



Young Ischemic Stroke as Presentation of Thrombotic Thrombocytopenic Purpura: A Case Report

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ABSTRACT

Thrombotic thrombocytopenic purpura (TTP) is a rare disorder with an estimated incidence of 3 - 7/1,000,000. It is an autoimmune disorder characterized by fever, neurological signs, microangiopathic hemolytic anemia, thrombocytopenia and renal failure. This case report will describe a young lady who presented with acute middle cerebral artery infarct and was subsequently diagnosed to have TTP. Therapeutic plasma exchange (TPE) did not improve the neurological deficit. This case highlights the importance of recognizing TTP as a possible differential diagnosis in young onset stroke.

Keywords: Young stroke, Thrombotic thrombocytopenic purpura (TTP), Therapeutic plasma exchange

INTRODUCTION

TTP is a rare autoimmune disorder affecting the coagulation system causing microscopic blood clots to form within any blood vessels including the cerebral arteries. This coagulation disorder is typically due to failure in cleaving the multimers of von Willebrand Factors (vWF) as a result of the absence or inhibition of enzyme ADAMTS-13. As red blood cells pass through these microscopic clots, hemolysis occurs. Reduce blood flow and thrombosis cause end organ damage giving rise to the clinical presentation in TTP. Microscopic clots in the cerebral arteries cause cerebral ischemia and the subsequent acute neurological deficit. As acute stroke is always the main presentation, recognizing TTP as a possible cause is crucial because early diagnosis is important as mortality usually exceeds 90% in untreated case.

CASE REPORT

A 38-year-old lady presented to the emergency department with sudden onset slurring of speech and right-sided body weakness. There was no fever or headache prior to the current symptoms. Apart from the current presentation, she was otherwise well.

On physical examination, she could open her eyes spontaneously. She had expressive aphasia but was able to follow simple one step command. She was pale and jaundiced. Multiple bruises were noted over the upper and lower limbs. Neurological examination revealed right hemiplegia with right extensor plantar response. Cardiovascular, respiratory, and abdominal examinations were unremarkable.

Laboratory findings revealed hemoglobin level of 6.0 g/L (normal values, 12-16) and platelet of $9 \times 10^9/L$ ($150-400 \times 10^9/L$). There were evidences for hemolysis suggested by low haptoglobin <0.2 g/L (0.43 to 2.12 g/L), and high lactate dehydrogenase (LDH) level, 1119 IU/L (<480). However, Coomb's test was negative. Peripheral blood film showed many fragmented cells and reduced platelet count, which was consistent with microangiopathic hemolytic anemia. Her renal profile was normal and urine full examination and microscopic examination (UFEME) showed no evidence of glomerulonephritis. CT brain revealed an ill-defined hypodense area over the left temporo-parieto-occipital region consistent with a left middle cerebral artery territory infarction. Transthoracic echocardiography was normal.



Figure 1 Encephalomalacic change seen in the left MCA territory in-keeping with previous infarct. There is associated ex-vacuo dilatation of the left lateral ventricle and midline shift of 3 mm to the left

In summary, our patient presented with acute left middle cerebral artery territory infarct, microangiopathic hemolytic anemia and thrombocytopenia. Thus, the diagnosis of TTP with left middle cerebral artery (MCA) stroke was made. She was given intravenous methylprednisolone and TPE was immediately commenced.

Subsequently, her blood profiles improved after TPE. Prior to discharge, her hemoglobin was 10.4 g/L and platelet of $433 \times 10^9/L$. Peripheral blood film showed only occasional schistocytes. Unfortunately, there was little recovery of her neurological symptoms. She remained dysphasic and weak on the right side of her body at discharge. She was discharged with oral prednisolone and subsequent follow up revealed stable condition with Modified Rankin Scale (MRS) of 4 (moderately severe disability with the need of assistance for daily activity). A repeat CT scan of the brain three months later showed encephalomalacic changes over the left MCA territory (Figure 1). She continued to receive an intensive course of physiotherapy and rehabilitation.

DISCUSSION

Stroke is a medical emergency. The incidence of stroke varies among countries and increase exponentially with age [1]. Eighty percent of strokes are caused by focal cerebral ischemia due to arterial occlusion, and the remaining 20% are caused by hemorrhages [2]. Making a diagnosis of stroke in this patient is straightforward; however, young onset, and unusual signs such as multiple bruises raised the possibility of hematological abnormality, which was confirmed by laboratory investigations as thrombocytopenia and hemolytic anemia. TTP is seen predominantly in women of 30 to 40 years of age. It is mainly idiopathic but may be triggered by other causes such as infections, pregnancy, drugs and autoimmune disorders. The pathogenesis is mainly due to the presence of unusually large von Willebrand Factor (vWF) multimers that lead to platelet clumping and subsequent microvascular thrombosis and ischemia. The vWF multimers are normally cleaved into smaller proteins by the vWF cleaving protease; ADAMTS-13. Impairment to ADAMTS-13 activity leads to an excessively large vWF, which can then lead to the onset of TTP [3]. Classically, the following pentads are indicative of TTP: neurological symptoms, kidney failure, fever, thrombocytopenia and microangiopathic hemolytic anemia [4]. In 90% of cases, there will be neurological symptoms during the course of the disease [5]. The exact pathophysiology of cerebral ischemia is unknown although it is generally accepted that pathological interactions between vascular endothelium and circulating platelets play a key role in producing profound dysregulation of coagulation. Due to the preferential involvement of the microcirculation, radiological

findings typically consist of subcortical or small cortical infarcts [6,7]. CT brain of this patient shows a large left MCA territory infarct that correlates with her clinical neurological findings. This is less typical for TTP related thrombosis. Sheid, et al. [8] reported a patient with bilateral and multiple large artery infarcts in TTP. Rinkel, et al. [9] and Wijdicks [10] reported 2 patients with PCA infarcts, while Kelly, et al. [11] studied 2 siblings with MCA main stem thrombosis and TTP. Although there is still a possibility of atherosclerosis causing cerebral infarction, her young age and the absence of cardiovascular risk factor would be against this.

A presentation of acute stroke within the first 3 hours is an indication for thrombolysis. The neurological manifestation of TTP as demonstrated by this patient can be easily be mistaken for an acute ischemic stroke. However, the role of thrombolytic therapy is controversial as it may cause bleeding. On the other hand, Boattini, et al., reported the recovery of neurological deficit in their TTP patient with acute ischemic stroke after successfully completing thrombolytic therapy and subsequent therapeutic plasma exchange (TPE) without any hemorrhagic complication [12].

There have been cases of TTP relapse without any evidence of thrombocytopenia and microangiopathic hemolysis [13]. Both cases were known cases of TTP presented with cerebrovascular events. Diagnosis of TTP was made on the basis of low plasma ADAMTS-13. Both patients had dramatic clinical improvement after TPE. The experience in these two cases suggests that TTP should be considered as a potential cause among patients presenting with stroke, particularly when there is a history of TTP.

TPE has become the treatment of choice for TTP since the 90's [14]. Unfortunately for this patient, even with early TPE, there was little recovery of her neurological deficit. Ozdogu, et al., in 2007, reported a case of resistant TTP who later developed acute stroke [15]. The patient had a dramatic response and a full recovery of her neurological deficit within days after an initiation with weekly rituximab for 4 weeks. Rituximab is a chimeric mouse and human monoclonal antibody directed to the surface molecule CD20 on pre-B, naive and memory-B lymphocytes. Although originally designed for the treatment of patients with B-cell lymphomas, it has been increasingly used to treat a variety of immune-mediated and autoimmune diseases [16]. Most TTP cases reported on rituximab are those who have been refractory to other forms of treatment. Tsai, et al., in 2003, for example, reported another case of patient with recurrent neurological symptoms despite several immunosuppressive therapies [17]. Her symptoms resolved after rituximab and she remained free of neurologic symptoms in the following 6-months of follow up. These cases suggest the effectiveness of rituximab on TTP with neurological involvement, at least in refractory cases.

In conclusion, TTP may mimic acute ischemic stroke. The diagnosis is made in the appropriate setting with supporting laboratory investigations. It should be considered in young patients with stroke. In terms of future treatment of TTP, current evidence suggests that rituximab is promising, at least in refractory cases with neurological involvement.

DECLARATIONS

Acknowledgement

We would like to thank the ward staffs for taking care of the patient and assisting us in collecting the patient's data for this report.

Conflict of Interest

The authors have disclosed no potential conflicts of interest, financial or otherwise

REFERENCES

- [1] Van der Worp, H. Bart, and Jan van Gijn. "Acute ischemic stroke." *New England Journal of Medicine* Vol. 357, No. 6, 2007, pp. 572-79.
- [2] Feigin, Valery L., et al. "Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century." *The Lancet Neurology* Vol. 2, No. 1, 2003, pp. 43-53.
- [3] Moake, Joel L. "Thrombotic thrombocytopenic purpura: the systemic clumping "plague"." *Annual Review of Medicine* Vol. 53, No. 1, 2002, pp. 75-88.
- [4] George, James N., et al. "Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: Diagnosis and management." *Journal of Clinical Apheresis* Vol. 13, No. 3, 1998, pp. 120-25.

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- [5] Meloni, Giovanna, et al. "Thrombotic thrombocytopenic purpura: prospective neurologic, neuroimaging and neurophysiologic evaluation." *Haematologica* Vol. 86, No. 11, 2001, pp. 1194-99.
- [6] Gruber, Oliver, et al. "Thrombotic thrombocytopenic purpura: MRI demonstration of persistent small cerebral infarcts after clinical recovery." *Neuroradiology* Vol. 42, No. 8, 2000, pp. 616-18.
- [7] Tardy, B., et al. "Thrombotic thrombocytopenic purpura: MR findings." *American Journal of Neuroradiology* Vol. 14, No. 2, 1993, pp. 489-90.
- [8] Scheid, Rainer, et al. "Major stroke in thrombotic-thrombocytopenic purpura (Moschowitz syndrome)." *Cerebrovascular Diseases* Vol. 18, No. 1, 2004, pp. 83-85.
- [9] Rinkel, G. J., E. F. Wijdicks, and Ronald J. Hené. "Stroke in relapsing thrombotic thrombocytopenic purpura." *Stroke* Vol. 22, No. 8, 1991, pp. 1087-89.
- [10] Wijdicks, Eelco Fm. "Silent brain infarct in thrombotic thrombocytopenic purpura." *Stroke* Vol. 25, No. 6, 1994, pp. 1297-98.
- [11] Kelly, P. J., et al. "Middle cerebral artery main stem thrombosis in two siblings with familial thrombotic thrombocytopenic purpura." *Neurology* Vol. 50, No. 4, 1998, pp. 1157-60.
- [12] Boattini, Matteo, and Gaetano Procaccianti. "Stroke due to typical thrombotic thrombocytopenic purpura treated successfully with intravenous thrombolysis and therapeutic plasma exchange." *BMJ Case Reports* Vol. 2013, 2013, p. bcr2012008426.
- [13] Downes, Katharine A., et al. "Relapsed thrombotic thrombocytopenic purpura presenting as an acute cerebrovascular accident." *Journal of Clinical Apheresis* Vol. 19, No. 2, 2004, pp. 86-89.
- [14] Zheng, X. Long, et al. "Effect of plasma exchange on plasma ADAMTS13 metalloprotease activity, inhibitor level, and clinical outcome in patients with idiopathic and nonidiopathic thrombotic thrombocytopenic purpura." *Blood* Vol. 103, No. 11, 2004, pp. 4043-49.
- [15] Ozdogu, Hakan, et al. "A dramatic response to rituximab in a patient with resistant thrombotic thrombocytopenic purpura (TTP) who developed acute stroke." *Journal of Thrombosis and Thrombolysis* Vol. 23, No. 2, 2007, pp. 147-50.
- [16] George, James N., et al. "Rituximab therapy for thrombotic thrombocytopenic purpura: A proposed study of the Transfusion Medicine/Hemostasis Clinical Trials Network with a systematic review of rituximab therapy for immune-mediated disorders." *Journal of Clinical Apheresis* Vol. 21, No. 1, 2006, pp. 49-56.
- [17] Tsai, Han-Mou, and Keith Shulman. "Rituximab induces remission of cerebral ischemia caused by thrombotic thrombocytopenic purpura." *European Journal of Haematology* Vol. 70, No. 3, 2003, pp. 183-85.