Cerebral Venous Sinus Thrombosis (CVST) in a Middle-Aged Female with Clustering of Risk Factors

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INTRODUCTION

Thrombosis of cerebral venous channel is a known complication of hypercoagulable states. Hyperhomocysteinaemia is a known hypercoagulable state. Obesity is a modern-day global epidemic. Disorders such as myocardial infarction (MI), stroke, and venous thromboembolism are on the rising trend and its increased morbidity and mortality is being associated with obesity. To date, however, the knowledge about the association between obesity and adult cerebral venous thrombosis (CVT) is sparse. We report a 44-year-old young morbidly obese metabolically unhealthy female who presented with headache, nausea, vomiting and giddiness. On evaluation, magnetic resonance venogram showed cerebral venous sinus thrombosis. On investigations, she had concomitant hyperhomocysteinaemia and metabolic syndrome.

Cerebral venous sinus thrombosis causing stroke in young adults is uncommon with various conditions precipitating it.1, 2, 3 Severe headache (70 - 90 %), focal lateralized signs (25 % - 75 %), seizures (30 - 40 %) as well as behavioural symptoms such as delirium, amnesia, and disturbances in consciousness are the various associated clinical symptoms.

The known inherited hypercoagulable risk factors that cause CVST are gain of function mutations in the genes encoding factor V (factor V Leiden) and prothrombin, Protein C, S and antithrombin III deficiency. Hyperhomocysteinaemia, is a known risk factor for causing venous thrombosis of the lower limbs. However, till date there is no data available showing its role in causing cerebral venous thrombosis. The interaction between genetic and acquired determinants result in high plasma levels of total homocysteine (tHcy).4, 5, 6 Vitamins such as folic acid, pyridoxine, and cobalamin are involved in the metabolic pathways of homocysteine and its deficiencies represent the acquired determinants.

Venous thromboembolism (VTE) comprises of deep vein thrombosis of the leg and pulmonary embolism and obesity is now being recognised as one of the risk factors causing it. The risk of VTE is approximately increased to 2-fold in an individual with a body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) of 30 or more compared with a normal BMI (< 25), and higher BMIs increase more risk with approximately 3 times higher risk in individuals with a BMI greater than 40.7, 8, 9 Again obesity as a risk factor for CVST is less known.
PRESENTATION OF CASE

A 44-year-old young female, vegan with morbid obesity (weight 112 kg, height 165 cm, BMI 41.1, waist circumference 118 cm) presented with complaints of headache, nausea, vomiting and giddiness since 3 days. The headache was continuous, diffuse with no aggravating of relieving factors. There was no history of fever, loss of consciousness, syncope, seizures, and weakness over limbs. There was no history of hypertension and diabetes mellitus too.

On examination, her pulse was 96/min, BP - 130/80 mm Hg. There were no signs of meningeal irritation, papilloedema or neurodeficit. Her other systemic examination was within normal limits. Her laboratory investigations revealed Hb of 8.9 %, mean corpuscular volume (MCV) – 119 fl, total leucocyte count (TLC) 7700/cumm. Peripheral smear showed macrocytosis. Fasting blood sugar was 108 mg % (impaired fasting glucose), Lipid profile - serum cholesterol 287 mg/dL, triglyceride 288 mg/dL, low density lipoprotein (LDL) 198 mg/dL, high density lipoprotein (HDL) 40 mg/dL. Her serum homocysteine levels were 46 µmol/L (normal 5 - 15 µmol/L), serum Vitamin B12 levels 102 pg/ml (normal 200 - 900 pg/ml), thyroid profile was normal.

Cerebral venous sinus thrombosis is a rare form of venous thromboembolism. Of all the types of stroke in young adults, CVST represents almost 0.5 % - 3 %, CVST has a female preponderance with a female to male ratio of 3 : 1.

Congenital thrombophilia is the most frequently associated factor. Homocystinaemia, factor V Leiden homozygous mutation, G20210A prothrombin gene and Methylene-Tetra-Hydro-Folate-Reductase 677TT mutations, protein C and S and anti-thrombin III deficiency, and positive anti-cardiolipin or anti-phospholipid antibodies are the various inherited prothrombotic risk factors for development of CVST.

Methionine is an essential amino acid that generates homocysteine (Hcy) which is a sulphur containing amino acid. The Hcy concentration is maintained and regulated by transsulfuration or remethylation pathway. With the help of folate and vitamin B12 as a cofactor, Hcy is remethylated back to methionine with the enzyme methionine synthase. Methyltetrahydrofolate reductase (MTHFR) and cystathione beta-synthase (CBS) enzyme activities can also affect Hcy levels. CBS controls the transsulfuration of Hcy to cystathione, and is dependent on Vitamin B6 as a cofactor. Increased levels of Hcy is a hypercoagulable state and a preclinical marker of stroke. Various prospective and retrospective clinical studies have provided evidence that Hcy may also cause stroke related thrombophilia.

CVST is one of the commonest cause of stroke in India with pregnancy and puerperum being the most common aetiologies in females. However, it is uncommon in nonpuerperal setting. The pathological hallmark of CVST is haemorrhagic infarction. It is by and large a disease of the young and it can present in protean ways having a wide spectrum of clinical manifestations which include headache, altered sensorium, seizures, focal neurological deficits, papilloedema and cranial nerve palsies. Headache is most frequent and is often the earliest manifestation.

The toxic effect of homocysteine on vascular endothelium can attenuate the oxidation of low-density lipoprotein cholesterol thus promoting thrombosis. There still remains a...
putative association between CVST and hyperhomocysteinaemia. Hyperhomocysteinaemia has a strong association with vitamin B12 deficiency. The association between Hcy and B12 levels in a study revealed that, there was a significant difference between HCy and B12 at 95% confidence level. Thus, homocysteine value tends to be high if vitamin B12 value is low. On the contrary, however, when homocystine is high, vitamin B12 need not be low. The study thus concluded that there is no evident association of vitamin B12 levels in patients of CVST and hyperhomocysteinaemia may not always be associated with low vitamin B12 level but it is definitely associated with CVST. Another study also had the similar conclusion. Our patient had lower Vitamin B12 and increased Hcy.

The change in coagulation factor levels is one mechanism which may increase the risk of thrombosis in obesity. Higher plasma concentrations of prothrombotic factors, such as plasminogen activator inhibitor 1 and Von Willebrand factor are found in obese women as compared to women having normal weight. Increased activated protein C resistance and higher concentrations of factor VIII, which are also the risk factors for thrombosis is associated with obesity. It is known that increased activated protein C resistance is caused by use of oral contraceptives which may justify the synergistic effect of both risk factors that we observed.

Of interest, idiopathic intracranial hypertension (IIH) also has obesity as a risk factor. They most often present with headache, decreased visual acuity and papilledema occurring due to impaired venous return in patients with chronic CVT. It is found that similar to CVST, IIH is fairly more common in women compared to men, and the association between IIH and obesity is also more stronger in women. It has been hypothesized that IIH is caused by decreased outflow from the cerebral venous system, possibly owing to stenosis of the transverse sinuses or insufficiency of the valves in the jugular veins. Our patient did not have papilloedema ruling out IIH, but she had jugular vein thrombosis.

Metabolic syndrome (MetS) is a distinct entity with conglomeration of vascular risk factors and metabolic abnormalities comprising of central obesity, atherogenic dyslipidaemia characterized mainly by elevated triglycerides and decreased high-density lipoproteins, high blood pressure, and hyperglycemia. MetS has been associated with an increased risk of prevalent stroke. In the National Health and Nutrition Examination Survey among 10,357 subjects, the prevalence of MetS was significantly higher in persons with a self-reported history of stroke (43.5%) than in subjects with no history of stroke (22.8%). MetS was independently associated with stroke history in all ethnic groups and in both sexes (OR 2.16; 95% CI, 1.48 to 3.16). Clinical studies have confirmed that frequency of MetS is markedly higher in patients with a history of atherothrombotic or non-embolic ischemic stroke. Long-term follow-up population-based studies have proven that healthy individuals having MetS are at a significantly increased risk for having major cardiovascular events, including stroke. Our case also had MetS.

CONCLUSIONS

Cerebral venous sinus thrombosis in our case had multiple coexisting risk factors like obesity, metabolic syndrome, hyperhomocysteinaemia and B12 deficiency. This case was rare to have clustering of more than one risk factors. Any obese female who presents with symptoms of CVST should be investigated for possible occurrence of other risks.

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Disclosure forms provided by the authors are available with the full text of this article at jemds.com.

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