Late onset and pregnancy-induced congenital thrombotic thrombocytopenic purpura

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Note added in revised manuscript: After submission of our manuscript (26 March, 2014) a paper by M. Scully et al. has been published electronically (27), reporting on 23 congenital TTP cases diagnosed during their first pregnancy. Several patients had the same ADAMTS13 mutation, c.C3178T leading to p.R1060W, as found in our patient

Thrombotic thrombocytopenic purpura (TTP) is an especially severe form of thrombotic microangiopathies (TMAs) with typical platelet and von Willebrand factor (VWF) rich microvascular thrombi. These microthrombi are found in arterioles and capillaries of multiple organs. Brain is particularly affected and this may result in variable neurological abnormalities (1) ranging from:

- headache,
- focal neurological signs to
- vigilance dysfunction,
- coma and
- seizures.

Keywords
Hereditary TTP, pregnancy, ADAMTS13 activity, ADAMTS13 mutation

Summary
We report on our patient (case 2) who experienced a first acute episode of thrombotic thrombocytopenic purpura (TTP) at the age of 19 years during her first pregnancy in 1976 which ended in a spontaneous abortion in the 30th gestational week. Treatment with red blood cell concentrates was implemented and splenectomy was performed. After having suffered from several TTP episodes in 1977, possibly mitigated by acetylsalicylic acid therapy, an interruption and sterilization were performed in 1980 in her second pregnancy thereby avoiding another disease flare-up. Her elder sister (case 1) had been diagnosed with TTP in 1974, also during her first pregnancy. She died in 1977 during her second pregnancy from a second acute TTP episode. Diagnosis: In 2013 a severe ADAMTS13 deficiency of <10% without detectable ADAMTS13 inhibitor was repeatedly found. Investigation of the ADAMTS13 gene showed that the severe ADAMTS13 deficiency was caused by compound heterozygous ADAMTS13 mutations: a premature stop codon in exon 2 (p.Q44X), and a missense mutation in exon 24 (p.R1060W) associated with low but measureable ADAMTS13 activity. Conclusion: Genetic analysis of the ADAMTS13 gene is important in TTP patients of all ages if an ADAMTS13 inhibitor has been excluded.

Schlüsselwörter
Hereditäre TTP, Schwangerschaft, ADAMTS13-Aktivität, ADAMTS13-Mutationen

Zusammenfassung
The patients typically present with
- consumptive thrombocytopenia,
- a non-immune haemolytic anaemia with schistocytes and increased LDH levels.

Further unspecific clinical symptoms are fatigue, petechiae, abdominal pain, nausea, vomiting, diarrhea and fever, as well as renal dysfunction and chest pain (2).

The initial diagnosis of TTP is based on a combination of clinical symptoms and laboratory parameters, obligatorily including thrombocytopenia and microangiopathic haemolytic anaemia (3). A rapid course of deterioration and death may occur without treatment of TTP. The mainstay of therapy for acute manifestations of TTP is plasmapheresis with replacement of fresh frozen plasma (FFP) alone or in combination with immunosuppressive drugs (4, 5).

TTP is often caused by a severe deficiency of the plasma enzyme, ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motifs 13) (6). ADAMTS13 deficiency is either due to mutations in the ADAMTS13 gene in case of hereditary TTP, or results from autoantibodies inhibiting the protease in the more frequent acquired TTP form.

Under physiological conditions ADAMTS13 cleaves high molecular weight, prothrombotic VWF multimers into smaller less adhesive molecules. Without proteolytic cleavage, the resulting unusually large VWF multimers initiate spontaneous VWF-platelet adhesion and aggregation, leading to widespread microvascular thrombosis in different organs (1, 3). This platelet clumping is often induced by certain trigger factors, especially infections and pregnancy (6). The underlying mechanism of these trigger factors is poorly understood.

Two sisters with severe pregnancy complications

We report on two sisters with severe, life-threatening pregnancy complications as a result of hereditary thrombotic thrombocytopenic purpura (TTP), also denoted as Upshaw-Schulman-syndrome (USS) (7). The family history of the two sisters revealed nothing conspicuous. The mother has had six normal pregnancies without any complications.

Case 1
First pregnancy
The older sister of our patient became pregnant in 1974 at age 19.5 years. The pregnancy was uneventful until gestational week (GW) 31 when she was admitted to a peripheral hospital for suspicion of pre-eclampsia (▶ Tab. 1). Four days later her medical condition deteriorated. She suffered from various neurological symptoms and the laboratory work-up showed severe thrombocytopenia, haemolytic anaemia and a considerably increased LDH level (▶ Tab. 1). She was treated with transfusion of two red blood cell concentrates. In gestational week 32 she had an initiated preterm birth. Unfortunately, the premature baby (1320 g, 40 cm) died after two days from the consequences of severe brain haemorrhage. Postpartum haemoglobin decreased rapidly to 5.3 g/dl whereupon she was moved to a tertiary care University hospital on the 29th of July 1974. Thrombocytes were less than 10 000/µl, Hb 4.0 g/dl, schistocytes and microspherocytes were present on the blood smear, reticulocytes were >300‰ and the Coombs-test was negative. She responded temporarily to red blood cell concentrates but the parameters deteriorated somewhat later. On the 21st of August 1974 she was splenectomized. The histology of the spleen showed some fresh and older arterial embolic occlusions. Ten days after splenectomy she was discharged with stabilized blood parameters (▶ Fig. 1a). The complications were first diagnosed as preeclampsia.

Tab. 1
Clinical signs and symptoms as well as laboratory findings upon admissions of cases 1 and 2

<table>
<thead>
<tr>
<th>case</th>
<th>pregnancy</th>
<th>date</th>
<th>gestational week</th>
<th>clinical signs and symptoms</th>
<th>laboratory findings</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>18.–22.07.1974</td>
<td>31</td>
<td>• blood pressure 140/80 mmHg&lt;br&gt;• oedema&lt;br&gt;• paraesthesia&lt;br&gt;• disorder of consciousness&lt;br&gt;• feeling of numbness&lt;br&gt;• weakness in the left side of her body</td>
<td>• thrombocytopenia 10000/µl&lt;br&gt;• haemoglobin 6.1 g/dl&lt;br&gt;• haematocrit 18%&lt;br&gt;• reticulocytes 285‰&lt;br&gt;• LDH 1830 U/l&lt;br&gt;• albuminuria</td>
</tr>
<tr>
<td>2</td>
<td>26.03.1977</td>
<td>32</td>
<td></td>
<td>• hypertensive crisis (BP 210/140 mmHg)&lt;br&gt;• headaches&lt;br&gt;• back pain&lt;br&gt;• pain in the limbs&lt;br&gt;• severe emesis&lt;br&gt;• brown urine</td>
<td>• thrombocytopenia 2000/µl&lt;br&gt;• haemoglobin 5.9 g/dl&lt;br&gt;• reticulocytes 44%&lt;br&gt;• schistocytes ++</td>
</tr>
<tr>
<td>2</td>
<td>05.11.1976</td>
<td>28</td>
<td></td>
<td>• visual disturbances (flickering, seeing stars)&lt;br&gt;• ringing in the ears&lt;br&gt;• swollen legs and arms&lt;br&gt;• fatigue&lt;br&gt;• weakness&lt;br&gt;• weight loss (5 kg in a few weeks)&lt;br&gt;• high blood pressure</td>
<td>• thrombocytopenia 20000/µl&lt;br&gt;• haemoglobin 5.5 g/dl&lt;br&gt;• decreased haaptoglobin&lt;br&gt;• increased LDH level</td>
</tr>
</tbody>
</table>
Second pregnancy

Two years later she was pregnant for the second time. In March 1977, at GW 32, she presented again with a blood pressure of 170/100 mmHg. The next day she was admitted as an emergency case to the University Medical Center because of progressively worsening general condition (a Tab. 1). Three hours after hospitalization, she gave birth to a stillborn child (1400 g, 41 cm). The placenta had only 50% of normal weight and the histology showed widespread infarctions and intervillous thrombi in 50% of the placenta. The patient’s medical condition rapidly deteriorated with severe anaemia and thrombocytopenia (Fig. 1a). Finally, she suffered from a respiratory and cardiac arrest which caused her death within 10 hours after admission. On autopsy widespread intravascular thrombosis in kidney, stomach, lung, intestine, pancreas, and multifocal inferior and anterior myocardial infarctions were noted along with petechiae and haemorrhages in several organs. Heart failure was considered to have caused her death.

Case 2
First pregnancy

The medical history of our patient began in November 1976 (Tab. 1). At that time, she was 19 years old and pregnant in GW 28. She suffered from high blood pressure, neurological symptoms and was consequently admitted to a University Medical Center (a Tab. 1). The medical examination revealed a severe haemolytic anaemia and thrombocytopenia (Tab. 1, Fig. 1b). Four red blood cell concentrates were transfused. Ten days later our patient had a spontaneous delivery in GW 30 (Fig. 1b). The male premature baby (1040 g) died after three days, due to a progressive sepsis and icterus. In addition the medical condition of the young woman deteriorated further. She developed motoric aphasia, disorder of consciousness and feeling of numbness and weakness in the right side of her body and she had oedema, high blood pressure and high temperature. The laboratory parameters exhibited a severe persisting anaemia, with signs of red blood cell fragmentation and thrombocytopenia. LDH level and bilirubin were increased. Most of the initiated therapies, such as heparin, corticosteroids and splenectomy were inefficient, only acetylsalicylic acid (ASA) seemed probably efficient. Red blood cell concentrates had a transient positive effect. She was discharged in March 1977 although her blood parameters had not normalized (Hb 6.6 g/dl, platelets 16 000/µl, BP 160/100 mmHg). She was seen every four weeks by her physicians. ASA was continued. Three days before menstruation in July and August 1977, Hb and platelet count sharply decreased on both occasions and spontaneous normalization was seen after seven days under ASA without other treatments (Fig. 1b).

Until October 1977 platelet counts were fluctuating and finally normalized as did Hb. In spring 1978 another TTP bout occurred, triggered by tonsillitis with fever during menstruation. The latter seemed always to be a critical phase, sometimes with petechial skin rash although platelet counts remained normal. Under ASA, 500 mg three times a day, a remission to normal blood count parameters was achieved after seven days.

Second pregnancy

In January 1980 the young woman was pregnant again. In view of her and her...
sister’s history an interruption of pregnancy was conducted in GW 8 and a tube sterilization was done without an ensuing TTP flare-up.

Since that time she never had suffered from an acute TTP episode. Several infections, including tooth abscesses, have not triggered any acute episode so far. Pregnancy was obviously a strong trigger factor in this family.

Results

In the medical report of our surviving patient from 1977, also based on the autopsy report of her elder sister, Moschowitz’s disease was first mentioned after her first acute TTP episode during pregnancy. 36 years later the patient consulted the Haemostaseology outpatient Clinic of the University Medical Center Mainz for final diagnosis.

ADAMTS13 activity as well as ADAMTS13 inhibitor (autoantibodies) were investigated. We repeatedly found a (borderline) severely reduced ADAMTS13 activity (3–9% of the normal) without detectable ADAMTS13 inhibitor. This was suggestive of congenital ADAMTS13 deficiency. Molecular analysis of the ADAMTS13 gene was initiated. It showed that the severe ADAMTS13 deficiency was caused by compound heterozygous ADAMTS13 mutations. One mutation, c.130C>T in exon 2, results in a premature stop codon (8). The second mutation, c.3178C>T in exon 24, results in ADAMTS13 R1060W, which is associated with late-onset, often pregnancy-induced TTP (9, 10). Residual ADAMTS13 activity of 5–10% was found in homozygous carriers of this mutation (11).

In conclusion, a pregnancy-induced hereditary TTP was diagnosed in our patient and this is also the likely diagnosis in her elder sister who had died during her second pregnancy.

Discussion

This report of two sisters underlines the importance of ADAMTS13 activity determination in pregnant patients with suspected preeclampsia. The HELLP (Hepatomegaly, Elevated Liver enzyme levels, Low Platelet count) syndrome is a very severe form of preeclampsia. In HELLP syndrome liver dysfunction, haemolytic anaemia and thrombocytopenia are present. These findings can be accompanied by non-specific symptoms ranging from nausea, vomiting and diarrhea to headaches, blurred vision and other neurological symptoms. This makes it difficult to distinguish HELLP syndrome from a TTP episode.

Studies have shown, however, that the number of TTP patients among women with preeclampsia or HELLP syndrome may be low (12). Conversely, the probability of serious maternal and fetal complications during pregnancy is high among hereditary TTP patients (12, 13).

The problem is that several patients with hereditary TTP have their first disease episode during their first pregnancy and consequently diagnosis will be made too late to avoid severe pregnancy complications. Still, in retrospect, it is striking that many of these patients had already had episodes of thrombocytopenia at a younger age (14). This is consistent with studies of Schneppenheim et al. who found that in a group of 83 children with episodes of thrombocytopenia and/or haemolysis, some patients had been misdiagnosed as immune thrombocytopenia (ITP) or Evans syndrome and suffered in fact from congenital ADAMTS13 deficiency (15). The risk of suffering a recurrent disease episode in patients with hereditary TTP during a next pregnancy without appropriate treatment is almost 100% (14, 16, 17), which is confirmed by the cases presented here. The prognosis for a fetus in cases of hereditary TTP is extremely poor, with a rate of miscarriages and stillbirths of 40–60% (10, 12, 14, 17). Fujimura et al. reported that, out of 15 pregnancies, eight children were already dead at the time of birth or died shortly afterwards (14). According to other reports, intrauterine fetal death had already been established at the beginning of a TTP bout (18). Historical examinations discovered infarcts in the placenta in cases of miscarriage and stillbirth (13, 19). The autopsy of the stillborn baby of the older sister of our patient also showed extensive placental infarcts leading to intrauterine asphyxia.

The importance of rapid diagnosis and initiation of treatment becomes clear when one considers the extremely rapid deterioration within hours after admission in both our cases. Before 1978 the cause of Upshaw-Schulman syndrome (7) and especially the beneficial effect of plasma therapy were not known. Even with immediate plasma treatment, acute episodes in hereditary TTP during pregnancy remain life-threatening, as evidenced by the case of a 23-year-old Japanese woman, who despite being treated with fresh frozen plasma (FFP), haemodialfiltration and plasma exchange, initiated within 5 hours of admission, nevertheless died after 32 hours (18).

In general, it is significantly more difficult to treat an acute TTP episode than to implement an early patient-tailored prophylaxis. Prophylactic treatment by regular FFP infusions was successful in a number of cases (13, 14). Overall the chances of survival for mothers today are quite good, with survival rates of over 80% (12, 14, 17).

A progressive increase of VWF in pregnancy and the associated decrease of ADAMTS13 may be considered a likely triggering mechanism for the acute episodes during pregnancy. Experiments with artificially raised levels of VWF show that ADAMTS13 behaves reciprocally to the increased VWF, be it by infusion of exogenous VWF or by desmopressin application (20).

As an acute-phase protein, VWF also increases during infections, which are also considered possible triggers for TTP episodes. A simultaneous decrease of ADAMTS13 levels is seen in sepsis and systemic inflammation (21, 22). The age at onset of hereditary TTP is variable (6). Infection is usually a trigger in early-onset cases, whereas pregnancy is often the trigger in late-onset cases (6, 13, 23). This is consistent with the course of the disease in our two sisters, who showed no symptoms before pregnancy. Astonishingly, the surviving sister had to this day, 36 years later, no further TTP bout, despite numerous infections, tooth abscesses and operations.

The period over which the level of VWF is increased may thus be an important factor. Often acute episodes are only reported in the second and third trimesters (14, 17), while another study did not observe a dif-
ference in the occurrence rate between the three trimesters (10).

The two mutations detected in our patient have already been discovered, along with more than 80 other ADAMTS13 mutations, but they have never before been found in this combination. Antoine et al. described the mutation c.130C>T leading to a premature stop codon (p.Q44X) in two brothers and their father in a Swiss family (8). The second mutation, c.3178C>T resulting in the amino acid exchange p.R1060W, is a common mutation in Europe and the USA (24–26). This point mutation in the TSP-7 domain causes intracellular retention of ADAMTS13 without affecting the activity of the enzyme itself (9). Residual ADAMTS13 activity may be present with this mutation, which would explain the observed ADAMTS13 activity of 3–9%. Moreover, this may be the reason why patients with USS having at least one allele coding for p.R1060W often suffer their first episode in adulthood, usually in combination with a strong trigger such as pregnancy or a severe infection (24).

Conclusion

These case reports emphasize the importance of further examinations in cases with thrombotic thrombocytopenia and haemolysis during pregnancy. In addition to preeclampsia / HELLP syndrome, the possibility of hereditary or acquired TTP must be considered. Tests should be carried out for ADAMTS13 activity and in case of severe deficiency for inhibitors (autoantibodies). Severely reduced ADAMTS13 activity without concurrent detection of ADAMTS13 inhibitors should lead to a molecular analysis of the ADAMTS13 gene and to the installation of FFP infusions in pregnant women as therapy as well as for prophylaxis. This simple treatment can save the lives of these rare patients with hereditary TTP. A correct and early diagnosis of hereditary TTP is instrumental for guiding therapy.

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Conflict of Interest

The authors state that they have no conflict of interest.

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