

## Thrombotic Thrombocytopenic Purpura

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*A 6-year-old boy presented with microangiopathic hemolytic anemia, thrombocytopenia, altered sensorium and intractable bleeding. A diagnosis of thrombotic thrombocytopenic purpura was made and the child recovered dramatically after plasmapheresis. Recent developments in the understanding of TTP are reviewed, including the importance of a metalloprotease required to cleave multimers of von Willibrand factor.*

**Keywords:** Purpura, Thrombosis.

Thrombotic thrombocytopenic purpura (TTP) is well described in adults, but there are scattered case reports and case series in children(1,2). Recent improvements in the understanding of the fundamental lesion in TTP have led to dramatic improvements in its diagnosis and treatment(3). We report a case in a child who responded to aggressive therapy and briefly review the current literature on TTP.

### Case Report

A 6-year-old boy presented with pro-

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gressive pallor for one month. His hemoglobin (Hb) was 5 g/dL, reticulocyte count was 2.5% and serum creatinine was 2.5 mg/dL. He received two blood transfusions. After the second transfusion he became disoriented and was referred to our hospital. At admission, he was febrile, his heart rate was 110/min and his blood pressure was 110/70 mm Hg. He had a few petechiae; his respiratory, cardiovascular and abdominal examination was normal. His higher mental functions were grossly abnormal with fluctuating consciousness, but his cranial nerve examination, motor and sensory system examination were within normal limits. Total leucocyte count was 7700/cu mm and platelet count was 30,000/cu mm. Peripheral smear showed schistocytes, suggesting microangiopathic hemolytic anemia (MAHA). Serum lactate dehydrogenase (LDH) was 782 units, serum creatinine was 2.9 mg/dL, total serum bilirubin was 4.0 mg/dL with a direct of 0.75. Prothrombin time was 28s against a control of 12s, PTT was 32s (control 14s) and fibrin degradation product (FDP) was 40U. Our initial clinical diagnosis was incompatible blood transfusion reaction with disseminated intravascular coagulation. Other post infectious causes like dengue and leptospirosis were ruled out by serology. Over the next few hours of admission, he developed nasal, oral and IV site bleeds, hematemesis, melena, and pulmonary hemorrhage. He received several units of fresh frozen plasma, platelet concentrates and fresh whole blood. His platelet counts decreased further and he continued to bleed profusely though PT, PTT became normal. He was electively ventilated. We reviewed our diagnosis. In view of microangiopathic hemolytic anemia, thrombocytopenia, diffuse CNS dysfunction and PT, PTT which was easily corrected, a diagnosis of TTP was considered. High dose steroids and plasmapheresis was started. Over the next 10 days

with five sittings of plasmapheresis, his bleeding gradually decreased, his platelet counts rose to 1.8 lakh/cu mm. He was weaned off from ventilator. After 3 days he had a relapse. He developed a massive left thalamic bleed with intraventricular extension with bilateral posterior territory infarction with tentorial herniation. His platelet count at this time was 19,000 and his PT was 52/12. Neurosurgical opinion was taken and he was treated conservatively with elective hyperventilation, antiedema measures and fresh frozen plasma. IV immunoglobulin was planned but his platelet counts picked up rapidly to 70,000/cu mm. Over the next few days, his general and neurological condition improved. He had a residual right hemiparesis with aphasia. He was slowly weaned off from ventilator and feeds and physiotherapy were started.

At discharge on day 30 there was no bleeding, power in right upper and lower limb was grade 2. He was aphasic, platelet counts were 2.9-lakhs/cu mm. At one month after discharge, power in right upper and lower limb is grade 4. He can walk with support and speak 20 words. Higher mental functions have nearly come to normal. His platelet counts are 1.7 lakhs/cu mm.

### Discussion

Our differential diagnosis in this child included TTP and post transfusion disseminated intravascular coagulation. This child had MAHA and elevated creatinine before transfusion. This could have been a sub acute onset of TTP(4). When he came to us, all the criteria for TTP were fulfilled including MAHA, thrombocytopenia, fever, diffuse neurological deficits, and mild renal involvement. TTP and hemolytic uremic syndrome (HUS) may at times be confused because the clinical spectrum is over-lapping(1).

However, if the neurological symptoms are over-whelming like in our patient, TTP is diagnosed, but when renal involvement including oliguria, hypertension and progressive azotemia are predominant, HUS is diagnosed. Our patient never had oliguria or hypertension and azotemia resolved in a few days; hence TTP is a more likely possibility than HUS. Two organs which are absolutely or relatively spared in TTP/sporadic HUS are the lung and liver respectively(5). Theoretically, protease levels in blood which are absent in TTP and present in HUS help in differentiating the two conditions but this is possible only in few laboratories(3). DIC is considered whenever PT, PTT, FDP are grossly deranged, whereas in TTP they are mildly abnormal, easily corrected or normal.

We now briefly review the recent developments in the pathogenesis of TTP. The disease was first described by Moscovitz in 1924 in a 16-year-old girl who presented with pallor, petechiae, and a rapidly fatal coma(6). The terminal capillaries and arterioles of this child were filled with hyaline thrombi without perivascular inflammation(3). In the 1980's plasma of patients with chronic relapsing TTP were found to have large multimers of von Willibrand factor unlike normal plasma(7). Since then many workers have proved that a metalloprotease is required to cleave these large multimers of vWF and this protease is consistently deficient in the plasma of patients with TTP(8). This deficiency may be a congenitally inherited mutation in the ADAMTS-13 gene as seen in relapsing TTP or acquired due to the development of autoantibodies against this vWF cleaving protease. Conditions and drugs associated with the development of TTP include HIV, pregnancy, bartonella infection, ticlopidine *etc.*(3,4). The clinical pentad of TTP is microangiopathic hemolytic anemia, thrombo-

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cytopenia, pyrexia, diffuse CNS involvement, and azotemia. The incidence of various symptomatology in TTP include fever (60%), rash, headache, fatigue, malaise, altered mental status (36%), seizures (16%), hemiplegia (12%), paresthesia (4%), abdominal pain (24%), arthralgias.

Treatment of a single acute episode of TTP includes infusion of large volumes of protease containing plasma products over days or weeks. Plasmapheresis is useful in removing autoantibodies and unusually large multimers of vWF. Two randomized control trials have demonstrated the superiority of plasma exchange over plasma infusion(9). Replacement of the protease in children with chronic relapsing TTP with only a few units of fresh frozen plasma, cryosupernatant or plasma treated with solvent or detergent induces a prompt response. Other drugs used include vincristine and cyclosporine(10). The mortality rate is approximately 95% for untreated cases and survival rate is 80-90% with early diagnosis and treatment with plasma-infusion and plasma-exchange. In a randomized trial, Rock and colleagues reported a mortality rate of 22% among persons who underwent plasma exchange compared with mortality rate of 83% among patient who underwent plasma-infusion(3). One third of patients experience a relapse within following 10 years

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