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Novel homozygous ADAMTS13 mutation with neonatal presentation of congenital thrombotic thrombocytopenic purpura in two Indian origin babies

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1. Introduction

Upshaw Schulman syndrome is the congenital form of thrombotic thrombocytopenic purpura (TTP) caused by a deficiency of ADAMTS13, a circulating zinc metalloprotease that cleaves multimers of von Willebrand factor (vWF) and thereby keeps a check on unregulated thrombus formation [1,2]. Decreased activity of the vWF-cleaving protease, ADAMTS13, results in abnormally high concentrations of ultra large von Willebrand factor (UL-vWF) molecules [3,4]. The uncleaved UL-vWF leads to inappropriate platelet activation and formation of platelet thrombi. Occlusive platelet thrombi cause mechanical damage to red cells resulting in a microangiopathic haemolytic anemia [5]. Congenital TTP is a result of a genetic mutation in the ADAMTS13 gene on chromosome 9. Inheritance is autosomal recessive, and homozygous or compound heterozygous genotypes are required to produce the clinical phenotype [5]. Neonatal presentation of congenital TTP is an established entity and may be fatal unless recognised promptly and treated appropriately [6]. There are limited reports of congenital TTP in children of Indian origin [7,8]. We report two cases of congenital TTP in Indian origin families with neonatal presentation, both carrying novel mutations of ADAMTS13.

2. Case report

2.1. Case 1

A preterm baby girl was delivered at 28 + 4 weeks of gestation via emergency Caesarean section for foetal distress. Her both parents are south Indian, Tamil in origin from the state of Tamilnadu and second degree consanguineous. Complete blood count at birth revealed anaemia (Hb-11.6g/dL), reticulocyte count of 19.0% and thrombocytopenia of 23 × 109/L. Peripheral blood film showed normochromic macrocytic red blood cells with few fragmented cells. Direct agglutination test was negative. Child was treated for presumed sepsis with antibiotics, platelets, red cells and fresh frozen plasma (FFP) with improvement of haematological parameters and normalization of platelet count. However on follow up persistent mild macrocytic anaemia and thrombocytopenia was observed. She developed urinary infection at 2 yrs of age and worsening bicytopaenia with haemoglobin of 6.6g/dL, elevated reticulocyte count of 13.4%, as well as thrombocytopenia with platelet count of 14 × 10^9/L. Peripheral blood film showed evidence of microangiopathic haemolysis with red blood cell fragmentation and reticulocytosis, as well as thrombocytopenia (Image 1). Bone marrow aspiration was done to exclude inherited bone marrow failure syndromes and it showed erythroid hyperplasia (Image 2). Congenital TTP was suspected and her ADAMTS-13 activity level was found to be 1.2% only. Direct DNA sequencing of 29 Exons of ADAMTS13 gene showed a novel homozygous mutation in Exon 14 (c.1639_1640delGT), that causes a frameshift with a premature termination of the protein (p.V547Vfs66×). Her parents were both heterozygous for the same ADAMTS13 mutation. She continues to be on treatment with FFP 15 ml/kg every 2–3 weeks. Presently, she is 6 years old and does not have any renal or neurological complications. Her haematological parameters are also stable.

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2.2. Case 2

A term baby boy, second child of non-consanguineous Indian parents from the state of Uttarpradesh developed haemolytic jaundice at 18 hours of life. The serum bilirubin value was 22.3 mg/dl (unconjugated - 21 mg/dl). There was a previous history of neonatal loss due to intracranial hemorrhage and multi-organ failure with deranged coagulation in the first week of life. Haemoglobin was 12.8 g/dl, reticulocyte count was 8.63%, Lactate dehydrogenase (LDH) was elevated, renal function was normal. G6PD estimation was normal (12.5 units/gm of Hb). Peripheral smear showed 24% schistocytes. Double volume exchange transfusion twice followed by intensive phototherapy was done. The initial platelet count was normal, but dropped to 10×10^9/L. With the clinical picture and laboratory findings a provisional diagnosis of congenital TTP was made and baby was transfused fresh frozen plasma following which jaundice subsided. LDH, platelet count and haemoglobin normalized and schistocytes in peripheral smear was reduced to 2.3%. Direct DNA sequencing of the gene for ADAMTS13 was carried out using Sanger sequencing. Results showed a novel homozygous missense mutation in exon 16 of the ADAMTS13 gene; c.1921G > A; p.Glu641Lys; resulting in substitution of lysine for Glutamic acid at codon 641. The parents were also tested and found to be heterozygous for the mutation. Presently, the child is 9 months old and receives FFP transfusion every 4 weeks. The child has stable haematological parameters and no renal or neurological complications.

3. Discussion

Upshaw Schulman syndrome was originally described separately by Upshaw in 1960 and Schulman in 1978 [9,10]. A landmark study by Moake et al., in 1982 identified unusually large multimers in patients with congenital TTP and predicted the absence of a factor required for the normal processing of VWF [11]. This factor was identified as ADAMTS13 in 2001 [12]. ADAMTS13 gene is a member of the ADAMTS family (a disintegrin-like metalloprotease with thrombospondin type 1 motif) which encodes for a plasma zinc metalloprotease responsible for the cleavage of von Willebrand factor (VWF). This is a large gene with 39 exons and multiple domains which encodes for a protein with 1427 amino acids. Till submission of this article 166 mutations in the ADAMTS13 gene have been reported [13,14]. Mutations are spread throughout the gene. Mutations resulting in absence of ADAMTS13 are likely lethal but no clear genotype-phenotype correlation has been established in patients with homozygous defects. The clinical presentation of congenital TTP is variable. The age of onset is usually at birth or during the neonatal period, but it can also be during infancy or childhood [4]. Even first clinical presentation in adult life with TTP or haemolytic uraemic syndrome (HUS) is well recognised. The clinical severity of disease episodes span from asymptomatic episodes of thrombocytopenia and anaemia to life-threatening multi-organ failure [13]. The organ involved depends on the location of microvascular thrombi. Renal and central nervous system involvements are the usual organs involved in congenital TTP patients. Timely diagnosis of congenital TTP is important, as it is a life-threatening but treatable disease. Patients usually respond to relatively small amounts of plasma (10–15ml/kg), which is sufficient to provide the increase in plasma ADAMTS13 activity to induce remission [15]. Normalization of LDH and platelet count are useful markers of efficacy of plasma which is necessary every 2–4 weeks for life. Intermediate purity factor 8 has been successfully used as prophylaxis in congenital TTP [16]. A recent phase 1 study of recombinant ADAMTS 13 was proven to be safe and effective [17]. Both cases described above had a neonatal presentation and high index of clinical suspicion, careful examination of the blood film was the key to accurate and early diagnosis in both cases.

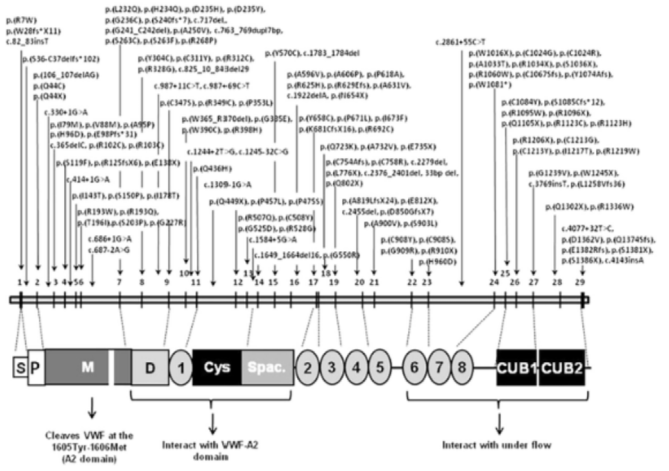

Fig. 1. *ADAMTS13* mutation responsible for congenital TTP. the upper part of the panel shows the *ADAMTS13* structure, with shaded bars representing exons 1–29. The lower panel represnets the *ADAMTS13* protien with its domains S, signal peptide; P, propeptide; M, metalloprotease; D, disintegrin domain; 1, first thrombospondin type 1(TSPI) repeat; Cys, cysteine Rich domain; Spac, spaxer domain; 2 through 8, the secound to eight TSPI repeats. The metalloprotease domain is the catalytic center that cleaves VWF at the 1605Tyr-1606Met peptide bond in the A2 domain. The proximal carboxyl-terminal domains from Dis to Spa intract with the A2 domain of VWF. more distal carboxyl-terminal domains (TSPI 2–8) interact with VWF under fluid shear stress.
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The rarity of congenital TTP combined with the similarity of its clinical picture to neonatal sepsis possibly accounts for under diagnosis and paucity of reports from Indian origin patients. The novel mutations identified add to the existing database of known genotypic mutations described in congenital TTP. However the long term prognosis of both children are guarded due to the possible complications of regular plasma infusions. Availability of a safe and affordable recombinant ADAMTS 13 will be extremely important for the long term survival of this group of children(see Fig. 1).

Declaration of patient consent

The authors certify that they have obtained appropriate parental consent for publication of clinical data and hematology slides of the children.

Conflicts of interest

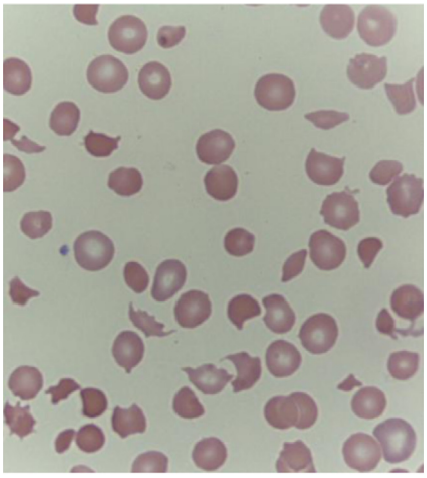
The authors have no conflicts of interest to report.

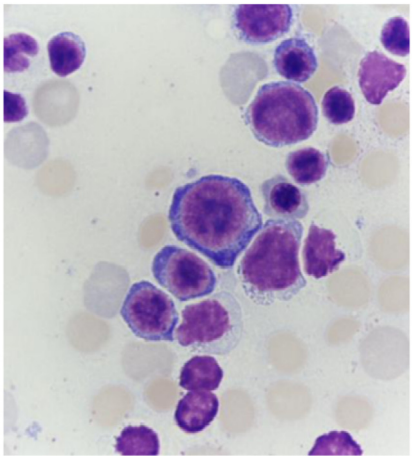
Contributors

All authors contributed to patient management and writing of the report.

Source of funding

Nil.





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