# Congenital thrombotic thrombocytopenic purpura

**BACKGROUND** Congenital thrombotic thrombocytopenic purpura (TTP) is a rare, hereditary disorder. Clinically it presents as episodic microangiopathic haemolytic anaemia and thrombocytopenia with varying degrees of damage to internal organs. The condition may present in neonates, but can also present for the first time in adulthood. The prevalence of congenital TTP is particularly high in Norway, and it is therefore important for Norwegian doctors to be aware of the condition. In this article we review the main characteristics of the disease, including its diagnosis and management, and introduce potential new treatments for the future.

**METHOD** The article is based on a literature search in PubMed as well as the authors' own research and clinical experience.

**RESULTS** There was great variation in the severity of congenital TTP: from neonatal mortality to disease-free intervals of several years. Episodes are generally precipitated by a trigger. Acute episodes are treated with plasma infusions, and approximately half of all patients experience frequent episodes and require prophylactic infusions to avoid organ damage. The risk of episodes is greatest in neonates, during pregnancy and in association with infections.

**INTERPRETATION** There is little research-based evidence regarding long-term prognosis in congenital TTP. There is also a need for guidelines to help identify candidates for prophylactic treatment. An international patient registry would provide useful information and form the basis for better guidelines on the monitoring and treatment of these patients.

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Congenital thrombotic thrombocytopenic purpura (TTP) was first described by Irving Schulman in 1960 in a young girl with haemolytic anaemia, recurrent thrombocytopenia and bleeding tendency (1). Jefferson D. Upshaw later described a similar case and suggested that deficiency of an unidentified plasma factor was responsible for the disorder, as administration of plasma-containing blood products resolved the thrombocytopenia in both his own patient and Schulman's (2). For many years the condition was known as Upshaw-Schulman syndrome.

These patients were subsequently found to have ultra-large, sticky von Willebrand factor multimers in their plasma. These were the result of mutations in the gene that encodes the protease ADAMTS13 (A Disintegrin And Metalloprotease with ThromboSpondin type 1 motif 13), which cleaves von Willebrand factor (3, 4). The condition is now known as congenital or hereditary TTP, but may also present in adulthood.

The disorder is characterised by episodic microangiopathic haemolytic anaemia, thrombocytopenia and varying degrees of organ damage. It is hereditary and affects both men and women. Left untreated, episodes of congenital TTP have high mortality, but prompt diagnosis and treatment allow most of those affected to survive (5). Little is known currently about long-term prognosis.

Congenital TTP has previously been featured in the Journal of the Norwegian Medical Association in the «case reports» section (6). The current article provides an overview of the disorder with emphasis on diagnosis and treatment, as well as on the unusually high prevalence of the condition in Norway.

## Method

The article is based on a literature search and a review of the bibliographies of relevant articles. We performed four different searches in PubMed with the keywords «thrombotic thrombocytopenic purpura», «Upshaw Schulman syndrome», «congenital» and «familial» (Fig. 1). The literature search was terminated on 15 March 2015. Articles were first assessed for relevance on the basis of the title and abstract. Articles in languages other than English or the Scandinavian languages were excluded.

There was extensive overlap in the search results. Of 131 articles reviewed in full text, 38 were deemed relevant on the basis of inclusion and exclusion criteria (Box 1). We included a further 12 articles from bibliographies and our own archives. These primarily concerned descriptions of disease mechanisms and treatment. An updated search was conducted for the period 16 March 2015 to 16 March 2016, and yielded a further three articles.

## Pathogenesis

Congenital TTP (OMIM# 274150) shows autosomal recessive inheritance and is caused by mutations in the *ADAMTS13* gene (OMIM* 604134) on chromosome 9q34 (4, 7). The mutations lead to a severe deficiency of the ADAMTS13 enzyme, either through

### KEY POINTS

**Congenital thrombotic thrombocytopenic purpura is a rare, hereditary disorder that causes thrombosis, increased bleeding tendency and anaemia**

**The condition may present for the first time in adulthood, often in association with pregnancy**

**Congenital thrombotic thrombocytopenic purpura is more prevalent in Norway than in other countries, but it is not known for certain why**

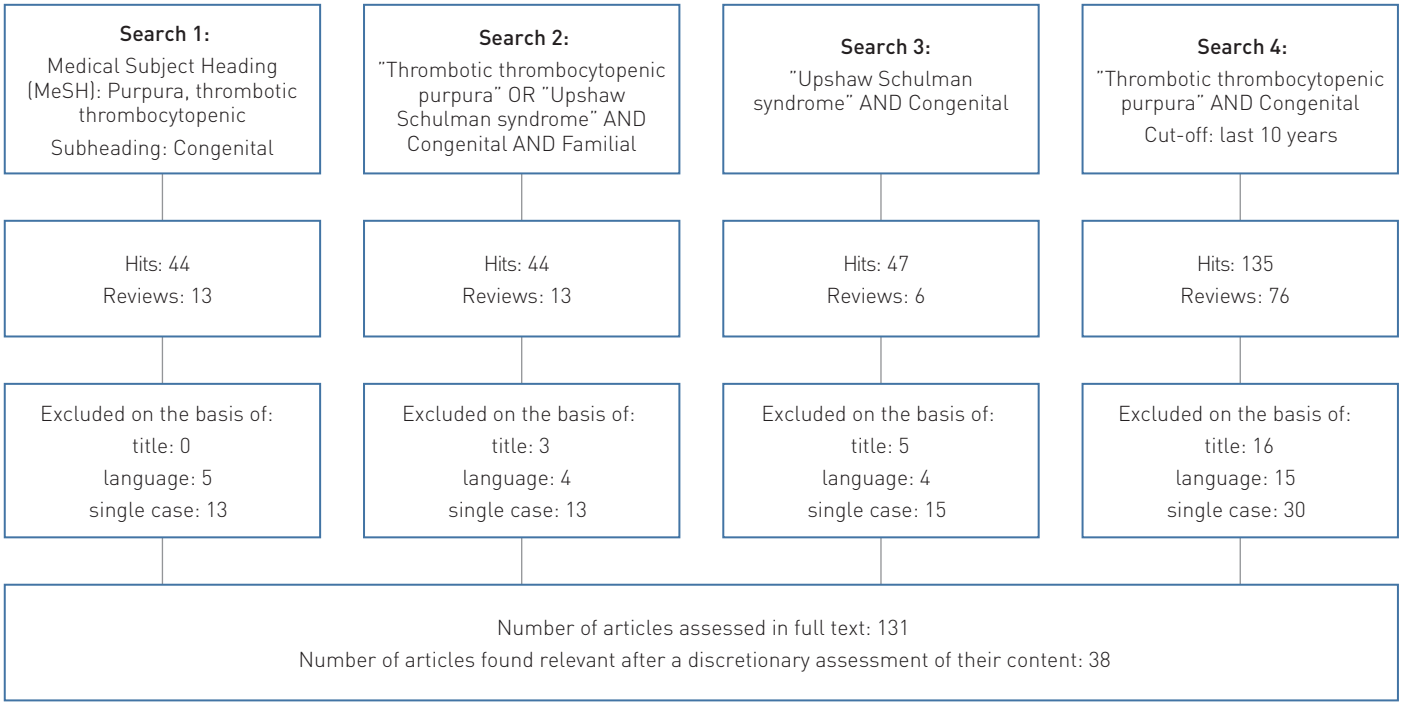


**Figure 1** *Summary of literature searches with number of hits at each step. Date ranges were specified only for search 4. Inclusion and exclusion criteria are shown in Box 1. In step 1, most articles were excluded because they were about individual cases or individual mutations of no relevance to the Norwegian population. In step 2, the main reason for exclusion was that articles primarily concerned acquired thrombotic thrombocytopenic purpura or contained no new patient data*

reduced synthesis and secretion or a reduction in specific activity.

ADAMTS13 plays an important role in haemostasis by regulating the size of von Willebrand factor multimers (8, 9). In the absence of ADAMTS13, ultra-large multimers of von Willebrand factor enter the circulation and stimulate platelet adhesion and aggregation, which can thus result in spontaneous thrombi in the microcirculation. These lead to consumption of platelets and ischaemia in affected organs, such as the kidneys, brain, heart and intestines.

ADAMTS13 is synthesised mainly in the liver and vascular endothelium, while von Willebrand factor is produced in endothelial cells and megakaryocytes, and is stored in Weibel-Palade bodies in endothelial cells and in platelet alpha-granules (10). Ultra-large multimers of von Willebrand factor enter the circulation only after endothelial activation. A stimulus is therefore required to activate the endothelium and release von Willebrand factor (e.g. trauma, infection, pregnancy or alcohol) prior to an episode of TTP (11).

## Other causes of TTP

ADAMTS13 deficiency may arise due to production of autoantibodies that inhibit the ADAMTS13 enzyme. TTP can also occur without ADAMTS13 deficiency – secondary to advanced malignancies, HIV infection, medication use or after allogeneic stem cell transplantation (12).

In this article we have focused on the genetic variant.

## Prevalence

The global incidence of TTP (all causes) is between 1.5 and 4 per million population per year (13, 14). Over 90 % of these cases are acquired TTP. The prevalence of the congenital form is estimated to be 1 per million population (15, 16). More than 150 different mutations in *ADAMTS13* have been described in connection with congenital TTP. Most have been observed in individual families, but two mutations of probable European origin have been described in various families from Northern and Central Europe, USA, Canada and Australia (7, 17, 18).

In Norway we know of 19 families with the disorder. A study conducted in the Central Norway Regional Health Authority revealed a prevalence of 16.7 per million population (19). This is 15 times higher than the rate reported in the international literature, and the congenital form was more common than the acquired.

The high prevalence was related to the *ADAMTS13* mutation NM_139025.4(ADAMTS13): c.4143-dupA (p.Glu1382Argfs), hereafter referred to as c.4143dupA. Of 18 patients who had been genotyped for *ADAMTS13*, eleven were homozygous and three were compound heterozygous for the c.4143dupA mutation. All patients with this mutation have the same haplotype, and a founder effect is therefore assumed to explain the high disease prevalence (17, 19).

A founder effect can occur when a new population is established from a small group of «founders» and thus loses some of its genetic variation. The prevalence of conge-

BOX 1

**Inclusion criteria**

Clinical studies that include patients with congenital thrombotic thrombocytopenic purpura

Consensus reports and treatment recommendations

Case series and review articles that contain phenotypic data

Single case studies relevant to the Norwegian patient population

**Exclusion criteria**

Reports that primarily concern acquired thrombotic thrombocytopenic purpura

Reports on single mutations that have not been described in the Norwegian population

Duplicate publications (previously published case in new context without new data)

nital TTP has not been systematically studied in the rest of Norway, but is probably closer to that seen worldwide.

## Clinical presentation at different life stages

*Neonatal period*

Prolonged icterus in neonates may be the first sign of congenital TTP. Of those who were subsequently diagnosed, 40–45 % had prolonged neonatal icterus that was treated with exchange transfusion (7, 20).

There are reports of unexplained deaths after anaemia in the neonatal period among the siblings of patients with known disease (20–23). In other cases, the haemolytic crisis may be self-limiting without organ manifestations or sequelae. ADAMTS13 activity should therefore be measured in neonates with haemolysis and thrombocytopenia in the absence of a clear explanation (e.g., rhesus incompatibility) (Fig. 1).

*Infancy*

In infants, the disease may present as episodes of haemolysis and thrombocytopenia after infections or trauma. An episode that occurs after a bout of gastroenteritis may be difficult to distinguish from conditions such as haemolytic-uraemic syndrome. Haemolytic anaemia with thrombocytopenia is also seen in Evans syndrome, and many children with TTP initially (and incorrectly) receive this diagnosis (24). Evans syndrome is a form of autoimmune haemolytic anaemia with concurrent or subsequent immune-mediated thrombocytopenia. Unlike patients with TTP, these patients will therefore have a positive direct antiglobulin test.

Patients with congenital TTP display an excess of neuropsychological developmental disorders. It is unknown whether this is due to episodes that affect the central nervous system in the neonatal period, or to repeated but less severe episodes subsequently.

*Pregnancy*

After the neonatal period, pregnancy is the next most common time for the disorder to present. Some patients will have been asymptomatic as neonates and in childhood and adolescence, and experience their first ever episode while pregnant. Women with known congenital TTP always experience episodes in pregnancy unless careful monitoring and prophylactic measures are implemented (25–27).

Pregnancy stimulates marked endothelial activation and the release of von Willebrand factor, and circulatory levels normally increase towards the end of pregnancy (2nd and 3rd trimesters and postpartum). It is typically in this period that episodes of TTP occur. This can make it difficult to distinguish them from other, far more common pregnancy complications that also occur in the same period, such as preeclampsia and HELLP syndrome (H = haemolysis, EL = Elevated Liver enzymes, LP = Low Platelets).

*Adolescence and adulthood*

At the end of childhood, many patients experience a reduction in the frequency of TTP episodes. Some continue to have episodes in response to clear precipitating factors – such as alcohol consumption – until the relationship is identified and the triggering factor eliminated. Others develop a form of remitting disease without clear precipitating factors or a state of persistent disease activity with signs of haemolysis and thrombocytopenia in laboratory tests. The development of late complications such as hypertension and progressive renal failure may occur during this period.

It remains unknown why patients in the same family with the same *ADAMTS13* mutations can develop such different disease severities (28). It is possible that unequal exposure to precipitating factors may play a role, as may comorbidity, polymorphisms in the *ADAMTS13* gene and mutations in other genes (29).

## Diagnostics

TTP is considered a medical emergency, and requires alertness on the part of the clinician and initiation of treatment upon suspicion of the disorder, often before a causal diagnosis is available (Fig. 2). TTP must be suspected whenever thrombocytopenia is seen in combination with microangiopathic haemolytic anaemia. Microangiopathy can be confirmed by showing the presence of fragmented erythrocytes (schistocytes and helmet cells) in a blood smear. A schistocyte count of greater than 1 % without other notable abnormalities in erythrocyte morphology is of significance.

Biochemical signs of activated coagulation (elevated activated partial thromboplastin time, prothrombin time, D-dimer) are rarely seen with TTP, unlike disseminated intravascular coagulation. Blood samples for detection of ADAMTS13 deficiency should be obtained prior to treatment with plasma-containing blood products. ADAMTS13 antigen levels or activity can be measured in citrated plasma with ELISA-based or FRET-based methods (30–32). St Olavs Hospital Trondheim University Hospital began offering the ADAMTS13 activity assay in October 2015, and accepts samples from all hospital laboratories in Norway.

Severe ADAMTS13 deficiency is defined as < 10 % normal activity. Samples are then examined for the presence of antibodies against ADAMTS13. If such antibodies are absent, congenital TTP is suspected if the disorder is otherwise indicated by the medical history; the diagnosis is confirmed by detection of a homozygous or compound heterozygous mutation upon sequencing of *ADAMTS13*. Molecular genetic diagnosis can be performed in a more targeted manner if the patient's blood type is known. This applies particularly to mutation c.4143dupA, which is associated with blood type B (19).

ADAMTS13 antibody testing and molecular genetic testing are not yet available in Norway, but are performed at Inselspital in Bern, Switzerland.

## Treatment

In patients with congenital TTP, acute episodes are treated using plasma infusion to replace the missing ADAMTS13. Fresh frozen plasma, solvent/detergent (SD)-treated plasma and intermediate purity factor VIII concentrate all contain ADAMTS13 (33–35). In Norway, Octaplas (Octapharma, Vienna) is used in practice for acute episodes, at a daily dose of 20–40 ml/kg body weight.

Plasma exchange, which is used in cases of antibody-mediated disease, is more expensive than plasma infusion and unnecessary for congenital TTP. Supportive therapy is provided for affected organs as required, such as dialysis in the event of acute anuric renal failure. The duration of treatment with plasma infusion is guided by its clinical effectiveness, whereby a rise in platelet count is often the best indicator of treatment response (5).

Patients (or their parents) must learn to recognise the symptoms of a TTP episode, and platelet count should always be measured in the event of other acute illness. Patients with repeated episodes, permanent organ damage or persistent subclinical signs of haemolysis and thrombocytopenia should be considered for prophylactic treatment.

Treatment is generally well tolerated but is time-consuming. Most patients achieve disease stabilisation with infusion of 10–15 ml Octaplas per kilogram every 2nd to 3rd week, but the treatment interval and volume must be tailored to the individual patient (36, 37). There are no reliable data on who should be offered prophylactic treatment, but a number of large case series have shown that approximately half of all patients receive plasma prophylaxis (19, 20, 29). There have been concerns that patients who are treated with prophylactic plasma infusions for a number of years may develop inhibitory alloantibodies against ADAMTS13, in line with what has been observed in patients with haemophilia treated with factor concentrate. However, to date this has not been seen in patients with congenital TTP.

Clinical trials are underway for congenital TTP treatments based on new principles. ARC1779 is a synthetic aptamer that binds to von Willebrand factor at the platelet bin-

ding site, and prevents von Willebrand factor-mediated platelet activation and thrombosis (38). Aptamers are oligonucleotides that bind with high affinity and specificity to binding sites, and can block protein-protein interactions. They have so far been tested only in a phase 1/phase 2 study (38).

Recombinant ADAMTS13 (rADAMTS13) has recently entered clinical trials in a phase 1 study (39). The drug may potentially ease the daily lives of patients who are today dependent on regular plasma infusions. The hope is that easier administration of treatments and possibly self-management may be the future for patients with congenital TTP, as has been achieved for many patients with haemophilia.

## Monitoring

Once TTP has been diagnosed, the patient and caregivers must receive training in how to quickly recognise the symptoms of an episode; when symptoms are present there must be a low threshold for attending hospital to receive plasma therapy. Early diagnosis is probably the most important measure to prevent the development of late effects.

Patients should be monitored regularly by a paediatrician or haematologist who can assess the need for prophylactic plasma infusions, the possibility of organ damage after episodes, and who can check renal functioning, general cardiovascular risk and neuropsychological functioning.

Pregnancy is a high-risk situation, and monitoring by a haematologist and obstetrician should begin as soon as the pregnancy is confirmed.

## Discussion

Congenital TTP is a rare hereditary disorder but one that is worth being aware of for several reasons. Firstly, it is a model disease that has provided insights into the interaction between von Willebrand factor and ADAMTS13 in normal haemostasis regulation. Secondly, congenital TTP is a relevant differential diagnosis at multiple life stages and in various clinical situations, and many patients experience delays in diagnosis. Thirdly, and of special relevance for Norwegian doctors, Norway has an excess of cases due to a founder effect of the mutation c.4143dupA in *ADAMTS13*.

Traditionally, TTP has been characterised by a collection of five signs and symptoms: fever, renal involvement, neurological symptoms, microangiopathic haemolytic anaemia and thrombocytopenia (40). However, only a minority of episodes will feature all five signs concurrently.

Attentiveness may be the key to early diagnosis, especially with regard to neonates with prolonged icterus, and pregnant women with thrombocytopenia and haemolysis. ADAMTS13 assays are now readily available and can within 2–4 weeks confirm or exclude the diagnosis. Siblings of patients should be offered genetic counselling. Because the expression of the disease may differ (its clinical presentation may vary), an asymptomatic sibling could have severely reduced ADAMTS13 activity and experience an episode if s/he is exposed to a sufficient stimulus, such as infection or pregnancy.

Our literature review shows that there has been little research on congenital TTP. Published treatment recommendations are based on experience from regional or national regis-

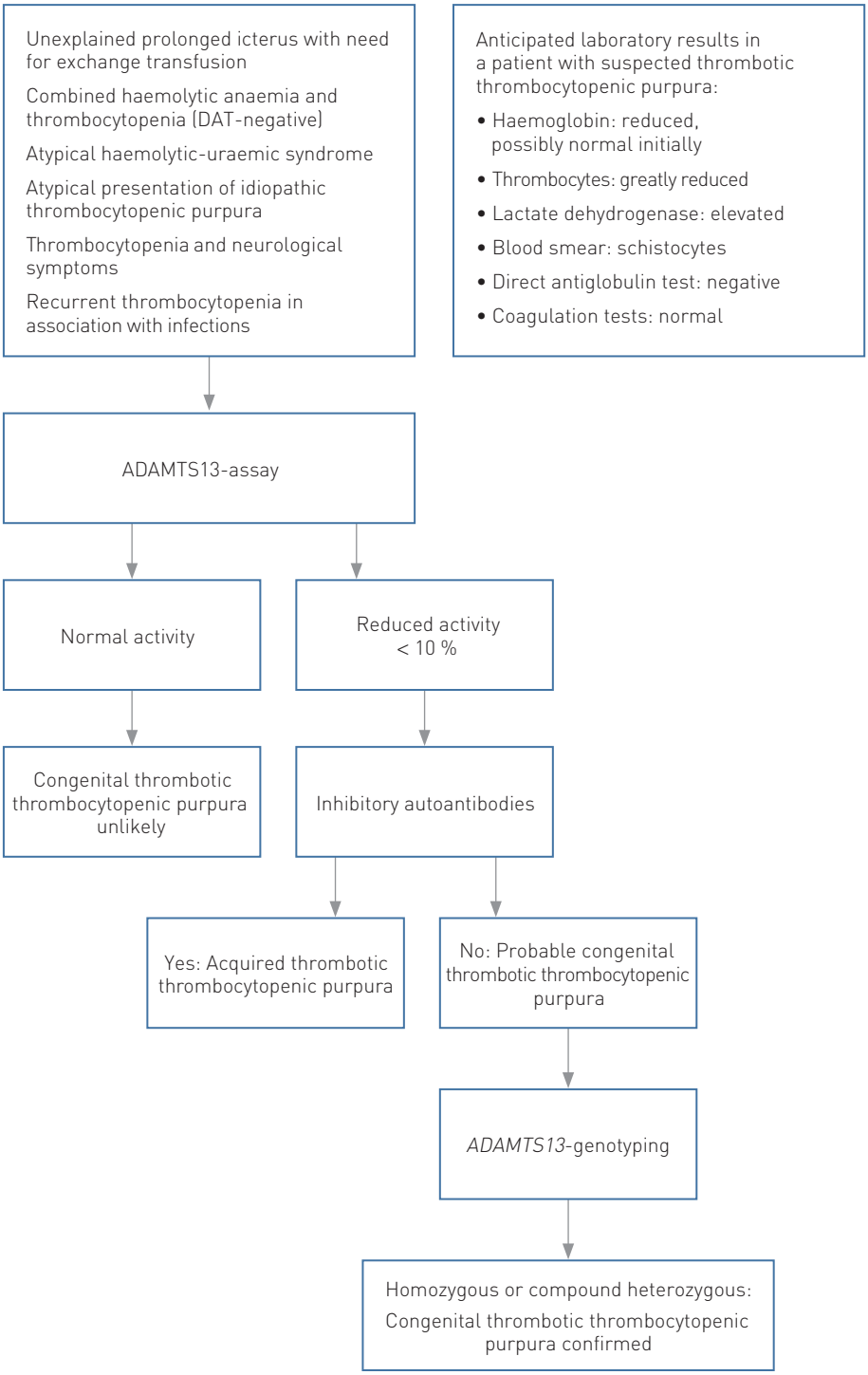


**Figure 2** *Conditions that should prompt assessment for thrombotic thrombocytopenic purpura, and an algorithm for use in the assessment. Typical laboratory results in a patient with congenital thrombotic thrombocytopenic purpura are shown on the right*

tries, or from major centres where these patients are treated. For very rare diseases, case series and single case histories can nevertheless be an important source of information.

There remain several unresolved issues: ADAMTS13 deficiency alone is insufficient to trigger episodes. Sites of predilection to organ damage vary from patient to patient. Such extensive variation in phenotype, even within the same family, raises the question of whether other disease-modifying genes or environmental factors may play a role. Prophylactic plasma therapy is probably beneficial, but we know little about its long-term effectiveness, nor whether those who currently do *not* receive prophylactic treatment should have done so. Cardio- and cerebrovascular deaths have been described, but it is unclear whether patients have excess mortality that is not directly related to TTP episodes.

For rare diseases, registry-based studies can provide valuable insights into the natural disease course. There is an international patient registry for congenital TTP that also includes Norwegian patients (41, 42). Systematic data collection is necessary to develop treatment guidelines and to form the basis for evidence-based practice.

## Conclusion

Congenital TTP is a rare, hereditary disorder with an unusually high prevalence in Norway. The diagnosis is based on demonstration of severely reduced ADAMTS13 activity and homozygosity or compound heterozygosity for mutations in *ADAMTS13*.

Acute episodes are treated with plasma infusion. The decision on whether to begin prophylactic plasma treatment must be tailored to the individual. A resource centre for patients with congenital TTP, similar to that which exists for patients with haemophilia, should be established.

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