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Case Series: 11 Cases of Hemolytic Disease of The Fetus And Newborn Due to Kell Blood Group Incompatibility

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ABSTRACT

Hemolytic disease of the fetus and newborn (HDFN) results from the destruction of the newborn's red blood cells or the fetus by the mother's immune globulin G antibodies. Although HDFN is often caused by RhD and ABO incompatibility, it can also be seen due to minor blood groups such as Kell, Kidd, Duffy, P, MNS, or Rh subgroup (C, c, E, e) alloantibodies. Our study aims to share our experiences regarding a rare cause of HDFN.

The files of patients who were followed up with the diagnosis of jaundice in a third-level Neonatology Unit of a university hospital between January 2014 and September 2023 were retrospectively examined. Eleven patients with Kell incompatibility were included in the study.

There was no ABO/RhD incompatibility in any case. RhD subgroup incompatibility and Kell incompatibility were present in four cases. Phototherapy was applied to all patients. The patient, whose total bilirubin level was high despite phototherapy, was treated with an exchange transfusion. No complications were observed due to treatment or high total bilirubin. No significant difference was observed between the parameters evaluated according to the gender variable.

It should be kept in mind that severe hemolysis and related deaths may occur due to Kell incompatibility. In order to reduce and prevent severe hemolysis due to Kell and other minor blood groups in newborns, transfusing blood products suitable for minor blood groups to women of childbearing age (especially pregnant women) may be a correct approach as a country policy.

Keywords: hemolytic disease, HDFN, Kell incompatibility, hyperbilirubinemia

Introduction

If the mother has received a blood product transfusion or has passed red blood cell antigen from the fetus to the mother in previous pregnancies, this causes the formation of immunoglobulin G (IgG) antibodies. Hemolytic disease of the fetus and newborn (HDFN) occurs when IgG antibodies transmitted from the mother cause hemolysis in the fetus or newborn. HDFN is caused primarily by the development of antibodies linked to RhD and ABO blood groups. However, minor blood group (Kell, Duffy, MNS, P, and Diego systems) incompatibilities can also cause HDFN (1). Kell is highly immunogenic after ABO and Rh blood group systems. IgG antibodies targeting Kell antigens are anti-Ks (anti-K1, anti-K2, anti-K3, anti-K7) that often become the cause of hemolytic disease and transfusion reaction in newborns (2). K antigen is one of the Kell blood group antigens, produced early in fetal development and expressed in bone marrow erythroid progenitor cells; thus, antibodies to K may also cause both hemolysis of mature erythrocytes and suppression of normal erythropoiesis. For this reason, HDFN due to anti-K can be serious. In Kell incompatibility where severe hyperbilirubinemia develops, a condition called bilirubin-induced neurological dysfunction (BIND) may ocur (3). Long-term morbidities in cases that develop BIND; Conditions such as hearing loss, athetoid cerebral palsy and intellectual disability may ocur (4,5). Phototherapy, hydration, intravenous immunoglobulin and exchange transfusion can be used to treat HDFN.

Materials and Method

The files of patients who were followed up with the diagnosis of jaundice in the Neonatology unit of xxx University Faculty of Medicine Hospital between January 2014 and September 2023 were retrospectively examined. 11 patients with Kell incompatibility were included in the study. Patients

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Table 1: Descriptive Statistical Results of The Patients

n=11	mean±std error (min-max)
Birth week	38.27±0.6 (34-40)
Birth weight (g)	3082.73±154.52 (1970-3850)
Hospitalization day	3.18±0.53 (1-6)
Total bilirubin (mg/dL)	16.56±1.67 (9.9-27.3)
Direct bilirubin (mg/dL)	0.5±0.02 (0.3-0.6)
Hemoglobin (g/dL)	17.89±0.9 (12-21.8)
Days in hospital	3.09±0.3 (2-5)

who were followed up for ABO, Rh and other identifiable causes of hyperbilirubinemia (G6PD deficiency, sepsis, hypothyroidism, etc.) were not included in the study. Data such as gestational age, gender, mode of delivery, birth weight, day of admission to the hospital and duration of hospital stay were evaluated. Hemoglobin, total and direct bilirubin levels were evaluated. Approval for the study was received from Van Yüzüncü Yil University Faculty of Medicine Clinical Research Ethics Committee.

Statistical Analysis: Descriptive statistics for continuous variables among the features emphasized; Expressed as Mean, Standard Error, Minimum and Maximum values, and as numbers and percentages for categorical variables. After testing whether the data showed normal distribution, an independent t-test was used for comparisons between continuous variables and categorical variables. In the calculations, the statistical significance level was taken as 0.05. SPSS (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp) statistical package program was used in the calculations.

Results

Two of our eleven patients diagnosed with Kell incompatibility were premature. Direct coobs test results were negative in all of our patients. None of our patients had elevated direct bilirubin. The descriptive statistical data of our cases are in Table 1 is also shown.

Six of our cases were boys and five were girls. All our patients were given phototherapy as the first treatment. One of our patients (admission total bilirubin level: 27.3 mg/dL, Hgb level: 12 g/dL) underwent blood exchange because the total bilirubin level was above the exchange limit despite phototherapy. None of our patients received intravenous immune globülin (IVIG) treatment. The percentage distribution of the patients' gender, mode of birth, type of treatment, and additional pathologies are shown in Table 2.

According to the gender variable, there was no statistically significant difference between boys and girls with Kell incompatibility in terms of week of birth, birth weight, postnatal day when they were admitted to the hospital with jaundice, total bilirubin, direct bilirubin and hemoglobin values measured at admission, and the number of days they were hospitalized due to this treatment (Table 3).

In four cases, there was Rh subgroup incompatibility as well as Kell incompatibility. One of them was the C and e incompatibility, and the other three were the E incompatibility. There was no statistically significant difference in terms of descriptive parameters between cases with only Kell incompatibility and cases with Rh subgroup (C, E, e) incompatibility in addition to Kell incompatibility (Table 4).

Discussion

HDFN may develop due to different blood group systems other than ABO and Rh during the neonatal period. These blood groups include blood group systems such as Kell, Duffy, Diego and MNS. Severe HDFN may develop especially against the K antigen, one of the Kell group antigens. This situation is explained by the fact that anti-K causes hemolysis and suppresses erythropoiesis (6). In a series examining pregnancies with K sensitivity, it was reported that HDFN developed at a rate of 26% (7). In another study, it was reported that severe fetal anemia developed in the early intrauterine period due to Kell isoimmunization (8). The most common cause of Kell isoimmunization is thought to be a previous transfusion of blood products. In a study, it was reported that the mothers of 12 newborns with K isoimmunization had previously received blood product transfusion (9). Some countries, such as the Netherlands and Australia, have adopted K-compatible blood product transfusion for women of childbearing age. This transfusion policy only exists in some countries, not including ours. It was shown in a study conducted in the Netherlands, where 1026

Table 2: Percentage Distribution of Patients' Gender, Birth Type, Treatment Method and Additional Pathologies

variables		N(%)
Gender	Girl	5 (%45.4)
	Boy	6 (%54.5)
Type of birth	Normal spontaneous vaginal delivery	8 (%72.7)
	Cesarean Section	3 (%27.2)
Treatment	Phototherapy Only	10 (%90.9)
	Phototherapy+Total Exchange	1 (%9)
Additional pathology	Prematurity	2 (%18.1)
	Transient tachypnea of the newborn	1 (%9)
	Infant of diabetic mother	1 (%9)
	Dehydration	1 (%9)
	No additional illness	6 (%54.5)

*sample size (percentage)

Table 3: Analysis of Parameters According to Gender Variable

	Girl (n=5) mean±std error	Boy (n=6) mean±std error	t	p
Birth week	38.4±0.87	38.16±0.9	0.18	0.859
Birth weight (g)	3120±221.6	3051.67±233.15	0.21	0.839
Hospitalization day	3.4±0.81	3±0.77	0.35	0.731
Total bilirubin (mg/dL)	18.88±2.8	14.63±1.83	1.26	0.223
Direct bilirubin (mg/dL)	0.54±0.02	0.47±0.04	1.25	0.241
Hemoglobin (g/dL)	16.78±1.83	18.81±0.95	-1.03	0.326
Days in hospital	3.2±0.37	3±0.51	0.30	0.770

*Independent t-test

Tablo 4: Analysis of parameters according to the presence of only Kell incompatibility and additional incompatibility accompanying Kell

	mean±std error		t	p
	Kell incompatibility only (n=7)	C,e,E subgroup incompatibility in addition to Kell incompatibility (n=4)		
Birth week	37.85±0.9	39±0.4	0.9	0.391
Birth weight (g)	2965.71±229.96	3287.5±108.73	1	0.343
Hospitalization day	2.85±0.59	3.75±1.1	0.78	0.452
Total bilirubin (mg/dL)	16.97±2.49	15.85±1.87	0.3	0.766
Direct bilirubin (mg/dL)	0.49±0.03	0.5±0.04	0.57	0.581
Hemoglobin (g/dL)	17.38±1.4	18.77±0.86	0.66	0.524
Days in hospital	3.14±0.45	3±0.4	-0.2	0.840

*****Independent t-test

pregnant women were examined, that HDFN, which develops due to K, one of the Kell group antigens, has a severe course (10).

Hydrops fetalis is an important cause of mortality and morbidity due to severe hemolysis in the intrauterine period. Hydrops may be seen in cases of Kell incompatibility. In a study conducted in 1992, it was reported that 15% of newborns with severe hemolysis due to Kell incompatibility died due to hydrops fetalis (11). In our study, hydrops was not observed in any of the HDFN cases due to Kell incompatibility. HDFN was not severe in patients other than the patient who underwent transfusion. We can list the possible reasons for this situation.

- There may have been moderate to mild Kell subgroup incompatibility in our cases.
- The number of cases is low.
- Our study does not include the intrauterine period.

The direct Coombs test was negative in all of our cases. This situation may be related to the fact that HDFN does not progress so severely. However, Barker et al. A study conducted, stated that direct Coombs positivity may not be correlated with the severity of hemolysis (12).

Intravenous immunoglobulin (IVIG) is thought to prevent hemolysis by blocking Fc receptors in the reticuloendothelial system. Therefore, in hemolysis due to ABO and RhD incompatibilities, IVIG is used before exchange transfusion. However, Cochrane analysis reported that publications claiming that IVIG reduces blood exchange are biased and have no benefit in reducing blood exchange[13]. We did not give IVIG treatment to any of our patients, and except for one of our patients (the patient who underwent transfusion), none of our patients needed additional treatment (transfusion, IVIG, etc.).

In cases of Kell incompatibility, the clinic may vary from mild jaundice to hydrops fetalis. Almost all of the cases in our study had mild-moderate HDFN. However, it should be kept in mind that serious hemolysis and related deaths may occur due to Kell incompatibility. Since our study does not include the intrauterine period, we do not know what proportion of the cases who died due to intrauterine severe hemolysis and hydrops in our hospital had Kell incompatibility and other minor blood group incompatibility. Conducting comprehensive studies on this subject may provide a better understanding of the importance of minor blood group incompatibilities. In our country and most European countries, minor blood group and Rh subgroup compatibility is not required when transfusing blood products. In order to reduce and prevent severe hemolysis due to Kell and other minor blood groups in newborns, transfusing blood products suitable for minor blood group to women of childbearing age (especially pregnant women) may be a correct approach as a country policy.

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