

## **Congenital Thrombotic Thrombocytopenic Purpura (CTTP) in Nine years old boy with Six years delayed in diagnosis**

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### **ABSTRACT**

Congenital thrombotic thrombocytopenic purpura (CTTP) is a rare disease due to mutations in genes that reduce the production of ADAMTS 13 (Metalloprotease). Metalloprotease deficiency causes large multimeres of Von Willebrand factor VWF not going to broken and result in anemia and thrombocytopenia (Microangiopathic hemolytic anemia) with renal involvement.

The case is a 9 years old boy who suffers from anemia, thrombocytopenia since age three with some courses of hematuria, BUN and creatinine rising period. He had different diagnosis such as ITP (Immune thrombocytopenic purpura), Fanconi anemia, autoimmune hemolytic anemia, Evans syndrome and has been taken various immunosuppressive therapy and frequent blood transfusion. After 6 years following HUS like crisis and due to congenital deficiency of ADAMs13 and normal antibody against it he was diagnosed as a CTTP and treated with regular injections FFP .

**Keywords:** ADAMTS13, congenital Thrombotic thrombocytopenic purpura, thrombocytopenia

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### **INTRODUCTION**

Congenital thrombotic thrombocytopenic purpura (CTTP) is a syndrome due to reversible platelet aggregation and cause micro-vascular ischemia in various organs.

Thrombocytopenia, microangiopathic hemolytic anemia, neurologic symptoms, fever and renal dysfunction are seen in most patients and without treatment, mortality is 90%. There are two main types of TTP acute acquired is type I and type II is a rare

hereditary recurrent disease. Type I is seen with no particular reason, idiopathic, or followed by a secondary bacterial infections, viral, pregnancy, collagen vascular disease, pancreatitis and certain drugs.<sup>1</sup>

In normal conditions, ADAMTS 13 as a Metalloproteinase is a VWF (VWF-cleaving) agent. It breaks and divides large multimeres to small one. In the absence of ADAMTS 13 activity large VWF formed and with production of fibrin within the vessels causing TTP. Reduced ADAMTS 13 activity is an inherited chronic and recurrent condition due to mutations in the gene for ADAMTS 13. It is transmitted by autosomal recessive trait.<sup>2,3</sup> Cell culture studies have shown that the basic physiopathology of the hereditary TTP is protein secretion inability and its catalytic inactivity by deficiency of ADAMTS 13.<sup>4</sup> Acquired and acute type often occurs in adults due to the production of IgG auto-antibodies against ADAMTS 13.<sup>5</sup>

TTP relatively is rare and occurs 4 to 5 per million per year and is more common in female.<sup>6</sup> Congenital form constitute 1% of the total TTP<sup>7</sup> and characterized by microangiopathic hemolytic anemia, often with fever, thrombocytopenia, renal and neurological

disorders.<sup>8</sup> Detection of the reduced activity of ADAMTS 13 in the absence of anti ADAMTS 13 antibodies lead to diagnosis.<sup>3</sup> Congenital TTP is well known Upshaw-Schulman syndrome too and may be symptomatic at birth or in early childhood and rarely will be asymptomatic till adulthood, the severity of the symptoms is highly variable. Congenital TTP can be confused with chronic ITP or Evans syndrome.<sup>9</sup> Treatment of congenital TTP is FFP transfusions to replace the protein ADAMTS 13 in long period empirically almost every few weeks to a month.<sup>9,10</sup>

In acquired type because of inhibitor antibodies, plasma exchange is required to remove the inhibitor.<sup>8</sup> ADAMTS13 inhibitors can be identified in most acquired cases but in Hemolytic - uremic syndrome (HUS) cannot be detected.<sup>12,11</sup> Mutations in factor H, a regulator of the complement alternative pathway and factor I mutations which is a complement inhibitor cause microangiopathic hemolytic anemia and atypical HUS.<sup>13-16</sup> Due to the rarity of congenital TTP and similarity of its symptoms with other common diseases, diagnosis is often delayed for long periods. The aim of this presentation is to bring attention of physicians to this rare condition

to prevent delayed and misdiagnosis of this condition.

**CASE REPORT**

A 9-years-old boy who presented for the first time in 3 years old with thrombocytopenia. After six months anemia was added to clinical findings. Anemia was hypochrome and macrocytic with corrected retic count 2.5%, B12 and folic acid blood levels were normal. The direct and indirect Coombs were negative, liver enzymes and urea, creatinine and LDH were normal but (Alkaline phosphatase) ALP has clearly increased. Initial diagnosis was ITP and patients was treated with prednisone but with a drop in hemoglobin and cytopenia diagnosis changed to Fanconi anemia and Oxymetholone added to therapy.

Abdominal ultrasound and blood tests for hepatitis C, and EBV (Epstein-Barr virus) were normal. Evaluation for SLE and ANA (Antinuclear antibody) and Anti ds DNA were normal. One-year patient was treated with CORTICOSTEROIDS, CYCLOPHOSPHAMIDE, AZATHIOPRINE, METHOTREXATE frequent blood and platelet transfusions because of drop in hemoglobin (up to 5.9) and platelets (below 10,000) counts. Bone

marrow aspiration in frequents samples were normal.

The patient found microscopic hematuria and Burr cell and Helment cell in the peripheral blood smear were reported. Reticulocyte increased up to 18% simetimes. Serum ferritin levels (Prothrombin time) PT, (Partial thromboplastin time) PTT, G6PD (Glucose - 6 - phosphatase dehydrogenase) and hemoglobin electrophoresis were normal. Urea was increased coincidentally with hematuria during the second year of disease. Because of positive results of coomb's test, panel test is done. The panel showed positive antibody to Anti-E/Anti-c/Anti-fya and positive direct Coombs test for Anti-IgG-c3b.

Because of the frequent findings of thrombocytopenia and platelet transfusions and weekly needs of the platelets transfusion Evans syndrome was considered again., reevaluations of lupus, hepatitis B, hepatitis C, HIV ,BM re-aspiration, Spiral chest and abdominal CT scan were normal. In the fourth year of illness due to lack of response to CORTICOSTEROIDS, CYCLOSPORINE, AZATHIOPRINE, DANAZOL, and RITUXIMAB was started. Following the injection patient showed gastrointestinal bleeding and further increase

in urea (130), creatinine (8.3), with increased blood pressure and hematuria. With probably ATN due to hemolysis patient was treated with pulse methylprednisolone, IVIG (Intravenous immunoglobulin) and plasmapheresis. Hematuria and nonnephrotic proteinuria were constant findings in patient.

Until the fifth year of the disease (8 years old age) because of the lack of correct diagnosis all medications were discontinued, and blood products were limited just in bleeding conditions if needed. Gradually the need of patient to blood products diminished. However, patient found new episode of hematuria hypertension and increased urea and creatinine again. Because of lack of blood products transfusion ATN was not considered, and due to fragmented RBC in PBS, microangiopathic hemolytic anemia, HUS and TTP were evaluated.

Normal I and B factors with low ADAMTS 13 clearly below the normal range 20ng/ml (630-850) and normal IgG auto antibodies against ADAMTS 13 resulted in diagnosis of congenital TTP. Amlodipine and atenolol are discontinued within 4 months. With serial FFP transfusion hemoglobin and platelets are in normal range. The patient now has the

history of seven years of disease (10 years old) and stay with his daily normal life with FFP infusion every 18 days.

### **DISCUSSION**

TTP is a life-threatening multi-system disease characterized with of microangiopathic hemolytic anemia, fever, thrombocytopenia, renal failure and neurological disorders. Platelet-rich thrombosis is caused kidney failure and nerve damage. Diminished metalloproteinase activity in break down VWF multimeres is the pathophysiology of TTP. (8).

Lack of renal and neurological findings during early course of disease in this patients lead to delayed in diagnosis. At first ITP and then with adding leukopenia other diseases such as autoimmune hemolytic anemia, Evans syndrome, Fanconi anemia were considered. After correct diagnosis, and holding of blood transfusions and immunosuppressive drugs leukopenia disappeared and coomb's changed to normal.

In thrombocytopenia and microangiopathic hemolytic anemia with negative comb's and elevated LDH, CTTP should be considered. Many patients do not show renal and neurologic symptoms (17,

18) After 5 years' anemia and thrombocytopenia by reducing the infusion of blood products and stopping the medications patients Coombs changed to normal. This result is not compatible with Evans and autoimmune hemolytic anemia<sup>17</sup>.

With sustained thrombocytopenia, anemia, hematuria, and the presence of Burr cells in peripheral blood and microangiopathic hemolytic anemia in a patient's blood smear, HUS and TTP are probable diagnosis. Because of frequent relapsing of disease and severe deficiency of ADAMTS 13 which is not common in HUS (8) and on the other hand, normal factors of H and I exclude HUS, low ADAMTS 13 activity with normal IgG-type autoantibodies against ADAMTS 13 suggests CTTP, which explain anemia, thrombocytopenia, hematuria, and increased urea, creatinine, and blood pressure of the patient. (18) One year therapy with FFP (15 cc/kg every 18 day) changed the thrombocytopenia proteinuria and hypertension of patient, although hematuria occurs occasionally.

We recommend that in every patient with thrombocytopenia and hemolytic anemia with unknown origin and poor response to therapy, CTTP should be

considered, it prevents complications and more additional unnecessary modality of therapy.

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