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Current Concepts in Thrombotic Thrombocytopenic Purpura

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Abstract

Recent advances have demonstrated that thrombotic thrombocytopenic purpura (TTP), characterized by widespread thrombosis in the arterioles and capillaries, is caused by deficiency of a circulating zinc metalloprotease ADAMTS13. Two types of TTP are recognized: Autoimmune TTP caused by inhibitory antibodies of ADAMTS13 and hereditary TTP in association with genetic mutations of the *ADAMTS13* gene. This article reviews the characteristic and function of ADAMTS13, the mechanism by which ADAMTS13 deficiency may cause thrombosis, and the causes of ADAMTS13 deficiency. It also discusses how the new knowledge may improve the diagnosis and treatment of this previously mysterious disorder.

Keywords

Thrombotic thrombocytopenic purpura; von Willebrand factor; ADAMTS13; Shear stress; Hemolytic uremic syndrome

INTRODUCTION

Thrombotic thrombocytopenic purpura, first described in 1924 by Moschcowitz, is characterized by the presence of hyaline thrombi in the arterioles and capillaries of multiple organs. The patients typically present with weakness, pallor, petechiae, headache or other subtle mental changes (1,2). If not treated, the disease may rapidly deteriorate to stupor, coma, cardiac arrest, and demise. The use of plasma infusion and plasma exchange as treatment has reduced the case fatality of TTP from > 90% to 10% – 20% (3). Because its etiologies were unknown, the pathogenesis was mysterious, and the response to plasma therapy was miraculous, TTP has been the subject of intense interest. In the last few years, advances in elucidating the molecular defects of TTP have raised new hopes of improving the diagnosis and treatment for the patients.

CLINICAL FEATURES

The incidence of TTP has been estimated to be 3 – 4 per million person-years (4,5). Blacks, and black females in particular, are affected at a disproportionately high rate. One study reported that between 1968 and 1991 there was an increasing trend of the disease (4). However, a more recent study failed to detect such a trend (5). These studies were based on death certificates, insurance claims, or practice management database, whose criteria of disease classification may differ and do not necessarily conform to the current disease definition.

Histopathologically, the changes of TTP are quite distinctive: widespread hyaline thrombi in the terminal arterioles and capillaries, and depending on the age of the lesions accompanied by variable fibroblastic infiltration and endothelial overlay. The thrombi are found most extensively in the brain (mainly cerebral cortex), heart, spleen, pancreas, adrenal gland and kidney, and are composed primarily of degranulated platelets and von Willebrand factor (6, 7). Small amount of fibrin may be present surrounding or sometimes penetrating the amorphous

or granular materials. This contrasts to the opposite results obtained in the thrombi of disseminated intravascular coagulation or the hemolytic uremic syndrome, which are characterized by prominent fibrin deposits (7,8). Endothelial or subendothelial swelling is minimal in TTP but more prominent in shiga toxin-associated or idiopathic HUS. Glomerular thrombi in the kidney per se are not pathognomonic of TTP as they are a common feature of the HUS. In contrast to HUS, TTP causes spotty rather than extensive glomerular thrombi.

Clinically, two types of TTP are recognized: a hereditary form that often present soon after birth, and an autoimmune form that affects adolescents or adults. Most cases of TTP are of the autoimmune type.

Autoimmune TTP

The classic features of TTP have been extensively reviewed (2). Thrombocytopenia, microangiopathic hemolysis, and fleeting neurological deficits (triad), plus fever and renal abnormalities (pentad) are characteristic but not pathognomonic of TTP. Other complications include abdominal pain with or without evidence of pancreatitis and EKG abnormalities. Pulmonary or liver dysfunction is rare. A constellation of vague, non-specific symptoms may precede the onset of seriously illness. These symptoms may be due to a prodrome event or the early stage of the disease. Occasionally a patient may present with isolated thrombocytopenia that lasts for weeks or months and incorrectly presumed to have immune thrombocytopenic purpura, before evolving to microangiopathic hemolysis and other complications. Although hematuria and proteinuria are common, overt renal failure or oliguria is rare in TTP, unless it is caused by a concurrent disorder.

Relapse of TTP occurs in 30%–60% of the cases (9,10), with most relapses occurring during the first month after the acute episode and less frequent thereafter. The periods between relapses may range from days to many years. Pregnancy, surgery, diarrhea and infection are suspected to trigger relapses. However, many cases do not have obvious precipitating events. A subset of the patients develops multiple relapses or has persistent disease, requiring long-term plasma exchange or other therapies.

Follow-up observations in patients that survive the acute episodes of TTP reveal that when the disease relapses, it often begins with a decline of the platelet count before hemolysis or other manifestations become apparent. The disease evolves variably, ranging from rapid deterioration within a few days to smoldering for weeks or months. Occasionally, focal neurological deficits such as hemiparesis, slurred speech or aphasia may occur early in the course. Such neurological complications may pose a diagnostic challenge when they precede thrombocytopenia or microangiopathic hemolysis (11,12).

The triad or pentad of manifestations is not pathognomonic of TTP as previously suggested; they may be present in patients with other disorders such as the hemolytic uremic syndrome, lupus erythematosus or allogeneic bone marrow transplantation (Table 1). The trend of making a diagnosis of TTP at an early stage further contributes to uncertainty or confusion in disease classification. The introduction of ADAMTS13 assay as a specific test of TTP has helped clarified the diagnosis in bewildering cases.

Hereditary TTP

Upshaw-Schulman syndrome, characterized by thrombocytopenia and microangiopathic hemolysis presenting soon after birth, represents the congenital form of TTP (13,14). The patients typically improve swiftly following infusion of small amount (10–15 mL/kg) of plasma infusion (13,14,15).

Most cases of hereditary TTP have evidence of the disease soon after birth, although its presence is not always recognized. The neonates typically develop within a few hours of birth hyperbilirubinemia and thrombocytopenia. Hemolysis with schistocytes on blood smears may be noted. Serious complications such as seizures and mental obtundation may raise suspicion of intracranial hemorrhage or sepsis. Improvement occurs promptly after simple blood transfusion or exchange transfusion. After variable periods ranging from weeks to years, the patients relapse with thrombocytopenia and anemia. Occasionally the course may be complicated with pancreatitis, focal neurological deficits, seizures, or acute renal failure. Because the disease is relatively obscure and a family history is often not available for this autosomal recessive disease, hereditary TTP might be mistaken as idiopathic thrombocytopenic purpura, Evan's syndrome, or the hemolytic uremic syndrome. When the disease presents or relapses after the first few years of life, a distinction with idiopathic TTP may not be obvious.

The severity of hereditary TTP varies. Many patients of hereditary TTP require regular plasma infusion every 2 – 4 weeks to prevent serious complications. These patients had been identified as chronic relapsing TTP in the literature. Others may maintain normal platelet counts and only require plasma infusion intermittently. Because some patients have mild or sub clinical disease, the hereditary form of TTP is likely more prevalent than currently recognized (16). It is important to establish the diagnosis in mild cases because it facilitates appropriate management when the patients do present with acute complications. No phenotypic abnormality has been established among carriers of one mutant *ADAMTS13* allele. Nevertheless, the family members with *ADAMTS13* deficiency were instrumental in cloning of the gene and establishing its role in causing TTP (17).

The variable severity of hereditary TTP suggests that other factors affect the manifestation of the disease. Three types of factors appear to contribute to the variability of TTP: the specific types of *ADAMTS13* mutations, other disease modifying genes, and environmental factors such as fever, infection, diarrhea, surgery, or pregnancy. Further studies are needed to delineate how these factors affect the phenotypic severity of *ADAMTS13* deficiency.

MOLECULAR MECHANISMS OF THROMBOSIS IN TTP

Molecular Biology and Biochemistry of *ADAMTS13*

The *ADAMTS13* gene contains 29 exons spanning approximately 37 kb on chromosome 9q34 (17,18,19). *ADAMTS13* encodes a 4.7-kb transcript that is expressed in the liver, and a 2.4-kb transcript detectable in placenta, skeletal muscle, and certain tumor cell lines. In the liver, *ADAMTS13* is expressed primarily in the retinoid-enriched stellate cells (also known as lipocytes, fat-storing cells, or Ito cells), which are located in the subendothelial space of Disse that separates the hepatocytes from the sinusoidal endothelium (20,21).

The full-length transcript encodes a precursor polypeptide with 1427 amino acid residues. *ADAMTS13* is synthesized in the cells as a 185-kd, instead of the calculated 145-kd protein, indicating that the protein undergoes extensive glycosylation and other post-translation modifications. The sequence of *ADAMTS13* exhibits a multi-domain structure that is common for proteases of the *ADAMTS* (a disintegrin and metalloprotease with thrombospondin type 1 motif) family and but also contains unique domains (Figure 1).

ADAMTS13 cleaves VWF at the Y1605-M1606 bond of the VWF polypeptide (22). Disulfide bond-reducing agents, tetracyclines, or cation chelators such as phenanthroline inactivate the VWF cleaving activity of *ADAMTS13*, suggesting that the Zn^{++} moiety of the metalloprotease domain and the intra chain disulfide bonds are critical for the protease activity. Although *ADAMTS13* is stable in normal plasma, its activity may deteriorate rapidly in plasma samples

obtained from patients with liver diseases or other pathological conditions. Thrombin, plasmin, and hemoglobin have been reported to inactivate the activity of ADAMTS13 (23,24).

Phylogenetic analysis indicates that ADAMTS13 diverges early from other members of the ADAMTS family of proteases (25,26). In particular, ADAMTS13 contains an unusually short (41 amino acid residues) propeptide whose cleavage does not appear necessary for expression of proteolytic activity (27). Enzymatic analysis of proteins expressed by mammalian cells reveals that the VWF cleaving activity decreases precipitously when ADAMTS13 is truncated proximal to spacer domain (28,29). It is possible that the sequence of the extra metalloprotease domain modulates the expression of the protease activity, perhaps by facilitating the binding between the spacer domain sequence the protease and its substrate, VWF(30).

VWF, platelet, shear stress, and microvascular thrombosis

von Willebrand factor (VWF), a glycoprotein synthesized in vascular endothelial cells and megakaryocytes, exists in the circulation as a series of disulfide-bonded multimers whose molecular weights range from 1×10^6 to greater than 20×10^6 daltons. The large multimers are essential for supporting platelet aggregation under high shear stress conditions. Endothelial cells account for > 90% of circulating VWF. Instead of being directly secreted from vascular endothelial cells, VWF multimers derive from an ultra large VWF polymer. This endothelial VWF and its large multimeric derivatives are cleaved in a shear dependent manner by ADAMTS13 to become smaller forms (31,32,33).

The complex interaction among VWF, platelet, ADAMTS13, and shear stress is depicted in Figure 2. Three-dimensionally VWF exists in a globular form that is conformationally flexible, and it unfolds in the direction of shear force to become an elongated form that is most active in aggregating platelets (panel A) (34). This elongated form of VWF would cause platelet thrombosis if it were allowed to accumulate in the circulation (panel C). The elongated form of VWF does not exist in the circulation because ADAMTS13 immediately cleaves VWF at the Y1605-M1606 bond whenever VWF is partially unfolded by shear stress (panel B). This proteolytic process is critical for keeping VWF in globular but progressively smaller, less flexible forms. The spectrum of VWF multimers is maintained in balance by continual secretion of ultra large VWF from endothelial cells. VWF multimers as detected in the plasma represent a snapshot of a dynamic process. A deficiency of ADAMTS13 diminishes VWF cleavage and favors the accumulation of elongated, hyperactive forms of VWF that are prone to bind platelets, causing microvascular thrombosis of TTP.

This scheme provides a basis for understanding some of the well-known peculiar features of VWF. (a) In a test tube, VWF and ADAMTS13 co-exist in the plasma without evidence of ongoing cleavage, because VWF exists in a globular conformation that is resistant to cleavage by ADAMTS13. (b) VWF-platelet adhesion and aggregation do not occur in the circulation because VWF is kept in globular forms that are incapable of binding platelet receptor Ib. (c) Shear stress enhances VWF-platelet adhesion and aggregation at sites of vessel injury because it causes rapid conformational unfolding of matrix-bound VWF, exposing its binding sites for platelet receptor Ib. (d) Large VWF multimers are hemostatically more effective than small multimers because large size confers higher flexibility and responsiveness to shear stress. The flexible conformation allows large VWF multimer to unfold in response to shear stress, forming the substrate for supporting platelet adhesion and aggregation.

This regulation of VWF-ADAMTS13 interaction is perhaps the nature's design to meet the need of immediate, effective hemostasis in the microvasculature. This scheme ensures that large VWF is instantly available at sites of vessel injury for supporting platelet aggregation, while it prevents unwarranted VWF-platelet binding in the circulation. It also takes advantage of shear stress profile in a vascular lumen: shear rate is highest at the endothelial surface,

declining toward zero at the center. Thus, after initial cleavage at the time of release from endothelial cells, VWF is exposed to high levels of shear stress only intermittently and very briefly during each cycle in the circulation, unless it is bound to a site of injury. This helps create a large safety margin: intravascular platelet thrombosis does not occur until ADAMTS13 is decreased to a very low (<10% of normal) level.

VWF multimer size in diseases

The balance of VWF-ADAMTS13 interaction may be disturbed if there is an abrupt rush of VWF secretion by endothelial cells in low-shear environments, deficiency of ADAMTS13, mutant VWF with enhanced susceptibility to cleavage by ADAMTS13, or abnormal shear stress.

Patients with ADAMTS13 deficiency are expected to have ultra large VWF multimers in their plasma. Indeed ultra large VWF multimers are present in patients with low ADAMTS13 activity levels during remission (35). Paradoxically, at the acute stage of TTP both ultra large and normally large multimers are missing (36,37). The scheme depicted in Figure 2 provides a framework for understanding the intriguing pattern of VWF multimers in TTP. In the absence of ADAMTS13, conformationally flexible large VWF multimers become progressively unfolded. These unfolded forms of VWF bind platelets, causing platelet thrombosis and a depletion of the large multimers from the circulation.

Infusion of desmopressin causes acute release of VWF from endothelial cells, resulting in the appearance of ultra large VWF multimers (38). Although infusion of desmopressin may decrease plasma ADAMTS13 level, the mild decrease is not sufficient to account for the appearance of ultra large multimers (39).

Certain mutations of the VWF gene (type 2A von Willebrand disease) enhance the susceptibility of VWF to cleavage by ADAMTS13 (40,41); as a consequence, VWF is continually cleaved by ADAMTS13 in the circulation to smaller multimeric forms.

The shear stress profile of the circulation also affects the efficiency of the cleavage. The hemolytic uremic syndrome and aortic stenosis are two examples in which abnormal shear stress in the microcirculation or at the aortic valve enhances cleavage of VWF, resulting in a decrease of large VWF multimers (8,42). Microangiopathic hemolysis often co-exists with loss of large VWF multimers, because abnormal shear stress contributes to the development of both conditions. The presence of ultra large multimers in neonates or the umbilical cord may result from lower shear stress profile of the fetal circulation (43).

CAUSES OF ADAMTS13 DEFICIENCY

Antibodies of ADAMTS13

Inhibitory antibodies of ADAMTS13 causes a profound deficiency of the protease among patients with the autoimmune TTP (44,45). The prevalence of ADAMTS13 deficiency among patients with TTP varies from 13% to 100% depending on the criteria used for including the study cases (44,45,46,47,48,49,50). Studies using less strict criteria of case inclusion inevitably report the lowest prevalence rates of ADAMTS13 deficiency. Since a clear distinction between TTP and HUS or other types of microvascular thrombosis is not always clinically feasible, TTP case series often include patients with other types of microvascular thrombosis. However, if a set of strict criteria is applied to define patients with unequivocal, idiopathic TTP, a profound deficiency in ADAMTS13 is detected in each case (51). In our experience, inhibitory activity mediated by IgG is detectable in every patient of TTP investigated. Nevertheless, this does not exclude the possibility that patients may also have non-inhibitory antibodies (52).

The inhibitors of ADAMTS13 are generally of very low (< 10 U/mL, using the same definition for factor VIII inhibitors) titers, suggesting that the antibodies are directed against other targets but cross-react with ADAMTS13. Because they appear suddenly, then decline gradually over a course of weeks to months, the inhibitors may represent a response to an otherwise innocuous infection or certain exogenous molecule. TTP may develop within 2 – 6 weeks after ticlopidine is used for cardiovascular indications (53,54). No other apparent etiologies of TTP have been identified.

TTP may develop in patients with HIV infection. Before the introduction of effective anti-retroviral treatment, HIV was present in up to 50% of the TTP cases at a major urban center (55). In recent years, the prevalence of HIV infection among TTP patients has declined to as low as 10% in some series. How HIV is related to the development of TTP remains poorly understood. Nevertheless its presence could pose challenges during the course of management. Because autoimmune thrombocytopenic purpura is common among patients with HIV infection, persistence of thrombocytopenia in a HIV patient with TTP may be mistaken as refractory TTP, leading to unnecessarily prolonged plasma exchange therapy.

When a patient is treated with plasma exchange, the rise in the platelet count is accompanied by a decrease of the inhibitor titer and an increase of the ADAMTS13 activity levels. It is believed that plasma exchange replenishes the missing ADAMTS13; it may also help remove the inhibitors. The protease activity level is usually not completely normalized and inhibitors of the protease may remain detectable when the patients are investigated during clinical remission, suggesting that the autoimmune reaction against ADAMTS13 persists. In such patients, a relapse of TTP due to increased inhibitor titers might represent anamnestic response to the same or similar inciting agents, or result from breakdown in the immune regulation, allowing a resurgence of the immunocytes.

The target epitopes of the ADAMTS13 inhibitors have not been definitively determined. Studies of recombinant ADAMTS13 or its truncated forms revealed that IgG molecules isolated from TTP patients react with recombinant ADAMTS13 proteins that include the sequence of the spacer domain (28,56,57). These observations suggest that the spacer domain is a potential target of TTP inhibitors. A systemic, prospective investigation is needed to determine the prevalence and duration of ADAMTS13 inhibitors among patients with TTP and the nature and etiology of the autoimmune reaction against ADAMTS13.

Genetic mutations

More than forty different mutations of the ADAMTS13 gene have been described (17,58,59, 60) and are shown in an extensive table available online (see the Supplemental Material link in the online version of this chapter or at <http://www.annualreviews.org>). The mutations, which include mis-senses, non-senses, frame-shifting deletions or insertions, and intronic splicing mutations, distribute throughout the various domains of ADAMTS13. The majority of the mutations affect the sequence of metalloprotease-spacer domains that are critical for expression of proteolytic activity. Eight mutations have been investigated in expression studies: one mutation creates a proteolytically inactive form, while the other seven mutations impede secretion of the protein. All five intronic mutations have been investigated by RT PCR and were confirmed to be associated with abnormal splicing.

Mutations of ADAMTS13 have been detected in individuals of various racial descents including African, American Indian, Asian, and Caucasian. There are at least 17 recurrent mutations, including 5 mutations detected in seemingly unrelated patients. Three reports have described the 4143insA mutation in multiple individuals. Nevertheless, it remains to be determined whether any of the recurrent mutations occurred independently. A correlation between the types of mutations and severity of hereditary TTP has not been identified.

In addition to mutations, multiple polymorphisms of the gene are detected in individuals from different geographic areas. Overall, each of the exons contains at least one genetic variation. The data suggest that variation in the *ADAMTS13* gene is not uncommon. Mutations that compromise the expression of ADAMTS13 protease activity may persist because a carrier of one mutant allele is not phenotypically disadvantaged.

DIFFERENTIAL DIAGNOSIS

TTP, HUS, or TTP/HUS?

Microangiopathic hemolysis and thrombocytopenia are not pathognomonic of TTP; instead, they are a hallmark of widespread microvascular thrombosis. Previously, because the pathogenesis of microvascular thrombosis was not known, classification of microangiopathic hemolysis and thrombocytopenia was based on phenotypic manifestations: TTP for patients with overt neurological dysfunction, and the hemolytic uremic syndrome (HUS) for patients with prominent renal failure. This seemingly simple scheme proves to be confusing and unattainable, as patients with recurrent TTP may present with overt neurological deficits or renal failure on some but not other occasions. As a result, it was not uncommon to encounter patients carrying both diagnoses of TTP and HUS. The development of thrombocytopenia and microangiopathic hemolysis in a patient with hereditary TTP after acute diarrhea may raise the suspicion of HUS. On the other hand, some cases of shiga-toxin associated thrombosis do not develop severe renal failure and consequently had been incorrectly given the diagnosis of TTP. Because of the overlapping manifestations, some investigators have used the term TTP/HUS to accommodate all patients presenting with microangiopathic hemolysis and thrombocytopenia. This approach obscures the distinct pathogenetic mechanisms or etiologies among different disorders. With advances in the molecular mechanisms of microvascular thrombosis, the term TTP/HUS has outlived its historic role.

Microvascular thrombosis is a pathological entity with multiple causes (Table 1). ADAMTS13 deficiency accounts for most of the cases of “typical” TTP, which is characterized clinically by the absence of certain features that suggest other disorders: a plausible cause of microvascular thrombosis, a prodrome of diarrhea, acute renal failure, hypertension, or acute respiratory syndrome. A patient with an age greater than 10 years but none of these excluding features is essentially certain to have TTP. Conversely, the presence of any of these features favors other diagnoses, although it does not exclude the diagnosis of TTP.

Shiga toxin is the etiologic agent of typical HUS that occurs after infection with *E. coli* O157:H7 or other related microorganisms (61). A defect in the regulation of the complement cascade, due to mutations in factor H, membrane cofactor protein (CD46), or serine protease factor I, or due to autoantibodies of factor H, accounts for approximately 30% of idiopathic atypical HUS (62,63). Table 2 summarizes some of the different features of TTP and HUS.

Thrombocytopenia and microangiopathic hemolysis occasionally occur in association with cancer chemotherapeutic agents (e.g. mitomycin, gemcitabine), bone marrow or solid organ transplantation (often in association with the use of calcineurin inhibitors) (64), lupus or other related autoimmune disorders. Generally, these disorders are accompanied by variable severity of renal failure and do not have antibody inhibitors of ADAMTS13. The molecular mechanisms of secondary HUS and many cases of idiopathic HUS remain unknown.

TTP and HUS do not encompass all patients that present with microangiopathic hemolysis and thrombocytopenia. HELLP syndrome, Paroxysmal nocturnal hemoglobinuria with widespread thrombosis in the mesenteric microvasculature, Rocky Mountain spotted fever, metastatic cancers and DIC are other disorders that may associate with the development of microvascular thrombosis or occlusion. These disorders are not caused by ADAMTS13

deficiency, and with normal renal function also do not belong to the category of the hemolytic uremic syndrome.

LABORATORY INVESTIGATION

A thorough assessment of a patient suspected of TTP includes assay of ADAMTS13 activity level, determination of ADAMTS13 inhibitors, and gel electrophoresis of VWF multimers. When hereditary TTP is suspected, study of the parents or other family members, complemented by DNA sequence analysis for mutation of the *ADAMTS13* gene, may help establish the diagnosis.

ADAMTS13 activity

A patient presenting with thrombocytopenia due to autoimmune inhibitors of ADAMTS13 typically has very low ADAMTS13 activity level in their plasma. A very low or absent ADAMTS13 activity level distinguishes TTP from shiga toxin-associated HUS, atypical HUS, and other microangiopathic disorders. Since some versions of the ADAMTS13 activity assay detect very low levels of protease activity among patients without TTP, the threshold value of ADAMTS13 activity for diagnosis of TTP varies and should be established in each laboratory.

Occasionally a patient may have concurrent ITP or other disorders that causes thrombocytopenia independent of TTP. If the platelet count does not respond satisfactorily to plasma exchange, a repeat analysis of ADAMTS13 activity may help reveal that the thrombocytopenia is due to the presence of another disorder.

Current assays of ADAMTS13 activity differ in design and the range of normal values observed, as recently reviewed (51). The protease activity in patients with various types of pathological conditions is not stable in vitro and may be lost during storage or incubation. This instability may explain at least in part why some assays detect very low activity levels without accompanying evidence of impaired VWF proteolysis. The combination of a very low ADAMTS13 value and a normal VWF multimer pattern should raise suspicion of the validity of the assay result.

ADAMTS13-inhibiting antibodies

A mixing study of patient plasma with normal plasma detects the presence of inhibitors of ADAMTS13 in most patients presenting with acute TTP. The prevalence of ADAMTS13 inhibitors depends on the sensitivity of the assay used. When a mixing study fails to detect the presence of inhibitors, IgG molecules purified from the patients' plasma or serum may bring out a positive result. Inhibitors of ADAMTS13 may persist with fluctuating titers for months to years during periods of clinical remission. Excessive increase of ADAMTS13 inhibitor titers may suppress ADAMTS13 activity below the threshold level and cause relapse of TTP.

Investigation of genetic ADAMTS13 deficiency

In hereditary cases, inhibitors of ADAMTS13 are not detected and the parents or children are partially deficient in ADAMTS13 activity. Since a slight decrease in ADAMTS13 activity level may be observed among patients with various types of medical illness, investigation of a potential carrier should be conducted in the absence of complicating illness. Assays that have a broad normal range will not distinguish carriers of ADAMTS13 mutant alleles from normal individuals. Nucleotide sequence analysis for mutations of ADAMTS13 gene remains an investigational tool.

VWF multimers

Analysis of the VWF multimers at the advanced stage of the disease usually detects a depletion of ultra large and large multimers. During the early stage of remission, an increase in the platelet count often coincides with the appearance of ultra large VWF multimers. This is because at this stage, the ADAMTS13 activity remains very low but is sufficient to ameliorate the binding between VWF and platelet. Ultra large VWF multimers are detected among patients in remission with persistently low ADAMTS13 activity levels. Interpretation of ADAMTS13 activity levels and VWF multimers should be correlated with the disease stage.

TREATMENT

Plasma exchange

Plasma exchange with fresh frozen plasma remains the mainstay of treatment, achieving remission in 70% – 90% of the patients (3,9). Because TTP may evolve rapidly at its advanced stage, any delay in treatment increases the risk of adverse outcomes. When plasma exchange is not immediately available, patients should be given fresh frozen while waiting for the institution of definitive treatment. Platelet transfusion should be avoided. Corticosteroids and anti-platelet agents are often used as part of the initial regimen, although their values have not been vigorously investigated. When patients do not respond satisfactorily to plasma exchange, second-line therapies including vincristine, splenectomy, cyclophosphamide, azathioprine, or cyclosporin A may be added to the therapeutic regimen. Only the efficacy of plasma therapy has been established in a randomized control study.

Patients with hereditary TTP respond readily to infusion of 10 –15 mL fresh frozen plasma, with the platelet count rising within a few hours or by the next day. For patients that maintain normal platelet counts between episodes of relapse, the indication of chronic plasma therapy is less obvious. Patients with a history of serious complications probably should be treated with maintenance therapy to prevent further complications.

Role of plasma therapy in other types of microvascular thrombosis

Because of uncertainty in diagnosis, patients with other types of microvascular thrombosis are often treated as TTP with plasma therapy. With new insights in the molecular mechanisms, it is now clear that management of the patients should be tailored to individual diagnosis. In pediatric practice, plasma therapy is generally not used for shiga-toxin associated HUS (61). Plasma therapy may be effective for patients with defects of circulating proteins such as mutations of factor H or serine protease factor I. However the optimal regimen for such patients has not been established. Plasma therapy is not expected to be effective for patients with mutations of the membrane cofactor protein (CD46); instead, such patients may be cured of the disease by renal transplantation. The use of plasma exchange for bone marrow transplantation-associated HUS has generally produced disappointing outcomes (65,66). Further elucidation of the underlying mechanisms responsible for microvascular thrombosis should facilitate the development of rationally designed targeted therapy for patients with idiopathic or secondary HUS.

Cryosupernatant plasma

Cryosupernatant fraction of fresh frozen plasma is depleted of large VWF multimers. Because large VWF multimers are involved in causing platelet aggregation, cryosupernatant of fresh frozen plasma has been advocated as a more effective alternative of fresh frozen plasma (67, 68). Cryosupernatant plasma contains the same amount of ADAMTS13 as fresh frozen plasma, and is not expected to be more effective in raising the ADAMTS13 levels. Two randomized studies have failed to confirm the superiority of cryosupernatant plasma over fresh frozen plasma in inducing remission or reducing mortality (69,70).

Immunomodulation

Since autoantibody inhibitors of ADAMTS13 cause TTP, suppression of immune responses with immunosuppressive molecules such as cyclosporin rituximab, a chimeric anti-CD20 monoclonal antibody that depletes B-cells from the circulation and lymphoid tissues, may be a rational approach. Case reports have described refractory patients that improved within 2 – 4 weeks of rituximab therapy (71). Rituximab appears to be valuable for patients that have persistent but low inhibitor titers but may be inadequate for patients with high titers of inhibitors. The role of rituximab in the acute or subacute setting for improving treatment outcome or preventing relapse is uncertain and will require vigorous evaluation in randomized trials.

PROSPECTIVES

Previously a perplexing disorder, TTP has been shown to be a single-molecule disease. Future challenges include the etiologies that induce the immune responses to ADAMTS13 among patients with TTP and the factors that affect the severity of thrombosis caused by ADAMTS13 deficiency. The identification of ADAMTS13 has raised expectations that it will be possible in the near future to provide molecular therapy for the treatment of TTP. This enthusiasm is hampered by the presence of ADAMTS13 inhibitors and the lack of effective measures to quickly eradicate the inhibitors. Through further structure-function analysis, it may be feasible to design ADAMTS13 variants that are proteolytically active but are not suppressible by the inhibitors of TTP. Such non-suppressible ADAMTS13 molecules might obsolete the need of plasma exchange and eliminate the risk of treatment failure due to potent ADAMTS13 inhibitors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

A schematic depiction of the homologous domain structure of ADAMTS13. The sequence of ADAMTS13 consists of a signal peptide, a propeptide that ends with a consensus RQRR sequence, a metalloprotease domain with zinc binding catalytic sequence motif (HE_xGH_{xx}G_{xx}HD), a disintegrin-like domain, a central thrombospondin type 1 repeat (TSR-1), a cysteine-rich domain, a cysteine-free spacer region, 7 additional TSR-1's, and two unique CUB (complement, uEGF, and bone morphogenesis) domains. The metalloprotease-disintegrin domain is essential for VWF cleaving activity. The cysteine-rich and spacer domain sequence markedly enhances the potency of the protease.

Figure 2.

A schematic depiction of the critical role that shear stress plays in enhancing VWF-platelet aggregation as well as in cleavage of VWF by ADAMTS13. **A.** At a site of vessel injury, VWF binds to extracellular ligands and quickly becomes unfolded by high levels of shear stress in the arterioles and capillaries. **B.** In normal circulation, ADAMTS13 cleaves partially unfolded VWF. This process progressively decreases the size of VWF but maintains the VWF molecules in a globular, inactive conformation. **C.** When ADAMTS13 is missing, VWF becomes unfolded to elongated forms, causing platelet aggregation and intravascular thrombosis characteristic of TTP.

Table 1

A classification of disorders associated with microvascular thrombosis

Disorder	Molecular or cellular defect
TTP	ADAMTS13 deficiency
Autoimmune	Inhibitors of ADAMTS13
Idiopathic	
Secondary	Ticlopidine-related
Hereditary	Mutations of ADAMTS13
Hemolytic uremic syndrome	
Typical	Shiga toxins
Atypical	1. Mutations of regulators of complement activation *
	2. Antibodies of factor H
Bone marrow transplantation	Unknown
Solid organ transplantation	Unknown
Drugs **	Unknown
Lupus and related disorders	Vasculitis?
Intravascular procedures	Unknown
Non-TTP, non-HUS	
Metastatic neoplasm	Embolism of cancer cells
Paroxysmal nocturnal hemoglobinuria	Somatic mutation of phosphatidylinositol glycan class A gene (<i>PIG-A</i>)
HELLP syndrome	Unknown
Disseminated intravascular coagulopathy	Miscellany
Rocky Mountain spotted fever, anthrax	Endothelial injury?

* Mutations in Factor H, membrane cofactor protein (CD46), or protein I.

** Examples include cyclosporin A, gemcitabine, mitomycin C, and cocaine.

Table 2

Different features of TTP and HUS

Feature	Autoimmune TTP	Hereditary TTP
Epidemiology	Sporadic	Sporadic
Age of onset	Adolescent - adult	Neonate – young child
Heredity	No	Autosomal recessive
Gastrointestinal prodrome *	Rare	Occasional
Recurrence	Common	Common
Renal failure	Rare	Uncommon
Composition of thrombi	VWF and platelets	VWF and platelets
VWF profile	Ultra large multimers; Depletion of ultra large and large multimers at advanced stage	Ultra large multimers; Depletion of ultra large and large multimers at advanced stage
Diagnosis	ADAMTS13 activity ADAMTS13 antibodies	ADAMTS13 activity Genetic analysis of ADAMTS13
Response to plasma therapy	Yes	Yes

* Acute gastrointestinal illness may exacerbate subclinical TTP or atypical HUS.

** Factor H, membrane cofactor protein (CD46), or serine protease factor I.

*** Patients with mutations of factor H or factor I may improve upon plasma therapy. The optimal regimen is unknown.