Clinical and subclinical features and results of treatment of neonatal unconjugated hyperbilirubinemia jaundice due to maternal child blood group incompatibility at Haiphong Children's Hospital from 2017 to 2022

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ABSTRACT

Objectives. The study was done to describe clinical and subclinical features and results of treatment of neonatal unconjugated hyperbilirubinemia due to maternal child blood group incompatibility at Haiphong Children's Hospital from 2017 to 2022. **Subjects and Methods.** Subjects included 51 infants with UHBJ due to maternal-child blood group incompatibility. The method was a case-series report. **Results and Conclusions**. The male/female ratio was approximately 1:1. The majority of patients were normal newborns. A history of having a sibling with neonatal jaundice accounted for a low rate. Most of the cases with jaundice occurred 24 hours after birth, the cases occurring 72 hours after birth accounted for a low rate. Jaundice in zones 3 and 5 accounted for the highest rate. ABO incompatibility accounted for 78.4%, and Rh was 22.6%. Which OA form accounted for 45.1%, and the OB form was 33.3%. The average concentration of UB on admission was about 23.27± 5.72 mg%. After 24 h of PT, the average UB reduced by 5.82± 1.3 mg%. At the end of PT, the average UB was very low: 8.12± 3.89 mg% (The average UB reduced by 60% compared to that before the PT). Exchange transfusion reduced 50% UB right after ET (from 28.12± 4.83 mg% to 13.02± 5.9 mg%). After 48 h of ET, the average UB reduced to 10.6± 4.28 mg%, and after 72 h, it decreased to a very low level 9.1± 3.21 mg%. 84.3% of patients recovered, 5.9% were referred to higher hospitals. The average hospitalization time was 6.47± 2.76 (days).

Keywords: Unconjugated hyperbilirubinemia Jaundice, kernicterus, phototherapy, exchange transfusion

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INTRODUCTION

Unconjugated hyperbilirubinemia Jaundice (UHBJ) is a common neonatal phenomenon that may account for up to 85% of live births, due to the particularity of the infants' bilirubin metabolism in the first few days of life. Of these, approximately 12% may develop kernicterus which can be fatal or leave severe neurological sequels affecting the physical, mental, and motor development of children [1]. The rate of newborns with pathological UHBJ in European countries and the United States accounts for 4-5% of the total number of

newborns and in Asia, it is about 14-16% [2]. According to the study of Wong in 2013 in Malaysia, the neonatal rate of pathological UHBJ was 16.4% [3]. In Vietnam, in a study by Tran Lien Anh in 2002 at the Vietnam National Pediatrics Hospital, among newborns who must be hospitalized, 17.9% had UHBJ. Among them, 28.8% required ET and 61.2% had neurological damage [4]. Another study done in this hospital by Khu Thi Khanh Dung in 2007, showed that the rate of UHBJ was 21.26% among the total number of newborns hospitalized for treatment [5]. At Children's Hospital in Ho Chi Minh City, the complications of nuclear jaundice tended to increase, with 170/550 cases of severe jaundice requiring ET [6].

At Haiphong Children's Hospital, UHBJ is a common disease and tends to increase. According to the statistics of Nguyen Thi Thanh, Dang Van Chuc, and Le Thi Minh Luyen, the rate of UHBJ increased from 12.8% in 2005 to 25.3% in 2006 [7]. UHBJ due to maternal-child blood group incompatibility is the most common cause among infants. However, there have not been any studies about clinical, and subclinical features and results of treatment of UHBJ due to this cause. Therefore, we conduct research on this topic: "Clinical and subclinical features and results of treatment of neonatal unconjugated hyperbilirubinemia jaundice due to maternal child blood group incompatibility at Haiphong Children's Hospital from 2017 to 2022" aims at the following objectives:

1. To describe clinical, and subclinical features and results of treatment of neonatal unconjugated hyperbilirubinemia due to maternal-child blood group incompatibility at Haiphong Children's Hospital from 2017 to 2022.

2. To comment on the results of treatment of the above patients

POPULATION AND METHODS

Subjects, research site, and time

Criteria for patients' selection

Newborns diagnosed with UHBJ due to maternal child blood group incompatibility were treated at Haiphong Children's Hospital from 2017 to 2022.

Evidence for neonatal UHBJ:

+ Early jaundice after birth or within 24 hours after birth

+ Bright yellow skin and rapidly increasing

+ Splenomegaly (±), not palpable liver

+ The concentration of UB above the physiological level recommended by the American Academy of Pediatrics (>5mg% in preterm, and >7 mg% in term)

ABO incompatibility is defined as maternal blood group O and child blood group A, B, or AB. Rh incompatibility is defined as maternal blood group Rh (+) and child blood group Rh (-).

Maternal serum resistant to fetus red blood cell (+)

The family agreed to participate in the study.

Exclusion criteria

Conjugated hyperbilirubinemia jaundice

Having severe and clear nuclear jaundice

Having congenital malformations such as cardiovascular, digestive, neurological malformations and some metabolic disorder diseases.

Research site and time

Research site: Neonate Department and Intensive Unit Care of Haiphong Children Hospital.

Research time: from 6/2022 to 1/2023.

Method

Study design

It was a case series report using retrospective and prospective data.

Sample size and sampling process

Sample size: all patients met the inclusion criteria

Sampling process: The sample size was selected according to the convenient method. We already selected 51 cases with all inclusion criteria.

Indices and variables regarding objectives

Clinical and subclinical features of jaundice

* Some information of study subjects

- Sex: boys, girls

- Premature /term

- History of having a sibling with UHBJ in the neonatal period

* Clinical features

- Time for beginning jaundice

- Icteric Zones (According to Cremer, there are 5 zones)

Zone 1: head and face.

Zone 2: Zone 1 and body upper umbilical Zone.

Zone 3: Zone 1 + Zone 2 and body inferior umbilical Zone to pubis bone.

Zone 4: Zone 1 + Zone 2 + Zone 3 and to ankle Zones of foot and hand.

Zone 5: whole body.

- Icteric Zones by hospitalization time

* Subclinical features

- Average red blood cell count, Hb, and Hct

- ABO and Rh incompatibility

- Average UB according to preterm and term baby

Comment on results of treatment

- Results of treatment: recovery, referral, asking for going home, death.

- Average hospitalization days.

- Average UB before and after PT at different points

- Average UB before and after ET at different points

Information collection

For retrospective data, we studied thoroughly medical records of patients with neonatal UHBJ due to maternal-child blood type incompatibility collected the necessary information, and filled out the questionnaire already designed

For prospective patients, we participated in asking, examining, doing tests, commenting on the results, and collecting information into predesigned medical records as mentioned above.

Data analysis

Entering and analyzing by using SPSS 22.0.

Computing percentage, comparing 2 percentages by $\chi 2$ test, there will be a significant difference if p value is less than 0.05.

Comparing 2 means by using T test, if p is less than 0.05, there will be a significant difference.

Comparing 2 means before and after treatment using Paired samples T test. The significant difference is when p value is less than 0.05.

RESULTS

Clinical and subclinical results

Some characteristics of research subjects

Table 3.1. Distribution of subjects according to sex

Sex	Number (n)	Percentage (%)
Boys	23	45.1
Girls	28	54.9
Total	51	100

Table 3.1 showed that unconjugated jaundice affected more girls than boys (54.9% versus 45.1%).

Table 3.2. Distribution of subjects according to gestational age

Gestational age	Number (n)	Percentage (%)
Term	44	86.3
Preterm	7	13.7
Total	51	100

Table 3.2 showed that unconjugated jaundice affected more term (86.3%) than preterm (13.7%).

Table 3.3. *History of having a sibling with unconjugated jaundice during the neonatal period*

History of having a sibling with UBHJ during the neonatal period	Number (n)	Percentage (%)
Yes	6	11.8
No	45	88.2
Total	51	100

According to table 3.3. 11.8% of patients had a sibling with UBHJ during the neonatal period.

Clinical features

Table 3.4*. Time beginning jaundice*

Time beginning jaundice after birth (h)	Number (n)	Percentage (%)
< 24	30	58.8
24-72	18	35.3
>72	3	5.9
Total	51	100

Table 3.4. showed that 58.8% of patients whose UBHJ occurred 24 h before birth, among 35.3% of patients, UBHJ occurred 24-72 h after birth, and the rest (5.9%) occurred 72h after birth.

Table 3.5. *Icteric Zones*

Yellow zone	Number (n)	Percentage (%)
Zone 1	3	5.9
Zone 2	8	15.7
Zone 3	17	33.3
Zone 4	9	17.6
Zone 5	14	27.5

Total	51	100

Table 3.4 revealed icteric zone 3 accounted for the highest rate 33.3%, then zone 5 27.5%, zone 2 and 4 were 15.7%, and 17.6% respectively, and the lowest rate of zone 1 was 5.9%.

Table 3.6. *Distribution of icteric zone according to time beginning jaundice*

Time beginning jaundice (h)	**Icteric zones**	**Number (n)**	**Percentage (%)**
<24	Zone 1	5	16.7
	Zone 2	6	20.0
	Zone 3	9	30.0
	Zone 4	2	6.7
	Zone 5	8	26.7
24-72	Zone 1	0	0.0
	Zone 2	2	11.1
	Zone 3	4	22.2
	Zone 4	7	38.9
	Zone 5	5	27,8
>72	Zone 1	0	0.0
	Zone 2	1	33.3
	Zone 3	1	33.3
	Zone 4	0	0.0
	Zone 5	1	33.3

Table 3.6 revealed that early jaundice at zone 3 accounted for 30.0%, zone 5 26.7%, zone 2 20.0%, zone 1 16.7%, zone 4 6.6%. In the 24-72 h group when jaundice began was the highest rate 38.9%, in zone 4, then zone 5 was 27.8%, zone 3 was 22.2%, zone 2 11.1%, and there was no icteric zone 1. In the group when the time beginning jaundice was more than 72 h, the rate of jaundice at zones 2, 3, and 5 were similar to each other about 33.3%. There were no icteric zones 1 and 4.

Subclinical features

Table 3.7*. Distribution of unconjugated hyperbilirubinemia jaundice patients according to ABO and Rh incompatibility*

		Number (n)	**Percentage (%)**
ABO system	OA	23	**45.1**
	OB	17	33.3
	OAB	0	0.0
Rh (-) system		11	21.6
Total		51	100

Table 3.7 showed that ABO incompatibility accounted for 78.4%, in which OA incompatibility was 45.1%; OB incompatibility was 33.3%; there was no OAB incompatibility. Rh incompatibility accounted for 21.6%.

Table 3.8. *Results of blood cell count, Hb, and Het*

Indicators	Number (n)	Mean	SD
HC (T/l)	51	3.8	0.9
Hb (g/l)	51	135.8	27.2
Hct (%)	51	38.5	9.6

Table 3.8 shows that the average red count blood cell count, Hb, and Hct were in normal values.

Table 3.9*. Average unconjugated bilirubinemia according to gestational age on admission.*

Average UB on admission (mg%) / Gestational age	Number (n)	Mean	SD	t, p
Preterm	7	27.09	5.85	3.957
Term	44	22.66	5.52	0.0045
Total	51	23.27	5.72	

Table 3.9 manifested that average UB by gestational age was significantly different with t= 3.957 and p<0.05.

Results of treatment

Table 3.10. Evolution of unconjugated bilirubinemia before and different points after phototherapy

Unconjugated bilirubinemia	Before PT (n=31)	24 hours after PT (n=31)	48 h after PT (n=31)	72 h after PT (n=31)
Average UB (mg%)	20.09	14.27	11.66	8.12
SD	3.62	4.92	3.84	3.89
The number of mg% UB reduced		5.82± 1.3		
p		0001		
The number of mg% UB reduced			2,.1± 1.08	
p			0.006	
The number of mg% UB reduced				3.54± 0.05
p				0.001

Table 3.10 showed that the average UB before PT was 20.09± 3.62 (mg%), 24 hours after PT average UB was 14.27± 4.92 (mg%) which reduced 5.82± 1.3 (mg%) (p<0.05). The average UB after 48 h PT was 11.66± 3.84 (mg%) p<0.05). The average UB 72 h after PT was 8.12± 3.89 (mg%), reduced by 3.54± 0.05 (mg%) compared to that after 48 h of PT (p<0.05).

Table 3.11. *Evolution of unconjugated bilirubinemia before and hours after exchange transfusion*

	Before ET (n=20)	**Right after ET (n=20)**	**24 h after ET (n=17)**	**48 h after ET (n=17)**	**72 h after ET (n=17)**
Average UB (mg%)	28.19	13.02	19.2	10.6	9.1
SD	4.83	5.9	3.72	4.28	3.21
p		0.002			
			0.001		
				0.001	
					0.006

Table 3.11 showed that the average UB before ET was 28.19 ± 4.83 (mg%), and right after ET, the average UB was 13.02 ± 5.9 (mg%) (p<0,05). The average UB after 24 h of ET was 19.2± 3.72 (mg%) higher than that of the average UB level after the ET (p<0.05). The average UB 48 h after ET was 10.6± 4.28 (mg%) (p<0.05). The average UB 72 h after ET was 9.1± 3.21 (mg%) (p<0.05).

Table 3.12. *Results of treatment*

Discharge from the hospital	**Number (n)**	**Percentage (%)**
Recovery	43	84.3
Transfer to a higher hospital	3	5.9
Asking for going home	5	9.8
Death	0	0.0
Total	51	100

Table 3.12. showed that patients recovered accounted for 84.3%, patients transferring to a higher level were 5.9%, patients asking to go home accounted for 9.8%, and there was no death.

Table 3.13. *Average hospitalization time according to gestational age*

Average hospitalization time (day) / **Gestational age**	**Number (n)**	**Mean**	**SD**	**t, p**
Preterm	7	6.68	3.93	0.396
Terms	44	6.41	2.58	0.178
Total	51	6.47	2.76	

Table 3.13 revealed that the average hospitalization time for preterm were similar to that of terms (p>0.05).

DISCUSSIONS

Clinical and subclinical features

Some characteristics of research subjects

Table 3.1 showed that among 51 patients with UHBJ due to maternal-child blood group incompatibility, boys accounted for 45.1% while girls accounted for 54.9%. This result was similar to that of Ngo Minh Xuan [8], and Ling Duan [9]. However, a study by Korejor HB in Karachi- Pakistan on 100 newborns with jaundice showed that the male/female ratio was 1.6/1 [10]. Up to now, there have been no studies that clearly explain the association of jaundice and sex in infants.

Table 3.2 revealed that term infants accounted for 86.3% while preterm infants were 13.7%. This result was similar to that of Tran Thị Hai Van [11] and Hoang Thi Lan [12]. According to a study by Ibrahim Qattea on newborns with jaundice in the United States, term infants accounted for 91.8% and preterm infants accounted for 8.2% [13]. According to Table 3.3, 11.8% of patients had a history of having a sibling with jaundice in the neonatal period.

Clinical features

Time beginning jaundice

Our results showed that 58.8% of patients had jaundice before 24 hours after birth, 35.3% had jaundice between 24 and 72 hours, and 5.9% had jaundice after 72 hours (table 3.4). According to Dang Van Chuc, the causes of early jaundice in infants were hemolytic or severely infective. Among hemolytic causes, ABO blood group incompatibility ranks first [7]. Our result was similar to that of Tran Thi Hai Van: the majority of infants with jaundice began 72 hours after birth [11]. According to Dang Van Chuc, up to 34% of infants showed early jaundice before 24 h and most of them appeared from the 3rd and 7th day, accounting for 59.5% [7]. The reason for the difference in the results of this study may be that the cause of our jaundice is simply hemolysis due to maternal-child blood group incompatibility, while the author studied many groups of causes of jaundice, so the time to appear jaundice will be different. Among 51 infants with UHBJ due to maternal-child blood group incompatibility, 78.4% belonged to ABO blood group incompatibility (table 3.7). In which, OA form was 45.1%, OB form was 33.3%. Early jaundice usually had bilirubinemia increase speed by more than 0.5mg%/h which may lead to nuclear jaundice.

Clinical Icteric Severity

Table 3.5 shows that on admission, there were 27.5% of patients with jaundice in Zone 5, 17.6% in Zone 4, and 33.3% in Zone 3. In other words, upon admission, bilirubin levels are above the threshold that requires treatment. When jaundice in zone 5, it corresponds to generalized jaundice, the bilirubin level is higher than 15 mg%, and the risk of nuclear jaundice occurring in these patients is very high. According to Nelson, at any time during the first 3 days after birth, if UB is more than 15mg% (clinical icteric zone 5-generalized jaundice), we must prepare the necessary conditions required for an ET.

Table 3.6 showed that before 24 h, early jaundice in zone 3 accounted for 30%, zone 5 accounted for 26.7%, zone 2 accounted for 20%, zone 1 accounted for 16.7%, and zone 4 accounted for 6.6%. In the group of onsets of jaundice within 24 and 72 h, zone 4 jaundice accounted for 38.9%, then zone 5 accounted for 27.8%, zone 3 accounted for 22.2%, zone 2 accounted for 11.1%, and

there was no zone 1. In the group of onsets of jaundice after 72 h, the rate of jaundice in zone 2, zone 3, and zone 5 was the same, accounting for 33,3%. There was no jaundice in zones 1 and 4. This result was similar to that of Bui Thi Thuy Duong and Dao Minh Tuyet [14]. According to the authors, on admission, there was mainly jaundice in zones 3, 4, and 5.

Clinical features

Rate of ABO and Rh incompatibility

Table 3.7 showed that among 51 jaundiced infants due to maternal child blood group incompatibility, 78.4% were ABO incompatibility and 22.6% were Rh one. Among them, the OA type accounted for 45.1%, the OB type accounted for 33.3%, and there was no OAB type. According to Chitty et al in 2013, Rh incompatibility was 71% and ABO incompatibility was 18% [15]. In a study by Gamaleldin in 2010 in Cairo, Egypt on 249 neonates with UHBJ, ABO incompatibility accounted for 23.7% and Rh incompatibility was 8.8% [16]. In research by Emal Okulu, Omer Erdeve et al on 80 jaundiced infants with UHBJ, ABO incompatibility accounted for 44.4%, and Rh incompatibility was 40.5% [17]. According to a study by David Sock about the distribution of the ABO blood group system on 34 jaundiced infants due to maternal-child blood group incompatibility in Yaoudé, Cameroon, A blood type accounted for the highest rate than B blood type accounted for 32.35% and AB accounted for 8.82% [18].

Result of a complete blood count

Table 3.8 shows that the average red blood cell count was 3.8 ± 0.9 T/l; the average Hb was 135.8 ± 27.2 g/l, and the average Hct was 35.8± 9.6 L/l. The result showed that the CBC values were mostly within the normal range. The results of this study were consistent with the comments of Dang Van Chuc in infants with jaundice who often have no anemia or only mild anemia. [7].

Average unconjugated bilirubinemia on admission

Table 3.9 showed that the average UB was 23.27± 5.72 mg%, in the preterm group, it was 27.09 ± 5,85 mg% higher than that of the full-term group 22.66 ± 5.52 mg% and the difference was statistically significant.

Our results were consistent with Khu Thi Khanh Dung 25.8 ± 9.2 mg% [5] and Emel Okulu 24.9 ± 9.1 mg% [17]. However, according to a study by Olufunmilola Olubisi Abolurin et al for 2 years in Nigeria manifested the average UB was 17.9 ± 6.3 mg% [19]. A study by Dao Minh Tuyet showed that the average unconjugated on admission was 17.1 ± 3.2 mg% [14]. The difference may be due to the different research objectives of authors and the criteria for selecting research subjects are different.

Comment on results of treatment

Results of phototherapy

Table 3.10 shows the average UB before PT, 24 h, 48 h, and 72 h after PT. The average UB before PT was 20.09± 3.62 mg%, 24 h after PT, this level decreased by 14.27 mg%, down 5.82± 1,3 mg% compared to before PT and this reduction was statistically significant ($p<0.05$). 48 h after PT, average UB reduced 11.66 ± 3.84 mg% (down 2.61± 1.08 mg% compared to 24 h before PT and $p<0.05$). After 72 h, average UB decreased to 8.12± 3,89 mg%, this level was statistically and significantly lower than that of 48 h after PT($p<0.05$). Thus, after PT, the average UB reduced by 3/5 compared to the level before PT.

According to this result, after 24 h PT, the average UB reduced to 14.72 ± 4.92 mg%,

with this UB, it was no longer a threat to the infant. By the end of PT (the infant was discharged from the hospital), the average UB was very low (8.12mg% ± 3.89 mg%), a safe threshold for the infants. According to a study by Khu Thi Khanh Dung [5] the average UB level after 12 of light exposure was 21.8± 6.4 mg%, after 24 h 20.7± 5.4 mg%, after 48 h: 18.1± 4.2 mg%, after 72 h 16.9± 4.1 mg%. The evolution of UB of Khu Thi Khanh Dung during PT was similar to our results. However, according to Muhammad Abdullah Nizam, the UB level decreased significantly after 24 h of PT to 6.35± 1.2 mg%, after 48 h, the average UB decreased to a very low level, even without needing to be re-quantified after 72 h of PT [20].

Result of exchange transfusion

Table 3.11 showed that the average UB was 28.19± 4.83 mg% and right after the ET was 13.02± 5.9 mg%. Thus, the average UB immediately after the ET decreased by more than half compared to before the ET and the change was statistically significant with $p<0.05$. However, after 24 h of ET, the average UB level was higher than that immediately after the ET but still lower than the average UB level before the ET. A study by Brinda Kakkar, Soma Agrawal et al on 14 infants with UHBJ in India who received ET showed that a total of 5912 ml blood was transfused (average 422 ml/infant). After the ET, the average UB reduced significantly, 46% lower than before ET [21]. A study by Min-Sun Kim, Heung-Bum Oh et al on 23 infants with UHBJ in Korea (among them, 2 infants need more than 2 times of ET) showed that the average UB level decreased by about 30% right after the ET and this concentration decreased gradually after 48 h and had very low value when the infant discharged from the hospital [22].

Final results of treatment

Table 3.12 shows that 84.3% of infants recovered, 5.9% were referred to higher hospitals, 9.8% asked to go home, and there was no death. A study by Olufunmilola Olubisi Abolurin in Nigeria showed that 97.2% recovered, and 2.8% died (1 infant died while preparing for ET) [19]. According to Tran Lien Anh, 1.96% of infants (3/145) have died during the treatment. Death during treatment may be due to the infant having severe jaundice with complications or due to other diseases associated with the collapse of the circulatory, respiratory, and nervous systems.

Table 3.13 shows that the average hospitalization time was 6.47± 2.76 (day) and the average hospitalization time in term infants did not differ from the average hospitalization time of preterm infants. After the treatment, jaundice severity reduced rapidly. When discharged from the hospital, most infants had no longer jaundice or mild jaundice.

CONCLUSIONS

Clinical and subclinical features

Clinical features

The male/female ratio was approximately 1:1. The majority of patients were normal newborns. A history of having a sibling with neonatal jaundice accounts for a low rate.

Most cases with jaundice occurred 24 hours after birth, the cases occurring after birth 72 hours accounted for a low rate. Jaundice in zones 3 and 5 accounted for the highest rate.

Subclinical features

ABO incompatibility accounted for 78.4%, and Rh was 22.6%. Which OA form accounted for 45.1%, OB form was 33.3%.

The concentration of UB on admission was about 23.27± 5.72 mg%.

Results of treatment

After 24 hours of PT, the average UB was reduced by 5.82± 1.3 mg%. At the end of PT, the average UB was very low: 8.12± 3.89 mg% (The average UB reduced by 60% compared to that before the PT). ET reduced 50% UB right after ET (from 28.12± 4.83 mg% to 13.02± 5.9 mg%). After 48 h of ET, the average UB reduced to 10.6± 4.28 mg% and after 72 h, it decreased to very low to 9.1± 3.21 mg%. 84.3% of patients recovered from the disease, and 5.9% were referred to a higher level. The average hospitalized time was 6.47± 2.76 (days).

ABBREVIATION

UHB: Unconjugated hyperbilirubinemia

UB: Unconjugated bilirubinemia

UHBJ: Unconjugated hyperbilirubinemia Jaundice

PT: Phototherapy

ET: Exchange transfusion

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