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ORIGINAL RESEARCH

Analysis of Co-Relation of Cerebral Venous Sinus Thrombosis with Vitamin B12 and Homocysteine Levels: An Institutional Based Study

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ABSTRACT

Introduction: Cerebral venous thrombosis is mostly an uncommon but severe thrombotic manifestation which has a high mortality rate, has the potential to end in disability and the greater tendency of recurrence. There are some coagulation abnormalities such as gain-of-function mutations in the genes that encodes factor V (factor V Leiden) and prothrombin[3] are presented with an increased risk of cerebral vein thrombosis[4-6] whereas there are no data currently reported on the role of hyperhomocysteinemia as a risk factor for cerebral venous thrombosis. High plasma levels of total homocysteine (tHcy) result from the connection between genetic and acquired determinants. Cerebral venous thrombosis is one of the commonest causes of stroke as far as Indian population is concerned. CVST usually predisposes in the state of pregnancy and puerperium. The pathological hallmark that is reported in CVST is haemorrhagic infarction. CVST predominantly occur in the young individuals and can present with a broad spectrum of clinical manifestations which include headache, altered sensorium, seizures, focal neurological deficits, papilloedema and cranial nerve palsies. Headache is the most frequent and often the first reported clinical manifestation. Homocysteine (Hcy) is a sulfhydryl amino acid compound that is generated from protein breakdown and the essential amino acid methionine as it is metabolized to cysteine. Hcy can be broken down in two pathways. When there is in excess methionine, Hcy is directed to transulphuration pathway where it is irreversibly conjugated to cysteine. Hcy can also be remethylated in a methionine conserving pathway and this pathway requires folic acid and MTHFR.

Methodology: For this study, 60 patients diagnosed with CVST who were admitted or in the outpatient department. There were 60 age matched selected patients as control group included in this study too. The duration of the study is 30 months and all the subjects included were above 18 years.All patients were subjected to neuroimaging before arriving at the diagnosis of CVST. Some differential diagnosis includes acute myocardial infarction, stoke may also have raised homocysteine levels. Patients were subjected to case history taking, physical examination, basic haematological examination include complete blood counts, peripheral blood smear, ESR< blood grouping and PT/APTT. Of all these, certain patients were sent for basic haemophilia testing, APLA series, factor VIII levels and d – dimer test.Data were collected and was put together in excel sheet. Correlation among various measurements were assessed

using pearson's correlation coefficients. P – value <0.05 was considered as statistically significant. One way ANOVA is also used to evaluate the relationship between control group with study group.

Results: The mean age of the patients in the study group was 35.4 years and median was 35 years. CVT is observed mostly in the age group of 31 – 40 years. The youngest being 18 years old whereas the oldest being 64 years old. The study population comprised of 27 women (45%) and 33 men (55%). The male to female ratio is 1:0.85. which depicts almost equal gender distribution.Patients who presented themselves within 48 hours were considered to have an acute onset whereas it can be considered subacute when the time of presentation ranges from >48 hours to <30 days and when the time frame ranges from >30 days is considered to be chronic. In the present study, subacute presentation was seen in 32 cases (54%) followed by 23 cases with acute onset. The most common clinical presentation includes headache (88%), altered sensorium (54%), motor neurological deficits (30%) and papilledema (54%). Motor neurological discrepancy occurred in 30% patients while cranial nerve palsies were seen in 10% cases. 20% cases reported visual disturbances.Most of the patients (86%) had more than 1 cortical venous sinus involvement and the commonest being transverse sinus (76%) followed superior sagittal sinus (60%). Almost 60% cortical veins are involved in this current study population.The mean Hb concentration was calculated to be 9.9 g% with SD 2.5, median being 9.5 g%. the lowest reported level being 4.8 g% and the highest to be 16g%. 18 patients were directed to CSF analysis to rule out meningitis condition of which 15 showed normal reading and 3 developed some abnormalities with pleocytosis.Elevated homocysteine levels were found in 42 cases and the values ranges from 11.2 – 65 with the mean being 25.69, median 23.615.One way ANOVA is used to evaluate the relationship between Hcy of control group with study group where p – value <0.05 makes statistical difference. Majority of the cases suffering from homocysteinemia was found to be 30 – 40 years in males and 50 – 60 in females. Vitamin B12 level was <200 in 28 patients and 32 patients have B12 level >200.From the total of 60 cases, 13(22%) patients were puerperal, 20(32%) were secondary to trauma and infections and 28(46%) were idiopathic. Almost all patients were on heparin therapy. 68% were already on anti-epileptic drugs and 7 patients were put on supportive ventilation.

Conclusion: There is no correlation between Vitamin B12 in CVST patients. Both Vit B12 and Hcy levels are inversely proportional, hyperhomocysteinemia is most of the times associated with CVT.

Keywords: Hyperhomocysteinemia, Cerebral Venous Thrombosis, Homocysteine.

INTRODUCTION

Cerebral venous thrombosis is mostly an uncommon but severe thrombotic manifestation which has a high mortality rate,[1] has the potential to end in disability and the greater tendency of recurrence.[2] There are some coagulation abnormalities such as gain-of-function mutations in the genes that encodes factor V (factor V Leiden) and prothrombin[3] are presented with an increased risk of cerebral vein thrombosis[4-6] whereas there are no data currently reported on the role of hyperhomocysteinemia as a risk factor for cerebral venous thrombosis.[7] High plasma levels of total homocysteine (tHcy) result from the connection between genetic and acquired determinants.[7] The latter are mostly the result of deficiencies of certain vitamins such as folic acid, pyridoxine and cobalamin, which play important roles in the metabolic pathways of homocysteine. Among genetic determinants, a homozygous substitution of cytosine by thymine at the 677th position of the gene encoding for methylenetetrahydrofolate reductase (MTHFR) causes a 50% reduction in the activity of this enzyme and is associated

with mild to moderate hyperhomocysteinemia in individuals with inadequate dietary intake of folic acid.[8]

Cerebral venous thrombosis is one of the commonest causes of stroke as far as Indian population is concerned. CVST usually predisposes in the state of pregnancy and puerperium. The pathological hallmark that is reported in CVST is haemorrhagic infarction. CVST predominantly occur in the young individuals and can present with a broad spectrum of clinical manifestations which include headache, altered sensorium, seizures, focal neurological deficits, papilledema and cranial nerve palsies. Headache is the most frequent and often the first reported clinical manifestation.[9]

Homocysteine (Hcy) is a sulfhydryl amino acid compound that is generated from protein breakdown and the essential amino acid methionine as it is metabolized to cysteine. Hcy can be broken down in two pathways. When there is in excess methionine, Hcy is directed to transulphuration pathway where it is irreversibly conjugated to cysteine. Hcy can also be remethylated in a methionine conserving pathway and this pathway requires folic acid and MTHFR. When there is a potential increase in the plasma levels of homocysteine associated with cerebral venous thrombosis, vitamin therapy has the potential to decrease the recurrence rates considerably.[10]

The diagnosis of CVST involves mostly with the high suspicion risk. CT image of brain affected with CVST may show direct or indirect manifestations of CVST but 10% of the population affected with CVST show normal findings. It has also been proved that early diagnosis of CVST is necessary to prevent morbidity and mortality.

The aim of this study is to evaluate the clinical profile of patients with CVST and to identify the presence of homocysteinemia and its correlation with Vitamin B12 levels.

METHODOLOGY

For this study, 60 patients diagnosed with CVST who were admitted or in the outpatient department. There were 60 age matched selected patients as control group included in this study too. The duration of the study is 30 months and all the subjects included were above 18 years.

All patients were subjected to neuroimaging before arriving at the diagnosis of CVST. Some differential diagnosis includes acute myocardial infarction, stoke may also have raised homocysteine levels. Patients were subjected to case history taking, physical examination, basic haematological examination include complete blood counts, peripheral blood smear, ESR< blood grouping and PT/APTT. Of all these, certain patients were sent for basic haemophilia testing, APLA series, factor VIII levels and d – dimer test.

Data were collected and was put together in excel sheet. Correlation among various measurements were assessed using pearson's correlation coefficients. P – value <0.05 was considered as statistically significant. One way ANOVA is also used to evaluate the relationship between control group with study group.

RESULTS

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Patients who presented themselves within 48 hours were considered to have an acute onset whereas it can be considered subacute when the time of presentation ranges from >48 hours to <30 days and when the time frame ranges from >30 days is considered to be chronic. (Bousser et al, 1985) In the present study, subacute presentation was seen in 32 cases (54%)

followed by 23 cases with acute onset. The most common clinical presentation includes headache (88%), altered sensorium (54%), motor neurological deficits (30%) and papilledema (54%). Motor neurological discrepancy occurred in 30% patients while cranial nerve palsies were seen in 10% cases. 20% cases reported visual disturbances.

Most of the patients (86%) had more than 1 cortical venous sinus involvement and the commonest being transverse sinus (76%) followed superior sagittal sinus (60%). Almost 60% cortical veins are involved in this current study population.

The mean Hb concentration was calculated to be 9.9 g% with SD 2.5, median being 9.5 g%. the lowest reported level being 4.8 g% and the highest to be 16g%. 18 patients were directed to CSF analysis to rule out meningitis condition of which 15 showed normal reading and 3 developed some abnormalities with pleocytosis.

Elevated homocysteine levels were found in 42 cases and the values ranges from 11.2 – 65 with the mean being 25.69, median 23.615.

One way ANOVA is used to evaluate the relationship between Hcy of control group with study group where p – value <0.05 makes statistical difference. Majority of the cases suffering from homocysteinemia was found to be 30 – 40 years in males and 50 – 60 in females. Vitamin B12 level was <200 in 28 patients and 32 patients have B12 level >200.

From the total of 60 cases, 13(22%) patients were puerperal, 20(32%) were secondary to trauma and infections and 28(46%) were idiopathic. Almost all patients were on heparin therapy. 68% were already on anti-epileptic drugs and 7 patients were put on supportive ventilation.

DISCUSSION

Out of 60 study patients, 42 patients were found to be having elevated levels of homocysteine resulting in the incidence of 44%. Values of homocysteine ranges from 11.2 – 65, mean being 25.69 and median is 23.615. These observations corroborate with those studies done by Cantu et all[3] where there was 13.58% of incidence with 45 patients developed CVT. *Marinelli* et al[4] reported elevated levels of homocysteine in 33 patients out of 121 patients with CVST. As per the available data in literature, hyperhomocysteinemia is an important cause of hypercoagulopathy and therefore it is prudent that high levels of homocysteine have unprovoked venous thrombosis.

This study reveals that hyperhomocysteinemia significantly increases the risk of cerebral venous thrombosis by 4 – fold. There are certain determinants of hyperhomocysteinemia which include low serum folate level and the homozygous 677 C>T mutation in the MTHFR gene which are most commonly associated with the increased risk of the disease. Boers et al showed that using a methionine loading test, identified hyperhomocysteinemia in 4 of 50 patients (28%) with premature peripheral and cerebral arterial disease under 50 years of age.[11]

Brattstrom et al reported methionine intolerance in 26 of 72 patients with cerebrovascular disease who were all below 55 years of age.[12] Malinow et al in their study reported with higher levels of fasting serum total homocysteine in 47 patients with peripheral occlusive vascular disease than in normal individuals.[13]

Araki et al concluded that high levels of serum homocysteine levels in 45 patients with cerebral infarction as compared with the same number of normal subjects, hypertension and cerebral bleeding.[14] The findings obtained from our study has profound evidence relating hyperhomocysteinemia to vascular disease and conclude that the relation is independent of the other risk factors associated.

There are certain limitations associated with this study which include that the patients referred for thrombophilia screening to our specialized centre are commonly selected. But, the exclusion of the most severe patients, such as those with previous history of venous

thrombosis, should have limited the possibility of risk over-quantification. A diagnostic bias is thought to be reduced by the recap of the existing previous medical records and imaging of patients with cerebral venous thrombosis by an expert radiologist/interpreter. The association between hyperhomocysteinemia and cerebral vein thrombosis was observed in both sexes. Whether hyperhomocysteinemia is a cause or merely a consequence of cerebral vein thrombosis cannot be established by studies with a retrospective study design. However, the rarity of cerebral vein thrombosis makes the organization of prospective and/or intervention studies cumbersome to carry forward.

Thrombophilia screening including the coagulation factor abnormalities such as factor V Leiden, prothrombin mutation, deficiencies of antithrombin, protein C, and protein S, and the presence of antiphospholipid antibodies, is recommended in the diagnostic work up in patients with cerebral vein thrombosis.[6] The results of this study suggest that measurements of plasma tHcy should be included in thrombophilia screening. At variance with other types of thrombophilia, hyperhomocysteinemia can be easily and safely treated with vitamin supplementation (folic acid alone o in combination with cobalamin and pyridoxine). Whether or not the correction of hyperhomocysteinemia with vitamin therapy will help to reduce the high risk of recurrent cerebral vein thrombosis (up to 20%)[2] is not demonstrated by this retrospective study, but it should be tested in proper studies.

CONCLUSION

There is no correlation between Vitamin B12 in CVST patients. Both Vit B12 and Hcy levels are inversely proportional, hyperhomocysteinemia is most of the times associated with CVT.

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