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HEMOLYTIC DISEASE OF THE NEWBORN DUE TO COMBINATION OF ANTI-E AND ANTI-S IN THE FIRST PREGNANCY*

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With the exception of ABO incompatibility, hemolytic disease of the newborn without previous isoimmunization occurs quite rarely in the first pregnancy. This paper presents an interesting case of a newborn infant with hemolytic disease caused by two different antibodies. The baby was the product of the mother's first pregnancy, and there was no history of transfusion, abortion or operation.

Material and Methods

Standard tube techniques were employed using prewashed 2% red cell suspensions for blood groups. For antibody identifications panels were performed with selected 0 group test red cells. Titration results were scored with the values recommended by Race and Sanger[1] (complete or C=12, +++=10, ++=8, +=5, ±=3, w=2, negative=0). Rubin's[2] ether technique was used for the elution studies.

Case Report

BC, a three-day-old full term baby, was admitted to the Hacettepe University Children's Hospital on August 2, 1977, because of severe jaundice which had become obvious at the end of the first day. She was born to a 17-year-old gravida 1, para 1, A Rh positive mother.

Physical examination of this 3 kg baby revealed enlargement of the liver and spleen, which were both palpable 2 cm below the respective costal margins.

Hemoglobin was 13.95 g/dl and bilirubin 29 mg/dl of which 0.8 mg/dl was the direct fraction. The blood group of the baby was B Rh positive (CDe/cDE) and the

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direct Coombs' test was (+ + +) positive. An exchange transfusion was performed immediately with one unit of B Rh positive blood. Bilirubin decreased to 13 mg/dl.

At this time a blood sample was obtained from the mother. Her blood group was rechecked. She was A Rh positive (CDe/cde), C+ E− c+ e+ M+ N+ S− s+ K− k+ Fy^a+ Fy^b+ Jk^a+ Jk^b+.

Antibody identification in the mother's serum showed the presence of two different IgG antibodies, anti-E plus anti-S, which were both eluted from the red cells of the baby also (Tables I, II). In the mother's serum, anti-E showed 1/512 titration with R_2R_2 and ss cells and anti-S showed 1/64 titration with rr and Ss red cells. Eluted antibody titrations from the red cells of the baby were 1/32 and 1/8 respectively.

TABLE I

Mother

Blood Group A Rh Pos. (R, r)

Panel Cells O	C	D	E	c	e	M	N	S	s	Fy^a	Fy^b	Jk^a	Jk^b	K	k	Mother's Serum Saline RT.	Saline 37°C	ICT
1. R_1r	o	•	o	•	•	o	•	•	•	•	•	•	•	o	•	o	o	••
2. R_2r	•	•	o	•	•	•	•	•	•	•	•	•	o	o	•	o	o	••
3. R_1r	o	•	•	•	•	•	•	o	•	•	•	•	•	o	•	o	o	•••
4. R_2r	•	•	o	•	•	•	•	•	•	•	•	•	•	o	•	o	o	••
5. R_1R_2	•	•	o	o	•	•	•	o	•	o	•	•	•	o	•	o	o	o
6. r r	o	o	o	•	•	•	•	•	•	•	•	•	•	o	•	o	o	••
7. r r	o	o	o	•	•	•	•	•	•	o	•	•	•	•	•	o	o	••
8. R_2R_2	o	•	•	•	o	•	o	o	•	•	o	•	•	o	•	o	o	•••

Anti-E • Anti-S

(Anti - E) - Titration with cDE / cDE (R_2R_2) and ss cells 1/512 Score. 61

(Anti - S) Titration with cde / cde (rr) and Ss cells 1/64 Score. 42

On the day after the first exchange transfusion, the infant's bilirubin increased again to 23.7 mg/dl with 1 mg/dl direct fraction. A second exchange transfusion with B Rh positive, E negative and S negative blood was performed. After transfusion, bilirubin was 11 mg/dl. Phototherapy was started. Bilirubin decreased more rapidly, and the patient was discharged on the fourth day after admission.

In reply to repeated questioning the young mother and her parents stated definitely that she had had no previous abortion, operation or blood transfusion.

Baby

TABLE II

Blood Group B Rh pos. (R_1R_2)

D.Coombs. +++

Panel Cells o.	C	D	E	c̄	e	M	N	S	s	Fy^a	Fy^b	Jk^a	Jk^b	K	k	Eluate ICT
1. R_oR	0	+	0	+	+	0	+	+	+	+	+	+	+	0	+	++
2. R_1r	+	+	0	+	+	+	+	+	+	+	+	+	0	0	+	+
3. R_2r	0	+	+	+	+	+	+	0	+	+	+	+	+	0	+	++
4. R_1r	+	+	0	+	+	+	+	+	+	+	+	+	+	0	+	+
5. R_1R_2	+	+	0	0	+	+	+	0	+	0	+	+	+	0	+	0
6. r r	0	0	0	+	+	+	+	+	+	+	+	+	+	0	+	+
7. r r	0	0	0	+	+	+	+	+	+	0	+	+	+	+	+	+
8. R_1R_2	0	+	+	+	0	+	0	0	+	+	0	+	+	0	+	++

Anti - E + Anti - S

(Anti - E) - Titration with cDE/cDE (R_2R_2) and ss cells 1/32 Score. 28

(Anti - S) - Titration with cde/cde (r r) and Ss cells 1/8 Score. 15

Discussion

In spite of the absence of a previous stimulus, the occurrence of two different IgG antibodies in this young mother is a puzzle. The usual immune stimuli observed are a previous abortion, pregnancy itself, and transfusions. There is also a possibility that these are "naturally occurring" antibodies.

Unfortunately, our knowledge concerning immunization caused by an abortion or a first pregnancy is mostly related with the Rh_o(D) antigen. Several reports[3,4] support the fact that at least 3% of Rh-negative women are immunized by an abortion.

Neubauer[5] reported nine firstborn infants with severe hemolytic disease (the total included three intrauterine deaths and one hydrops fetalis), and all the mothers had a history of previous abortion. Thus primary immunization or hemolytic disease is seen to be induced by an abortion. But there is no history of an abortion in our case, and because of social pressures in the Turkish society, the incidence of unmarried adolescent abortions and pregnancies is extremely low in this country.

In Rh-negative women with no history of transfusion or abortion, anti-D has been found to be less than 1% at the end of a first pregnancy resulting in an Rh-positive

infant[6]. The incidence of anti-Rh antibody positivities in Rh-negative women six months after the birth of an Rh-positive, ABO-compatible first infant ranges from 4.3%[7] to 9.0%[8].

Hemolytic disease due to anti-D rarely occurs during a first pregnancy. Because the Rh_o(D) antigen is more than 30 times as immunogenic as (c) and (E), the next two most immunogenic antigens, one can easily consider that hemolytic disease due to anti-E or anti-S, as in our case, must be extremely rare in a first pregnancy.

However, in routine screening of the serum of pregnant women for the presence of incomplete blood group antibodies, Giblett[9] found that in 93% of the cases the antibodies were anti-D or anti-CD, approximately 6% were anti-c, anti-E or anti-Ce, and the remaining 1% were antibodies of other specificities. The prevalence of anti-S, as an immune red cell isoantibody, is found to be 0.2% in various studies[4].

In general, isoimmunization occurs only as a consequence of exposure to human blood group antigens, generally through transfusion or pregnancy. Levine and Waller[10] pointed out that severe hemolytic disease due to anti-Rh in a firstborn infant was frequently associated with a history of previous transfusion of Rh-positive blood. Anti-S is also known to have caused hemolytic disease of the newborn. Levine et al[11] reviewed 12 cases and reported one fatal case due to anti-S, but that baby's mother had previously received a transfusion. There is definitely no history to associate transfusion with our case. Because of the severity of the disease with a single pregnancy, it would seem reasonable to consider that the antibodies were present before the pregnancy, and in the absence of a history of immune stimulus, we should consider that these were "naturally occurring" antibodies.

An antibody is said to be naturally occurring if it is found in the serum of an individual who has never received a transfusion or been injected with red blood cells containing the related antigen or been pregnant with a fetus carrying the related antigen. It is concluded that naturally occurring antibodies such as anti-A and anti-B are heteroagglutinins produced as an immune response to substances in the environment which are antigenically similar to the human blood group substances[12]. Several naturally occurring antibody examples (anti-B, anti-K, anti-M) supporting this hypothesis have been reported[13-15]. The occurrence of anti-D in a person who has never received Rh positive red blood cells is extremely rare[16,17].

Although substances other than red cells capable of stimulating the formation of Rh antibodies in man have not been described, it seems possible that they exist in view of the interesting finding of anti-E in only one of identical twins[18]. Anti-E is found not infrequenly in patients who have not had transfusions or been pregnant[19-22]. At one center, about 60 examples of this kind of anti-E were detected in the course of routine antenatal examinations[23]. The highest incidence was in primigravidae, 40%

of whose husbands were E-negative, reinforcing the conclusion that most examples of anti-E encountered in pregnant women are naturally occurring.

Virtually all naturally occurring antibodies are either wholly IgM or at least partly IgM. Occasionally, examples of antibodies which are apparently naturally occurring are found to be IgG[4]. In another study of 218 anti-E examples, 14% gave a positive indirect antiglobulin reaction, and 46 women denied provious transfusion or pregnancy[24].

Although anti-E is a relatively common antibody, it rarely causes hemolytic disease of the newborn, even if the fetal red blood cells carry the corresponding antigen. Anti-S has occasionally been found as a naturally occurring antibody[25], but is more commonly found as an immune antibody in cases who have received many transfusions.

In conclusion, although several cases of hemolytic disease of the newborn due either to anti-E or anti-S have been reported, the antibodies in these cases are the immune antibodies that occurred as a result of multiple transfusions or pregnancies. We did not find any case in the literature in which the combination of these two antibodies is the cause of hemolytic disease in a first pregnancy.

In our case, anti-E and anti-S in combination, in the absence of an obvious antigenic stimulus, were IgG fraction, which caused the hemolytic disease in this newborn baby; in other words, two probably naturally occurring IgG antibodies are the most likely cause of hemolytic disease in the product of this first pregnancy.

Summary

Hemolytic disease in a newborn infant, the product of a first pregnancy, is reported. A combination of anti-E and anti-S is shown as the cause of the disease. In view of the absence of a previous antigenic stimulus, the antibodies present are most probably naturally occurring IgG antibodies.

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