



“CO-RELATION OF HOMOCYSTEINE WITH VITAMIN B12 LEVEL IN PATIENTS OF CEREBRAL VENOUS SINUS THROMBOSIS”

1 Dr. Jyoti Kharche, 2 Dr. Virendra Yadav., 3 Dr. Mahesh Dalvi., 4 Dr. Dhananjay Patil.

1 Professor Internal Medicine, 2 Resident Doctor Internal Medicine, 3 Resident Doctor Internal Medicine 4
Resident Doctor Internal Medicine.

1MGM Medical College And Hospital, Sambhajinagar. ,

2MGM Medical College And Hospital, Sambhajinagar. ,

3MGM Medical College And Hospital, Sambhajinagar,

4MGM Medical College And Hospital, Sambhajinagar.

Abstract:

Background: Hyperhomocysteinemia is a risk factor for arterial and venous stroke, coronary artery disease and dementia. Risk factors for hyperhomocysteinemia is old age, smoking, chronic renal failure, and deficiency or defective metabolism of folic acid, vitamin B12 or pyridoxine. In the remethylation and trans-sulphuration pathways of Hcy metabolism the vitamin B12, folic acid and pyridoxine are co-factors.

In rural and urban indians, hyperhomocysteinemia is caused by the vitamin B 12 deficiency.

Hence the present study was done at our tertiary care centre to assess the clinical profile of Cerebral Venous Sinus Thrombosis patients and the Co-relation of Homocysteine with Vitamin B12 level in Patients of Cerebral Venous Sinus Thrombosis.

Material and methods: Present study was hospital based cross sectional observational study conducted in patients of age more than 18 years of both gender admitted to Department of General Medicine, MGM Medical college & Hospital with proven Cerebral Venous Sinus Thrombosis diagnosed with MRI Brain Imaging with MR Venogram were enrolled as study population.

Result: The mean vitamin B12 level in patients with normal serum homocysteine levels was 615.93 ± 281.70 pg/ml and was comparable to mean vitamin B12 levels in patients with mild hyperhomocysteinemia (434.06 ± 377.17 pg/ml) and in patients with moderate hyperhomocysteinemia (564.33 ± 360.73 pg/ml) as per ANOVA test ($p > 0.05$). As $P > 0.05$, there was no significant co-relation of serum homocysteine with vitamin B12 level in CVST patients.

Conclusion: Hyperhomocysteinemia is a one of the risk factor for Cerebral Venous Sinus Thrombosis. Thus, hyperhomocysteinemia should be investigated and treated timely in every CVST patients. But the association of homocysteine with vitamin B 12 deficiency in CVST patients is not proven by this study, as association is not statistically significant. So, there is no significant co-relation of homocysteine with vitamin B 12 level in CVST patients.

INTRODUCTION

In venous thromboembolism (VTE), cerebral venous sinus thrombosis (CVST) is rare form. In all types of stroke, 0.5% - 3% cases are CVST, which affect predominantly to younger people, incidence for adult is 3-4 per million, and for children is 7 per million. ¹⁻⁴

CVST is caused by the septic process in the pre-antibiotic era, but now most common cause of CVST is aseptic form ⁵.

Common Risk factor for CVST are Hyperhomocysteinemia, use of Oral contraceptive pills, pregnancy, Head trauma, local and generalised infection, prothrombotic state, hormone replacement therapy, antiphospholipid syndrome, antithrombin III deficiency, protein c and s deficiency, factor V Leiden mutation, lupus anticoagulant, Cancer, Bechet syndrome, Wegener's granulomatosis, Intracranial hypertension, Inflammatory bowel disease, Hematological disorder.

Common manifestation of CVST patients are presents with headache, vomiting, convulsions, focal neurological deficit, etc. ⁶

Transverse sinus (76%) is most common sinus involved followed by superior sagittal sinus (60%) and lateral sinus. ⁷

In CVST patient risk factor for hyperhomocysteinemia is folic acid deficiency and methylene-tetra-hydro-folate- reductase (MTHFR) 677C→T mutation. ⁷

Hyperhomocysteinemia is one of the risk factor for arterial and venous stroke, coronary artery disease and dementia. ⁸ Sulphydryl group containing Amino Acid Homocysteine (Hcy) is toxic to neurons and vascular endothelium which is derived from methionine.

Patients have an increased risk of developing venous sinus thrombosis recurrence or other forms of venous thromboembolism (VTE) in about one-third of cases. ⁹

Risk factors for hyperhomocysteinemia is old age, smoking, chronic renal failure, and deficiency or defective metabolism of folic acid, vitamin B12 or pyridoxine. In the remethylation and trans-sulphuration pathways of Hcy metabolism the vitamin B12, folic acid and pyridoxine are co-factors. Impairment of Hcy metabolism causes oxidative stress, endothelial dysfunction and prothrombotic state.

In rural and urban indians, hyperhomocysteinemia is caused by the vitamin B 12 deficiency. In a study on CVST from south India, there is co-relation of low plasma folate level with hyperhomocysteinemia but not with serum vitamin B12 level.

Hence the present study was done at our tertiary care centre to assess the clinical profile of Cerebral Venous Sinus Thrombosis patients and the Co-relation of Homocysteine with Vitamin B12 level in Patients of Cerebral Venous Sinus Thrombosis.

METHODOLOGY

The study was hospital based cross-sectional, observational study conducted in 43 patients to analyse the co-relation of Homocysteine with Vitamin B12 level in patients of Cerebral Venous Sinus Thrombosis (CVST). Cases enrolled in study after taking written informed consent from the patients of age more than 18 years of both gender admitted with proven Cerebral Venous Sinus Thrombosis diagnosed with MRI Brain Imaging with MR Venogram were enrolled as study population. In each patient, serum homocysteine levels and serum vitamin B12 levels were done. The serum homocysteine levels were done by

kinetic biochemistry using R1 and R 2 reagents.

OBSERVATIONS AND RESULTS

A hospital based cross-sectional, observational study was conducted in 43 patients to analyse the co-relation of Homocysteine with Vitamin B12 level in patients of Cerebral Venous Sinus Thrombosis (CVST).

Majority of the patients 37.4% were in the age group of 21-30 years followed by 32.5% in the age group of 31-40 years with male preponderance 62.8% while female patients constituted 37.2% of the study group. The mean age of the patients was 36.58 ± 11.64 years.

Out of the total 43 patients under study 27(62.8%) were having comorbidity diabetes being more common and 16 (37.2%) patients had no co-morbidities.

The most common clinical presentation in the present study was headache followed by others like vomiting , seizures, and altered mental status.

From 43 patients, 76.7 % patients were having addictions like alcohol and smoking.23.3% patients had no addiction.

Distribution of patients according to Magnetic Resonance Imaging (MRI) and Magnetic Resonance Venography (MRV) findings:

23 (53.6%) patients had left transverse and sigmoid sinus and 15 (34.9%) patients right transverse and sigmoid sinus. 2 (4.6%) patients each had inferior Sagittal & right sinuses and inferior Sagittal& left sinuses while 1 (2.3%) patient had bilateral transverse & sigmoid sinuses.

Table 8: Distribution of patients according to MRI and MRV findings

MRI and MRV findings	n	%
Left transverse & sigmoid sinus	23	53.6%
Right transverse & sigmoid sinus	15	34.9%
Inferior Sagittal & right sinuses	2	4.6%
Inferior Sagittal & left sinuses	2	4.6%
B/L transverse & sigmoid sinuses	1	2.3%
Total	43	100%

Distribution of patients according to Serum Homocysteine levels:

14 (32.5%) patients had normal serum homocysteine levels while 29 (67.5%) had hyperhomocysteinemia. Out of 29 patients with hyperhomocysteinemia, 9 (20.9%) and 20 (46.6%) patients had mild and moderate hyperhomocysteinemia respectively. No patients had severe hyperhomocysteinemia.

Table 6: Distribution of patients according to Serum Homocysteine levels

Serum Homocysteine levels	n	%
Normal (5-15 $\mu\text{mol/L}$)	14	32.5%
Mild (16-30 $\mu\text{mol/L}$)	9	20.9%
Moderate(31-100 $\mu\text{mol/L}$)	20	46.6%
Severe (>100 $\mu\text{mol/L}$)	0	-
Total	43	100%

Distribution of patients according to Vitamin B12 levels:

14 patient have vitamin B12 deficiency, out of which 4 (9.2%) patients had severe deficiency of vitamin B12 while 10 (23.2%) patients had mild vitamin B12 deficiency. 17 (39.5%) patients had normal vitamin B12 levels and 12 (28.1%) patients had high levels of vitamin B12. The mean vitamin B12 level of patients was 564.33 ± 360.73 pg/ml.

Table 7: Distribution of patients according to Vitamin B12 level

Vitamin B12 levels	n	%
Severe Deficiency (<100 pg/ml)	4	9.2%
Mild Deficiency (100-189 pg/ml)	10	23.2%
Normal (190-900 pg/ml)	17	39.5%
High (>900 pg/ml)	12	28.1%
Total	43	100%
Mean \pm SD	564.33 ± 360.73	

Association of Vitamin B12 levels and serum Homocysteine levels:

The mean vitamin B12 level in patients with normal serum homocysteine levels was 615.93 ± 281.70 pg/ml and was comparable to mean vitamin B12 levels in patients with mild hyperhomocysteinemia (434.06 ± 377.17 pg/ml) and in patients with moderate hyperhomocysteinemia (564.33 ± 360.73 pg/ml) as per ANOVA test ($p > 0.05$).

As $P > 0.05$, there was no significant co-relation of serum homocysteine with vitamin B12 level in CVST patients.

Table 12: Association of Vitamin B12 levels and Serum Homocysteine levels in patients

Vitamin B12 levels	Serum Homocysteine levels								Total	p Value	
	Normal		Mild		Moderate		Severe				
	n	%	n	%	n	%	n	%			
Severe Deficiency	0	-	0	-	4	9.2%	0	-	4	9.2%	>0.05
Mild Deficiency	2	4.6%	5	11.7%	3	6.9%	0	-	10	23.2%	
Normal	10	23.2%	2	4.6%	5	11.7%	0	-	17	39.5%	
High	2	4.6%	2	4.6%	8	18.8%	0	-	12	28.1%	
Total	14	32.5%	9	20.9%	20	46.6%	0	-	43	100%	
Mean ± SD	615.93 ± 281.70		434.06 ± 377.17		586.85 ± 403.62		-		564.33 ± 360.73		

DISCUSSION

Cerebral venous sinus thrombosis (CVST) is an uncommon condition, with extremely diverse clinical features ranging from an isolated headache to focal neurological deficits to encephalopathy to psychiatric manifestation to coma, predisposing factors, brain imaging findings, and outcome².

In the present study, majority of the patients 37.4 % were in the age group of 21-30 years followed by 32.5 % in the age group of 31-40 years. The mean age of the patients was 36.58 ± 11.64 years. There was male preponderance (62.8%) while female patients constituted 37.2% of the study group. This is similar to the studies of Kamran S et al¹⁰, Khosya S¹¹, Kalita J et al¹², Patil VC et al¹³ and Kalita J et al¹².

The present study observed male preponderance (62.8%) compared to female patients. Kamran S et al¹⁰ also reported 60.53% of patients were male, whereas Khosya S¹¹, Patil VC et al¹³ and Kalita J et al¹² studies showed female preponderance because CVST more often occurs during pregnancy, multiparity, and infection.

The present study reported most common comparable clinical presentation as headache(67.4%) followed by vomiting (58.1%). Khosya S¹¹ and Appenzeller S et al¹⁴ study also reported similar finding in which 30 (42%) and 33% had vomiting respectively.

It was observed in the present study that 15 (34.9%) patients were alcoholic while 10 (23.2%) patients were smokers. 8 (18.6%) patients were both smokers and alcoholic, and 10 (23.3%) patients had no addiction.

In our study, 23 (53.6%) patients had left transverse and sigmoid sinus and 15 (34.9%) patients right transverse and sigmoid sinus. 2 (4.6%) patients each had inferior Sagittal & right sinuses and inferior Sagittal & left sinuses while 1 (2.3%) patient had bilateral transverse & sigmoid sinuses. This is concordant to the studies of Khosya S¹¹, Kamran S et al¹⁰ and Kalita J et al¹⁷.

The major route of homocysteine clearance from plasma is the kidney, and the rise is due to defective metabolism of homocysteine by the kidney.¹⁵ Total homocysteine levels are found to be considerably higher in patients with chronic renal disease than the moderately raised concentrations commonly found in patients with atherothrombotic vascular disease, and this may be the probable cause that contributes to the high incidence of vascular complications in patients with chronic renal failure.¹⁵ Plasma homocysteine concentrations can be increased by various drugs and diseases that interfere with folate, vitamin B6, and B12 metabolism, hence an abnormal homocysteine concentration may have a probable use as a

diagnostic aid for some of these conditions.¹⁵

In the present study, 14 patients have vitamin B12 deficiency. The mean vitamin B12 level of patients was 564.33 ± 360.73 pg/ml. Kamran S et al¹⁰ and Kalita J et al¹⁷ noted similar observations in their studies.

In our study, the mean vitamin B12 level in patients with normal serum homocysteine levels was 615.93 ± 281.70 pg/ml and was comparable to mean vitamin B12 levels in patients with mild hyperhomocysteinemia (434.06 ± 377.17 pg/ml) and in patients with moderate hyperhomocysteinemia (564.33 ± 360.73 pg/ml) as per ANOVA test ($p > 0.05$).

As $P > 0.05$, there is no significant co-relation of homocysteine with vitamin B12 levels in CVST patients. Similar observations were noted in the studies of Kamran S et al¹⁰ and Kalita J et al¹⁷.

Our study results co-relate with Kamran S et al¹⁰ and show that hyperhomocysteinemia and vitamin B12 levels do not co-relate with CVST.

CONCLUSION

Hyperhomocysteinemia is one of the risk factors for Cerebral Venous Sinus Thrombosis. Thus, hyperhomocysteinemia should be investigated and treated timely in every CVST patient. But the association of homocysteine with vitamin B12 deficiency in CVST patients is not proven by this study, as the association is not statistically significant. So, there is no significant co-relation of homocysteine with vitamin B12 level in CVST patients.

REFERENCES

1. Bousser MG, Crassard I. Cerebral venous thrombosis, pregnancy and oral contraceptives. *Thromb Res.* 2012;130(Suppl): S19–22.
2. Bousser MG, Ferro JM. Cerebral venous thrombosis: An update. *Lancet Neurol.* 2007; 6:162–170.
3. Ruiz-Sandoval JL, Chiquete E, Bañuelos-Becerra LJ et al. Cerebral venous thrombosis in a Mexican multicenter registry of acute cerebrovascular disease: The RENAMEVASC study. *J Stroke Cerebrovasc Dis.* 2012;21:395–400.
4. Stam J. Thrombosis of the cerebral veins and sinuses. *N Engl J Med.* 2005;352:1791–1798.
5. Guenther G, Arauz A. Cerebral venous thrombosis: A diagnostic and treatment update. *Neurologia.* 2011;26:488–498.
6. Ferro JM, Canhão P, Stam J et al. Prognosis of cerebral vein and dural sinus thrombosis: Results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) Stroke. 2004;35:664–670.
7. Harale M, Alurkar A, Basavaraj A et al. Co-relation of Cerebral Venous Sinus Thrombosis with Vitamin B12 and Homocysteine Levels in a Tertiary Care Centre. *The Journal of the Association of Physicians of India.* 2019; 67(1):34-75.
8. Ganguly P, Alam SF. Role of homocysteine in the development of cardiovascular disease. *Nutr J.* 2015; 14:6.
9. Miranda B, Ferro JM, Canhão P, Stam J, Bousser MG, Barinagarrementeria F, Scoditti U. Venous thromboembolic events after cerebral vein thrombosis. *Stroke* 2010; 41: 1901–6.
10. Kamran S, Sharma S, Banerjee S et al. Correlation Between Cerebral Venous Sinus Thrombosis And Serum Homocysteine Levels In A Tertiary Care Hospital, India A Prospective Observational Study. *International Journal of Advanced Research.* 2021; 9(01):251-274.
11. Khosya S. A Study of Clinical Profile, Risk Factors and Outcome of the Cerebral Venous Sinus Thrombosis (CVST): An Experience at a Tertiary Care Center, INDIA. *Austin J NeuroDisord Epilepsy.* 2018;5(2):1041.
12. Kalita J, Bansal V, Misra UK et al. Cerebral venous sinus thrombosis in a tertiary care setting in India. *QJM.* 2006; 99: 491-492.
13. Patil VC, Choraria K, Desai N et al. Clinical profile and outcome of cerebral venous sinus thrombosis at tertiary care center. *Journal of Neurosciences in Rural Practice.* 2014; 5: 218- 224.
14. Appenzeller S, Zeller CB, Annichino-Bizzachi JM et al. Cerebral venous thrombosis: Influence of risk factors and imaging findings on prognosis. *Clin NeurolNeurosurg.* 2005; 107: 371–378.
15. Hankey GJ, Eikelboom JW. Homocysteine and vascular disease. *Lancet.* 1999;354:407–413.

16. Rigamonti A, Carriero MR, Boncoraglio G et al. Cerebral vein thrombosis and mild hyperhomocysteinemia: Three new cases. *Neurol Sci.* 2002;23:225–227.
17. Kalita J, Singh VK, Misra UK. A study of hyperhomocysteinemia in cerebral venous sinus thrombosis. *Indian J Med Res.* 2020;152(6):584594.

