Case Report

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Cerebral Venous Thrombosis and Hyperhomocysteinemia, How Important is the Co-Relation?: A Review of 3 Cases

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Abstract

Thrombosis of the cranial venous sinuses and the cerebral cortical veins can lead to a distinct cerebrovascular disorder, which unlike arterial stroke, most often affects even young adults and children. Symptoms and clinical courses are highly variable, etiological factors are even more heterogeneous making cerebral cortical vein thrombosis (CVT) a unique clinical entity.We report three cases in which the initial presentation in our Emergency Department (ED) led to suspicion of CVT, had it diagnosed and recognised hyperhomocysteinemia.

Keywords: Cerebral Venous Thrombosis; Hyperhomocysteinemia; Headache.

Introduction

Thrombosis of the cranial venous sinuses and the cerebral cortical veins can lead to a distinct cerebrovascular disorder, which unlike arterial stroke, most often affects even young adults and children. Symptoms and clinical courses are highly variable, etiological factors are even more heterogeneous making cerebral cortical vein thrombosis (CVT) a unique clinical entity. Common presenting symptoms in the International Study on Cerebral Venous and Dural Sinuses Thrombosis (ISCVT) were headache (89%); seizures (39.3%); unilateral or bilateral weakness (37.2%); papilledema (28.3%); and mental status changes (22%)[6]. Unusual presentations that can present with CVT include acute subdural haematoma[16], cerebellar ataxia and cortical blindness[13], subarachnoid haemorrhage[12], Paroxysmal Nocturnal Hemoglobinuria (PNH)[19] and Homocystinuria [14] among others.

Because of the heterogeneity in the clinical presentation and etiology, the diagnosis of CVT is often missed, and even if a diagnosis is made the contributory factors which are often subclinical are also missed or overlooked [15]. It can present to various specialists apart from emergency physicians such as general physicians, obstetricians and neurologists. Diagnosis is often missed unless clinicians maintain a high index of suspicion and be aware of the varied clinical presentations to be able to recognize and manage by prompt and proper application of clinical skill, rather than depending heavily on investigations alone for effective management of these patients.

After making a diagnosis of CVT the clinician should apply clinical skill and common sense with which it is possible to arrive at oneor more completely correctable common etiological factors contributing to the development of CVT, even if there isan underlying inherited disorder which cannot be corrected, and thus can avoid recurrences in future. Once the diagnosis of CVT is made it is easily managed if we know all the contributory factors and almost always has a good prognosisas compared to other cerebrovascular accidents [14]. It is alsoan observation that in many patients with the so called idiopathic CVT, nutritional deficiencies and life style issues are more important basic etiological factors in pathogenesis, at least in some epidemiological settings as strict vegetariansand those who consume an unbalanced diet. Research byobservation and studying the patients for their diet, lifestyle and environment might give the answer to the several etiological factors in cerebral cortical vein thrombosis, as inall other clinical problems, rather than depending on thecostly laboratory investigations alone[1].

The main progress in CVT study has been focused on identification of thrombophilic factors. Epidemiological studies have suggested that even mild Hyperhomocysteinemia (hyper-Hcy) is associated with occlusive arterial vascular disease and venous thromboembolism. Little information about the role of homocysteine in CVT is available. A systematic study on CVT and hyper-Hcy has been published in which Martinelli et al found that hyper-Hcy increases the risk of CVT by approximately 4-fold [5]. Vitamin supplementation with folic acid, pyridoxine, and cobalamin lowers the plasma levels of total homocysteine (tHcy) in most cases.Therefore, if hyperhomocysteinemia is associated with cerebral vein thrombosis, vitamin therapy has the potential to decrease the risk of recurrence.

We report three cases in which the initial presentation in our Emergency Department (ED) led to suspicion of CVT, had it diagnosed and recognized hyperhomocysteinemia.

Case Reports

Patient 1

A 24-year-old male came to the Emergency Department (ED) with complaint of headache and vomiting (projectile in nature)for the past 2 days. He had no co-morbidities. His neurological examination was normal. NCCT head was done because of the unexplained headache, which was suggestive of CVT (left transverse, left sigmoid and straight sinuses with dense clot sign as seen in Fig.1). He was assessed by neurology and admitted in Intensive Care Unit (ICU). MRI venography was advised, which confirmed the diagnosis. He was treated with injection Heparin with 6hourly APTT monitoring. His thrombocheck panel was normal except for raised S Hcy level (>50 micro mol/l). His vitamin B12 and D3 levels were also in the lower range (130.7pg/ml and 4.4 ng/ml respectively). His condition improved and on discharge he was put on tablet acenocoumarol 1 mg/ day prophylactically along with oral Vitamin B12 and vitamin D3 and to consume a diet low in vitamin K. He was advised for follow up and explained about the morbidity and mortality of the condition

Patient 2

The second patient, a 38-year-old male patient presented to our ER with complaint of headache followed by diplopia and blurred vision for the past 3 days. He had history of fever a week back which was of moderate gradeand intermittent in nature. It had subsided on self-medication. NCCT head was done which was suggestive of CVT in the right transverse, right sigmoid and superior sagittal sinuses (Fig. 2). He then underwent MRI venography, which showed hypointense-filling defectsuperior sagittal, bilateral transverse and sigmoid sinuses which confirmed the diagnosis. He was also admitted in Intensive Care Unit (ICU) under neurology team and put on intravenous heparin with regular APTT monitoring. His lipid profile, Complete Blood Count (CBC), Lupus Anticoagulant, Antiphospholipid Antibody (APLA) was normal except forelevated Serum Homocysteine (28.84 micro mol/l). He was discharged after a week without any complication with improved vision. He was also started on tablet acenocoumarol 3 mg/day, vitamins and advised for regular follow up.

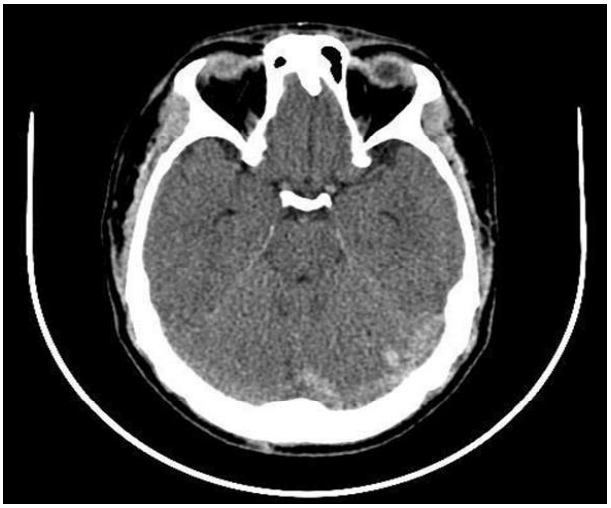

Fig. 1: Left transvere sinus CVT with dense clot sign

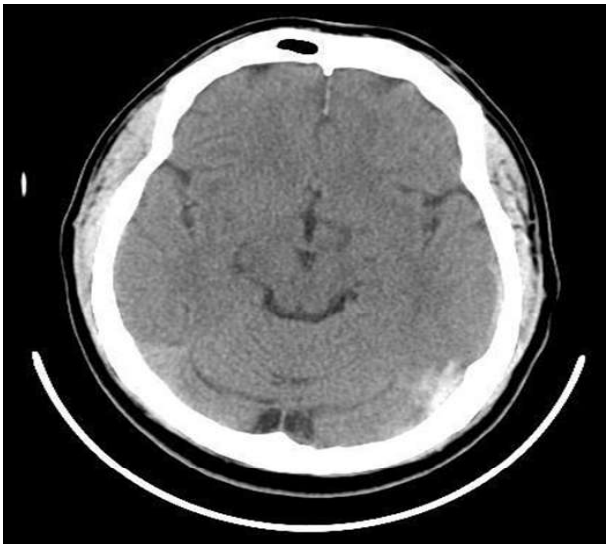

Fig. 2: Image showing infarction in the area of the vein of Labbe

Patient 3

The third patient, a 21-year-old male patient, had chief complaint of headache, neck pain with recurrent vomiting for the past 4 days. It was associated with bilateral lower limb weakness. NCCT head was done which was suggestive of CVT in the sagittal sinus. He then underwent MRI venography, which showed hypointense-filling defectin the transverse, right sigmoid and posterior part of superior sagittal sinuses. In the Intensive Care Unit (ICU) he put on intravenous heparin with regular APTT monitoring. His serum homocysteine level was high (28.18 micro mol/l) and his vitamin B12 and D3 were on the lower side. He was discharged with the same advice as the above 2 patientwith tablet acenocoumarol in a dose of 4 mg/day.

Discussion

Headache is one of the most frequent presentation in our emergency department. Etiology of headache varies and generally it is due to meningitis, cerebral tumors, hydrocephalus, intoxications, overwork-stress related, stroke or just migraine.The varied presentations in our patients led to the inclusion of CVT in our differentials. The symptom and clinical course of CVT are highly variable and can range from isolated headache and visual or auditory problems, to serious symptoms such as hemiparesis and coma. Its incidence is reported as 0.5 of 100,000 annually, more frequently diagnosed in women, accounting for 0.5% to 1% of all strokes[10]. Young age group with varied causes ranging from taking hormones to recreational drugs and chronic alcohol abuse are at risk for CVT. As this is a potentially life-threatening condition with high mortality rate in untreated patients, early diagnosis and treatment are important. None of our patient had any risk factors ranging from APLA, Lupus Anticoagulant except for raised Serum Homocysteine. All the three patients in our study were discharged with similar diagnosis of CVT with hyperhomocysteinemia with hypovitaminosis B12 and D3. All of them were non-smoker, non-alcoholic and had no co-morbidities.

Hyperhomocysteinemia can lead to vascular events like acutecoronary syndromes, recurrent coronary events, stroke andvenous thrombosis. It can be familial or acquired due to vitamin deficiencies. Homocysteine has primary atherogenicand prothrombotic properties. Histopathologic hallmarks of homocysteine-induced vascular injury include intimal thickening, elastic lamina disruption, smooth muscle hypertrophy, marked platelet accumulation, and the formationof platelet-enriched occlusive thrombi [15]. Vitamin B12, folate and pyridoxine deficiency contributes to development of hyperhomocysteinemia.

To date, thrombophilia screening, including coagulation factor abnormalities such as factor V Leiden, prothrombin mutation,deficiencies of antithrombin, protein C, and protein S, and thepresence of antiphospholipid antibodies, is recommended in the diagnostic work up in patients with cerebral vein thrombosis. The cases that we have taken up further support the evidences that measurements of plasma tHcy are an important entity in thrombophilia screening. At variance withother types of thrombophilia, hyperhomocysteinemia can be easilyand safely treated with vitamin supplementation as stated above. Hyper-Hcy has proved to be a strong and independent factor associated with ischemic stroke.The probable causal link is also observed in young patients and children, suggesting a thrombogenic rather than anatherogenic effect in these young subjects. The findings of Carlos Cantu et al were consistent with the hypothesis that high blood concentrations of tHcy are associated with increased risk of CVT [7]. Furthermore, low plasma folate levels were alsoassociated highly with an increased risk for CVT in this population in which low socioeconomic conditions and deficient nutritional status may contribute to its relatively high incidence.

Spence et al [9] found that in the era of folate fortification, B12 plays a key role in vitamin therapy for total Hcy. Higher doses of B12, and other treatments to lower total Hcy may be needed for some patients. Thus inthe western world, effective vitamin intervention has shifted from folateto vitamin B12 in post fortification era unlike what was seen in 2002 where intervention with folate reduced the incidence of stroke, cardiovasculardisease and venous thrombosis effectively. That B12 and folate deficiency canlead to hyper-homocysteinemia and venous thrombosis has been welldocumented [2,4,8] and its role cannot be ignored.

Conclusion

CVT should be considered in any young patient who presents with an unexplained headache. Patients should be started on treatment as soon as the diagnosis is made to improve the outcome and thereby decrease morbidity and mortality. Stress is made once again

on the importance of measurements of plasma tHcy and its role in development of CVT. Its role in CVT diagnosis and prognosis cannot be overlooked.

References

1. M. G. Bousser, J. Chiras, J. Bories, and P. Castaigne. Cerebral venous thrombosis—a review of 38 cases. Stroke, 1985;16(2):199–213.
2. J.B. Ubbink, W.J. Vermaak, M.A. Vander, et al. Vitamin B12, VitaminB6 and folate nutritional status in men with hyperhomocysteinemia. Am. J. Clin. Nutr. 1993;57:47–53.
3. M. Cataneo. Hyperhomocysteinemia: a risk factor for arterial and venous thrombosis. Int J Clin Lab Res 1997;27:1139-1144.
4. M.A. Mansoor, O. Kristen Sen, T. Hervig, et al.Total plasma homocysteine response to oral doses of folic acid and pyridoxine hydrochloride (vitamin B6) in healthy individuals: oral doses of vitamin B6 reduce concentrations of serum folate.Scand. J.Clin. Lab. Invest. 1999;59:139–146.
5. Martinelli I, Battaglioli T, Pedotti P. Hyperhomocy-steinemia in cerebral vein thrombosis. Blood 2003;102:1363–6.
6. Ferro JM, Canhao P, Stam J, et al, ISCVT Investigators. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). Stroke 2004;35(3):664–70.
7. Carlos Cantu,Elisa Alonso, Aurelio JaraLeticia Martý´nez, Camilo Rý´os, Marý´a de los Angeles Ferna´ndez, Irma Garcia, Fernando Barinagarre menteria. Hyperhomocysteinemia, Low Folate and Vitamin B12 Concentrations, and Methylene Tetrahydrofolate ReductaseMutation in Cerebral Venous Thrombosis. Stroke, 2004;35:1790-1794.
8. C. Fernandez-Miranda, M. YebraYebra, C. Ribera Casado, T. Toledo Urgarte, M.MartinMola, P. Gomez Gonzalez. Venous throm boem bolism and hyperhomocy-steinemiaas first manifestation of pernicious anemia. Rev. Clin. Esp. 2005Oct;205 (10):489–492.
9. J.D. Spence, H. Bang, L.E. Chambless, M.J. Stampfer. Vitamin Intervention For Stroke Prevention trial: an efficacy analysis. Stroke2005 Nov;36(11):2404–2409.
10. Bousser MG, Ferro JM. Cerebral venous thrombosis: an update. Lancet Neurol 2007;6:162–70.
11. P. K. Sasidharan and A. Mohammed. Cortical vein thrombosisdue to acquired hyperhomocyseteinemia. The National Medical Journal of India, 2009;22(6).
12. Yves Benabu, Levental Mark, Suissa Daniel, Rafael Glikstein. Cerebral venous thrombosis presenting with subarachnoid hemorrhage Case report and review. American Journal of Emergency Medicine 2009;27:96–106.
13. Samia Ben Sassi,HabibaMizouni, FatmaNabli,Lamia Kallel,MounirKefi, and Fayc 'al Hentati. Cerebral Venous Thrombosis Presenting With Cerebellar Ataxia and Cortical Blindness. Journal of Stroke and Cerebrovascular Diseases, 2010 Nov-Dec;19(6): 507-509.
14. Parveen Bhardwaj, Ravi Sharma, and Minoo Sharma. Homocystinuria: A rare condition presenting as stroke and megaloblastic anemia. J PediatrNeurosci. 2010 Jul-Dec;5(2):129–131.
15. P. K. Sasidharan. Cerebral Vein Thrombosis misdiagnosed and mismanaged. Thrombosis, 2012; 1-11.
16. Satoshi Takahashi, Jun ShinodaandTakuro Hayashi. Cerebral Venous Sinus Thrombosis in an Adult Patient Presenting as Headache and Acute Subdural Hematoma. Journal of Stroke and Cerebrovascular Diseases, 2012 May;21(4):338-340.
17. M. Sayadnasiri, A.A. Taheraghdam, M. Talebi. Cerebral venous thrombosis presenting as subarachnoid hemorrhage: Report of two cases. Clinical Neurology and Neurosurgery 2012;114:1099–1101.
18. Piazza G. Cerebral venous thrombosis. Circulation 2012;125:1704-9.
19. H. Sumbul, O. Taktakoglu, M. Buyuksimsek, B. Guven. Paroxysmal Nocturnal haemoglobinuria presenting as cerebral venous sinus thrombosis. Leukemia Research 2014;38(S1): S1–S65.
20. Sofia E. Thorell, Adrian R. Parry-Jones, Martin Punter, Robert Hurford,JeckoThachil. Cerebral venous thrombosis—A primer for the haematologist. Blood Reviews. 2015;29:45–50.