahore from 13th October 2017 to 12th April 2018.

Methodology: Two hundred and fifty subjects of ischemic cerebral stroke were included in this study using non probability sampling technique. Diagnosis of ischemic stroke was confirmed by CT brain and serum homocysteine level was measured in micromoles/L.

Results: The average age of our studied population was 64.9±11.5 years with 141 males (56.4%) and 109 (43.6%) females. Mean total homocysteine levels were 55.5±2.9 µm/L and the range was 8-148.7. Elevated homocysteine levels were found in 239 (95.6%) and were normal in 11 (4.4%). Highly elevated levels were present in 18 (7.5%), moderately elevated in 179 (74.9%) and lightly elevated levels were found in 82 (17.6%).

Conclusion: The elevated homocysteine levels are a strong risk factor for ischemic cerebral Stroke. About 74.9% of the patients with ischemic stroke had moderately elevated levels whereas 7.5% had highly elevated serum homocysteine levels.

Key words: Ischemic stroke, Elevated homocysteine levels

INTRODUCTION

Stroke, specifically cerebral infarction, remains an important cause of morbidity and mortality all over the world. Stroke is generally classified into ischemic and hemorrhagic varieties. Ischemic brain injury is thought to result from a cascade of events from energy depletion to cell death. Intermediate factors include an excess of extracellular excitatory amino acids, free radical formation, and inflammation.¹ Established predisposing factors for ischemic cerebrovascular event include old age, high blood pressure, type 2 diabetes mellitus, hypercholesterolemia and heart diseases. Latest research have pointed out possible contribution from environmental factors, poor nutritional habits, chronic alcohol use, tobacco chewing, sedentary lifestyle and poor socioeconomic status.²

Homocysteine levels have a pivotal role in ischemic events anywhere in the body. According to the latest data from different populations, recent studies from several populations, high serum homocysteine levels constitute an independent predisposing factor for cerebral infarction, ischemic heart disease, deep venous thrombosis, and cerebral venous sinus thrombosis.^{3,4}

The primary substrate for Homocysteine synthesis is methionine. Primary enzymatic defects responsible for homocysteinemia are 5, 10-methylenetetrahydrofolate reductase (MTHFR) and cystathionine-beta synthase (CBS). Also folic acid and vitamin B12 (methylcobalamin) have an important role in homocysteine metabolism and their deficiency can lead to high plasma homocysteine levels.⁵ An elevated homocysteine level induces thrombogenicity, causes procoagulant states and promotes the proliferation of smooth muscle cells.⁶

A healthy level of homocysteine in the blood is less than 10 µm/L and data shows that every 5 micromoles/L elevation in plasma homocysteine levels, incidence of

ischemic cerebrovascular event increases proportionately (OR 2.3).⁷

Lowering of homocysteine with folic acid, vitamin B6 and B12 did reduce the risk of overall stroke.⁸ In chronic renal failure/ESRD patients, the oral intake of vitamin pyridoxine (B6), cyanocobalamin (B12) and folic acid ameliorates the hyperhomocysteinemia; a risk factor for coronary artery disease in such patients.⁹ Folic acid fortification of food is already practiced in some countries, including the USA. Folic acid supplementation results in significant Intima Media Thickness reduction after 18 months in patients with at least one cardiovascular risk.¹⁰

Many studies have now proved that hyperhomocysteinemia is an independent risk factor for carotid artery atherosclerosis and the degree of carotid artery atherosclerosis is highly correlated with the level of homocysteine in serum.¹¹⁻¹² Both homocysteine and lipoprotein(a) have been shown to be risk factors for coronary artery disease and may directly promote atheroma development through several mechanisms.¹³ A study conducted to find the association between homocysteine levels and stroke revealed slightly elevated levels in 56.3% and moderately elevated levels in 8.3% while normal levels were found in 35.4%.¹⁴ The relationship between elevated homocysteine and ischemic stroke has not been studied extensively in Pakistani population.

MATERIALS AND METHODS

This cross-sectional study was conducted in Medical Unit II, Jinnah Hospital Lahore from 13th October 2017 to 12th April 2018. A total 250 patients of ischemic stroke admitted in Medical II of Jinnah Hospital, Lahore who had evidence of ischemic stroke on CT brain, both male and female and aged between 30-80 years were included. After written informed consent from the study subjects, detailed history

and examination was done. A diagnosis of stroke was made by the presence of focal deficit, exaggerated deep reflexes and positive Babinski's sign on clinical examination. Cerebral ischemia was confirmed on noncontract CT-scan of brain. About 5 cc blood was taken in a serum vial and sent for total homocysteine levels. Results were noted down on a proforma which were used for future analysis. Data was entered and analyzed in SPSS-20

RESULTS

The average age of our studied population was 64.92 ± 11.540 years. There were 141 (56.4%) males and 109 (43.6%) were females. Two hundred and thirty nine (95.6%) have total homocysteine level and 11 (4.4%) patients have no total homocysteine level with mean total homocysteine level was 55.55 ± 2.94 (Table 1). Highly elevated levels were found in 18 (7.5%), moderately elevated levels were found in 179 (74.9%), slightly elevated levels were found in 42 (17.6%) [Table 2].

Table 1: Demographic information of the patients (n=250)

Variable	No.	%
Age	64.92 ± 11.54	
Gender		
Male	141	56.4
Female	109	43.6
Total homocysteine level		
Yes	239	95.6
No	11	4.4

Table 2: Frequency of elevated homocysteine levels (n=239)

Elevated homocysteine level	No.	%
Highly	18	7.5
Moderately	179	74.9
Lightly	42	17.6

DISCUSSION

Pathophysiology of Ischemic Stroke involves acute cerebral vascular insufficiency to certain areas of the brain, leading to neurological dysfunction of that affected area. Stroke is a nonspecific term with diverse etiology including hemorrhagic events, thrombotic episodes and embolic phenomenon.¹⁵⁻¹⁷

Stroke has two major types depending upon the etiopathogenic mechanisms, it can be either ischemic or hemorrhagic. Ischemic stroke is more prevalent in the general population as compared to hemorrhagic CVA with approximately 82-92% of the strokes being documented as ischemic. Contrary to this popular opinion, recent studies have shown a slightly high prevalence for hemorrhagic CVA (40.9%) necessitating further studies in this regard. The authors are of the opinion that this increased prevalence of hemorrhagic CVA in the general population may in fact be due to easy availability of the CT scan and better understanding of disease pathology in recent times. Increase in the use of antiplatelet therapy and anticoagulants may be the other explanation for this increased prevalence of hemorrhagic strokes in modern era.^{18,19}

Homocysteine levels are found to be elevated in patients deficient in vitamins B₁₂ and B₆, elderly population (above 70), chronic kidney disease, high coffee consumers,

and those on medications altering folic acid metabolism like methotrexate and bile acid sequestrants. Alcohol use in excess, cigarette smoking, and sedentary lifestyle also affect Homocysteine metabolism in diverse ways.²⁰⁻²² Data shows effectiveness of folic acid and vitamin B₆, B₁₂ supplementation in reducing homocysteine levels.²³ However, a karachi based study denied the possible role of vitamin supplementation in preventing stroke necessitating further studies on this controversy.²⁴ In the present study, the average age was 64.9 ± 11.5 as compared to the study of Goksel et al¹⁴ the mean age was 64.0 ± 8.2 , which is comparable to our study.

In our study there were 141(56.4%) males and 109(43.6%) females. As compared to the study of Saposnik et al⁸ there were 146 (58.4%) males and 104(41.6%) females, which is comparable to our study.

In this study elevated homocysteine levels were found in 239 (95.6%) and were normal in 11(4.4%). As compared to the study of Kang et al²⁵ elevated levels were found in 210 (79.8%) and were normal in 53 patients (20.2%), which is comparable to our study.

In the current study the mean total homocysteine levels was $55.5 \pm 2.9 \mu\text{m/L}$. Kang et al²⁵ reported that mean homocysteine levels were $49.8 \pm 3.7 \mu\text{m/L}$, which is comparable to our study.

This study showed that moderately elevated levels were found in 179 (74.9%), highly elevated levels were found in 18(7.5%) and slightly elevated levels were found in 42 (17.6%). As compared to the study of Goksel et al¹⁴ moderately elevated levels were found in 8.3%, slightly elevated in 56.3% and highly elevated in 3.9%, which is comparable to our study.

CONCLUSION

Elevated homocysteine levels in 95.6% and only 4.4% of the patients had a normal level. Whereas mean homocysteine level was found to be 55.5% with a range of 8-148.7. Highly elevated levels were found in 7.5%, moderately elevated levels in 74.9% and slightly elevated in 17.6%. These are quite significant findings and suggest that homocysteine levels are significantly higher in patients of ischemic cerebral stroke. This also implies that significant modification of the diet as in fortification of food with folic acid, vitamin B₆ and B₁₂ should be done in all the elderly and in all those who are at an increased risk of stroke due to other risk factors. This category of the patients should be educated and regular tests should be carried out.

REFERENCES

1. Worp van der HB, Gijn van J. Acute ischemic stroke. *NEJM* 2007;357:572-9.
2. Galimanis A, Mono ML, Arnold M, Nedeltchev K, Mattle HP. Lifestyle and stroke risk: a review. *Curr Opin Neurol* 2009;22(1):60-8.
3. Cui R, Moriyama Y, Koike KA, Date C, Kikuchi S, Tamakoshi A, et al. Serum total homocysteine concentrations and risk of mortality from stroke and coronary heart disease in Japanese: The JACC study. *Atherosclerosis* 2008;198(2):412-8.
4. Sheerani M, Khealani BA. Hyperhomocysteinemia and cerebral venous sinus thrombosis. *Pak J Neurological Sci* 2006; 1(3):136-7.

5. Pezzini A, Del Zotto E, Padavoni A. Homocysteine and cerebral ischemia: pathogenic and therapeutical implications. *Curr Med Chem* 2007;14(3):249-63.
6. Atif A, Rizvi MA, Tauheed S, Aamir I, Majeed F, Siddiqui K, et al. Serum homocysteine concentrations in patients with hypertension. *Pak J Physiol* 2008;4(1)21-2.
7. Nura HA, Hillary W, Sunday AB, Amos G. Association of plasma homocysteine and ischemic stroke in a Nigerian population. *Pak J Med Sci* 2006;22:405-8.
8. Saposnik G, Ray JG, Sheridan P, McQueen M, Lonn E; the HOPE 2 Investigators. Homocysteine-lowering therapy and stroke risk, severity, and disability. Additional findings from the HOPE 2 trial. *Stroke* 2009.
9. Naqib M, Naveed AK, Waheed P, Masood M, Khan A, Ahmad I. Oral intake of vitamins cocktail ameliorates hyperhomocystenemia in chronic renal failure/ ESRD patients. *Pak J Pathol* 2008;19(1):16-9.
10. Ntaios G, Savopoulos C, Karamitsos D, Economou I, Destanis E, Chrysogonidis I, et al. The effect of folic acid supplementation on carotid intima-media thickness in patients with cardiovascular risk: A randomized, placebo-controlled trial. *Int J Cardiol* 2009;143(1):16-9.
11. Wang H, Zhang H, Fu Y, Zhang J, Shen Y. Serum level of homocysteine is correlated to carotid artery atherosclerosis in chinese with ischemic stroke. *Neurol Res* 2006;28(1):25-30.
12. Yokote H, Shiraishi A, Shintani S, Shiigai T. Acute multiple brain infarction in large-artery atherosclerosis is associated with hyperhomocyst(e)inemia. *Acta Neurologica Scandinavica* 2007;116(4)243-7.
13. Arenillas JF, Candell-Riera J, Romero-Farina G, Molina CA, Chacon P, Agude-Bruix S, et al. Silent myocardial ischemia in patients with symptomatic intracranial atherosclerosis. *Stroke* 2005;36(6):1201-6.
14. Somay G, Aliskan T, Erenoglu NY. Carotid artery stenosis and homocysteine in ischemic stroke; A case-control study. *J Neurol Sci [Turkey]* 2005;22(4):394-402.
15. AyH. Pathogenic ischemic stroke phenotypes in the NINDS-stroke genetics network. *Stroke* 2014; 45: 3589-96.
16. Hindy G, Engström G, Larsson SC, et al. Role of blood lipids in the development of ischemic stroke and its subtypes: a mendelian randomization study. *Stroke* 2018;49(4):820-27.
17. Lubitz SA, Parsons OE, Anderson CD, et al. Atrial fibrillation genetic risk and ischemic stroke mechanisms. *Stroke* 2017;48(6):1451-56.
18. Regenhardt RW, Das AS, Ohtomo R, Lo EH, Ayata C, Guroil ME. Pathophysiology of lacunar stroke: history's mysteries and modern interpretations. *J Stroke Cerebrovasc Dis* 2019; 28(8):2079-97.
19. Cipolla MJ, Liebeskind DS, Chan SL. The importance of comorbidities in ischemic stroke: Impact of hypertension on the cerebral circulation. *J Cereb Blood Flow Metab* 2018;38(12):2129-49.
20. Chen PJ, Lu YC, Wang PM, Huang CF, Loke SS. Factors associated with hyperhomocysteinemia in relatively healthy Taiwanese adults: A retrospective medical record study. *Medicine (Baltimore)* 2021; 100(3):e23829.
21. Stover PJ. Vitamin B12 and older adults. *Curr Opin Clin Nutr Metab Care* 2010; 13(1):24-27.
22. Kapur V, D'Cruz S, Kaur R. An uncommon presentation of hyperhomocysteinemia and vitamin B₁₂ deficiency: a case report. *J Med Case Rep.* 2019;13(1):36.
23. Barnabé A, Aléssio AC, Bittar LF, et al. Folate, vitamin B12 and Homocysteine status in the post-folic acid fortification era in different subgroups of the Brazilian population attended to at a public health care center. *Nutr J* 2015;14:19.
24. Khan M, Raza E, Kamal AK. What is the role of B-vitamins in stroke prevention in Pakistan?. *J Pak Med Assoc* 2011;61(8):825-6.
25. Kang SS, Wong PW, Malinow MR. Hyperhomocyst(e)inemia as a risk factor for occlusive vascular disease. *Annu Rev Nutr* 1992;12:279.