CASE REPORT

Hereditary Thrombotic Purpura

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Abstract

Congenital Thrombotic Thrombocytopenic Purpura (TTP) is a rare disease with diverse presentation that can also mimic Idiopathic Thrombocytopenic Purpura (ITP) and be misdiagnosed. After confirming diagnosis with ADAMTS13, it can simply be treated with FFP transfusion and complications can be prevented.We describe an eight year old girl previously managed as ITP and referred to Children Cancer Hospital for opinion. History, clinical examination and laboratory findings were not consistent with ITP. History of neonatal jaundice, microangiopathic haemolytic anaemia and thrombocytopenia favoured congenital TTP. Low ADAMTS13 level and improvement in platelet counts after FFP transfusion confirmed the diagnosis of congenital TTP. So cases with atypical presentation of ITP should be properly investigated to make correct diagnosis and avoid unnecessary exposure to drugs and their complications.

Keywords: Thrombotic Thrombocytopenic Purpura (TTP), Idiopathic Thrombocytopenic Purpura (ITP), ADAMTS13, FFP Transfusion.

Introduction

Thrombotic thrombocytopenic purpura (TTP), congenital or acquired, is characterized by microangiopathic haemolytic anaemia, thrombocytopenia with fever, renal failure and neurological deficits. Until recently, the pathophysiology of TTP was largely unknown. But now Ultralarge von Willebrand factor (ULVWF) multimers are considered as causation of TTP by promoting uncontrolled platelet agglutination and thrombosis. Congenital TTP is associated with a deficiency in a plasma metalloprotease, ADAMTS 13, that cleaves a specific peptide bond in the von Willebrand factor (VWF) subunit, thereby decreasing the size of VWF multimers. Acquired TTP, seen more often in adolescents and adults, is associated with auto-antibodies neutralizing the metalloprotease.[1,2]

We present a report of a child with congenital TTP that initially presented with a misdiagnosis of ITP. The purpose of this case report is to spread awareness amongst paediatricians regarding this rare syndrome which can be treated simply and effectively but also be fatal if left untreated.

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Case Report

An 8-year-old girl, diagnosed with idiopathic thrombocytopenic purpura (ITP) elsewhere was referred to the Children Cancer Hospital (CCH), Karachi, for an opinion of splenectomy. She presented with reported petachiae and pallor for the past 6 years.

History revealed that the patient had severe neonatal jaundice for which she had exchange transfusion and was discharged without confirmatory diagnosis. She was also deaf and dumb most likely due to complicated jaundice. Family history was significant with consanguineous marriage, one abortion and death of a sibling at 3years of age due to jaundice and low platelet count without any definitive diagnosis.

The child had been on steroids since one and a half years of age for five years and then switched to azathioprine for the last one and a half years. During the past six and a half years, she had episodes of pallor and petechiae and received packed cell transfusion twice with no platelet transfusion.

On presentation, she had normal vital parameters with no positive systemic findings except some bruises. Her previous investigations revealed thrombocytopenia, schistocytic anaemia with fragmented RBCs on peripheral smear and reticulocytosis. Renal function tests, haemoglobin electrophoresis, Coomb's and osmotic fragility tests done in the past were normal.

We re-investigated the child as clinical scenario and previous investigations were not favouring ITP. All medications were stopped. Investigations at CCH revealed haemoglobin of 7.7g/dl, total leucocytes count of 3,300/cumm, platelet count of 20,000/cumm, 14% corrected reticulocyte count and peripheral blood smear (PBS) suggestive of microangiopathic haemolytic anaemia with schistocytes and thrombocytopenia. Urine microscopic examination revealed haemoglobinuria. Liver function test (LFT) showed un-conjugated bilirubinaemia (bilirubin 5.4 mg/dl, un-conjugated

1.2mg/dl) with normal protein and enzyme levels. Prothrombin time and activated partial thromboplastin time were normal. The renal function and serum electrolytes were normal. The lactate dehydrogenase (LDH) level was elevated to 1014U/L and direct coombs test (DAT) was repeated and again negative. Her bone marrow showed erythroid hyperplasia and increased megakaryocytes.

The clinical and laboratory evidences were not consistent with ITP, rather suggestive of congenital TTP. So ADAMTS13 level sent. Low ADAMTS13 level and improvement in platelet counts from 12,000/cumm to 334,000/cumm after FFP transfusion confirmed the diagnosis of congenital TTP.

Discussion

The purpose of this case report is to increase awareness amongst paediatricians regarding this rare syndrome which has a simple and effective treatment. In neonates, clinicians can suspect congenital TTP with jaundice, haemolytic anaemia and thrombocytopenia. In children, Congenital TTP can be suspected with unexplained repeated episodes of thrombocytopenia and with a picture of TTP since acquired TTP is rare in children.[3]

Thrombotic Thrombocytopenic Purpura (TTP) is a rare life threatening disease with an estimated incidence of 2-10 cases/million/year in all racial groups. TTP classically consists of pentad of fever, microangiopathic haemolytic anaemia, thrombocytopenia, and variable renal and neurologic dysfunction. But majority lack this classical presentation.[1,2] The revised diagnostic criteria include thrombocytopenia and microangiopathic haemolytic anaemia along with raised LDH and negative coombs test.[3,4] TTP is less common in children and frequent in women in their 3rd or 4th decade.[1]

There are two forms of TTP; acquired and inherited. Inherited TTP, initially reported by Schulman et al in 1960 and Upshaw in 1978, is also known as Congenital TTP or Upshaw-Schulman syndrome and is less common than the acquired form.[1,5] Over 100 cases of congenital TTP have been reported worldwide but this is underestimated due to varied presentation.[3] TTP is an autosomal recessive disease.[2,6]

In the last decade it has been recognized that TTP is due to a deficiency of von Willebrand factor (VWF) cleaving protease, ADAMTS13, (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) resulting in ultra-large multimers of VWF (ULVWF).[3,4] In physiological states, ULVWF released by the endothelium induce platelet aggregation in areas of high shear stress, but this only occurs briefly as VWF is rapidly broken down by ADAMTS-13.[1] In the absence of ADAMTS13, ULVWF are not cleaved appropriately, and cause spontaneous platelet aggregates in the microvasculature of the brain, heart and kidneys.[3] Thrombocytopenia results from consumption of platelets in the thrombotic process, while erythrocyte fragmentation and haemolysis are believed to result from mechanical injury induced by abnormally high shear stress in the microvasculature.[3,7]

ADAMTS13 gene is located on chromosome 9q34.[5] It is derived primarily from the stellate cells of the liver and its elimination half-life is 1-2 days.[6] Auto antibodies against ADAMTS13 in acquired TTP and mutations in ADAMTS 13 gene in congenital TTP cause its deficiency.[2,6] More than 90 different ADAMTS13 mutations have been identified.[2,7]

Congenital TTP has variable presentations. It usually manifests as neonatal jaundice secondary to haemolytic anaemia along with thrombocytopenia[1,3] and may be discharged without a correct diagnosis as occurred in our case.[6] It may present as recurrent episodes of thrombocytopenia and may be misdiagnosed as idiopathic thrombocytopenic purpura similar to our case.[3,7,8] Some cases of congenital TTP may be first diagnosed in adulthood usually during pregnancy.[1,3,8] Patients may also be asymptomatic and are detected because they have affected siblings making testing of the asymptomatic sibling and first degree relative at risk to be important.[3,7]

Diagnosis of inherited TTP can be confirmed by ADAMTS13 levels <10% of normal control which is available in Pakistan.[1,6,7]

Plasma exchange with fresh frozen plasma is a first-line treatment for TTP and this has decreased the mortality in TTP to 10%.[1,5] But regular plasma infusions have logistical problems and potential risks that may be minimized by future availability of recombinant ADAMTS13.[8] Many patients of hereditary TTP require regular plasma infusion every 2-4 weeks to prevent serious complications.[6] These patients should be regularly assessed for renal or neurologic abnormalities that could develop later due to microvascular thrombosis.[4]

Conclusion

Atypical presentation of ITP should always be investigated thoroughly as congenital TTP can mimic ITP. Thus, proper

diagnosis is essential for optimal treatment and prevention of its late complications.

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ERRATA

In the Case Report Titled: **"Use of vascularised free fibula in limb reconstruction (for non-malignant defects)"** which appeared on pages 1549-1554 of December 2013 issue (Volume 63), the acknowledgmenet was inadvertently left out.
The acknowledgement should be included as:

Acknowledgement
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The Journal regrets the error.