Original Research Article

Study of Hyperhomocystienemia as a cause/effect in venous thrombosis

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Abstract

Background: Hyperhomocysteinemia has been hypothesized to be associated with heightened risk of venous thromboembolism. Hence the study has been conducted to study association of hyperhomocysteinemia as a cause/effect in venous thrombosis. **Materials And Methods:** It is an observational study conducted in a tertiary care setup of 42 patients over a period of 18 months. Patients with cortical venous thrombosis, pulmonary vein thrombosis, deep vein thrombosis, hepatic vein thrombosis were included in the study and their clinical history, detailed investigations, course in the ward noted and patients who found to have hyperhomocysteinemia were evaluated for its causative role in thromboembolism. **Observation And Results:** Out of 42 patients (13 females and 29 males) with mean age being 42.22 with standard deviation of 7.24, 19 patients had hyperhomocysteinemia in patients with B12 levels less than 180, 15 had high homocysteine in patients with B12 between 180-210, 2 patients had B12 level between 210-350pg/ml. It is significantly associated with MTHFR gene mutation with p value of less than 0.001 which is statistically significant. **Conclusions:** Cyanocobalamine deficiency, folic acid deficiency and MTHFR gene mutation has probably got causal relationship with hyperhomocysteinemia and that detection of b12, folic acid level and gene mutation should be done in all patients to optimize therapy.

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INTRODUCTION

Homocysteine is an intermediary product of methionine metabolism. Elevated homocysteine level may result from deficiency or impaired function of enzymes and cofactors in these pathways. Plasma homocysteine level is influenced by many factors, genetic as well as environmental. The role of homocysteine in venous thrombosis has been studied less extensively than its role in arterial diseases and nowadays it seems quite controversial. In vitro, it is possible to demonstrate multiple prothrombotic action of homocysteine. However, the results of epidemiologic studies are not so clear. Most of them found an association of hyperhomocysteinemia with venous thromboembolism (VTE) but the association was quite weak and moreover, it was much weaker in prospective than in retrospective studies. It is not quite clear whether elevated homocysteine level is the cause of thromboembolic event or the consequence of it. It is also possible that hyperhomocysteinemia plays a role in the pathogenesis of VTE only as an additional risk factor in the presence of other thrombophilic disorders. Homocysteine level can be lowered by vitamin supplementation, especially with folic acid and vitamin B12.

So far, the benefit of lowering homocysteine level in primary and secondary VTE prevention has not been clearly proven.

Aims and Objectives: To study level of homocysteine in venous sinus thrombosis. To evaluate other factors contributing to increased homocysteine levels, and hyperhomocysteinemia as a incidental finding or causal relation. To study reduction in homocysteine levels after

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treatment for 6 months and correlation with primary disease. To obtain correlation between homocysteine levels and prognosis of the disease.

MATERIALS AND METHODS

This is an observational study, conducted in an tertiary care centre. Patients admitted with thromboembolic episodes over 1 year in general medical ward or intensive care unit were screened for venous thromboembolism. Patients with cortical venous thrombosis, pulmonary vein thrombosis, deep vein thrombosis, hepatic vein thrombosis were included in the study. Their clinical history, detailed investigations, course in the ward noted and patients who found to have hyperhomocysteinemia were evaluated for its causative role in thromboembolism. Study was conducted over 18 months. 42 patients with venous thrombosis and raised serum homocysteine levels were included. These patients were treated with anticoagulants and combination of Pyridoxine/folic acid/cyanocobalamine for lowering homocysteine levels. These patients were followed up for 3 to 6 months on out patient basis. Their clinical improvement along with normalisation of homocysteine levels was noted. Patients were evaluated for complications, recurrence and improvement.

Inclusion criteria: All those cases present with venous thrombosis with age >12 yrs with valid consent are included. Those willing to follow up. Patients with above normal levels of homocysteine.

Exclusion criteria: All those not willing to participate in study. All the cases not willing for follow up. All the patients with arterial thrombosis. Clotting disorders and normal homocysteine levels.

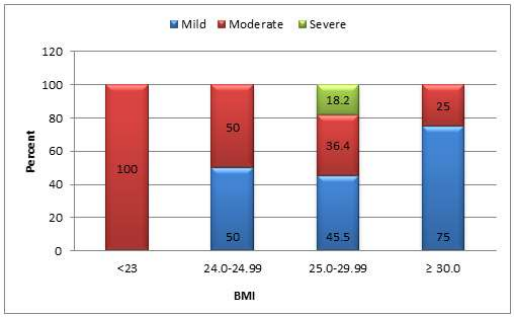
RESULT

Present study is an observational study done in a tertiary care hospital in Maharashtra between April 2019 and September 2020. The total number of patients in the study were 42. These patients were venous thrombosis in the form of either Cortical venous thrombosis, pulmonary embolism, Deep Venous thrombosis or Hepatic vein thrombosis.

Table 1

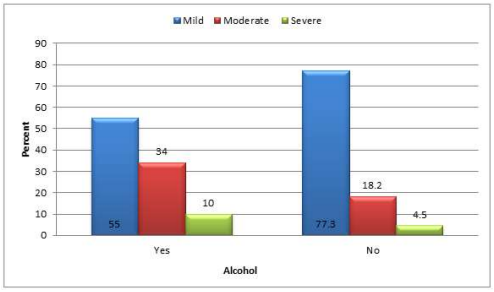
Age (Years)	Mild (n=28) n (%)	Moderate (n=11) n (%)	Severe (n=3) n (%)	Total
≤ 40	17 (68.0)	5 (20.0)	3 (12.0)	25
41-50	8 (72.7)	3 (27.3)		11
51-60	3 (75.0)	1 (25.0)		4
61-70		2 (100.0)		2
Mean (SD)	41.21 (7.49)	45.82 (13.32)	38.67 (1.15)	42.24 (9.24)
Chi-Square Test, P Value = 0.237, Not Significant				

Table 1 suggests the mean age of presentation of hyperhomocysteinemia, among 25 patients with age less than 40, 68% of them had mild, 20% had moderate and 12 % had severe homocysteinemia. Among age group 41-50, 72 percent had mild, 3 percent had moderate hyperhomocysteinemia. Among age group 51-60yrs, 75 percent had mild, 25% had moderate homocysteinemia. Among elderly people with age group 61-70yrs, 2 of them had moderate hyperhomocysteinemia. Mean age of presentation for mild was 41.21 with SD 7.49, for moderate 45.82 with SD 13.32 and severe 38.67 with SD 1.15, overall mean being 42.24 with SD 9.24.



Graph 1: BMI and Homocysteinaemia

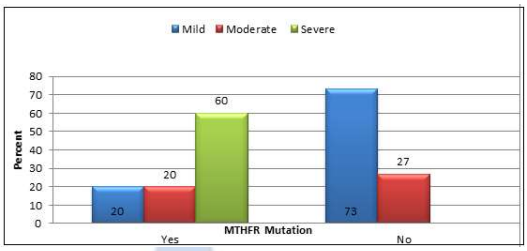
Graph 1 studies the BMI correlation between hyperhomocysteinemia and CVST. Results are for BMI less than 23, only one patient had hyperhomocysteinemia (moderate). For BMI of 24 to 29, around 16 patients had hyperhomocysteinemia. For more than 30 BMI, 4 patients had hyperhomocysteinemia, with mean BMI being 27.31 with SD 3.39



Graph 2: Alcohol and Homocysteinaemia

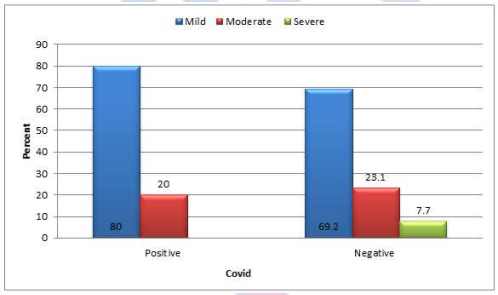
Chi-Square Test, P Value = 0.309, Not Significant

graph 2 with Alcohol and homocysteinemia, among alcohol drinkers, 20 had hyperhomocysteinemia, 22 were non alcoholics.



Graph 3: MTHFR Mutation and Homocysteinaemia

Above graph shows correlation between MTHFR gene mutation and hyperhomocysteinemia, showing hyperhomocysteinemia is significantly associated with MTHFR gene mutation with p value of less than 0.001.



Graph 4: Covid and Homocysteinaemia

Graph 4 shows Covid positive and negative patients data with hyperhomocysteinemia, 5 were covid positive having mild, 1 had moderate hyperhomocysteinemia, 13 patients were negative.

Table 2

B12 pg/ml	Mild (n=28) n (%)	Moderate (n=11) n (%)	Severe (n=3) n (%)	Total
<180	13 (68.4)	5 (26.3)	1 (5.3)	19
180-210	8 (53.3)	5 (33.3)	2 (13.3)	15
210-350	1 (50.0)	1 (50.0)		2
Chi-Square Test, P Value = 0.042, Significant*				

Above table shows association of B12 level and hyperhomocysteinemia, with 19 patients had hyperhomocysteinemia in patients with B12 levels less than 180, 15 had high homocysteine in patients with B12 between 180-210, 2 patients had b12 level between 210-350pg/ml.

Table 3

Clinical Recovery	Mild (n=28) n (%)	Moderate (n=11) n (%)	Severe (n=3) n (%)	Total
Yes	5 (17.9)	6 (54.5)	1 (33.3)	12
No	23 (82.1)	5 (45.5)	2 (66.7)	30
Chi-Square Test, P Value = 0.072, Not Significant				

Above table shows association of clinical recovery and homocysteine levels, with 12 patients had complete clinical recovery, 30 did not. P value- 0.072

DISCUSSION

Our study had 42 patients with 13 females and 29 males, with mean age being 42.22 with standard deviation of 7.24. 8 of them were diabetic, 5 were hypertensives. Chi square test showed that there is no statistically significant correlation between age, gender, Diabetes mellitus, hypertension and hyperhomocysteinemia. Most of the patients were of age less than 40 suggesting that high prevalence of hyperhomocysteinemia in young patients presenting with venous thrombosis.

2) smoking, tobacco, alcohol Our study had 42 patients, of which, 20 were alcoholics 22 were non alcoholics. 9 of 42 gave history of tobacco intake and 14 of 42 of smoking. Chi square test was applied and it showed there was no statistically significant correlation between smoking, tobacco and alcohol intake suggesting smoking, alcohol and tobacco intake was not a risk factor. Current smokers tended to have lower levels of folate, and vitamin B6 and vitamin B12 than never smokers. The risk of vascular disease associated with smoking was not significantly altered by adjustment for levels of B-vitamins using a conditional regression model.[11]

3) Nephrotic syndrome and hyperhomocysteinemia: In our study of 42 patients, 1 patient had nephrotic syndrome with p value 0.184 being statistically non significant. This was the only patient with hyperhomocysteinemia and nephrotic syndrome so correlation was not possible.

4) Clinical features: In our study, duration of symptoms and time of presentation, 18 presented immediately (less than 1 hour) to the hospital, 2 patients presented with history of 3-4 hrs duration, 6 with less then 7 days history, 2 with 10-15 days history, 1 patient with 1 month history of presentation. P value was found out as 0.233, statistically non significant.

Among patients presented early, 16 were patients of cerebral venous sinus thrombosis, 2 were of Pulmonary embolism. Patient with delayed presentation of 1 month of onset was the one with Budd Chiari syndrome with ascites who had mild abdominal pain.

5)In our study, Distribution of venous thrombosis among patients with hyperhomocysteinemia, 47.6 percent had thrombosis in superior sagittal sinus thrombosis, 9.5 % had Pulmonary embolism, 7.1% Hepatic vein thrombosis, 11.9% had transverse sinus thrombosis, 9.5% had sigmoid sinus thrombosis, 9.5% had deep venous thrombosis, 4.8% had multiple venous thrombosis with presentation of cerebral venous sinus thrombosis being acute and hepatic vein thrombosis presentation being late.

6)In our study, various CNS manifestations of patients presenting with CVST, out of them 25 had headache, 7 had Diplopia, 5 had blurring vision, 25 had convulsion and 7 had limb weakness, with p value for headache being 0.901, diplopia – 0.582, blurring of vision 0.488, convulsion 0.529, limb weakness 0.693.

7) MTHFR mutation, Protein C and S, Factor V Leiden mutation, JAK 2 mutation

Above tables shows correlation between MTHFR gene mutation, Protein C and S, Factor V Leiden mutation, JAK2 mutation and hyperhomocysteinemia, showing hyperhomocysteinemia is significantly associated with MTHFR gene mutation with p value of less than 0.001 which is statistically significant while others were not statistically significant. Low protein C and low protein S was found in 3 and 1 patient respectively with their correlation with hyperhomocysteinemia being statistically insignificant. This could probably be due to comsumption of Protein C and S in acute venous thrombosis. In other patients, gene mutation could not be tested.

8) Cyanocobalamine and folic acid: In our study, shows association of Cyanocobalamine level(pg/ml) and hyperhomocysteinemia, with 19 patients had hyperhomocysteinemia in patients with B12 levels less than 180, 15 had high homocysteine in patients with B12 between 180-210, 2 patients had b12 level between 210-350pg/ml. Among the 42 patients with hyperhomocysteinemia, severe folic acid deficiency was associated with 12 patients, 9 had sufficient folic acid level, 1 had adequate folic acid level, with p value for B12 being 0.042 and Folic acid being 0.048 which are statistically significant. Folic acid and vitamin B_{12} are two vital regulators in Homocysteine metabolic process with B12 and Folic acid acting as cofactor and important intermediate products.[22]

9) In our study of 42 patients, 5 had critical illness requiring ICU care and ventilator while 37 had non critical illness and were managed in ward with p value being 0.651 which is statistically non significant. Among patients with CVST and venous hemorrhagic infarct with limb weakness, 3 had residual paralysis on discharge and follow up. However, there were no deaths in our study.

10) In our study, follow up homocysteine were available for 3 patients who followed up in OPD with their mean homocysteine after treatment was 16mcmol/L, they were started on Folic acid/cyanocobalamin/pyridoxine tablet and anticoagulation with heparin and oral anticoagulant with target INR of 2-3. Their mean homocysteine before treatment was 43mcmol/L on presentation. These patients had radiological improvement in CT scan with distribution being Superior sagittal sinus thrombosis being most common site (47.6%) followed by transverse sinus thrombosis (11.9%) and others being in Hepatic vein, multiple dural sinuses, sigmoid sinus. After 3 months of Rx patient were then kept on Folic acid/cyanocobalamin/pyridoxine tablet only and withholding anticoagulation. These patients didn't

complain of further deterioration of symptoms or readmitted with similar complaints suggesting benefit of Folic acid/cyanocobalamin/pyridoxine tablet in patients with concomitant vitamin deficiencies. Use of anticoagulation and specific complication with each of them, among the complication we observed in 42 patients on these drugs, IC bleed was seen in 2 patients among Dabigatran with p value 0.034, Acitrom was associated with mucosal bleed and PR bleed in 1 patient each p value 0.704, warfarin was associated with 1 patient having mucosal bleed p value being 0.505 being statistically insignificant.

CONCLUSION

In our study of venous thrombosis with hyperhomocysteinemia, mean age of presentation was 42.22, with maximum number of patients being less than 40 years of age, suggesting the importance of checking homocysteine in younger age group without comorbidities. There were no gender differences in homocysteine value, presentation, prognosis, and critical illness. Catastrophic presentation was present in 11.90% of population with some requiring ventilator and ICU care. CVST and other venous sinus thrombosis can occur at various levels of homocysteine and that severity of presentation is not related to the value of homocysteine and neither it is related to smoking, alcohol, drugs intake. B12 deficiency, folic acid deficiency and MTHFR gene mutation has probably got causal relationship with hyperhomocysteinemia and that detection of b12, folic acid level and gene mutation should be done in all patients to optimize therapy. Reduction in homocysteine levels with Folic acid/cyanocobalamin/pyridoxine tablet and anticoagulation resulted in complete clinical and radiological resolution of disease in those with associated b12, folic acid deficiency and those on drugs causing decrease in b12 and folic acid levels leading to hyperhomocysteinemia. CT scan (Computed Tomography) during 3 months and 6 months follow up of patients of CVST and PTE showed complete resolution. These patients were discharged home with anticoagulation and Folic acid/cyanocobalamin/pyridoxine tablet, had good prognosis with 35 of 42 patients and having only 3 patients with minimal focal neurological deficit. In patients with MTHFR gene mutation and hyperhomocysteinemia, there were recurrent admissions, suggesting need for lifelong anticoagulation.

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