A rare case of cerebral venous thrombosis in male with secondary thrombophilia

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Abstract:
Cerebral venous thrombosis is a rare cause of stroke. The incidence is 1-3 per million people. 75 percent of cerebral venous thrombosis cases occurs in females. Here we present a case of male cerebral venous thrombosis with secondary thrombophilia who presented with seizures.

Keyword: Cerebral venous thrombosis, Diabetes mellitus, Dyslipidemia, Hyperhomocysteinemia, Seizure

Introduction:
Compared to arterial thrombosis venous thrombosis is rare and the ratio between venous and arterial thrombosis in the central nervous system is 1: 62.5²; though rare CVT is associated with an equal degree of morbidity and mortality; the risk factors are many for cerebral venous thrombosis with an elevated homocysteine due to secondary causes is a rare cause; we present a 38 year old male with cerebral venous thrombosis with secondary hyperhomocysteinemia who presented with seizures and cranial nerve palsy;

Case report: Mr Sigamani, 38 year old male, who was not a smoker nor an alcoholic, a diabetic for 3 years on oral hypoglycaemic agents presented with seizures for the last 2 days; The first episode of seizure lasted about 5 minutes; it was a generalized tonic clonic seizures (GTCS) with transient loss of consciousness; he regained consciousness with no residual neurologic deficits other than mild postictal confusion which lasted for a short time;

Figure 1
Subsequently he had 4 episodes of GTCS on the day of admission, each lasting 5-10 minutes, lost consciousness since then. He had severe throbbing head ache and vomiting which was non projectile & non bilious. He had no fever, no visual symptoms prior to admission; Attenders denied any high risk behavior; Family history was not contributory. On initial examination he was drowsy, disoriented, afebrile; there was no pallor, no cyanosis, no clubbing, no lymphadenopathy, no pedal edema; Pulse: 82/min; BP 120/86 mm Hg; respiratory rate 18/mnt; Cardiovascular, respiratory and abdominal examination were normal; Pupils were 2mm and reacting, no cranial nerve, motor or sensory deficits. DTRs were normal and bilateral flexor plantar. He had no meningeal signs. Fundoscopy also was normal. 

Hb 13 g%, PCV 39%, TC: 6100, DC: P50L48E2, ESR 6/14), RFT, ECG and CXR were normal. CBG was 186 mg%, Urine sugar was 2+; ketones negative. FLP ( TC:226, TGL: 222, HDL: 50, LDL: 132, VLDL :44 mg ) was abnormal. Ultrasound abdomen showed fatty liver; CT brain revealed hypodensity in left parietal region (figure 1).

Patient recovered from post ictal state during first 24 hrs. He was persistently complaining of head ache, severe enough to disturb even during sleep.

On day 4 patient developed focal seizures involving his left upper limb. Seizure was not getting controlled with AED; On 7th day of admission he developed multiple cranial nerve palsies with left side LMN VI, VII, IX, X and XII CN involved. He also developed “left hemiparesis” (figure 2,3 and 4). An urgent MRI was taken which showed venous infarct in the left frontal lobe with superior sagittal and superficial sinus thrombosis (figure 5 and 6).

Patient was shifted to IMCU due to intractable seizures and was sedated, intubated and ventilated for airway protection. Patient recovered over the next couple of days. Seizures stopped, CN palsies significantly improved, with mild hemiparesis. Patient was shifted back to ward on day 12. The seizure episodes continued for another 6 days but episodes were less frequent and less severe, with occasional worsening of cranial nerve symptoms and hemiparesis. Glycemic status was strictly monitored and managed with insulin. Further investigations were done. Cardiac status was normal and ECHO showed no RWMA, normal LV function. Carotid doppler was normal. EEG: Bilateral potential epileptiform pattern. Ophthalmologic evaluation and fundoscopy was normal. Mantoux done was negative, HIV ELISA and HBsAg were negative.

Thrombophilia profile: Protein C 184% (70-140), Protein S 158%(60-150), Homocysteine- 43.43 (5.9-16), Anti Cardiolipin IgG 1.27 (<10), Anti Cardiolipin IgM 1.6(<7), Lupus anticoagulant-negative, Serum Fibrinogen:382 mg/dL (180-350), ANA -negative, RA Factor-negative, CRP -24 mg/L
(<6mg/L) There is elevated homocysteine and CRP levels. 

**DISCUSSION:**

The most common symptoms and signs of CVT are headache, seizures, focal neurological deficits, altered consciousness and papilloedema. Four main patterns have been identified 1. Isolated intracranial hypertension 2. Focal syndrome, 3. Cavernous sinus syndrome and 4. Subacute encephalopathy. Rare presentations include subarachnoid haemorrhage, thunderclap headache, attacks of migraine with aura, transient ischaemic attacks, tinnitus, isolated psychiatric symptoms and isolated or multiple cranial nerve palsies. Clinical presentation of CVT is affected by age of patient, time between onset and admission to hospital, location of CVT and the presence of parenchymal lesions. Patients with chronic course or delayed clinical presentation may show papilloedema on fundoscopy but this finding is less common in acute cases.

Isolated headache cases (headache in the absence of intracranial hypertension, subarachnoid haemorrhage, or meningitis) are essentially associated with lateral sinus thrombosis, which should not be mistaken for lateral sinus hypoplasia (too difficult to differentiate even in an MRI). The exact mechanism of the headache remains unknown, but proposed theories include stretching of nerve fibres in the walls of the occluded...
sinus and a local inflammatory reaction. Neuroimaging of the thrombosed vessel: The current gold standard is MRI with MRV (MRI to visualise the thrombosed vessel and MRV to detect the non-visualisation of the same vessel). MRI alone is limited by flow artifacts that can lead to false positives and the absence of hyperintense signal on T1 and T2-weighted images at the onset of acute thrombosis. During the first 3–5 days the thrombosed sinus is isointense on T1 and hypointense on T2, and thus very difficult to differentiate from normal veins. Again with MRV alone it is difficult to differentiate between thrombus or sinus hypoplasia. Echoplanar Susceptibility-weighted images (T2*SWI) are more sensitive than T2WI especially within 3 days of onset. Diffusion weighted images (DWI) are exceptionally good at imaging of the parenchymal lesions. Contrast enhancement of the sinus wall surrounding the clot - the “empty delta sign” is characteristic of CVT. Prognosis is very good compared to arterial events with 15% overall death/dependency.

Poor prognostic factors include CNS infection, any type of cancer, deep venous system thrombosis, intracranial haemorrhage, mental status disorder, age >37 years and male gender. The progression of superficial sinus thrombosis to sigmoid sinus would have resulted in the ipsilateral cranial paresis and hemiparesis in the patient under discussion, complete reversal again favouring the same.

Homocysteinemia: Homocysteine is an intermediary amino acid formed by the conversion of methionine to cysteine. Normal level is 5-15 mol/L. Homocystinuria or is a rare autosomal recessive disorder characterized by severe elevations in plasma and urine homocysteine concentrations. Mounting evidence suggests that moderate hyperhomocysteinemia is an independent risk factor for atherosclerotic vascular disease and for recurrent venous thromboembolism. Homocysteinemia can be Moderate (15 to 30 µmol/L), Intermediate (30 to 100 µmol/L) or Severe (>100 µmol/L) according to blood levels.

Vitamin B12 (cobalamin) is the precursor of methylcobalamin, which is the cofactor for methionine synthase. This enzyme is important in the metabolism of homocysteine; thus vitamin B12 plays an important role in homocysteine metabolism, with a deficiency state causing raised homocysteine levels. Hyperhomocysteinemia can be due to 1. Genetic defects 2. nutritional deficiencies 3. drugs like fibrates 4. cigarette smoking 5. chronic kidney disease. Apart from myocardial infarction, other cardiovascular morbidity and stroke homocysteine is associated with Venous thromboembolism, obstetric complications, birth defects, osteoporosis and dementia. Treatment: Correcting nutritional inadequacy of folic acid, vitamin B12, and choline (betaine) will lower homocysteine levels. A diet rich in fruits, vegetables, and low-fat dairy products, and low in saturated and total fat also can lower fasting serum homocysteine. Folic acid (1 mg/day), vitamin B6 (10 mg/day) & vitamin B12 (0.4 mg/day) will normalize homocysteine usually in two weeks. Folic acid can be increased
to 5 mg/day as needed (till level <15 µmol/L). If homocysteine level is >30 µmol/L or patient is having CKD the initial dose of folic acid is 5 mg/day. Genetic testing is available for inherited or familial cases (MTHFR mutation). This 38 year old diabetic had multiple risk factors for a secondary thrombophilia which resulted in cortical venous thrombosis. The clinical evolution was dramatic. Recent insight and research towards hyperhomocysteinemia emphasizes the nutritional inadequacy prevalent in low to middle socio-economic groups though the disease can be inherited and lead to accelerated athero-thrombosis. Diabetes, associated dyslipidemia and acquired coagulation abnormalities (like decreased protein C concentration) in addition lead to thrombophilia, according to recent reports.

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