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COMMENTARY

Hereditary thrombotic thrombocytopenic purpura: The risk for death at birth

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Hereditary thrombotic thrombocytopenic purpura (hTTP) is a rare disorder. Patients with hTTP have insufficient plasma ADAMTS13, the enzyme required for cleavage of von Willebrand factor (VWF) after it is released by endothelial cells.[1] The result of ADAMTS13 deficiency is the circulation of ultra-large multimers of VWF (ULVWF).[2] When blood flow becomes turbulent, the coiled molecules of ULVWF unwind, exposing platelet-binding sites. Adherent platelets become activated, creating platelet aggregates attached to the long strings of ULVWF.[3,4] These ULVWF-platelet aggregates can obstruct circulation. Newborn infants always have turbulent circulation at birth; therefore, infants with hTTP have great risk for systemic thrombosis and ischemia during the first days of their lives.

Before birth, the infant receives maternal ADAMTS13. Fetal circulation bypasses the lungs because right atrial blood crosses through the foramen ovale and pulmonary arterial blood flows into the aorta through the ductus arteriosus. Immediately after birth, the umbilical cord is clamped, and the infant breathes. Pulmonary vascular resistance decreases. The foramen ovale closes. Blood flow through the ductus arteriosus reverses and begins to flow through the lungs. The ductus arteriosus flow remains bidirectional and turbulent until closure occurs.[5] Closure of the ductus arteriosus usually occurs within 48 hours after birth, although it may remain open for several days or longer, especially in premature infants.[6] Thus, until ductus arteriosus closure occurs, infants with hTTP are at great risk for arteriolar thrombosis, microangiopathic hemolytic anemia, and thrombocytopenia.

Historically, the most important cause of severe hemolysis and hyperbilirubinemia at birth was RhD alloimmunization. Before treatment with plasma exchange treatment began a century ago, most infants with RhD alloimmunization died.[7] When immunization with Rho(D) immune globulin became available in 1968, severe hemolysis and hyperbilirubinemia in newborn infants became rare.[8] ABO alloimmunization may now be the most common cause neonatal hemolysis and hyperbilirubinemia, but it is rarely severe.[9] When severe hemolysis with hyperbilirubinemia occurs soon after birth, it is often assumed that blood group alloimmunization is the cause. hTTP is rarely considered.

Although hTTP can cause severe hemolysis, hyperbilirubinemia, and thrombocytopenia soon after birth, to the best of my knowledge there have been no published comparisons to distinguish hTTP from ABO alloimmunization until now. In this issue of *RPTH*, Liu and colleagues describe the distinguishing clinical features of infants with hTTP and ABO incompatibility.[10] Their data document the clear differences between these two causes of neonatal hyperbilirubinemia and provide criteria for recognition of hTTP in newborn infants.

Liu et al. present clinical and laboratory data of infants who were hospitalized at the Peking Union Medical College Hospital in Beijing, China, 2013–2021. Four infants had hTTP. None were correctly diagnosed during their initial neonatal hospitalization. The diagnosis of hTTP was established at ages 1–48 months, when symptoms recurred. Their data were compared to the data of 20 infants with ABO incompatibility (Table 1). The gestational age of birth for these infants with hTTP and ABO incompatibility was the same, 39 weeks (median range, 37–41 weeks). No infants died.

The first distinguishing feature between these two groups of infants was their family history. Two of the four infants with hTTP

TABLE 1 Comparison of key distinguishing clinical features of hereditary TTP and ABO incompatibility from the study of Liu et al[10]

Clinical feature	Hereditary TTP (4 infants)	ABO incompatibility (20 infants)
Family history	2 patients each had 1 older sibling who died 2 days after birth with jaundice, hemolysis	No infant deaths
Jaundice onset (h)	10 (5–13)	69 (18–82)
Bilirubin (mg/dl, maximum)	24 mg/dl (38 h after birth)	16 mg/dl (74 h after birth)
Bilirubin response to phototherapy, IVIg[a]	0	20 (100%)
Hemoglobin (g/dl, mean, minimum)	10.6	16.3
Platelet count (/μl, mean, minimum)	17,000	291,000

Note: These data are from tables 1 and 3 and supplemental table 1 of Liu et al's publication.[10]

[a]All 20 patients with ABO incompatibility were treated only with phototherapy and IVIg. All four patients with hTTP were also treated with phototherapy and IVIg. Three patients with hTTP also had whole blood exchange transfusion; in the other patient, bilirubin decreased following platelet transfusions.

had older siblings who both died without a diagnosis at age 2 days; both had severe jaundice, hemolysis, and thrombocytopenia. This is the inevitable fate of untreated newborn infants with hTTP.[11–13] No neonatal deaths were reported among the siblings of the 20 patients with ABO incompatibility.

Increased serum bilirubin is common in healthy newborn infants. However, bilirubin levels >5 mg/dl at 24 h or >12 mg/dl at any time are probably pathological.[14] Among the four infants with hTTP, the bilirubin concentration was 10–23 mg/dl at 12 h. The median maximum bilirubin concentration was 24 mg/dl, occurring at 39 h. Among the 20 infants with ABO incompatibility, the median maximum bilirubin concentration was 16 mg/dl, occurring at 74 h after birth. The increased bilirubin was not only greater in patients with hTTP; it was refractory to the routine treatment with phototherapy and IVIg. All 24 infants received these two treatments; in the 20 patients with ABO incompatibility, the bilirubin concentration decreased. Bilirubin concentrations in the four patients with hTTP continued to increase until they received additional treatments.

Platelet counts were dramatically decreased in the four infants with hTTP; they were normal in infants with ABO incompatibility. Anemia occurred in all four infants with hTTP and in five of the infants with ABO incompatibility.

These distinguishing clinical features would seem to make the diagnosis of hTTP easily apparent. But the first criterion for any diagnosis is to consider it. Because hTTP is rare, it may be rarely considered. The current estimate of the prevalence of hTTP is 0.5–2.0 patients/10^6 people.[15] Data from Norway suggest that the prevalence may be much higher, 16.7/10^6 people.[11] The prevalence may be even greater because infants with hTTP may not be recognized and die within the first days after birth.

Until hTTP is considered in all infants with severe hyperbilirubinemia, it will remain rare. Prompt suspicion of hTTP and treatment with plasma infusion or whole blood exchange transfusion is lifesaving; recovery is complete. Suspicion of hTTP is sufficient for initiating treatment; diagnosis of hTTP by documentation of ADAMTS13 deficiency requires several days. Early diagnosis and close follow-up of infants with hTTP would prevent the recurrences that occurred in the four patients reported by Liu et al.[10]

Neonatal intensive care is a unique specialty. Hematologists, even pediatric hematologists, may not become involved in the care of newborn infants with severe thrombocytopenia. Therefore, I ask all hematologists who read the report of Liu et al[10] to share it with their colleagues in neonatal intensive care units. hTTP may not be as rare as we think it is.

RELATIONSHIP DISCLOSURE

I have no conflicts with the content of this Commentary.

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