Hereditary thrombotic thrombocytopenic purpura and the hereditary TTP registry

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Summary
Hereditary thrombotic thrombocytopenic purpura (TTP), also known as Upshaw-Shulman syndrome, is a rare recessively inherited disease. Underlying is a severe constitutional deficiency of the von Willebrand factor-cleaving protease, ADAMTS13, due to compound heterozygous or homozygous mutations in the ADAMTS13 gene. The clinical picture is variable and more and more patients with an adult-onset are diagnosed. In the majority of countries the only available treatment is plasma, which when administered regularly can efficiently prevent acute disease bouts. The decision to initiate regular prophylaxis is often not easy, as evidence based guidelines and long term outcome data are lacking. Through the hereditary TTP registry (www.ttpregistry.net, ClinicalTrials.gov identifier: NCT01257269), which was initiated in 2006 and is open to all patients diagnosed with Upshaw-Shulman syndrome and their family members, we aim to gain further information and insights into this rare disease, which eventually will help to improve clinical management of affected patients.

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Thrombotic thrombocytopenic purpura (TTP), sometimes dubbed “the systemic clumping plague” (1), is characterized by an acute onset of

• thrombocytopenia,
• microangiopathic haemolytic anaemia with schistocytes on the blood smear and
• ischaemic end organ damage due to microvascular thrombosis, notably in brain, heart and kidneys.

Underlying is an impaired size regulation of von Willebrand factor (VWF), which persists in the circulation in the form of unusually large, sticky multimers as a result of a severe deficiency of the VWF-cleaving protease, now denoted as ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motifs-13) (1–5). Two forms of severe ADAMTS13 deficiency (<5% of the normal) are recognized:

• severe acquired ADAMTS13 deficiency as the result of circulating anti-ADAMTS13 autoantibodies inhibiting ADAMTS13 activity and/or increasing ADAMTS13 cleavage; see M. Schaller et al. in this issue of Hämostaseologie (6) for details on the deregulated immune response in acquired or idiopathic TTP, and
• severe constitutional ADAMTS13 deficiency, in hereditary TTP (Upshaw-Shulman syndrome [USS]) due to compound heterozygous or homozygous ADAMTS13 mutations (7).

This review focuses on the current definition and knowledge of Upshaw-Shulman...
syndrome (OMIM #274150) and presents the hereditary TTP registry (www.ttptregistry.net, ClinicalTrials.gov identifier NCT01257269).

**Historical aspects**

The first case of hereditary TTP was reported by Irving Schulman and coworkers in 1960 (8). They studied a girl of German origin over a period of several years. From age 1 year, she suffered from recurrent episodes of thrombocytopenia, abnormal bruising and epistaxis which eventually led to the diagnosis of thrombocytopenic purpura. Splenectomy was performed because of chronic persistent thrombocytopenia but had no effect on the clinical course nor had corticosteroids. On several occasions signs indicative of haemolytic anaemia were present in addition. The turnarounds came, when the authors realized that always following the administration of plasma containing blood products the platelet count rapidly recovered and the hypothesis of a missing plasma factor important for megakaryocyte maturation and platelet production was then meticulously investigated over several years. Nearly two decades later Jefferson D. Upshaw described a very similar case and realized that his and Irving Schulman’s case likely were the result of the same congenitally missing plasma factor (9). Both reports excel by an excellent clinical dissection and foreclose a result of the same congenitally missing plasma factor postulated to exist so many years ago (16).

The two cases were also instrumental in the next step as they participated as patient B (case of Schulman et al.) and as patient D (Upshaw’s case) in the landmark study of Moake et al. in 1982, who demonstrated that the lacking VWF multimer size regulation was central in the pathophysiology of TTP (13). Nearly 15 years later the principal regulator of VWF size was described and termed the VWF-cleaving protease (14, 15). One year later the first link between a severe deficiency of this VWF-cleaving protease (<5% of the normal) and chronic recurring TTP was established in four patients, including two brothers suffering from hereditary TTP (2).

The next highlights were the identification of the ADAMTS13 gene and the first ADAMTS13 mutations in USS families (7) as well as the cloning, expression of ADAMTS13 and formal proof of principal when VWF-cleaving protease activity was restored upon addition of recombinant ADAMTS13 to an USS plasma that ADAMTS13 indeed was the missing plasma factor postulated to exist so many years ago (16).

**ADAMTS13 and USS**

The ADAMTS13 gene is located on chromosome 9q34, contains 29 exons, and encodes a multidomain protein of 1427 amino acids. Up to date, more than 150 different ADAMTS13 mutations have been identified. The mutations are distributed throughout the whole ADAMTS13 gene and consist of missense mutations (~60%), small deletions and insertions (~20%), as well as nonsense and splice site mutations. Large deletions have not been described so far and the causative nature of the found mutations has been demonstrated by expression studies for only about one third of mutations.

While the majority of mutations are confined to single families and homozygous mutations are found primarily in consanguineous background, two mutations in Europe stick out; for particularities in Japanese USS cases see Miyata et al. (17) in this issue of Hämostaseologie. The single nucleotide insertion in exon 29, 4143insA resulting in a frameshift and subsequent premature termination codon at amino acid 1386; and the missense mutation Arg1060Trp (R1060W) in exon 24, reported in a number of cases with adult onset hereditary TTP. Both mutations have been observed in homozygous state or together with a second mutation in a large number of unrelated families in different countries in Europe as well as on other continents.

The exon 29 mutation seems to cluster around the Baltic sea, in Scandinavia and in Moravia (18–21), but was also found in Croatia, Italy, the United States and Canada as well as in Australia (in the latter three countries families traced ancestors to Germany, the Baltic sea basin or Scandinavia). The distribution area of the second mutation, R1060W seems to be even larger (18, 22–24).

Summing up reported cases and personal knowledge of the hereditary TTP registry steering committee worldwide more than 150 patients diagnosed with USS are alive.

The prevalence of USS is, however, unknown. An estimate based on the number of diagnosed cases in certain areas results in a prevalence of 0.5 to 4 cases / million in Europe (this projects to a number of 250–2000 cases among the 500 million inhabitants of the EU) with a higher prevalence in Scandinavia and in countries around the Baltic Sea, than for instance in Switzerland. USS may be more prevalent than anticipated so far because of the:

- large geographic distribution areas of the ADAMTS13 mutations, 4143insA and R1060W,
- occurrence of homozygous mutations in unrelated families (18, 23, 25, 26),
- increasing numbers of patients identified with a disease onset in adulthood.

**Clinical aspects of USS**

Although Upshaw-Schulman syndrome is considered as a monogenic disorder, the clinical courses are often very variable and differ in the:

- time point of a first disease episode,
- recurrence,
- organ involvement,
- need for regular prophylactic plasma infusions.
Onset of disease

One third to 50% of USS patients experience their first acute TTP episode within their first days of life up to five years of age (early onset) (27). The other half of patients remain asymptomatic into adulthood, when they present with a first acute episode often triggered by well recognized risk factors, such as pregnancy, alcohol binge drinking or other situations known to be associated with VWF release and high VWF levels (24–28).

A few patients have been observed who had their first acute TTP bout at the age of 60 years or older, and in a number of families siblings of USS patients remained asymptomatic into their fourth to fifth decade despite a severe ADAMTS13 deficiency and proven ADAMTS13 mutations. Residual ADAMTS13 activity, as determined by new generation ADAMTS13 activity methods, employing a VWF A2 domain peptide of 73 amino acids as a substrate, is observed in the plasma of a number of USS patients, including R1060W carriers and seems to delay disease onset, to reduce the number of recurrences and the need for regular prophylactic plasma infusions (26, 29).

Organ involvement

While some patients present with neurological symptoms and never show renal complications, renal involvement is the predominant manifestation in others (19, 23, 25, 27, 30–32). Moreover, patients with neurological involvement tend to present with neurological symptoms also during subsequent episodes, the same applies for renal involvement.

Thus far, no genotype-phenotype correlation explaining organ predilection is cognizable and the clinical presentation may vary in unrelated carriers of the same two ADAMTS13 mutations and even within families (18).

Meticulous investigation of patient histories often reveals that incomplete pictures have been present many years before a diagnosis of USS has been established. A number of patients have had (severe) hyperbilirubinemia, once in a while necessitating exchange transfusions during the neonatal period. In addition, episodes of thrombocytopenia are frequent, and many patients have been misdiagnosed with immune thrombocytopenic purpura (ITP) or Evans’ syndrome leading to futile treatment with corticosteroids or even splenectomy, as seen in Schulman’s case (8).

Irrespective of the age at disease onset and of organ tropism, most USS patients present with a chronic relapsing course once they have experienced an acute TTP bout, though recurrence may be triggered by risk factors, such as pregnancy (this is particularly true for carriers of the R1060W mutation) (23, 24, 28, 33–35).

Disease modifying factors

Additional factors besides ADAMTS13 are likely to have an impact on the phenotypic presentation of USS. In one Italian family diagnosed with hereditary TTP with three affected siblings, one sibling was asymptomatic into his fourth decade, a second patient presented with classical TTP while the clinical picture in the third was suggestive of atypical haemolytic uremic syndrome (aHUS). In this latter patient an additional heterozygous mutation in complement factor H was found, known to be associated with atypical HUS (36). Whether mutations in complement factors, known to be associated with aHUS, shape the clinical picture in other USS families remains to be determined.

Other possible disease modifiers are individual variability in levels of β2 glycoprotein I, shown to bind to the A1 domain of VWF and to prevent the binding of platelets to VWF (37), or the AB0 blood groups, with their known impact on VWF levels.

Heterozygous mutation carriers

Obligatory heterozygous ADAMTS13 mutation carriers, such as parents or offspring of USS patients, typically have half-normal ADAMTS13 activity levels and are generally asymptomatic (7, 18, 27, 30, 32, 33, 38, 39). It is noteworthy that among women with severe pregnancy complications the number of heterozygous mutation carriers seems to be increased (23, 24). Whether the reported patients are true heterozygotes or a second mutation was missed due to the strategy used to analyze the ADAMTS13 gene (i.e. often only exons with flanking intron/exon boundaries are analyzed, by this approach large deletions can be overlooked) is currently unknown. In some USS families we have seen mild thrombocytopenia in heterozygotes during (viral) infections or during pregnancies.

Treatment

For detailed information on treatment modalities for TTP including hereditary TTP the reader is referred to the “How I treat” series in Blood (40) and the paper by Paul Knöbl in this issue of Hämostaseologie (41).

Here, we want to mention only a few points.

Acute TTP episodes can be prevented in USS patients by regular plasma infusions every 2–3 weeks (10–12, 27).

In contrast to other hereditary coagulation factor deficiencies, e.g. haemophilia, there is neither plasma-purified nor recombinant ADAMTS13 available. In most countries, ADAMTS13 can thus only be replaced by the administration of plasma.

Plasma therapy in USS is generally well tolerated (apart from incidental allergic reactions) and no patient has emerged to date who developed an ADAMTS13 inhibitor despite frequent plasma transfusions and thus opportunity for alloimmunization (a frequent problem in haemophilia A). Fluctuating titer of non-inhibitory anti-ADAMTS13 antibodies of isotype IgG have been observed in some frequently transfused USS patients in Japan and Europe (25, 42). The significance of these antibodies is currently unknown.

A diagnosis of USS is not synonymous with instalment of regular prophylaxis with plasma infusions.

As a considerable number of patients experience relapses only in situations of increased risk, such as pregnancy (25, 26),...
The hereditary TTP registry

The hereditary TTP registry evolved from the local registry in Bern, Switzerland, which had been operational since the identification of the two brothers, who were instrumental in establishing a link between a severe deficiency of the VWF-cleaving protease and TTP (2, 10, 43) and gathered new patients mainly through diagnostic activities of the Hemostasis Research Laboratory in Bern. This local registry was put on a new basis with the approval by the Kantonale Ethikkommission Bern in 2006. At this time, the registry contained 45 families from 18 countries in Europe, the Americas and in Asia, with one affected family member in 39 families, two affected siblings in four and three USS patients in two families, respectively. Two of the patients had died of (unrecognized) acute TTP bouts and in the 45 families at least 7 siblings of patients had died before the age of two years due to a TTP-like disease (most often severe haemolytic anaemia and thrombocytopenia in the first days of life), generally not recognized as TTP.

During these first years it became apparent, that a number of USS families were studied by different groups simultaneously, that there were more reports than actual patients and that for this rare disorder forces should be joined to create a multinational registry. Baxter Healthcare offered to help and in a first step the approved patient questionnaire was distributed among members of Baxter Healthcare’s clinical advisory board for recombinant ADAMTS13 to have their opinion and input – the ten-page original patient questionnaire increased to 20 pages to include all suggestions and national requirements. Transcription of this extended questionnaire into an electronic database proved difficult as did the different national and local requirements of ethic committees (EC) and institutional review boards (IRB), but the efforts put into this project and the commitment of national and international experts was very helpful.

The electronic database is operational since Q1/2012.

For participating centers it is possible to perform data entry electronically or by using the paper questionnaire and data entry is performed at the central coordination site in Bern, Switzerland. As requested by several ECs and IRBs patient data are processed exclusively in a pseudonymised manner to create a nine digit pseudonym on the basis of a hash-algorithm by personal data: first and last name, birth name (surname), date of birth and gender. The goal of the hereditary TTP registry is to gather as much information as possible on

- natural history and clinical course of USS in different patients,
- factors that may trigger acute episodes (i.e. pregnancy, infections),
- treatment modalities, including plasma therapy and
- possible side effects of therapy.

Through an investigator-initiated research grant for the registry from Baxter Healthcare it is possible to offer laboratory investigation and molecular analysis of the ADAMTS13 gene free of charge to participants and their interested family members.

In a second step we hope then to be able to increase knowledge on this rare disease and thereby to prevent futile treatment (e.g. splenectomy for a misdiagnosis of ITP or Evans’ syndrome), to provide diagnostic tools to confirm diagnosis in suspected patients, to help to identify situations with increased risk for USS patients and to establish evidence based recommendations on plasma prophylaxis and therapy and last but not least to provide a discussion platform for affected patients.

The eligibility criteria for the hereditary TTP registry are summarized (Tab. 1). Individuals fulfilling criteria A and two or all of the remaining three criteria are enrolled as confirmed patients; patients meeting less criteria can be enrolled as suspected patients. Their status can be revised where appropriate when additional information becomes available (e.g. molecular analysis of the ADAMTS13 gene).

Tab. 1. Eligibility criteria for the hereditary TTP registry (clinicaltrials.gov identifier: NCT01257269).

<table>
<thead>
<tr>
<th>Enrollment into the hereditary TTP registry</th>
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<tbody>
<tr>
<td>1. patients* with hereditary TTP having a</td>
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<tr>
<td>A suitable patient history with one or more episodes of acute TTP, or having been identified through a family screening (history of an acute TTP episode not required, that is the patient may as yet be asymptomatic)</td>
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<tr>
<td>B severe ADAMTS13 deficiency (&lt;10% of the normal) in the absence of a functional ADAMTS13 inhibitor, documented on two or more occasions at least one month apart</td>
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<tr>
<td>C molecular analysis of the ADAMTS13 gene documenting two or more ADAMTS13 mutations</td>
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<td>D plasma infusion trial documenting a</td>
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<tr>
<td>- full recovery of infused ADAMTS13 and</td>
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<tr>
<td>- plasma half-life of infused ADAMTS13 of 2–4 days</td>
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<tr>
<td>2. all family members of patients with hereditary TTP</td>
</tr>
</tbody>
</table>

* patients fulfilling A and at least two of the remaining three criteria are enrolled as confirmed patients; patients meeting less criteria can be enrolled as suspected patients. Their status can be revised where appropriate when additional information becomes available (e.g. molecular analysis of the ADAMTS13 gene).

The hereditary TTP registry is to gather as much information as possible on natural history and clinical course of USS in different patients, factors that may trigger acute episodes (i.e. pregnancy, infections), treatment modalities, including plasma therapy and possible side effects of therapy. The eligibility criteria for the hereditary TTP registry are summarized (Tab. 1). Individuals fulfilling criteria A and two or all of the remaining three criteria are enrolled as confirmed patients; patients meeting less criteria can be enrolled as suspected patients. Their status can be revised when additional information or results, e.g. of molecular analysis, become available. The cutoff of a severe ADAMTS13 deficiency was set at 10% because there exist USS patients with some residual ADAMTS13 activity.

Because we are very much interested to increase knowledge on the fate of heterozy-
gous ADAMTS13 mutation carriers and other possible disease modifiers, family members interested in the project are invited to participate in addition.

During the past twelve months further individuals have been enrolled in the hereditary TTP registry (72 in total) and we aim for a number of 100 at the end of the year, when a first analysis is planned. As transition from the existing local registries in Bern (currently 80 families) and Nara is not yet complete, among the 72 individuals there are also patients identified as a result of the increased knowledge of the project through presentations at congresses and meetings.

Additional information is available on the hereditary TTP registry’s website (http://www.ttregistry.net), where basic information including patient information is posted in many languages (e.g. English, German, French, Italian, Spanish, Czech, Croatian) or on ClinicalTrials.gov (http://clinicaltrials.gov/ct2/results?term=NCT01257269).

The physicians enrolling patients retain the possibility to publish their cases on their own if they wish to do so, participate in future activities of the registry and can request a small compensation for their work upon completion of the baseline questionnaire.

Conflict of interest

YF, JNG, PNK, RS, BL and JAKH have served as consultants for Baxter Healthcare for the development of rADAMTS13 as a potential treatment for TTP.

References

Dabigatran, a new oral anticoagulant, is increasingly used to prevent thrombosis. In case of an emergency there are – despite the lack of a specific antidote – effective ways to quickly lower plasma dabigatran concentrations, as published in Thrombosis and Haemostasis by Prof. Harm Peters, MD, Department of Nephrology, Charité – Universitätsmedizin Berlin, Germany.

Dabigatran is a specific reversible oral direct thrombin inhibitor approved for prevention of venous thromboembolism and of stroke in patients with non-valvular atrial fibrillation. Dabigatran is highly water soluble, has low plasma protein binding, and a half-life of 12 to 17 hours (creatinine clearance > 60 ml/min) which is roughly doubled in patients with severe renal insufficiency (creatinine clearance < 30 ml/min). Since a specific antidote to reverse dabigatran’s effects on haemostasis is currently lacking, substantial clinical experience with non-specific reversal agents such as fresh frozen plasma or factor concentrates (e.g. PCC) are not available, and since haemodialysis data about removing dabigatran at therapeutic levels from the body are sparse, Peters and his team initiated an open-label trial to gather information about reductions of the anticoagulatory effects of dabigatran in humans via haemodialysis. They investigated the pharmacokinetic, dynamic and safety profiles of dabigatran and the reduction of plasma concentrations in seven clinically stable end-stage renal disease patients without atrial fibrillation. The study was designed to determine the efficiency of a single optimized haemodialysis session in removing dabigatran from the circulation with dabigatran being administered for a period of three days to achieve peak plasma concentrations comparable to those observed in atrial fibrillation patients receiving 150 mg b.i.d. Haemodialysis turned out as an effective method to remove dabigatran from the body. A single 4-hour dialysis session will rapidly eliminate at least 50% of dabigatran plasma levels, substantially reducing its anticoagulatory activity. There was a negligible redistribution of dabigatran after haemodialysis.

Haemodialysis can be a suitable approach to eliminate dabigatran in emergency situations. The low protein binding of dabigatran allows its rapid elimination at least 50% of dabigatran plasma levels, substantially reducing its anticoagulatory activity. There was a negligible redistribution of dabigatran after haemodialysis.

Effective elimination of dabigatran during bleeding or surgery

**Haemodialysis works for reducing dabigatran levels**

Reference


Die *Thrombosis and Haemostasis* erhalten GTH-Mitglieder mit 40% Rabatt im Abonnementspreis.

Interessenten wenden sich bitte an Frau Kluge (cornelia.kluge@schattauer.de).