AMPATHCHAT no. 83

DIAGNOSIS OF THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

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KEY MESSAGES

- Thrombotic thrombocytopenic purpura (TTP) is a rare disorder with high mortality. A high index of suspicion and early communication with the haematologist is pivotal to improve outcome.
- Confirmation of diagnosis depends on signs and symptoms of a Coombs-negative microangiopathic haemolytic anaemia (MAHA), organ involvement and thrombocytopaenia with an ADAMTS13 activity level of less than 10%.
- In acquired TTP (iTTP), antibodies against ADAMTS13 are often present, which is not the case with hereditary TTP (hTTP). A negative antibody test does not indicate hTTP, as mechanisms other than antibodies against ADAMTS13 may play a role.
- Long-term follow up of these patients is essential, both to distinguish between hTTP and iTTP, and to monitor activity of the disease.
- Various other conditions must be considered if ADAMTS13 activity is greater than 10% (see Figure 2).

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a rare disorder that forms part of the heterogenous group disorders of thrombotic microangiopathies (TMA). The hallmarks of the TMAs are:

- Occlusion of the arterioles and capillaries leading to dysfunction of the organ it supplies.
- Non-immune thrombocytopenia.
- Microangiopathic hemolytic anaemia (red cells broken up in the small vessels by the fibrin strands).

The first clinical description of TTP was given in 1924 by Eli Moschcowitz in a 16-year-old girl who died from a stroke and myocardial infarction 14 days after she presented with fever, weakness and transient neurological symptoms. Today, it is still a life-threatening disease, with mortality of 10 to 20%, despite our knowledge of pathogenesis and newer therapies. Long-term complications in survivors include neurocognitive defects, arterial hypertension and major depression. Therefore, these patients need careful follow up. This disease has a relapsing tendency. A high index of suspicion is needed when evaluating patients. ADAMTS13 antigen and antibody testing are done, not only to distinguish between acquired versus congenital forms of the disease, but also to monitor disease activity.

PATHOPHYSIOLOGY

Endothelial cells normally release von Willebrand Factor (vWF), which is a large multimeric glycoprotein protein that functions as an activator and anchor for platelets (leading to platelet activation) and stabilises FVIII (and increases the half-life of this clotting factor). It is released as large vWF multimers that need to be cleaved by a protease known as ADAMTS13 (a disintegrin and metalloprotease with thrombospondin Type 1 repeats, member 13). Decreased ADAMTS13 due to either a genetic (hereditary) abnormality, or antibodies made against ADAMTS13 that neutralise it, or antibodies that lead to increased clearance of ADAMTS13 lead to the presence of ultra-large vWF in the vessel. Platelets bind to these large vWF multimers, forming platelet-rich thrombi that obstruct blood flow with end-organ ischemia (Figure 1).

MECHANISM OF TTP

The primary cause is low ADAMTS13 levels, which may be due to:

- **Hereditary TTP (hTTP) low levels:** This is also called Upshaw-Schulman syndrome and constitutes approximately 2% of cases. More than 150 distinct genetic mutations in the ADAMTS13 gene have been described and are inherited recessively (patients are homozygous or compound heterozygous). The clinical phenotype varies, and a trigger is often necessary to precipitate the disorder (such as pregnancy, infection, trauma). It is a rare genetic disorder, with an incidence of 0.4 to 1 million people. A diagnosis can only be made if the ADAMTS13 levels are constantly low and ADAMTS13 IgG antibodies are persistently absent during relapses and long-term monitoring. ADAMTS13 gene analysis is the ideal confirmation test, but is not yet available in South Africa.

- **Acquired TTP:**
  - Immune-mediated TTP (iTTP): Antibodies against ADAMTS13 are present. In primary iTTP, no obvious underlying associated disease is present.
  - Unknown mechanism TTP: Possible insensitivity of vWF to ADAMTS13.

Conditions that increase vWF release, such as inflammation, infection and pregnancy, may precipitate the acute TTP event. Some predisposing factors, including obesity and gender (e.g. female patients and patients of African ancestry) may also play a role. Due to these predisposing and precipitating factors, some authors subclassify acquired TTP into various groups such as drug-induced TTP (ticlopidine,

case reports of Pfizer-BioNTech COVID-19 vaccine), obstetric TTP, auto-immune associated TTP (especially SLE), cancer- and organ transplantation-associated TTP, HIV-related TTP and others.

CLINICAL PICTURE

The known pentad of thrombocytopenia, fever, microangiopathic haemolytic anaemia (MAHA), renal insufficiency and neurological symptoms are rarely seen today. The most constant signs and symptoms are:

- Thrombocytopenia (often <30 x10^9/L);
- Haemolytic anaemia (fragmentation with red cell fragments on the peripheral blood smear);
- High D-dimer levels, PT, aPTT normal or mild increase;
- Neurological symptoms (headache, confusion, seizures, stroke, coma);
- Mesenteric ischaemia (abdominal pain and diarrhoea);
- Heart ischemia (myocardial infarction); and
- Renal injury (proteinuria/hematuria).

The **PLASMIC** score has been developed as a clinical prediction tool and as a prognostic indicator in TTP. This score must only be applied when a thrombocytopenia and MAHA is present (Table 1). This scoring tool does not replace clinical judgement. When a TMA is present, but the ADAMTS13 level is greater than 10%, various other disorders should be suspected (Figure 2).

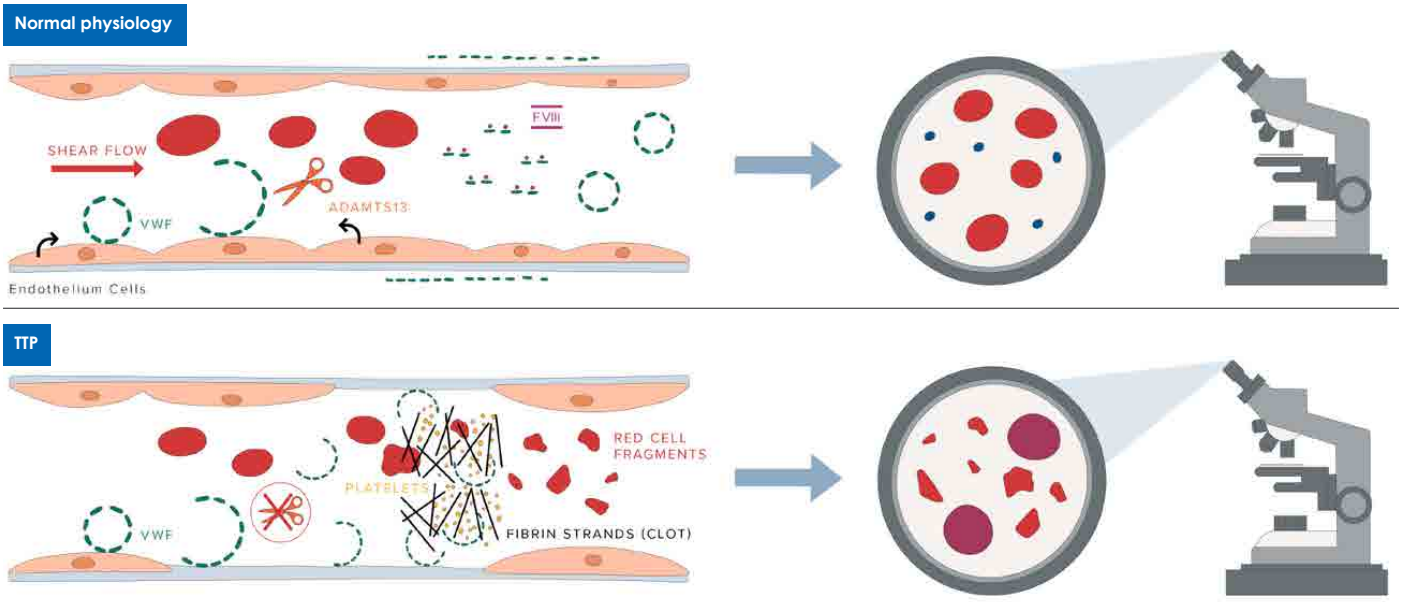

FIGURE 1: PATHOPHYSIOLOGY OF TTP

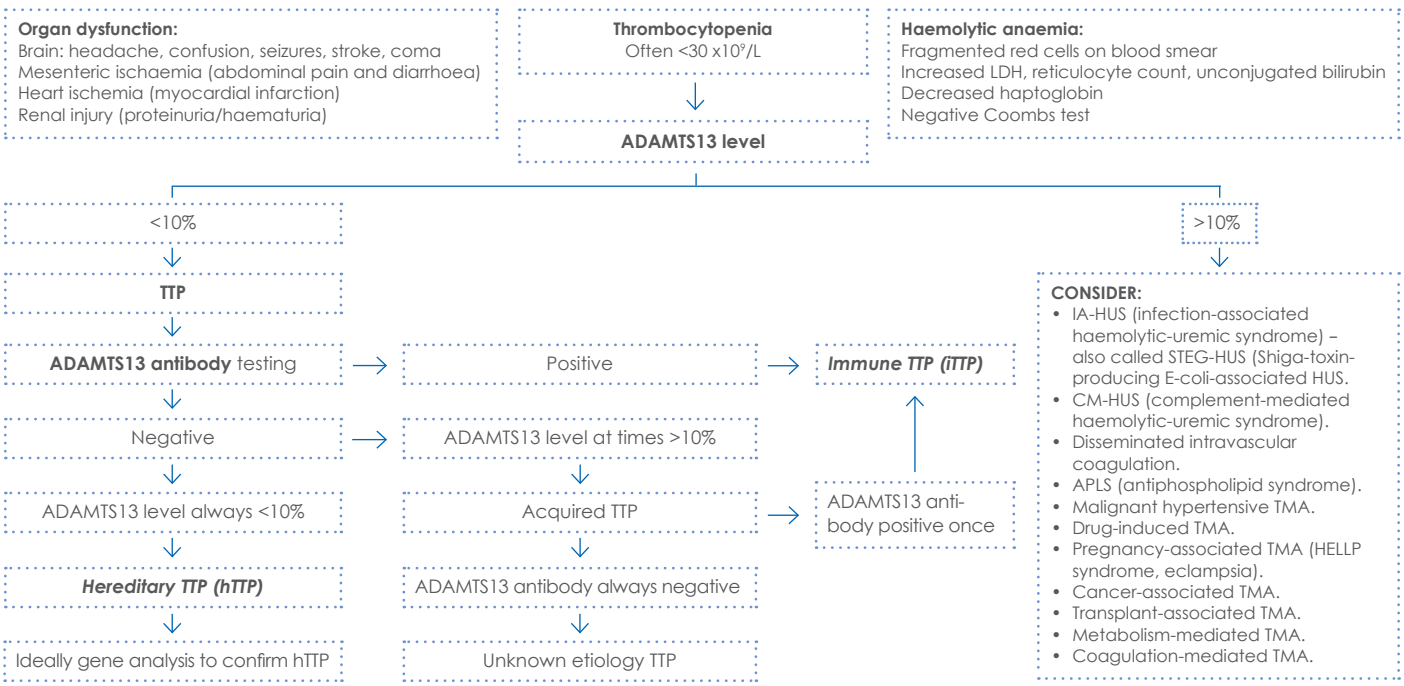

FIGURE 2: APPROACH TO DIAGNOSTIC WORKUP OF TTP

Adapted from references mentioned in text.

MANAGEMENT PRINCIPLES

As soon as the diagnosis of TTP is clinically suspected, input from a haematologist is suggested, especially in the evaluation of peripheral blood smear (red cell fragmentation evaluation). Laboratory testing should include ADAMTS13 activity levels, Coombs, reticulocyte count, haptoglobin, LDH, D-dimer, INR, PTT and fibrinogen. Treatment includes plasma exchange and immunosuppression without delay (see references).

PRACTICAL ISSUES REGARDING ADAMTS13 ANTIBODY TESTING

ADAMTS13 antibody testing will only be done if the activity (ADAMTS13) level is below 10% or when specifically requested (e.g. a known patient with iTTP). Samples containing EDTA cannot be used and a citrate tube is required for testing. Samples with very high concentrations of other autoantibodies may result in a weak false positive or borderline result.

TABLE 1: PLASMIC SCORE PARAMETERS

A score of >5 is indicative of TTP, and values of 6 to 7 have been shown to correlate with ADAMTS13 levels of <10%.

Parameter	Absent	Present
Platelet count <30 x10^9/L	0	+1
Haemolysis Reticulocyte count >2.5% Haptoglobin undetectable Indirect bilirubin >34.2 umol/L	0	+1
Active cancer (treated in last year)	+1	0
History of solid organ/stemcell transplant	+1	0
MCV <90 fL	0	+1
INR <1.5	0	+1
Creatinine <176.8 umol/L	0	+1

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