

Thrombophilia - Some Interesting Case Reports of Cerebral Venous Thrombosis

Selvaraj Pitchai^{1*}, Kalaimani², Akshay chowdary³, Swathi⁴, Vignesh⁴, Lavanya⁴, Sneha⁴, Gadam chakkradhar⁴

¹Professor, ²Assistant professor, ³Senior Resident, ⁴PG students, M.D (GM); Department of General Medicine, Mahatma Gandhi Medical College & Research Institute, Pondicherry, Pincode – 607403, India

*Corresponding Author

Selvaraj Pitchai

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Abstract: Thrombophilia causes venous thrombosis predominantly, sometimes arterial thrombosis in susceptible individuals causing increased morbidity and mortality. Cerebral venous thrombosis (CVT) is the commonest complication resulting from thrombophilia in young patients that can lead to diagnostic confusion. The treatment is either replacement therapy with prothrombotic factors that are deficient or anti coagulants if CVT occurs. Here we present some interesting three cases of CVT admitted and treated in a tertiary care hospital in South India.

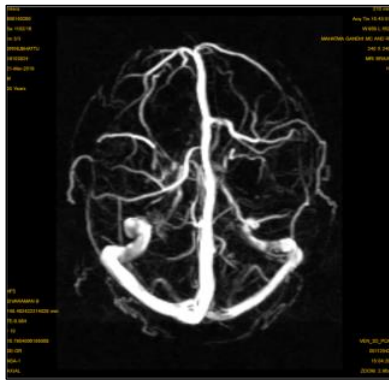
Keywords: Thrombophilia, Cerebral venous thrombosis (CVT), prothrombotic factors

INTRODUCTION

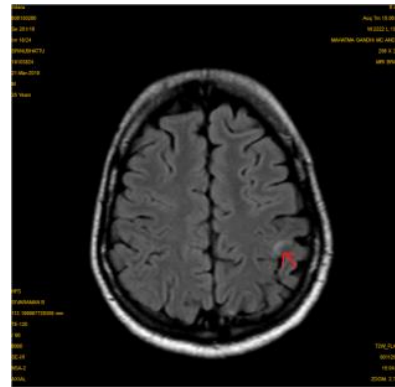
Thrombophilia also called prothrombotic state syndrome is an abnormality of blood coagulation that increases the risk of thrombosis in blood vessels. Thrombophilia has been recognized as one of the most important risk factors for CVT, DVT, DIC, Recurrent abortions, still birth, sometimes stroke, coronary vascular and peripheral vascular disease. Of late thrombophilia has shown a steep rise in the incidence of such clinical syndromes with different modes of presentation. Thrombophilia increases the risk of CVT, DVT, Stroke, and acute MI when it is associated with other risk factors like dyslipidemia, alcohol, smoking. Thrombophilia should be considered as a cause particularly when young individuals develop CVT, MI or the causes unknown. The clinical features of CVT vary and may include Headache (90%), focal or lateralizing neurological deficit (50%), seizures (40%), behavioral symptoms of delirium, amnesia and altered sensorium (10%). In about 70% of thrombophilia the causes are secondary and in 30% of cases the etiology may be congenital or hereditary thrombophilia. Thrombophilia is more common in males and the annual incidence is 3-5 per million. Complete blood count, prothrombin time, APTT, thrombin time, antiphospholipid antibodies such as lupus anticoagulants, anti-cardiolipin antibodies and anti beta-2 glycoprotein-1 antibodies, fibrinogen factor v Leiden, protein c, protein s, AT111, ANA, HIV, homocysteine, prothrombin 20210 gene mutation, USG, CT/MRI, CTV/MRA or MRV are the mainstay of diagnostic tools and investigations.

CASE REPORT

Case 1: 35 year old male presented with history of sudden onset of numbness, headache, involuntary movements of right upper and lower limbs and seizure of one day duration. Examination showed the patient was conscious, oriented and other neurological examination was normal, fundus normal, vitals and other system examinations were normal. Routine blood chemistry were normal and procoagulable factors namely protein C was reduced (35.2), protein S was reduced (42.1) normal value (60-140), serum homocysteine was elevated (18.96) (normal value : 5-16), patient also had elevated beta-2 glycoprotein-1 Igm antibody (70.08) (normal value <13). Hepatitis B HbsAg was positive, ECG/ECHO were normal, MRI revealed isolated cortical venous thrombosis with venous infarct in left parietal lobe, Diagnosis – CVT.

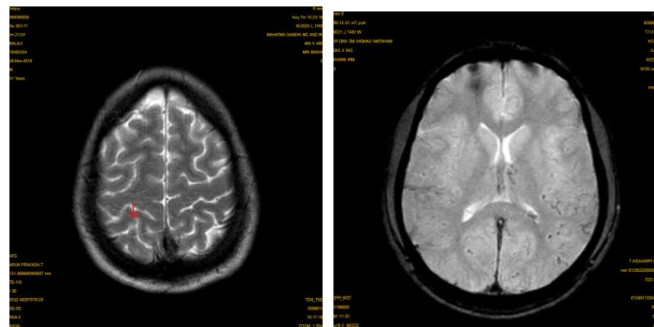


CT Brain with left parietal lobe infarct

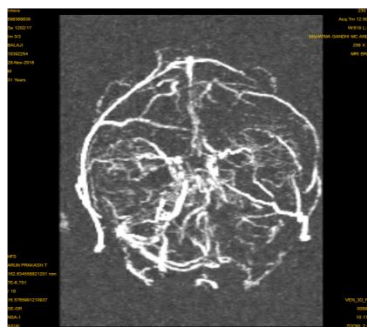


MRV showing extensive CVT.

Case 2: 31 year old male an alcoholic, smoker was admitted for severe throbbing headache of 10 days duration. History of involuntary movements both upper and lower limbs 5 days prior to headache was present. History of vomiting and two episodes of seizures present. No history of fever, trauma or altered sensorium, no similar previous episodes. On examination, patient was conscious, oriented, DTR brisk, bilateral plantar extensor, pupils normal, fundus bilateral papilloedema. Otherwise no focal neurological deficit. ENT opinion was normal. Other systemic examinations and vitals were normal. ECG/ECHO normal. Procoagulable factors work up showed elevated serum homocysteine level (38.2) (normal value : 5-16). Serum B12 was low (150) (normal value: 190-990), prothrombin time was 14.2 sec, INR : 1.9. LFT, ANA, CBC, APTT, PCV, Platelets were normal. CT brain showed diffused cerebral venous thrombosis with right parietal lobe intra parenchymal haemorrhage. MR venogram of neck/thorax revealed extensive thrombosis in superior sagittal sinus, bilateral transverse sinus, sigmoid sinus. Thrombus was also seen extended into right internal jugular vein for a length of 8cm from skull base, entire length of left internal jugular vein, left internal jugular vein was collapsed. Partial thrombus is also seen extending to left brachiocephalic vein and SVC and left subclavian vein. There was partial thrombus in the right pulmonary artery extending into right lower branches, other veins were normal. No lung infarction or pleural effusion noted. Aorta was normal. Diagnosis – CVT.



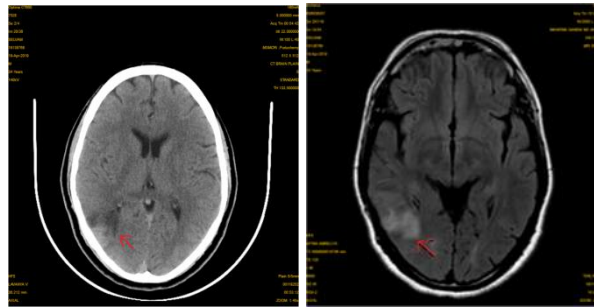
CT Brain right parietal lobe infarct



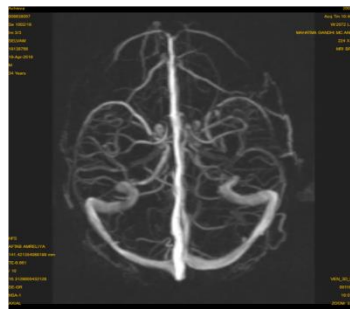
MRV showing extensive CVT.

Case 3: 34 year old male admitted for severe headache, giddiness of 2 days duration. History of weakness left upper limb and paraesthesia lasting for 3 hours. History of seizure present. No other symptoms. Neurological examination and systemic examination were normal except mild weakness left upper limb with power 4/5. Fundus is normal, vitals were normal, all routine biochemical analysis such as CBC, ANA, HIV were normal, lipid profile was slightly elevated, ECG/ECHO was normal, CT brain revealed wedge shaped infarct in right parieto-occipital lobe. MRV showed venous haemorrhagic infarct in right temporo-occipital lobe and subcortical hyperintensity in white matter of both frontal lobes suggesting small vessel ischemic changes. Most prothrombotic

factors were normal, serum B12 was elevated (2000mcg), serum homocysteine was normal, factor V Leiden mutation showed wild Type and MTHFR A1298C heterozygous mutant was positive. Diagnosis – CVT.



CT brain showing wedge shaped infarct in right parieto-occipital lobe.



MRV showing venous haemorrhagic infarct.

DISCUSSION

Pathophysiological

Thrombophilia may be congenital (hereditary) or acquired. Hereditary thrombophilia (type 1) is caused by deficiency of natural anti-coagulants namely protein C, S, AT3, XIII factor mutation, familial dysfibrinogenemia, congenital deficiency of plasminogen. Type 2 hereditary thrombophilia occurs as a result of over activity of clotting factors. The most common are factor V Leiden and prothrombin G 20210 mutation. ABO, and non-O groups and patients with factor VIII are at 2-4 fold relative risk for thrombosis. It has been well established that there is association between CVT and methylene tetrahydro folate reductase A1298C mutation (MTHFR A1298C).

Thrombophilia due to acquired causes consist of APLA syndrome- hence considered as auto immune disease. APLA usually causes venous thrombosis, recurrent abortions, but occasionally arterial thrombosis or migraine. Heparin induced thrombocytopenia (HIT) and paroxysmal nocturnal haemoglobinuria (PNH) also can cause venous thrombosis or CVT. Numerous haematological conditions – sickle cell disease, polycythemia vera, essential thrombocythosis, IBS, predispose to thrombosis of veins. Though the association between increased homocysteine and CVT is not clear, but several cases have been reported, linking increased homocysteine and CVT [1]. Homocysteine level is determined by mutation in MTHFR A1298C and CBS genes and by the levels of folic acid, B12, B6 in diet. Folate or B12 regulate the metabolism of homocysteine and low levels of folate/ B12 will be associated with increased serum homocysteine. Severity of imbalance between procoagulant and anti-coagulant activity determines that someone develops thrombosis and more importantly hyper coagulable states may accelerate the development of atherosclerosis of arteries. Hyper homocystenemia is well associated with premature atherosclerosis and cardiovascular risks. MTHFR A1298C mutation is potentially a risk factor for CVT. Thrombophilia occurs in all racial groups and pregnancy associated CVT, Puerperal water restriction a cultural habit in India may be a modifiable risk factor for venous thrombosis/CVT in addition to the presence of prothrombotic factors [3]. Besides, pregnancy accentuates hypercoagulability and increased viscosity of blood by prolonged bed rest, puerperal water restriction, and this predisposes to venous thrombosis/CVT in susceptible individuals [2].

Clinical Discussion

Thrombophilia by and large presents clinically like CVT, DVT, DIC, or sometimes arterial thrombosis. Thrombophilia also causes recurrent abortions, still birth etc. Arterial thrombosis due to pro thrombotic state can cause stroke or acute coronary syndrome and peripheral vascular disease. Incidence of venous thrombosis in rare sites like hepatic veins, portal veins, splenic veins has also been reported in large number of cases.

In our case presentation thrombophilia has manifested as CVT in three young males in the age group of 30-35 years age. All the three patients who were admitted for CVT had headache, giddiness. One patient had seizure and two patients had blunting of sensation, weakness of limbs for few hours. One patient had bilateral papilloedema but none of them had persistent focal neurological

deficit. All the three patients were admitted for first time episode, two patients had slightly elevated lipid profile, one patient had several prothrombotic factors namely protein C, protein S deficiency, hyperhomocysteinemia (level 18.96) and anti-phospholipid antibodies elevated (beta 2 glycoprotein-1 IgM – 70.58). Same patient had HbsAg antigen positive. The prothrombotic factors were repeated after about two months and they were found to be decreased, since these prothrombotic factors may fall soon after arterial or venous thrombosis due to consumption. CVT is caused by elevated homocysteine and decreased B12 /folate levels. In our study one male patient age 31 years had elevated homocysteine (18.96) and decreased B12 level (<150). He had extensive CVT involving right and left internal jugular veins, subclavian veins and thrombosis in main pulmonary artery, superior sagittal sinus, bilateral transverse sinus, sigmoid sinus, innominate vein, SVC etc. No lung infarct was noted and he had right parietal lobe haemorrhage in the CT. In spite of his extensive CVT, patient did not have any neurological deficit except constant headache.

It has been reported that Hyperuricemia and gouty arthritis may increase the risk of venous thrombosis in some patients because, hyperuricemia itself has proinflammatory effect on vascular cells leading to venous thrombosis [4], even though there is no major study investigating these associations. In another case of our CVT study, MTHFR A1298c mutation was positive along with factor V Leiden mild type – heterogenous. Numerous studies had reported that heterogenous MTHFR A1298c mutation is a significant risk factor for CVT [5] and Soleiman *et al.* [7]. Chitraloka *et al.* [6] reported a case of AIDP (GBS) with CVT and this type of presentation was very unusual and the mechanism is uncertain. However the highly elevated level of CSF protein and increased viscosity of blood and vasculitis may predispose to CVT since GBS is regarded as immune mediated disease which is known to produce venous or arterial thrombosis.

Discussion on Management

No Treatment is generally required in thrombophilia except those who are at risk of developing clot or thrombosis or who have developed clot/thrombosis. Anti-coagulants are generally used, either unfractionated or LMW heparin for short period and the oral anticoagulants are continued for 3-6 months.. Anti coagulants either injections or oral drugs can be safely used during pregnancy or breastfeeding. Dose of anticoagulants can be adjusted according to INR (2-3) is the aim. Sometimes replacement therapy with prothrombotic factors can also be undertaken in selective cases. Long term therapy with anticoagulants or antiplatelets may be needed in certain prothrombotic clinical conditions.

Life Style Modifications Advice

1. Weight reduction
2. Stop smoking
3. Exercise
4. Healthy and balanced diet
5. Avoid prolonged bedrest or immobility
6. Avoid oral contraceptives and hormone replacement therapy
7. Aspirin/heparin during pregnancy.

CONCLUSION

Thrombophilia is a blood disorder that has an increased tendency to form clot/ thrombosis either in veins/ arteries due to the combination of platelet activation and coagulation factors. They may remain largely asymptomatic in both congenital and acquired types of thrombophilia unless provoked or precipitated by environmental, autoimmune or genetic factors. Prompt recognition and understanding of the clinical state and institution of appropriate therapy and proper follow up will ameliorate the patient's suffering or disability and it will prevent recurrent thrombophilia. It is therefore important to recognize prothrombotic states as a significant risk factor in young patient presenting with CVT/stroke/ACS and peripheral vascular diseases.

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