Inherited thrombotic thrombocytopenic purpura in pregnancy

Krzysztof Drews 1, Agnieszka Seremak-Mrozikiewicz 1, Sławomir Sobieszczyk 2, Magdalena Barlik 1

1 Department of Perinatology and Women's Diseases, Poznan University of Medical Sciences, Poland
2 NZOZ Solumed, Poznan, Poland

Correspondence to: Magdalena Barlik
Department of Perinatology and Women's Diseases
University of Medical Sciences
ul. Polna 33, 60-535 Poznań, Poland.
tel: +48 618419613; fax: +48 0618474651; e-mail: magda.barlik@op.pl

Submitted: 2013-05-13 Accepted: 2013-07-18 Published online: 2013-11-25

Key words: thrombotic thrombocytopenic purpura; Upschaw-Schulman Syndrome; pregnancy

Abstract

OBJECTIVE: The primary pathologic reason for thrombotic thrombocytopenic purpura (TTP) lies in the systemic formation of platelet aggregations in association with endothelial cells damage. Endothelial damage is a result of an abnormal synthesis and metabolism of unusually large von Willebrand Factor (ULvWF) multimers. In normal conditions vWF cleaving metalloprotease, known as ADAMTS-13 (A Disintegrin And Metalloproteinase with Thrombospondin type-1 motif, member 13) prevents the ULvWF entrance in the circulation. It already has been proven that thrombotic thrombocytopenic purpura is strongly correlated with severe congenital or acquired deficiency of ADAMTS-13. Congenital ADAMTS-13 deficiency is known as Upshaw-Schulman Syndrome and it accounts for only 2–4% of all TTP cases. It is conditioned by genetic variants of the ADAMTS-13 gene causing reduced ADAMTS-13 synthesis and shows an autosomal recessive type of inheritance. CASE PRESENTATION: We present an interesting case of a 20 year old patient, primigravida, nulliparous, in 28th gestational week of twin pregnancy with undiagnosed Upshaw-Schulman Syndrome. The patient was transferred from the district hospital to the Tertiary Perinatal Care Center because of thrombocytopenia and suspicion of hemolytic-uremic syndrome. Genetic analysis performed 5 years after patient's death (before 2008 that kind of genetic analysis had not been available in Poland) showed a homozygotic mutation in the ADAMTS13 gene (4143insA) which confirmed the diagnosis of Upshaw-Schulman Syndrome. CONCLUSIONS: 1. TTP, especially hereditary Upshaw-Schulman Syndrome, is extremely rare and complicates the course of pregnancy. It is usually very sudden and dramatic; 2. Differential diagnosis of this disease is difficult and treatment strategy very burdensome for the patient. For this reason, diagnosis of micro-angiopathic disorders need to be simultaneously based on both clinical symptoms and laboratory findings; 3. Genetic diagnosis that confirms exact recognition of Upshaw-Schulman Syndrome is not commonly available; 4. The described case was a huge diagnostic challenge, and actually the final diagnosis was published until five years after the patient's death. Before 2008, that type of genetic analysis had not been available in Poland; 5. Despite the enormous progress in medical knowledge and experience, the exact diagnosis of TTP, including Upshaw-Schulman Syndrome, of this condition remains very difficult.
INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is referred to as thrombotic micro-angiopathy and was first described by Moschowitz in 1925. TTP is mainly characterized by micro-angiopathic hemolytic anemia, thrombocytopenia, micro-vascular thrombosis and multiorgan dysfunction. The most common clinical manifestation of TTP is neurologic dysfunction, but it also concerns other organs such as heart, pancreas and kidneys. These disturbances lead to many complications such as pancreatitis, acute renal failure, cerebral ischemia, myocardial infarction and cardiac arrhythmias. Without appropriate treatment, death from disseminated micro-vascular thrombosis occurs (Tamizi-Far et al. 2007; D'Angelo et al. 2009).

Classic diagnosis of TTP involves Coomb's negative hemolytic anemia, thrombocytopenia, neurological symptoms, fever and renal insufficiency. Unfortunately, these symptoms are present in 40% of cases. Most often, signs and symptoms are very non-specific, such as abdominal pain, nausea, vomiting, weakness, dizziness – flu-like symptoms.

The primary pathologic reason for TTP lies in the systemic formation of platelet aggregations within arterioles and capillaries in association with endothelial cells damage. Endothelial damage is a result of an abnormal synthesis and metabolism of unusually large von Willebrand factor (ULvWF) multimers. These molecules are responsible for systemic platelet aggregation by increasing platelet adhesiveness, which results in mechanical damage of erythrocytes (anemia), thrombocytopenia and impairment of fibrinolytic activity (Sadler et al. 2004; Sibai 2007). In normal conditions, a vWF cleaving metalloprotease, known as ADAMTS-13 (A Disintegrin And Metalloproteinase with Thrombospondin type-1 motif, member 13) prevents the ULvWF entrance in the circulation (Sibai 2007; Stella et al. 2009). ADAMTS-13, an enzyme produced mainly by hepatocytes, degrades vWF multimers by cleaving the Tyr842-Met843 bond in the vWF A2 domain directly on to the surface of the endothelial cells. The ADAMTS-13 gene is localized on chromosome 9q34, contains 29 exons, and is expressed mainly in the liver (Soejima & Nakagaki 2005).

It already has been proven that TTP is strongly correlated with severe congenital or acquired deficiency of ADAMTS-13 (Soejima & Nakagaki 2005; McCrae 2010). There have been observed reduction of ADAMTS-13 plasma activity, even less than 5% of normal, in patients with TTP (Sibai 2007). An acquired form of TTP is conditioned by the presence of inhibitory autoantibodies against vWF multimers cleaving protease. It has been suggested that a trigger for anti-ADAMTS-13 antibody production may be viral infections, malignancy, stem cell transplantation, pregnancy, certain drugs and auto-immune diseases (Soejima & Nakagaki 2005; Gerth et al. 2009).

Congenital ADAMTS-13 deficiency is known as Upshaw-Schulman Syndrome and it accounts for only 2-4% of all TTP cases. It is conditioned by genetic variants of ADAMTS-13 gene causing reduced ADAMTS-13 synthesis and shows autosomal recessive type of inheritance (Kato et al. 2009). ADAMTS-13 gene mutation in inherited TTP are distributed along an entire gene and are correlated with secretion abnormalities or activity loss of ADAMTS-13. In 2001, Levy et al. revealed 12 genetic variants of the ADAMTS-13 gene conditioning Upshaw-Schulman Syndrome in 7 families (Levy et al. 2001). One of the mutations is 4143insA polymorphism located in 29 exon of the ADAMTS-13 gene.

CASE PRESENTATION

A 20 year old patient, primigravida, nulliparous, in her 28th week of twin pregnancy was admitted to the Tertiary Perinatal Care Center in Poznan, Poland at 00:15 am on November 26, 2006. At 09:20 am on November 26, 2006, the patient was transferred from the district hospital to the Tertiary Perinatal Care Center because of chronic thrombocytopenia and suspicion of hemolytic-uremic syndrome (HUS). What is important is that at the time of admission there were no other known facts concerning the patient. There was no specific information as to the personal history of the patient or her family history.

At admission to hospital, vital parameters were within normal limits. Gynecological and ultrasound examinations were normal for the 28th week of twin pregnancy. Internal Medicine and Anesthesiology examinations took place just after admission to the Delivery Ward. Because of a lack of typical HUS Syndromes (mild anemia, mild thrombocytopenia PLT 66 G/L, normal urinary output, normal urine color; there was no fever, neurological symptoms, abdominal pain, nausea or vomiting) the diagnosis of HUS was excluded. At 09:20 am, on November 26, 2006, the patient was transferred from the Delivery Ward to the Obstetric-Gynecological Ward for further treatment and differential diagnostic. The General condition of the patient was very good and raised no concerns. Internal Medicine and gastroenterological examinations took place. Results of the blood tests and treatment are listed in Tables 1 and 2.

At 03:30 pm on November 27, 2006, during the standard cardio-tocography test there was no fetal heart rhythm (FHR) of the fetus I (confirmed with ultrasound examination), FHR of the fetus II was within normal limits. There was no signs of preterm placental ablation in the ultrasound. Internal Medicine and Anesthesiology examinations took place which did not reveal any disturbances.

At 07:30 pm the same day patient was transferred to the Intensive Care Unit because of unclear and alarming symptoms – back pain, abdominal pain, nausea, vomiting. FHR of the fetus II was controlled each 30 minutes.
At admission to the Intensive Care Unit, vital parameters were within normal limits (heart rate 100/min, blood pressure 120/80 mmHg, blood saturation 98%, temperature 36.9 °C). There had been slight symptoms of jaundice (the skin color was slightly yellow). Abdominal palpating examination was normal. One of the distressing symptoms was the decreased urinary output and the very dark color of the urine. After pharmacological treatment (Table 1) abdominal and back pain was significantly diminished. At 3:00 am, the patient started to feel disturbed and very anxious. Standard neurological examination was within normal limits. At 4:00 am the intrauterine death of fetus II was declared. There were no symptoms of preterm placental abruption in the ultrasound.

In the meantime some facts of the patient's personal history were delivered to our clinic. On that basis initial diagnosis of thrombotic micro-angiopathy was declared. Because of the sudden and dramatic course of the still undiagnosed disease, the diagnostic procedure had not been finished. The patient presented extreme, non-specific signs and symptoms. Moreover, results of the laboratory tests were not immediately available but some of the results were only known after one day delay.

At 5:50 am, the patient presented fluctuating neurological symptoms and finally did not react to external stimuli. Sudden Bradycardia occurred (heart rate 40/min) followed by sudden cardiac arrest. There was no response to pharmacological treatment nor cardiopulmonary resuscitation. A cesarean section was performed as a life saving effort (fetus I – son, 1380 g, fetus II – daughter, 1100 g). Time of patient’s death was at 07:15 am on November 28, 2006.

Post mortem examination
The autopsy revealed genetically conditioned liver disease characterized by an accumulation of very large concrements of alpha1-antitrypsin. Failed liver function was accompanied by pathologic changes in lungs interalveolar septa (focal thickening of elastic fibers, lack of filaments in blood-air barrier) and thrombocytopenic coagulopathy. The direct cause of death was acute heart failure with massive pulmonary edema. In the heart, there were found changes specific to acute ischemic-hypoxic damage (thrombosis in the blood capillaries, disseminated necrotic areas).

Genetic analysis performed in 2011 (5 years after patient’s death) with a usage of tissue preparation collected during the autopsy showed homozygotic mutation in ADMTS13 gene (4143insA) which allowed us to declare a final diagnosis of Upshaw-Schulman Syn-
Thrombotic thrombocytopenic purpura in pregnancy

The patient's older sister (born in 1986), since the age of 2, presented symptoms of chronic thrombocytopenia, recurrent hemorrhagic diathesis and anemia. In 2008, she was finally diagnosed with Upshaw-Schulman Syndrome. During pregnancy (2008), she was treated with fresh frozen plasma 10 mg/kg each 14 days, acetylsalicilic acid 150 mg per day and was under intensive care of a Hematologist and a Gynecologist.

The patient's brother (born in 1989), since the age of 2, suffered from chronic thrombocytopenia, hemorrhagic diathesis, anemia, he presented neurological symptoms (cerebral ischemia). He was also diagnosed with acute renal insufficiency, pulmonary edema and auricular fibrillation. Finally, in 2008, he was diagnosed with Upshaw-Schulman Syndrome.

DISCUSSION

Since early childhood, the analyzed patient was misdiagnosed with idiopathic thrombocytopenia, the diagnosis determined her pregnancy. There are several reasons for thrombocytopenia in pregnancy. Most common of them are pregnancy induced thrombocytopenia, preeclampsia, HELLP Syndrome (hemolysis, elevated liver enzymes, low platelet count), acute fatty liver, disseminated intravascular coagulation (DIC), antiphospholipid syndrome, folic acid deficiency and idiopathic thrombocytopenic purpura (ITP). A very rare cause of thrombocytopenia in the course of pregnancy may be thrombotic microangiopathies (TMA).

In a diagnosis of thrombocytopenia both personal and family history of a patient are very important. Characteristic are hemorrhagic diathesis since early childhood and in case of familial disease – similar symptoms in

Table 3. Family of the patient.

<table>
<thead>
<tr>
<th>Family members</th>
<th>ADAMTS-13 concentration (75–110)</th>
<th>ADAMTS-13 activity (50–150%)</th>
<th>ADAMTS-13 antigen (50–150)</th>
<th>ADAMTS-13 inhibitors (&lt;12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother (healthy)</td>
<td>–</td>
<td>85.77</td>
<td>31.85</td>
<td>0</td>
</tr>
<tr>
<td>Father (healthy)</td>
<td>–</td>
<td>85.77</td>
<td>43.75</td>
<td>0</td>
</tr>
<tr>
<td>Recent advances in thrombotic thrombocytopenic purpura</td>
<td>–</td>
<td>&lt;2.0</td>
<td>&lt;2.0</td>
<td>2.25</td>
</tr>
<tr>
<td>Brother (born in 1989, USS)</td>
<td>0.0</td>
<td>0.0</td>
<td>–</td>
<td>6.105</td>
</tr>
<tr>
<td>Brother (born in 1993, healthy)</td>
<td>–</td>
<td>72.16</td>
<td>38.37</td>
<td>0</td>
</tr>
<tr>
<td>Reported Patient (USS)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

USS – Upshaw-Schulman Syndrome

Table 3.

<table>
<thead>
<tr>
<th>Family members</th>
<th>ADAMTS-13 mutation 4143insA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
<td>(healthy) – 85.77 31.85 0 heterozygotic</td>
</tr>
<tr>
<td>Father</td>
<td>(healthy) – 85.77 43.75 0 heterozygotic</td>
</tr>
<tr>
<td>Brother (born in 1989, USS)</td>
<td>0.0 0.0 – 6.105 homozygotic</td>
</tr>
<tr>
<td>Brother (born in 1993, healthy)</td>
<td>– 72.16 38.37 0 heterozygotic</td>
</tr>
<tr>
<td>Reported Patient (USS)</td>
<td>– – – – homozygotic</td>
</tr>
</tbody>
</table>
family members. On physical examination, attention also should be paid, as often there is hepato- and splenomegaly or lymphadenopathy. Very often, when the only dominant symptom is thrombocytopenia, those kinds of diseases are misdiagnosed.

TMA are groups of rare, very severe disorders of diverse etiology. They are characterized by forming in arterioles and small capillaries thrombi formed by platelets, von Willebrand factor and fibrin, which result in failed organ perfusion. Clinically, it is manifested by Coomb’s negative microangiopathic hemolytic anemia (MHA), thrombocytopenia and multiorgan dysfunction. Laboratory test results usually reveal thrombocytopenia, anemia, elevation of lactate dehydrogenase (LDH) serum concentration, presence of fragmented erythrocytes (helmet cells), negative Coomb’s test, increased white blood cell count, urine color is usually dark (hemoglobinuria, hematuria, proteinuria). Liver function tests may be within normal limits and concentration of coagulation factors is not significantly changed. There are no markers of coagulation system activation. Unfortunately, laboratory findings are not always definitive.

There are a few TMA that may occur in pregnancy. These are thrombotic thrombocytopenic purpura (TTP), HUS, ITP, HELLP syndrome and acute fatty liver in pregnancy. Differential diagnosis of TMA is very difficult because of overlapping laboratory and clinical symptoms. Exact diagnosis is extremely important as management and treatment strategies differ among those diseases. The rarity of these disorders during pregnancy results in a lack of systemic reviews and randomized trials on that issue.

The available literature presents the diverse frequency of TTP during pregnancy although it is always underlined that it is an extremely rare state. Sibai (2007) assumed that the risk of development of TTP or hemolytic uremic syndrome during pregnancy or postpartum is probably less than one case in 100,000 pregnancies. Similar estimation also may be found in other publications (Stella et al. 2009). According to Crowther & George (2008) annual incidence of TTP in the general population is about 11 cases per million and incidence of severe deficiency of ADAMTS-13 is about 2 per million. The rarity of familial TTP, which accounts for only 2–4% all TTP cases, must be noted. Maternal mortality is very high in pregnancies complicated with TTP, it even has been 60% before the use of plasma infusions. Nowadays, in spite of usage of proper treatment which is plasma transfusions, the maternal mortality rate is still very high, reaching even 10%. Moreover, recent case series report estimated fetal death rate at 20% (George 2003).

Hypercoagulability, with an increased risk of thrombotic disorders, which is a physiologic change during pregnancy, may contribute to the risk of TTP development, especially in women with congenital or acquired ADAMTS-13 deficiency. Moreover, ADAMTS-13 activity decreases during pregnancy, which probably is correlated with physiologic increase vWF concentration. This is because ADAMTS-13 activity is inversely correlated with vWF concentration in serum (George 2003).

To date, precise diagnostic criteria of TTP has not been established, especially during pregnancy. Thrombocytopenia, hemolytic anemia, fluctuating neurological abnormalities, renal failure and fever are classic pentad of TTP symptoms. But, above all, these symptoms are not specific only to TTP and they are seen in only 40% of patients with TTP. Other signs and symptoms that may be present in TTP patients are abdominal pain, nausea, vomiting, gastrointestinal bleeding, epistaxis, petechiae and purpura (Sibai 2007). It is suggested that in case of TTP suspicion, routine laboratory tests should include full blood count, film clotting screen, LDH, direct anti-globulin test, plasma haptoglobin, urea, electrolytes, liver function tests and urine dipstick for protein (D’Angelo et al. 2009).

It is worth noting, that even without severe thrombocytopenia, decreased ADAMTS-13 activity in consumptive coagulopathy is associated with altered platelet dynamics (Song et al. 2008). It is suggested to use decreased plasma concentration of ADAMTS-13 as a marker of TTP. But, first of all, ADAMTS-13 deficiency is present in other symptoms, such as disseminated intravascular coagulation (DIC) and co-existent sepsis. Moreover, tests evaluating ADAMTS-13 concentration are not comprehensively available (Kato et al. 2009).

Plasma transfusions and exchanges are essential points in the management of thrombotic thrombocytopenic purpura. Fresh frozen plasma, cryoprecipitate-poor plasma and plasma treated with a mixture of solvent and detergent are used in therapy. All these preparations contain deficient ADAMTS-13. Plasma exchange leads to removal of ULvWF multimers and supplements metalloproteinase deficiency (Sibai 2007). Some patients with acquired TTP and high concentration of antibody against ADAMTS-13 may need additional immuno-suppressive therapy. Transfusion of platelet preparations is absolutely contraindicated. Erythrocytes transfusion are allowed and their use depends on clinical need. Recognition of TTP in a pregnant patient is not an indication for terminating the pregnancy. In opposition to some other states correlated with pregnancy, such as preeclampsia, eclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count) delivery does not influence the disease course. Pregnant patients with TTP who respond to plasma transfusions may continue pregnancy. Because the risk of relapse of TTP during pregnancy is high, these patients require close observation. Proposed treatment strategy of a pregnant women with TTP includes serial plasma exchange, weekly plasma infusions, corticosteroids and antiplatelet agents. Plasma therapy reduced the mortality rate of TTP from 80–90% to 10–20% (Kato et al. 2009).
CONCLUSIONS

TTP, especially hereditary Upshaw-Schulman Syndrome, is extremely rare and complicates the course of pregnancy. It is usually very sudden and dramatic.

Differential diagnosis of this disease is difficult and treatment strategy very burdensome for the patient. For this reason, diagnosis of micro-angiopathic disorders need to be simultaneously based on both clinical symptoms and laboratory findings.

Genetic diagnosis that confirms exact recognition of Upshaw-Schulman Syndrome is not commonly available.

The described case was a huge diagnostic challenge, and actually the final diagnosis was not published until five years after the patient’s death. Before 2008, that type of genetic analysis had not been available in Poland.

Despite the enormous progress in medical knowledge and experience, the exact diagnosis of TTP, including Upshaw-Schulman Syndrome, of this condition remains very difficult.

REFERENCES