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Inherited thrombotic thrombocytopenic purpura

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Thrombotic thrombocytopenic purpura (TTP) is a life-threatening disorder characterized by thrombocytopenia and microangiopathic hemolytic anemia accompanied by variable neurological dysfunction, renal failure and fever.[1]

Lesions consist of vessel wall thickening (mainly arterioles or capillaries), with endothelial cell swelling and/or detachments from the basement membrane with accumulation of fluffy material in subendothelial space, intraluminal platelet thrombosis and partial or complete obstruction of the vessel lumina. Thrombocytopenia is the likely consequence of platelet consumption in the microcirculation. The reason for hemolytic anemia is not as clear, but it may be a consequence of the mechanical fragmentation of erythrocytes as they flow through partially occluded microvessels.

TTP is a rare disease, with an estimated incidence of 2-10 cases per million/year in all racial groups. Recently, a greater awareness and perhaps improved diagnostic facilities have given the impression that the incidence is increasing.

In the microvasculature of patients with TTP, systemic platelet thrombi develop, mainly formed by platelet and von Willebrand factor (VWF). This protein plays a major role in primary hemostasis forming platelet plugs at sites of vascular injury under high shear stress. VWF is a large glycoprotein secreted by endothelial cells as ultra large (UL) multimers.

A major contribution to the understanding of VWF processing has been provided by Furlan *et al.*[2] and Tsai[3] who partially purified and characterized a plasma metalloprotease that physiologically reduces UL-VWF multimers by cleaving VWF at the peptide bond between 842Y and 843M residues in the A2 domain of the subunit. The activity of this protease was found deficient in the majority of patients with TTP leading to accumulation of UL-VWF multimers that are highly reactive with platelets.

In 2001 the protease was identified as ADAMTS13, the thirteenth member of the ADAMTS (a disintegrin and metalloprotease with thrombospondin type 1 domains) family.[4] This metalloprotease is encoded by the homonymous gene restricted on chromosome 9q34.[5] ADAMTS13, expressed predominantly in liver, is one of the largest proteins of the ADAMTS family, contains 1,427 amino acid residues and consists of a N-terminal signal peptide, a propeptide, a reprolysin-like metalloprotease domain, a disintegrin-like domain, a first thrombospondin type-1 motif (TSP1), a cysteine-rich domain, a spacer domain, seven additional TSP1 repeats and two CUB domains.

Two primary mechanisms for deficiency of the ADAMTS13 activity have been identified in TTP patients. In 70-80% of patients ADAMTS13 deficiency is acquired and is caused by the presence of circulating autoantibodies that develop transiently and tend to disappear during remission.[2,3] These inhibitory anti-ADAMTS13 antibodies are mainly IgG,[2,3,6] although IgM and IgA anti-ADAMTS13 antibodies have also been described.[6] Recent studies demonstrated that in patients with acquired TTP there were inhibitory antibodies reacting chiefly against the cysteine-rich and spacer domains of recombinant ADAMTS13.[7,8] In some cases the antibodies were directed only against these epitopes, but in the majority of patients different combinations of antibodies against the propeptide, the TSP1 and the CUB domains[8] were found suggesting a polyclonal autoantibody response.

In rare cases (about 10%), mutations in the *ADAMTS13* gene cause a congenital deficiency of the protease[9,10] and result in a familial recessive form of TTP. More than 80 different mutations have been identified in families with hereditary TTP.

Studies on secretion and activity of the mutated forms of the protease showed that most of these mutations led to an impaired secretion from the cells, and, when the mutated protein is secreted, the proteolytic activity is greatly reduced.[11-14]

Approximately 60% of these mutations are missense causing single aminoacid substitutions, and the remaining are nonsense, deletions or insertions causing frameshifts, or splice site mutants leading to a truncated protein. Although the mutations that result in a truncated protein are equally distributed throughout the molecule, more than 75% of the missense mutations cluster in the first half of the protein.

Most patients are carriers of compound heterozygous mutations. Only 15 mutations have been observed in homozygous form, including the one described in this issue of the journal by Palla *et al.*,[15] who found a homozygous deletion of nucleotides 2930-2935 in exon 23 of *ADAMTS13* in a South Iranian family. Interestingly, the deletion does not result in a frameshift and in protein interruption but it causes the replacement of C977 by a W and the deletion of A978 and R979 in the sixth TSP1 repeat domain where no mutations had so far been described.

The role of the seven TSP1 domains (TSP1-2-8) located on the C-terminal of ADAMTS13 on protease activity is controversial. Direct binding data[16] suggested that the C-terminal TSP1 domains and CUB domains may modulate ADAMTS13 interaction with VWF. Indeed truncation after the eighth TSP1 repeat reduced the binding affinity, and truncation after the seventh TSP1 repeat in addition to the CUB domains increased the affinity for VWF.[16] No data however were provided for the role of the sixth TSP1 domain on ADAMTS13 binding affinity. Another study from Soejima *et al.*[7] on recombinant proteins showed that mutants truncated after the spacer domain cleaved the Y842-M843 peptide bond of VWF, suggesting that all the C terminal TSP1 repeats and the CUB domains are dispensable for the proteolytic activity. In agreement with this finding, the report of Palla *et al.*[15] shows that the recombinant 2930-2935del GTGCCC mutant protein has normal specific activity. On the other hand this mutation, by substituting the C977 with a W, probably alters the folding of the protease by disrupting a disulphide bond within the sixth TSP1 domain. The recombinant mutated molecule is synthesized, although to a lesser degree than the wild type (wt) protein, but is secreted to very low levels. Immunofluorescence studies showed a diffuse presence of the mutant protein into the cytoplasm, with only a minimal staining at the endoplasmic reticulum and cis-Golgi compartments. These results suggest that the disulphide bridges in the sixth TSP1 repeat are important for the proper intracellular handling and secretion of the protein.

Of note, the 2930-2935delGTGCCC mutation was found in homozygosity in two brothers who developed TTP in adulthood but also in their asymptomatic 24-year old sister. This finding confirms previous data in literature reporting that penetrance of TTP in carriers of homozygous or compound heterozygous *ADAMTS13* mutations is variable. In the majority of patients the onset is in the neonatal period or during infancy, but a second group (10-20% of cases) remain asymptomatic until the third decade of life.[17] In addition, while some patients with complete congenital ADAMTS13 deficiency are plasma dependant and require frequent plasma infusion to prevent disease recurrences, many patients who achieved clinical remission after plasma treatment remain in a disease free status for long periods of time despite the absence of protease activity.[10,18] Emerging data suggest that the type and location of *ADAMTS13* mutations may influence the age of onset of TTP and the penetrance of the disease in mutation carriers. One of the most frequently reported *ADAMTS13* mutations, the 4143-4144insA in the second CUB domain, leading to a frameshift and loss of the last 49 aminoacids of the protein, is associated with neonatal-childhood onset, indeed only one out of 16

reported carriers, either homozygous or compound heterozygous with other *ADAMTS13* mutations, reached adulthood without developing TTP. [17,19,20] *In vitro* expression studies revealed that the mutation causes a severe impairment of protein secretion combined with a strongly reduced specific protease activity.[20] On the other hand, mutations in the seventh TSP1[21] and the newly reported mutation in TSP1-6[15] appear to lead to a later onset and a milder course of TTP. The R1060W mutation in TSP1-7 domain has been reported overall in 12 patients with adult onset TTP, but not in any published childhood cases.[17,21,22] Some patients carry the mutation in homozygosity (n=3), 4 are compound heterozygous, but 5 patients are heterozygous and no other causative mutations have been identified despite the fact that they had undetectable ADAMTS13 activity levels at presentation. Of note, inhibitory antibodies to ADAMTS13 were detected in 3 out of 5 heterozygous patients.[22] The reason for adult onset phenotype in patients with the R1060W and the 2930-2935delGTGCCC mutations is not yet clear. Expression studies revealed that both mutations result in severe defects in secretion of the metalloprotease, although a small fraction of the mutant protein is released in the supernatant, but the mutants maintain normal specific protease activity.[15,23] It is possible to hypothesize that in carriers of these mutations residual ADAMTS13 activity may be present in the circulation, which cannot be detected with the methods currently employed, but is however enough to prevent onset of the disease in childhood or even in adulthood. The latter possibility is supported by the asymptomatic 24-year old carrier of the 2930-2935delGTGCCC mutation described by Palla *et al.*[15] Additional cases of carriers of *ADAMTS13* mutations who never developed TTP have been previously reported (Table 1), including 2 twins with the R1060W and the 82-83insT mutations.[14]

Thus, ADAMTS13 deficiency alone is not sufficient to cause TTP. Environmental factors may contribute to induce full-blown manifestation of the disease. According to this *two hit model*, deficiency of ADAMTS13 predisposes to microvascular thrombosis and thrombotic microangiopathy supervenes after a triggering event that activates microvascular endothelial cells and causes the secretion of UL-VWF multimers and P-selectin expression. Platelets in flowing blood adhere transiently to secreted VWF anchored on P-selectin expressed by activated endothelium.[25] In normal subjects ADAMTS13 cleaves VWF multimers, thus limiting the thrombus growth.[25] Instead, in the absence of ADAMTS13, long strings of secreted UL-VWF and platelets remain bound to endothelial cells initiating the formation of thrombi.

Potential triggers of the above phenomena are infections and pregnancy. Indeed, one of the 2930-2935delGTGCCC mutation carriers in Palla's report developed the first TTP episode in association with pneumonia, which was also the triggering event in an adult case with the R1060W mutation.[21] Six additional carriers of the R1060W change developed the disease during pregnancy.[14,22]

Also genetic modifiers may be implicated in susceptibility to develop thrombotic microangiopathy in conditions of ADAMTS13 deficiency, which may include genes encoding proteins involved in the regulation of the coagulation cascade, VWF, or platelet function, components of the endothelial vessel surface or the complement cascade.

An example of this principle can be found in a report[24] on 2 sisters with the same compound heterozygous ADAMTS13 mutations, namely the V88M and the G1239V heterozygous changes, but dramatically different clinical manifestations. Both sisters developed TTP in adulthood following their first pregnancy and had several relapses concomitant with pregnancies, spontaneous abortions or infections. In one of them neurological symptoms were dominant, renal function remained normal and remission was achieved with plasma infusion, antiplatelet agents and anticoagulants. The sister, who had a more severe course of the disease, including severe renal involvement requiring chronic dialysis and eventually death attributable to cerebral stroke, was found also to carry a heterozygous mutation in the gene encoding complement factor H, a plasma factor inhibiting the activation of the alternative pathway of complement.[24] Since mutations in factor H gene have been

Table 1. Asymptomatic relatives of TTP patients carrying homozygous or compound heterozygous mutations in *ADAMTS13*.

Gender/age		aa change	Consequences (*in vitro*)	Activity/antigen (*in vivo*)	Ref.
1) M/37		ND	Unknown	Severe deficiency	18
2) M/53	Comp hetero	V88M G1239V	20% secretion *vs.* wt 35% activity *vs.* wt no secretion 66% activity *vs.* wt	<6%/<10%	14,24
3) F/25	Comp hetero	R1060W 82-83 insT	11% secretion *vs.* wt 35% activity *vs.* wt unknown	<6%/ND	14,23
4) F/25 (twin of n.3)	Comp hetero	R1060W 82-83 insT	11% secretion *vs.* wt 35% activity *vs.* wt unknown	<6%/ND	14,23
5) F/24	Homo	2930-2935 delGTGCCC	5% secretion *vs.* wt normal activity	<6%/<1%	15

Comp hetero: compound heterozygous; homo: homozygous, wt: wild type, ND: not done.

found in around 30% of familial cases of HUS, it was hypothesized that in the above patient, factor H haploinsufficiency had a role in determining the renal complications that superimposed on the systemic disease caused by ADAMTS13 deficiency.

This finding suggests that abnormalities in factors that control complement activation may contribute to development of thrombotic microangiopathy in patients with ADAMTS13 deficiency. That this may be the case is documented by the occasional finding of platelet-associated C3 in patients with TTP. In addition lower than normal serum levels of C3 (an index of complement activation) were found during the acute phase of the disease in half the patients with TTP and ADAMTS13 deficiency.[26]

Recently, two mouse models of ADAMTS13 deficiency[27,28] have been described, which underline the requirement for further genetic and environmental factors in addition to lack of ADAMTS13 for the full manifestation of TTP.

Deletion of *Adamts13* gene on a 129/Sv background resulted in mice that were viable and fertile without any evidence of thrombocytopenia, hemolytic anemia or microvascular thrombosis.[28] Thrombocytopenia was more severely induced in ko than in wild-type mice after injection of collagen and epinephrine, indicating that a complete ADAMTS13 deficiency in mice caused a prothrombotic state, but not TTP. ADAMTS13 deficiency in the mixed strain C57BL/6J-129/Sv was associated with normal survival, although VWF-mediated platelet-endothelial interactions were prolonged. Backcrossing to CASA/Rk (a mouse strain with elevated plasma VWF) resulted in the appearance of spontaneous thrombocytopenia in a subset of *Adamts13* deficient mice.[27] When Shiga toxin was infused intravenously, TTP-like symptoms were observed in *Adamts13* deficient mice with the mixed CASA/Rk background, but not in C57BL/6J-129/Sv mice.[27] No correlation was observed between plasmatic levels of VWF and severity of TTP, implying the existence of TTP modifying genes distinct from VWF.

Thus *Adamts13* ko mice appear to recapitulate the situation in humans in which deficiency of ADAMTS13 is not sufficient for TTP pathogenesis. They may be useful models for investigating TTP genetic modifiers and environmental triggers.

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Hepatitis C virus and allogeneic stem cell transplantation still matters!

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Allogeneic Hematopoietic Cell Transplantation (HCT) is widely used to cure patients with hematologic disorders. Nearly 90% of the patients who survived free of their original disease more than two years after the procedure are expected to become long-term survivors, leading to thousands of cured patients worldwide.[1] Liver complications influence morbidity and mortality in patients undergoing HCT. Liver injury is common early after HCT because of sinusoidal obstruction syndrome (SOS; formerly known as veno-occlusive disease), Graft-versus-Host Disease (GvHD), drug toxicity, post-transplantation viral hepatitis and disease relapse. Among long-term survivors, cirrhosis is an important late complication of HCT.[2,3]

The hepatitis C virus (HCV), identified in 1989, is an enveloped RNA-virus with a 9.6kb single strand genome. A significant proportion of long-term HCV-infected HCT survivors, primarily contaminated through blood exposure, develop cirrhosis and hepatocellular carcinoma during the long-term follow-up.[4,5] Moreover, HCT recipients showed a higher rate of liver fibrosis progression as compared with HCV-infected patients who did not receive a transplant.[5] HCV-related disorders and the prognostic implications of hepatitis C seropositivity after allogeneic HCT will be shortly summarized here, more detailed reviews can be found in recent publications.[2,3] Hepatitis C virus (HCV) is a major cause of liver disease worldwide. HCV is the most common chronic blood-borne infection in the United States. The Centers for Disease Control estimated that during the 1980s, an average of 230,000 new infections occurred each year. Although the annual number of new infections has declined by more than 80% since the 1990s, population-based studies indicate that 40% of chronic liver diseases are HCV related. HCV is transmitted primarily through blood exposure. However, blood transfusion, which accounted for a substantial proportion of cases of HCV infections acquired more than ten years ago, rarely accounts for recently acquired infections owing to systematic screening of blood products for HCV.[2,3]

Hepatitis C in allogeneic hematopoietic cell transplant donors

It may turn out that the only available donor is HCV antibody and RNA positive. Regulatory issues may then arise in some countries knowing that HCV will usually be transmitted, and that the rate of spontaneous viral clearance is likely to be low. Treatment of the donor with pegylated interferon plus ribavirin prior to harvest of donor cells may render them non-viremic and much less likely to transmit infection. If the virus is transmitted, the acute phase of HCV infection may cause elevated liver enzymes at 2–3 months post HCT, after recovery of T-cell function; however, severe hepatitis is rare, and the outcome in ten years of follow-up is no different than in transplant recipients without hepatitis C infection.[6] In the long-term, treatment should be offered to the recipient who remains with active hepatitis as such a patient is at risk for development of cirrhosis and hepatocellular carcinoma.

Chronic hepatitis C in candidates for hematopoietic cell transplant

Patients with active liver disease, particularly those with severe hepatic fibrosis or cirrhosis, are at increased risk for fatal sinusoidal obstruction syndrome (SOS) following some myeloablative regimens, (notably regimens that contain cyclophosphamide or total body irradiation over 12 Gy), and the presence of cirrhosis may provide a contraindication to any high-dose conditioning regimen. Patients with cirrhosis are at risk for fatal hepatic decompensation after HCT even if given a reduced-intensity conditioning regimen.[7] Liver biopsy should be considered before the start of conditioning therapy if there is a clinical suspicion of cirrhosis or extensive fibrosis resulting from chronic viral infection.

Prognostic implications of hepatitis C virus infection after allogeneic hematopoietic cell transplant

Short-term outcome

In the first three months after transplant, liver dysfunctions related to HCV are usually mild[6,8-10] limited to