1955

Hemolytic disease of the newborn due to ABO incompatibilities

Richard George Gere
University of Nebraska Medical Center

HEMOLYTIC DISEASE OF THE NEWBORN DUE TO ABO INCOMPATIBILITIES

Richard George Gere

Submitted in Partial Fulfillment for the Degree of Doctor of Medicine

College of Medicine, University of Nebraska

April 1, 1955

Omaha, Nebraska

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INTRODUCTION

The fact that hemolytic disease of the newborn can be caused by ABO incompatibilities is a relatively recent discovery, and is probably not generally known. The purpose of this paper is to discuss certain pertinent aspects of the disease, as compiled through a review of the literature, and to present a proven case of of hemolytic disease of the newborn due to ABO incompatibilities. Throughout this paper the disease will be referred to as it is stated in the title rather than erythroblastosis fetalis as many investigators designate it. This is because some confusion may result due to the fact that the term erythroblastosis fetalis has become so closely associated with hemolytic disease as caused by Rh sensitization.

ABO hemolytic disease, along with sufficient supportive evidence, was first reported by Polayes (1) in 1945. At that time he reported six cases of hemolytic disease in Rh positive mothers. Shortly thereafter, Halbrecht (2) reported similar findings. There have been many case reports in which the investigators were of the opinion that the hemolytic disease they described could be attributed to ABO incompatibilities. However, investigators such as Pickles (3) and Boorman (4) think that many of these reports did not contain suffi-

cient evidence to support the diagnosis. Since the initial report in 1945 much work has been done on the subject and many new, previously unknown, facts have been discovered and have been substantiated.

PATHOGENESIS

While the mechanism for production of ABO hemolytic disease is not entirely known, there are two entities that have been shown to be necessary. They are heterospecific pregnancy and iso-immunization.

Heterospecific pregnancy has been defined as one in which the fetus exhibits a blood group antigen of the ABO classification which is absent from the maternal red blood cells. (5) In the United States, among the white population, 35% of all matings will fall into the heterospecific group. (5) Since most of group A and group B are heterozygous, incompatibility of the child's red cells with the mother's serum occurs in approximately 25% of all births. (2)(6) An incompatibility could not be produced if the mother were AB because there are no antigens in that group to which she might be sensitized. (7)(8)

It is a known fact that iso-immunization takes place, but it has not been shown to the satisfaction of everyone how and why it occurs. Ottenberg (9), in a review on the etiology of eclampsia, stated that in 1905

Dienst recognized the possibility that maternal iso-immunization might be a factor in the production of certain morbid conditions during pregnancy and the neonatal period. It was Dienst's idea that an imperfect placenta, allowing transfusion of incompatible blood between the mother and fetus, was the mechanism for production of antibodies in the maternal blood against the red blood cells of the child. This concept, while seemingly plausible, is not thought to be the mechanism by the investigators doing the majority of the research in the field at this time.

The best way in which to show the most popular concept of iso-immunization is with the following diagram. The mother is designated as being of group O, but iso-immunization and an incompatibility could result if she were either group A or B. (7)

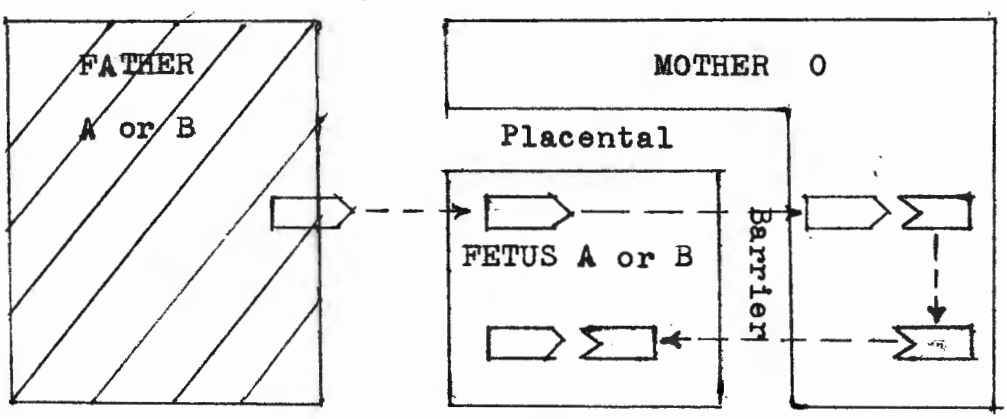

Fig. 1: Diagram of Mechanism of Iso-immunization (10)

As will be noted by the above diagram no explana-

tion is advanced as to how the placental barrier is crossed. Wiener (11)(12) in his observations, notes that A and B agglutinogens (antigens) are numerous and are good antigens. Further work by him, with agglutinin and conglutinin titers, led him to believe that univalent antibodies traversed the placenta more readily, as evidenced by a higher conglutinin titer. This titration is specific for univalent antibodies. He speculated that this phenomenon probably took place because they were smaller molecules. (11)(13)

Reports from many sources state that the process of iso-immunization occurs only when the infant is a secretor of group-specific substances containing A or B antigens. (7)(14) According to Schiff, secretors constitute 80% of all humans. Smith (7) postulated, that since iso-immunization occurs regularly when soluble group-specific substances are present in the saliva of the infant and fails to appear when they are absent, perhaps this is the substance that traverses the placenta into the maternal circulation and stimulates antibody formation.

Why do some infants born of mothers who have been shown to have a high anti A or B agglutinin titer fail to show any evidence of hemolytic disease? There is much speculation as to this and a few ideas will be dis-

cussed. Tovey (15) suggests that there is a protective mechanism that prevents anti A and anti B agglutinins from damaging the fetal erythrocytes, because there are twice as many mothers with an incompatible agglutinin for an A or B agglutinogen in the fetus than there is for an Rh negative mother with an Rh positive fetus, yet ABO hemolytic disease of the newborn is noted less often. Others (2)(6)(7)(16) are of the same opinion and think that perhaps the maternal agglutinins are specifically inhibited from acting on the fetal erythrocytes because of the wide distribution of the A and B antigens in the tissues and body fluids. In other words, the group-specific substances act as a buffering agent against the maternal agglutinins, and if the quantity of this is insufficient, hemolytic disease of the newborn will result. This, however, is pure speculation. Lack of permeability of the human placenta to the anti A and anti B agglutinins, lack of sensitivity of the fetal erythrocytes to the incompatible agglutinins, and diminished activity of the anti A and anti B agglutinins at body temperature have also been suggested as possible mechanisms for protection. (3)(15)

Needless to say there is much yet to be done before the entire pathogenesis of hemolytic disease of the newborn due to ABO incompatibilities is known.

FEATURES OF THE DISEASE

Although there are many variants in this disease, as there are in all medical entities, there have been sufficient case reports and studies to enable one to state the characteristic findings.

FREQUENCY- A review of the literature places the frequency of hemolytic disease of the newborn due to ABO incompatibilities somewhere between 5 and 20% of all newborn hemolytic diseases. (7)(17)(18)(19) Whether this represents the true frequency is yet to be determined, as a systematic study has not been done.

CLINICAL AND PATHOLOGICAL FINDINGS- All the findings that have been observed in Rh-Hr hemolytic disease have been reported in connection with this disease. However the clinical course is, in the most part, less severe although deaths and incapacitation have been been reported. Of interest is the fact that this disease occurs quite commonly when the mother is a primigravida. (20) Some sources report the incidence in primigravidas as high as 50%. (14)(17) Subsequent pregnancies have been shown to have little or no effect on the incidence. (20)

The most common clinical feature that has been observed is that of jaundice appearing during the first 24 hours of life. (14)(21)(22)(23) This occurs in 100% of the cases that have been proven and reported. It can

be differentiated from physiologic jaundice because the latter does not generally appear until 48-72 hours after delivery. (19) Halbrecht (2) has designated the jaundice that appears with this disease, as icterus neonatorum precox. Boorman et al suggest that some cases of physiologic jaundice might in fact be mild cases of hemolytic disease of the newborn due to the destruction of the fetal erythrocytes by anti A or anti B agglutinins. The jaundice usually clears by the end of one weeks time.

Splenomegaly and hepatomegaly may or may not be present. (22)(24)

Kernicterus is far from a rare finding, the incidence having been reported as high as 15%. (22) In one study, the patients developed the symptoms of this entity between 3-6 days. (22) That this feature does occur has been proven at autopsy, where brain changes were found that were consistent with kernicterus. (1)(22)

The least common finding is fetal hydrops; however, Aubert (25) reported this in 1945.

Pathologic variants have been reported by Zuelzer (22) describing two infants that had mild edema of the face and hands but did recover. He also reported a case that came to autopsy, at which time the findings were those of pulmonary edema, hemosiderosis, and hematopoiesis in an enlarged liver and spleen. (22)

LABORATORY FINDINGS- The laboratory findings will be discussed in an order that seems to be the logical manner in which they would be carried out.

One of the simplest, yet important, determinations is the blood type of both the mother and infant. According to most of the reports in the literature the mother will be type O Rh positive and the infant type A Rh positive. (13)(19)(23)(26) However, as mentioned previously, any heterospecific pregnancy can result in ABO hemolytic disease of the newborn. This is witnessed by the fact that cases have been reported in which: the mother was group O and the infant group B; the mother was group A and the infant group B (23); and the mother was group B and the infant group A. (26)

The usual form of the disease shows little or no anemia. (13)(19)(22)(27) The average hemoglobin value varied from 15.5 to 12.8 grams per cent in one study. (15)

The diagnosis is greatly facilitated by the careful examination of a peripheral blood smear from the infant. The most common finding is that of a notable degree of microspherocytosis. (17)(19)(22)(23) Further serial studies have shown that the spherocytes generally disappear in one to two weeks. (27) This is in direct contrast to Rh-Hr hemolytic disease, but does simulate the findings in congenital hemolytic anemia. (17)

Reticulocytosis has been reported to be found in varying degrees. (17)(19) A reticulocyte count greater than 5% is noticed in most cases. (27) The severity of the disease may be evaluated by the degree of reticulocytosis. (17)

On some occasions nucleated red blood cells have been seen but this is not at all common, or at least has not been reported as being significant. (17)(22)(26)

Whereas the Direct Coombs Test is a valuable indicator in the diagnosis of Rh hemolytic disease, it has proven variable in ABO incompatibilities. For the most part it is negative, but it has been shown to be weakly positive in some studies. (4)(17)(19) In the face of a negative Direct Coombs Test, Hsia and others have shown that a two stage Coombs was positive in a fair percentage of cases. (14)(21)

The seriousness of possible sequelae in this disease is dependent on the bilirubin concentration. Serum bilirubin levels are higher than the maximum levels that are seen in normal infants. (14)(17)(21) A serum bilirubin level of 10 mgs. per cent or higher at 24 hours or less post partum, along with other characteristic findings of the disease, is sufficient evidence to warrant the diagnosis of ABO hemolytic disease of the newborn. (21) Another useful guide to the severity of the disease is

the rate of increase of serum bilirubin. An increase of 0.5 to 1.0 mgs.% per hour is considered significant. (17) If at all possible the serum bilirubin concentration should be kept below 20 mgs.%, by exchange transfusion if necessary. (14) Kernicterus is related to bilirubinemia and has been observed in 15% of the cases. (22)

Extensive work has been done on the anti A and anti B agglutinin titers as related to this disease. It has been concluded that the finding of high titers during pregnancy has limited diagnostic value and frequently occurs in a mother who later gives birth to a normal offspring. (18)(24)(27) The fact should be appreciated that these titers are difficult to evaluate because of the occurence of natural anti A and anti B iso-antibodies. Nonetheless, it has been shown that an unusual or immune antibody is not present. (19)(24) However, it has been suggested that a maternal, perhaps natural, antibody with special immune characteristics is present. (22) Although variable titers are found in mothers whose infants show ABO hemolytic disease, these titers are generally higher than the average normal. (19)

It is difficult to state just what are significant maternal anti A and anti B agglutinin titers because reports have ranged from 1:16 to 1:82,000,000, depending upon how soon after delivery the titration was done and

whether saline, albumin, or human serum was used as a diluent, the latter two giving considerably higher titers. (21)(24)(28) In general the maximum concentrations in the maternal serum are reached between the fifth and twentieth day post partum. (29) The previously mentioned titer of 1:82,000,000 was done on the fortieth day after delivery.

The secretor status of the infant, as discussed in pathogenesis, is all important. When saliva of an infant whose mother showed a high agglutinin titer is tested it is found that in all cases they are secretors. (8)

Fetal anti A and anti B agglutinin titers are also present although most reported cases make no mention of them. An anti A titer of 1:128 was reported in conjunction with a case of fetal hydrops due to ABO hemolytic disease. (25) In general a fetal titer of 1:4 or over is considered significant. (14)

Hemolysin titers against fetal group A and B erythrocytes have been shown in the maternal serum in most cases. Anti A or anti B hemolysins have been found in all cases of ABO hemolytic disease of the newborn, if complement was present. However, some of the control groups showed similar findings. Therefore this test was considered to be of greatest value when negative, as it would appear to rule out the disease. (14)(26)

Zuelzer (22) was able to demonstrate only A_1 hemolysin in the maternal serum when the infant was of group A. He speculated that perhaps A_2 infants might not be susceptible.

It has been shown that there is increased fragility of the fetal erythrocytes in a high percentage of the cases. (14)(17)(21)(23)(26) Some investigations have shown that there is increased mechanical as well as osmotic fragility present, only in a lesser degree. (21(14)

TREATMENT

The treatment, as would be expected, is on an individual basis and depends on the severity of the disease. The majority of the cases require no treatment, as the course of the disease is usually benign. (13)(17)(23) When it is moderately severe, as evidenced by a rising fetal serum bilirubin level or a falling hemoglobin level, a simple transfusion usually abates the hemolytic process. (17)(26) In case the bilirubin and hemoglobin values are nearing dangerous levels, an exchange transfusion will be necessary. (17)(23) Group O Rh negative or positive blood, depending on the Rh typing of the infant, should be used for the transfusions. (17)(20)

PROGNOSIS

The prognosis for hemolytic disease of the newborn

due to ABO incompatibilities is usually good, again depending on the severity of the disease. (20)

PRESENTATION OF A CASE

The case to be presented is that of R.J., a white male child, case number 116660 who was born at the University of Nebraska Hospital on December 3, 1953.

HISTORY- The mother was a white 27 year old gravida IV para III. The entire pregnancy was uneventful. Labor was of 4 hours duration and uncomplicated. Delivery was spontaneous and the immediate post natal condition of the infant was satisfactory. The mother was group O Rh positive and the infant was group A Rh positive.

CLINICAL COURSE- The skin of the infant developed a yellow-orange tinge within the first 24 hours. The remainder of the physical exam at that time was negative with the exception of the liver being palpable one-half fingersbreadth below the right costal margin.

SUMMARY OF FINDINGS- A summary of the pertinent aspects of the clinical course and the laboratory findings are as follows:

a. The mother is type O Rh positive and the infant type A Rh positive.

b. Jaundice was present in the first 24 hours.

c. Mild anemia was present.

d. Peripheral blood smears showed microspherocytes and 9.4% reticulocytes.

e. The Direct Coombs Test was negative on two occasions.

Date	12-4	12-6	12-7	12-8	12-9	12-11	12-14
Hgb. Gms.%	19.2	16.8	17.5	15.7		14.8	12.8
RBC	5.12		4.43				
M'spherocytes		/			/	/	
Retics.					9.4%	9.0%	6.3%
Direct Coombs	Neg.				Neg.		
Serum Bilirubin mgs.%			1'-3.4 T-21.6		1'-5.7 T-27.4	1'-2.9 T-17.8	1'-1.6 T-8.6
Anti A Titer					1:320		
A_1 Hemol.				/		/	
Os.Frag. %Nor.Sal.					B-0.58 C-0.22		
Bleed. Time			2 min.				
Clot. Time			4 min. 30 sec.				

Table 1- Summary of laboratory Findings

f. The serum bilirubin was greatly elevated.

g. An anti A agglutinin titer of 1:320 was present.

h. An A_1 hemolysin was demonstrated on two occasions.

i. The fetal red blood cells showed an increased osmotic fragility.

Due to these findings there is sufficient evidence to warrant the diagnosis of hemolytic disease of the newborn due to ABO incompatibilities.

The patient did well and was dismissed on December 15, 1953. He was readmitted on January 5, 1954 for evaluation to determine if a transfusion was necessary. Physical exam at that time revealed no jaundice, but there was pallor of the skin and mucous membranes. Hemoglobin on two consecutive days was 9.0 grams and 9.8 grams respectively. The leucocyte count and the differential were within normal limits. The patient was deemed to be in good condition and that no transfusion was necessary. He was discharged for the second time on January 7, 1954.

SUMMARY AND CONCLUSIONS

Since Polayes reported the first case of hemolytic disease of the newborn due to ABO incompatibilities in 1945, extensive work has been done on the subject.

While the pathogenesis of the disease has not been entirely worked out, it has been shown that heterospecific pregnancy and iso-immunization are major factors. That iso-immunization takes place only in infants who are secretors of A or B antigens has been established, but whether these are the substances that traverse the

placental barrier is not known, although there are some theories to that effect.

The most common clinical and pathologic finding in this disease is the appearance of jaundice within the first 24 hours of life.

Laboratory examinations are of great aid in confirming the diagnosis. The positive points as determined by the laboratory are: little or no anemia; reticulocytosis; microspherocytosis; negative or weakly positive Direct Coombs Test; increased serum bilirubin; the presence of an anti A or anti B agglutinin titer; the demonstration of an anti A or anti B hemolysin; and the increased fragility of the infant's red blood cells.

Treatment is generally not necessary, but this is determined by the severity of the disease. When the disease is of a more severe nature a simple or exchange transfusion of type O blood is indicted.

The prognosis is very good as the disease process is usually benign, however, kernicterus and deaths have been reported.

A case was presented in which there was sufficient positive evidence to warrant the diagnosis of hemolytic disease of the newborn due to ABO incompatibilities.

ACKNOWLEDGEMENT

I wish to take this opportunity to thank Dr. Morton

Kulesh for his assistance and guidance in the preparation of this paper. The assistance rendered by the library and medical records staffs is also greatly appreciated.

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