Clinical Case Study of ABO Hemolytic Disease in Full-term Newborns Complicated with Neonatal Pneumonia and Intracranial Hemorrhage

Yan Jin[a]
Department of Neonatology, the People's Hospital of Baise, Baise, Guangxi, China

Keywords: Newborn, ABO Hemolytic Disease, Neonatal Pneumonia, Intracranial Hemorrhage.

Abstract: ABO Hemolytic Disease of Newborn (ABO-HDN) is the most common cause of blood-incompatible Hemolytic Disease in China. In this paper, the clinical characteristics of full-term ABO-HDN complicated with pneumonia and intracranial hemorrhage were summarized, and the corresponding clinical data were collected by using retrospective study methods, and the full-term infants meeting the ABO-HDN diagnostic criteria were selected as research objects. The differences in minimum hemoglobin, age at onset (h), and incidence of anemia among ABO-HDN patients with or without complications (neonatal pneumonia, intracranial hemorrhage) were compared. To investigate the influence of pneumonia and intracranial hemorrhage on the clinical manifestations of term ABO-HDN.

1 INTRODUCTION

Hemolytic disease of the newborn (HDN), caused by inconsistent maternal and infant blood groups, is one of the common causes in neonatal hyperconjugated bilirubinemia (Jeon, Calhoun, Pothiawala, et al 2000). There are different degrees of clinical manifestations of neonatal hemolytic disease. The fetus may have varying degrees of anemia after delivery. The clinical manifestations are pale, jaundice, hypoglycemia and edema. However, when the hemolytic immune response is severe, hyperunconjugated bilirubinemia will occur, and bilirubin encephalopathy may occur, resulting in damage to the central nervous system, More serious cases can occur early spontaneous abortion or late stillbirth (Li 2020). This study retrospectively analyzed the clinical data of ABO-HDN children who met the diagnosis and treatment criteria in full-term neonatal Pediatrics, and discussed the clinical manifestations and influence of ABO hemolytic disease complicated with pneumonia and intracranial hemorrhage.

2 SUBJECTS AND METHODS

2.1 Study Subjects

2.1.1 Selection of the Study Subjects

According to the diagnostic criteria of ABO-HDN of newborns in practical neonatology (4th Edition), according to the ABO blood group of mother and child (the mother is type O blood, the child is type A or B blood, and the mother and child Rh blood group are positive), jaundice ABO-HDN was diagnosed as positive by serological test, antibody release test (ART) or direct antiglobulin test (DAT); 127 full-term newborns who met the diagnostic criteria of ABO-HDN were selected from the neonatal department of the people's Hospital of Baise City in 2020.

2.1.2 Diagnosis Criteria for Related Comorbidities and Complications

Diagnostic criteria for anemia: anemia was diagnosed according to the diagnostic criteria in Pediatrics (8th Edition) for neonatal anemia, which was defined as hemoglobin <145g/L, and could be classified into 4 degrees according to the hemoglobin content: mild in patients with a range of

[a] https://orcid.org/0000-0002-3465-7057

Jin, Y.
Clinical Case Study of ABO Hemolytic Disease in Full-term Newborns Complicated with Neonatal Pneumonia and Intracranial Hemorrhage.
DOI: 10.5220/0011370300003438
In *Proceedings of the 1st International Conference on Health Big Data and Intelligent Healthcare (ICHIH 2022)*, pages 367-372
ISBN: 978-989-758-596-8

144-120g/L, moderate in those with a range of ~ 90g/L, severe in those with a range of <60g/L, and extremely severe in those with a range of <60g/L.

Neonatal pneumonia (NP) diagnostic criteria: according to the practical neonatology fourth edition neonatal pneumonia section, eligible for the following ① mother has a history of vaginitis in the third trimester, or the presence of premature rupture of membranes for more than 24 hours before delivery, or the newborn has a history of close contact with respiratory tract disease after delivery; ② Clinically, they had symptoms and signs of exocytosis and foam, nasal obstruction, rhinorrhea, cough, shortness of breath, cyanosis, and rales in lungs; ③ Sputum culture may reveal pathogenic bacteria, chest radiograph or chest CT suggests increased lung texture, blurring, disturbance or patchy hyperdense shadow, etc; ④ Except for neonatal wet lung, congenital lung disease, the clinical diagnosis was neonatal pneumonia.

Diagnostic criteria of Intracranial hemorrhage (ICH) : according to the 4th edition of Practical Neonatology, Intracranial hemorrhage refers to hemorrhage caused by Intracranial blood vessel rupture, including ① periventricular - intraventricular hemorrhage; ② Subdural hemorrhage; ③ Subarachnoid hemorrhage; ④ Parenchymal hemorrhage; ⑤ Hemorrhage in cerebellum, thalamus and basal ganglia. The diagnosis can be made with characteristic imaging changes of intracranial hemorrhage on head CT examination.

Diagnostic criteria for bilirubin encephalopathy (Du, Ma, et al 2014): ① have hyperbilirubinemia with peak total bilirubin > 342 umol / L or (and) a rise velocity > 8.5 umol/L, > 35 weeks' gestation; ② The early clinical manifestations are characterized by poor mental responsiveness, drowsiness, poor sucking, a weak cry, and hypotonia, followed by irritability, fever, convulsions, hypertonia, and opisthotonus, and in severe cases, death; ③ On cranial MRI, the basal ganglia globus pallidus appears hyperintense on T1WI (acute phase) and weeks later on T2WI; ④ Prolongation of all wave latencies or even hearing loss can be seen at brainstem auditory evoked potentials (BAEP), and the early changes of BAEP are mostly reversible.

2.2 Research Methods

SPSS statistics 16.0 software was used for statistical analysis. The counting data were described by the number of cases and percentage (n,%). The measurement data were described by mean±standard deviation ($\overline{X} \pm S$), and the differences between groups were compared by independent sample t-test, analysis of variance and chi square test.

3 ANALYSIS OF CLINICAL DATA

In this study, there were 68 cases of complicated neonatal pneumonia and 59 cases of uncomplicated neonatal pneumonia, which accounted for 53.5%, 46.5% of the total cases, respectively; There were 24 cases of combined intracranial hemorrhage and 103 cases without combined intracranial hemorrhage, accounting for 18.9% and 81.1% of the total, respectively. Of the children with combined intracranial hemorrhage, 21 had subarachnoid hemorrhage and 3 had patchy hemorrhages in the brain parenchyma.

In this study, there were 127 cases of ABO-HDN, 50 cases (39.4%) were complicated with mild anemia, 22 cases (17.3%) with moderate anemia, 1 case (0.8%) with severe anemia, and 8 cases (6.3%) with bilirubin encephalopathy.

4 GROUPING ANALYSIS OF ABO-HDN

4.1 Comparison of the Effects of Having and not Having Neonatal Pneumonia on Minimum Hemoglobin, Age at onset (h), and Incidence of Anemia

Included studies were stratified into no neonatal pneumonia group and combined neonatal pneumonia group using independent samples t-test to compare the lowest hemoglobin between the two groups Differences in age at onset (h), chi square test was used to compare the differences in the incidence of anemia. As can be seen from table 1, the combined neonatal pneumonia group had a lower nadir hemoglobin than the group without neonatal pneumonia, and the results were statistically significant (P<0.05), but there was no statistical difference in age at onset (h), incidence of anemia (P>0.05).

Table 1: Comparison of the incidence of neonatal pneumonia in minimum hemoglobin, age at disease onset (h) and anemia incidence.

class (n)	Minimum Hb (g / L) ($\bar{x} \pm s$ [1])	Age at disease onset(h) ($\bar{x} \pm s$ [1])	Anemia incidence[2] (%)
neonatal pneumonia (n=68)	134.88±22.26	21.88±12.32	63.2%
No neonatal pneumonia (n=59)	142.61±19.09	27.28±19.94	50.8%
t value/χ2value	-2.08	-1.86	1.98*
P value	0.04	0.07	0.16

Note: * Use the chi-square test;1 x refers to the mean, s refers to the standard deviation; 2 The denominator of the incidence of anaemia was 127 term ABO-HDN cases enrolled.

4.2 Comparison of Effects of Presence or Absence of Concomitant Intracranial Hemorrhage on Minimum Hemoglobin, Age at Onset (h), Anemia

Patients were divided into no intracranial hemorrhage and intracranial hemorrhage groups using independent samples t-test to compare the lowest hemoglobin between the two groups Difference in age at onset (h), chi square test was used to compare the difference in anemia incidence. As can be seen from table 2, there was no significant difference in the lowest hemoglobin, age at onset (h), anemia incidence between the groups (P > 0.05).

Table 2: Comparison of the incidence of intracranial hemorrhage in minimum hemoglobin, age at onset (h) and anemia.

class (n)	Minimum Hb (g / L) $\bar{x} \pm s$ [1]	Age at disease onset (h) $\bar{x} \pm s$ [1]	Anemia incidence2 (%)
Have intracranial hemorrhage (n=24)	131.83±25.48	20.95±13.84	70.8%
No intracranial hemorrhage (n=103)	140.02±19.80	25.19±16.97	54.4%
t value/χ2value	-1.72	-1.14	2.16*
P value	0.09	0.26	0.14

Note: * Use the chi-square test;1 x refers to the mean, s refers to the standard deviation; 2 The denominator of the incidence of anaemia was 127 term ABO-HDN cases enrolled.

4.3 ABO-HDN Characteristics in Concurrent Bilirubin Encephalopathy

There were 8 full-term abo-hdn cases complicated with bilirubin encephalopathy, including 2 cases without complications and 6 cases with complications. Among the full-term abo-hdn cases with complications, there were 2 cases of neonatal pneumonia, 1 case of intracranial hemorrhage and 3 cases of neonatal pneumonia + intracranial hemorrhage.

Among the 8 cases, the highest total bilirubin value was 207.0 umol/L, the highest value was 587.3 umol/L, the lowest hemoglobin value was 100 g/L, and the high value was 150g/L. Anemia occurred in 7 cases, including mild anemia in 3 cases and moderate anemia in 4 cases. Age at onset (h) as early as 9 h, as late as 27 h, age at first presentation (h) as early as 21 h, and as late as 168 h. There were 2 cases without comorbidities and 6 cases with comorbidities, including 2 cases with complicated neonatal pneumonia, 1 case with combined intracranial hemorrhage, and 3 cases with combined neonatal pneumonia + intracranial hemorrhage, see tables 3.

Table 3: Concurrent bilirubin encephalopathy ABO-HDN.

Project	Maximum total bilirubin (umol/L)	lowest Hb (g/L)	Age at disease onset (h)	Age at first visit (h)	Combined with neonatal pneumonia	Concomitant intracranial hemorrhage
case 1	291.9	150	20.27	32.27	+	-
case 2	244.7	123	23.5	35.5	+	+
case 3	284.0	117	9	21	+	+
case 4	207.0	111	14	26	-	-
case 5	348.9	132	16	40	-	+
case 6	587.3	121	24	168	+	+
case 7	277.1	100	27	39	+	-
case 8	362.1	112	24	58	-	-

Note: -indicates unmerge, + indicates merger.

5 UNIVARIATE ANALYSIS OF MODERATE AND SEVERE ANEMIA IN ABO-HDN

The 127 full-term ABO-HDN cases included in the study were analyzed according to whether moderate or severe anemia occurred.The relevant values are shown in Table 4.

As shown in Table 5, there was no statistical difference in the results of moderate and severe anemia caused by neonatal pneumonia and intracranial hemorrhage at term ABO-HDN (P > 0.05).

Table 4: Table of Related Factors.

project	assignment
Combined with neonatal pneumonia	not have =0 have =1
Concomitant intracranial hemorrhage	not have =0 have =1

Table 5: Results of a univariate analysis affecting the moderate and severe anemia of ABO-HDN at term.

project	classify	No moderate or severe anemia occurred (n=104)	Moderate and severe anemia occurred (n=23)	χ2value	P value
Combined with neonatal pneumonia	have	52	16	2.90	0.09
Concomitant intracranial hemorrhage	have	17	7	2.44	0.12

Note: * P <0.05 has statistical differences.

6 CONCLUSIONS

This study discusses whether full-term ABO-HDN children are grouped with neonatal pneumonia and intracranial hemorrhage, and compares the differences in minimum hemoglobin, age at onset (h) and incidence of anemia. Through analysis, it is found that the full-term ABO-HDN group with neonatal pneumonia treated in Baise people's hospital is lower than the group without neonatal pneumonia in minimum hemoglobin, The results were statistically significant (P<0.05). There was no significant difference in the lowest hemoglobin, age at onset (h) and incidence of anemia in patients with

intracranial hemorrhage (P> 0.05).The analysis is as follows:

6.1 Complications Associated with ABO-HDN Hemolysis

Among the cases enrolled in this study, 68 cases (53.5%) were complicated with neonatal pneumonia, and 59 cases (46.5%) were not. 24 cases (18.9%) had intracranial hemorrhage, 103 cases (81.1%) had no intracranial hemorrhage.

Hemolytic disease of newborn is a kind of passive immune disease, the occurrence of which depends on whether maternal and infant blood groups are inconsistent (Simmons, Savage 2015, Wei, Saller, Sutherland 2001). The pathogenesis is that maternal blood group antibody IgG, which can destroy fetal red blood cells, enters the child's body and causes hemolysis(Yogev-Lifshitz, Leibovitch, Schushan-Eisen, et al 2016).There was no statistical significance in minimum hemoglobin, age at onset (h) and incidence of anemia in patients with ABO-HDN complicated with intracranial hemorrhage (P>0.05).Intracranial hemorrhage can cause extravascular hemolysis, jaundice, when the amount of bleeding, also can be accompanied by anemia. There are more kinds of the disease, such as periventricular - intraventricular hemorrhage, subdural hemorrhage, subarachnoid hemorrhage, parenchymal hemorrhage, cerebellum, thalamus, basal ganglia and other parts of the hemorrhage. Among them, subarachnoid hemorrhage is more common in infants, most of which are small and clinically asymptomatic. A few of which are large and stimulate the brain parenchyma, causing corresponding nervous system symptoms, such as lethargy, low response, repeated convulsions, and central respiratory abnormalities. This study combined intracranial hemorrhage cases, 21 cases of subarachnoid hemorrhage, less blood loss, hemolysis reaction was not significant, outside the blood vessels to term ABO-HDN anemic, onset time have a significant impact, whether other types of intracranial hemorrhage in full-term ABO-HDN anemic, onset time, remains to be further validation.

The lowest hemoglobin in the group with neonatal pneumonia was lower than that in the group without neonatal pneumonia (134.88±22.26, 142.61±19.09), and the results were statistically significant (P<0.05). Although there was no difference in the incidence of anemia, it was still necessary to be vigilant that the ABO-HDN with neonatal pneumonia was more prone to anemia. Because when the body with infection, will produce the INF alpha, IL - 1, TNF and other cytokines, these cytokines can activate mononuclear macrophage, the macrophage chemotaxis, devouring, such as immunity strengthening, lead to increased red blood cells in the spleen, liver damage, extravascular hemolysis, aggravating the pathophysiology of hemolysis, so still need to the attention of the clinicians.

6.2 Factors Associated with Concurrent Bilirubin Encephalopathy

Bilirubin encephalopathy, generally seen in neonates with severe or very severe hyperconjugated bilirubinemia. The occurrence of the disease is closely related to serum free bilirubin, albumin, blood-brain barrier integrity.

Serum free bilirubin is lipid soluble and can penetrate the blood-brain barrier, and when conjugated with albumin is converted into water-soluble conjugated bilirubin, it cannot cross the blood-brain barrier and achieves the effect of protecting nerve cells. The rate of movement of free bilirubin from plasma to brain is limited by (1) surface area and permeability of the capillary endothelium, (2) transit time through the capillary bed, (3) albumin / bilirubin conjugation and dissociation rates, and (4) blood flow per unit area(Wennberg 2000).

Serum free bilirubin usually exists in the form of conjugation with albumin, when the body causes a rapid increase in free bilirubin for a short period of time because of some diseases, such as hemolytic disease of the newborn, or some substances compete with free bilirubin for the albumin binding site, resulting in decreased binding of albumin to free bilirubin, such as some cephalic antibiotics, sulfonamides, indomethacin and other drugs, And when the integrity of the BBB is compromised, conditions such as intercurrent infections, intracranial hemorrhage, or increased blood flow, such as hypercapnia, promote the transport of free bilirubin to the brain(Govaert, Lequin, Swarte, et al. 2003).

Most of the early neonatal BBB development is not perfect, especially the newborns less than 72 hours after birth, the BBB is not yet intact, the endothelium is fenestrated, the endothelial basement membrane is thin, part of the endothelium has no continuous basement membrane, glial membrane is not complete, etc., can affect the BBB integrity. At this time, serum free bilirubin rapidly increases and can be at risk for concurrent bilirubin

encephalopathy. The age at onset of the eight cases in this study complicated by bilirubin encephalopathy were all within 48 hours of birth and required attention from clinicians. For newborns less than 72 hours after birth, close monitoring of bilirubin should be performed, along with observation for clinical signs of early presentation of bilirubin encephalopathy, and aggressive intervention to try to prevent the emergence of bilirubin encephalopathy.

Studies have shown (Ma, Shi, et al. 2012) that the risk of developing bilirubin encephalopathy increases with comorbid infections, intracranial hemorrhage, and other conditions. There were 8 cases of concurrent bilirubin encephalopathy in this study, 2 cases without comorbidities, and 6 cases with existing comorbidities, including 2 cases of combined neonatal pneumonia, 1 case of combined intracranial hemorrhage, and 3 cases of combined neonatal pneumonia+intracranial hemorrhage, which was in keeping with related studies. The small number of cases with concurrent bilirubin encephalopathy in this study precludes further statistical testing, and further analyses with larger samples are warranted in the future. In clinical practice, attention should be paid to the presence of comorbidities such as: neonatal pneumonia, intracranial hemorrhage in abo-hdn cases, and vigilance for concurrent bilirubin encephalopathy.

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