ANTENATAL SELECTION OF DONORS FOR EXCHANGE TRANSFUSION IN ERYTHROBLASTOSIS

A. S. WIENER, M.D., AND I. B. WEXLER, M.D.*

Brooklyn, New York

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THE recent demonstration (1, 2, 3, 4) that two varieties of antibodies are formed as the result of Rh sensitization has suggested to one of us that the pathogenesis of erythroblastosis and its various clinical manifestations are dependent upon the kind and concentration of these antibodies in the maternal and consequently also the fetal organism (5, 6). Furthermore, by antenatal Rh testing it is possible to predict before birth, with a high degree of accuracy, whether an infant will have the disease and also in general what the clinical picture will be both in type and severity (7, 8).

The two varieties of antibodies resulting from Rh sensitization are known as agglutinins and blocking antibodies (or glutinins). The available evidence indicates that the latter are comprised of smaller molecules readily capable of traversing the placenta and of "coating" the erythrocytes of the infant in utero (7). It has been demonstrated, furthermore, that clumping of the coated cells does not take place except in the presence of an additional substance found in normal blood plasma which has been named conglutinin and seems to be identical with the X-protein of Pedersen (2, 8, 10). Conglutinin is a conglomerate of plasma proteins which is absent or deficient in the blood of the fetus and also the newborn for a short time after birth. On this basis the fact may be explained that frequently no clinical symptoms are evident in the erythroblastotic infant until this complex is formed. When conglutinin reaches an effective concentration in the infant's blood, either as a result of the normal process of maturation or because of dehydration, clumping of the erythrocytes in the vascular bed with extensive tissue damage may take place. Until that time hemolysis owing to trauma of the circulation on the coated and consequently fragile cells is the dominant pathologic process. Therefore, the finding of blocking antibodies in the mother's plasma indicates that either an hydropic stillbirth or an anemic child is to be expected, depending upon the titer of the maternal antibodies. If after birth excessive conglutinin is formed or if the child is permitted to become dehydrated, intravascular clumping occurs leading to the syndrome of icterus gravis.

* From the Transfusion Division and Department of Pediatrics, Jewish Hospital, Brooklyn, N. Y.

In the case in which the antibodies consist of agglutinins, a different variety of clinical erythroblastosis is to be expected. The agglutinating antibody is assumed to be larger than the blocking antibody because, as a rule, it does not gain entrance to the infant's circulation until the time of birth when it is milked into the circulation by the action of the contracting uterus. The infant in such cases often appears normal at first, indicating that no clumping of the erythrocytes with resulting tissue damage has as yet taken place. Within a few hours or days, however, jaundice sets in and the typical symptom complex of icterus gravis unfolds. Liver damage and sometimes nuclear jaundice, as a rule without anemia, dominate the picture. Where only small quantities of agglutinins gain access to the infant's body, the agglutination of the infant's erythrocytes is weak and readily reversed by the circulation of the blood. In such cases, the repeated clumping and tearing apart of the red cells may lead to an abrupt breakdown of the cells so that hemolytic anemia results instead of icterus gravis.

Simple transfusions of Rh-negative blood will help only those infants with hemolytic anemia uncomplicated by intravascular clumping. To prevent tissue damage in instances in which clumping is likely to occur, the infant's sensitized Rh-positive cells must be removed and replaced with inagglutinable Rh-negative cells.* This is the rationale of replacement transfusion (11, 12, 13, 14, 15) which must be carried out as soon after birth as possible if it is to be successful. Once intravascular clumping has taken place, the tissue damage that results may be permanent.

In view of the considerations presented, the ideal time for the institution of therapy is immediately after birth. For this reason we have attempted to select compatible donors before the baby is born, and to be in the delivery room ready to start the procedure within minutes after delivery. The purpose of this paper is to explain how it is possible to select donors antenatally in the majority of cases (20, 21). For our purposes the cases can be divided into two categories, namely, those in which it is possible to select a suitable donor for the baby before it is born and those in which the group of the infant must be determined before the donor can be chosen. In tables 1 and 2 the various possible combinations in each category are summarized. In constructing the tables it was necessary to bear in mind that the newborn infant and the fetus are incapable of producing antibodies, and that any antibodies present in the infant's serum at birth are derived passively from the mother. Thus the mother's group is an important consideration. In addition, because of the relatively large amount of blood introduced during an exchange transfusion, the agglutinins present in the donor's serum cannot be ignored even though they may be present in low titer.

* The other alternative, namely, to attempt to desensitize the infant by massive transfusions of Rh-positive blood (16, 17, 18), has proved to be too dangerous and has succeeded only in the most mildly affected infants (19).

In table 1, for example, when the father belongs to group O and the mother to group A, the baby may belong to group O or to group A. In either event, the infant's blood can contain only beta (anti-B) and not alpha (anti-A) antibodies because the latter are lacking from the maternal plasma. Therefore, if a donor with group A, Rh-negative blood

TABLE 1

COMBINATIONS IN WHICH THE DONOR CAN BE SELECTED WITHOUT WAITING FOR A DETERMINATION OF THE BABY'S BLOOD GROUP

Father	Mother	Donor
O	O	O
O	A	A
A	A	A
O	B	B
B	B	B
O	AB	AB
A	AB	AB
B	AB	AB
AB	AB	AB

TABLE 2

COMBINATIONS IN WHICH THE BABY'S GROUP MUST BE DETERMINED BEFORE A COMPATIBLE DONOR CAN BE SELECTED

Father	Mother	Infant	Donor
A	O	A	A
		O	O
B	O	B	B
		O	O
A	B	O	O or B
		A	A or AB
		B	B
		AB	AB
B	A	O	O or A
		A	A
		B	B or AB
		AB	AB
AB	A	A	A
		B	B or AB
		AB	AB
AB	B	A	A or AB
		B	B
		AB	AB

is at hand in such a case, one may proceed with the transfusion without waiting for the infant's blood group to be determined. On the other hand, the donor cannot be selected in advance if the mother belongs to group O and the father to group A. In such an instance, if the infant belongs to group O, its serum would contain both alpha and beta antibodies and hence only a group O donor would be compatible, while if

the infant belonged to group A, a group O donor would not be acceptable because of the presence of alpha agglutinins in the donor's plasma and only a group A donor may be used. The remainder of the combinations in the table can be analyzed in the same way.

In cases of great urgency when compatible donors are not at hand, group O blood to which Witebsky's A and B substance * has been added and the alpha and beta antibodies neutralized, may be used to start the procedure and matched blood used to complete the transfusion.

TABLE 3

HEMATOLOGIC FINDINGS FOLLOWING EXCHANGE TRANSFUSION

	Before Transfusion 1/25	After Transfusion 1/27	2/9	3/4	3/15	3/29	4/22
Hemoglobin, per cent	96	118	85	56	57	69	74
Grams per 100 cc.	13.9	17.2	12.3	8	8	10	10.7
Erythrocytes, millions	4.0	5.28	3.9	3.46	3.07	3.54	3.83
Leukocytes	—	4,900	10,000	6,300	10,150	—	10,900
Polymorphonuclear cells	55	48	27	11	18	32	23
Band forms	3	22	0	3	1	—	1
Lymphocytes	27	12	47	76	69	56	71
Monocytes	—	2	11	6	10	7	2
Eosinophils	9	16	15	4	2	5	2
Basophils	1	0	0	0	0	0	1
Myelocytes	5	0	0	0	0	0	0
Normoblasts	8	0	0	0	0	0	0
Reticulocytes	—	—	1/2%	2%	1%	1/2%	1/2%
Icteric Index	24	—	—	—	—	—	—
Differential agglutination	100% BMRhurh	2% BMRhurh 98% A_1BMNrh	—	—	2/3 BMRhurh 1/3 A_1BMNrh	9/10 BMRhurh 1/10 A_1BMNrh	100% BMRhurh

It is our practice to test the serum of all Rh-negative donors used for transfusions to Rh-positive infants for the presence of Rh antibodies. If antibodies are found, the donor is rejected, but his blood may be used for transfusing sensitized Rh-negative adults. Also, Rh-negative donors giving a history of having received a transfusion in the past that might have sensitized them, particularly ex-service men, are not used by us for transfusions to infants, even though antibodies are not demonstrable in their sera [cf. Kelsall (22)].

Those physicians who have been reared under the dictum that patients must never be given blood of groups containing agglutinogens lacking from their own blood, may find it difficult to convince themselves that, for example, it is safe at times to give to group O infants O blood from group A, B or AB donors (20, 21). Therefore, one of our cases will be described which illustrates the successful application of the principles outlined.

CASE REPORT

A pregnant white woman was referred to us with the following obstetrical history. Her first pregnancy, in 1943, ended at term with the birth of a normal male infant who is now living and well. At the time of her first visit to us she

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was in the seventh month of her second pregnancy. Routine Rh tests performed during the sixth month of her pregnancy showed her to be Rh negative; however, no Rh antibodies were demonstrable in her serum up to this time despite several examinations. One month later she took a long automobile trip, and shortly thereafter she experienced an attack of giant urticaria which lasted for about a week. When her serum was retested two weeks later for the presence of Rh antibodies, positive results were obtained. She was then referred to us for further study.

Results of grouping and Rh-Hr tests on the father, mother, and the four year old son were as follows:

Blood of	Group and Subgroup	M-N Type *	Rh-Hr Type
Father	A_1	M	Rh_1rh
Mother	A_1B	MN	rh
Son	A_1B	MN	Rh_1rh

* The M–N types are not of clinical importance but are given for the sake of completeness.

Anti-Rh agglutinins were found to be present in the mother's serum in a titer of 2 units. By the standard plasma conglutination technic (8) the anti-Rh titer was 3 units while by the plasma-albumin conglutination technic (23) the anti-Rh titer was 4 units.

These results indicated that the mother was mildy sensitized to the Rh factor. From the sequence of events it seemed probable that she was originally "primed" by the birth of her previous Rh positive infant, and had received the second stimulating inoculation of Rh-positive blood during the second pregnancy in the course of her automobile trip (24).

A course of counter immunization injections with typhoid and pertussis antigen (21) was undertaken but was of no avail because on restudy two weeks later, anti-Rh agglutinins of 16 units titer were found in the patient's serum. Because of the rise in titer it could be predicted with reasonable certainty that the fetus was Rh positive and also would be erythroblastotic. Furthermore, because of the nature of the antibodies (agglutinins) the type of manifestation in the infant was likely to be icterus gravis.

It was decided to induce labor two weeks before term and to perform an exchange transfusion on the infant immediately after birth. Inasmuch as the mother belonged to group AB and the father to group A, the infant would have to belong to group A, group B, or group AB. In any event, no agglutinins against A or B could be present in the infant's plasma because the mother belonged to group AB so that her plasma contained no alpha or beta agglutinins. Whatever group the infant belonged to, blood of group AB would be compatible (cf. table 1). Accordingly, a donor was selected who belonged to group AB, type rh. When the patient went into labor 500 cc. of blood was withdrawn from the donor, half the plasma removed, and saline solution added to make up the original volume. (This was done to reduce the conglutinin content of the transfused blood.) When the baby, a female weighing 6 pounds and 3 ounces, was born her color was good, but respirations were grunting and she appeared to be lethargic. Cord blood was collected for studies to be carried out at a more convenient time, and an exchange transfusion was begun, using the method described in our previous papers. The infant's general condition remained unchanged during the procedure but on the following day the baby appeared much improved.

Laboratory studies done on the cord blood showed: icterus index, 24 units; hemoglobin concentration 13.9 Gm. per 100 cc.; red blood count, 4,000,000. The differential white count was as follows: polymorphonuclear cells, 55; lymphocytes, 27; eosinophils 9; basophils, 1; juveniles, 3; myelocytes, 5; normoblasts, 8 per 100 white blood cells. The baby's blood proved to belong to group B, type M and type Rh,rh; the complete classification of the donor's blood was group A_1B, type MN, type rh. Forty-eight hours following the exchange transfusion the blood examination showed: hemoglobin concentration, 17.2 Gm. per 100 cc. and leukocyte count, 4,900. The differential white count was as follows: polymorphonuclear cells, 48; band forms, 22; lymphocytes, 12; eosinophils, 16; monocytes 2. No nucleated red blood cells were seen.

The infant's subsequent course was uneventful except for the development of moderate jaundice that lasted for about four days. Further transfusions were not required. After leaving the hospital her blood was examined on several occasions. At 15 days of age the hemoglobin concentration was 12.3 Gm., and the erythrocyte count 3,900,000. The smear showed 15 per cent eosinophils, indicating that the antigen-antibody reaction in the infant's body was still going on. When the child was seen at the age of 40 days, the hemoglobin had fallen to 8 Gm. per 100 cc. and the erythrocyte count was 3,600,000, but the smear showed 2 per cent reticulocytes and only 4 per cent eosinophils. The drop in the eosinophil count indicated that the Rh antibodies were no longer present in the infant's body and that recovery was to be expected without further treatment. This prediction proved to be correct, for when the baby was seen at the age of 2 months the hemoglobin has risen to 10 Gm. per 100 cc., and when last seen at the age of 3 months, the count had risen slightly higher. Differential agglutination tests to determine the survival of the donor's blood in the circulation were particularly easy to carry out in this case because the blood of the donor and that of the infant differed not only in the Rh type but also in the blood group and the M–N types. Tests performed two days after the transfusion showed that scarcely any of the infant's blood remained in the circulation. The donor's blood cells could be detected in the circulation for more than two months thereafter although the donor belonged to group AB and the baby to group B, so that the survival time of the transfused cells compares favorably with that obtained when blood of the homologous group is transfused.

SUMMARY

The rationale of exchange transfusion treatment for erythroblastosis is briefly discussed. Since the treatment must be carried out as soon after birth as possible, any means that would serve to shorten the time between the birth of the child and the institution of treatment is of value. In many instances the group of blood that will be compatible with that of the infant can be predicted if the groups to which the mother and the father belong are known. These are tabulated. A table is also given listing those instances in which the infant's group must be determined before a compatible donor can be selected. A case is presented illustrating the selection of a donor for an exchange transfusion before the birth of the infant. The mother belonged to group AB and the father to group A and an Rh-negative donor belonging to

group AB was chosen. The infant later proved to belong to group B. Nevertheless, the donor's blood survived in the infant's circulation for more than two months, a survival time that compares favorably with that obtained when blood of the homologous group is used.

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