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REVIEW ARTICLE

Thrombotic thrombocytopenic purpura and its diagnosis

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Introduction

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening illness whose mortality rate exceeds 90% in the absence of rapid appropriate treatment. Empirical plasma-therapy instituted in the 1970s has reduced the death rate to approximately 25% and both plasma infusions and plasma exchanges remain the only efficient treatments so far. TTP prevalence is about four per one million with a preference for women of childbearing age [1]. To diagnose TTP implies to face a first challenge: to define it. The definition criteria for TTP have significantly evolved as a result of a 20-year retrospective accurate analysis of North American [2,3], European [4–8] and Japanese [9] patients registries and cohorts and a better understanding of TTP pathogenesis.

Historically, TTP was originally described in 1924 by Eli Moschcovitz in a 16-year-old girl who presented with fever, anemia, central nervous system impairment, renal insufficiency and both respiratory and cardiac failure related to hyaline platelet thrombi in the terminal arterioles and capillaries of most organs [10]. Several case-reports and reviews of the literature have followed the initial description [11] leading to a definition concept focused on the following pentad: fever, microangiopathic hemolytic anemia, thrombocytopenia, central nervous system abnormalities and renal impairment. TTP, also called 'Moschcovitz syndrome', was described as a disease affecting primarily adults, but, interestingly, a rare pediatric form of the disease was also reported as early as 1960 [12] and named 'Upshaw-Schulman syndrome' in 1978 [13]. However, further large retrospective analysis of patients' clinical features showed that neither fever nor neurologic abnormalities and renal impairment were constant, especially during the early stage of the disease [14]. This observation led to the proposal that the association of microangiopathic hemolytic anemia and unexplained thrombocytopenia are sufficient and essential criteria to suspect TTP at an early stage in order to institute timely plasmatherapy [15,16].

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In parallel to the evolution of the standard clinical and biological criteria required for a solid TTP suspicion, the pathophysiological mechanisms for TTP were further elucidated recently. Until the 1980s, the pathogenesis for TTP remained very unclear although numerous candidates like endothelium, platelets or plasma proteins were suggested to participate in the triggering of the disease [17]. The role of von Willebrand factor (VWF), a plasma multimeric protein essential for platelet adhesion and aggregation at the high shear rates of blood flow present in the microvessels, was first put forward in 1982 by Moake *et al.* [18] who found abnormally large VWF multimers in the plasma of TTP patients. These hyperadhesive ultralarge multimers of VWF were suspected to be directly responsible for spontaneous platelet clumping in the microcirculation leading to ischemic visceral dysfunction. This hypothesis was further supported in 1985 by Asada *et al.* [19] who demonstrated that platelet thrombi in TTP were enriched in VWF (and not in fibrin) using an immunohistochemistry study of vascular lesions. In 1996, Furlan *et al.* [20] and Tsai [21] independently isolated and partially characterized a new metalloprotease from human plasma that specifically cleaves VWF at Tyr842-Met843, the peptide bond known to be cleaved *in vivo*. This enzyme was identified as the 13th member of the ADAMTS (A Disintegrin And Metalloproteinase with ThromboSpondin type 1 repeats) family of metalloproteases and the corresponding gene was cloned in 2001 [22]. In 1998, Furlan *et al.* [23] and, Tsai and Chun-Yet Lian [24] revealed that most adult patients with acute TTP had a severe functional deficiency of ADAMTS-13 in plasma (< 5% of the activity of a normal pooled plasma), most often related to inhibitory IgG autoantibodies. Further studies of patients with miscellaneous diseases, including other thrombotic microangiopathies like hemolytic uremic syndrome (HUS), confirmed that ADAMTS-13 severe deficiency was about 90% sensitive and specific for TTP [8,25–27]. In addition, Levy *et al.* [22] found that patients with hereditary TTP associated with a severe ADAMTS-13 functional deficiency were doubly heterozygous or homozygous carriers of mutated *ADAMTS-13* alleles. Thus, in 2005, ADAMTS-13 severe deficiency (< 5%), either acquired via circulating autoantibodies or more rarely inherited via recessive *ADAMTS-13* mutations, appears as a major specific risk factor for TTP. However, this observation does not allow TTP to be redefined by an undetectable ADAMTS-13 activity in plasma because other

mechanisms either involving ADAMTS-13 or other systems cannot be excluded from participation in TTP pathogenesis (see infra).

Diagnosing TTP usually proceeds with two main steps: (i) by identifying the first acute episode of the disease and (ii) by predicting the evolutionary form of the disease. Both steps require specific clinical and biological tools whose interests and limits will be discussed in this review. Perspectives concerning the potential interests of ADAMTS-13 testing to further support TTP diagnosis will be discussed at the end of the review.

Diagnosis of the first TTP acute episode

To identify the first TTP acute episode is very challenging because of the great variety of presenting features and the potential confusion with other diseases [28]. Indeed, no clinical symptom or biological criterion available in emergency is specific for TTP. However, a fast and appropriate diagnosis is urgent considering the severe prognosis in the absence of correct treatment. In this difficult context, TTP suspicion relies on the association of several clinical and biological symptoms and also on the exclusion of a list of differential diagnoses.

Clinical presentation

In probably more than 90% of cases, the onset of TTP occurs in adulthood, usually between 30 and 40 years of age, and preferentially in women (sex ratio of about 3F/1M) and in subjects from Afro-Caribbean origin [1]. In about 10% of cases, TTP appears initially in infancy (sometimes as soon as the neonatal period) or in childhood [7,8]. Rare familial forms of TTP (affecting mainly the siblings) are commonly observed in infancy or childhood but can also occur initially in adulthood [29].

The acute episode of TTP is usually characterized by non-specific presenting complaints like weakness (often anemia-related), arthralgia, myalgia, abdominal pain, nausea, vomiting, diarrhea and fever (Table 1). Some skin and mucosal bleeding secondary to the thrombocytopenia (purpura, ecchymosis, menorrhagia) are also common. Other symptoms linked to the systemic platelet clumping-induced ischemia may be associated. The brain is the most common target for ischemia (present in 75% of TTP cases) translating either in headache, confusion, severe mental status abnormalities, focal abnormalities (i.e. aphasia, focal motor deficits) or seizures. Ischemia of both the gastrointestinal tract and kidneys also occurs frequently. Renal manifestations consist in an isolated proteinuria, a renal insufficiency or more rarely an oliguric acute renal failure (Table 1). The median duration of symptoms prior to diagnosis is about 1 week with extreme values ranging from 1 day to 3 weeks [1].

In the infancy-onset TTP, the first acute episode may occur spontaneously as soon as birth and usually consists of a major hemolysis requiring an exsanguino-transfusion [7,9]. In other cases, the disease begins later and is often triggered by a viral or bacterial infection [30].

Table 1 Main clinical and standard biological features of TTP

Clinical/biological features	Approximate prevalence (%)
Presenting symptoms	
Headache, confusion	60
Digestive symptoms (nausea, vomiting, diarrhea, abdominal pain)	50
Weakness, fever	20
Bleeding symptoms (purpura, ecchymosis, menorrhagia)	20
Neurologic abnormalities	
Mild (headache, confusion)	25
Severe (coma, focal abnormalities, seizures)	50
Renal abnormalities	
Mild (proteinuria, renal insufficiency)	40
Severe (acute renal insufficiency)	5
Hematologic abnormalities	
Platelet count < 20 giga L^{-1}	95
Hemoglobin < 8 g L^{-1}	80

In adults, TTP is idiopathic in about one third of cases and thus occurs abruptly and independently of any other associated condition. In contrast, in about two thirds of cases, TTP is encountered in a variety of clinical situations, potentially involved in the triggering of the acute episode, which should be an additional criteria to suspect TTP: *bacterial or viral infections*, *pregnancy* (especially during the last trimester and also the postpartum period) [31,32], *drug ingestion* (involving either an acute immune-mediated toxicity: quinine [33], ticlopidine, clopidogrel [34] or an insidious dose-related toxicity: mitomycin C, alpha-interferon, cyclosporin, tacrolimus and other immunosupressive and chemotherapeutic agents [1]), *autoimmune disorders* [mainly systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APL)] [35–37], *disseminated malignancy*, *bone marrow transplantation* [38] (Table 2).

Table 2 TTP subtypes based on ADAMTS-13 activity and clinical backgrounds

TTP subtypes	Frequency (% of all TTP)	Main clinical backgrounds
ADAMTS-13-undetectable TTP	90	
Idiopathic	30	None, 'out-of-the-blue'
Clinical context-associated	60	Conditions stimulating an autoimmune process and/or an endothelial release of UL-VWF Infections Pregnancy Autoimmune diseases Drugs (immune toxicity)
ADAMTS-13-detectable TTP	10	Disseminated malignancies Organ transplantations Drugs (dose-related toxicity)

Complementary exams

Standard analysis In addition to the clinical symptoms, the following standard biological parameters are crucial to establish the emergency diagnosis of TTP. Hematological abnormalities (i.e. thrombocytopenia and microangiopathic hemolytic anemia) are the most common symptoms in the acute phase of TTP and their severity actually reflects the extent of the microvascular aggregation of platelets. A consumption thrombocytopenia is present in almost all cases, with a platelet count most often below 20 giga L^{-1}. The mechanism for the anemia is a mechanical hemolysis where fragmented red cells (schistocytes usually > 1% of total erythrocytes) are produced as blood flows through the microvessels partially occluded by platelet aggregates [17]. The hemoglobin count may be variable, usually below 8 g L^{-1} (Table 1).

Classical parameters for hemolysis show a high reticulocyte count (higher than 120 giga L^{-1}), an undetectable serum haptoglobin concentration and an elevated serum lactate deshydrogenase level derived from both ischemic necrotic tissue and lysed red cells. Except in some associated autoimmune context (SLE), the erythrocyte Coombs' test is negative. Standard coagulation parameters are usually normal. Renal testing may show several degrees of abnormalities (proteinuria, hematuria, increased plasma urea and creatinine) in about half cases (Table 1). Tomodensitometry may be helpful to localize the various visceral ischemic lesions.

Specialized analysis

Assays for ADAMTS-13 activity Since the first functional assays for ADAMTS-13 plasmatic activity were described in 1998 by Furlan *et al.* [23] and, Tsai and Chun-Yet Lian [24], many methods have been developed both to improve the sensitivity threshold for VWF proteolysis by ADAMTS-13 and to decrease the time required for the testing [39]. In 2004, the sensitivity threshold of most methods is admitted to be 5%.

About 90% of patients in the acute phase of a syndrome diagnosed as TTP, using both the clinical and the biological criteria described previously, exhibit a severe functional deficiency of ADAMTS-13 in plasma defined by levels lower than the usual 5% sensitivity threshold (Table 2). Undetectable ADAMTS-13 levels have been found mainly in idiopathic TTP [1] and also in TTP associated with infections, pregnancy, autoimmune diseases [lupus, antiphospholipid (APL) syndrome] and anti-aggregant drugs (ticlopidine, clopidogrel) [1] (Table 2). The 10% of patients whose ADAMTS-13 plasma activity is detectable and thus probably not involved in TTP pathogenesis are limited to TTP associated with disseminated malignancies, organ transplantations and both immunosuppressive and chemotherapeutic agents [1] (Table 2).

Undetectable plasma ADAMTS-13 activity (< 5%) also appears specific for TTP as it has very exceptionally been found in other pathological conditions and has never been found in any physiological condition [27].

Also, focusing on the development of new recombinant VWF-substrates, some laboratories were able to significantly decrease the time required for the global testing making a reliable result potentially available in a few hours [1,40]. ADAMTS-13 measurement thus appears as a very attractive complementary biological parameter to support TTP diagnosis. However, considering that all ADAMTS-13 assays are still available only in very specialized research laboratories and time-consuming for most of them, ADAMTS-13 activity is not used as a parameter helpful for diagnosing TTP in emergency yet.

Assays for anti-ADAMTS-13 autoantibodies In more than 90% of cases, ADAMTS-13-undetectable types of TTP are acquired and related to an autoimmune mechanism [23,24,41]. Most autoantibodies to ADAMTS-13 are inhibitory and thus, they can be detected and titrated *in vitro* using classical mixing studies [6,23,24]. Less frequently, autoantibodies to ADAMTS-13 are non-neutralizing and they can be detected with more sophisticated methods using recombinant fragments of ADAMTS-13 [41,42]. Similar to ADAMTS-13 functional assays described previously, testing for autoantibodies to ADAMTS-13 would be of great interest to corroborate TTP diagnosis as soon as the first acute episode occurs; however, simple assays adaptable in clinical laboratories are not available yet. Nonetheless, it appears appropriate to systematically collect blood before any treatment (especially before plasmatherapy that provides exogenous ADAMTS-13 [15,16]) in all patients with a TTP suspicion. Then, a delayed ADAMTS-13 activity measurement and testing for autoantibodies will be performed in order to retrospectively document the definitive diagnosis of the first acute phase.

Differential diagnoses

The diagnosis criteria for TTP (thrombocytopenia, microangiopathic hemolytic anemia and no other clinically apparent etiology) are not specific. As TTP diagnosis will translate in the decision of plasmatherapy, an efficient but potentially risky treatment, it is crucial to consider carefully alternative diagnoses before holding TTP as the ultimate diagnosis in some specific clinical contexts. Some differential diagnoses are particularly slippery and will be discussed in the following paragraphs (Table 3).

Pregnancy/postpartum context In women, TTP is diagnosed during pregnancy or postpartum in 12% to 25% of cases, with 75% of episodes occurring around the time of delivery [43]. The distinction between TTP and pregnancy-related complications like pre-eclampsia/eclampsia/HELLP (hemolysis elevated liver enzymes and low platelet count) syndrome may be impossible. In all cases, a severe thrombocytopenia often associated with a hemolytic anemia is present. Seizures defining eclampsia may also occur in TTP as a symptom of the brain ischemia. By definition, the entity pre-eclampsia/eclampsia/HELLP

Table 3 Slippery differential diagnoses for TTP

Clinical contexts	Differential diagnosis for TTP
Pregnancy/postpartum	Eclampsia HELLP syndrome
Autoimmune diseases (SLE, APL syndrome)	Own evolution of the disease (aggravation of thrombocytopenia and/or anemia) Catastrophic APL syndrome
Disseminated malignancies Bone marrow transplantation	Immunosuppressive agents toxicity Chemotherapeutic agents toxicity Opportunistic infections

HELLP, hemolysis elevated liver enzymes low platelet count; SLE, systemic lupus erythematosus; APL, antiphospholipid.

spontaneously resolves after delivery in contrast to TTP which systematically worsens in the absence of plasmatherapy.

Autoimmune diseases At the very initial phase of the disease, the severe thrombocytopenia present in TTP may be confused with an immune thrombocytopenic purpura (ITP), if isolated, or Evan's syndrome, if associated with a hemolytic anemia [7]. Also, the initial clinical presentation of some patients with severe multiorgan failure related to a previously established SLE, APL syndrome and potentially its catastrophic variant (catastrophic APL syndrome) or scleroderma may be indistinguishable from an acute TTP episode [44]. What makes the differential diagnosis even more tricky is that TTP may also be a complication of these autoimmune diseases [45,46]. In these patients, a trial of plasma exchange for presumed TTP associated with intensive immunosuppressive treatment is considered as the most rational management by most authors [14].

Multiorgan failure related to disseminated malignancy and bone marrow transplantation As the diagnostic criteria for TTP are not specific, the distinction with conditions associated with multiorgan failure like disseminated malignancies and bone marrow transplantation (which also share the use of multiple high toxicity-drugs and a high risk for opportunistic infections) is very difficult. In addition, disseminated malignancy and bone marrow transplantation [38] have been classically described as clinical contexts frequently associated with TTP. However, recent retrospective analysis of registries of large series of patients with thrombotic microangiopathies actually reveals that these pathological conditions are rather alternative disorders that may mimic TTP rather than TTP-associated (and potentially inducing) disorders [14]. Indeed, a crucial common point of these conditions is inefficiency of plasmatherapy.

Hemolytic-uremic syndrome A clinical overlap of TTP and hemolytic-uremic syndrome (HUS) may occur. Indeed, an acute renal failure, the clinical feature used to define HUS, may also be present in TTP in about 5% of cases (even in the ADAMTS-13-deficient adult and pediatric forms). In adults and children with non-enterotoxin related HUS (atypical HUS), the distinction between HUS and TTP is actually not important for the initial management decision regarding plasma exchange [1].

Diagnosis of the TTP evolutionary form

The major concern of patients who experience a first TTP acute episode and had clinical remission is the risk for relapse. Longitudinal studies involving a long follow-up of a large series of patients with TTP are obviously the only ones to be able to answer the crucial question of the risk for relapse, but they are still very limited. However, data from the Oklahoma TTP-HUS registry including a 1–9 years follow-up of 301 consecutive patients with TTP-HUS bring interesting information [1]. Relapses do not usually appear in patients with disseminated malignancies, bone marrow transplantation and dose-dependent drug toxicity associated-TTP. These TTP types have not only a usually detectable ADAMTS-13 activity in plasma in common, but also a high mortality rate, which may partially explain the rarity of relapses. Thus, relapses appear restricted to patients with a severe ADAMTS-13 deficiency during the acute episode. Although ADAMTS-13-undectectable TTP is very heterogeneous, two subgroups respectively associated with a low risk of relapse and a high risk for relapse, can be identified on the basis of the clinical background.

ADAMTS-13-undetectable TTP associated with a low risk for relapse

Adult idiopathic TTP (with no identified clinical background) is associated with a risk of relapse of 11% to 36% [1]. Data from the Oklahoma TTP-HUS registry report a similar rate of about 20% [1]. In most cases, the initial relapse will occur within the first year. Next relapses are usually unpredictable and occur at irregular intervals. The frequency of relapses does not seem to be correlated to either the presence or the strength of an inhibitory autoantibody to ADAMTS-13 during the acute episode [1]. However, this lack of correlation may be partially related to the heterogeneity of this group presenting as an 'idiopathic TTP first acute episode' but potentially including both acquired TTP with various mechanisms and inherited TTP with an adulthood-onset.

Ticlopidine- and clopidogrel-associated TTP is also associated with a low risk for TTP relapse provided the patient is not re-exposed to the drug. This data is supported by small series as only a small fraction of patients treated for arterial thrombosis with ticlopidine (Ticlid) or clopidogrel (Plavix) have developed TTP, usually a few weeks after initiation of therapy. An immune-mediated drug reaction is likely as transient anti-ADAMTS-13 inhibitory antibodies have been detected during the acute episode of TTP [34].

ADAMTS-13-undetectable TTP associated with a high risk for relapse

Adult TTP occurring concomitantly with another clinical condition (especially pregnancy and autoimmune diseases) are associated with a potentially high risk of relapse. In women whose initial TTP acute episode was associated with a *pregnancy*, the risk of relapse for a future pregnancy is very concerning. The latter is very controversial and ranges from 26% [1] to 73% [32]. However, the authors admit that these percentages are probably overestimated as patients involved in these studies had very complex outcomes and more encouraging practical experiences are suggested [1]. Also, pregnancy is admitted to be associated with TTP acute episodes in either acquired ADAMTS-13 deficiencies (pregnancy being considered as a classical triggering factor for autoimmune processes) or familial inherited ADAMTS-13 deficiencies [47]. This data suggests that the relationship between pregnancy and risk for TTP relapse should also be modulated as a function of other criteria. Patients whose initial TTP acute episode was associated with a *previously established autoimmune disorder* (SLE, APL, scleroderma) seem to have a significant risk of relapse [1]. The accurate rate of relapse in this context is not known as TTP associated with an autoimmune disorder has been described mainly in case-reports. Again, the predictive value for relapse of anti-ADAMTS-13 antibodies, both in the acute phase and in clinical remission, has not been established yet.

Infancy- and childhood-onset TTP is, in almost all cases, an autosomal recessive inherited familial form of the disease corresponding to *Upshaw-Schulman syndrome*. The constant undetectable plasma ADAMTS-13 activity is a consequence of homozygous or double heterozygous mutations of the *ADAMTS-13* alleles, located all along the gene [48]. The disease usually recurs as 'chronic relapsing TTP' episodes at about 3- or 4-week intervals, thus requiring monthly plasmatherapy. In some of these inherited cases, however, the disease exhibits a different relapsing clinical course with irregular and unpredictable relapses. In some very rare cases, acquired TTP related to transient ADAMTS-13 severe functional deficiencies and associated mainly with infections, have been reported in children [30,49,50], but the risk of relapse has not been determined.

Interests of ADAMTS-13 analysis in TTP diagnosis: perspectives

Perspectives for plasma ADAMTS-13 activity

Plasmatherapy is the only efficient treatment in ADAMTS-13-undetectable acute TTP provided it is introduced as early

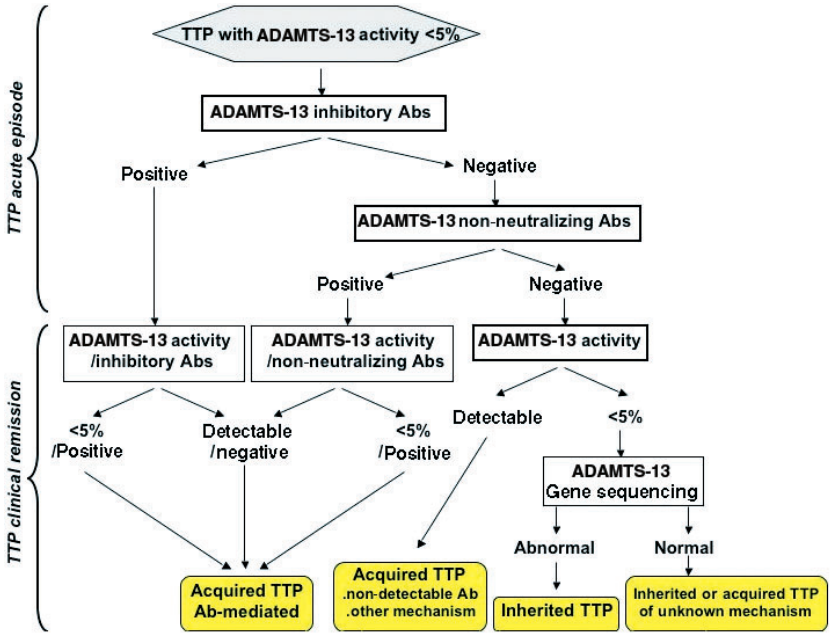

Fig. 1. Flow chart to illustrate possible mechanisms for ADAMTS-13 severe functional deficiency in ADAMTS-13-undetectable TTP. During a TTP acute episode where ADAMTS-13 activity has been found undetectable (< 5%), testing for ADAMTS-13 inhibitory antibodies (Abs) should be systematic. ADAMTS-13 inhibitors may be positive or negative, thus requiring a testing for non-neutralizing antibodies. In clinical remission, ADAMTS-13 activity should be performed in all cases in association with a testing for inhibitory or non-neutralizing Abs if they were positive during the acute episode. If anti-ADAMTS-13 Abs (either inhibitory or non-neutralizing) were detected in the acute phase, whatever their course in remission, an acquired TTP mediated by anti-ADAMTS-13 Abs is diagnosed (the reversibility of both ADAMTS-13 activity and the Abs may be useful for prognostic evaluations). If no antibody was detected in the acute phase and ADAMTS-13 activity is reversible in remission, an acquired TTP should be diagnosed too, related to either undetectable Abs or another mechanism still unidentified. If no antibody was detected in the acute phase and ADAMTS-13 activity remains undetectable in remission, *ADAMTS-13* gene should be sequenced: (i) if homozygous or double heterozygous mutations are found, an inherited TTP (Upshaw-Schulman syndrome) is diagnosed or (ii) if no *ADAMTS-13* mutation is found, an inherited or acquired TTP related to a still unidentified mechanism is likely.

as possible. In addition, plasmatherapy may be inappropriate and potentially dangerous in ADAMTS-13-detectable TTP and in some differential diagnoses for TTP. Thus, rapid assays for ADAMTS-13 activity may be crucial for an early sensitive and specific TTP diagnosis in the acute phase leading to an optimal therapeutic management. A Japanese group [1,40] has been working on the development of a promising bed-side assay for ADAMTS-13 activity for a few years. This assay is using VWF73, a fragment of VWF-A2 domain that constitutes an original minimal substrate for ADAMTS-13 proteolysis *in vitro*. However, 'beginning plasmatherapy on the basis of undetectable plasma ADAMTS-13 activity that supports TTP diagnosis' should certainly not mean 'excluding plasmatherapy if ADAMTS-13 activity is detectable.' Indeed, plasmatherapy may be efficient in other diseases, like HUS or HELLP syndrome, associated with detectable plasma ADAMTS-13 levels [1]. The interest of ADAMTS-13 monitoring during plasmatherapy to adjust the treatment remains to be established. In contrast, ADAMTS-13 monitoring has been proposed by a Japanese pharmaceutical company for the early diagnosis of patients with suspected ticlopidine-associated TTP in order to prevent the morbidity caused by drug-associated TTP [1].

The prognostic value of ADAMTS-13 activity in the acute phase of TTP is more controversial. Several case series [28,47,51] have reported a lower mortality but a higher frequency of relapses in ADAMTS-13-undetectable TTP when compared with ADAMTS-13-detectable TTP. These observations may be explained only by the serious conditions (disseminated malignancies, systemic infections, organ transplantations) associated with ADAMTS-13-detectable TTP and may not be correlated with ADAMTS-13 levels at all. Another argument that supports the lack of correlation between ADAMTS-13 levels and the clinical course is the extreme variability of the clinical phenotype of patients with persistent plasma ADAMTS-13-undetectable activity (inherited TTP and some acquired TTP). In some cases, the disease is almost chronic with very recurrent relapses and very short clinical remissions; in other cases, clinical remissions may last several years [29].

Perspectives for plasma ADAMTS-13 inhibitory antibodies

In 37 patients with ADAMTS-13-undetectable acute TTP, the presence of a high titer of inhibitory activity has been shown to be associated with a higher risk of prolonged course, relapses and a higher mortality when compared with patients with no inhibitor [52]. Thus, an undetectable ADAMTS-13 activity associated with a high titer inhibitor may be an appropriate indication for both plasma exchanges (vs. plasma infusions) and intensive immunosuppressive treatment at once. However, the follow-up of 18 patients from the Oklahoma TTP-HUS Registry showed that the occurrence of relapses was not related to the strength of the inhibitor activity detected during the acute phase [1]. In addition, neither the interest for treatment adjustment of ADAMTS-13 inhibitory antibodies monitoring during plasmatherapy nor the prognostic value of a persistent ADAMTS-13 inhibitor during clinical remission have been determined yet.

Obviously, future studies involving a long follow-up of a large series of TTP patients appears crucial to further determine predictive values for morbidity (response to treatment, course, risk for relapse) and mortality of ADAMTS-13 inhibitors and, consequently, to define new therapeutic guidelines.

Beyond the previous perspectives, a better understanding of TTP pathophysiology focused on (i) the correlation of the phenotype to the *ADAMTS-13* genotype in inherited TTP, (ii) the correlation of the phenotype to ADAMTS-13 autoantibodies features (inhibitory/non-neutralizing effect, titer, epitope mapping) in acquired TTP and (iii) the identification of other mechanisms for ADAMTS-13 deficiencies, will be a crucial tool to further clarify the relationship of ADAMTS-13 deficiency to TTP clinical course (Fig. 1). Elucidation of ADAMTS-13-independent mechanisms for TTP should also bring new clues for both diagnosis and therapeutic management.

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