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ROLAND B. SCOTT, M.D.
MELVIN E. JENKINS, M. D.
and
ALTHEA D. KESSLER, M.D.
Washington, D. C.

From the Department of Pediatrics, Howard University School of Medicine and the Pediatric Service of Freedmen's Hospital

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ERYTHROBLASTOSIS FETALIS IN THE NEGRO INFANT

Report of Five Cases, Including Four Cases Due to A-B-O Incompatibilities

Roland B. Scott, M.D., Melvin E. Jenkins, M.D., and
Althea D. Kessler, M.D.
Washington, D. C.

ERYTHROBLASTOSIS fetalis is considered a rare entity among infants of Negro descent. The frequency of Rh-negative individuals has been variously reported as from 5 to 10 per cent among American Negroes.[1, 2] Of 3,615 Negroes typed on the laboratory service of our hospital there was an incidence of 7.1 per cent Rh-negative individuals. At Gallinger Municipal Hospital an incidence of 6.5 per cent Rh-negative individuals was found among 1,000 Negro blood donors.[3] However, the incidence of the disease is not nearly so high as one would expect from the above figures. Another interesting observation of Wiener[1] and Zuelzer[4] is that most of the cases of erythroblastosis occurring in Negroes are not due to Rh sensitization. Contrariwise, in the white race about 95 per cent of the cases can be explained on the basis of isoimmunization with the Rh group.

During the past seven years we have encountered five cases of erythroblastosis fetalis in Negro infants. During this period (1942 to 1948) there were 11,217 infants (all Negro) delivered at Freedmen's Hospital including 448 stillborn infants. These figures represent an incidence of 0.45 cases of erythroblastosis per thousand deliveries. Potter[5] reports an incidence of hemolytic disease (erythroblastosis) among 22,742 white infants delivered at the Chicago Lying-in Hospital (1940 to 1946) as one case per 252 births (approximately four cases per 1,000 births). Similarly, Diamond[6] and Pickles[7] state that the incidence of the disease in white infants is about one in 200 births or five per 1,000 deliveries.

From the Department of Pediatrics, Howard University School of Medicine and the Pediatric Service of Freedmen's Hospital.

CASE REPORTS

Case 1.—A. N., a full-term male infant weighing 2,951 grams, became jaundiced several hours after birth. The infant was born at Freedmen's Hospital by a spontaneous breech delivery on March 20, 1942. Amniotic fluid was described as meconium colored. The mother had had no illnesses during this gestation and one previous pregnancy produced a normal infant. No jaundice or blood dyscrasia was described in the family history and the maternal Wassermann test was negative. The exact description of the vernix caseosa and placenta was not recorded.

Physical examination revealed a very icteric newborn infant who was well nourished and in no apparent distress. The spleen extended about 1 cm. below the left costal margin while the liver was not palpable. Stools and urine were yellow.

Initial laboratory findings were red blood count 2.36 million per cubic millimeter, hemoglobin 6.7 Gm., white blood count 43,900 with 42 per cent polymorphonuclears, 43 per cent lymphocytes, 12 per cent myelocytes, and 3 per cent basophiles. Icterus index 110 units with indirect van den Bergh 3.8 mg., urine positive for bile.

The moist preparation for sickling of red blood cells was negative.

Serologic studies were done by Dr. Karl Landsteiner who reported that the blood of the mother was Rh negative while that of the father and infant was Rh positive. The serum of the mother gave positive agglutination reactions with the baby's blood and with other Rh positive bloods.

The patient responded well to five transfusions of type O blood and was discharged on April 23, 1942, with a hemoglobin of 12.4 Gm.

CASE 2.—W. B., a 12-day-old male, was admitted to the pediatric service on Dec. 27, 1948, because of hematemesis and melena which had begun on the third day of life. The mother was a 37-year-old para iii whose pregnancy was normal. The birth weight was 4,342 grams and the neonatal course was uneventful until the third day of life. The urine was intensely yellow on admission. A paternal grandmother had had viral hepatitis about six months previously but there was no family history of jaundice or syphilis.

This well-developed and well-nourished infant showed intense jaundice as the outstanding finding. The temperature was normal. The liver and spleen were not palpable and there was no evidence of hemorrhage.

Laboratory findings on admission were red blood count 2.7 million per cubic millimeter, hemoglobin 13.7 Gm. white blood count 6,050 with 28 per cent polymorphonuclears, 66 per cent lymphocytes, and eosinophiles 6 per cent. The bleeding time was 15 seconds, clotting time 22 minutes.

When clinical and laboratory studies ruled out the more common causes of neonatal jaundice, erythroblastosis was suspected. Blood samples were submitted to Dr. A. S. Wiener for serologic investigation. His report follows:

BLOOD OF	GROUP	M-N TYPE	Rh-Hr TYPE
Father	B	MN	Rh_oRh_o
Mother	O	N	Rh_o
Patient	B	MN	Rh_o

The above findings excluded the Rh-Hr factors as having any bearing on the baby's jaundice and suggested a possible B sensitization. This was confirmed by titration of the mother's alpha and beta antibodies:

Agglutination method
(average normal titer—40 units)
Anti A—30 units
Anti B—160 units

Plasma conglutination method
Anti A—128 units
Anti B—500 units

Acacia conglutination method
Anti A—80 units
Anti B—500 units

These results revealed a definite sensitization to B agglutinogen.

The patient recovered fully after three transfusions with type O blood. At present the child, who is 2 years of age, is developing normally, weighs 36 pounds, and has a hemoglobin of 15.5 Gm.

CASE 3.—S. H., a 17-day-old male, was admitted because of jaundice which first appeared about the fifth day of life. The infant was delivered spontaneously in another local hospital after an uneventful gestation period. The birth weight was 3,147 grams. There was no history of jaundice or syphilis in the family.

Physical examination disclosed a moderately icteric infant showing signs of an upper respiratory infection. The heart and lungs were normal. The liver and spleen were not enlarged. There was a small granuloma of the umbilicus but no evidence of infection.

Initial laboratory findings included red blood count 4.8 million per cubic millimeter, hemoglobin 15 Gm., white blood count 7,650 with 13 per cent polymorphonuclears, 80 per cent lymphocytes, 5 per cent monocytes, and 2 per cent eosinophiles. The urine was negative. Icterus index was 38 units with an indirect van den Bergh of 6.1 mg.

Serologic studies by Dr. A. S. Wiener were reported as follows:

BLOOD OF	GROUP	M-N TYPE	Rh-Hr TYPE
Father	B	M	Rh_2rh
Mother	O	MN	Rh_2rh
Infant	B	MN	Rh_2rh

Titration of the mother's alpha and beta antibodies showed:

Agglutination method
(average normal titer—40 units)
Anti A—100 units
Anti B—192 units
Plasma conglutination method
Anti A—96 units
Anti B—400 units
Acacia conglutination method
Anti A—96 units
Anti B—500 units

In view of the above findings a diagnosis of icterus precox due to B sensitization as the cause of the baby's jaundice seemed justified.

The upper respiratory tract infection responded satisfactorily to penicillin therapy. No transfusions were necessary. He was discharged on March 26, 1949, much improved with a hemoglobin of 15 Gm.

CASE 4.—A. T., a 5-day-old male infant, was admitted to the Pediatric Service on March 1, 1949, because of failure to feed well and an unexplained cyanotic episode on the day of admission. The infant was born spontaneously at this institution and although he was resuscitated with difficulty, his stay in the newborn nursery was uneventful. The birth weight was 2,951 grams. The mother was a 38-year-old primipara who suffered no prenatal abnormality. There was no history of familial anemia or syphilis.

On admission the infant showed definite evidence of dehydration and pallor. However, there was no visible jaundice. The heart and lungs as well as the liver and spleen revealed nothing unusual.

The admission laboratory studies revealed red blood count 3.56 million per cubic millimeter, hemoglobin 11.5 Gm., white blood count 12,500 with a normal differential. The urine and stools were normal.

Serologic studies by Dr. A. S. Wiener were reported as follows:

BLOOD OF	GROUP	M-N TYPE	Rh-Hr TYPE
Father	A	N	Rh_o
Mother	O	MN	Rh_o
Patient	A	MN	Rh_o

The alpha and beta antibodies in the mother's serum were titrated giving the following results:

Agglutination method
(average normal titer—40 units)
Anti A—24 units
Anti B—20 units
Plasma conglutination method
Anti A—56 units
Anti B—12 units
Acacia conglutination method
Anti A—128 units
Anti B—24 units

These results showed a mild sensitization to the A agglutinogen. The infant received two transfusions with type O Rh-negative blood and made an uneventful recovery.

At the age of 21 months the child is developing normally. The hemoglobin is now 12.5 Gm.

CASE 5.—J. T., female, was born at Freedmen's Hospital on July 3, 1949. On the third day of life the infant developed jaundice and fever. The temperature returned to normal on the following day but the jaundice persisted. Some increasing muscle spasticity of the upper and lower extremities was noticed at this time. On the eighteenth day of life the infant again developed a fever which remained elevated for five days. A blood culture at this time was negative. The intense jaundice meanwhile remained unchanged.

The initial hemogram taken on the third day of life revealed red blood count 2.5 million per cubic millimeter, hemoglobin 5 Gm., white blood count 12,800 with 37 per cent polymorphonuclears and 63 per cent lymphocytes. The infant and maternal Wassermann reactions were negative. Icterus index was 73 units with an indirect van den Bergh of 29 mg.

Serologic studies by Dr. A. S. Wiener were reported as follows:

BLOOD OF	GROUP	M-N TYPE	Rh-Hr
Mother	O	MN	Rh_1rh
Patient	B	N	Rh_o

Rh agglutinin studies were negative.

The mother's alpha and beta antibodies were titrated with the following results:

Agglutination method
- Anti A—80 units
- Anti B—640 units

Plasma conglutination method
- Anti A—110 units
- Anti B—1920 units

Acacia conglutination method
- Anti A—200 units
- Anti B—2560 units

The results indicated that the mother was strongly sensitized to the B agglutinogen, confirming the impression that the infant's condition was due to B-O incompatibility.

After numerous transfusions with type O blood, the child began to improve steadily and was discharged seventy-three days after birth. There was still some residual spasticity which we attributed to probable kernicterus. The child has not been available for follow-up study.

DISCUSSION

Erythroblastosis fetalis can assume one of several forms; namely, icterus gravis, congenital hemolytic anemia, and hydrops fetalis.[2, 8] In addition to the classical types another variety has been reported.[1, 8, 9, 10, 11, 12] This latter type which has been called icterus precox by Halbrecht[11] is characterized by:

1. A-B-O incompatibilities (infants usually belong to blood groups A or B. Mothers usually group O with elevated titers of anti-A or anti-B agglutinins in their serums).
2. Mildness of symptoms as a rule.
3. Spontaneous recovery in most cases.
4. Relative high frequency with which first born are affected in contrast with Rh cases.
5. High incidence of Rh-positive mothers.
6. Relatively more common in races which have a low incidence of Rh-negative individuals such as Negroes, Mongolians, and American Indians.

The cases herein reported are in keeping with the above characteristics and with the observations of Wiener and Zuelzer that most cases of erythroblastosis in Negro infants are due to antigenic factors other than Rh. Only one of our five cases could be attributed to Rh sensitization. One was due to A-O incompatibility. B-O incompatibilities were responsible for the disease in three cases. Other conditions capable of producing jaundice, anemia, or erythroblastemia in the newborn infant (congenital syphilis, sepsis, atresia of bile ducts, etc.) were excluded by appropriate clinical and laboratory studies.

As early as 1923, Ottenberg[13] suggested the possibility of interaction of the A and B agglutinogens with resultant pathologic processes. Jansson[14] (1936) concluded that A and B agglutinogens in human beings have an antigenic effect. In 1945, Polayes[10] reported six cases of isoimmunizations with A and B agglutinogens. Nance[15] (1946) reported four cases of icterus precox. Nathan, Greene, and Weiss[16] reported a case of congenital hemolytic anemia caused by isoimmunization with agglutinogen B. We have added four cases of icterus precox to the relatively small number reported in the literature. Wiener[12] believes that incompatibilities due to A-B-O sensitization are relatively frequent but have been overlooked because the manifestations are usually milder than in cases of Rh sensitization.

As to therapy each case of erythroblastosis has to be individually appraised. Allen and associates[17] have furnished statistical evidence which suggests that Rh-negative blood from young adult females is the treatment of choice in hemolytic disease of the newborn due to the usual Rh factor. A or B, certain authors[18] have suggested the use of type O Rh-negative blood in order to avoid the possibility of giving the infant blood to which he has circulating isoagglutinins. Sanford[19] on the contrary prefers to transfuse the infants' own type blood, either A or B, rather than type O blood.

TABLE I. SUMMARY OF CLINICAL FINDINGS IN FIVE CASES OF ERYTHROBLASTOSIS FETALIS

FINDINGS	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5
1. Maternal age	22	37	25	38	24
2. Maternal parity	1	3	2	0	0
3. Miscarriages or stillbirths	0	0	0	0	0
4. Gestation (months)	9	9	9	9	9
5. Type of delivery	Breech	Cephalic	Cephalic	Cephalic	Cephalic
6. Sex	Male	Male	Male	Male	Female
7. Birth weight (grams)	2,951	4,342	3,147	2,951	2,963
8. Onset of symptoms	Birth	3rd day	5th day	5th day	3rd day
9. Family history of anemia	None	None	None	None	None
10. Hemoglobin (grams)	6.7	13.7	15	11.5	5.0
11. Icterus index (units)	110	76	38	—	73
12. Van den Bergh (units)	3.8	—	6.1	—	29
13. Erythroblasts (%)	1.6	10	2	1	11
14. White blood count (uncorrected for immature red blood cells)	43,900	6,050	7,650	12,500	12,800
15. Blood Kahn or Wassermann	Negative	Negative	Negative	Negative	Negative
16. Rh factor (mother)	Negative	Rh_0	Rh_2rh	Rh_0	Rh_1rh
17. Rh factor (infant)	Positive	Rh_0	Rh_2rh	Rh_0	Rh_0
18. Blood group (father)	Not known	B	B	A_1	—
19. Blood group (infant)	O	B	B	A_1	B
20. Blood group (mother)	Not known	O	O	O	O
21. Maternal agglutinins	Anti-Rh	Anti-B 500 units	Anti-B 400 units	Anti-B 128 units	Anti-B 2,560 units
22. Bleeding time	2 minutes	15 seconds			
23. Clotting time	1.5 minutes	22 minutes			
24. Sedimentation rate	—	24	10	0	5
25. X-ray long bones	Normal	Normal	Normal	Normal	Normal
26. Sickling test (RBC)	Negative	Negative	Negative	Negative	Negative
27. Outcome	Recovered	Recovered	Recovered	Recovered	Recovered
28. Complication	None	None	None	None	Kernicterus

Repeated small transfusions produce satisfactory results for relatively mild cases. Diamond and others advocate exchange transfusions for infants severely affected at birth.

In the relatively milder icterus precox type of erythroblastosis fetalis due to isoimmunization with agglutinogen However, he admits that it probably makes little practical difference especially in an emergency.

More recently Seigneurin, Roget, Groulade, and Viallet[20] have reported the successful treatment of a case of hemolytic disease of the newborn due to B-O incompatibility with trans-

fusions of blood artificially composed of group O red cells and group A-B plasma.

The icterus precox variety of erythroblastosis fetalis in general has a better prognosis than the typical Rh hemolytic disease presumably because the anti-A and anti-B antibodies are weaker hemolytic agents than anti-Rh agglutinins.

SUMMARY

Five cases of erythroblastosis fetalis have been presented in Negro infants. Four cases had clinical and serologic findings consistent with the type described by Halbrecht as "icterus precox." Only one case exhibited typical Rh sensitization. That A-B-O sensitization can occasionally cause severe damage is reflected in one case which developed kernicterus but survived. Polayes[10] similarly reported kernicterus in an infant who died on the fifth day of life with hemolytic disease produced by anti-A agglutinins. The pertinent clinical features of our cases are summarized in Table I. It is noted that all patients recovered. Only one infant exhibited a complication (kernicterus). The infant with Rh sensitization presented characteristic symptoms at birth; however, the cases due to A-B-O sensitization did not develop significant findings until three to five days following delivery.

On the basis of our experience with erythroblastosis in Negro infants, we are inclined to concur with the observation of Wiener and Zuelzer that most cases of erythroblastosis in Negro infants are due to A-B-O incompatibilities (icterus precox) and not to Rh sensitization which is rare in this race.

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