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Case Report

Cerebral sinovenous thrombosis in a child with homocystinuria

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Introduction

Cerebral sinovenous thrombosis (CSVT) is a potentially fatal condition which can have multiple etiologies and varied presentation in children. Management of CSVT is incomplete without a search for possible etiology. Sébire et al (2005) found that the incidence of pediatric CVST is at least 0.67 per 100,000 children per year.¹ We present an interesting case of a six-year old-boy with extensive CSVT who was diagnosed to be suffering from homocystinuria.

Case report

A six year old patient was brought to hospital with complaints of multiple episodes of vomiting for two days. He had no

diarrhea, fever, oliguria or high-colored urine. The child was a second product of non-consanguineous marriage. He had moderate mental subnormality (IQ: 50). A child psychologist had worked him up at the age of five years when his thyroid status, karyotype, blood lead levels, parental questionnaire for autistic spectrum disorder were detected to be normal. Perinatal, family, socioeconomic, immunization and treatment history was unremarkable.

On admission, he was irritable, pale and had tachycardia (120/min). Temperature, respiration, blood pressure, capillary filling time, oxygen saturation (SaO₂) and skin turgor were normal. He did not have icterus, cyanosis, lymphadenopathy, rash and neck rigidity. He had hyper-pigmentation over dorsa of fingers, axilla and groin as shown in [Fig. 1]. His parents and sibling did not have similar hyper-pigmentation. His weight and height at admission were 16.8 kg (81.95% of 50th centile of WHO reference i.e. 20.5 kg) and 115 cm (99.13% of 50th centile of WHO reference i.e. 116 cm). His arm-span was 114.5 cm and ratio of upper body segment to lower body segment was 1.1:1 (both normal for age). His systemic examination was normal. The boy was managed as a case of acute gastritis with mild dehydration with Oral Rehydration Solution and anti-emetics. He became asymptomatic within 12 h of admission. After about 30 h of admission; he became irritable and febrile. He had hair-pulling and head-banging which were suggestive of headache. After about 2 h of the first spike of fever, he had an episode of vomiting. Fever, intermittent in type, lasted for about 12 h (maximum temperature: 101 °F). He had no meningeal signs. Fundoscopy was normal. Investigations

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Fig. 1 – Photograph showing hyper-pigmentation over the dorsa of fingers.

revealed Hb: 9.8 g/dl Total Leukocyte Count: 14,200/mm³ Differential Leukocyte Count: P₈₀L₁₄M₀₂E₀₄ Platelets: 1,90,000/mm³. Peripheral blood smear showed microcytic hypochromic anemia with anisocytosis, poikilocytosis and leukocytosis with leftward shift. No hemoparasites were seen. Liver Function Test, Blood urea, Serum creatinine, Blood sugar, Serum electrolytes, urinalysis and Blood culture were within normal limits. Lumbar puncture released CSF with high pressure (not quantified). Cerebro-spinal fluid studies were normal. On day 3 of admission, the patient had generalized tonic clonic seizures lasting 3 min followed by drowsiness, bradycardia and projectile vomiting. He was managed with intravenous phenytoin sodium, mannitol, broad spectrum antibiotics and intravenous fluids. Neuroimaging was locally not available. Due to rapid clinical deterioration with signs of raised ICT, he was electively ventilated for 72 h. After extubation, the boy was asymptomatic with no signs of neurological impairment. CT scan brain showed thrombosis of superior sagittal and right transverse sinuses [Figs. 2 and 3]. His PT-INR was 0.8 and d-dimer levels were 8.8 µg FEU/ml (>0.5 µg FEU/ml). Hb electrophoresis, echocardiography, urine for homocystinuria and reducing substances, Mantoux test, sickle screen, HIV (I & II) screen, serum cortisol, aldosterone, T₃/T₄/TSH, ANA profile, ECG, chest radiograph, USG abdomen and Doppler study of renal, abdominal and neck vessels were essentially normal. Low Molecular Weight Heparin (LMWH) (1 mg/kg/dose 12 hrly s) was initiated which was substituted

Fig. 2 – CT Scan brain showing thrombosis of the superior sagittal sinus.

Fig. 3 – CECT brain showing the enhancing dura around the thrombosed superior sagittal sinus, the “empty delta sign” (white arrow). Multiple hypodense (black arrows) are noted involving the centrum semiovale on left side.

one week later with oral coumarol. He was discharged home after two weeks on oral iron, phenytoin sodium, acenocoumarol with PT-INR of 1.5.

The child was readmitted after two weeks with headache, vomiting and irritability followed by generalized status epilepticus, right sixth cranial nerve palsy and decorticate posturing. He was managed with Inj Midazolam, Phenytoin Sodium, Phenobarbitone and Propofol in stepwise fashion. Cerebral decongestive therapy including head elevation,

Fig. 4 – MRI sagittal FLAIR image of brain which reveals irregular and expansile hyperintense thrombus (black arrow) in the superior sagittal sinus and an ill defined hypointensity (white arrow) in the superficial part of the frontal lobe, consistent with venous infarct.

mannitol, hypertonic (3%) sodium chloride infusion, sedation and mechanical ventilation were instituted. He responded and could be weaned off from mechanical ventilation after five days. Subsequent clinical examination was normal. MRI brain findings were similar to earlier CT findings as shown in Fig. 4. Qualitative test for urinary homocysteine excretion was positive. Serum homocysteine was 23.10 $\mu\text{mol/l}$ (ref range: 5–15 $\mu\text{mol/l}$). Tandem mass spectroscopy (TMS) revealed serum methionine levels of 836.66 $\mu\text{mol/l}$ (Ref range <77 $\mu\text{mol/l}$). He was diagnosed as a case of classical homocystinuria due to cystathionine β -synthase (CBS) deficiency. His skeletal survey and detailed ophthalmological examination were unremarkable. Protein C and Protein S levels done after three months of discharge are normal.

His parents and sibling have been subjected to anthropometric evaluation, ophthalmological examination and urine for homocystinuria screening and have been found to be normal. His parents have been counseled about prevention of dehydration and prompt treatment of fever. He has been prescribed therapy in the form of Vitamin B₆ (1000 mg/day), folic acid (5 mg/day), oral anticoagulants (to target INR between 1.5 and 2.0), iron and phenytoin sodium. Oral anticoagulation has been planned for a period of twelve months.

The patient's parents have been sensitized about the supportive role of nutritional therapy and a model diet has been planned keeping in view the child's caloric and protein requirement as well as acceptability. Methionine rich foods such as mutton, fish, beans, eggs, onion, garlic, lentils and sesame seeds have been restricted. Foodstuff rich in cysteine such as poultry and wheat have been recommended.

The child is under monthly clinical review. He is scheduled to undergo six-monthly review by ophthalmologist and an MRI imaging at a later date to demonstrate recanalization of thrombosed cerebral venous sinuses. Child is asymptomatic till date.

Discussion

Incidence of childhood CSVT has been seen by deVeber et al (2001) to range between 0.4 and 0.7 per 100,000 children per year.² Our case outlines the basic management plan in CSVT.

Symptoms and signs of CSVT are non-specific and diagnosis is often delayed and may be missed altogether.³ It is recommended that CSVT should be considered in the differential diagnosis of all unexplained CNS disorders of sudden onset.⁴ Our patient's initial presentation mimicked acute gastritis.

Cerebral venous drainage occurs via superficial (cortical veins, superior sagittal sinus) and deep (internal cerebral veins, straight sinus) systems that converge at the torcula to exit via the paired transverse and sigmoid sinuses and jugular veins.⁵ The study by Teksam et al demonstrated that commonest sites of CSVT are the transverse, superior sagittal, sigmoid, and straight sinuses.⁶ Our patient had involvement of transverse and superior sagittal sinus.

Einhauptl et al strongly outlines the merits of heparin therapy in CSVT.⁷ Though use of heparin in CSVT has been questioned, consensus across published guidelines now uniformly recommends anticoagulation with unfractionated or low molecular weight heparin in most children.⁵

Homocystinuria is an inborn error of methionine metabolism. There are three major types of homocystinuria, namely:

- (a) Cystathionine β -Synthase (CBS) Deficiency (Classic Homocystinuria)
- (b) Defects in Methylcobalamin Formation. This can be of five sub-types.
- (c) Deficiency of Methylenetetrahydrofolate Reductase (MTHFR).

Classical homocystinuria is the commonest type of homocystinuria. This is an autosomal recessive condition and the gene involved is localized to 21q22.3. About 40% of affected patients respond to high doses of Vitamin B₆ and usually have milder clinical manifestations than those unresponsive to Vitamin B₆ therapy. Our patient had mental subnormality as the only feature of this condition. Mental subnormality is a common accompaniment of homocystinuria.⁸ Etiology of his hyper-pigmentation could not be ascertained. Urine for homocystinuria screening may be falsely negative if the examination is not done on a freshly voided sample because of the instability of the compound. This may explain the initial negative result of urinary screening test for homocystinuria in our patient.

Homocystinuria and iron deficiency anemia are known risk factors for CSVT.^{1,9} CSVT in our patient could have arisen from an interplay of dehydration, homocystinuria and anemia. Regular follow-up has been emphasized upon in order to detect recurrence of CSVT as well as development of other complications early.

Conflicts of interest

All authors have none to declare.

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