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Case Report

A case of acquired thrombotic thrombocytopenic purpura (TTP) mimicking transient ischemic attack (TIA)

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ABSTRACT

Background: TTP is a rare multisystem disease among children due to dysfunction of ADAMTS 13 enzyme in plasma causing defective vWF cleavage, thus giving rise to platelet aggregation, micro thrombi formation, platelet consumption, capillary blockage and finally organ dysfunction leading to a severe life-threatening condition with mortality around 90% if untreated. It can be congenital (5%) or acquired (95%) and Plasmapheresis works wonder for both the subtypes.

Clinical Description: Here we have described a case of acquired TTP masquerading TIA in an 8-year-old girl child who had attacks of sudden onset aphasia and upper limb weakness lasting for few hours with spontaneous recovery. On detailed examination we found pallor and few petechial spots on face and upper limbs with a peripheral blood picture suggestive of thrombocytopenia with microangiopathic hemolytic anemia but a normal renal function. We sent blood for ADAMTS 13 activity which reported a critically low level of ADAMTS 13 enzymatic activity with presence of inhibitors and absent genetic mutation.

Management: Immediate Plasmapheresis was started along with oral prednisolone therapy for a span of one month which resulted both clinical and hematological recovery. Platelet count acted as a good indicator of clinical remission.

Conclusion: A high degree of clinical suspicion is required to make a prompt diagnosis of this life threatening disease (TTP) since this carries a very high mortality rate and can mimic a more common disease HUS.

1. Introduction

Thrombotic Thrombocytopenic Purpura (TTP) is a rare life-threatening disease among children characterized by thrombocytopenia, nonimmune microangiopathic hemolytic anemia (MAHA) and reduced activity of ADAMTS 13 (a disintegrin & metalloproteinase with a thrombospondin type 1 motif member 13).[1] This current definition of TTP omitted fever, renal and neurological dysfunction from the classical pentads of TTP, which was conceptualized since TTP was considered as a separate disease from HUS (Hemolytic uremic syndrome) rather than its variation. HUS is more common in children and shares clinical criteria with TTP.[2] Since they differ significantly in terms of pathophysiology and management, exclusion of HUS is mandatory to diagnose TTP, which is done by documenting reduced ADAMTS 13 activity in blood. The absence of ADAMTS 13 activity causes inappropriate cleavage of ultra large multimers of Von Willebrand Factor (vWF) thus triggering unregulated platelet activation, aggregation, thrombi formation and blocking microvasculature causing both platelet deficiency and organ dysfunction. TTP may be Congenital or Familial due to inborn deficiency of ADAMTS 13 enzyme from genetic error causing early manifestation of TTP as happens in children or may be Acquired type where indigenous

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production of antibodies directed against ADASMTS 13 precipitates TTP which we get commonly in adults and adolescents.[3] Here we will report an 8-year-old child who presented at the neurology OPD for repeated attacks of transient weakness involving upper limbs and aphasia on several occasions with spontaneous recovery, mimicking Transient Ischemic Attack (TIA) later confirmed as a case of acquired TTP.

1.1. Clinical description

This 8 years old girl presented to us with increasing generalized weakness for last 1 month with few episodes of sudden onset weakness of upper limbs and transient aphasia, lasting for few hours. She had spontaneous recovery in less than 24 hours without any residual neurodeficit. She gradually started developing few petechial spots, predominantly involving face and upper extremities without any history of frank bleeding. No other symptom suggestive of any other systemic involvement recorded. Examination revealed presence of severe pallor, mild jaundice and few petechial spots, without fever, joint pain, and edema. Her vitals were stable with intact sensorium, normal pupillary reaction and no sign of neurodeficit. From the history we thought it could be a sickle cell anemia or any cerebral arteriopathy.

1.2. Management and outcome

Initial laboratory investigations showed anemia (Hb% 6 gm./dl), with raised RBC hemolysis indices like reticulocytosis (9.7%), elevated LDH (4321 IU/L), total bilirubin (4.2 mg/dl), peripheral blood smear showing normochromic normocytic anemia with schistiocytosis (13.6%) and fragmented RBCs, all pointing towards MAHA along with a platelet count of 27000/ cc and a normal leukocyte count. Bone marrow aspiration showed erythroid hyperplasia, megakaryocytosis and less than 2% blast cells. Apart from unconjugated hyperbilirubinemia, both liver and renal function tests were within normal range all along. To find out the cause behind hemolysis we send blood for DCT (direct comb test), C3, C4, ANA, anti DsDNA, APLA and subsequently all reports came negative. Screening for HIV, Hepatitis B and C was negative and brain imaging studies like MRI, MR Angiography and EEG all were normal.

The child deteriorated further with increasing thrombocytopenia as low as 10000 / cc though there were no bleeding episodes. Hb% level dropped to 3 mg% and one more attack of aphasia without paresis occurred during hospital stay prompted us to start empirical treatment with IvIG and Methyl prednisolone. But, as the clinical downhill course continued and consecutive two peripheral blood smears showed increasing schistocytes fraction, amounting to 20%, we decided to send blood for ADAMTS 13 activity with inhibitor study, entailing a complex method of blood collection and processing in order to put an end to the clinical quagmire and speed up diagnosis. The ADAMTS 13 activity came out to be less than 1% with presence of inhibitors, confirming the diagnosis of Acquired TTP. We immediately started Plasmapheresis on alternate day with fresh frozen plasma and daily oral prednisolone at the dose of 2 mg/kg body weight for 4 weeks. After 3 weeks of treatment, the child showed recovery with a platelet count of 1.6 lakhs/cc, Hb of 12% and no further episodes of neurodeficit attacks. She was discharged on oral prednisolone at the dose of 1 mg/kg body weight for a total period of 6 months and advised for periodic monitoring of platelet counts as it's an easy and inexpensive method to monitor disease activity. ADAMTS 13 assay being expensive and cumbersome to arrange so we couldn't perform a repeat test. However, we did a clinical exome sequencing to rule out congenital origin of the disease as all the auto immune markers were negative.

2. Discussion

Child- onset TTP (initial episode before 18 years age) is itself a very rare entity accounting only about 10% of total TTP cases with incidence of <1 case per million children per year.[4,5] The first published case of TTP in 1924 by Moschcowitz was a 16year old girl who developed sudden onset hemiparesis, fever with pallor and petechial rashes and subsequently died and her autopsy finding showed presence of disseminated hyaline thrombi in multiple organ.[6] TTP should be suspected whenever a child presents with fever and neurodeficit having blood pictures of microangiopathic haemolytic anemia and consumptive thrombocytopenia with or without renal impairment. It very closely mimics HUS but in HUS there is an invariable renal involvement and ADAMTS 13 activity is normal. Basic pathology of TTP is based on the underlying functional deficiency (activity <10%) of ADAMTS 13 enzyme which may be either congenital (resulting from biallelic mutation of ADAMTS13 gene) or acquired (having autoantibodies against ADAMTS13) associated with other autoimmune disease.[2] Brain is the commonest organ affected producing several neurological features of TTP, however heart, kidney and even gastrointestinal tract may be affected in disseminated disease.

In our case we had an 8 years old developmentally normal girl without any previous history of major illness suddenly presented with intermittent attack of aphasia, limb paresis and progressively increasing pallor & petechial spots. Suspicion of TTP aroused when we found evidence of microangiopathic haemolytic anaemia with about 13% schistocytes and reduced platelets in peripheral smears without any renal impairment and absent hypertension but having neurodeficit. HUS is the closest differential diagnosis and to establish TTP we moved further for ADAMTS 13 enzymatic activity estimation and inhibitors

study. The result showed a critically low level of ADAMTS 13 activity (< 0.2%) the reference range being 60-130% and presence of inhibitors. We also performed direct coomb's test to rule out autoimmune haemolytic anaemia and Evans syndrome (autoimmune cytopenias), bone marrow biopsy to exclude haematological malignancy and C3, C4, ANA, APLA (to rule out lupus and antiphospholipid syndrome), and all reports came negative. We also did exome sequencing to find out genetic mutation for ADAMTS 13 enzyme as congenital TTP is more common among children, but this report also came negative. So our case is an idiopathic acquired TTP which may be around 55% of total cases of acquired TTP and the rest are due to malignancy or autoimmune diseases.[6–8] The child had a good response to Plasmapheresis with both symptomatic improvement and recovery from anaemia, thrombocytopenia achieved within one month, and so we didn't use Rituximab. In a French study with a cohort of 45 children onset acquired TTP, they found that TTP is more common in girls (M: F: 1:2.5) and median age is 13 years with the lowest one at 4 months of age. 55% are idiopathic and the rest are associated with auto immune and malignant diseases.[5] The frequency of organ involvement were, Brain (64%) being the commonest organ followed by, kidney (40%) heart (7%) liver (3%). They also documented a high kidney (80%) involvement in non-idiopathic type TTP, which is identical to our case where kidney was spared and brain got maximally affected. The child is under follow-up and still under remission.

3. Conclusion

To conclude, TTP is a life threatening haematological disease with 90% mortality in the absence of Plasmapheresis. So a quick diagnosis a strong suspicion is mandatory to deal with its fatality, however the outcome is good on Plasmapheresis. Immunomodulators like Rituximab is the next line therapy if there is a relapse.

3.1. Lessons learnt

1. All microangiopathic haemolytic anaemia cases with systemic features are not HUS.
2. ADAMTS 13 activity assay differentiates HUS from TTP as both have different treatment protocol
3. Plasmapheresis is an emergency lifesaving procedure in both congenital and acquired TTP.
4. Platelets are inexpensive and surrogate markers for TTP disease status.
5. A strong clinical suspicion can detect disease mimickers.

4. Source of Funding

None.

5. Conflict of Interest

The author declares that there is no conflict of interest.

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