

# A rare cause of relapsing thrombocytopenia during childhood: Congenital thrombotic thrombocytopenic purpura

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## ABSTRACT

Congenital thrombotic thrombocytopenic purpura is a rare, life-threatening disease with relapsing thrombocytopenia episodes accompanied by less prominent hemolytic anemia. Here we report a 9-year-old Turkish boy with congenital TTP with homozygosity for the ADAMTS-13 gene with the p.Pro671Leu (c.2012C>T) mutation. He had recurrent episodes of thrombocytopenia, diagnosed as chronic immune thrombocytopenic purpura, and treated with IVIG and steroids. After he was diagnosed with congenital TTP, he has been given fresh frozen plasma every three to four weeks, and he has been in good clinical condition since then.

**Keywords:** ADAMTS-13; congenital thrombotic thrombocytopenic purpura; Immune thrombocytopenic purpura.

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# Çocukluk çağında tekrarlayan trombositopeninin nadir bir sebebi: Konjenital trombotik trombositopenik purpura

## ÖZET

Konjenital trombotik trombositopenik purpura (TTP), nadir görülen, tekrarlayan trombositopeni atakları ve hafif hemolitik anemi bulguları ile seyreden, hayatı tehdit edici bir hastalıktır. Burada, ADAMTS-13 geninde homozigot p.Pro671Leu (c.2012C>T) mutasyonu saptanmış olan konjenital TTP tanısı alan 9 yaşında bir erkek hasta sunulmuştur. Öncesinde tekrarlayan trombositopeni atakları olan hasta, kronik immün trombositopenik purpura tanısı ile IVIG ve steroidlerle tedavi edilmiştir. Konjenital TTP tanısı aldıktan sonra hastanın 3–4 haftada bir taze donmuş plazma ile tedavisine devam edilmekte olup, trombositopeni ve hemolitik anemi atakları tekrarlamamış ve klinik durumu iyi olarak izlemi devam etmektedir.

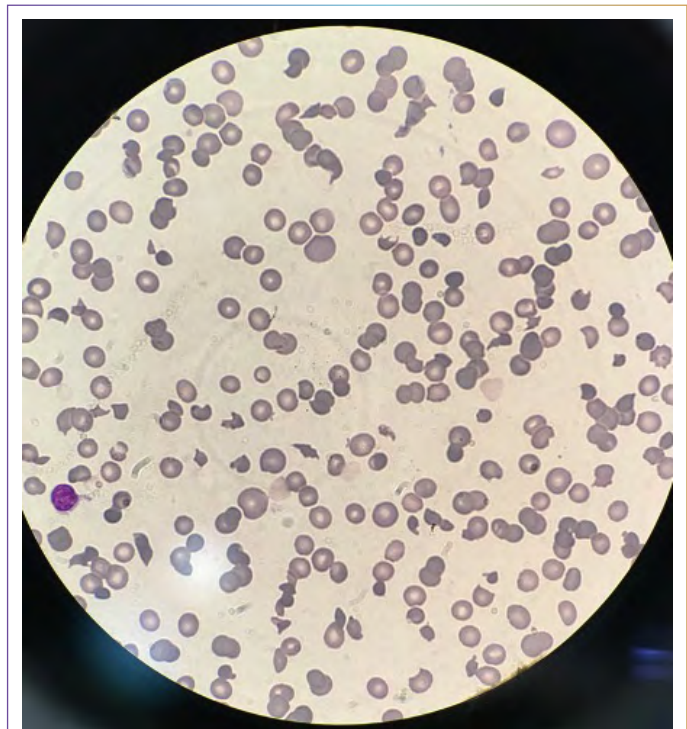
**Anahtar Kelimeler:** ADAMTS-13; immün trombositopenik purpura; konjenital trombotik trombositopenik purpura.

## INTRODUCTION

The most common cause of thrombocytopenia during childhood is Immune Thrombocytopenic Purpura (ITP), which is usually diagnosed when other etiologies have been ruled out (1). Congenital Thrombotic Thrombocytopenic Purpura (TTP), a rare life-threatening disease, represents a severe form of microangiopathy in the microcirculation. It is characterized by platelet clumping, resulting in thrombocytopenia, microangiopathic hemolytic anemia, and multiorgan failure (2, 3). The disease itself is potentially fatal in the absence of treatment and is typically presented with severe thrombocytopenia and hemolytic anemia. TTP is caused by the deficiency of ADAMTS-13 (A Disintegrin and Metalloprotease with Thrombospondin 1 repeats Nr. 13), a von Willebrand Factor cleaving metalloproteinase. The majority of TTP cases are acquired, while a minority are congenital, known as Upshaw-Schulman Syndrome (4, 5). ADAMTS-13 deficiency causes ultra-large von Willebrand multimers to accumulate in small blood vessels, leading to thrombus formation in areas with shear stress (5). The inheritance of congenital TTP is thought to be autosomal recessive, with homozygous or compound heterozygous mutations in the ADAMTS-13 gene (3). Here, we report a child with congenital TTP, formerly diagnosed and treated as chronic ITP.

## CASE REPORT

A 9-year-old boy was admitted to our emergency department with complaints of nausea, vomiting, abdominal pain, and dark urine. His history revealed that he was born healthy to healthy and third-degree consanguineous parents. His medical history included indirect hyperbilirubinemia and thrombocytopenia, treated with thrombocyte suspension and phototherapy during the newborn period. At the age of two, he was admitted with complaints of petechiae and diagnosed with ITP. He had experienced similar complaints once or twice a year and had been treated with either intravenous immunoglobulin G (IVIG) or steroids under the diagnosis of chronic ITP at another center. His blood tests and bone marrow aspiration results were indicative of chronic ITP.



**Figure 1.** Prominent anisocytosis, poikilocytosis, schistocytes, and rare spherocytes with 4% normoblasts on peripheral blood smear.

At his admission to our emergency department, his physical examination showed no abnormalities except for hepatomegaly of 2 cm below the costal margin. His complete blood count revealed mild anemia with a hemoglobin level of 10.5 g/dl, a decrease from 12.4 g/dl within a few days, a thrombocyte count of 9000/mm<sup>3</sup>, a leukocyte count of 4300/mm<sup>3</sup>, and an absolute neutrophil count of 2190/mm<sup>3</sup>. His peripheral blood smear showed prominent anisocytosis, poikilocytosis, schistocytes, polychromasia, and rare spherocytes with 4% normoblasts (Fig. 1). There were few, large to giant-sized thrombocytes on the peripheral blood smear. His reticulocyte count was 3.5%,

and his haptoglobin level was 8 mg/dl (normal: 30–270). Biochemical tests showed increased lactate dehydrogenase (LDH) of 755U/l (normal range: 110–295), total bilirubin of 3.38 mg/dl (normal range: 0–1.2), and indirect bilirubin of 2.64 mg/dl (normal range: 0–0.8), indicating hemolysis. His urine analysis revealed hematuria with 3+ erythrocytes. His renal function tests were normal. The direct Coombs test was negative. Since his diagnosis was known as chronic ITP, he was given IVIG at a dose of 1g/kg. After 24 hours, his thrombocyte level was still 10000/mm<sup>3</sup>, anemia was more profound, and hematuria continued. For differential diagnosis, complement activity tests (C3, C4), CH50 were normal. Antinuclear antibody (ANA), anti-dsDNA, PNH (Paroxysmal Nocturnal Hemoglobinuria) clone, and genetic testing for HUS (Hemolytic Uremic Syndrome) and aHUS (atypical HUS) were negative. With a history of hemolytic anemia and relapsing thrombocytopenia, ADAMTS-13 activity was also studied, resulting in <0.2%, and the inhibitor test was negative. During the period of awaiting the result of ADAMTS-13 plasma level, he was transfused with erythrocyte suspension because his anemia deepened to a Hb of 7 g/dl, and he developed symptoms of cardiac insufficiency with tachycardia and headache due to anemia. After the ADAMTS-13 result was achieved, he was administered fresh frozen plasma (FFP) two times a day, after which his clinical condition improved immediately. His thrombocyte levels increased to 313000/mm<sup>3</sup>, and his Hb level to 11.4 g/dl, without any further transfusion.

His mutation analysis revealed homozygosity for the ADAMTS-13 gene with p.Pro671Leu (c.2012C>T) mutation through PCR-DNA gene analysis. For our patient's diagnosis, an atypical hemolytic uremic syndrome (aHUS) panel by Next Generation Sequencing (NGS) analysis was planned to clarify the molecular etiology. The gene panel included 11 genes (CFH, CFI, CFB, CD46, C3, C5, DGKE, CFHR3, CFHR1, THBD, ADAMTS13) associated with aHUS. Sequence analysis covered the coding regions of each gene, including all coding exons and +/- 10 base pairs of adjacent intronic sequences. A homozygous missense c.2012C>T, p.Pro671Leu variant was detected in ADAMTS13 (NM\_139025). This variant, absent in the homozygous state from controls in the 1000 Genomes Project and GnomAD, was previously reported as a disease-causing mutation associated with TTP in the Human Genome Mutation Database. The variant was confirmed by Sanger sequencing. Primer sequences and reaction conditions are available upon request.

Since the diagnosis of congenital TTP was confirmed, the patient was placed on a prophylactic regimen with monthly FFP infusions. Despite the FFP therapy, a hemolytic crisis triggered by a respiratory infection occurred, likely due to a delay in FFP infusion beyond one month for once. Afterwards, no delays were allowed, and he has maintained good physical and clinical condition and academic performance since then. Written informed consent was obtained from the patient's parents.

## DISCUSSION

TTP is a well-described, life-threatening, rare hematologic disease characterized by fatal thrombotic microangiopathy, severe thrombocytopenia, microangiopathic hemolytic anemia, and transient neurological symptoms that tend to relapse (6). A quite frequent presentation of congenital TTP is recurrent episodes of acute thrombocytopenia and anemia during the neonatal period, which is usually underdiagnosed (1, 3, 5). Most patients remain asymptomatic, but some are admitted to the hospital with recurrent episodes of thrombocytopenia, usually misdiagnosed as immune thrombocytopenic purpura.

Severe ADAMTS-13 deficiency is defined as <10% of normal activity (7). The diagnosis of congenital ADAMTS-13 deficiency is based on severe deficiency of ADAMTS-13 (<5%) with the lack of inhibitors against ADAMTS-13 (1). Diagnosis is confirmed by the detection of a homozygous or compound heterozygous mutation upon sequencing of the ADAMTS-13 gene (7). Most patients are diagnosed during early childhood, mostly presented with hyperbilirubinemia, anemia, and thrombocytopenia, mostly treated by exchange transfusion during the newborn period (1). Our patient was also hospitalized during the newborn period with jaundice accompanied by thrombocytopenia, treated by phototherapy and thrombocyte transfusion. After the newborn period, the clinical manifestations vary and show no correlation between mutation type and severity of symptoms (1, 5). On the other hand, in a recent cohort of congenital TTP patients from the United Kingdom, it was shown that there is evidence of genotype-phenotype correlation in congenital TTP, where pre-spacer mutations are associated with earlier development of symptoms during the childhood period (8). A rare cause of admission to the hospital is recurrent episodes of thrombocytopenia with mild anemia, drawing less attention than thrombocytopenia, which usually causes underdiagnosis. Our patient was also admitted to a different center with the signs and symptoms of thrombocytopenia repetitively and treated with either IVIG or steroids with the diagnosis of chronic ITP. During his admission to our hospital, thrombocytopenia and mild anemia, which deepened during his stay within hours accompanied by prominent hematuria, helped us think about hemolytic uremic syndrome and ADAMTS-13 deficiency in the differential diagnosis. But it is very important to pay attention to other components of blood tests, such as anemia, even if it is mild, and accompanying symptoms during thrombocytopenia episodes. A regional study from the UK TTP registry by Scully M et al. (9) emphasized that the diagnosis of TTP was made by the presence of thrombocytopenia, anemia, fragmentation, and polychromasia confirmed on the peripheral blood smear, increased levels of LDH, reticulocytosis, negative direct Coombs test, and normal clotting screen. Mutations that cause congenital TTP are located on chromosome 9 in the ADAMTS-13 gene, leading to ADAMTS13 deficiency, which is usually inherited in an autosomal recessive pattern (10). The widely accepted treatment of symptomatic congenital ADAMTS-13 deficiency is FFP infusions with 10 ml/kg every 2–4 weeks, usually containing enough ADAMTS-13 to subside recurrent episodes of the disease. FFP is also effective during the acute period of the disease, reverting the hematological alterations (1).

Although the treatment of congenital TTP via plasma infusions is generally effective, the therapy is frequently complicated by allergic and anaphylactic reactions or volume overload. Plasma infusions also carry risks for infections as a result of blood-borne pathogens. It can also be time-consuming and stressful for both parents and the patient himself. Marie Scully et al. (11) investigated rADAMTS13 in patients diagnosed with severe congenital TTP deficiency for future studies and found it to be safe and well tolerated with compatible activity of ADAMTS13 levels in vivo. We plan to give FFP until rADAMTS-13 is widely used and becomes available in our country.

## CONCLUSION

During the newborn period and childhood, congenital TTP should be kept in mind with thrombocytopenia, Coombs-negative hemolytic anemia, and hematuria. It is very important to consider the diagnosis as early as possible since FFP is both a curative and preventive treatment for life-threatening attacks when applied on a monthly basis. The ideal treatment for congenital TTP would be recombinant human ADAMTS-13 or genetic therapy, but none are currently available. Until then, the treatment should be tailored for each patient, and the therapy schedule should be discussed properly with the patients and parents.

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**Hasta Onamı:** Yazılı hasta onamı bu çalışmaya katılan hastaların ailelerinden alınmıştır.

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**Çıkar Çatışması:** Yazarlar çıkar çatışması bildirmemişlerdir.

**Mali Destek:** Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

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