

## CASE REPORT

# Large vessel stroke as initial presentation of thrombotic thrombocytopenic purpura

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## SUMMARY

A 67-year-old right-handed woman presented with dysarthria, left upper extremity weakness and right-sided neglect of 3 hours duration. Imaging of the brain revealed acute right middle cerebral artery stroke; however, tissue plasminogen activator could not be administered due to severe thrombocytopenia. A peripheral smear revealed schistocytes and the patient was treated empirically for thrombotic thrombocytopenic purpura (TTP) with therapeutic plasma exchange. An extensive workup revealed no embolic source or other cause for stroke, and a diagnosis of large vessel infarct secondary to TTP was made. After a prolonged hospital course, the patient had partial neurological recovery and was discharged to a rehabilitation facility. Although transient neurologic deficits due to small vessel occlusions are well described in TTP, large vessel infarct can occur as well. This diagnosis should be considered in patients presenting with concomitant stroke and thrombocytopenia, as untreated TTP is nearly always fatal.

## BACKGROUND

Thrombotic thrombocytopenic purpura (TTP) is an uncommon disease with an incidence of approximately four cases per million adults per year.<sup>1</sup> It is characterised by the classic pentad of thrombocytopenia, microangiopathic haemolytic anaemia, acute kidney injury, fever and neurological symptoms. TTP results from inherited deficiency or acquired inhibition of the enzyme ADAMTS13, which is responsible for cleaving von Willebrand factor (vWF) into smaller multimers. Diminished ADAMTS13 activity results in larger multimers of vWF, which cause increased platelet adhesion at sites of endothelial injury, resulting in thrombi formation. The mortality of untreated TTP is approximately 90%; however, prognosis is markedly improved when diagnosed early and treated with therapeutic plasma exchange (TPE).<sup>1,2</sup> Approximately, 50% of acquired TTP cases have neurological involvement at the time of presentation. This is believed to be secondary to thrombi development in the small vessels of the brain. Neurological symptoms include fluctuating or persistent alterations of level of consciousness, confusion, aphasia, visual disturbances, paresthesias, motor deficits and seizure.<sup>3</sup> These can be attributed to ischaemia of the cerebral cortex and/or subcortical white matter causing transient occlusions or microinfarcts. However, these symptoms tend to be reversible in

most patients who survive the acute presentation.<sup>4</sup> In contrast, large cerebral artery occlusion (LCAO) in TTP is very rare, with only nine prior reports identified after extensive literature review.<sup>5–12</sup> Here, we report a patient with TTP who presented with right middle cerebral artery (MCA) occlusion that caused permanent neurologic deficit.

## CASE PRESENTATION

A 67-year-old right-handed female with prediabetes presented to the Emergency Department with a chief complaint of sudden onset slurred speech. Physical examination revealed a partial right gaze palsy, asymmetric smile, left arm motor drift, dysarthria and right-sided neglect, consistent with National Institute of Health Stroke Score of 7.

## INVESTIGATIONS

A stroke workup was performed with several imaging studies. Non-contrast head CT revealed no ischaemia or haemorrhage (figure 1). CT angiography showed normal carotid and vertebral arteries but revealed an occlusion of the right MCA at the level of the right MCA bifurcation (figure 2). Blood work revealed severe thrombocytopenia, acute kidney injury, an elevated lactate dehydrogenase and diminished haptoglobin (table 1). Schistocytes were identified on microscopic evaluation of a peripheral smear.

## TREATMENT

The patient was transferred to the intensive care unit where TPE and high-dose corticosteroid therapy was initiated; tissue plasminogen activator (tPA) was held due to thrombocytopenia.

## OUTCOME AND FOLLOW-UP

Diagnosis of TTP was confirmed when the ADAMTS13 assay resulted (figure 1). While the platelet count and kidney function recovered with TPE, the patient had a functional decline from the time of admission with the development of left-sided hemiparesis and dysphagia.

Brain MRI revealed the known right MCA occlusion, as well as scattered infarcts in the cerebellum, left frontal and occipital regions (figure 3), suggestive of an embolic source of stroke. The patient tested negative for antiphospholipid syndrome; however, other causes of hypercoagulable state such as antithrombin III deficiency, protein C and S deficiencies were not tested for at the time of presentation because their



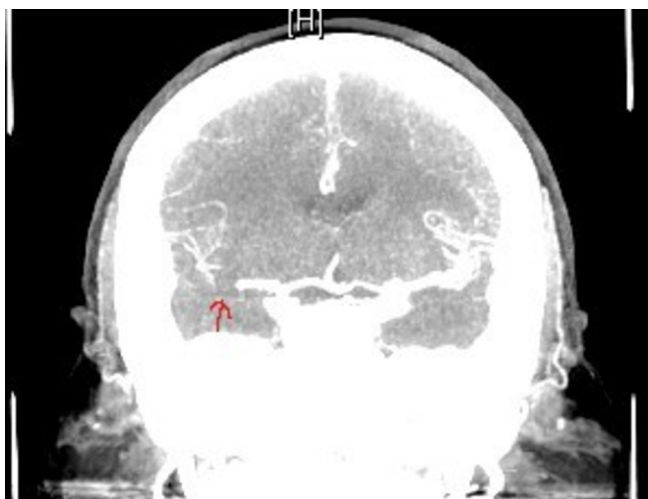
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**Figure 1** CT brain on admission showed no acute haemorrhage or infarct.

levels may be diminished in the setting of acute clot. Extensive workup with 3-month loop recorder, transoesophageal echocardiogram and CT angiography of the neck revealed no other cause of stroke and the patient was discharged to a subacute rehabilitation facility with a diagnosis of cerebrovascular accident secondary to TTP. At the time of discharge, the patient was using wheelchair and received nutrition through a percutaneous gastrostomy tube.

Nearly 3 years later, the patient has had significant neurological recovery and no longer suffers from dysphagia. While her strength has improved, residual left upper extremity weakness persists.



**Figure 2** CT angiography of the brain on admission revealed occlusion of the right middle cerebral artery at the M1 segment (red arrow).

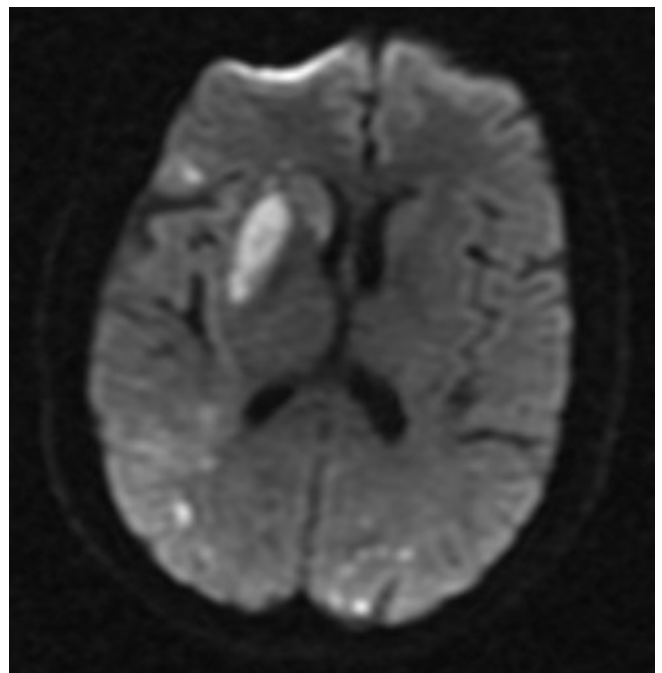
**Table 1** Initial laboratory findings

Laboratory studies	Patient values (reference range)
Haemoglobin	14.1 (11.5–15.5 g/dL)
Platelet count	19 (150–400 10 <sup>9</sup> /L)
Creatinine	1.63 (0.5–1.3 mg/dL)
Lactate dehydrogenase	1250 (122–222 U/L)
Haptoglobin	<3 (34–200 mg/dL)
ADAMTS13 Activity	5% (≥70%)
ADAMTS13 Inhibitor	7.4 (≤0.4)
Total bilirubin	1.5 (0.2–1.2 mg/dL)

**DISCUSSION**

Central nervous system involvement causing headache, confusion, seizures and focal deficits are common in TTP. The mechanism is believed to be occlusion by the platelet–fibrin complex. However, it is very rare to have permanent neurologic deficit secondary to large cerebral artery occlusion.<sup>3</sup> In a 2009 retrospective study by Burrus *et al*, brain MRI in 33 patients newly diagnosed with TTP revealed acute change in 83% of cases, with no instances of large ischaemic infarct.<sup>13</sup> Our patient suffered LCAO stroke and was left with permanent neurologic deficit. We believe that the MCA occlusion was thrombotic in origin, as extensive workup for embolic source was negative.

On review of the literature, we could only identify nine cases that reported LCAO in the context of TTP (table 2). Of these, only four cases reported cerebrovascular accident occurring as initial presentation of TTP.<sup>5–8</sup> Notably, one case report described two siblings with TTP with stroke, suggesting the role of inherited ADAMTS13 deficiency in this rare presentation. However, since none of the other case studies reported testing for the presence of the ADAMTS13 inhibitor, we are unable to establish an association between the type of TTP (primary vs secondary) and large vessel stroke presentation.



**Figure 3** Brain MRI showed acute infarcts in the right basal ganglia, corona radiata and right frontal parietal regions, as well as scattered infarcts in the cerebellar hemispheres, occipital lobes and left frontal lobe suggestive of embolic stroke.

**Table 2** Literature reported cases of large vessel cerebrovascular occlusion in TTP

Publication year	Country of reported case	Age	Gender	Stroke location	Schistocytes present on blood smear	Platelet count (10 <sup>9</sup> u/L)	ADAMTS13 activity	Treatment	Outcome	Reference
1991	USA	44	F	L parietal	Yes	30	Not reported	TPE	Permanent L eye blindness	Rinkel <i>et al</i> <sup>5</sup>
1994	USA	38	M	R thalamic	Yes	24	Not reported	Heparin	Permanent aphasia	Wijdicks <sup>6</sup>
1998	Switzerland	46	F	L MCA	Yes	57	Not reported	TPE+splenectomy	Permanent aphasia and R upper extremity weakness	Kelly <i>et al</i> <sup>7</sup>
1998	Switzerland	27*	F	R MCA	Yes	19	Not reported	TPE+steroids	Expired during hospital course	Kelly <i>et al</i> <sup>7</sup>
2004	Germany	46*	M	R PCA	Yes	<20	<5%	TPE+steroids	Permanent neurologic deficit	Scheid <i>et al</i> <sup>8</sup>
2005	Spain	36	M	Bilateral cerebral large arteries	Yes	52	Not reported	TPE	Expired during hospital course	Ibernon <i>et al</i> <sup>9</sup>
2011	France	30	F	R MCA	Yes	252	<5%	tPA+heparin	Permanent L upper extremity weakness	Sevy <i>et al</i> <sup>10</sup>
2013	Portugal	39	M	L MCA	Unknown	27	Not reported	tPA then TPE	Full neurological recovery	Boattini and Procaccianti <sup>11</sup>
2015	Hong Kong	58	F	L MCA	Yes	8	Not reported	TPE	Permanent R-sided paralysis	Yu <i>et al</i> <sup>12</sup>
2017	USA	67	F	R MCA	Yes	67	<5%	TPE+steroids	Permanent L upper extremity weakness	Current case report

\*Siblings.

F, female; L, left; M, male; MCA, middle cerebral artery; PCA, posterior cerebral artery; R, right; tPA, tissue plasminogen activator; TPE, total plasma exchange; TTP, thrombotic thrombocytopenic purpura.

Management of TTP varied. Seven patients received TPE, two received corticosteroids, two received heparin, one received cryoreduced plasma and one underwent splenectomy. Additionally, two patients received thrombolytic therapy with Alteplase. In one case, the patient had a normal platelet count at the time of tPA administration and developed thrombocytopenia later in the course. Ultimately, this patient had residual left arm weakness. In the other case, documented by Boattini *et al*, administration of tPA was done in the setting of a platelet count of 27 000, as well as TPE and resulted in restored cerebral blood flow as well as full neurological recovery.<sup>11</sup> While successful in that case, it is difficult to recommend tPA in this setting as TPE alone may have caused reversal of the neurological symptoms, and thrombolysis in the setting of severe thrombocytopenia could lead to a life-threatening haemorrhage.

Although there is limited follow-up data on patients with TTP and stroke, the outcome tends to be poor. Only one patient achieved complete recovery and two patients expired. This case illustrates that TTP can cause large vessel infarct, and plasma exchange should not be delayed for embolic workup or ADAMTS13 assay result. Thrombolytic therapy should only be considered in select cases where the benefit of treating a large vessel stroke outweighs the risk of a life-threatening bleeding event.

### Learning points

- ▶ To recognise the incidence of large cerebral artery occlusion (LCAO) as a rare but possible presentation of thrombotic thrombocytopenic purpura (TTP).
- ▶ To manage LCAO secondary to TTP with plasma exchange.
- ▶ To consider the use of thrombolytic therapy in cases of LCAO as previously described in literature.

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