

Hereditary TTP and Hemolytic Anemia in Newborns

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Hereditary thrombotic thrombocytopenic purpura (hTTP) is a thrombotic microangiopathy due to severe ADAMTS13 deficiency. hTTP typically presents in adulthood with thrombocytopenia, hemolytic anemia, and/or neurologic abnormalities. However, nearly half of the patients with hTTP are symptomatic at birth, most commonly presenting as severe jaundice secondary to hemolysis. Turbulent blood flow during birth puts neonates at high risk for thrombotic events and subsequent hemolytic anemia. We present a case series of 3 siblings with ADAMTS13 loss-of-function variants, all of whom required neonatal exchange transfusion. These siblings are now in their 30s and were diagnosed with hTTP between the ages of 13 and 18. One sibling experienced a neonatal stroke, while another sibling required a leukemia workup in her childhood because of hTTP. They remain in good health as adults. Two of them receive recombinant ADAMTS13 treatment for their deficiency. A recent report found that only 5% of patients with hTTP were correctly diagnosed at birth—underscoring the importance of having a high index of suspicion in the neonatal period for the anemic and thrombocytopenic newborn with nonimmune hemolytic anemia. With newly Food and Drug Administration–approved recombinant ADAMTS13 therapy and rapid diagnostic testing for ADAMTS13 levels, it is imperative that pediatricians and neonatologists recognize this rare but treatable form of recalcitrant jaundice. We propose a diagnostic algorithm to assist clinicians in neonatal diagnosis of hTTP in hopes of mitigating the need for exchange transfusions and extensive hematologic workups later in life. Timely diagnosis would prompt targeted treatment, which can prevent long-term neurologic and renal sequelae.

INTRODUCTION

Hereditary thrombotic thrombocytopenic purpura (hTTP) is a rare thrombotic microangiopathy resulting from congenital deficiency of ADAMTS13. ADAMTS13 cleaves von Willebrand factor (vWF), a cofactor for platelet adhesion during primary hemostasis. Lack of ADAMTS13 leads to an increase in ultra-large vWF multimers and formation of microthrombi in small vessels. Manifestations of hTTP include microangiopathic hemolytic anemia, thrombocytopenia, and renal/neurologic dysfunction. The neonate with hTTP is at particularly high risk for microangiopathic thrombotic events because the shear stress from turbulent blood flow experienced during fetal transitional physiology can trigger catastrophic microvascular thrombosis.

The estimated prevalence of hTTP is 0.5 to 2.0 per million patients.¹ However, hTTP may be 30 to 40 times more prevalent than previously recorded, because genome aggregation data indicate that the prevalence of pathogenic biallelic ADAMTS13 gene variation occurs at a prevalence between 2.3 and

abstract

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4 per 100 000 patients.² This places hTTP at similar frequency to other rare diseases tested on the federal Recommended Uniform Screening Panel.³ We propose that the discordance between the genetic and clinical prevalence of hTTP is due to underdiagnosis in the newborn period owing to its clinical overlap with hemolytic disease of the newborn (HDN). Underdiagnosis may also result from variable penetrance or genotypic heterogeneity because more than 200 ADAMTS13 variants, spread over all ADAMTS13 protein domains, have been identified in patients with hTTP.¹ A recent report of 226 patients with hTTP described that 83 (37%) had severe jaundice at birth; hTTP was suspected and effectively treated in only 3 (4%) of these 83 patients.⁴

We describe a case series of 3 siblings, born approximately 30 years ago, who presented with hTTP in the neonatal period. Each patient received an exchange transfusion for hyperbilirubinemia secondary to presumed HDN. They were diagnosed with severe (<10%) ADAMTS13 protein deficiency following recurrence of disease in adolescence. Notably, the siblings experienced similar presentation of hTTP at birth; however, variable disease penetrance was observed despite conserved ADAMTS13 variants. The goal of this case series is to highlight this underrecognized cause of neonatal illness and provide clinicians with a toolkit for distinguishing hTTP from more common neonatal diseases.

CASE SERIES

Patient A

Patient A is a term female newborn who presented with jaundice in the newborn nursery; she is the oldest of the 3 siblings described here. She was admitted on phototherapy, but total bilirubin levels peaked at greater than 30 mg/dL, requiring an exchange transfusion. She was likely misdiagnosed with HDN because the patient and her parents had the same blood type (A-positive), although minor antigen testing was unavailable.

Her laboratory results were also notable for anemia and severe thrombocytopenia. Her platelet count fell from 146 000 to 23 000 cells/mm³ and hematocrit fell from 47% to 27% during her admission. At 20 hours old, she suffered a focal seizure manifested by left hand twitching. A head computed tomography scan demonstrated a small right hemispheric cortical infarct. She required physical therapy for her first year of life and recovered without long-term weakness.

When she was 19 years old, patient A was diagnosed with hTTP. She presented to her primary care physician with neck pain, weakness, near-syncope episodes, and dark-colored urine. She was diagnosed with a urinary tract infection and received a course of nitrofurantoin. She was severely thrombocytopenic (platelets of 19 000 cells/mm³) and anemic (hemoglobin of 9.3 g/dL). Her lactate dehydrogenase (LDH)

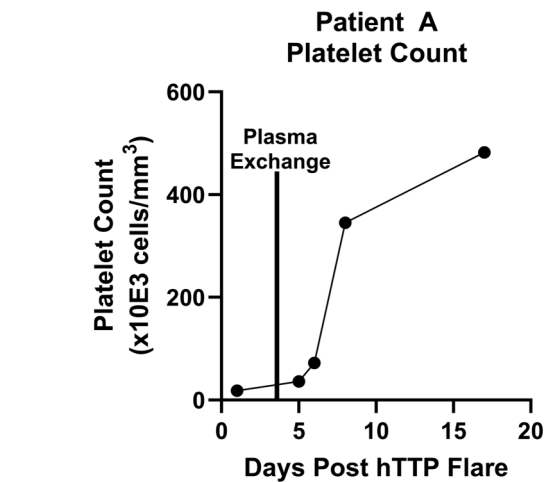


FIGURE 1. Platelet trend for patient A during hTTP flare as an adult. Abbreviation: hTTP, hereditary thrombotic thrombocytopenic purpura.

Patient	ADAMTS13 Mutation	ADAMTS13 Activity	Presentation at Birth
Father	R1060W (heterozygous)	56%	Asymptomatic
Mother	I1217T (heterozygous)	65%	Asymptomatic
Patient A	R1060W, I1217T	<5%	Severe hyperbilirubinemia Severe thrombocytopenia Cortical infarct with seizures
Patient B	R1060W, I1217T	<5%	Severe hyperbilirubinemia Severe thrombocytopenia
Patient C	R1060W, I1217T	<5%	Severe hyperbilirubinemia Severe thrombocytopenia

was 644 U/L and indirect bilirubin was 8.1 mg/dL, consistent with hemolytic anemia. She was treated with 1 round of plasma exchange and corticosteroids and her platelet count improved to 72 000 cells/mm³ at time of discharge (Figure 1). Further workup revealed undetectable ADAMTS13 activity (<5%) with negative testing for an ADAMTS13 inhibitor. She underwent next-generation DNA sequencing, which revealed compound heterozygous variations in the *ADAMTS13* genes, R1060W, and I1217T (Table 1). This established her diagnosis of hTTP, and she was the first in her family to receive this diagnosis. Patient A is now 33 years old. She remains in good health and requires occasional treatment with recombinant ADAMTS13 (rADAMTS13) for hTTP flares.

Patient B

Patient B, who is 2 years younger than her sister, also experienced jaundice shortly after birth. Her bilirubin level

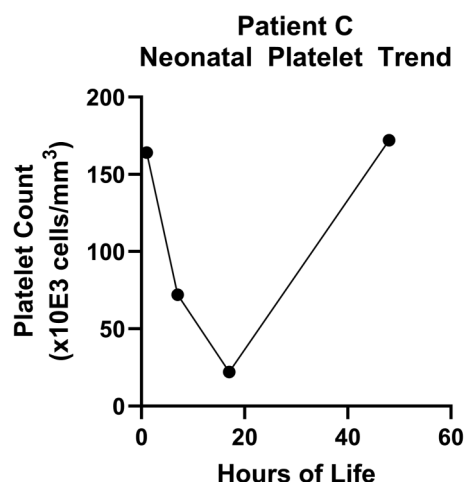


FIGURE 2. Platelet trend for patient C during the neonatal period.

reached 23.4 mg/dL (exact age in hours is unknown), necessitating an exchange transfusion with subsequent improvement. At birth, Patient B had a platelet count of 41 000 cells/mm³ with a hematocrit of 46%. She recovered following the exchange transfusion and was eventually discharged home.

When Patient A was diagnosed with hTTP, Patient B was tested and carried the same variants (Table 1). Patient B's adult hTTP flares occurred only during her 4 pregnancies, for which she required prophylactic plasma infusions. Today, she is 29 years old and remains asymptomatic with a milder disease course than her siblings. Despite having the same genotype as her siblings, she does not require rADAMTS13 treatment.

Patient C

Patient C, the youngest sibling, also presented with neonatal jaundice. She was born at 38 weeks following an uncomplicated pregnancy. Her bilirubin levels increased from 1.7 mg/dL at birth to 7.4 mg/dL at 7 hours of life. She was initially treated with phototherapy, but she required an exchange transfusion for hyperbilirubinemia. The exact bilirubin level at transfusion and its timing are unknown. The patient developed anemia and thrombocytopenia by 7 hours of life (Figure 2). The platelet count reached its nadir of 22 000 cells/mm³ at 17 hours after birth but improved to 172 000 cells/mm³ on day 2. The patient was diagnosed with HDN and eventually discharged.

At 5 years of age, she underwent a workup for leukemia because a screening complete blood count included white blood cells of 20 200 cells/μL, hemoglobin of 7 g/dL, platelets of 28 000 cells/mm³, and LDH of 1639 U/L. A bone marrow biopsy showed trilineage hematopoiesis without a hematologic malignancy. She was diagnosed with immune thrombocytopenic purpura (ITP). She presented again with

severe thrombocytopenia at 7 years of age with platelets of 13 000 cells/mm³. She was diagnosed with ITP and monitored outpatient where her counts recovered over the course of 2 months. Finally, at the age of 13, she was diagnosed with hTTP via genetic testing following her sister's diagnosis.

Throughout adolescence, she had episodes of abdominal pain, visual floaters, headaches, and focal neurological deficits such as slurred speech and anisocoria. She required plasma infusions with full recovery in symptoms. Today, she is 27 years old and requires occasional rADAMTS13 treatment.

DISCUSSION

Hereditary TTP, although rarely diagnosed in the neonatal period, is a particularly high-risk disease for neonates. Retrospective studies of patients with hTTP have shown that 35% to 45% of these patients receive exchange transfusions in the neonatal period.^{5,6} In a study evaluating reports of 226 patients with hTTP, 9 patients died within the first 17 days of birth, suggesting a 4% mortality rate in the reported patients.⁴ Case reports of neonatal hTTP have previously been described. This study adds to existing literature as we present a case series of 3 siblings who experienced neonatal complications and survived to be diagnosed with hTTP in their adulthood. The patients described here were born in the 1990s; thus, we relied on paper hospital records and correspondence with hematologists. We acknowledge the limitations surrounding exact age (in hours) of exchange transfusion and the transfusion thresholds; however, these hospital records no longer exist. Differences may exist today regarding exchange transfusion thresholds since revised hyperbilirubinemia algorithms were published in 2022.⁷

The cases described highlight 2 themes in hTTP: (1) variable disease penetrance despite conserved genetic variants and (2) developmental variation in ADAMTS13 levels dictating disease manifestation. In patients with hTTP, identical variations can be asymptomatic, requiring no treatment, or highly symptomatic, requiring lifelong fresh frozen plasma (FFP) infusions or rADAMTS13 treatment.⁸ Some of these variations can be attributed to developmental time points. For example, in the vulnerable perinatal period, term neonates have reduced ADAMTS13 activity, despite comparable protein levels to adults.⁹ In children/adults, ADAMTS13 deficiency alone is insufficient to cause disease, but prothrombotic states such as pregnancy or clinical illness can trigger flares with renal and neurologic complications despite targeted treatment.

Recently, 2 seminal advances have revolutionized diagnosis and treatment of hTTP. First, rapid testing for ADAMTS13 activity using 7 μL to 300 μL blood volume with a turnaround time of 1 hour (in-house) to 24 hours (send-out) testing is now available.¹⁰ Previous ADAMTS13 activity

TABLE 2. Parental, Fetal, or Neonatal Factors Suggesting hTTP as a Cause of Jaundice, Anemia, and Thrombocytopenia in a Neonate

- Presence of severe thrombocytopenia (platelet count $<25\text{--}50\,000\text{ cell/mm}^3$)
- Coombs/direct antiglobulin test negative
- Severe hyperbilirubinemia threatening exchange transfusion
- Rh-negative fetus
- Rh-negative father, with assured paternity
- Rh-positive mother
- Severe fetal anemia in the first pregnancy with no history of serological findings to suggest parvovirus B19 infection
- Evidence of microvascular and macrovascular thromboses in the fetus
- Evidence of microangiopathic hemolytic anemia in the neonate
- Documented hTTP in the first-degree relatives
- Documented severe ADAMTS13 deficiency in the family in absence of inhibitors to ADAMTS13
- History of previous fetal/immediate neonatal demise in the first-degree family with evidence of thromboses or severe thrombocytopenia

Abbreviation: hTTP, hereditary thrombotic thrombocytopenic purpura.

assays required 3 to 5 days. Second, rADAMTS13 is now Food and Drug Administration approved for patients with hTTP aged 2 years and older, and emergency

compassionate use of rADAMTS13 in the prenatal setting has successfully treated fetal complications of maternal hTTP.^{11,12} Given the rarity of the disease and recent development of recombinant protein therapy, the field is several years away from an absolute risk reduction or numbers needed to treat analysis. Still, specific testing in the high-risk neonate presenting with the unique constellation of hTTP symptoms can reduce potential complications of hTTP by prompting timely treatment, reducing subsequent diagnostic workups, and preventing morbidities such as pregnancy loss and stroke.¹³

To reduce unnecessary hTTP testing in infants with physiologic/breastfeeding jaundice or HDN, pertinent distinguishing features are noted in Table 2. Compared with HDN, patients with hTTP experience higher indirect (unconjugated) bilirubin levels with a rapid rate of rise (24 mg/dL with mean maximum occurring 38 hours after birth vs 16 mg/dL with a mean maximum occurring 74 hours after birth), with worsened anemia (hemoglobin of 10.6 g/dL vs 16.3 g/dL), and with worsened thrombocytopenia (platelets of $17\,000\text{ cells/mm}^3$ vs $291\,000\text{ cells/mm}^3$).^{14,15}

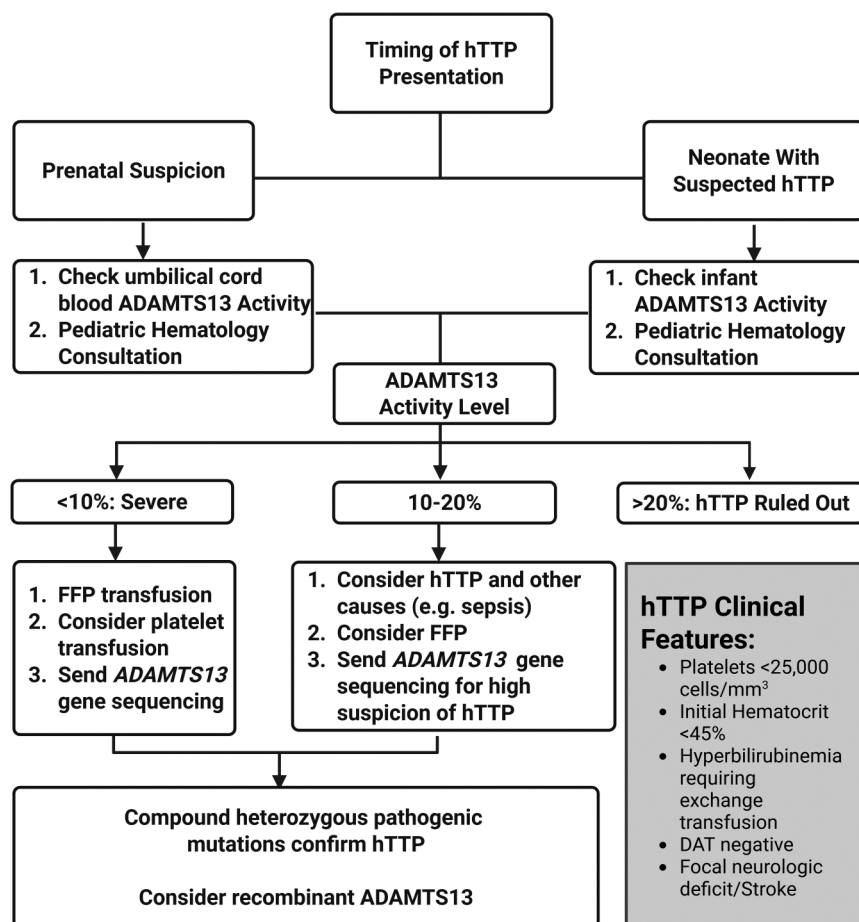


FIGURE 3.

Proposed diagnostic algorithm for hTTP and nonimmune hemolytic anemia.

Abbreviations: DAT, direct antiglobulin test; FFP, fresh frozen plasma; hTTP, hereditary thrombotic thrombocytopenic purpura.

Other identifying features of hTTP are provided in Table 2, including Coomb's negative status, need for an exchange transfusion, a notable family history, and absence of infectious risk factors.

Although neonatal disease has significant clinical overlap for hTTP and HDN, the lifelong disease course differs significantly. Intravenous immunoglobulin and exchange transfusion are mainstays of treatment for HDN, but for hTTP, treatment is primarily FFP. To complicate the clinical picture, plasma received during exchange transfusion for HDN can improve thrombocytopenia and hemolysis by providing ADAMTS13. The major difference is that high-risk exchange transfusions and repeat hospital admissions may be avoided with timely hTTP diagnosis. When hTTP is suspected in recalcitrant jaundice or nonimmune hemolytic anemia, prompt hematology consult, evaluation of ADAMTS13 activity, and FFP transfusion are warranted (Figure 3). Although different recommendations exist regarding prophylactic vs symptomatic treatment of hTTP, patients with hTTP can have long-term neurocognitive problems or chronic renal insufficiency.¹³ Therefore, early diagnosis during infancy and targeted treatment can improve long-term outcomes in this unique population.

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ABBREVIATIONS

FFP: fresh frozen plasma
HDN: hemolytic disease of the newborn
hTTP: hereditary thrombotic thrombocytopenic purpura
ITP: immune thrombocytopenic purpura
LDH: lactate dehydrogenase
rADAMTS13: recombinant ADAMTS13
vWF: von Willebrand factor

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