

Novel mutation of Upshaw-Schulman syndrome associated with coarctation of aorta in Palestinian child

Mahdi Zaid¹, Sultan Musleh², Tahani Sarrawi², Maysa Alawneh¹, Reem Sawafta¹, Honood AbuRas³

¹Department of Paediatrics, An-Najah National University Hospital, Nablus, Palestine

²Department of Paediatric Haematology-Oncology, An-Najah National University Hospital, Nablus, Palestine

³Department of Histopathology, An-Najah National University Hospital, Nablus, Palestine



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Received: 2020-03-08

Accepted: 2020-03-15

UDC: 616.1

J Clin Med Kaz 2020; 1(55):27-31

Corresponding Author: Mahdi Mohammed Zaid, Department of Paediatrics, Pediatric Resident MD, An-Najah National University Hospital, Palestine. Tel.: 00972568210002

Email: Dr.mahdiz@yahoo.com

Abstract

Upshaw-Schulman syndrome is a rare inherited form of thrombotic thrombocytopenic purpura disease caused by deficiency of ADAMTS13 and reversible by fresh frozen plasma infusions. Unlike the more common acquired thrombotic thrombocytopenic purpura, patient with Upshaw-Schulman syndrome generally presents early life with a repeated episodes of microangiopathic haemolytic anaemia, usually triggered by acute illness. There are few reported cases about congenital thrombotic thrombocytopenic purpura and long term prognosis.

We describe a 16 months old Palestinian male patient with history of severe neonatal jaundice, microangiopathic haemolytic anaemia and thrombocytopenia triggered by febrile illness associated with facial palsy as neurological manifestation favoured congenital thrombotic thrombocytopenic purpura. Low ADAMTS13 level and improvement in platelet counts after fresh frozen plasma infusion with novel mutation of Leu209Pro in exon 6 of the ADAMTS13 gene confirmed the diagnosis of congenital thrombotic thrombocytopenic purpura in our patient who later on developed coarctation of aorta suggested thrombotic complication of ADAMTS13/VWF missing axis dysfunction.

Key words: Upshaw-Schulman syndrome (USS), congenital thrombotic thrombocytopenic purpura (TTP)

ПАЛЕСТИНАЛЫҚ БАЛАДАҒЫ ҚОЛҚА ТАРЫЛУЫМЕН БАЙЛАНЫСТЫ АПШОУ-ШУЛЬМАН СИНДРОМЫНЫҢ ЖАҢА МУТАЦИЯСЫ

М. Зайд¹, С. Муслех², Т. Саррауи², М. Алауних¹, Р. Сауафта¹, Х. АбуРас³

¹Педиатрия бөлімі, Ан-Наджа Ұлттық Университеттік ауруханасы, Наблус, Палестина

²Педиатриялық гематология және онкология бөлімшесі, Ан-Наджа Ұлттық Университеттік ауруханасы, Наблус, Палестина

³Гистопатология бөлімі, Ан-Наджа Ұлттық Университеттік ауруханасы, Наблус, Палестина

ТҰЖЫРЫМДАМА

Апшоу-Шульман синдромы - ADAMTS13 жетіспеушілігінен туындаған және жаңа мұздатылған плазманың инфузиясы арқылы қайтымды болатын тромботикалық тромбоцитопениялық пурпураның сирек кездесетін тұқым қуалайтын түрі. Жиі кездесетін тромботикалық тромбоцитопениялық пурпурадан айырмашылығы, Апшоу-Шульман синдромы бар науқастың балалық шағында әдетте өткір аурудан туындаған микроангиопатиялық гемолитикалық анемия жиі кездеседі. Туа біткен тромботикалық тромбоцитопениялық пурпураның және ұзақ мерзімді болжамның бірнеше тіркелген жағдайлары бар.

Бұл зерттеуде ауыр неонатальды сарғаю, туа біткен тромботикалық тромбоцитопениялық пурпураға тән неврологиялық көрінісі ретінде бет парализімен байланысты фебрильді аурудан туындаған микроангиопатиялық гемолитикалық анемиямен және тромбоцитопениямен ауыратын 16 айлық палестиналық баланың жағдайы сипатталады.

ADAMTS13 деңгейінің төмендігі және ADAMTS13 6 генінің экзонда Leu209Pro жаңа мутациясымен жаңа мұздатылған плазманы инфузиялағаннан кейін тромбоциттер санының жақсаруы біздің науқаста туа біткен тромботикалық тромбоцитопениялық пурпураның диагнозын растады, ол науқаста кейінірек қолқа тарылуы анықталды, болжам бойынша жоқ ADAMTS13/VWF осьтік дисфункциясының тромботикалық асқынуы болуы мүмкін.

Негізгі сөздер: Апшоу-Шульман синдромы, туа біткен тромботикалық тромбоцитопениялық пурпура, жаңа мутация, ADAMTS13, фон Виллебранд факторы, қолқа тарылуы

НОВАЯ МУТАЦИЯ СИНДРОМА АПШОУ-ШУЛЬМАН, СВЯЗАННАЯ С КОАРКТАЦИЕЙ АОРТЫ У ПАЛЕСТИНСКОГО РЕБЕНКА

М. Заид¹, С. Муслех², Т. Саррауи², М. Алауних¹, Р. Сауафта¹, Х. АбуРас³

¹Отделение педиатрии, Национальная университетская больница Ан-Наджа, Наблус, Палестина

²Отделение педиатрической гематологии и онкологии, Национальная университетская больница Ан-Наджа, Наблус, Палестина

³Отделение гистопатологии, Национальная университетская больница Ан-Наджа, Наблус, Палестина

РЕЗЮМЕ

Синдром Апшоу-Шульмана является редкой наследственной формой тромботической тромбоцитопенической пурпуры, вызванной дефицитом ADAMTS13 и обратимой с помощью инфузий свежезамороженной плазмы. В отличие от более распространенной приобретенной тромботической тромбоцитопенической пурпуры, пациент с синдромом Апшоу-Шульмана обычно в детстве имеет частые эпизоды микроангиопатической гемолитической анемии, обычно вызванной острым заболеванием. Есть несколько зарегистрированных случаев врожденной тромботической тромбоцитопенической пурпуры и отдаленного прогноза.

В настоящем исследовании описывается случай пациента, 16-месячного палестинского мальчика с тяжелой неонатальной желтухой в анамнезе, микроангиопатической гемолитической анемией и тромбоцитопенией, вызванной фебрильной болезнью, связанной с параличом лица, как неврологическим проявлением, характерным врожденной тромботической тромбоцитопенической пурпуры. Низкий уровень ADAMTS13 и улучшение количества тромбоцитов после инфузии свежезамороженной плазмы с новой мутацией Leu209Pro в экзоне 6 гена ADAMTS13 подтвердили диагноз врожденной тромботической тромбоцитопенической пурпуры у нашего пациента, у которого позднее выявилась коарктация аорты, предположительно тромботическое осложнение отсутствующей осевой дисфункции ADAMTS13/VWF.

Ключевые слова: Синдром Апшоу-Шульмана, врожденная тромботическая тромбоцитопеническая пурпура, новая мутация, ADAMTS13, фактор фон Виллебранда, коарктация аорты

Introduction

Upshaw-Schulman syndrome (USS) or Congenital thrombotic thrombocytopenic purpura (TTP) is a rare life-threatening recessively inherited disease characterized by thrombocytopenia, microangiopathic haemolytic anaemia, microvascular thrombosis and ischemic damage of multiple organs with end stage renal failure or neurological sequelae in the absence of appropriate treatment. It can be congenital or acquired; Congenital TTP is associated with a genetic mutation in ADAMTS13, which cuts von Willebrand factor into smaller pieces, thereby formation of unnecessary blood clots. Acquired TTP, seen more often in older age secondary to anti-ADAMTS13 autoantibodies [1,2]. Congenital TTP is a rare genetic disorder with an estimated incidence of 4-10 cases per million/year [3]. Diagnosis can be suggested by the normalization of platelet count after fresh frozen plasma infusion, which may have a dual therapeutic and diagnostic advantage [4].

Case report

We report a 16 months old Palestinian male patient, full term with uncomplicated pregnancy, weighted 3100 gm at birth. Patient was admitted at NICU with severe indirect hyperbilirubinemia developed during first 24 h of life, associated with fever, cyanosis and tachycardia. Therefore, urgent blood exchange transfusion was done and patient improved. Both maternal and infant's blood groups were A+ with negative Coombs test. G6PD enzyme assay level was normal. During infancy, patient was in a good health condition except for a two episodes of mild febrile illness associated with hypoactivity, decrease feeding and occasional isolated low platelets counts, ranges between 50-150 X 10⁹ (Normal 135-465 X 10⁹/L).

At age of 16 months, patient presented with high grade fever and sudden onset right sided facial palsy associated with severe thrombocytopenia, platelet counts 34x 10⁹/L. So, he referred to our Paediatric Haematology and Oncology Department for further evaluation and management.

At presentation, patient was irritable, pale with loss of forehead wrinkling, inability to close eyes and absent naso-labial fold on right side. No palpable lymph nodes or hepatosplenomegaly.

Initial laboratory evaluation revealed isolated thrombocytopenia, Platelets count 25 X10⁹, Reticulocytic count 7.5%, negative direct Coomb's test, Haptoglobin 0mg/dL (normal, 22-164), lactate dehydrogenase (LDH) level 1417U/L (normal = 180-430 U/L), Peripheral smear showed numerous schistocytes and helmet cells with few nucleated red cells.

Bone marrow biopsy and aspirate showed hypercellularity with increase erythroid precursors and adequate megakaryocytes in keeping with peripheral consumption. Blood cultures revealed no growth. Other labs as renal function tests, coagulation profiles, antinuclear antibodies (ANA), iron profiles, immunoglobulins levels and Haemoglobin electrophoresis all were all within normal.

Brain MRI and MR angiography were done to rule out upper motor neuron lesion as CNS tumour, thrombosis or focal lesions which causing this facial palsy, which showed few small acute lacunar infarcts seen scattered in both cerebral hemispheres (cortical, white matter and right basal ganglia) in addition to abnormal bilateral cerebral white matter signal intensities (Figure 1). CSF glucose, protein WBC, culture and PCR for Herpes simplex I and II were within normal.

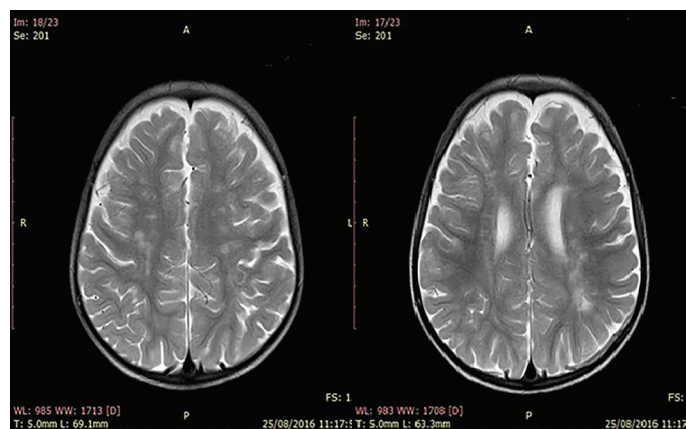


Figure 1 - Small acute lacunar infarcts seen scattered in both cerebral hemispheres (cortical, white matter and right basal ganglia) in addition to abnormal bilateral cerebral white matter signal intensities.

The diagnosis of thrombotic thrombocytopenic purpura (TTP) was made based on clinical presentation, laboratory findings and neurological sequel (facial palsy). Therefore, plasma infusion in addition to 3 sessions of plasma exchange was done. So ADAMTS13 activity assay sent and showed low ADAMTS13 level without ADAMTS13 antibodies. Genetic study for ADAMTS13 gene mutation was sent for confirmation. Platelet counts started to increase gradually with rapid improvement of facial palsy till it recovered completely.

After one month with regular plasma exchange every

two weeks, genetic test result confirmed the diagnosis of congenital Thrombocytopenic Purpura showing homogeneous ADAMTS13 gene mutation of Leu209Pro at exon 6, which was not documented before.

Patient was kept on regular plasma transfusion every 2 weeks till age of 31 months, by this time when he presented for routine plasma transfusion, he was drowsy and hypoactive. His vital signs showed high blood pressure reading in the arms with low blood pressure in the lower extremities, (right arm 150/91 mmHg, left arm 155/94 mmHg, right leg 97/71 mmHg, and left leg 95/68 mmHg).

Urgent echocardiogram was done that showed narrowed segment of the aortic arch and descending aorta with near occlusion of the distal part. So patient underwent aorta resection and end to end anastomosis.

Discussion

Upshaw-Schulman Syndrome (USS) is a synonym for Congenital thrombotic thrombocytopenic purpura (CTTP), was first described in 1960 by Schulman et al in an 8-year-old girl born in Germany with bleeding tendency, recurrent thrombocytopenia and microangiopathic haemolytic anaemia (MAHA), but without specific clotting factor abnormalities. The episodes were transiently but dramatically corrected by the infusion of fresh frozen plasma (FFP). Therefore, the authors expected a congenital deficiency of a plasma platelet-stimulating factor [5]. In 1978, Jefferson D. Upshaw described a 29-year-old woman who had a history of recurrent bleeding episodes from the age of 6 months to 12 years, characterized by thrombocytopenia and MAHA, similar to Schulman's case [6]. Furthermore, they submitted the appellation of Upshaw-Schulman syndrome (USS) for such cases.

USS is a rare life-threatening disease which inherited through an autosomal recessive pattern. It is caused by mutations in the gene encoding ADAMTS13 on chromosome 9q34, and to date, there have been many distinct reported mutations spreading all over the ADAMTS13 gene [7]. The most commonly reported mutation of ADAMTS13 is c.4143dupA (p.Glu1382Argfs) mostly in Northern and Central European countries [8,9]. In this Palestinian case, we found homogeneous mutation of Leu209Pro in exon 6 of the ADAMTS13 gene, which is unreported before.

ADAMTS13 enzyme, which is synthesised mainly in the liver and vascular endothelium, plays an important role in haemostasis by regulating the size of von Willebrand factor (VWF) that is produced in endothelial cells and megakaryocytes [10]. ADAMTS13 cleaves hyperactive ultra-large von Willebrand factor (ULVWF) multimers into smaller and less active multimers [11]. ADAMTS13 deficiency is prothrombotic, where excessive amounts of ULVWFs result in platelet aggregation by binding circulating platelets spontaneously and causing systemic microvascular platelet thrombi that induce embolic ischemic damage to end organs as brain, heart and kidney, which defining TTP [12]. But this alone is unable to precipitate acute symptoms. Thus, usually prompted by stress-inducing triggers that required to activate the endothelium and release von Willebrand factor (e.g. hyperbilirubinemia, infection, trauma or pregnancy) [13].

The most common presentation of USS is the neonatal onset of severe hyperbilirubinemia requiring an exchange blood transfusion with negative Coombs test and thrombocytopenia, haemolytic anaemia and the presence of schizocytes on the peripheral smear. Repeated episodes of thrombocytopenia occur in 80% of patients that reversed by FFP infusion [14-16]. The classical pentad of fever, MAHA, thrombocytopenia, neurological and renal abnormalities is found in up to 9% of

cases [17].

TTP crises can be associated with progressive renal deterioration in approximately 50% of cases, where 20% of them deteriorated to chronic or end-stage renal disease. Cerebral vascular accidents progressed in about one third of patients, with a risk of neurologic sequelae in approximately 20% of patients [18,19]. In our case, patient had bell's palsy at time of diagnosis, which resolved gradually after two sessions of plasma exchange. It is unknown whether this is due to episodes that affect the central nervous system in the neonatal period with severe hyperbilirubinemia, or on top of repeated but less severe episodes subsequently.

It is unknown whether neurological, renal, cardiac, cognitive, or vascular complications can be prevented by prophylactic plasma therapy [20]. In this case, after one year of diagnosis with regular plasma transfusion every 2 weeks, patient accidentally noticed to have high blood pressure that was found later due to narrowed segment of the aortic arch and near occlusion at distal part of descending aorta, so patient underwent urgent repair by coarctation of aorta resection and creation of end to end anastomosis.

There are two possible explanations for this vascular complication. First, it could be an accidental combination and the systemic deficiency of ADAMTS13 has no impact on developing coarctation of aorta. Second, ADAMTS13 and VWF play an opposite role in thrombosis and systemic inflammation [21]. ADAMTS13 deficiency lead to an increase in leukocyte adhesion and extravasation under acute inflammatory conditions [21,22]. It also results in an accumulation of ultra large VWF multimers on endothelial cell surfaces and in plasma, which enhances both platelet aggregation and systemic inflammation. This hypothesis is based on a number of published studies showing the accumulation of ULVWF strings on endothelial cells upon injury in Adamts13^{-/-} mice mainly in the regions of disturbed blood flow, which are highly prone to atherosclerotic lesion development as carotid sinus, aorta and aortic sinus [21-26].

TTP is considered a medical emergency, so plasma therapy (plasma exchange or plasma infusion) should be obtained immediately if we suspect TTP. The correction of thrombocytopenia by plasma therapy has a dual diagnostic and therapeutic action in TTP. ADAMTS13 activity provides valuable information contributing to the diagnosis of TTP. Severe deficiency in ADAMTS13 considered if it less than 10%, which is highly indicative of congenital thrombotic thrombocytopenic purpura (TTP) in an appropriate clinical setting [27]. Not all patients with a clinical diagnosis of thrombotic thrombocytopenic purpura (TTP) have severe ADAMTS13 deficiency, other non-TTP conditions might have mild to moderate ADAMTS13 deficiency ($\leq 10\%$). These conditions include haemolytic uremic syndrome, disseminated intravascular coagulation, sepsis, pregnancy, liver diseases or certain medications. Therefore, TTP remains a clinical diagnosis and should be confirmed by detection of a homozygous or compound heterozygous mutation upon sequencing of ADAMTS13 gene on chromosome 9q34 to prove hereditary form and exclude acquired TTP and other non-TTP conditions having ADAMTS13 activity deficiency [28-31].

Nowadays, plasma therapy (plasma exchange or plasma infusion) alone, is the mainstay of treatment and prevention of acute episodes of USS. Although ADAMTS13 has a half-life of only 2–3 days, plasma infusions (10-15mg/kg) every 2–3 weeks are sufficient to prevent relapse episodes of the disease and maintain normal platelets count. Approximately 50% of USS patients exhibit relapses especially with neonatal onset

that clearly requires regular prophylaxis and close observation after stress situations (e.g. infection, vaccination, trauma and pregnancy) [32].

Rituximab administration showed by several reports a favourable outcomes in prevent relapse of TTP among more than 90% of patients with relapsed or refractory TTP by depleting anti-ADAMTS13 antibodies [33,34].

Nowadays, Recombinant ADAMTS13 replacement instead of plasma infusion in the treatment and prophylaxis is a clinical trial which can be applied in near future, this can minimize the potential risks of recurrent plasma infusions as infections, circulatory overload and anaphylactic reactions [35].

Conclusion

USS is a rare congenital TTP diagnosis based on the clinical presentations and confirmed by genetic finding. An ADAMTS13 gene mutation of Leu209Pro at exon 6 is novel one that was not reported before, and this is the first reported case that showed the association with coarctation of aorta.

Disclosures: There is no conflict of interest for all authors.

Patient informed consent: obtained.

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How to cite this article: Mahdi Zaid, Sultan Musleh, Tahani Sarrawi, Maysa Alawneh, Reem Sawafta, Honood AbuRas. Novel mutation of Upshaw-Schulman syndrome associated with coarctation of aorta in Palestinian child. *J Clin Med Kaz*. 2020; 1(55):27-31