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ORIGINAL ARTICLE

Early indicators of neonatal-onset hereditary thrombotic thrombocytopenia purpura

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Abstract

Background: Neonatal-onset hereditary thrombotic thrombocytopenia purpura (hTTP) is often misdiagnosed due to its rarity. It begins with jaundice, similar to infants with ABO incompatibility.

Objective: To explore early indicators of neonatal-onset hTTP.

Methods: This study was a retrospective case series of newborns with hTTP and ABO incompatibility. We compared the clinical characteristics and laboratory test results in these two groups.

Results: This study included four hTTP patients and 20 ABO-incompatible newborns. All patients manifested disease during the neonatal period. There were equal numbers of males and females in each group. hTTP newborns showed earlier (median difference, 57.0 h; 95% confidence interval [CI], 24.0–65.0) and more severe hyperbilirubinemia (mean difference, 8.0 mg/dl; 95% CI, 3.8–12.1) than ABO-incompatible newborns. In hTTP newborns, anemia was more common within 7 days after birth than in ABO-incompatible newborns (odds ratio, 25.4; 95% CI, 1.2–551.6), and platelet counts were lower than in ABO-incompatible newborns ($17 \pm 12 \times 10^9$/L vs. $291 \pm 76 \times 10^9$/L). The levels of serum creatinine (median difference, 51.8 μmol/L; 95% CI, 16.0–109.4) and blood urea nitrogen (median difference, 5.7 mmol/L; 95% CI, 2.8–38.7) were higher in hTTP newborns than in ABO-incompatible newborns. There were no significant differences in white blood cell counts, C-reactive protein, alanine aminotransferase, or albumin levels.

Conclusions: Severe jaundice soon after birth, early anemia, and severe thrombocytopenia were more common in newborns with hTTP than ABO incompatibility. These are distinguishing early features of hTTP.

KEYWORDS
ADAMTS-13, hemolysis, hereditary thrombotic thrombocytopenia purpura, jaundice, newborn

Jing Liu and Yuelun Zhang contributed equally as co-first authors.

Essentials

- Hereditary thrombotic thrombocytopenia purpura (hTTP) is a rare disorder that is often missed.
- hTTP manifests similarly to ABO incompatibility in newborns.
- Jaundice was more severe and occurred earlier in hTTP than in ABO incompatibility.
- Anemia occurred earlier and thrombocytopenia was more severe in hTTP.

1 | INTRODUCTION

Hereditary thrombotic thrombocytopenia purpura (hTTP), also known as Upshaw-Schulman syndrome, is an inherited thrombotic microangiopathy, and has an estimated prevalence of 0.5–16.7 cases per million people.[1,2] A study from Japan showed that 42% of hTTP patients (18/43) had undergone neonatal exchange transfusion for severe jaundice, but only 4 were diagnosed as hTTP within 6 months after birth.[1] A study from Norway also reported that 45% of hTTP patients (9/20) underwent neonatal exchange transfusion for jaundice, but diagnosis of hTTP was delayed until after 1 year of age.[2] ABO incompatibility, on the other hand, is one of the most common causes of neonatal jaundice.[3,4] The prevalence of ABO incompatibility is 54.4 per 1000 births and 17.3 per 100 neonates with blood group A or B born to mothers with blood group O.[5] Unlike ABO incompatibility, delayed diagnosis or misdiagnosis of hTTP can lead to infant death soon after birth due to severe thrombocytopenia and vital organ damage.[6,7] Therefore, prompt identification and treatment of hTTP in newborns is of paramount importance.

Neonatal jaundice is a common manifestation of both hTTP and ABO incompatibility. This study aimed to establish distinguishing clinical features and routine laboratory characteristics to differentiate hTTP from ABO incompatibility given the limited access to ADAMTS-13 testing, the variable sensitivity of direct antiglobulin test (DAT) in ABO incompatibility, and the possibility of concomitant hTTP and ABO incompatibility given the high prevalence of the latter condition.

2 | METHODS

2.1 | Patients

We performed a retrospective comparative case series of newborns with a subsequent diagnosis of hTTP and newborns with ABO incompatibility. The medical records of patients with hTTP from the Peking Union Medical College Hospital in Beijing from 2013 to 2021 were reviewed. For each patient with hTTP, we randomly sampled five newborns with confirmed ABO incompatibility balanced for patient sex. Newborns with severe infection, asphyxia, or premature birth were excluded from the ABO incompatibility group. This study was conducted with the approval of the Institutional Review Board of Peking Union Medical College Hospital (reference number: S-K1978), and informed consent was obtained from their guardians.

2.2 | Definitions

The diagnosis of hTTP was confirmed by documentation of ADAMTS-13 activity (less than 10% of normal) and clinical responsiveness to ADAMTS-13 supplementation.[8] Neonatal ABO incompatibility was defined by maternal-fetal ABO antigen incompatibility and a positive indirect antiglobulin test (IAT) or DAT[9,10] as well treatment with intravenous immunoglobulin (IVIG), phototherapy, and/or exchange transfusion per American Academy of Pediatrics guidelines.[11–13]

2.3 | Data collection

Data collection was performed by chart review and confirmed with guardians of the affected patients when applicable. Demographic and clinical characteristics were collected, including onset time of jaundice, which was confirmed through total serum bilirubin (TSB) measurement[13]; TSB levels; time to the maximum levels of TSB; DAT; IAT; complete blood count (including hemoglobin level, white blood cell count, and platelet count); C-reactive protein (CRP) level; liver enzyme and function biomarker levels (including albumin and alanine aminotransferase levels); renal function biomarker levels (including serum creatinine and blood urea nitrogen levels); ADAMTS-13 activity; ADAMTS-13 inhibitor; *ADAMTS-13* gene mutation analysis; treatments administered; and responses to treatments.

2.4 | Statistical analysis

Descriptive statistics were used and expressed as mean ± standard deviation, median (range), or count (frequency). Demographic and clinical characteristics were compared between the two groups using the *t* test, Mann–Whitney test, and chi-square test. The mean difference, median difference, and odds ratio with their corresponding 95% confidence intervals (CIs) were used to evaluate the effect size between groups. The median difference was estimated using the Hodges–Lehmann method. We did not adjust multiplicity given the exploratory nature of our study, and we did not conduct multivariate regression analysis due to the small sample size. A two-sided *p* value of less than 0.05 was considered statistically significant. We used IBM SPSS Statistics software 26 (IBM Corp) for all analyses.

3 | RESULTS

Four patients with neonatal-onset hTTP and 20 newborns with ABO incompatibility were included in this study. All four patients with neonatal-onset hTTP were identified within a short time frame (2020–2021), which may be explained by some previously missed or misdiagnosed cases, while the 20 newborns with ABO incompatibility were identified over the entire study period (2013–2021). All participants developed clinical manifestations of disease within the first day or days of their life. There was an equal number of males and females in the hTTP and ABO incompatibility groups. All participants were of Han Chinese ethnicity.

3.1 | Clinical characteristics

The clinical characteristics of the four patients with neonatal-onset hTTP are listed in Table 1, and the clinical characteristics of the 20 newborns with ABO incompatibility are listed in Table S1. Neonatal manifestations of patients with hTTP included severe jaundice (4/4), weakness (2/4), ecchymosis (1/4), fever (1/4), and seizures (1/4). All ABO-incompatible newborns had jaundice but no other clinical manifestations. Subsequently, the infants' blood group, IAT, and DAT were tested. Patient 2 with hTTP was diagnosed with ABO incompatibility due to a positive IAT, while the other three patients had undiagnosed hyperbilirubinemia and thrombocytopenia. DAT was negative in 35% (7/20) of newborns with ABO incompatibility and 100% of newborns with hTTP. None of the four patients with hTTP received the correct diagnosis during the neonatal period. Patient 4 with hTTP was the earliest to be diagnosed with hTTP at the age of 30 days via genetic testing due to persistent unexplained symptoms after birth, while the other three patients were diagnosed when there were recurrent hTTP manifestations at ages of 13–48 months. In contrast, all 20 newborns with ABO incompatibility received the correct diagnosis several days after birth.

All 24 newborns were treated with phototherapy and IVIG soon after birth. There was clinical improvement in all newborns with ABO incompatibility after phototherapy and IVIG. One of four newborns with hTTP (Patient 3) improved after phototherapy, IVIG, antibiotics, and platelet transfusion without whole-blood exchange transfusion. The remaining three newborns with hTTP clinically improved only after whole-blood transfusion. Patients 3 and 4 with hTTP received platelet transfusions due to severe thrombocytopenia (19 h and 38 h after birth, respectively).

All four patients with hTTP had a clinical recurrence after the neonatal period. None of the newborns with ABO incompatibility

TABLE 1 Characteristics of patients with neonatal-onset hTTP

Patients	1	2	3	4
Sex	Girl	Girl	Boy	Boy
Ethnicity	Han Chinese	Han Chinese	Han Chinese	Han Chinese
Gestational age (weeks, +days)	38	38+2	39+4	40+5
Birth weight (g)	3130	2940	3000	3390
Age at diagnosis (months)	14	13	48	1 (30 days)
Clinical manifestations after birth	Jaundice, weakness	Jaundice	Jaundice, skin ecchymosis	Fever, jaundice, weakness, seizures
Patient blood group	O Rh+	B Rh+	O Rh+	O Rh+
Maternal blood group	O Rh+	O Rh+	A Rh+	O Rh+
DAT	Negative	Negative	Negative	Negative
IAT	Negative	Anti-B antibody ++	Negative	–
Peripheral red blood cell fragmentation	No	Yes	Yes	–
Family history	A brother died of severe jaundice and hemorrhage on the second day after birth	A sister died of hemolysis and thrombocytopenia on the second day after birth	No	No
Treatment	Phototherapy, IVIG, antibiotics, albumin transfusion, exchange transfusion	Phototherapy, IVIG, albumin transfusion, exchange transfusion	Phototherapy, IVIG, antibiotics, platelet transfusion	Phototherapy, IVIG, antibiotics, platelet transfusion, exchange transfusion
Age of first recurrence (months)	14	12	36	3

Abbreviations: –, not available; DAT, direct antiglobulin test; hTTP, hereditary thrombotic thrombocytopenia purpura; IAT, indirect antiglobulin test; IVIG, intravenous immunoglobulin.

had a recurrence. Patients 1 and 2 with hTTP had older siblings who had died on the second day after birth with manifestations consistent with hTTP, recorded as death from severe jaundice and hemorrhage in Patient 1's brother and death from hemolysis and thrombocytopenia in Patient 2's sister. There was no family history of infant sibling death in newborns with ABO incompatibility.

3.2 | ADAMTS-13 activity, inhibitor, and *ADAMTS-13* mutations in patients with hTTP

ADAMTS-13 activity was less than 5%, and the ADAMTS-13 inhibitor was negative in all four patients with hTTP. Genetic test results showed compound heterozygous *ADAMTS-13* gene mutations (Table 2). Of the eight *ADAMTS-13* gene mutations, c.330+1G>A and c.1335delC had been reported previously.[1,14]

TABLE 2 Gene mutations of four patients with neonatal-onset hTTP in the study

Patients	Nucleic acid changes	Amino acid changes	Source
1	c.2731+1G>A	Splicing	Mother
	c.2364-2365delGG	p.G788Gfs*56	Father
2	c.330 + 1G > A [a]	Splicing	Mother
	c.1564T>C	p.C522R	Father
3	c.623G>C	p.C2085	Mother
	c.1335delC[a]	p.F445Lfs*52	Father
4	c.3639-3640delTG	p.A1214Sfs*17	Mother
	c.2364-2365delGG	p.A789Pfs*55	Father

Abbreviation: hTTP, hereditary thrombotic thrombocytopenia purpura.
[a]Genetic mutation reported previously.

3.3 | Comparison of clinical characteristics in neonatal-onset hTTP and ABO incompatibility groups

3.3.1 | Jaundice

Jaundice occurred earlier in newborns with hTTP than in newborns with ABO incompatibility (Table 3; median difference, 57.0 h; 95% CI, 24.0–65.0). All patients with hTTP had jaundice within 24 h after birth. Newborns with hTTP had a higher bilirubin peak than newborns with ABO incompatibility (mean difference, 8.0 mg/dl; 95% CI, 3.8–12.1). Time to bilirubin peak was shorter in newborns with hTTP than in newborns with ABO incompatibility (38.5 ± 15.8 h vs. 74.0 ± 26.8 h; mean difference, 35.5 h; 95% CI, 6.4–64.6). All newborns had undergone phototherapy and received IVIG within 24 h of admission. After 24 h of treatment, TSB levels increased by 3.3 ± 3.8 mg/dL in the hTTP group but decreased by 4.0 ± 2.8 mg/dl in the ABO incompatibility group (mean difference, 7.3 mg/dl; 95% CI, 4.0–10.6). Figure 1 shows the temporal trends of TSB in the two groups, and Figure 2 shows the temporal trends of TSB and platelet counts after birth in each patient with hTTP.

3.3.2 | Complete blood counts

There were some differences in the complete blood counts between groups, especially in the early neonatal period (within 7 days of birth and before exchange transfusion) (Table 3). Anemia was more common in newborns with hTTP than in newborns with ABO incompatibility (odds ratio, 25.4; 95% CI, 1.2–551.6). The minimum level of hemoglobin within 7 days after birth was lower in newborns with hTTP than in newborns with ABO incompatibility (mean difference, 57.4 g/L; 95% CI, 31.2–83.7). Platelet counts were significantly lower in newborns with hTTP than in those with ABO incompatibility ($17 \pm 12 \times 10^9$/L vs. $291 \pm 76 \times 10^9$/L; mean difference, 274.4×10^9/L; 95% CI, 194.3×10^9/L to 354.4×10^9/L).

3.3.3 | Renal and liver function

There were higher levels of serum creatinine (median difference, 51.8 μmol/L; 95% CI, 16.0–109.4) and blood urea nitrogen (median difference, 5.7 mmol/L; 95% CI, 2.8–38.7) in newborns with hTTP than in newborns with ABO incompatibility, but there were no differences between the two groups for alanine aminotransferase, CRP, or albumin levels.

4 | DISCUSSION

This retrospective case series comparing the clinical course of newborns with hTTP and ABO incompatibility found earlier and more severe jaundice, earlier anemia, more severe thrombocytopenia, and negatively affected renal function in hTTP. To the best of our knowledge, this is the first study to compare neonatal-onset hTTP with ABO incompatibility.

Severe jaundice can occur soon after birth in newborns with either hTTP or ABO incompatibility,[1,2,15] but here we found earlier-onset jaundice in newborns with hTTP, all within 24 h, than in newborns with ABO incompatibility. Consistent with these findings, Tsujii et al.[16] reported a case of hTTP with jaundice at 6 h after birth, and Tanabe et al.[17] reported a case of jaundice 11 h after birth. Furthermore, we found that the jaundice was more severe in the hTTP group than in the ABO incompatibility group, prompting clinicians to provide exchange transfusion for severe jaundice in three of the four newborns with hTTP compared with none in the ABO incompatibility group. This is consistent with previous reports of patient with hTTP receiving exchange transfusion in the neonatal period,[1,2,18] while 4.8% of newborns with ABO-incompatibility requiring this treatment.[5,19] Different responses to phototherapy plus

TABLE 3 Comparison of laboratory test results between the hTTP group and the ABO incompatibility group

Characteristics	hTTP group ($n = 4$)	ABO incompatibility group (n = 20)	Effect size[a] (95% CI)	*p* value
Male sex	2	10		
Onset time of jaundice (h)	10.0 (5.0 to 13.0)	68.5 (18.0 to 82.0)	57.0[c] (24.0 to 65.0)	<0.001
TSBmax (mg/dl)	24.0 ± 6.3	16.0 ± 3.0	8.0[d] (3.8 to 12.1)	0.001
Time to TSBmax (h)	38.5 ± 15.8	74.0 ± 26.8	35.5[d] (6.4 to 64.6)	0.02
Response of TSB to treatment[b] (mg/dl)	3.3 ± 3.8	−4.0 ± 2.8	7.3[d] (4.0 to 10.6)	<0.001
Presence of anemia	4 (100%)	5 (25%)	25.4[e] (1.2 to 551.6)	0.01
Hemoglobin minimum (g/L)	105.7 ± 24.1	163.2 ± 22.9	57.4[d] (31.2 to 83.7)	<0.001
Platelet count minimum (10^9/L)	17 ± 12	291 ± 76	274.4[d] (194.3 to 354.4)	<0.001
WBC (10^9/L)	22.2 ± 7.9	20.0 ± 9.3	2.2[d] (−8.2 to 12.5)	0.67
CRP (mg/dl)	3.9 (0.5 to 18.5)	5 (1.0 to 28.0)	0.5[c] (−5.9 to 11.5)	0.79
ALT (U/L)	16.5 (6 to 21)	8.5 (6 to 19)	6.5[c] (−2.0 to 12.0)	0.18
Alb (g/L)	35.9 ± 2.6	34.6 ± 2.5	1.2[d] (−1.6 to 4.1)	0.37
Cr (μmol/L)	92.8 (58.0 to 149.4)	41.0 (28.0 to 75.0)	51.8[c] (16.0 to 109.4)	0.02
BUN (mmol/L)	8.2 (4.9 to 41.9)	2.5 (1.2 to 4.2)	5.7[c] (2.8 to 38.7)	<0.001
DAT				
Positive	0 (0%)	13 (65%)	0.1[e] (0.0 to 1.3)	0.07
Negative	4 (100%)	7 (35%)		

Abbreviations: −, not available; Alb, albumin; ALT, alanine aminotransferase; BUN, blood urea nitrogen; Cr, serum creatinine; CRP, C-reactive protein; DAT, direct antiglobulin test; hTTP, hereditary thrombotic thrombocytopenia purpura; TSB, total serum bilirubin; TSBmax, maximum levels of TSB; WBC, white blood cell count.

[a]We use absolute numbers for effect sizes.

[b]Change in TSB after the first 24-h treatment of phototherapy and IVIG.

[c]Median difference.

[d]Mean difference.

[e]Odds ratio.

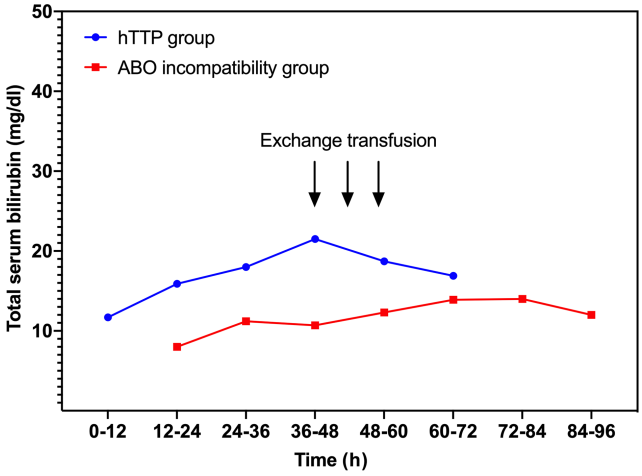

FIGURE 1 Temporal trend of total serum bilirubin (TSB) levels in newborns with hereditary thrombotic thrombocytopenia purpura (hTTP) and ABO incompatibility. The blue line represents the neonatal-onset hTTP group. The red line represents the ABO incompatibility group. Each point represents the mean levels of TSB during that period. The arrow respectively represents the start time of exchange transfusion for Patients 4, 2, and 1 from left to right (43, 48, and 59 h after birth, respectively).

IVIG in newborns with hTTP versus ABO incompatibility were also noted, with newborns with hTTP responding poorly to phototherapy and IVIG. The administration of exogenous ADAMTS-13 through plasma infusion during the exchange transfusion likely explains the good response to exchange transfusion of newborns with hTTP in this study.[20,21]

Hemolytic anemia is another feature of both hTTP and ABO incompatibility.[22] We found that anemia within 7 days after birth was more common in the hTTP group than in the ABO incompatibility group. This is similar to the findings of Fujimura et al.,[18] where 6 of 10 neonates with hTTP had anemia prior to exchange transfusion. Early anemia is uncommon in ABO incompatibility, which typically manifests with delayed anemia.[19] Therefore, early anemia may herald consideration of hTTP in neonates.

In this study, severe thrombocytopenia during the neonatal period was present in all patients with hTTP but in none of the newborns with ABO incompatibility. Thrombocytopenia has previously been described as a common feature in neonates with hTTP.[18,20] Thrombocytopenia can also occur in neonates with ABO incompatibility when additional factors such as severe infection, asphyxia, or intrauterine growth restriction are present.[23,24] Pediatricians should consider the possibility of hTTP in neonates when they have

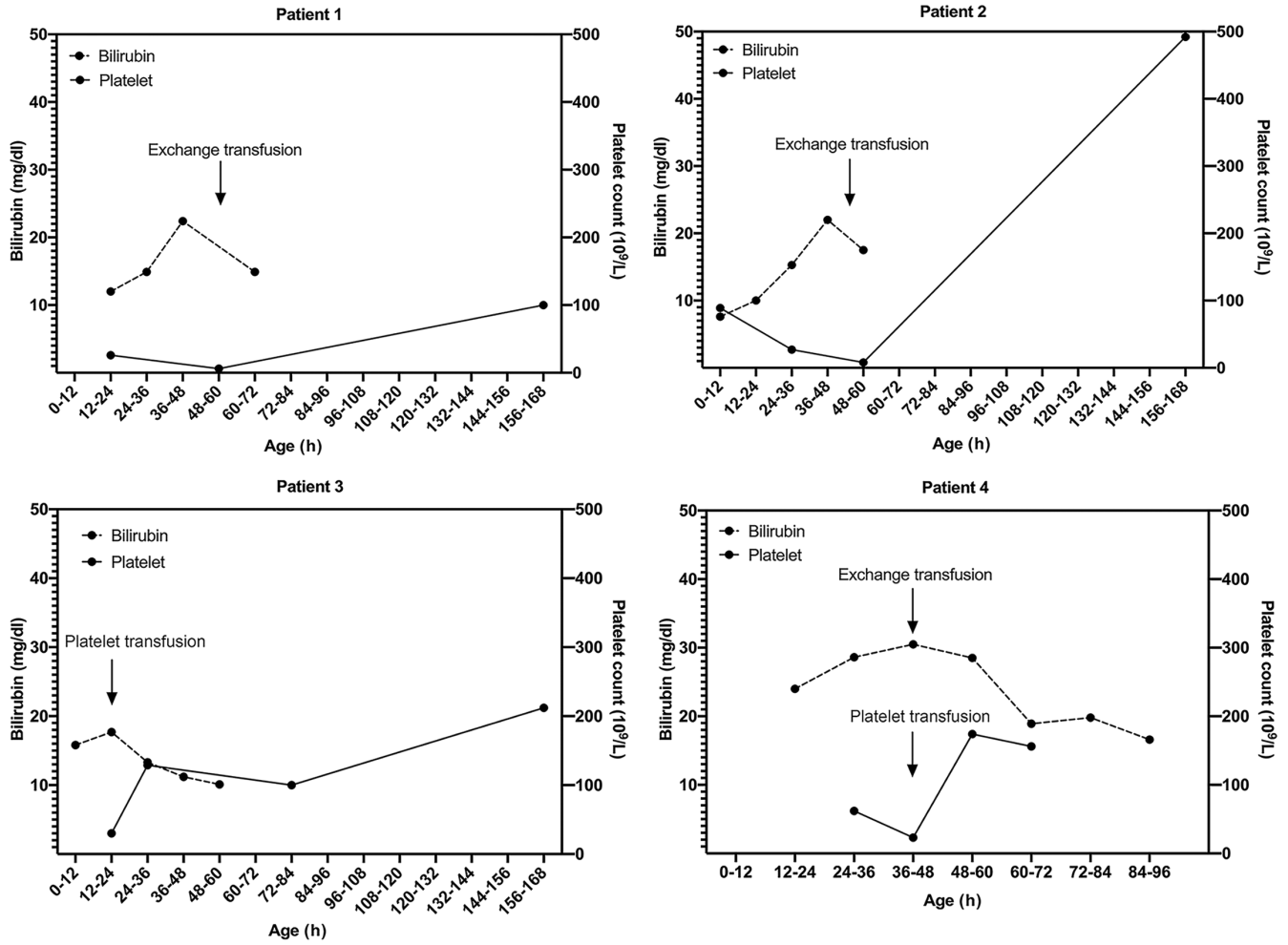

FIGURE 2 Temporal trend of total serum bilirubin and platelet levels in each patient with hereditary thrombotic thrombocytopenia purpura (hTTP). The arrow represents the time of exchange transfusion for Patients 1, 2, and 4, respectively (59, 48, and 43 h after birth, respectively) and the time of platelet transfusion for Patients 3 and 4 (19 and 38 h after birth, respectively).

thrombocytopenia after birth in the absence of severe infection, asphyxia, or intrauterine growth restriction. Thrombocytopenia is one of the common complications of exchange transfusion, with incidence ranging from 38% to 64%.[25,26] But in this study, thrombocytopenia was present in all newborns with hTTP before exchange transfusion, and the platelet count gradually returned to normal after the exchange transfusion. Therefore, considering the timing of thrombocytopenia around exchange transfusion is important in neonates with severe jaundice.

In this study, the mean levels of serum creatinine and blood urea nitrogen were higher in newborns with hTTP than in newborns with ABO incompatibility, but not high enough to meet criteria for neonatal acute kidney injury.[27,28]

hTTP may progress rapidly after birth and lead to death within hours of birth in severe cases.[29,30] In this study, two patients with hTTP had a sibling who likely died of manifestations of hTTP on the second day of life. Children with ABO incompatibility may also have a family history of neonatal jaundice, but the course is usually benign and without recurrence after the neonatal period.[31,32]

RhD incompatibility, another neonatal hemolytic disease occurring in Rh+ fetuses born to Rh− mothers, often presents with severe jaundice and anemia soon after birth, similar to hTTP. Only 0.45% of people in China are Rh−, and RhD incompatibility is estimated to affect 0.06% of newborns (10,825/16,700,000 in 2010),[33] which is far lower than the prevalence of ABO incompatibility. Pregnant patients who are Rh− in China with Rh+ partners typically receive Rh immunoglobulin, undergo regular monitoring of Rh antibody titers and fetal ultrasounds to facilitate the prenatal diagnosis of clinically relevant Rh incompatibility and to institute treatment if necessary. Newborns with Rh incompatibility may have manifestations before birth, such as fetal edema and ascites, while severe hemolysis in hTTP mainly manifests soon after birth, possibly triggered by (delayed) changes of the fetal circulation[18] or by events such as neonatal asphyxia and infection. The careful prenatal diagnosis procedure makes it easy to identify Rh hemolytic disease. Therefore, the careful care provided to those at risk of RhD-related hemolytic disease of the fetus and newborn has become extremely rare and is the reason why we chose not to compare hTTP to RhD incompatibility.

There are several limitations of this study that mostly relate to the small sample size. As hTTP is an extremely rare blood disorder, this limitation is challenging to overcome. Due to the small sample size and diminished statistical power, we were unable to conduct multiple analytical comparisons. Larger international registry–based studies are warranted.

5 | CONCLUSIONS

Severe jaundice requiring exchange transfusion soon after birth, early anemia, severe thrombocytopenia, and previous sibling death in the neonatal period from manifestations suggestive of hTTP are warning signs of possible neonatal-onset hTTP. Testing of ADAMTS-13 activity and genetics are required for diagnostic confirmation of hTTP and appropriate, potentially lifesaving, treatment.

AUTHOR CONTRIBUTIONS

Jing Liu carried out the initial analyses and drafted the initial manuscript; Yuelun Zhang checked the initial analyses, reviewed, and revised the manuscript; Juan Xiao designed the study and revised the manuscript; Zhuo Li and Lejia Zhang supervised data collection and critically reviewed the manuscript for important intellectual content; Zhenghong Li, Shan Jian, Changyan Wang, Lijuan Gou, and Xiaoyan Tang provided clinical care to patients and coauthored the paper; Yuqing Song and Zichao Lv coordinated and supervised data collection and provided statistical support.

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RELATIONSHIP DISCLOSURE

The authors declare no conflicts of interest.

ETHICAL APPROVAL

Ethical approval was obtained from the Peking Union Medical College Hospital Institutional Review Board (reference number: S-K1978).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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