International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2020): 7.803

Isolated Protein S Deficiency Leading to Cerebral Venous Sinus Thrombophlebitis in Young Male

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Abstract: ***Protein S is a potent anticoagulant that downregulates thrombin formation and is a vitamin K-dependent glycoprotein which is primarily synthesized in the liver. A deficiency in this protein or decreased activity, as seen in hereditary protein S deficiency, can lead to life-threatening thrombosis. Hereditary protein S deficiency is a rare disease as listed by the National Organization for Rare Disorders (NORD). Dural venous sinus thrombosis is a rare consequence of protein S deficiency and is associated with a risk of increased morbidity and mortality.It is also known to cause venous as well as arterial thromboembolic events commonly occurring in the deep leg and pelvic veins. We are reporting a case of 17 years old male without any risk factors and comorbidities presented with headache, giddiness and diplopia who has been diagnosed with cerebral venous sinus thrombosis and associated protein s deficiency.***

Keywords: proteins, cerebral venous sinus thrombosis

1. Introduction

Protein S is a vitamin K dependent anticoagulant that works in conjunction with activated protein C to inhibit activated procoagulant factors V and VIII restricting clot formation. A deficiency in protein S causes a hypercoagulable state with increased risk of thromboembolism. Protein S deficiency is a rare condition as noted by the National Organization for Rare Disorders (NORD). It can be hereditary or acquired. Acquired protein S deficiencies can occur with oral contraceptive use, estrogen therapy, pregnancy, liver disease, and acute inflammatory processes. Dural venous sinus thrombosis, with an overall incidence of 1.32 per 100,000 person years, is a known but relatively uncommon occurrence in patients with thrombophilia [(1)] Cerebral sinus venous thrombosis (CSVT) is a uncommon form of venous thromboembolism (VTE)[(2)] with varied clinical presentation, predisposing factors ,imaging findings and clinical outcomes. Cerebral sinus venous thrombosis represents almost 0.5% -3%[(3)] of all the types of stroke which affects predominantly younger people [(4)] with an estimated incidence of 3-4 per million for adults[(5)]. Female are three times more commonly affected than males with majority of female belong to child bearing age group[(6)]. The International Study on Cerebral vein and Dural Sinus thrombosis determine the prevalence of CSVT in different sinuses- Transverse sinus (86%), superior sagittal sinus (62%), straight sinus (18%), cortical veins (17%), jugular veins (12%),vein of Galen and internal cerebral vein (17%)[(6)] The prevalence of peripartum cerebral venous thrombosis is 11.5 cases per 100,000 deliveries of pregnant female [(7)]. The prevalence of protein S deficiency in patients with history of recurrent thrombosis or with family history of thrombosis is 3-6%.Protein S deficiency is rare in healthy adults without any abnormalities [(8)].

2. Case Report

17 years old male patient presented to us with complain of headache in bilateral fronto- parietal region since 10 days and fever which was low grade since 3 days. Patient had 2-3 episodes of vomiting since 5 days which was projectile, non-billious. Patient had developed diplopia since 1 day. Patient had no history of seizure, photophobia, phonophobia, loss of consciousness, diminished vision and no any drug history. On examination patient was T-afebrile, P-54/min regular, B.P-120/70 patient was conscious & oriented to time, place & person. CNS examination shows tone/power/reflexes-normal. Plantars-bilateral flexors, pupils -bilateral reacting to light. Other systemic examination was normal. On clinical suspicion of vascular event in young male we did routine investigation which showed Hb-14.8, TLC-10900, PLT-2.39, INR-1.2, lipid profile-normal, sickling & Hb electrophoresis- normal, homocysteine- normal. MRI showed loss of flow signal is seen in almost entire superior sagittal sinus, straight sinus , vein of galen ,bilateral transverse and sigmoid sinuses on MR venogram. These venous sinuses show hyperintense signal on T1 weighted and FLAIR images suggestive of acute thrombosis and mild cerebral edema is also seen in high frontal and parietal region. On further evaluation his ANA was negative, APLA was negative and protein c -68.7%(65-140), protein s -46.7%(67.5-139) ,Antithrombin III-86.2%(80-120). Patient was started on injectable conventional heparin therapy &injectable mannitol. Within 3 days patient started showing improvement & there is improvement in headache & diplopia. Patient was discharged with warfarin therapy and continuous follow up of patient was done and patient did not develop any new symptoms.

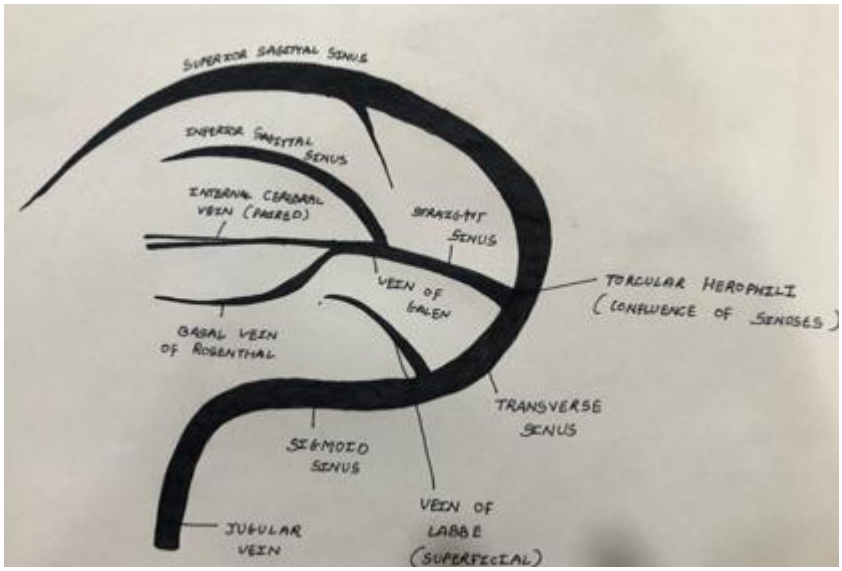

Figure A: Normal anatomy of Dural sinus (self drawn)

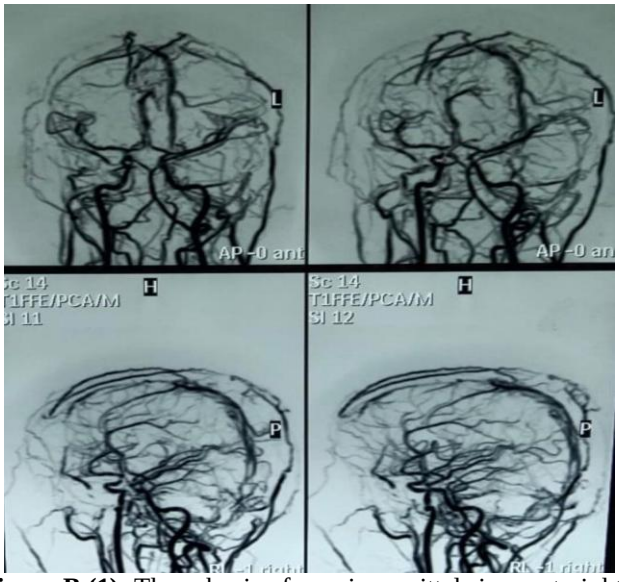

Figure B (1): Thrombosis ofsuperior sagittal sinus , straight sinus , vein of galen ,bilateral transverse and sigmoid sinuses

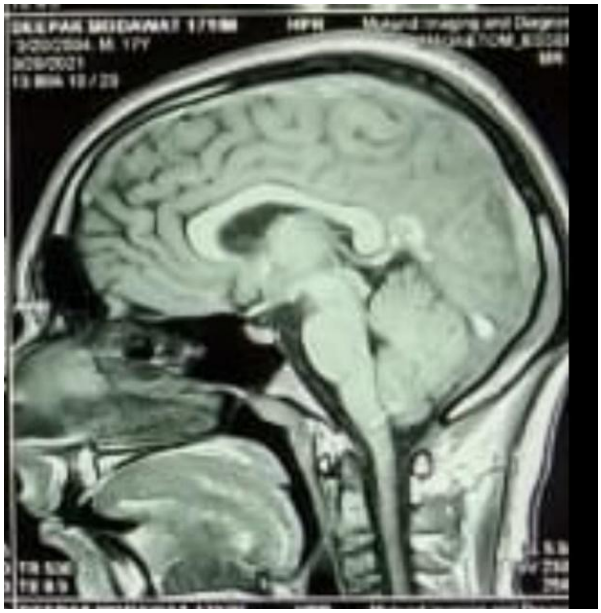

Figure B (2): Early venous infarct in left Thalamus

3. Discussion

Cerebral venous systems are group of venous channels which are between endosteal and meningeal layers of dura matter. Tese cerebral veins lack valves. The cerebral veins are divided in superficial and deep veins [(9-11)]. These venous system drains blood into superior sagittal sinus (sss), inferior sagittal sinus (iss), lateral sinus (ls), straight sinus (ss), cavernous sinus (cs) and then into internal jugular vein.superficial venous system includes dural sinus and cortical veins. Two major dural sinuses are superior sagittal sinus and cavernous sinus. SSS drains into transverse sinus which then drains into straight sinus. Cavernous sinus drains poster laterally into transverse sinus and inferior laterally into sigmoid sinus. Deep venous system include straight sinus, lateral sinus and sigmoid sinus as well as deeper cortical vein .these vessels drains into basal ganglia, thalamus, upper brainstem, deep white matter. There are two pathophysiologic mechanisms which contribute to the clinical manifestations of cerebral venous thrombosis. The thrombosis of cerebral veins leads to increase in venular and capillary pressure. Cerebral sinus occlusion leads to disruption of arachnoid granulations leading to decrease in CSF absorption. Both of these leads to increase in intracranial pressure. Increase in intracranial pressure for longer time leads to disruption of blood brain barrier, leading to leakage of capillary components producing cytotoxic and vasogenic oedema and parenchymal tissue damage[(12)].[(13)]Various types of risk factors have been identified in development of venous sinus thrombosis.they are infective causes which includes (a) local - direct septic trauma, intracranial infection like abscess, subdural empyema, meningitis regional infection: Otitis, sinusitis, orbital cellulitis, tonsillitis, dental infection, stomatitis, cutaneous cellulitis. (b) general- bacterial- septicaemia, endocarditis, typhoid, tuberculosis, parasitic- malaria, trichinosis, toxoplasmosis fungal- cryptococcus, aspergillosis.

Noninfective causes: (a) local - head injury , post neurosurgery tumours (cholesteatoma, meningioma, metastasis, jugular tumours),occlusion of internal jugular vein, post lumbar puncture, post epidural or spinal

anaesthesia (b) general: any surgery with or without thrombosis, pregnancy and postpartum, oral contraceptives, cardiac insufficiency, severe dehydration of any cause, malignancies, inherited thrombophilia like anti thrombin deficiency, protein C and S deficiency, factor v leiden mutation, prothrombin mutation (substitution of a to g at position 20210), homocysteinemia caused by gene mutation in methylenetrahydrofolate reductase. Acquired coagulation disorders like nephrotic syndrome, antiphospolipid antibodies, homocysteinemia, hyperviscosity (monoclonal gammapathy). digestive includes cirrhosis, crohn disease, ulcerative colitis. inflammatory disorders: systemic lupus erythematous, behcet's disease, wegener's granulomatosis, giant cell arteritis, sarcoidosis. medications like steroids, aminocaproic acid, l-asparaginase, methotrexate, cisplatin. The presentation of cerebral sinus thrombosis occurs in three forms i.e. acute form (<48 hours) which occurs in 30% of populations, subacute form (48 hours to 30 days) which occurs in 50% of population, chronic form (30 days to 6 months) which occurs in 20 % of populations[13].[14] there are 4 clinical patterns of CSVT which include (1) focal syndrome: presence of focal signs associated with headache, seizures or changes in mental state. (2) Isolated ich: with headache, nausea, vomiting and papilledema. (3) diffuse sub-acute encephalopathy: with changes in mental state. (4) Cavernous sinus syndrome : painful ophthalmoplegia, chemosis, proptosis. Headache is the most common presenting symptom in CSVT. It was present in almost 90% of patients; this symptom is more frequent than in cerebrovascular ischemic arterial disease.

4. Conclusion

Cerebral dural venous sinus thrombosis is a rare occurrence in patients with protein S deficiency. A high degree of suspicion, especially in young population presenting with unusual headache and neurologic signs and symptoms, will help facilitate timely diagnosis and management of the condition, potentially avoiding serious complications. Anticoagulant is main line of treatment in these patients. They are not contraindicated even if there is haemorrhagic transformation in these patients.The chances of recurrences are high in these patients depending upon the cause of the thrombosis.patient education on potential need for life-long therapy, treatment compliance, and avoidance of risk factors, thus preventing recurrent thrombotic events.

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