

Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome: Pathogenesis and Therapy

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Abstract

Thrombotic thrombocytopenia purpura (TTP) and hemolytic uremia syndrome (HUS) are rare and closed-related disorders with similar clinical features. They are characterized by thrombocytopenia and microangiopathic hemolytic anemia in different severity. TTP was conventionally described as a pentad of microangiopathic hemolytic anemia, thrombocytopenia, neurological symptoms, renal involvement and fever. HUS affects mainly children and presents with microangiopathic hemolytic anemia, thrombocytopenia and a clinical picture dominated by renal insufficiency. Clinically, various denominations have been used to describe these similar syndromes with variable combinations of neurologic and renal manifestations. Because of without definitive pathogenetic evidence to support a clear distinction among the various clinical entities, some given such disorders the generic term TTP-HUS. In a recent decade, the pathogenesis of those disorders have been described: First, defective regulation of von Willebrand factor activity by a severe deficiency of A Disintegrin and Metalloprotease with ThromboSpondin, type I repeat, member 13 (ADAMTS13) is found in most patients with congenital and acquired idiopathic TTP. Second, mutations in the genes for complement proteins, including Complement 3, factor H, B and I, and membrane cofactor protein are associated with dysregulation of alternative complement pathway in many patients with Atypical HUS. These advances, along with well-known association between Shiga toxins and Diarrhea positive HUS (D⁺ HUS), provide the better understanding of variable disease processes and the further directions of diagnosis and treatment in TTP-HUS. TTP in adult typically follow a progressive course, irreversible renal failure, progressive neurologic deterioration, cardiac ischemia, and death are common outcome. Plasma exchange is associated with a high response rate, therefore, aggressive plasma exchange should be initiated in all patients as soon as the clinical dyad of microangiopathic hemolytic anemia & thrombocytopenia present. (J Intern Med Taiwan 2013; 24: 299-308)

Key Words: Thrombotic thrombocytopenic purpura, Hemolytic uremic syndrome, Thrombotic microangiopathy, Plasma exchange therapy, ADAMTS13, von Willebrand factor

Introduction

Thrombotic thrombocytopenia purpura (TTP) and hemolytic uremia syndrome (HUS) are rare

and closed-related disorders with similar clinical features. They are characterized by thrombocytopenia and microangiopathic hemolytic anemia in different severity^{1,2}. TTP, first reported by

Moschowitz in 1924, affects mainly female between the ages of 10 and 39 years with an annual incidence of 2 to 11 per million-year. The clinical presentation was conventionally described as a pentad of microangiopathic hemolytic anemia, thrombocytopenia, neurological symptoms, renal involvement and fever. HUS, first described by Gasser et al. in 1955, affects mainly children. It presents with microangiopathic hemolytic anemia, thrombocytopenia and a clinical picture dominated by renal insufficiency; its presence is often preceded by a diarrheal illness^{3,4}. Clinically, similar syndrome with variable combinations of neurologic and renal manifestations have also been reported in patients with disseminated intravascular coagulation (DIC), disseminated malignancies, stem cell transplantation, pregnancy, and a variety of drug-related disorders, such as mitomycin C, tidopidine, clopidogrel, cyclosporine, and quinine. Therefore, Secondary TTP has been used to refer to these similar disorders^{5,6}, and thereby differentiated it with idiopathic TTP, including congenital and acquired.

Typical HUS, also termed Shiga toxin-associated HUS or Diarrhea positive HUS (D⁺ HUS), has been recognized since 1983 as a complication of infection caused by Shiga toxin-producing *E. coli* of the serotype O157:H7 or, in some cases, by *Shigella dysenteriae*, that involves approximately 90% of children with HUS that have diarrhea as a prodrome, usually with blood. Atypical HUS^{3,7,8}, also termed non Shiga toxin-associated HUS or Diarrhea negative HUS (D⁻ HUS), involves a heterogeneous group of patients without antecedent diarrhea, not infected by Shiga toxin-producing bacterium, and may present as sporadic or familial form. It accounts for 10% of the patients with HUS. Some sporadic cases of atypical HUS can be found in patients with *Streptococcus pneumoniae* infection. Streptococcal pneumonia associated HUS accounts for 5% of childhood cases of HUS, children less than 2 years are most commonly affected, and HUS usually develops 3 to 13 days after infection starts^{3,8}.

Clinically, patients with these syndromes can have both, or none, neurologic and renal abnormalities. Some cases of TTP may present only with neurologic manifestation, such as transient ischemic attack or stroke, without thrombocytopenia or microangiopathic hemolysis, or patients with HUS present without diarrhea or renal failure. Therefore, the differential diagnosis between TTP and HUS based on clinical features without definitive pathogenetic evidence is usually difficult. Because of the various denominations and without definitive pathogenetic evidence to support a clear distinction among the various clinical entities, some given such disorders the generic term TTP-HUS.

Advances of the pathogenesis in recent years, a molecular mechanism was believed to be responsible for both congenital and acquired idiopathic TTP and that TTP and HUS have independent pathogenesis and non-related outcome, changing the conceptual basis of diagnosis and therapeutic strategies of these related disorders^{9,10}.

ADAMTS13 and the Pathogenesis of TTP

A variety of early studies used glucocorticoids at various dosages as the mainstay of therapy, whose advent in the 1950s seemed to change the course of the disease and has since been considered to be the only effective therapy at that period^{9,10}. The clinical advance was dramatic in 1976; Murkowski et al. published the experience of treatment of TTP with whole blood exchange transfusion. Eight of 14 patients respond quickly with remissions lasted from several months to more than 13 years. They denoted that the active principle in blood was shown to be in the plasma fraction^{11,12}.

In 1982, Moake et al. noted circulating ultra large von Willebrand factor (ULVWF) multimers in the plasma of patients with relapsing TTP. The first time linked VWF to the pathogenesis of TTP. It was postulated that these multimers were responsible for

platelet aggregation in small blood vessels and that patients lacked a VWF multimers depolymerase responsible for controlling multimer size, possibly a protease that normally cleaved ULVWF to prevent it from causing the intravascular platelet aggregation and thrombosis. He found relapsing acquired or congenital TTP had circulating ULVWF multimers that absent from the plasma of healthy persons¹³.

In 1991, Rock GA et al demonstrated the value of plasma therapy conclusively in a randomized, prospective study. In their study, survival rate was 78% in plasma exchange group and 63% in plasma infusion group, a significant difference in favor of plasma exchange. Since the trial published, the numbers of plasma exchange therapy for TTP-HUS increase 7-fold and mortality rate decrease to 20-30%¹⁴.

In 1998, two independent investigations revealed the significance of a metalloproteinase in the pathogenesis of TTP-HUS^{15,16}. They identified a 200 KD metalloproteinase whose activity was abnormally low in familial and non-familial TTP. In some cases, an inhibitor to the protease was also identified. Patients with HUS, however, demonstrated normal enzyme activity and seemed to have a different disease. They finally concluded that adult acquired TTP have severe deficiency of VWF-cleaving protease caused by IgG autoantibodies that inhibits the enzyme. In 2001, VWF-cleaving protease was purified, cloned, and named ADAMTS13 (A Disintegrin and Metalloprotease with ThromboSpondin, type I repeat, member 13, family of metalloproteases), and the ADAMTS13 gene mutations were found to cause congenital TTP by Levy G, et al^{17,18}. With the advances of the recent studies, it is known that severe deficiency of a VWF cleaving protease, ADAMTS13, is the main cause of platelet thrombosis in patients with idiopathic TTP and now possible to define TTP at the molecular level^{19,20}.

ADAMTS13 is a circulating metalloprotease

synthesized primarily by the hepatic stellate cells and rarely by platelets and endothelial cells. The ADAMTS13 gene contains 29 exons placed on chromosome 9q34. In normal conditions, ADAMTS13 degrades Ultra-large VWF (ULVWF) multimers released from endothelial cells into small units in the circulation before it unfold by shear stress, thereby reducing their ability to induce platelet adhesion and aggregations.

However, there is evidence that suggest the inhibition of ADAMTS13 by plasmin and thrombin. It appears to be a physiological regulation that these coagulation proteins may modulate the activity of ADAMTS13 at the sites of hemostatic plug formation²¹. Thus, the process of proteolytic cleavage by ADAMTS13 is in a delicate balance between reducing the size of VWF multimers. So that they remain sufficiently function to establish hemostasis, but also cleaving them appropriately to avoid unwanted thrombosis²²⁻²⁷. Another important control mechanism for ADAMTS13 appears to be its endothelial localization²⁸⁻³¹. ADAMTS13 bound to endothelial surfaces show to facilitate the cleavage of ULVWF multimers released from endothelial cells, allowing control of multimers length at their released sites, and explain the prolongation of half-life of bound ADAMTS13 in vivo³²⁻³⁵.

It is generally accepted that a severe deficiency of ADAMTS13 activity, defined as less than 5% to 10% of normal controls, is the cause of TTP, either congenital or acquired. In TTP, the ULVWF multimers are not cleaved due to severe deficiency of ADAMTS13. It leads to accumulation of ULVWF multimers and unfolded in the microcirculation, resulting in abnormal platelet aggregation and occurrence of microvascular thrombosis and occlusions. [Figure 1]. Because of microangiopathic damage of the erythrocytes ongoing, plasma level of free hemoglobin and lactate dehydrogenase are elevation and haptoglobin reduced or absent with negative Coomb's test and normal prothrombin

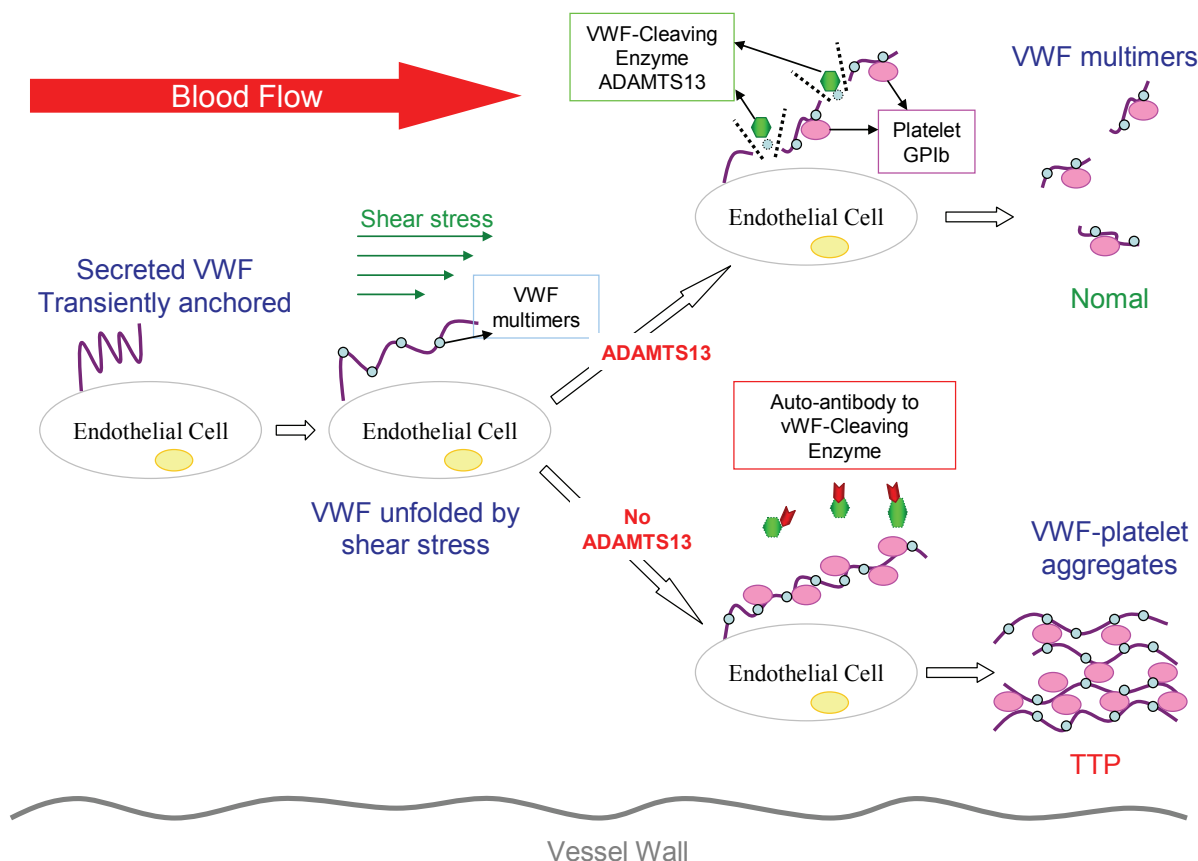


Figure 1. Pathogenesis of idiopathic thrombotic thrombocytopenic purpura: idiopathic TTP caused by ADAMTS13 deficiency due to gene mutations or autoantibodies. Multimeric VWF adheres to endothelial cells or to connective tissue exposed in the vessel wall. Platelets adhere to VWF through platelet membrane GPIb. In circulation, VWF is unfolded by shear stress and cleaved by ADAMTS13, limiting thrombus growth. If ADAMTS13 is severe deficiency, accumulation of VWF-platelet aggregation continues, eventually causing microvascular thrombosis and TTP.

time (PT) and activated partial thromboplastin time (aPTT). It may affect numerous organs, such as peripheral circulation, central nervous system and kidneys, consequently, with the presence of the characteristic manifestations of TTP^{24,26,36}.

As noted, congenital TTP is a disorder of homozygous or compound heterozygous gene mutations and acquired TTP caused by an IgG autoantibody (mainly IgG4); the common consequence of severe deficiency of ADAMTS13 explains the pathogenesis of the disease. At present, at least 99 of gene mutation polymorphism were identified. However, ADAMTS-13 activity can be severely deficient in asymptomatic patients, patients with the

characteristic syndrome of TTP can have normal or nearly normal ADAMTS-13 activity, or in some individuals carrying gene mutations but show no symptoms. So that, an additional triggering event or some yet undefined factors must be involved in the patients to develop this syndrome^{23,24,26}. Other causes of ADAMTS13 deficiency have been found in a variety of pathological conditions, such as sepsis, DIC, liver cirrhosis, and plasmodium falciparum infection. However, the decreased level of ADAMTS13 activity is unlikely to contribute to thrombosis in these cases^{10,24}, whereas, ADAMTS13 activity is relatively reserve in HUS^{8,23,26}.

The Relationship between Thrombotic Microangiopathy (TMA) and TTP-HUS

TMA, first described by Smmers in 1952, is the pathological process that represents the final common pathway of many disease entities, mostly associated with TTP and HUS. Clinically, TMA is considered as a family of closed-related syndromes recognized by the development of new onset thrombocytopenia, microangiopathic hemolytic anemia with schistocytes in the peripheral blood, and multiple organ thrombosis^{9,22,37,40}.

The pathological process of TMA begins with an abnormal biochemical triggering or pathological insult, that damage the endothelium via multiple and varied mechanisms. Then, functionally altered endothelium provokes intravascular platelet aggregation or activation of coagulation factors that leads to widespread microvascular thrombosis^{10,21,41}. The clinical spectrum of TMA includes a group of disorders, such as: TTP-HUS, catastrophic antiphospholipid antibody syndrome, systemic vasculitis, malignant hypertension, scleroderma in renal crisis, disseminated malignancy, pre-eclampsia/eclampsia, stem cell transplantation related TMA, cancer and chemotherapy related TMA, HIV infection, H1N1 influenza A, DIC, or even, drugs induced TMA^{20,25,40}.

TTP and HUS manifest the similarity of clinical features of TMA, but the pathways evolved to microvascular thrombosis are different and the organ systems involved are variable. Comparing with TTP, mutations in the genes for complement proteins, including complement 3, factor H, B and I, and membrane cofactor protein, which result in dysregulation of alternative complement pathway, can be detected in many patients with Atypical HUS⁹. These advances, along with well-known association between shiga toxins and D⁺ HUS, provide the better understanding of variable disease processes and the further directions of diagnosis and treatment in TTP-HUS^{9,10,34,37}.

The Evolution of Conceptual Basis for Diagnosis of TTP

In the period prior to the effective treatment with plasma exchange, the majority of patients with TTP died from systemic microvascular thrombosis that cause myocardial and cerebral infarction and renal failure. In clinical practice, TTP-HUS remains a clinical diagnosis and no clinical parameters at diagnosis predict for response and survival^{1,3}. Because of rapid progression of clinical course, high mortality rate in untreated TTP patients and the disease response well to plasma exchange, it is important to adopt the more concise criteria for the immediate recognition of patients.

Clinically, the presence of pentad is found only in 40% of the patients with TTP. The triad, comprised of microangiopathic hemolytic anemia, thrombocytopenia and a markedly increased level of plasma LDH that is unexplained by another conditions, is found in proximally 70% of the patients, its presence allow a tentative diagnosis of TTP⁴². In 1991, Rock GA et al had shown the efficacy of the plasma exchange therapy only for the presence of clinical dyad of microangiopathic hemolytic anemia and thrombocytopenia, without apparent alternative causes. The trial established plasma exchange as the standard of care for idiopathic TTP today⁴³⁻⁴⁶. Therefore, for marking the decision of plasma exchange rapidly, the diagnostic criterion is revised from pentad, triad, to dyad without alternative causes such as secondary TTP, these patients, however, with the clinical similarity but almost never having severe ADAMTS13 deficiency^{6,42,47,48}. At present, some believe the efficacy of early treatment with plasma exchange adopted clinical dyad criteria rather than awaiting additional symptoms and signs, which may be lethal.

With the advances of pathogenesis, assays for ADAMTS-13 activity and inhibitors may be clinically helpful in diagnosis and treatment⁴⁹⁻⁵³.

Congenital TTP does not always present during childhood and may be difficult to distinguish from acquired TTP, the detection of autoantibodies against ADAMTS13 supports a diagnosis of acquired TTP. In Japan, a registry of 919 patients with TMA during 1998-2008 from a database revealed 11.5%, 31% and 50% of the 919 patients were idiopathic HUS, idiopathic TTP and secondary TMA, respectively, and idiopathic TTP patients have severe deficiency of ADAMTS13 activity⁵⁴. In this database, 58 patients including 41 congenital TTP and 17 acquired TTP were diagnosis with a severe deficiency of ADAMTS13 activity during childhood, which cause a paradigm shift in our concept of TTP do mainly occurred in adults⁵⁵.

The value of distinguishing patients with or without severe deficiency of ADAMTS13 activity seems to be that ADAMTS13 assays at diagnosis provide useful prognostic information. At initial presentation, patients with severe deficiency of ADAMTS13 have a significantly increased risk of TTP relapsing (30%). whereas, patients without severe deficiency of ADAMTS13 rarely relapse (9%)⁶. However, in clinical practice, very few laboratories can perform ADAMTS13 assays rapidly enough; the clinician must make a diagnosis and initiate therapy without this information. For idiopathic TTP, patients with or without severe deficiency of ADAMTS13 have had similar response rates and short-term survival (80-90%) to plasma exchange. In Taiwan, the available information of patients with TTP has been very limited and most of them were in the form of single case reports^{56,57}. A retrospective cohort study by Chang et al in 2012 showed 77% of response rates and 7.7% of relapse rates with treatment of combination of plasma exchange and corticosteroid, which were relatively similar to those reported literatures. In this study, sporadic or idiopathic TTP accounted for 70% of the patients overall⁵⁷. In china, a retrospective study from 1998 to 2006 showed that most of patients had

secondary TTP-HUS; SLE-associated TTP-HUS is the most common form of TTP-HUS²². In a Korean TTP registry experience from 2005 to 2008 revealed 59% of patients were idiopathic TTP and there was not any independent risk factors for TTP-associated mortality appeared⁵⁸.

Some studies reported that the fraction of severe deficiency of ADAMTS13 activity vary from 34% to 91% in patients with apparent idiopathic TTP. This lower prevalence of ADAMTS13 deficiency was no unexpected because patients who had HUS or other TMA were no rigorously excluded in these studies. The variation of the fraction in those studies may also reflect difference in assays or case definitions, variable attention to secondary causes of TMA or the application of additional criteria for case selection^{17,47,48,50,59}.

Biologic Plausibility Supporting the Therapeutic role of Plasma Exchange in TTP

Therapeutic principles of TTP and TMA are to distinguish these disorders based on underlying pathogenetic mechanism and to ensure appropriate management. Plasma exchange therapy has become a standard of care and with a high response rate in patients with TTP. Even in patients with different molecular defects, some of them may share the benefit of plasma infusion or exchange therapy⁶⁰⁻⁶³.

Present practice is to treat TTP and HUS in similar fashion at initial unless the clinical features are clear, such as in Shiga toxin-associated HUS. Plasma exchange therapy should starts within 24-48 hours of the appearance of the clinical dyad even though the diagnosis is uncertain, a delay in initiation of therapy could be one of the factors responsible for treatment failure. An inappropriate delay in the diagnosis and initiating plasma exchange may occurs in hospitalized patients admitted for other conditions that may trigger the onset of an acute episode of TTP-HUS, such as hemorrhagic colitis,

recent surgery, acute pancreatitis, or cirrhosis of liver. The role of plasma exchange in malignancy, blood stem cell transplant and chemotherapy associated TMA is limited and the utility of plasma exchange in HUS is controversial^{21,61,62}.

The role of plasma exchange in treatment of idiopathic TTP is mainly with daily plasma exchange, depending upon the removal of the patient's plasma to deplete the circulating ADAMTS13 inhibitors and the circulating ultra-large VWF multimers, and to replenish the normal plasma to supply the missing ADAMTS13, treated until clinical symptoms improve and laboratory values normalize. Some patients with TTP require prolonged plasma exchange to achieve a sustained remission and prevent a fatal outcome.

Platelet transfusions should be avoided unless severe thrombocytopenia results in bleeding risk⁴. The roles of ADAMTS13 assays in choosing therapy remains uncertain, but most believe that severe deficiency of ADAMTS13 is specific for idiopathic TTP and identifies a subgroup with a well response to plasma exchange^{50,54,56,63,64}.

The manifestations that suggest the responses to the treatment of plasma exchange therapy can include: 1. neurologic symptoms and serum LDH level tend to improve dramatically within 1-3 days; 2. thrombocytopenia start to rise after several days; 3. Parameters of hemolysis improve promptly, yet anemia may continue to worsen. However, recovery from renal failure is unpredictable and often incomplete. Prolonged courses of plasma exchange therapy and with frequent exacerbations are characteristic of idiopathic TTP; relapse usually occurs after beyond 30 days of complete remission with no plasma exchange^{4,56}. The most important predictor of mortality was the presence or absence of a serious underlying disorder.

Clinically, a variety of adjunctive immunosuppressive treatment, including corticosteroids, cyclophosphamide, azathioprine, cyclosporine A,

high-dose intravenous immunoglobulin or splenectomy, have been used with variable results. Use of rituximab, a monoclonal antibody against B cell CD20, has shown promise in a small prospective cohort study of the patients with acute refractory and severe relapsing TTP. However, clinical use of rituximab, or combination of rituximab and plasma exchange, for refractory or relapsing idiopathic TTP or as adjuvant or salvage therapy remains to be investigated^{29,53,55,65}.

Because of severe deficiency of ADAMTS-13 caused by autoantibody in acquired idiopathic TTP, it is likely that this disorder has an autoimmune etiology. Consequently, corticosteroid has its rationale basis for reduction of ADAMTS13 autoantibody. The timing of corticosteroid used is suggested in such conditions as no evidence of drug-induced etiology, bloody diarrheal prodrome and severe renal failure; poor response to initial treatment with plasma exchange; platelets do not increase within several days of treatment with plasma exchange; thrombocytopenia recurs when plasma exchanges are diminished or discontinued.

Conclusion

It is generally accepted that defective regulation of VWF activity by a severe deficiency of ADAMTS13 is the cause of TTP, either congenital or acquired. TTP typically follow a progressive course if untreated, irreversible renal failure, progressive neurologic deterioration, cardiac ischemia, and death are common outcome. Therapeutic principles of TTP are to distinguish these disorders based on underlying pathogenetic mechanism. Plasma exchange therapy has become a standard of care with a high response rate in patients with TTP; it should start within 24-48 hours of the appearance of the clinical dyad even though the diagnosis is uncertain.

Severe deficiency of ADAMTS13 is thought to be a biomarker for a high risk of relapsing disease, so that, the detection of ADAMYS13 level at diagnosis

and monitoring it during treatment could be useful to determine whether plasma exchange should be intensified, decreased, or discontinued^{66,67}. However, the usefulness of assays of ADAMTS13 activity or antibody in diagnosis of TTP is controversial, but it should permit early diagnosis and could speed the institution of plasma exchange therapy for the occasional patients with ADAMTS13 deficiency, which presents with atypical manifestations, and could prevent misdiagnosis of idiopathic TTP with symptoms suggesting gastroenteritis, sepsis, or transient cerebral ischemia.

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血栓性血小板減少紫斑症 - 溶血性尿毒症候群： 疾病發生論和血漿置換術治療

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摘要

血栓性血小板減少紫斑症 (TTP) 和溶血性尿毒症候群 (HUS) 是罕見又密切相關的疾病，具有不同嚴重度的臨床相似性，特點為血小板減少和微血管病變溶血性貧血。血栓性血小板減少紫斑症，傳統上將其描述為五種徵候為一組的表現，即血小板減少、微血管病變溶血性貧血、神經的症狀、腎臟的侵犯和發燒。溶血性尿毒症候群，主要侵犯小孩，呈現血小板減少、微血管病變溶血性貧血和以腎功能不全為主的臨床表現。臨床上有各種不同的命名來表述這些相似但結合不同程度腎臟和神經症狀的症候群。因為無確定的疾病發生論的證據來支持各種不同疾病類別的分辨，因此有學者將這些不同疾病類別統稱為 TTP-HUS。近 10 年來，學者們對這些異常類別的疾病發生論有所論述：一，大部分先天性和後天性血栓性血小板減少紫斑症病人的血循環中可發現 ADAMTS13 嚴重缺乏，此導致 von Willebrand factor 調解缺陷；二，許多非典型溶血性尿毒症候群的病人與補體替代路徑調解異常有關，乃補體蛋白基因突變，包括 C3，因子 H，B，I 及胞膜補體輔因子蛋白。這些進展，及對 Shiga 毒素和下痢相關的溶血性尿毒症候群之間關係的相當認知，提供了我們對這些多變的疾病過程更多的了解，也提供了 TTP-HUS 診斷和治療的進一步方向。假如未治療，血栓性血小板減少紫斑症的病程將快速進行；不可逆腎衰竭、進行性神經異常、心肌缺血及死亡是常見的後果。血漿置換術具有高度反應率，因此，當病人出現二位組的徵候時，即血小板減少和微血管病變溶血性貧血，就應起動血漿置換術。