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TITLE OF CASE
Congenital thrombotic thrombocytopenic purpura presenting in adulthood with recurrent cerebrovascular events
AUTHORS OF CASE <i>Please indicate corresponding author by *(after the author's name)</i>
Emma Tenison*, Ashar Asif, Mathew Sheridan
SUMMARY <i>Up to 150 words summarising the case presentation and outcome</i>
<p>Congenital thrombotic thrombocytopenic purpura (cTTP) is a rare, life-threatening disease, characterised by episodes of microangiopathic haemolytic anaemia (MAHA), thrombocytopenia and small vessel thrombosis.</p> <p>We describe a case of cTTP first diagnosed at age 70 in a female presenting with an acute ischaemic stroke and thrombocytopenia, in whom ADAMTS13 levels were less than 10%, suggestive of TTP. The patient underwent plasma exchange (PEX) and started Rituximab for presumed immune TTP, however anti-ADAMTS13 antibody titres were negative on 2 occasions. This, together with a history of pregnancies complicated by presumed disseminated intravascular coagulation (DIC), and 2 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 (FFP), 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.</p>
BACKGROUND <i>Why you think this case is important – why you decided to write it</i>

up

Congenital TTP, 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.

Whilst 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 *Presenting features, medical/social/family history*

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. Past 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; 2 miscarriages and 1 successful pregnancy, each complicated by a disseminated intravascular coagulation (DIC) picture requiring haemodialysis some four decades previously. She had had 2 previous transient ischaemic attacks and had been diagnosed with a left occipital infarct 7 months prior to this presentation, for which she received 75mg 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 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 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 *If relevant*

On admission to the tertiary centre, platelet count was $49 \times 10^9/L$, haemoglobin 93 g/L, mean corpuscular volume (MCV) 91.8 fL, lactate dehydrogenase (LDH) 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 (**A** Disintegrin **A**nd **M**etalloproteinase with a **T**hrombospondin type 1 Motif, member 13) 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).

DIFFERENTIAL DIAGNOSIS *If relevant*

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

A computerised tomography 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 pre-treatment sampling, ruling out an autoimmune cause of TTP. Genetic testing later identified the pathogenic p.R1060W mutation, confirming the diagnosis of congenital TTP.

TREATMENT *If relevant*

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 (FFP) as Octaplas, a good source of ADAMTS13. This was given alongside the dual antiplatelet therapy for ischaemic stroke; 75mg aspirin and 75mg 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 neurone 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 four weeks and had been extended because of the associated burden and because the patient had been stable 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 electrocardiogram showed no evidence of atrial fibrillation and recent Hba1c 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 7 units every fortnight due to recurrent events and subsequent episodes of thrombocytopenia.

DISCUSSION *including very brief review of similar published cases (how many similar cases have been published?)*

TTP is a rare, life-threatening syndrome. Historically described as a pentad of microangiopathic haemolytic anaemia, thrombocytopenia, fever, renal impairment and neurological involvement, diagnosis is only dependent on the first two criteria.[1] 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.[2, 3] 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.[4] 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 congenital TTP 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, whilst the partial 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.[1] Whilst 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.[5] 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.[5]

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 female with acute right proximal MCA occlusion and normal initial platelet count underwent intravenous thrombolysis, with no subsequent haemorrhagic transformation, but six days later developed thrombocytopenia and a MAHA; ADAMTS13 levels were found to be low and anti-ADAMTS13 autoantibodies detected, confirming a diagnosis of TTP.[6] A 48-year-old woman presented with features of acute right MCA stroke, on a background of 2 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.[7] 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.[8]

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.[6,7] Rojas *et al.* present the case of a 29-year-old lady with cryptogenic stroke who represented 2 months later, with new findings of thrombocytopenia, anaemia and red cell fragments on the blood film. ADAMTS13 levels were undetectable.[9] The authors summarise 8 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.[5, 6, 7, 8, 9]

When considering TTP as a possible diagnosis, the PLASMIC score 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.[10]

Whilst adult-onset TTP is generally acquired, at least 50% of cTTP patients present in adulthood also, particularly in primiparous women.[11, 12] Pérez-Rodriguez *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.[13] 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.[14] 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.[13]

LEARNING POINTS/TAKE HOME MESSAGES 3 to 5 bullet points

- Although adult-onset TTP is generally acquired, at least half of cases of 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 ADAMTS13 in congenital TTP.
- In stroke of unclear aetiology, TTP should be considered even in the context of normal haematological values

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Figure captions

Figure 1: T2-weighted MRI head images showing multiple acute and subacute

infarcts in both hemispheres, midbrain and right cerebellum.

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.

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

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