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Homocystinuria Presenting as a Simultaneous Dual-Site Venous Thrombosis

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Abstract

We report a case of a 32-year-old male who presented with acute neurological and gastrointestinal symptoms, including seizure and abdominal pain and was found to have Budd-Chiari syndrome and cerebral cortical venous thrombosis simultaneously.

The patient was subsequently diagnosed with Homocystinuria, a rare genetic disorder caused by cystathionine beta-synthase deficiency that increases the risk of thrombosis. The patient responded well to anticoagulation and homocystinuria treatment and was discharged.

While previous case reports have linked homocystinuria to venous thromboembolism, this is the first known case to present with simultaneous dual venous site thrombosis. This study emphasizes the importance of maintaining a high index of suspicion for homocystinuria to prevent severe thromboembolic complications.

Keywords

Cerebral cortical venous thrombosis; Neurological; Bacterial Peritonitis

Introduction

Case Report

A 32-year-old gentleman was brought into the Emergency Department with a history of sudden- onset abdominal pain. His past medical history included a low trauma fracture of his right wrist about 1 year before this presentation and had cholecystectomy due to gallbladder disease at the age of 15 years (no further details could be elicited about it). He was not on any regular medications.

He was married, had no children; denied any history of smoking/alcohol or illicit drug use. He worked as a Chef in a restaurant. In regards to the family history- both his parents had early dementia at the age of 50 and 55 years. While in the emergency department, the patient developed a generalized tonic-clonic seizure and was stabilized with intravenous diazepam and levetiracetam. The seizure was subsequently aborted after 2 minutes. The patient woke up confused and with worsening abdominal pain.

A general physical examination showed Marfanoid features with-

- High arched palate, marked pectus excavatum, few striae noted on the back
- Bilateral arachnodactyly- with positive Walker- Murdoch sign and Steinberg Signs
- His Arm Span: height ratio was 1.25 (Height-120cm and Arm Span-150cm) and his Upper segment: Lower segment ratio was 0.7 (50cms:70cm)

Neurological examination was essentially normal with

- No signs of meningeal irritation;
- Cranial nerves were intact
- Motor and sensory examinations of both the Upper and Lower Limbs were Normal- with normal power/reflexes/bulk and tone
- Co-ordination of upper and Lower limbs was normal with no features of Cerebellar pathology

Abdominal examinations showed tender hepatomegaly with mild ascites with no other clinical evidence of chronic liver disease. Cardiac and Respiratory examinations were unremarkable. The patient was admitted to the high dependency unit (HDU) and his initial CT Brain with angiogram did not show any acute pathology. He had a second episode of generalised tonic-clonic seizure in the HDU requiring Clonazepam/ Sodium Valproate along with Levetiracetam to control the seizure. Following this, he had CT cerebral venogram which confirmed superior sagittal vein thrombosis and was commenced on unfractionated heparin.

Subsequently, the patient had Doppler US of the abdomen and Liver Fibroscan, which showed hepatic vein occlusion and mild ascites without hepatic fibrosis/cirrhosis. MR hepatic angiogram and venography confirmed hepatic veins thrombotic occlusion with spider web pattern without evidence of Hepatocellular carcinoma (HCC). The transthoracic echocardiogram was essentially normal with no evidence of heart failure or constrictive pericarditis.

Ascites fluid analysis showed Transudative ascites with SAAG of (Serum-to-ascites gradient) of >1.1 g/dl;

suggestive of portal hypertension possibly due to hepatic venous occlusion, no microbial growths in the culture; negative cytology and negative for Spontaneous Bacterial Peritonitis.

Other investigations listed below were essentially normal/unremarkable-

- Full blood count, renal function, C-reactive protein (CRP); Erythrocyte Sedimentation rate (ESR); blood and urine culture
- Negative thrombophilia screening including lupus anticoagulants, Beta2 microglobulin antibodies, anticardiolipin IgG and IgM, factor V Leiden, protein C, Protein S, antithrombin III, Prothrombin gene mutation
- Flow cytometry and JAK2 screening- ruled out Paroxysmal Nocturnal Hemoglobinuria (PNH), myeloproliferative and lymphoproliferative disease
- Serum and urine electrophoresis and light chain assay showed no evidence of paraproteinemia
- CT of neck/thorax/abdomen and pelvis- revealed no new pathology or solid organ malignancy.

Unfractionated heparin was changed to apixaban. He gradually recovered with no further episodes of seizures and abdominal pain improved with the resolution of ascites. The patient was reviewed by a haematologist and was suggested to have serum Vitamin B12/B6/B1, Folate, Methionine, and Homocysteine levels as well as genetic study for FBN1 genetic testing (Marfan Syndrome (MFS) gene which encodes fibrillin-1). The result of blood tests showed hyperhomocysteinemia with a homocysteine level of 200µmol/L (Normal range <15µmol/L) and Methionine of 80µmol/L(14-18umol/L) with a normal level of Vitamin B1/B6/B12/Folate and no mutation for FBN1.

Subsequently, the patient was seen by a clinical geneticist and had a genetic study for mutation of CBS (Cystathionine B- synthase), which confirmed positivity for P.G3075 mutation. Moreover, he was reviewed by an ophthalmologist and had confirmed ectopia lentis with downward dislocation in both eyes, high myopia, bullous keratopathy, iris atrophy, and secondary glaucoma which are all the classic ocular signs of homocystinuria. In addition to these, he had osteoporosis in the DEXA scan with a T-Score of less than -2.5. Hence, the diagnosis of homocystinuria was confirmed and the patient was treated with folate, Vitamin B12, and B6. However, there was no improvement in the homocysteine level, so he was labelled as nonresponsive to B6 and was later commenced on Betaine with dietary modification (LowMethionine diet) with a good response. Calcium and vitamin D were added to his medication with regular Denosumab injections every 6 months and indefinite apixaban.

Discussion

Our patient had both the hepatic and cerebral cortical veins thrombosis and was ultimately diagnosed with Homocystinuria. The fact that the patient had venous thrombosis in multiple sites without any identifiable common risk factors prompted us to consider the possibility of rarer causes of venous thrombosis, such as homocystinuria. Additionally, the patient had Marfanoid features, osteoporosis, a history of gall bladder disease, and a family history of dementia, all of which have been associated with Homocystinuria, further supporting this potential diagnosis [1-2].

However, we first ruled out the more common causes of venous thrombosis, including inherited thrombophilia, as well as acquired risk factors such as prior thrombotic events, recent surgery, trauma, immobilization, malignancy, myeloproliferative disorders, Paroxysmal Nocturnal Hemoglobinuria, antiphospholipid syndrome (APS), congenital heart disease, severe liver disease, and obesity.

Homocystinuria is a rare inherited metabolic disorder that affects methionine metabolism through abnormalities in the transsulfuration or re-methylation pathway. It is autosomal recessive and has a prevalence estimated at 1 in 344,000 (3). The transsulfuration process, which converts homocysteine to cysteine, requires pyridoxal phosphate (vitamin B6) as a cofactor. Methionine is produced through the remethylation of homocysteine, catalyzed by methionine synthase or betaine-homocysteine methyltransferase, with vitamin B12 (cobalamin) serving as the precursor of methylcobalamin, which is the cofactor for methionine synthase. Abnormalities in these pathways result in hyperhomocysteinemia.

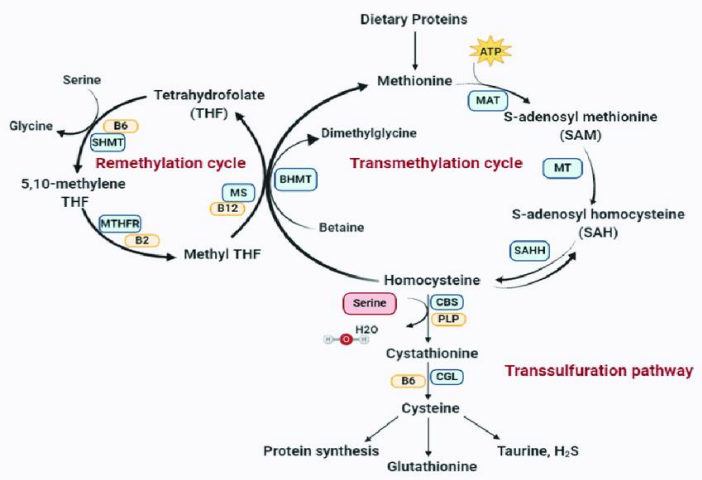

Figure 1: Homocysteine metabolism pathway.

Methionineadenosyltransferase (MAT); methyltransferase (MT); S-adenosylhomocysteinase hydrolase (SAHH); betaine-homocysteine methyltransferase (BHMT); pyridoxal-phosphate (PLP); cystathionine gamma-lyase (CGL); methionine synthase (MS); serine-hydroxymethyltransferase (SHMT); methyl-tetrahydrofolate-reductase (MTHFR), hydrogen sulfide (H2S)[4].

Plasma homocysteine levels can be elevated due to various factors such as genetic defects (cystathionine beta-synthase deficiency), vitamin deficiencies (folate, vitamin B6, or vitamin B12), chronic kidney disease, certain drugs used in the treatment of hypercholesterolemia (Fibrates, Nicotinic acid), and smoking. Hyperhomocysteinemia has been associated with venous thromboembolism (VTE) [5-11] due to its primary atherogenic and prothrombotic properties. The precise mechanisms behind thrombus formation in hyperhomocysteinemia are not fully understood, but proposed mechanisms include increased platelet activation, decreased expression of the anticoagulant protein thrombomodulin, and endothelial dysfunction resulting from a relative lack of endothelium-derived nitric oxide (NO) [12].

The histopathologic characteristics of homocysteine-induced vascular damage include intimal thickening, disruption of the elastic lamina, smooth muscle hypertrophy, significant platelet accumulation, and formation of thrombi that are rich in platelets [13-17].

These observations were presumed to explain the association between hyperhomocysteinemia and various other diseases like cardiovascular/cerebrovascular/venous thromboembolism/osteoporosis and Dementia. Several studies have confirmed the association of Homocystinuria with vascular complications [18-19]. Vascular complication continues to be a major cause of morbidity and mortality. It has been shown that before the age of 30 years, more than half of the affected patients will suffer at least one thromboembolic event [12]. Although theoretically, the thromboembolic event occurs in any vein or artery, the most commonly reported sites are the central nervous system, lungs, carotids, and renal arteries [20].

The treatment goal for Homocystinuria is to lower the plasma total homocysteine (tHcy) concentration to the level below the therapeutic target to limit the severity of complications and reduces the risk of a further vascular event [21].

When a patient is diagnosed with the condition, it is important to determine their responsiveness to pyridoxine. Patients can be categorized as fully or partially responsive, or non-responsive. Depending on their responsiveness, treatment with pyridoxine alone may be sufficient, or they may require betaine in addition to pyridoxine. For those who are non-responsive, a low-methionine diet and a methionine-free amino acid formula, along with betaine, can be used to lower homocysteine levels via a remethylating pathway that does not depend on vitamin B12 or folate. (Figure1).

The e-HOD (European Network and Registry for Homocystinurias and Methylation Defects) guideline suggests the following targets for plasma total homocysteine (tHcy) –[22]

- For patients who are responsive to pyridoxine, the target is to keep the plasma tHcy levels below 50µmol/L. If the levels stay above 50µmol/L, other medications such as diet and betaine can be considered.
- For patients who are not responsive to pyridoxine, the target is to keep the plasma tHcy levels below 100µmol/L.

Additionally, various trials like the Heart Outcomes Prevention Evaluation 2 trial, the French trial of folic acid and omega three oils, and the Vitamins to Prevent Stroke subgroup excluding antiplatelet therapy all showed a significant reduction of stroke with reduction of Homocysteine levels [23].

In conclusion, although Homocystinuria is a very rare condition, it is a treatable and preventable cause of thromboembolism. Physicians should be aware of this underlying cause for unprovoked thromboembolism to introduce timely and effective treatment and prevent further events, as well as future neurologic and vascular complications. Additionally, an early diagnosis will facilitate timely genetic counselling for the family given its autosomal recessive nature.

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