

## Case report

# Congenital thrombotic thrombocytopenic purpura presenting in adulthood with recurrent cerebrovascular events

Emma Tenison ,<sup>1,2</sup> Ashar Asif ,<sup>3</sup> Mathew Sheridan ,<sup>4</sup>

<sup>1</sup>Translational Health Sciences, University of Bristol Musculoskeletal Research Unit, Bristol, UK

<sup>2</sup>Older People's Unit, Royal United Hospitals Bath NHS Foundation Trust, Bath, UK

<sup>3</sup>Medical School, University of Bristol, Bristol, UK

<sup>4</sup>Bristol Haematology and Oncology Centre, University Hospitals Bristol NHS Foundation Trust, Bristol, UK

**Correspondence to**  
Dr Emma Tenison,  
et6915@bristol.ac.uk

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## SUMMARY

Congenital thrombotic thrombocytopenic purpura (cTTP) is a rare, life-threatening disease, characterised by episodes of microangiopathic haemolytic anaemia (MAHA), thrombocytopenia and small vessel thrombosis. We describe a case of cTTP first diagnosed at age 70 years in a female presenting with an acute ischaemic stroke and thrombocytopenia, in whom A Disintegrin And Metalloproteinase with a Thrombospondin type 1 Motif, member 13 (ADAMTS13) levels were <10%, suggestive of thrombotic thrombocytopenic purpura (TTP). The patient underwent plasma exchange and started rituximab for presumed immune TTP; however, anti-ADAMTS13 antibody titres were negative on two occasions. This, together with a history of pregnancies complicated by presumed disseminated intravascular coagulation, and two previous episodes of sepsis with MAHA, prompted investigation for cTTP, which was confirmed by genetic testing. Despite treatment with infusions of solvent/detergent-treated, virus-inactivated fresh frozen plasma, she has re-presented with further neurological deficit, associated with new infarcts on imaging. cTTP has a varied phenotype which, as demonstrated in this case, can include large vessel occlusion.

## BACKGROUND

Congenital thrombotic thrombocytopenic purpura (cTTP), also known as Upshaw-Schulman syndrome, has an approximate incidence of one case per million per year and, despite being congenital, can present at any age, from the neonatal period through to adulthood.

While neurological involvement, including transient neurological deficit, is well-recognised in TTP due to occlusion of small vessels, large vessel occlusion is less typical.

The case highlights how a rare disease can present with a common syndrome (stroke) which necessitates specialised treatment. Knowledge of this will enable inclusion of TTP and cTTP in the differential diagnosis when appropriate, leading to better patient care.

## CASE PRESENTATION

A 70-year-old right-handed female presented to a district general hospital with diarrhoea and vomiting, together with acute confusional state and fever. Infective causes of diarrhoea were excluded

and she was treated for urosepsis. She was noted to be thrombocytopenic and developed epistaxis for which platelets were transfused.

She was a hypertensive, tee-total, never-smoker, diet-controlled type 2 diabetic. She had no history of hyperlipidaemia or ischaemic heart disease. Previous medical history was notable for unilateral mastectomy for breast adenocarcinoma, followed by adjuvant radiotherapy but no hormonal therapy, 7 years prior to this presentation; seronegative rheumatoid arthritis; two miscarriages and one successful pregnancy, each complicated by a disseminated intravascular coagulation picture requiring haemodialysis some four decades previously. She had had two previous transient ischaemic attacks and had been diagnosed with a left occipital infarct 7 months prior to this presentation, for which she received 75 mg aspirin. She had no known family history of haematological or oncological disease and there is no known consanguinity. During treatment for urosepsis, she developed a microangiopathic haemolytic anaemia (MAHA) and was transferred to a tertiary centre for treatment of TTP. She was initiated on plasma exchange (PEX), rituximab and steroids, for presumed immune TTP with A Disintegrin And Metalloproteinase with a Thrombospondin type 1 Motif, member 13 (ADAMTS13) assays confirming reduced activity (8.5%), supportive of this diagnosis. Despite improving platelet count, she deteriorated neurologically, with fluctuating Glasgow Coma Score and new onset left upper and lower limb weakness with spasticity.

## INVESTIGATIONS

On admission to the tertiary centre, platelet count was  $49 \times 10^9/L$ , haemoglobin 93 g/L, mean corpuscular volume 91.8 fL, lactate dehydrogenase 2431 U/L and blood film showed red cell fragments. CT head at this time showed established left occipital infarct and chronic parietal infarct, consistent with the previously diagnosed cerebrovascular event.

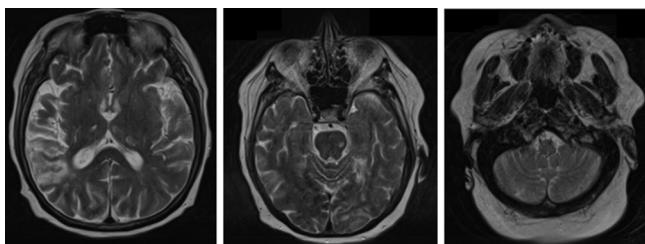
ADAMTS13 levels and platelet counts initially improved with PEX.

MRI head, after the onset of new left-sided neurological deficit, confirmed multiple acute and subacute infarcts in both cerebral hemispheres, midbrain and right cerebellum (figure 1).



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**Figure 1** T2-weighted MRI head images showing multiple acute and subacute infarcts in both hemispheres, midbrain and right cerebellum.

## DIFFERENTIAL DIAGNOSIS

The main differential in one with MAHA and thrombocytopenia is of TTP and malignant bone marrow infiltration.

A CT scan of the chest, abdomen and pelvis showed no evidence of malignancy and ADAMTS13 levels of <10% are suggestive, though not diagnostic, of TTP.

The finding of thrombocytopenia, together with evidence of haemolysis, originally raised suspicion of immune thrombocytopenic purpura or Evan's syndrome; however, direct Coombs test was unremarkable. Blood film showed schistocytes, suggesting a microangiopathic process. Dacrocytes were also seen on blood film which, in the context of a negative bone marrow aspirate, are of unclear significance.

Given the pregnancy-related morbidity and strokes in later life, catastrophic antiphospholipid syndrome was an important consideration, although lupus anticoagulant results, anti-cardiolipin antibody and anti-beta2-glycoprotein antibody titre were not performed at presentation. Subsequent PEX and immunosuppression precluded the diagnostically mandated repeat testing for the anti-cardiolipin and anti-beta2-glycoprotein antibodies.

Anti-ADAMTS13 antibody levels were negative on pretreatment sampling, ruling out an autoimmune cause of TTP. Genetic testing later identified that she is homozygous for the pathogenic p.R1060W mutation, confirming the diagnosis of cTTP. She was also identified to be homozygous for a missense variant in p.A1033T but, while this has been described in cTTP, the clinical significance is currently not known.

## TREATMENT

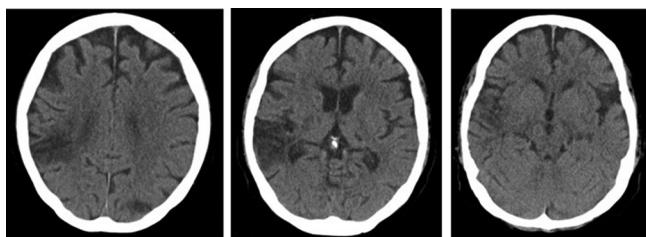
PEX and immunosuppression were discontinued once immune TTP was no longer felt to be causative as they have no role in the context of cTTP.

Treatment of cTTP was initially with fortnightly infusions of solvent/detergent-treated, virus-inactivated fresh frozen plasma as Octaplas, a good source of ADAMTS13. This was given alongside the dual antiplatelet therapy for ischaemic stroke; 75 mg aspirin and 75 mg clopidogrel.

The patient also received regular physiotherapy and occupational therapy to overcome the left-sided weakness.

## OUTCOME AND FOLLOW-UP

Less than 1 year post discharge, the patient was admitted with new neurology and diagnosed with an acute right middle cerebral artery (MCA) territory infarct (figure 2). A few weeks' later, she was admitted again with acute onset left-sided weakness, dysarthria and cranial nerve VII upper motor neuron palsy and MRI with diffusion-weighted imaging revealed areas of acute infarction in the right basal ganglia, corona radiata and temporo-parietal lobe (figure 3). At the time, the interval of regular plasma infusions was 4 weeks and had been extended because of the associated burden and because the patient had been stable



**Figure 2** CT head showing established right parietal and left occipital lobe infarct with new hypoattenuation in the anterior right temporal lobe, suggestive of acute ischaemia.

clinically with stable blood counts. On both occasions, there were no fragments on blood film, normal platelet count and no evidence of haemolysis. However, carotid Doppler ultrasonography showed no significant stenosis, no cardiac thrombus was identified on echocardiogram, 48 hour ECG monitoring showed no evidence of atrial fibrillation and recent HbA1c (glycosylated haemoglobin) was 39 mmol/mol, suggesting excellent glycaemic control. Her strokes are presumed to be related to cTTP and she continues on Octaplas infusions which, having been reduced to monthly for a period in an attempt to reduce the burden of treatment, have now increased to seven units every fortnight due to recurrent events and subsequent episodes of thrombocytopenia.

## DISCUSSION

TTP is a rare, life-threatening syndrome. Historically described as a pentad of MAHA, thrombocytopenia, fever, renal impairment and neurological involvement, diagnosis is only dependent on the first two criteria.<sup>1</sup> TTP may be acquired or congenital.

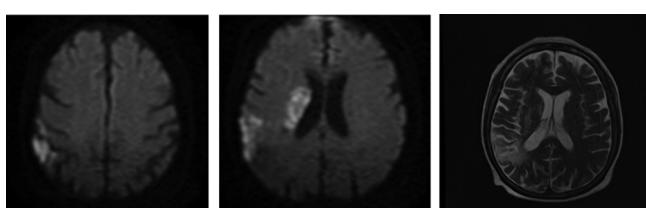
Acquired TTP has an incidence of 6 cases per million in the UK and cTTP, which is inherited in an autosomal recessive pattern, is even rarer, accounting for no more than 5% of cases of TTP and estimated to have an approximate prevalence of one case per million.<sup>2 3</sup> Whether congenital or acquired (excepting pancreatitis and malignancy-mediated disease), TTP is due to low levels of ADAMTS13.

ADAMTS13 cleaves ultra-large multimers of von Willebrand Factor (vWF) into smaller units, which are important ligands for platelet adhesion in normal haemostasis.<sup>4</sup>

Inhibition of ADAMTS13 activity therefore causes increased numbers of ultra-large multimers of vWF, which are haemostatically very active and cause formation of large platelet aggregates within vessels, including the cerebral, renal and cardiac microvasculature.

Large platelet aggregates are prothrombotic. vWF is an acute phase protein—hence, if a patient with cTTP is unwell, they may increase vWF levels beyond a critical concentration for their ADAMTS13 to cleave.

Formation of platelet rich thrombi causes consumption of platelets resulting in thrombocytopenia, while the partial



**Figure 3** Diffusion-weighted and T2-weighted MRI head images showing high signal in the right temporo-parietal region and right basal ganglia.

occlusion of high shear, small vessels causes haemolysis with red cell fragmentation.

Up to 35% of patients do not have neurological impairment at presentation; if neurological involvement occurs, it can be in a variety of forms including headache, confusion, visual disturbance, transient ischaemic attack, seizures and coma.<sup>1</sup>

While neurological involvement including transient neurological deficit, is well-recognised in TTP due to occlusion of small vessels, large vessel occlusion is less typical, although has been previously recognised.<sup>5</sup> Sugarman *et al* report a case of a 67-year-old patient presenting with right MCA territory infarct, in whom no embolic source was found, but in whom thrombocytopenia and presence of schistocytes led to a diagnosis of TTP, complicated by large vessel occlusion.<sup>5</sup>

Thrombolysis is controversial in the context of TTP due to potential thrombocytopenia. There are no clinical trials investigating its use, likely on account of the low incidence of TTP. Several case reports exist in which patients have been thrombolysed and subsequently diagnosed with TTP: a 30-year-old woman with acute right proximal MCA occlusion and normal initial platelet count underwent intravenous thrombolysis, with no subsequent haemorrhagic transformation, but 6 days later developed thrombocytopenia and a MAHA; ADAMTS13 levels were found to be low and anti-ADAMTS13 autoantibodies detected, confirming a diagnosis of TTP.<sup>6</sup> A 48-year-old woman presented with features of acute right MCA stroke, on a background of two previous ischaemic strokes and underwent thrombolysis and thrombectomy with no neurological improvement. Collateral history latterly confirmed a diagnosis of TTP. Imaging post-thrombolysis showed haemorrhagic transformation in the context of progressive thrombocytopenia.<sup>7</sup>

A third case in the literature describes a 39-year-old man with occlusion of the temporal stem of the left MCA, together with MAHA and thrombocytopenia (platelet count  $27 \times 10^9/L$ ), in whom recanalisation was achieved post-thrombolysis without any evidence of haemorrhage on repeat imaging.<sup>8</sup>

Our patient had normal platelet count on the two most recent presentations with stroke and, although anaemic, had no features of haemolysis. Two cases also demonstrate that haematological investigations, including haemoglobin and platelet count, may be normal, at least at presentation—so-called ‘atypical’ TTP.<sup>6,7</sup>

Rojas *et al* present the case of a 29-year-old woman with cryptogenic stroke who re-presented 2 months later, with new findings of thrombocytopenia, anaemia and red cell fragments on the blood film. ADAMTS13 levels were undetectable.<sup>9</sup> The authors summarise eight other cases, of atypical TTP, with only mild or absent thrombocytopenia and haemolytic anaemia, presenting with stroke; all patients were young or middle-aged women without other cardiovascular risk factors.

These cases suggest that, in patients with unexplained stroke and an absence of other risk factors, TTP should be considered, even in the absence of typical haematological derangement.<sup>5-9</sup>

When considering TTP as a possible diagnosis, the PLASMIC score (named after the 7 components of the score: platelets, lysis, active cancer, stem cell or solid organ transplant, MCV, INR, and creatinine) may help determine the likelihood of low ADAMTS13 levels necessitating urgent treatment, but it requires further validation and is in no way a replacement for diagnostic ADAMTS13 levels.<sup>10</sup>

While adult-onset TTP is generally acquired, at least 50% of cTTP patients present in adulthood also, particularly in primiparous women.<sup>11,12</sup> Pérez-Rodríguez *et al* highlight homozygosity or heterozygosity for the p.R1060W mutation in ADAMTS13 may be associated with late-onset cTTP and often initially presents

during a first pregnancy.<sup>13</sup> Camilleri *et al* showed the high prevalence of the p.R1060W mutation in adult onset cTTP with an absence of this mutation in cTTP presenting in childhood.<sup>14</sup> Through in vitro studies, they showed that the p.R1060W mutation causes intracellular retention of ADAMTS13 but has no effect on the metalloproteinase activity of the expressed protein. Given this residual ADAMTS13 activity, it is suggested that individuals with the p.R1060W mutation require an additional factor, such as pregnancy, to trigger TTP.<sup>13</sup>

## Learning points

- ▶ Although adult-onset TTP is generally acquired, at least half of cases of congenital thrombotic thrombocytopenic purpura (cTTP) have been shown to be adult-onset.
- ▶ TTP can present with large vessel occlusion.
- ▶ The usual management of stroke with intravenous thrombolysis can be risky in this patient group, hence the need to recognise promptly when TTP may be the underlying aetiology and then obtain early specialist haematology input.
- ▶ When stroke occurs in the context of immune TTP, treating the underlying disease with plasma exchange and immunosuppression can bring about resolution of neurological symptoms. Plasma infusion aims to replenish levels of A Disintegrin And Metalloproteinase with a Thrombospondin type 1 Motif, member 13 in cTTP.
- ▶ In stroke of unclear aetiology, TTP should be considered even in the context of normal haematological values.

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## ORCID iDs

Emma Tenison <http://orcid.org/0000-0003-2330-8844>

Ashar Asif <http://orcid.org/0000-0002-9361-1083>

Mathew Sheridan <http://orcid.org/0000-0003-0628-7674>

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