Survey of the incidence of ABO haemolytic disease of the newborn in one institution in northern China

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Abstract

Background: Haemolytic disease of the newborn is often secondary to ABO incompatibility, the routine practice of early discharge of newborns leads to a higher occurrence rate for hyperbilirubinemia. We aim to compare the probability of ABO incompatibility and the prevalence of ABO haemolytic disease of the newborn (ABO HDN) and investigate the clinical characteristics of ABO HDN to identify risk factor for ABO HDN. Procedure: The blood type of 85 590 blood donors and the inpatient medical records of 471 ABO HDN were analysed retrospectively. Results: The possibility of a blood group O woman giving birth to a non-group-O infant should be 13.28%; however, only 6.03% of newborns had ABO HDN. 49.46% of total ABO HDN newborns developed disease due to anti-A antibody and 50.54%, due to anti-B. No significant difference was found in group A and B newborns in haemoglobin and peak total serum bilirubin (TSB) levels, but lower haemoglobin values were observed in ABO HDN infants with a positive direct anti-globulin test (DAT). Furthermore, the correlation coefficient between the postnatal age of admission and peak TSB levels was 0.54. When severe hyperbilirubinemia developed, the peak TSB levels increased gradually with the increase in postnatal age of admission. Conclusion: For ABO-incompatible mother-infant pairs, timely monitoring is advised, since early hospitalization and appropriate interventions, if necessary, can reduce the risk of severe hyperbilirubinemia, especially for DAT-positive newborns.

Introduction

Haemolytic disease of the foetus and newborn(HDFN) due to maternofoetal blood group incompatibility was once a significant factor in perinatal morbidity and mortality [1]. However, the widespread adoption of antenatal and postpartum use of Rh immune globulin in most western countries has resulted in a decrease in the incidence of Rh(D) alloimmunization [1, 2]. ABO incompatibility has become the most common cause of haemolytic disease of the newborn (HDN) [3].

HDN is an immune-mediated haemolytic disease, almost exclusively limited to ABO neonates with blood groups A or B delivered by women with group O. ABO-incompatible newborns with haemolytic disease are at risk for various degrees of anaemia and subsequent hyperbilirubinemia caused by immune-induced haemolysis [4]. Toxic bilirubin can occasionally cross the immature neonatal blood-brain barrier, resulting in kernicterus and subsequent life-long disabilities such as hearing impairment [5]. In a previous study, approximately one-third of ABO-incompatible newborns had significant hyperbilirubinemia and required phototherapy [6]. Phototherapy provided by modern equipment has been proven to be effective by decreasing the need for exchange transfusion (ET) in the treatment of hyperbilirubinemia [5]. However, severe subjects with dramatic haemolysis and hyperbilirubinemia, which require ET, have also been reported in clinical studies [7, 8]. In addition, the routine practice of early discharge of newborns at postnatal <48 hours lead to a higher readmission rate for hyperbilirubinemia within 14 days of birth and brings extra unnecessary expense [9, 10]. Among the identified causes of hyperbilirubinemia, ABO incompatibility was the most common [11].

ABO incompatibility cannot always be avoided, but the severity of ABO incompatibility in neonates varies greatly from region to region. Italian mothers experience a major ABO incompatibility with their newborns at a rate of approximately 11%, but haemolytic disease occurs in only 2.5% of births [12]. Both ratios are higher in Blacks, with the former farther than the latter [13]. Meanwhile other studies show that Asians have an increased likelihood of extreme neonatal hyperbilirubinemia and hospital readmission rates due to jaundice [9, 14]. However, the circumstance of ABO incompatibility remains unknown in northern China.

Our objective was to estimate the frequency of ABO incompatibility among infants, survey the incidence of haemolytic disease due to ABO incompatibility, compare the risk of haemolysis and jaundice between O-A/B and DAT-pos/neg subgroups, and assess the proportion of neonates developing ABO-incompatible haemolysis with neonatal severe hyperbilirubinemia in a single institution.

Methods

The probability of ABO incompatibility

A total of 85 590 blood donors in Qingdao, Shandong Province were recruited from the Affiliated Hospital of Qingdao University between May 2018 and November 2019. EDTA-anti-coagulated peripheral blood samples were obtained from all enrolled participants, and standard serological typing methods were used to test their blood types for ABO antigens and antibodies. All participants were negative for irregular antibodies. This study protocol was approved by the ethics committee of the Affiliated Hospital of Qingdao University.

According to Akanmu. A.S. et al. [13], the ABO blood-group gene frequencies of the population are calculated using data for the prevalence of blood group phenotype obtained from ABO typing of blood donors based on the Hardy-Weinberg equilibrium. Further, the occurrence rates of OO and non-OO (AA, BB, AO, and BO) blood type genotypes in the population were obtained. The possibility of ABO incompatibility is the sum of the product of the probability that the father of blood group genotypes is non-OO combined with the probability that the mother is OO.

The prevalence of ABO-HDN

We carried out screening on 7 513 mothers and 7 810 newborns between November 2016 and April 2020. Hospitalization information was collated from all neonates diagnosed with "ABO haemolytic disease of the newborn" (including "ABO haemolytic jaundice" and/or "ABO haemolytic anaemia"), including maternal blood group, gestation at delivery, mode of delivery, the infant's sex and birth weight, date of birth, time of admission, blood type, direct anti-globulin test (DAT), indirect anti-globulin test (IAT), eluate test, peak total serum bilirubin (TSB, μmol/L), haemoglobin (Hb, g/L), and treatment measures. All maternal blood groups, including Rh and irregular antibody screens, were tested at least once during pregnancy.

Neonates were assessed for blood type and subjected to DAT, IAT, and the eluate test if the newborn ABO was incompatible with that of the mother and the newborn developed neonatal jaundice simultaneously. Once the eluate test was positive and clinically significant jaundice occurred, infants were continuously monitored in an inpatient setting, whereas those who did not develop clinically significant jaundice were evaluated as outpatients. TSB and Hb were tested anytime when visual assessment and transcutaneous bilirubin were abnormal during hospitalization. "ABO haemolytic jaundice" was defined when the eluate test was positive and the infant developed clinically significant jaundice, which was judged as any single total bilirubin result above the newborn infant 35 or more weeks of gestation phototherapy treatment threshold on charts from the American Academy of Paediatrics on Neonatal Jaundice [15]. "ABO haemolytic anaemia" was defined as eluate test positive and Hb [?] 145 g/L.

DAT and IAT tests were performed routinely at the blood bank of the Affiliated Hospital of Qingdao University on umbilical cord blood with an agglutination technique. The eluate test was performed by the heat dispersion method to remove RBC-bound antibodies. EDTA-anti-coagulated peripheral whole blood was centrifuged at 1 760 ×g for 5 min, drawing at least 2 ml of erythrocytes with a pipette tip for testing. After six washes of erythrocytes with 0.9% normal saline, the last release solution was used as the negative control. An equal volume of saline was added, and samples were incubated with shaking in a 56°C water

bath for ten minutes. Samples were next centrifuged at 1 000 ×g for three minutes, immediately followed by transferring the supernatant red emission solution to the other three test tubes. One drop of A, B, and O RBC reagent (Changchun Boxun Biotechnology, Changchun, China) was added to the test tube, after which the samples were centrifuged and observed. Agglutination indicated that the RBC was attached to the corresponding antibodies and the eluate test was regarded as positive.

Statistics

Statistical analysis was performed using the Statistical Package for the Social Sciences version 26.0 software (SPSS Inc., Chicago, IL, USA). The chi-square or Fisher's exact tests for categorical variables were used. The Shapiro–Wilk test was used to test the distribution of normality. The differences between groups were analysed using Student's t-test or the Mann–Whitney U test when only two groups were compared, or by the Kruskal-Wallis H test when more than two groups were compared. If there was a significant difference between multiple groups, the Bonferroni correction for post hoc multiple comparisons was used. Correlations between variables were analysed using the Spearman correlation test. P-values < 0.05 (two-sided) were considered statistically significant.

Results

The probability of ABO incompatibility

The blood group phenotypes were used to calculate ABO gene frequencies of 85 590 blood donors. The prevalence of blood group B (31.44%) was slightly higher than that of blood groups A (29.05%) and O (28.54%), and the distribution characteristics were B > A > O > AB in the Affiliated Hospital of Qingdao University in northern China (Fig. 1).

The probabilities of genes A, B, and O were 0.2253, 0.2409, and 0.5338, derived from the population frequencies of ABO blood group phenotypes in the recruited blood donors at the Affiliated Hospital of Qingdao University (the detailed calculation procedure is shown in Supplementary Information A).

The probability of a blood group O woman giving birth to an infant who was non-group-O was predicted to be 13.28% at the Affiliated Hospital of Qingdao University in northern China (the detailed calculation procedure shown in Supplementary Information B).

The prevalence of ABO-HDN

From November 2016 to April 2020, 471 (6.03%) infants from 7 810 live births were confirmed to have ABO haemolytic disease. Among them, 46.50% (219/471) infants were male, 8.07% (38/471) were premature, 4.88% (23/471) weighed less than 2 500 g and 45.44% (214/471) were first-borns. Of newborns, 42.04% (198/471) were admitted with jaundice occurring in <24 hours and the median postnatal age of admission (days) was two (interquartile range (IQR) was one-three days; 15 neonates were re-admitted, with a median age at re-admission of 10 days, and IQR of 8-12 days). The baseline demographic characteristics of the newborns with ABO HDN are presented in Table 1. Moreover, two neonates were diagnosed with Trisomy 21 syndrome and Gilbert syndrome, respectively, in addition to ABO HDN. Four mother-infant pairs were also diagnosed with Rh(D) incompatibility. Twenty-seven (5.73%) neonates had severe hyperbilirubinemia (TSB [?] 342 μmol/L) of which five (18.52%) had extreme hyperbilirubinemia (TSB [?] 428 μmol/L, one of the patients was also diagnosed with Gilbert syndrome). Finally, 99.15% (467/471) of infants underwent intervention with phototherapy, 57.54% (271/471) underwent invasive treatments (intravenous immunoglobulins), and only two were subjected to ET.

Excluding subjects with congenital disease and combined with Rh(D) incompatibility, 465 cases whose mothers were all blood group O were identified, of which 49.46% (230/465) had blood type A and 50.54% (235/465) had blood type B. Median peak TSB was 206.80 μmol/L (IQR was 160.08 to 262.16 μmol/L), and mean Hb was 142.58 g/L (standard deviation (SD) was 23.76 g/L). No significant difference was found between the O-A incompatibility group and the O-B incompatibility group in Hb and peak TSB. Sixty-seven (14.41%) newborns were DAT positive. DAT-positive neonates (mean Hb value was 133.00 g/L) had

lower Hb levels than DAT-negative neonates (mean Hb value was 144.50 g/L) (P <0.05) (Fig. 2a), but no difference was observed in peak TSB between the two groups. In addition, the DAT positive rate of group A was higher than that of group B (P <0.05) (Fig. 2b).

The peak TSB was significantly different between the several different age groups of postnatal admission (P <0.001), and the median peak TSB level was higher in the older postnatal age of admission group than in the younger group between each two groups, except the two-three days group and [?] 14 days group, and the 4-13 days group and [?] 14 days group (Fig. 4a). Furthermore, the correlation coefficient between the postnatal age of admission and peak TSB levels was 0.54 (P <0.001) (Fig. 3). The severe hyperbilirubinemia groups had a later postnatal age of admission than ABO HDN neonates that did not develop severe hyperbilirubinemia (P <0.001) (Fig. 4b). In addition, neither gender, gestational age, birth weight, the mode of delivery, blood type, or DAT results were related to severe hyperbilirubinemia (P >0.05).

Discussion

In this study, we systematically assessed the possibility that group O mothers would give birth to non-group-O infants and the incidence of an infant actually developing haemolytic disease due to ABO incompatibility. Depending on the genotype frequencies, the likelihood of ABO incompatibility between a mother and her infant was 13.28%, but the occurrence rate of ABO HDN was 6.03%. There was no significant difference in severity between O-A and O-B incompatibility groups, and the frequency of maternal-foetal blood group mismatch in O-A and O-B was almost equal. The DAT positive neonates were more prone to haemolysis and led to even lower Hb. Moreover, we found that the later the postnatal age of admission, the higher the peak TSB level, whether a newborn develops severe hyperbilirubinemia.

Disparities between regions and ethnicities are conspicuous factors affecting the prevalence of haemolytic diseases. Our data showed that 13.28% of newborns have a major ABO incompatibility with mothers, while haemolytic disease was observed in only 6.03% of newborns, which is different to the incidence of HDN due to ABO incompatibility in Singapore [16]. In Caucasians, ABO incompatibility between the neonate and mother occurs in 10-25% of pregnancies and only 1-2.5% of infants are complicated by haemolytic disease [12, 17]. The reason for this discrepancy may be that A and B antigens are expressed at different frequencies and strengths in different populations. The results of Sebija Izetbegovic et al. [18] from Sarajevo showed an ABO incompatibility in 15% of pregnancies an ABO HDN of 0.67% in all newborns included in the study.

The variance in the incidence of blood group incompatibility and haemolytic disease can be attributed to the weak expression of major blood group antigens A and B on foetal erythrocytes; blood group antigens A and B are also expressed in other tissues, to which antibodies could bind. In addition, the immunoglobulin subclasses each have differing biological properties affecting their pathogenic potency. IgG3 has more effective transported across the placenta [19], compared with other subclasses of IgG, which may be responsible for whether the disease is present.

The American Academy of Pediatrics has reported blood group incompatibility with positive DAT as one of the most important risk factors for severe hyperbilirubinemia [15]. Clinically observable ABO HDN is usually diagnosed by severe jaundice within the first few days of life, followed by a positive laboratory test. DAT as a screening test for incomplete antibodies present on an individual's RBCs has poor sensitivity (50%) in identifying neonates that will develop clinically significant jaundice [15] and does not determine the specificity of the antibody attached to red blood cells. The eluate test is performed if DAT results are negative in our institution, which makes up for the defects of the DAT test in HDN identification caused by ABO antibody. We observed that DAT-positive neonates with haemolytic disease had lower Hb concentrations, so even at lower sensitivity, DAT was an invaluable screening tool for HDN. As other studies show, ABO incompatibility with positive DAT infants is at increased risk of receiving phototherapy and invasive treatment when compared with DAT-negative infants [20], and the increasing strength of DAT positivity is associated with phototherapy need [21].

The results of this study showed that the frequencies of O–A and O–B incompatibility and the severity of haemolysis between group A and group B were almost the same, as also observed in the study of Y. R.

Bhat et al. [6]. Many investigators in Western countries suggest that O-A blood group incompatibility has a higher morbidity and forms a majority of the ABO HDN, but haemolysis due to IgG anti-B is more severe [20, 22]. This divergence may be due to the difference in the distribution of blood type phenotypes between the other regions and ours [23]. However, the higher incidence of positive DAT in O-A blood group incompatibility that we observe is similar to the results of Kaplan, M. et al. [21]. Michael Kaplan et al. [22] conducted a retrospective study of the incidence of hyperbilirubinemia in neonates who were DAT-positive, ABO incompatible and compared O-A and O-B groups; the condition was more prevalent in the group B neonates and hyperbilirubinemia developed in more O-B newborns than O-A newborns at <24 hours.

Hyperbilirubinemia in the first week of life occurs in more than 60% of otherwise healthy infants and usually resolves within 7–10 days of age [5, 24]. In our research, the peak TSB levels increased gradually with the prolonging of postnatal age of admission and a good correlation was observed. The onset of hyperbilirubinemia caused by ABO incompatibility was most likely to occur prior to 72 hours of age and is associated with increased bilirubin production [5]. A study conducted by R. D. Christensen et al. [25] found that group A and B neonates, born to O (+) mothers, had higher peak TSB levels during the first 10 days after birth than did group O neonates. Due to the immature liver function of newborns, the level of bilirubin is markedly elevated with the duration of jaundice. Moreover, among ABO HDN newborns with severe hyperbilirubinemia, the age at admission was significantly higher than that of newborns without severe hyperbilirubinemia, which indicated that early admission might reduce the risk of severe hyperbilirubinemia for infants with ABO incompatibility, although the sample size needs to be larger for confirmation of this result.

Although we recognize that A, B, or AB mothers can deliver neonates with ABO haemolytic disease, those incompatibilities very infrequently have any clinical significance. The probability of ABO incompatibility, which represents the possibility of an O-type mother giving birth to a non-O-type baby, has been calculated using genetic frequencies from the 8 5590 blood donors in the Affiliated Hospital of Qingdao University in northern China. With respect to the prevalence of ABO HDN, an estimate of the incidence in northern China would be 1 in 6 live births (471 in 7 810 over the 3-year study period). It is anticipated that any infant born in the Affiliated Hospital of Qingdao University complicated by haemolytic disease due to ABO incompatibility would be referred to a doctor for treatment. However, some newborns may go to other hospitals or even no hospital. The estimate of 1 in 6 live births is likely conservative given that this is based on hospital medical records.

Neonatal haemolytic disease caused by ABO incompatibility of mother and infant is not infrequent in northern China. Although not all neonates develop neonatal haemolytic disease and the disease process is usually benign, it can be devastating if left untreated. For DAT positive newborns with ABO incompatibility, timely monitoring is advised, because early hospitalization and appropriate interventions, if necessary, can reduce the risk of severe hyperbilirubinemia.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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Legends

FIGURE 1 The distribution of blood type in the Affiliated Hospital of Qingdao University. The percentage of type-O (O pos.), type-A (A pos.), type-B (B pos.) and type-AB (AB pos.) of blood donors in the Affiliated Hospital of Qingdao University in northern China was 28.54%, 29.05%, 31.44% and 10.97%.

FIGURE 2 Significant differences between O-A/B and DAT-pos/neg subgroups. (a) The Hb levels in DAT-positive (DAT-pos.) group (135.3±21.2 g/L) were lower than that in DAT-negative (DAT-neg.) group (143.8±24.0 g/L). Values are expressed as the mean ± SD. *$P<$ 0.05 by Student's t-test. (b) Infants with blood type$A$ (18.26%) have a higher DAT positive rate than those with blood type B (10.64%). *P < 0.05 by chi-square test.

FIGURE 3 The correlation analysis between peak TSB levels and postnatal age of admission. The postnatal age of admission was positively correlated with the levels of peak TSB (r = 0.54, P<0.001).

FIGURE 4 Significant differences between the non-/severe hyperbilirubinemia groups and different postnatal age of admission groups. (a) Peak TSB levels were significantly lower in the postnatal age of admission less than 1-day group than in the other three groups, as well as in infants admitted at 2-3 days postnatal than in those admitted at 4-13 days postnatal. Values are expressed as the median ± 95%CI. *P < 0.05 and **P < 0.001 by Kruskal-Wallis H test and P value adjusted by Bonferroni correction. (b) The severe hyperbilirubinemia infants had a later postnatal age of admission than infants that did not develop severe hyperbilirubinemia. Values are expressed as the mean ± SEM. *P < 0.001 by Mann–Whitney U test.

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