Case report:

1. Upshaw Schulman syndrome: A rare cause for recurrent strokes in paediatric age

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Abstract:

Introduction: The incidence of Congenital TTP (Thrombotic Thrombocytopenic Purpura) i.e. Upshaw Schulman syndrome is less than 1/1,000,000person/year.It may leadto thromboembolic phenomena which may cause end organ damage and is life threatening condition. Prothrombotic conditions remain one of the major causes for paediatric recurrent stroke.

Case Summary: A five year old male child presented with recurrent episodes of stroke, anaemia and thrombocytopenia. On analysing the clinical presentation and laboratory investigations, diagnosis of Congenital TTP was accomplished. Child responded to Plasmapheresis with improvement in chief complaint of right sided hemiparesis.

Discussion: Neurological symptoms occur in 35% of the cases of TTP. Patients with Congenital TTP remain asymptomatic until an acute precipitating event (fever, infectionsand vaccinations) occurs. The diagnosis of Congenital TTP must be considered in a child presenting with unexplained thrombocytopenia and stroke. With timely intervention and treatment, this disorder can be dealt with, as occurred in described case.

Keywords: Congenital TTP, Thrombocytopenia, Recurrent stroke

Introduction:

Thrombotic Thrombocytopenic Purpura (TTP) is a rare disease ofvariable severity with incidence of 1-8/1,000,000person/year and its congenital form-Upshaw Schulman syndrome's incidence is less than 1/1,000,000 person/year.[1]TTP occurs due to deficiency of Von Willebrand factor (vWF) cleaving protein also known as ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type1 motif, member 13) which regulate the interaction between vWF and platelets in the circulation. [2]Incidence of recurrent stroke is 2-8 per 100,000 children and causes are heart diseases, prothrombotic conditions, sickle cell disease, and vascular malformations. [3]Among causes of recurrent paediatric stroke;prothrombotic abnormalities were found in 11% cases and time of recurrence was 5 days to 18 months (median 6 months) after first stroke. [4]Due to initial subtle and nonspecific presentations, diagnosis of paediatric stroke is generally delayed.A five year old male child presented with history of recurrent episodes of stroke with thrombocytopenia. This patient had microangiopathic haemolytic anaemia, thrombocytopenia and stroke which supported the rare diagnosis of Congenital TTP - Upshaw Schulman syndrome.

Case Summary:

A three and half years old male child presented to our emergency department withacute onset, rapidly progressive right sided hemiparesis, ipsilateral upper motor neuron (UMN) facial nerve palsy, fever, anaemia (Hb –5.8g/dl) and thrombocytopenia (Platelet count – 53,000 per cu.

mm).On examination, the patient's blood pressure was 102/60 mm Hg(within normal centiles) , pulse 94 beats/min, respiratory rate 24 breaths/min, and temperature 38.0°C. Neurological examination revealed right upper limb weakness (ABR power grade 2/5), right lower limb weakness (ABR power grade 3/5) and UMN facial nerve palsy. There were no meningeal signs or cerebellar abnormalities.

The child had been admitted twice in the past at six month and one year of age with similar complaints of fever, anaemia and thrombocytopenia for which symptomatic treatment was given. In the prior admissions, as the child had bicytopenia, bone marrow aspiration and biopsy was done which revealed erythroid hyperplasia. Although Lactate dehydrogenase (1990 units/l) and Indirect Bilirubin (2.4 mg/dl) were elevated; peripheral smear was not suggestive of haemolytic anaemia. Computed Tomographic(CT) angiography showed subacute infarct in the left Middle Cerebral Arteryterritory.Clotting factors assays were normal.Further work up was done to find out the causes of stroke. It includedPT (14 seconds), INR (1), aPTT (32 seconds), Von Willebrand levels (100 IU), Immunoglobulin levels (to rule out common variable immunodeficiency),ANA (negative), anti-dsDNA (negative),Serum homocysteine levels (10 micrmoles/litre) and Haemoglobin Electrophoresis which were within normal limits. Lipid profile was deranged. Two dimensional Echocardiography was normal. Workup for Antiphospholipid Syndrome was also negative [Anti phospholipid antibodies-Negative, Anti cardiolipin antibodies-1.0(<7U/ml), Anti Beta 2 glycoprotein-0.16(<1.0)].Child improved with physiotherapy and symptomatic treatment, thusdischarged. Post-discharge asymptomaticthrombocytopenia was persistent and got admitted again at four years of age (fourth admission) with similar presentation during which, right sided weakness lasted for 2 days and improved thereafter. Carotid and Hepatoportal Doppler was normal (to rule out vasculitis).

At four and half years of age (fifth admission), child was readmittedwithacute onset bilateral loss of vision and anaemia(Hb–6.8 g/dl). Ophthalmic examination and Visual Evoked Potential (VEP) were normal. Repeat peripheral smear showed schistocytes with microangipathic haemolytic anaemia with corrected reticulocyte count of 22.64%. Hence, on analysing the clinical presentation and laboratory investigations, a diagnosis of CongenitalTTP with recurrent strokes was reached. Intravenous Methylprednisolone was started at 30 mg/kg/day initially, however as he developed hypertension, it was withheld and antihypertensivedrug started. Plasmapheresis was commencedand after two cycles the patient showed improvement. Thrombocytopenia resolved (Platelet counts – 4,53,000/mm^3), Reticulocyte count improved(3%) and LDH decreased(640 units/l).As vision improved during the hospital stay, child wasdischarged. Genetic work up for TTP could not be done due to financial constraints.

Discussion:

There are two types of TTP described in literature: Autoimmune TTP (caused by inhibitory antibodies of ADAMTS13) and Hereditary TTP (due to genetic mutations of the *ADAMTS13* gene)**.** Hereditary or Congenital TTP is much less common than the acquired form accounting for only 5% of all TTP. In 1978, Upshaw reported a female who had episodes of thrombocytopenia and microangiopathic hemolytic anemia since age 6 months which was similar to the age of presentation of our patient.[10]

During the initial two presentations (at 6 and 12 month of age) our patient had anaemia with thrombocytopenia and at third episode, he developedneurological involvement in the form of right sided hemiparesis with UMN facial nerve palsy similar to case reported by Rabkin Y et al.[5] 35% of the cases do not have neurological involvement at onsetwhich is similar to the described patient.[6] There was no renal involvement in our patient as is consistent with Congenital TTP.[6]

During the afterwards relapse, the peripheral smear revealed a microangiopathic haemolytic anaemia and on collating the clinical and laboratory picture, the diagnosis of Congenital TTPwas reached.In order of frequency, neurologic manifestationsinclude confusion, headache, altered mental state, paresis, aphasia, coma, seizures, and visual problems.[6]

TTP leads to microthrombi formation in the microvasculature of various vital organs.**[7]** It clinically presents asa pentad of fever, microangiopathichaemolytic anaemia, thrombocytopenia, neurological signs and renal impairment (proteinuria, microhaematuria). However, TTP must be considered in the presence of thrombocytopenia and microangiopathic haemolytic anaemiaalone. [8]The diagnosis of congenital TTP is confirmed by ADAMTS13 activity <5%, absence of antibody and confirmation of homozygous or compound heterozygous defects of the ADAMTS13 gene.

Relapse of TTP generally occurs early, after the first acute episode and then less frequently (months to years)which matches the pattern of described patient.[9]

Plasma exchange should be performed immediately if clinical suspicion is high.[6] Daily plasma exchange should be continued for a minimum duration of 2 days after increment of platelet counts to >1.5 lac and then stopped.[6] FFP infusion (20-30 ml/kg) may be started if there is a delay in initiation of plasma exchange or if no facility is available.

Folate supplementation was startedduring active haemolysis as per British Journal of Hematologyguidelines.[6] Platelet transfusions are contra-indicated in TTP unless there is life-threatening haemorrhage. Thromboprophylaxiswith LMWH (Low Molecular Weight Heparin) is recommended once platelet counts reached to >50× 10^9 /l as was done in our patient. Rituximab should be administered immediately after plasma exchange in order to maximize its duration of actionbut due to non-affordability the drug was not used in this patient.

Conclusion:

Upshaw Schulman Syndrome is rare but fatal disease.Increased awareness will lead to augmented frequency of diagnoses for disorders that can be simply and effectively treated. Early administration of plasmapheresis gives excellent outcome. Thus the possibility of TTP as a differential diagnosis must be considered in a child with thrombocytopenia and microangiopathichaemolytic anaemia presenting with CNS manifestations.

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