MEDICINE

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) AND MODERN APPROACH TO ITS INVESTIGATION AND TREATMENT*K. Ukleba, L. Gvetadze,**Department of Clinical Medicine, Medical faculty, Akaki Tsereteli state University Kutaisi, Georgia*DOI: https://doi.org/10.31435/rsglobal_sr/31032019/6381**ARTICLE INFO****Received** 16 January 2019**Accepted** 16 March 2019**Published** 31 March 2019**KEYWORDS**Thrombocytopenic Purpura,
Microangiopathic hemolytic
anemia,
ADAMTS13.**ABSTRACT**

Thrombotic thrombocytopenic purpura (TTP) is a rare and life-threatening thrombotic microangiopathy characterized by microangiopathic hemolytic anemia, severe thrombocytopenia, and organ ischemia linked to disseminated microvascular platelet rich-thrombi. TTP is specifically related to a severe deficiency in ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 repeats, member 13), the specific von Willebrand factor-cleaving protease. ADAMTS13 deficiency is most frequently acquired via ADAMTS13 autoantibodies, but rarely, it is inherited via mutations of the ADAMTS13 gene. The first acute episode of TTP usually occurs during adulthood, with a predominant anti – ADAMTS13 autoimmune etiology. In rare cases, however, TTP begins as soon as childhood, with frequent inherited forms. TTP is 2 – fold more frequent in women, and its outcome is characterized by a relapsing tendency.

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Introduction. TTP is thought to be a rare disease. Over one series, the frequency was approximately 1 in 50000 hospital admissions. Over a 25 year period in the Sacramento, California region (population at risk, 1.2 million) at least 176 documented cases of TTP were reported. Analysis of a French national registry found that the rate of TTP in France was 13 cases per million population.

Untreated TTP has a mortality rate of as high as 90%. With plasma exchange the mortality rate is reduced to 10-20%. Patients with TTP have unusually large multimers of von willebrand factor (WF) in their plasma and the lack a plasma protease that is responsible for the breakdown of these ultralarge WF multimers. In the congenital form of TTP, mutations in the gene encoding this protease have been described. This protease has been isolated and cloned and is designated ADAMTS13. To make an accurate diagnosis, the clinician must recognize the similarity between thrombotic thrombocytopenic purpura (TTP) and hemolytic – uremic syndrome (Hus). The differential diagnosis also includes immune thrombocytopenic purpura (ITP) and disseminated intravascular coagulation (Dic).

In addition to the microangiopathic hemolytic anemia and consumption thrombocytopenia, classical parameters for hemolysis show a high reticulocyte count ($>120 \times 10^9/L$), an undetectable serum haptoglobin concentration, and an elevated lactate dehydrogenase level, a marker for tissue damage. The presence of schistocytes on the blood smear (helmet cells; small, irregular triangular, or crescent – shaped cells; pointed projections; and lack of central pallor) with a confident threshold value of 1% is the morphologic hallmark of the disease. Except in some associated autoimmune contexts (SLE), the erythrocyte Coombs' test is negative, Standard coagulation parameters are usually normal.

Renal testing may show proteinuria, hematuria, and sometimes increased plasma urea and creatinine levels. An increased cardiac troponin level ($>0.1 \mu\text{g/L}$) is present in up to 60% of cases, the majority of whom have no clinical cardiac involvement. Electrocardiogram changes, mainly repolarization disorders, are present in 10% of cases. Point-based TTP prediction scores have been validated to predict an acquired ADAMTS13 deficiency. These scores include platelet count, serum creatinine level, and either detectable antinuclear antibodies or d-dimer, reticulocytes, and indirect bilirubin.

As these standard investigations are not specific for TTP and may be present in the miscellaneous differential diagnosis for TTP, they should be complemented by analysis of ADAMTS13, the unique marker sensitive and specific for TTP.

Clinical spectrum of TTP

Today, the historical clinical pentad of fever, thrombocytopenia, microangiopathic hemolytic anemia, neurological symptoms, and renal insufficiency that used to define TTP appears obsolete, as several cohort studies have clearly demonstrated that these 5 symptoms were present in less than 10% of patients with an acute TTP. The almost constant signs of TTP remain severe thrombocytopenia (typically $<30 \times 10^9/\text{L}$) and microangiopathic hemolytic anemia characterized by schistocytes on the blood smear, often associated with corresponding symptoms (ie, skin and mucosal hemorrhage, weakness, and dyspnea). Symptoms related to ischemia/infarction mostly concern the brain (~60% of patients have neurologic symptoms at presentation, with a broad range from headache and confusion to stroke, coma, and seizures). Heart ischemia is also frequent (~25% of patients, ranging from isolated electrocardiographic abnormalities to myocardial infarction), as well as mesenteric ischemia (~35%) causing abdominal pain and seizures. Heart ischemia is also frequent (~25%) of an isolated proteinuria/hematuria; acute renal failure is unusual in TTP, with typically a serum creatinine level below 2 mg/dL at presentation.

Rapid recognition of TTP is crucial to initiate appropriate treatment. The first-line therapy for acute TTP is based on daily therapeutic plasma exchange supplying deficient ADAMTS13, with or without steroids. Additional immune modulators targeting ADAMTS13 autoantibodies are mainly based on steroids and humanized anti-CD20 monoclonal antibody rituximab. In refractory or unresponsive TTP, more intensive therapies including twice-daily plasma exchange; pulses of cyclophosphamide, vincristine, or cyclosporine A; salvage splenectomy are considered. New drugs including N-acetylcysteine, bortezomib, recombinant ADAMTS13, and caplacizumab show promise in the management of TTP. Also, long-term follow-up of patients with TTP is crucial to identify the occurrence of other autoimmune diseases, to control relapses, and to evaluate psychophysical sequelae. The overall response rate to plasma exchange is 75-90%. The early mortality rate is 10-20%.

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