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Erythroblastosis fetalis : a review of recent literature with specific emphasis to serologic principles and review of irregular antibody screening at UNMC

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ERYTHROBLASTOSIS FETALIS

REVIEW OF RECENT LITERATURE WITH SPECIFIC EMPHASIS TO SEROLOGIC PRINCIPLES

AND

REVIEW OF IRREGULAR ANTIBODY SCREENING AT THE UNIVERSITY OF NEBRASKA COLLEGE OF MEDICINE

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The discovery of blood groups in man is a relatively new finding. Since 1900 when Landsteiner made his Nobel Prize-winning discovery of the ABO system, this field has expanded to such a degree that it is now a highly specialized area of clinical and investigative science. The relation of hemolytic disease of the newborn to the field of blood groups was not realized until 1939 when Levine and Stetson published their historic paper[1]. The investigation for this paper was stimulated by a severe hemolytic transfusion reaction suffered by a mother of a stillborn fetus to her husband's blood which was compatible with respect to blood groups recognized at that time. These investigators proposed that a "new" antibody had originated from fetal sensitization of the mother to a factor inherited from the father. A year later in 1940, Landsteiner and Weiner identified a new antibody which agglutinated eighty-five percent of a population group studied and was found to be responsible for many severe transfusion reactions of "compatible" ABO blood types. This antibody, the Rh or rhesus, was subsequently proven identical to that one found by Levine and Stetson. Furthermore, in 1941, Levine, Burnham, Katzin and Vogel showed that the Rh factor was responsible for some cases of erythroblastosis fetalis. This historic breakthrough in the

etiology of hemolytic disease of the newborn led the way for further studies regarding other blood groups resulting in fetal-maternal sensitization. This latter topic will be covered later in this paper.

Due to the scope of this paper and the vast quantity of material written on the subject, the general considerations of pathologic physiology will be presented in severely abbreviated form to serve as a lead into the main topic i.e. serologic aspects of hemolytic disease of the newborn. Erythroblastosis fetalis is the condition resulting from antenatal transmission of antibody from the mother to the fetus. The antibody causes hemolysis of the antigen bearing fetal red blood cells producing varying degrees of anemia and stimulation of ectopic hematopoesis. Normally erythrocytes are produced only in the liver and bone marrow during the latter one half of pregnancy. When the anemia due to hemolysis is present, the fetus must increase production of erythropoetic tissue and thus maintain the blood forming mesenchymal tissue used in the first half of pregnancy and form additional tissue from totipotential cells located about the smaller vessels[2]. These ectopic areas of hematopoesis tend to release immature

forms of cells more readily than the bone marrow and liver and hence cells such as hemacytoblasts (erythroblasts) and mitotic immature cells of the erythroid series may be found in the peripheral circulation. Hence, the term erythroblastosis was derived. This condition is one of the few anemias in which hemacytoblasts and mitoses may be found in the peripheral circulation.

The pathophysiology of this disease has as a common denominator, the anemia resulting from destruction of red blood cells.and the increased bilirubin resultant from the destruction of erythrocytes. The anemia is the condition which first threatens the life of the fetus. It results in an anoxemia which endangers those tissues most sensitive to hypoxia, i.e. liver, brain and endothelial cells. The response of the organism is increased production of erythroid elements, and when it is severely affected by hemolytic disease, additional sources of red blood cells are required. The ectopic hematopoesis which results affects many of the organs of the fetus, most prominently the kidneys, liver, spleen and lymphopoetic sites. Hypoxia results in cardiac failure which further aggravates an already

serious anemia and produces further tissue hypoxia, peripheral edema, liver failure and endocardial damage.

Hyperbilirubinemia and its sequelae, kernicterus, are postnatal complications of hemolytic disease of the newborn and occur in those infants who survive the ravages of the disease in utero.

Further discussion of diagnosis, treatment and complications of hemolytic disease of the newborn will be deferred from this paper. Reference is made, however, to the December 1964 issue of Clinical Obstetrics and Gynecology for an excellent seminar on the subject of erythroblastosis fetalis.

The discovery of the ABO system in 1900 was only the beginning of the identification of a large number of serologically identifiable antigens in human blood. At the present time there are approximately fourteen separate blood group systems. In addition there may be added two unique groups of antigens. They may be categorized in this way: 1)very infrequent or "private" antigens (about one dozen) and 2) frequent or "public" antigens (about a half dozen). These "public" and "private" categories as their name implies refer to the incidence of these antigens in the general public and are important only rarely but have caused hemolytic

transfusion reactions and hemolytic disease of the newborn in isolated instances.

Among the fourteen recognized blood group systems, two in particular have been identified as causing the majority of maternal-fetal incompatibility resulting in hemolytic disease of the newborn. These two systems are the ABO and Rh systems and account for about ninty-eight per cent of cases of this disease. It is beyond the scope of this paper to consider in depth ABO hemolytic disease. For the sake of completeness, however, a few basic facts regarding the ABO system are included.

Approximately twenty-two per cent of all pregnancies in this country are ABO incompatible between mother and fetus[3]. The incidence of hemolytic disease of the newborn due to ABO incompatibility, however is much less than that number of ABO incompatible pregnancies. Somewhat greater than one per cent of all newborns are affected[3].

The ABO system, as do most other blood groupings, contains a wide variety of antibodies. Among these antibodies are naturally occuring or saline reacting antibodies which rarely cross the placenta and are

for all practical purposes not associated with hemolytic disease of the newborn. The acacia reacting or 7s gamma$_2$ globulins are most consistently correlated with hemolytic disease of the newborn in the ABO system and should be searched for in group O and A_2 mothers prior to delivery in the third trimester. The latter reccommendation is in contradistinction to suspected Rh incompatibility in which much earlier detection of the disease is mandatory to the proper management. This is due to the rarity of hydrops fetalis from pure ABO incompatibility. ABO hemolytic disease produces a milder anemia.

The discovery of the Rh blood group system was alluded to earlier in this paper. Since its discovery in 1939, this blood group system has greatly increased in complexity. Controversy still exists regarding genetic determination of the antigenic factors of this system. This is evidenced by the Wiener and Fisher theories regarding the inheritance of Rh system blood factors.

The Rh_o (D antigen of Fisher) antigen is by far the most familiar antigen of the Rh system. There exist, however many more antigens in the Rh system and

for the purpose of this paper we will consider only those which are more common.

Five identifiable antigens and one antigen to which no antisera has yet been found constitute the greatest majority of genotypes found in the Rh system. These antigens and their frequencies in a caucasian population are listed in the table below[5]:

SEROLOGICAL CONFIRMATION OF FISHER'S THEORY

Antibodies	Anti-C	Anti-D	Anti-E	Anti-c	Anti-d	Anti-e
English % positive	70	85	30	80	65	96
CDe	+	+	-	-	-	+
cDE	-	+	+	+	-	-
cde	-	-	-	+	+	+
cDe	-	+	-	+	-	+
cdE	-	-	+	+	+	-
Cde	+	-	-	-	+	+
CDE	+	+	+	-	-	-
CdE	+	-	+	-	+	-

genes & antigens

The above antigens were considered by Fisher to be allelic and to occur in combinations of three, determining eight phenotypes. Immune antisera to any

of these antigens could develop upon stimulation by antigen to which the host has no naturally occuring counterpart e.g. anti-c in an individual homozygous "C". This occurs in incompatible transfusions and transplacentally during pregnancy, especially at the time of delivery.

Although Rh_o (D) is the antigen to which sensitization occurs most frequently and with the most dire results, sensitization to other factors such as "c"[6], "E", "e", "C" also occurs. The severity of hemolytic disease produced by these factors can vary from mild, requiring no exchange transfusion, to severe, resulting in intrauterine death.

The antibodies of the Rh system which cross the placenta and cause erythroblastosis fetalis are of the incomplete or blocking type and are best detected by means of the Coomb's antihuman globulin test.

Hemolytic disease of the newborn can be accounted for in the great majority of cases by the two preceding systems and more specifically by the Rh_o and AB antigens.

The remainder of this paper will consider those

antibodies other than anti-D and anti-A and B known henceforth as "irregular" antibodies. The various blood group systems will be of necessity reviewed briefly. Any pertinence of their component antibodies to hemolytic disease of the newborn will be discussed and data on incidence of the irregular antibodies and hemolytic disease of the newborn due to irregular antibodies will also be presented.

The MN blood group was discovered in 1927 by Landsteiner and Levine. The system was subsequently proven to be the result of two codominant alleles and the blood types M, MN, and N were the phenotypes produced by these genes. Walsh and Montgomery found a "new" antibody, anti-S, in 1947 which was later associated with the MN blood groups. It was the work of these investigators that led to the classification of the MNSs system.

Other antibodies have been shown to be related to the MNSs system. Some of these have only been found in immune sera of rabbits injected with human blood e.g. anti-He and anti-Hu. Others are fairly common in the human population e.g. anti-Mg^a.

Rare cases of hemolytic disease of the newborn

have been associated with antibodies of the MNSs system. Many of the antibodies of this system are "naturally occuring"antibodies and therefore do not cross the placental barrier[7].

Anti-M[8], anti-S[9] anti-s[10], and anti-U of this system have been associated with hemolytic disease of the newborn. Other antibodies of this system have also caused hemolysis of fetal blood e.g. anti-Vw, and anti-Mi^{a}, although their occurance is rare.

The Lutheran blood groups were first recognized in 1945 by Callander, Race and Paykoc[11] and described in more detail by Callander and Race in 1946. The antibodies occurring in this blood group system can be of either the natural or immune varieties. It is the immune variety which is associated with hemolytic disease of the newborn. Detection of immune antibodies of this group may be done with the Coombs antihuman globulin techniques.

The incidence of hemolytic disease of the newborn due to sensitization by Lutheran antibodies is rare and, when it does occur, subclinical or mild cases are the result.

The two antigens of the Lutheran system Lu^{a}and Lu^{b} are recognized by their specific antibodies

anti-Lu^a and anti-Lu^b. Their notation therefore is combined to Lu(a+ b+), Lu(a- b+), Lu(a+ b-) etc. depending on the presence or absence of the particular antigens of the system.

Most of the cases of hemolytic disease of the newborn due to the Lutheran blood groups are due to anti-Lu^b.[12] A case of hemolytic disease of the newborn due to anti-Lu^a was reported in 1959 by Francis and Hatcher.

The occurrence of hemolytic disease of the newborn due to sensitization to Kidd blood group system antigens has been reported in several cases.[13 14 15] The Kidd blood group system was discovered by Allen, Diamond and Niedziela in 1951[16] as a result of investigation of the serum of a mother, Mrs. Kidd, whose child suffered from hemolytic disease of the newborn.

The incidence of the Kidd antigens in the caucasian population is approximately as follows:

Jk(a+ b-) 25% Jk(a+ b+) 52% Jk(a- b+) 23%

Therefore about 77% of the white population is Jk^a positive.

An absence of reaction to either Jk^a or Jk^b has been found in some Filipinos.

Anti-Jk^a has been the cause of rare hemolytic disease of the newborn cases and hemolytic transfusion

reactions. Anti-Jk^b on the other hand has been recognized on several occasions as producing hemolytic disease of the newborn. Kornstad and Havorsen, Geczy and Leslie, Wagman and Bove, Zodin and Anderson have reported cases of hemolytic disease of the newborn due to the latter antibody. The severity of the disease has been mild and it may be suspected that many cases of sensitization go unrecognized.

Sensitization of maternal serum to Kidd blood group antigens is not totally understood. Evidence indicates, however, that transplacental passage of antigen was responsible for at least one case of hemolytic disease of the newborn due to anti-Jk^b.[17]

Identification of Kidd antibodies is possible by a variety of methods including saline, the trypsin antiglobin test of Unger, Löw's papain test and a modification of the antiglobin test.[18]

The discovery of the Duffy blood group system was made in 1950 by Cutbush, Mollison and Parkin. The system received its name from the individual in whom the antibody was first identified, a man suffering from hemophila who had had numerous transfusions. Two antibodies anti-Fy^a and anti-Fy^b were eventually identified. The frequency of these phenotypes as

listed by Race and Sanger[19] are as follows:

Fy(a+ b+)	48%	Fy(a+ b-)	19%
Fy(a- b+)	32.5%	Fy(a- b-)	0%

The above frequency figures are for caucasian populations only. In 1955, however, Race Sanger and Jack[20] noted that many negroes did not react to either anti-Fy^a or anti-F^b and another genotype Fy(a- b-) or Fy was postulated. Seventy percent of negroes were found to give no reaction to the presently identified Duffy antibodies and were therefore Fy(a- b-).

Information concerning the effects of Duffy blood group sensitization is not yet sufficient for generalizations concerning their significance. Anti Fy^a has been the cause of severe transfusion reactions. Somewhat greater than a dozen cases of hemolytic disease of the newborn due to anti-Fy^a had been reported by Race and Sanger[21] by 1958. No cases of hemolytic disease of the newborn have been attributed to anti-Fy^b at the time of the latter text.

Identification of the antibodies of this system is best accomplished by means of the antiglobulin technique due to their occurrence in the incomplete form.

Shortly following the availability of the anti-

globulin test, the Kell blood group system was uncovered. The first antibody of this system was discovered by Coombs, Mourant and Race in 1946 upon the investigation of the serum of a mother whose child was suffering with hemolytic disease of the newborn.[22] The antibody that was discovered by these investigators sensitized the cells of 7% of a random population and was named anti-Kell with the permission of the mother in whom it was found. Other antibodies of this system were identified. In 1949 the antithetical antibody "k" or Cellano was discovered by Levine, Backer, Wigod and Ponder.[23] In 1951 anti-Kp^a or Penny and anti-Kp^b or Rautenberg were uncovered by Allen and Lewis.[24]

At present with the addition of a fifth antiserum there are eight phenotypes of the Kell system as shown in Table 1, by Allen and Rosenfield (1961).[25]

Kell and Cellano are potent antigens and have caused hemolytic disease of the newborn and hemolytic transfusion reactions. Anti-Rautenberg, which occurs in 99% of all bloods tested, has also been associated with hemolytic disease of the newborn.[26]

The antibodies of this system are for the most part immune in nature and react best with the indirect Coombs technique.

TABLE 1

Known Phenotypes of the Kell Blood-Group System–1960

(From Allen and Rosenfield–1961)

Short name	Full name	Actual phenotype-reactions with various antibodies (indicates antigens present on red cells)					Approximate frequency
		K1 Kell	K2 Cellano	K3 Penney	K4 Raut.	K5 Peltz	
Kell+	K:1, 2, -3, 4, 5	+	+	0	+	+	.09
Kell-	K:-1,2,-3,4,5,	0	+	0	+	+	.88
Cellano-	K:1,-2,-3,4,5,	+	0	0	+	+	.0025
Penney+	K:-1,2,3,4,5	0	+	+	+	+	.02
Kell+, Penney+	K:1,w2,3,4,5	+	weak	+	+	+	.004
Rautenberg-	K:-1,w2,3,-4,5	0	weak	+	0	+	.0002
Peltz type	K:-1,-2,-3,-4,-5	0	0	0	0	0	.0001
McLeod type	K:-1,w2,-3,w4,-5	0	weak	0	weak	0	.0001

Other blood group systems have been associated with hemolytic disease of the new born. Among these are anti-Tj^a of the P blood group, some of the "private" antigens such as Wr^a, Good, Bi, Be^a and Levay,and rarely public antigens may stimulate antibodies in a woman who lacks the particular antigen possessed by the fetus. Di^a of the Diego blood group system has also been implicated in hemolytic disease of the newborn but its incidence is rare. This antibody reats best by the indirect Coombs test at 37^oC. It is rarely found in caucasians.

Although the resumé of the blood groups given above is by no means complete, it is obvious that hemolytic disease of the newborn is no longer simply a disease associated with fetal-maternal incompatibility. It is instead an increasingly comples situation and will continue to increase in complexity due to the relative safety of blood transfusion in modern hospital practice. It therefore will be the duty of physicians to be aware of the possible complications of blood transfusion,both immediate and future, and also to be aware of the fact that sensitization may occur "naturally" to blood group systems other than Rh and ABO.

In view of the fore-going information, it is

readily seen that hemolytic disease of the newborn can occur from sensitization to antigens other than D of the Rh system. Indeed, a great majority of cases of hemolytic disease of the newborn of severity requiring intervention by the physician during the prenatal period are due to D(Rh_o) sensitization. However, some of the "irregular antibodies" produce disease of such severity as to result in intra-uterine death. Such a case was sited by Pirofsky due to anti-Kell sensitization.[27]

The prenatal antibody screen is a procedure in which the mother's serum is checked against cells of known antigen content for the purpose of detecting "irregular antibodies." Such a procedure has a several-fold value.. The most obvious value of the screen is detection of immune antibodies that may result in hemolytic disease of the newborn. The fact that with pregnancy and increasing with subsequent pregnancies goes a potential hazard of hemorrhage either pre-or post-partum is also well established. If at the detection of pregnancy an antibody screen is performed routinely, any antibody which could result in an hemolytic transfusion reaction would be known. If this factor were of rare type, blood could be obtained

more rapidly from a preexisting rare donor file. The fact that many cases of neonatal jaundice have gone and are still going unexplained is another value of routine screens for antibodies prenatally. Much is yet to be learned of hemolytic disease of the newborn, and the prenatal identification of antibodies would lead to further identification of predisposing factors and responsible blood group systems.

The performance of the antibody screen is a relatively short and inexpensive laboratory procedure. In the test used at the University of Nebraska Hospital two samples of mixed cells containing known antigens are used. Each of these suspensions are examined under three different conditions: 1) albumin at 20°C, 2) albumin at 37°C for 60 minutes and 3) antihuman globulin. After each of the three situations the cells are centrifuged and examined for agglutination.[28]

By evaluating the tubes in which agglutination occurs and the conditions which favored agglutination, the "MOST PROBABLE ANTIBODY" can be determined. Antibodies reacting at low temperatures are found by the room temperature examination e.g. Le^a, Le^b and P. Warm reacting antibodies are found after 60 minutes

of incubation at 37°C. e.g. Rh system antibodies. Antibodies detected by the Coombs test are found when the antihuman globulin is added e.g. K, k, Jk^a, Jk^b etc.

For reasons of practicality, the antibody screen does not include all known blood group factors. Many of the private and weak reacting antibodies are not included. If hemolytic disease of the newborn results therefore in a woman with a negative antibody screen, further study after a repeated screen is needed.

Although investigations of blood group immunology started in 1900 and made rapid progress to the present date, the literature is conspicuously sparse regarding erythroblastosis due to less common blood group systems. This could be the result of failure to identify sensitized patients and incomplete follow-up of mild neonatal jaundice which might be due to mild hemolysis.

The screening of maternal serum on a routine basis prepartum is a relatively new procedure. Good obstetric care however, will require such a test on all prepartum women regardless of their parity. Smith, Haber and Queenan reviewed the results of routine screening for irregular antibodies at the New York

Hospital of the Cornell University Medical College for the five year period 1960 to 1964.[29]

In their review, the authors screened every pregnant woman who presented for care at this facility for the five year period, a total of 12,297 screens. Irregular antibodies were defined as those other than anti-A, anti-B or anti-Rh_0. Their results showed a total of 113 irregular antibody positive screens representing 0.92% of the screened population. The incidence of Rh_0 (D) sensitization of this same series was 173 or about 1.4% . It was also noted that of the 113 patients with irregular antibodies, 104 or 92% were Rh_0-positive. Forty-two of the 113 immunized patients had a history of previous blood transfusions.

The antibodies and their incidence for the entire period 1960-1964 are shown in the accompanying table. (see table 2.)

The incidence of erythroblastosis fetalis in this study attributable to irregular antibodies was seven, or an incidence of 6.2% of screen positve pregnancies.

Another article reviewing hemolytic disease and the antibody screen was published by Eilers and Brown[30].

TABLE 2

SERUM ANTIBODIES IDENTIFIED[29]

Antibody	Total 1960-1964
Anti-Rh_o	173
Anti-rh''	19
Anti-Kell	17
Anti-Le^b	13
Anti-Le^a	11
Anti-M	8
Anti-Fy^a	4
Anti-Lu^a	3
Anti-hr'c	3
Anti-S	3
Anti-rh'C	2
Anti-Jk^a	2
Anti-hr''e	2
Anti-P	3
Anti-I	2
Anti-V	3
Unidentified	28

Their data on screening for all specific antibodies in both a general and obstetric population for one years time is as follows:

SUMMARY OF ANTIBODY SCREENING-1964 #0

	General	Obstetric
No. screen	4,330	2,257
Per cent spec. antibod. ident.	2.2	6.5
SPECIFIC ANTIBOD. FREQ.	TOTAL	TOTAL
Anti-Rh_o alone	24.2	24.7
Anti-c alone	3.2	1.4
Other Rh-hr antibod.	10.5	2.0
Antb. outside Rh-hr sys.	62.1	71.9
Lewis	31.6	59.6
P	11.6	3.4
Kell	7.4	2.7
Antb. in Rh_o pos women		66.5
Antb. in Rh_o neg women		33.6

These authors also reviewed 210 cases of erythroblastosis fetalis from the years 1955 to 1965. The results of their series are listed below.

ERYTHROBLASTOSIS FETALIS (210 CASES)

ANTIBODIES OBSERVED[30]

Antibody	Total	1955-1965	%
ABO	99		47.2
Anti-D	97	46.2	
Anti-D+C	7	3.3	50.0
Anti-D+E	1	0.5	
Anti-c+E	2	0.9	1.4
Anti-c	1	0.5	
Anti-E	1	0.5	
Anti-e^S	1	0.5	
Anti-K+Fy^a	1	0.5	
Other than Rho and ABO	6		2.9

The "antibody screen" has been a routine procedure at the University of Nebraska Hospital since July, 1964. All women seen in the prenatal obstetric clinic have, in addition to other routine laboratory procedures, a prenatal screen for specific antibodies.

During the two and one-half years of the study, 2275 women have been tested using a commercial test of antigens. From this population a total of ninety-six positive screens were obtained. This represents an incidence of 4.2%. The chart below shows the incidence of the antibodies uncovered by the screens. The reader will note that the total number of antibodies present exceeds the number of positive screens. This was due to the frequent finding of two antibodies in a single patient's serum.

ANTIBODY SCREENING--JULY, 1964, TO JANUARY, 1967

Number screened	2275
Number pos. screens	96

SUMMARY OF ANTIBODIES FOUND

Anti-Le^a	46
Anti-D	19
Anti-Le^b	12
Anti-C	9
Anti-OorH	9
Anti-E	5
Anti-K	3
Anti-c	3
Anti-e	1
Anti-Jk^a	1
Anti-I	1

The significance of antibodies in the serum of prenatal women is well established regarding the "D" antigen of the Rh system. Irregular antibodies, however, have been shown by many investigators to produce hemolytic disease of the newborn . The severity of the disease due to these antibodies depends upon several factors, among which are the antibody to which sensitization has occurred, the maturity of the neonate, and prior pregnancies in which sensitization may have occurred.

The statistics regarding hemolytic disease of the newborn at the University of Nebraska Hospital are unfortunately only partial due to a variety of reasons not to be enumerated. However, a case of neonatal jaundice occurred in a pregnancy in which anti-c+E were detected prenatally. No exchange was needed.

The prenatal screen for antibodies will be found, in the author's opinion, to be of increasing value in the fields of obstetrics and pediatrics in predicting possible sensitized mothers and perhaps in elucidating the causes of heretofore unexplained cases of neonatal jaundice.

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