View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by eCommons@AKU

Pakistan Journal of Neurological Sciences (PJNS)

Volume 10 | Issue 2 Article 2

6-2015

Hyperhomocysteinemia - An unidentified risk factor for stroke in our population

Sabaa Asif
Ziauddin Medical University Hospital

Bashir A Soomro
Ziauddin Medical University Hospital

Kanwal Sartaj
Ziauddin Medical University Hospital

Shafaq Alvi
Ziauddin Medical University Hospital

Follow this and additional works at: http://ecommons.aku.edu/pjns

 Part of the Neurology Commons

Recommended Citation

Asif, Sabaa; Soomro, Bashir A; Sartaj, Kanwal; and Alvi, Shafaq (2015) "Hyperhomocysteinemia - An unidentified risk factor for stroke in our population," *Pakistan Journal of Neurological Sciences (PJNS)*: Vol. 10: Iss. 2, Article 2.
Available at: http://ecommons.aku.edu/pjns/vol10/iss2/2

HYPERHOMOCYSTEINEMIA- AN UNIDENTIFIED RISK FACTOR FOR STROKE IN OUR POPULATION

Sabaa Asif[1], Bashir A.Soomro, Kanwal Sartaj[1], Shafaq Alvi
[1]Resident, Department of Medicine, Ziauddin Medical University Hospital.

Correspondence to: *Bashir A.Soomro, 43/II Zulfiqar Street No: 03, PhaseVIII DHA, Karachi, Postal Code: 75500, Email: Basoomro@gmail.com*
Date of Submission: *29 August 2014,* ***Date of Revision:*** *7 January 2015,* ***Date of Acceptance:*** *6 February 2015*

ABSTRACT

Introduction: Various studies show that moderate elevation of plasma homocysteine level has been associated with increased risk for cardiovascular and cerebrovascular disease. **Objective:** To observe the frequency of increased homocysteine level in ischemic stroke patients; and its association with other risk factors. **Methodology:** Observational pilot study was conducted on a sample of 75 ischemic stroke patients, enrolled regardless of their age, gender and comorbidities, at Ziauddin university hospital, Karachi. Fasting serum homocysteine, folate and vitamin B12 levels were measured. Results were interpreted using spss 20.0. **Results and Discussion:** Mean homocysteine level in our population was 19.51 (SD: 11.47)micromol/l. It was higher in groups with vitamin B12 and folic acid deficiency, difference being statistically significant (p=0.013 and 0.017, respectively). Males had greater propensity to hyperhomocysteinemia; the mean homocysteine value being higher, and the difference, statistically significant (p=0.010). Other factors that affect homocysteine levels were also evaluated, that is hypertension, increased cholesterol levels and smoking. There was no significant statistical difference in the homocysteine value between the groups of patients who had these risk factors and the groups that did not (p=0.747, 0.252 and 0.565, respectively). **Conclusion:** It was speculated that hyperhomocysteinemia is an imperative risk factor for stroke.

INTRODUCTION

Homocysteine has gained significant attention in the last decade for its atherogenic properties. Various studies have shown that moderate elevation of the plasma level of this metabolite has been associated with increased risk for cardiovascular and cerebrovascular disease [1,2,3]. Besides causing atherosclerosis, raised homocysteine levels also increase the risk of vascular dementia and Alzheimer's disease [3] Homocysteine levels may be moderately elevated secondary to deficiency of enzyme co-factors involved in homocysteine metabolism (i.e. Vitamin B12, B6 and folate) and genetic polymorphism in methylenetetrahydrofolatereductase (enzyme involved in homocysteine metabolism) [3,4]. In addition, plasma levels of homocysteine are influenced by other factors. Increased levels are associated with high blood pressure, elevated cholesterol levels,[5] smoking, increasing age and gender (more prevalent in males) [3,6] Vascular injury induced by moderately elevated levels of homocysteine is characterised by intimal thickening, disruption of elastic lamina, smooth muscle proliferation, platelet accumulation, and formation of platelet plugs [7,8]. Studies are now being done to determine whether vitamin therapy reduces the risk of ischemic stroke and stroke-related disability [9]. HOPE-2 (Heart Outcomes Prevention Evaluator 2) study shows that although homocysteine-lowering therapies did not improve the outcome of cardiovascular death, MI and stroke, but the risk of stroke was reduced by around 25%, after a fair duration of treatment of three years in persons younger than 70 years with untreated hyperlipidemia, not receiving antiplatelets and with hyperhomocysteinemia or folate and vitamin B12 deficiency[10,11]. Although the VISP (Vitamin Intervention for Stroke Prevention) trial showed that high-dose multivitamin therapy did not help in preventing recurrent stroke, the control agent used in the trial contained small doses of vitamin B6, B12, and folic acid, and the reduction of homocysteine level was less than that expected in the study. 12 Besides these, four meta-analyses reporting on the benefit of folic acid or vitamin B supplementation have been published in 2010[13,14,15,16].

OBJECTIVE

To observe the frequency of increased homocysteine levels in patients with ischemic stroke, presenting to our private tertiary care centre, regardless of their age, gender, race and social status; and its association with other risk factors.

RESULTS

Out of the 75 enrolled patients, 33(44%) had moderately elevated homocysteine level, 10(13.3%) had severely elevated level of more than 30□mol/l (Table 1). The mean homocysteine level was 19.52 (SD: +/- 11.47)□mol/l, with the minimum being 7.02□ mol/l and the maximum 50□mol/l. The mean folate level was 7.15 (SD: +/- 4.51)ng/ml, with a minimum of 1.12ng/ml and a maximum of 21.50ng/ml. The mean vitamin B12 level was 432.55 (SD: +/- 293.53) pg/ml; minimum, 150pg/ml and maximum, 1000pg/ml

Table 1

Homocysteine level (□mol/l)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Normal <14	32	42.7	42.7	42.7
	Moderately Elevated >14	33	44.0	44.0	86.7
	Severely Elevated >30	10	13.3	13.3	100.0
	Total	75	100.0	100.0	

Table 2

Statistics

	Homocysteine level (□mol/l)	Folate level (ng/ml)	Vitamin B12 level (pg/ml)
N Valid	75	75	75
Missing	0	0	0
Mean	19.5152	7.1527	432.5467
Median	16.1500	6.0700	294.0000
Std. Deviation	11.46664	4.50741	293.53122
Minimum	7.02	1.12	150.00
Maximum	50.00	21.50	1000.00

Thirty-four of our patients were less than 60 years of age and the mean homocysteine level in this group was 21.26 (SD: +/-13.55) □mol/l. In the 41 patients who were more than and equal to 60 years, the mean homocysteine level was 18.07(SD: +/- 9.32) □mol/l. The difference in the two groups was statistically not significant (p= 0.250). The mean homocysteine level of the male patients (41 in number) was 22.44(SD: +/-13.38)□mol/ l and that of the female patients was 15.98(SD: +/- 7.37), with a significant statistical difference between the two (p=0.010). There were 15 patients who had folic acid deficiency and the mean homocysteine level in this group was 27.49(SD: +/- 13.83)□mol/l, compared to the 60 patients with normal folic acid levels, whose mean homocysteine level was 17.52(SD: +/-9.97)□mol/l. The difference among the two groups was statistically significant with a p-value of 0.017. 15 of the patients who were vitamin B12-deficient had a mean homocysteine level of 28.41(SD: +/- 14.80)□mol/l, and those with normal values had a mean level of 17.29(SD: +/- 9.37)□mol/l. Statistical difference was significant between the two groups (p=0.013). Out of the 75 patients, 70 were hypertensive, with a mean homocysteine level of 19.40(SD: +/-11.52) □mol/l. The mean homocysteine value of the 5 non-hypertensive patients was 21.13(SD: +/-11.87) □mol/l, with no significant statistical difference between the two groups (p=0.747). Increased cholesterol level was present in 20 patients and their mean homocysteine value was 16.99(SD: +/-11.99) □mol/l. In the group of patients with normal cholesterol level (55 patients), the mean homocysteine level was 20.44(SD: +/-11.24) □mol/l; the statistical difference being not significant between the two groups (p=0.252). Similarly, no significant statistical difference was present between the smokers and non-smokers (p=0.565). There were 14 smokers, with a mean homocysteine value of 17.91(SD: +/- 13.60) □mol/l, and 61 non-smokers, with mean homocysteine level of 19.88(SD: +/-11.02) □mol/l.

DISCUSSION

The study showed a strong association between hyperhomocysteinemia and stroke, with 44%of the patients having moderately elevated levels and 13.3% having severely elevated levels of more than 30□mol/l, making a total of 53.3% of patients. Various studies have shown that homocysteine levels increase with age [3,6], although our study speculates that there is no association between hyperhomocysteinemia and increasing age, as the difference in mean homocysteine levels was statistically not significant. We also looked for association between increased homocysteine levels and gender. As described in different studies previously [3,6], our study also showed a significant difference in mean homocysteine levels between males and females. Males had higher propensity to hyperhomocysteinemia than females. Deficiency of enzyme co-factors involved in homocysteine metabolism (i.e. Vitamin B12, B6 and folate) and genetic polymorphism in methylenetetrahydrofolatereductase (enzyme involved in homocysteine metabolism) are alleged to cause hyperhomocysteinemia [3,4]. In our patients, the patients who were deficient in vitamin B12 and folic acid had a greater predilection to hyperhomocysteinemia than those having normal vitamin B12 and folic acid values, with a significant statistical difference in the mean homocysteine value between the two groups. Similarly, other variables that are individually associated with both hyperhomocysteinemia and ischemic stroke, were evaluated, that is hypertension, increased cholesterol

Table 3

Variables	Subgroups	Frequency	Mean Homocysteine level	Standard Deviation	p- value
Age groups	Age less than 60	34	21.26	+/-13.55	0.250
	Age more than and equal to 60	41	18.07	+/-9.32	
Gender	**Male**	41	22.44	+/-13.38	0.010
	Female	34	15.98	+/-7.37	
Folic acid	Deficiency	15	27.49	+/-13.83	0.017
	Normal level	60	17.52	+/-9.97	
Vitamin B_{12}	Deficiency	15	28.41	+/-14.80	0.013
	Normal level	60	17.29	+/-9.37	
Hypertension	Present	70	19.40	+/-11.52	0.747
	Absent	5	21.13	+/-11.87	
Increased Cholesterol	Present	20	16.99	+/-11.99	0.252
	Absent	55	20.44	+/-11.24	
Smoking	Smoker	14	17.91	+/-13.60	0.565
	Non-smoker	61	19.88	+/-11.02	

levels [5] and smoking [3,6]. The group of patients that were non-hypertensive also had an elevated mean homocysteine value and the difference in the mean level between the hypertensive and non-hypertensive group was statistically not significant. In the same way, there was no significant statistical difference in the mean homocysteine value between the group of patients having increased cholesterol levels and that with normal cholesterol levels. So, it can be speculated that increased cholesterol levels do not directly relate to hyperhomocysteinemia. Non-smokers had a higher mean homocysteine value, compared to the smokers, the difference being statistically non-significant, showing that there is no association between this variable and hyperhomocysteinemia.

CONCLUSION

It is speculated that hyperhomocysteinemia is an imperative risk factor for stroke in our population. Although the patients had other risk factors as well that individually contribute to stroke but the role of homocysteine in vascular diseases should be considered. Large studies should be conducted on our local population, to determine the absolute risk of having high levels of homocysteine on stroke, and trials should be conducted to observe the effect of homocysteine-lowering therapy on its incidence. Many studies have shown that the routine use of such therapies does not decrease the risk of stroke,[17] but there is evidence that homocysteine-lowering therapy helps in secondary prevention in individuals with ischemic stroke. Since homocysteine-lowering therapy does not appear to have any major side effects and is rather cost-effective, it should be considered for use in these patients (though with caution in patients with renal failure or decreased glomerular filtration rate, in whom more active forms i.e. methylcobolamin and tetrahydrofolate are recommended).[17]

REFERENCES

1. Perry IJ, Refsum H, Morris RW, Ebrahim SB, Ueland PM, Shaper AG. Prospective study of serum total homocysteine concentration and risk of stroke in middle-aged British men. Lancet. 1995;346: 1395–1 398.
2. Graham IM, Daly LE, Refsum HM, Robinson K, Brattstrom LE, Ueland PM, Palma_Reis RJ, Boers GH, Sheahan RG, Israelsson B, Uiterwaal CS, Meleady R, McMaster D, Verhoef P, Witteman JC, de Valk HW, Sales Luis AC, Parrot Rouland FM, Tan KS, Higgins I, Garcon D, Andria G. Plasma homocysteine as a risk factor for vascular disease: the European Concerted Action Project. JAMA. 1997;277:1775–1781.
3. McIlroy SP, Dynan KB, Lawson JT, Patterson CC, Passmore AP. Moderately Elevated Plasma Homocysteine, MethylenetetrahydrofolateReductase Genotype, and Risk for Stroke, Vascular Dementia, and Alzheimer Disease in Northern Ireland. Stroke, 2002;33:2351-2356.
4. Stabler SP, Marcell PD, Podell ER, Allen RH, Savage DG, Lindenbaum J. Elevation of total homocysteine in the serum of patients with cobalamin or folate deficiency detected by capillary gas chromatography-mass spectrometry. J Clin Inv est. 1988;81:466–474.
5. Nygard O, Vollset SE, Refsum H, Stensvold I,

Tverdal A, Nordrehaug JE, Ueland PM, Kvale G. Total plasma homocysteine and cardiovascular risk profile: the HordalandHomocysteine Study. JAMA. 1995;274: 1526–1533.
6. Boushey CJ, Beresford SA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease: probable benefits of increasing folic acid intakes. JAMA. 1995;274: 1049–1057.
7. Rolland PH, Friggi A, Barlatier A, et al. Hyperhomocysteinemia-induced vascular damage in the minipig. Captopril-hydrochlorothiazide combination prevents elastic alterations. Circulati on 1995; 91:1161.
8. Tsai JC, Perrella MA, Yoshizumi M, et al. Promotion of vascular smooth muscle cell growth by homocysteine: a link to atherosclerosis. ProcNatl-AcadSci USA 1994; 91:6369.
9. Saposnik G, Ray JG, Sheridan P, McQueen M, Lonn E. Homocysteine-lowering therapy and stroke risk, severity, and disability: additional findings from HOPE2 trial. Stroke. 2009;40:1365-1372.
10. Lonn E, Yusuf S, Arnold MJ, Sheridan P, Pogue J, Micks M, McQueen MJ, Probstfield J, Fodor G, Held C, Genest J, Jr. Homocysteine lowering with folic acid and b vitamins in vascular disease. N Engl J Med. 2006;354:1567–1577.
11. Lonn E, Held C, Arnold JM, Probstfield J, McQueen M, Micks M, Pogue J, Sheridan P, Bosch J, Genest J, Yusuf S. Rationale, design and baseline characteristics of a large, simple, randomized trial of combined folic acid and vitamins b6 and b12 in high-risk patients: The heart outcomes prevention evaluation (HOPE)-2 trial. Can J Cardiol. 2006;22:47–53.
12. Toole JF, Malinow MR, Chambless LE, Spence JD, Pettigrew LC, Howard VJ, Sides EG, Wang CH, Stampfer M. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: The vitamin intervention for stroke prevention (VISP) randomized controlled trial. JAMA. 2004;291:565–575.
13. Lee M, Hong KS, Chang SC, Saver JL. Efficacy of homocysteine- lowering therapy with folic acid in stroke prevention: a meta-analysis. Stroke. 2010;41:1205–1212.
14. Clarke R, Halsey J, Lewington S, Lonn E, Armitage J, Manson JE, Bonaa KH, Spence JD, Nygard O, Jamison R, Gaziano JM, Guarino P, Bennett D, Mir F, Peto R, Collins R. Effects of lowering homocysteine levels with b vitamins on cardiovascular disease, cancer, and cause-specific mortality: meta-analysis of 8 randomized trials involving 37 485 individuals. Arch Intern Med. 2010;170:1622–1631.
15. Mei W, Rong Y, Jinming L, Yongjun L, Hui Z. Effect of homocysteine interventions on the risk of cardiocerebrovascular events: a meta-analysis of randomised controlled trials. Int J ClinPract. 2010;64:208–215.
16. Miller ER III, Juraschek S, Pastor-Barriuso R, Bazzano LA, Appel LJ, Guallar E. Meta-analysis of folic acid supplementation trials on risk of cardiovascular disease and risk interaction with baseline homocysteine levels. Am J Cardiol. 2010;106:517–527.
17. Saposnik G. The role of vitamin B in stroke prevention: A journey from observational studies to clinical trials and critique of the VITAmins TO Prevent Stroke (VITATOPS). Stroke. 2011;42:8 38-842.

Conflict of Interest: Author declares no conflict of interest.

Funding Disclosure: Nil

Author's contribution:

Dr.Sabaa Asif: Study concept and design, protocol writing, data collection, data analysis, manuscript writing, manuscript review

Dr. Bashir Soomro: Study concept and design, protocol writing, data collection, data analysis, manuscript writing, manuscript review

Dr. Kanwal Sartaj: Data collection, data analysis, manuscript writing, manuscript review

Dr.Shafaq Alvi: Data collection, data analysis, manuscript writing, manuscript review