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# Full neurologic recovery after fulminant thrombotic thrombocytopenic purpura with status epilepticus

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**KEYWORDS**
Thrombotic thrombocytopenic purpura;
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**Summary** Thrombotic thrombocytopenic purpura (TTP) is an ischemic vasculopathy frequently associated with neurological dysfunction including seizures. However, status epilepticus (SE) has rarely been reported in this condition. We report on a 70-year-old woman with fulminant TTP who developed convulsive SE despite high therapeutic serum levels of phenytoin and phenobarbital. Her electroencephalogram (EEG) was characterized by bilateral independent periodic lateralizing epileptiform discharges (BIPLEDs) propagating into clinical and electrographic seizures. She recovered completely after intensive plasmapheresis and treatment with pentobarbital induced coma for 5 days. This case illustrates that aggressive treatment with pentobarbital and plasmapheresis may prevent permanent neurologic deficits when TTP is complicated by SE and that periodic lateralizing epileptiform discharges (PLEDs) in this syndrome can be the manifestation of a reversible ischemic insult.


## Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare syndrome of unknown etiology characterized by thrombocytopenia, microangiopathic hemolytic anemia, neurological abnormalities, renal impairment and fever. In its fulminant form, diffuse thrombotic lesions in the central nervous system cause seizures and coma.[1] Its prognosis was once considered uniformly poor, with a high mortality rate.[2,3] Since the introduction of plasma infusions and exchanges, the prognosis of the disease has improved dramatically; remissions now occur in 80—90% of patients.[3]

Neurologic symptoms and signs are amongst the most common presentation of TTP, including alteration in the level of awareness, waxing and waning neurological deficits, headaches and coma.[4] Although seizures have been described in patients with TTP,[5—7] status epilepticus (SE) is rarely reported.[8,9]

We describe an elderly woman with TTP who developed convulsive SE during her illness associated with bilateral independent periodic lateralizing epileptiform discharges (BIPLEDs) on EEG. She completely recovered and the electroencephalo-

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gram (EEG) normalized following treatment with pentobarbital-induced coma and intensive plasmapheresis.

## Case report

A 70-year-old woman with a history of diverticulitis and peptic ulcer was admitted to a community hospital because of abdominal pain and bloody diarrhea. Her platelet count was 53,000 $mm^{-3}$ and creatinine level was 210 $\mu$mol/l. One week earlier, her platelet count was 290,000 $mm^{-3}$. Brain computed tomography (CT) and cerebrospinal fluid examination were normal. Two days after admission, she was transferred to the University of Michigan Medical Center because of progressive confusion and focal motor seizures. On admission, her temperature was 100.2 °F, blood pressure 120/72 mmHg, and pulse rate 82 $min^{-1}$. She was lethargic, disoriented to time, and complained of abdominal and back pain. She was unable to look past midline on attempted left lateral gaze and her left plantar response was equivocal. Physical examination was otherwise unremarkable.

Laboratory results revealed hemoglobin 10.8 g/dl, hematocrit 27.7%, white blood cell count 9100 $mm^{-3}$, platelet count 27,000 $mm^{-3}$, creatinine 270 $\mu$mol/l, LDH 1326 IU/l (normal 60—200), fibrinogen 2.7 g/l (normal 1.5—3.5), erythrocyte sedimentation rate 15 mm/h (normal 0—20), prothrombin time 13.4 s, partial thromboplastin time 22 s and reticulocyte count 2.9% (normal 0.5—1.5). A peripheral blood smear revealed moderate numbers of schistocytes and few helmet cells. Bone marrow aspiration and biopsy showed an increased number of megakaryocytes.

Treatment for TTP began immediately with plasma infusions. The following day, her mental status was normal, but during the next few days, despite a decrease in serum creatinine levels, she was intermittently confused. Three days after admission, the patient experienced a single generalized tonic-clonic (GTC) seizure for which she received an intravenous loading dose of phenytoin. Repeat brain CT was normal except for a small low density lesion in the hypothalamus. She was started on daily plasmapheresis for 3 days. Six days after admission, she was found stuporous, responding to painful stimuli only with eye opening, moaning and withdrawal of the extremities. Both plantar responses were extensor. Another brain CT did not show any changes compared to the previous scan. Lumbar puncture yielded clear, colorless fluid with a protein level of 0.85 g/l (normal 0.15—0.4), normal glucose, seven red blood cells and two white blood cells per high power field. A few hours later, the patient had serial GTC seizures and received an intravenous loading dose of phenobarbital. Despite a serum phenytoin level of 100 $\mu$mol/l and phenobarbital level of 150 $\mu$mol/l, she developed SE. Over 8 h she had approximately 40 seizures, each beginning with clonic activity of the left arm that secondarily generalized. EEG revealed BIPLEDs and in a 25 min recording, five clinical and two electrographic (subclinical) seizures occurred (Fig. 1). Laboratory studies revealed a platelet count of 190,000 $mm^{-3}$, creatinine 270 $\mu$mol/l, and fibrinogen of 2.6 g/l. Blood, sputum and urine cultures were negative.

Treatment with intravenous pentobarbital infusion was initiated to induce a burst suppression pattern on EEG, after which her seizures ceased. Plasmapheresis was resumed daily for 3 days followed by three more sessions every other day. The pentobarbital infusion was gradually tapered and discontinued after 5 days and the EEG was monitored to ensure no return of electrographic seizures. The next day she opened her eyes to loud voices but did not follow commands. EEG revealed

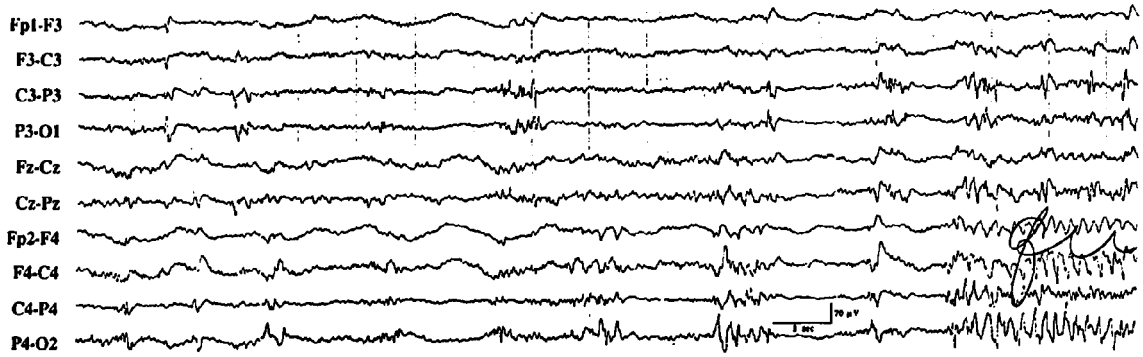


**Figure 1** EEG during SE showing markedly disorganized background, BIPLEDs and onset of a focal seizure in the right hemisphere.

diffuse slowing without epileptiform activity. Over the next several days her mental status gradually improved, blood counts and clotting studies returned to normal, and she was discharged from the hospital without neurological deficits. A subsequent EEG was normal. At last follow-up, 3 years after the illness, she remained seizure free with a normal neurological examination.

## Discussion

Our patient demonstrated the diagnostic pentad for TTP, including the presence of thrombocytopenia, microangiopathic hemolytic anemia, neurological abnormalities, renal impairment and fever. This syndrome usually occurs in younger individuals. The median onset is 35 years; only 6% of the patients are older than 60 years.[5] While only 50% of patients have neurological manifestation at presentation, 90% developed them during the course of the illness.[1,4,6] In a review of 529 patients with TTP, the most common neurological manifestations were alteration of mental status (35%), headache (32%), coma (24%), focal weakness (24%), aphasia (19%), seizures (15%), and visual changes (10%).[4]

These and other clinical features are believed to be due to widespread vascular occlusions caused by characteristic hyaline thrombi in terminal arterioles and capillaries.[3,4] The most frequently involved organs are the heart, brain, kidneys, pancreas and adrenals.[10] Neuropathological changes include small vessel occlusion in the cortical and subcortical grey matter, some of which are associated with small infarctions.[6]

Although, seizures have been reported in 12—41% of patients with TTP,[2,5—7] SE is rarely diagnosed.[8,9] In one study, two patients with TTP and altered mental status were diagnosed to be in non-convulsive SE.[9] One patient died and the other recovered with mild neurologic deficit following treatment with pentobarbital induced coma.[9] There is another published report of an elderly woman with TTP and intermittent stupor, who was found to be in non-convulsive SE.[8] The status was aborted following treatment with anticonvulsants. The patient subsequently expired because of respiratory failure.[8] Seizures are probably secondary to widespread ischemia of the cerebral cortex and are most commonly generalized.[2] Although our patient was in convulsive SE, two of her seizures were subclinical. This stresses the importance of a high level of suspicion for the possibility of SE in patients with TTP, especially in those with alteration in level of awareness or those in coma.[9] To our knowledge, no case with EEG findings of PLEDs or BIPLEDs associated with TTP has been reported in the literature. PLEDs are usually associated with seizures and carry an increased risk of mortality.[11,12] Although they usually occur in the setting of a acute structural lesions, cases due to toxic or metabolic abnormalities have also been reported.[11,13] The BIPLEDs seen in our patient's EEG suggested an acute and multifocal ischemic insult. The subsequent disappearance of those discharges and the return of normal background activity, coinciding with clinical improvement, indicate that the ischemic insult in this patient was largely reversible and that PLEDs in this syndrome are not necessarily indicative of a permanent structural lesion.

Despite her advanced age, our patient responded to treatment with plasmapheresis and pentobarbital induced coma. In the past, recurrent seizures and progression into coma constituted a frequent terminal event.[2] Improved survival has been attributed to treatment with plasma infusions and plasmapheresis. Current recommendations for treatment also include antiplatelet agents, corticosteroids, and in resistant cases, splenectomy and vincristine.[3,14]

This case illustrates that complete neurological recovery is possible even when fulminant TTP is complicated by convulsive SE. It also suggests that the presence of PLEDs in this syndrome is not necessarily indicative of a permanent structural lesion. The transient nature of this EEG finding is fully consistent with a reversible ischemic insult.

## References


1. Ruggennenti P, Remuzzi G. Thrombotic purpura and related disorders. *Hematol/Oncol Clin North Am* 1990;**4**:219—41.
2. Amorosi EL, Ultmann JE. Thrombotic thrombocytopenic purpura: report of 16 cases and review of the literature. *Medicine* 1966;**45**:139—59.
3. Elliott MA, Nichols WL. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. *Mayo Clin Proc* 2001;**76**:1154—62.
4. Sills RH. Thrombotic thrombocytopenic purpura. I. Pathophysiology and clinical manifestations. *Am J Pediatr Hematol Oncol* 1984;**6**:425—30.
5. Ridolfi RL, Bell WR. Thrombotic thrombocytopenic purpura: report of 25 cases and review of the literature. *Medicine* 1981;**60**:413—28.
6. Silverstein A. Thrombotic thrombocytopenic purpura: initial neurologic manifestations. *Arch Neurol* 1968;**18**:358—62.
7. Kennedy SS, Zacharski LR, Beck JR. Thrombotic thrombocytopenic purpura: analysis of 48 unselected cases. *Semin Thromb Hemost* 1980;**4**:341—9.
8. Blum AS, Drislane FW. Nonconvulsive status epilepticus in thrombotic thrombocytopenic purpura. *Neurology* 1996;**47**:1079—81.
9. Garrett WT, Chang CWJ, Bleck TP. Altered mental status in thrombotic thrombocytopenic purpura is secondary to nonconvulsive status epilepticus. *Ann Neurol* 1996;**40**:245—6.

10. Byrnes JJ. Thrombotic thrombocytopenic purpura. *Adv Intern Med* 1980;**26**:131—57.
11. Garcia-Morales I, Garcia MT, Galan-Davila L, et al. Periodic lateralized epileptiform discharges. Etiology, clinical aspects, seizures, and evolution in 130 patients. *J Clin Neurophysiol* 2002;**19**:172—7.
12. Walsh JM, Brenner RP. Periodic lateralized epileptiform discharges. Long term outcome in adults. *Epilepsia* 1987;**28**:533—6.
13. Raroque HG, Gonzales PCW, Jhaveri HS, et al. Defining the role of structural lesions and metabolic abnormalities in periodic lateralized epileptiform discharges. *Epilepsia* 1993;**34**:279—83.
14. Shepard KV, Bukowski RM. The treatment of thrombotic thrombocytopenic purpura with exchange transfusion, plasma infusion, and plasma exchange. *Semin Hematol* 1987;**24**:178—93.