Original Research Article

Co-relation of cerebral venous sinus thrombosis with vitamin B12 and homocysteine levels in a tertiary care centre

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Abstract

Background: Cerebral Venous Sinus Thrombosis still remains the most common cause of treatable and reversible causes of stroke in young. High levels of homocysteine cause oxidative damage to vascular endothelium with the proliferation of vascular smooth muscle and create a prothrombotic environment through its action on platelets, thrombin, and fibrin. Present study was aimed to study co-relation of cerebral venous sinus thrombosis with vitamin b12 and homocysteine levels in a tertiary care center. **Material and Methods:** Present study was hospital based, prospective and observational study, conducted in patients aged above 18 years, of either gender, diagnosed clinically and radiologically as cerebral venous sinus thrombosis. **Results:** In present study 62 patients of CVST were considered. Majority were from age group of 31- 40 years (33.87 %) followed by 19-30 years (25.81%). Male patients (66.13 %) were more than females (33.87 %). Smoking (24.19 %) and alcohol consumption (33.87 %) were also noted. In present study, most common sign and symptoms were headache (69.35 %), visual disturbance (46.77 %), nausea/vomiting (37.10 %), hemiparesis (19.35 %), unconscious (12.90 %), seizure (8.06 %) and speech disturbance (4.84 %). In present study, Hyperhomocysteinemia (HHCy) was noted in 36 patients (58.06 %). GCS score, Motor deficit, Cranial nerve involvement, Seizure, Mechanical ventilator, Sinus (types) involvement and Outcome were significantly associated with hyperhomocysteinemia levels. In present study, Vitamin B12 deficiency was noted in 26 patients (41.94 %). GCS score, Motor deficit, Cranial nerve involvement, Seizure, Mechanical ventilator, Sinus (types) involvement and Outcome were not significantly associated with Vitamin B12 deficiency. **Conclusion:** Hyperhomocysteinemia is significant in CVST patients and serum hyperhomocysteinemia is a risk factor in the etiology of Cerebral Venous Sinus Thrombosis patients.

Keywords: Hyperhomocysteinemia, Cerebral Venous Sinus Thrombosis, Vitamin B12 levels young patients.

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INTRODUCTION

Cerebral Venous Sinus Thrombosis still remains the most common cause of treatable and reversible causes of stroke in young. Cerebral venous thrombosis represents 0.5–3% of all cases of stroke affecting mainly the younger population with an incidence of 3–4 per million in adults.[1] Hyperhomocysteinemia (hHcy) is observed in approximately 5% of the general population and is associated with an increase in risk of many disorders, including vascular and neurodegenerative diseases, autoimmune disorders, birth defects, diabetes, renal diseases, osteoporosis, neuropsychiatric disorders and cancer.[2] Homocysteinaemia is also one of the modifiable

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risk factors of stroke. In one study, moderate hyperhomocysteinemia was an independent stroke risk factor seen in 30% of a group of Malaysian ischemic stroke patients.[3] High levels of homocysteine cause oxidative damage to vascular endothelium with the proliferation of vascular smooth muscle and create a prothrombotic environment through its action on platelets, thrombin, and fibrin.[4] Other possible mechanisms by which homocysteine may contribute to thrombosis include activation of factor V, increased oxidation of low-density lipoprotein, and inhibition of plasminogen activator binding and of protein C activation, or direct damage to the vascular endothelium.[5] Present study was aimed to study co-relation of cerebral venous sinus thrombosis with vitamin b12 and homocysteine levels in a tertiary care center.

MATERIAL AND METHODS

Present study was hospital based, prospective and observational study, conducted in Department of General Medicine, Sri Siddhartha Institute of Medical Sciences & Research Centre, T.Begur, Nelamangala. India. Study duration was of 2 years (January 2020 to December 2021). Study approval was taken from institutional ethical committee.

Inclusion criteria: Patients aged above 18 years, of either gender, diagnosed clinically and radiologically as cerebral venous sinus thrombosis, willing to participate in study

Exclusion criteria: Patients with ischemic/hemorrhagic stroke, transient ischemic attack, extradural hemorrhage, subdural hemorrhage, aneurysmal bleed and subarachnoid hemorrhage

Study was explained to patients/relatives and a written informed consent was taken. All patients were evaluated thoroughly by clinical examination by neurological assessment of the study subjects along with laboratory and radiological methods.Laboratory investigation (Hb%, TC, DC, ESR, Platelet count, BT, CT, PT, INR, APTT, Blood urea, serum creatinine and electrolytes, Urine routine, ECG, Chest x ray, FBS, Lipid profiles, LFT) and Radiological investigations (CT Scan/MRI of the brain) were done in all patients. CSF analysis, 2D ECHO and MRI with MR venography were done as and when needed, In each patient fasting serum homocysteine levels and serum B12 levels were done by kinetic biochemistry and ELISA Technique respectively. On the basis of serum homocysteine levels, the patients were divided

1. Normal Levels: 4 -15 nmol/L.
2. Mild Hyperhomocysteinemia: 15 – 30 nmol/L
3. Moderate Hyperhomocysteinemia : 30 – 100 nmol/L
4. Severe Hyperhomocysteinemia : >100 nmol/L

On the basis of serum B12 levels, the patients were again divided into

1. Severe Deficiency: <100 pg/ml
2. Mild Deficiency: 100-189 pg/ml
3. Normal Range: 190-900 pg/ml
4. High levels: >900 pg/ml

Data was analyzed using SPSS 22 version software. Categorical variables were summarized as proportions. The difference between categorical variables was analyzed using chi-square test. P value <0.05 was considered as statistically significant.

RESULTS

In present study 62 patients of CVST were considered. Majority were from age group of 31- 40 years (33.87 %) followed by 19-30 years (25.81%). Male patients (66.13 %) were more than females (33.87 %). Smoking (24.19 %) and alcohol consumption (33.87 %) were also noted.

Table 1: Age and Gender distribution

Characteristic	No. of patients	Percentage
Age (Years)		
19 – 30	16	25.81
31 – 40	21	33.87
41 – 50	12	19.35
51 – 60	7	11.29
61 – 70	4	6.45
≥71	2	3.23
Gender		
Male	41	66.13
Female	21	33.87
Addictions		
Smoker	15	24.19
Alcoholic	21	33.87

In present study, most common sign and symptoms were headache (69.35 %), visual disturbance (46.77 %), nausea/vomiting (37.10 %), hemiparesis (19.35 %), unconscious (12.90 %), seizure (8.06 %) and speech disturbance (4.84 %).

Table 2: Sign and symptoms

Sign and symptoms	No. of Cases	Percentage
Headache	43	69.35
Visual disturbance	29	46.77
Nausea/Vomiting	23	37.10
Hemiparesis	12	19.35
Unconscious	8	12.90
Seizure	5	8.06
Speech disturbance	3	4.84

In present study, Hyperhomocysteinemia (HHCy) was noted in 36 patients (58.06 %). GCS score, Motor deficit, Cranial nerve involvement, Seizure, Mechanical ventilator, Sinus (types) involvement and Outcome were significantly associated with hyperhomocysteinemia levels.

Table 3: Hyperhomocysteinemia (HHCy) and clinical association

Parameter	Normal (n=26)	Mild HHcy (n=13)	Moderate HHcy (n=21)	Severe HHcy (n=2)	P value
GCS score (n=62)					<0.001
<9	22 (35.48 %)	4 (6.45 %)	6 (9.68 %)	0	
≥9	4 (6.45 %)	9 (14.52 %)	15 (24.19 %)	2 (3.23 %)	
Motor deficit (n=7)	2 (28.57 %)	2 (28.57 %)	1 (14.28 %)	1 (14.28 %)	<0.001
Cranial nerve involvement (n=32)	8 (25 %)	11 (34.38 %)	11 (34.38 %)	2 (6.25 %)	<0.001
Seizure (n=5)	0	1 (20 %)	3 (60 %)	1 (20 %)	<0.001
Mechanical ventilator (n=11)	1 (9.09 %)	3 (27.27 %)	6 (54.55 %)	1 (9.09 %)	<0.001
Sinus (types) involvement (n=62)					<0.001
Superficial	21 (33.87 %)	10 (16.13 %)	13 (20.97 %)	0	
Deep	5 (8.06 %)	3 (4.84 %)	7 (11.29 %)	0	
Both	0	0	1 (1.61 %)	2 (3.23 %)	
Outcome (n=62)					<0.001
Good	24 (38.71 %)	12 (19.35 %)	19 (30.65 %)	1 (1.61 %)	
Poor	2 (3.23 %)	1 (1.61 %)	2 (3.23 %)	1 (1.61 %)	

In present study, Vitamin B12 deficiency was noted in 26 patients (41.94 %). GCS score, Motor deficit, Cranial nerve involvement, Seizure, Mechanical ventilator, Sinus (types) involvement and Outcome were not significantly associated with Vitamin B12 deficiency.

Table 4: Severity of Vitamin B12 levels and clinical association

Parameter	Normal (n=36)	Mild Deficiency (n=15)	Severe Deficiency (n=11)	High levels (n=0)	P value
GCS score					>0.05
<9	20 (32.26 %)	7 (11.29 %)	5 (8.06 %)	0	
≥9	16 (25.81 %)	8 (12.9 %)	6 (9.68 %)	0	
Motor deficit (n=7)	3 (42.86 %)	2 (28.57 %)	2 (28.57 %)	0	>0.05
Cranial nerve involvement (n=32)	19 (59.38 %)	7 (21.88 %)	6 (18.75 %)	0	>0.05
Seizure (n=5)	1 (20 %)	1 (20 %)	3 (60 %)	0	>0.05
Mechanical ventilator (n=11)	2 (18.18 %)	5 (45.45 %)	4 (36.36 %)	0	>0.05
Sinus (types) involvement (n=62)					>0.05
Superficial	28 (45.16 %)	11 (17.74 %)	5 (8.06 %)	0	
Deep	8 (12.9 %)	3 (4.84 %)	4 (6.45 %)	0	
Both	0	1 (1.61 %)	2 (3.23 %)	0	
Outcome (n=62)					>0.05
Good	34 (54.84 %)	13 (20.97 %)	9 (14.52 %)	0	
Poor	2 (3.23 %)	2 (3.23 %)	2 (3.23 %)	0	

DISCUSSION

Patients with CVT often have headaches, seizures, altered consciousness, and neurological focal signs, all of which are non-specific manifestations, making it difficult to diagnose this disease. Thrombosis of cerebral veins causing localized edema of the brain and venous infarction and thrombosis of major sinuses leading to elevated intracranial pressure as result of increased venous pressure and impaired absorption of cerebrospinal fluid.[6] The metabolism of Hcy is regulated by 2 major pathways for remethylation and trans-sulfuration. Folate, vitamin B12 and Vitamin B6 play roles through the conversion or catalytic process in these pathways. Thus, the deficiencies of these vitamins induce hyper-Hcy. Raised levels are found in some chronic diseases such as DM, and malignancy; after the administration of certain drugs such

as oral contraceptives, AEDs, and methotrexate; and in patients of older age, male sex, postmenopausal status, heavy smoking history, etc.[7] A meta-analysis of 17 clinical studies showed that oral contraceptive use, Leiden mutation of Factor V, and hyper-Hcy were recognized as statistically significant risk factors.[8] Acquired thrombophilia was found in 15% of the cases in the ISCVT cohort. Fasting hyperhomocysteinemia has been associated with CVT, and in the ISCVT cohort the prevalence was 4.5%.[9] In two studies fasting hyperhomocysteinemia was present in 27 to 37% of CVT patients, compared to 10% of controls. Blood homocysteine levels are affected by both genetic and environmental factors. However, the methylene tetrahydrofolate reductase gene C677T mutation that leads to elevated levels of homocysteine was not itself associated with CVT risk in these two studies.[10,11] In the largest hospital-based prospective cohort study by Narayan *et al.*,[12] in 428 consecutive patients with CVT, the mean age of the patients was 31.3 years, male dominance, clinical presentation was stroke-like (28.5%), isolated seizures (29.4%), benign intracranial hypertension (18.2%), encephalopathy (25.2%) and psychosis (1.8%). In study by Chouksey D *et al.*,[13] 58.33% were diagnosed with acute ischemic stroke as compared to cerebral venous thrombosis 41.66% from a total of 72 patients. The statistical analysis projected that the HHcy diagnosed among more (45, 62.5.0%) cases with stroke who had aged ≤45 years as compared to cases who had aged >45 years (17, 23.6%). Jayantee K *et al.*,[14] studied 96 CVST patients, 73% patients had risk factors; hyperhomocysteinemia (52.1%), protein S deficiency (47.8%), protein C deficiency in (19.4%). 32% patients with hyperhomocysteinemia had no other thrombotic cause, and 22 % of them had either vitamin B12 and or folic acid deficiency only. The patients with hyperhomocysteinemia more frequently had vitamin B12 deficiency (70 vs. 13%), MTHFR 677C→T mutation (47.5 vs. 9.1%) and superior sagittal sinus thrombosis (78 vs. 56.5%) than normal Hcy group. In study by Panigrahi I *et al.*,[15] 32 acute ischemic stroke patients (aged 1-44 years) were studied. 43.8 % had recurrent stroke, 28% had multiple infarcts and 12.5% had high homocysteine levels. Three out of these 4 hyper-homocysteinemia patients were homozygous (*TT*) for *MTHFR* polymorphism (2 with recurrent stroke). Two of three homozygous cases with TT genotype had low serum folate. Five of 32 stroke cases (18.8%) were heterozygous (*CT*) genotype. Primary hyper-homocysteinemia appears to be an important risk factor for ischemic stroke in North Indians, most due to *MTHFR C677T* homozygosity. Folate levels may modify the presentation of the MTHFR TT genotype. Hyperhomocysteinemia could be a risk factor accounting for Cerebral Venous Sinus Thrombosis. The results of this study have shown that homocysteine levels were significantly higher in CVST patients and serum hyperhomocysteinemia is one of the risk factor in the etiology of Cerebral Venous Sinus Thrombosis patients. Though, Serum B12 levels showed no correlation in patients of CVST. Thus, Serum homocysteine estimation needs to be sent from emergency department of all patients with diagnosis of Cerebral Venous Sinus Thrombosis.[16] Clinical presentation is varied and with a high index of suspicion and newer imaging modalities the long term prognosis is excellent in CVST. Vitamin B12 and folate supplements, and acetylsalicylic acid, may be administered to reduce the serum concentration of homocysteine and thereby reduce the risk of CVST and stroke. It is necessary to perform larger scale based prospective and interventional studies to clarify the independent risk of homocysteine in patients of Cerebral Venous Sinus Thrombosis.

CONCLUSION

Hyperhomocysteinemia is significant in CVST patients and serum hyperhomocysteinemia is a risk factor in the etiology of Cerebral Venous Sinus Thrombosis patients. While Vitamin B12 levels are not associated with Cerebral Venous Sinus Thrombosis patients.

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