Fatal Transfusion Reaction Due to the Kell Factor

By F. Ottensooser, M.D., Ph.D., O. Mellone, M.D., and A. Biancalana, M.D.

THE KELL FACTOR, which has proved to be of considerable clinical interest, was discovered by Coombs, Mourant, and Race when they introduced the direct antiglobulin test in the diagnosis of hemolytic disease of the newborn. Until 1950, seven cases of this disease due to the Kell factor had been published and recently two more cases were added. Seven transfusion reactions have been observed in which the sera of the patient contained Kell antibody; however, three cases were not “pure”, for anti-Kell occurred together with other antibodies which masked the harmful effects of anti-Kell.

Brief reference is made below to four transfusion reactions attributable to isoimmunization by the Kell factor.

Wiener and Sonn-Gordon described, in 1947, the case of a woman with four children who suffered from subacute bacterial endocarditis and received four blood transfusions, the last two followed by severe hemolytic reactions. One of the children and the last donor were Kell positive, but the other children and donors were not examined. The patient whose serum contained anti-Kell was later given two uneventful transfusions of compatible Kell negative blood. A second transfusion reaction due to the Kell factor has been mentioned but not described. Mollison reported a hemolytic transfusion reaction caused by the Kell factor occurring after about thirty blood transfusions in the course of eight years. Wiener et al. investigated a case of autohemolytic disease with anemia in which more than fifteen blood transfusions had been given. Serologic tests were complicated by the presence of autoantibodies and survival of transfused cells. The next blood transfusion caused a mild hemolytic reaction, and at this time the patient was shown to be Kell negative and to have a strong incomplete Kell antibody in her serum. Thereafter, transfusions of Kell negative blood were well tolerated.

In two of the four cases the hemolytic reactions were not severe, but in at least one of the remaining cases the incompatible transfusion together with the generalized infection could have contributed to the fatal outcome. In the case to be presented, the Kell factor was doubtless the essential cause of death.

CLINICAL OBSERVATION

Patient, R. B., 50 years of age, had a normal child in 1928 and received, in 1929, after a spontaneous abortion, five blood transfusions of 100 ml. each, two of which were from the same donor. Subsequently, the patient had three normal children and one induced abortion. Since May 1952, the patient had had slow continuous bleeding due to uterine fibroma and surgical treatment was required. In November 1952, one of us (A. B.) gave her 500 ml. of blood which was B, M, Rh, and which corresponded to the antigens in the patient's serum.
red cells. A direct compatibility test was not carried out. About forty-five minutes after the
completion of the transfusion, the patient had a violent reaction with chills and vomiting,
and twenty minutes later, generalized pains, more severe in the lumbar region and the legs.
Two hours later, her temperature rose to 38.5°C. The pains which persisted during the night,
despite analgesics, diminished the following day. She eliminated only 180 ml. of black urine
of specific gravity 1.018 and containing 8 Gm./liter protein and 30 red cells per microscopic
field. On each of the third and fourth days, 45 ml. urine were passed and subsequently there
was complete kidney shut-down. Tests showed 3,360,000 red cells, 6.75 Gm./100 ml. or 45
per cent hemoglobin, and a hematocrit value of 26 per cent. On the fifth day, packed cells
were transfused, 470 ml. from one donor, and 370 ml. from another, while 700 ml. of the
patient's blood was withdrawn. Catheterization yielded only 75 ml. of urine. On the sixth
day, 350 ml. of packed cells from one donor and 400 ml. from another were administered to
replace 600 ml. patient's blood withdrawn. The compatibility tests for the last four donors
were controlled by antiglobulin tests of donor's red cells and patient's serum. Apparently
these transfusions were well tolerated, although the anuria continued. Further progress
seemed to be satisfactory, without toxic symptoms of retention, but on the eighth day the
patient developed a cerebral vascular accident and died suddenly.

**Table 1.—Blood Groups of the Patient, Her Family, and the Donors**

<table>
<thead>
<tr>
<th></th>
<th>ABO</th>
<th>MN</th>
<th>Rh</th>
<th>Standard anti-Kell</th>
<th>Patient's serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>B</td>
<td>M</td>
<td>+Rh_1rh</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Most recent donor</td>
<td>B</td>
<td>M</td>
<td>+Rh_1rh</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Patient's husband</td>
<td>A</td>
<td>MN</td>
<td>+Rh_1Rh_2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Her children</td>
<td>A</td>
<td></td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>O</td>
<td></td>
<td>+Rh_1rh</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td></td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>O</td>
<td></td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Three donors (donated in 1929)</td>
<td>O</td>
<td>O</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>O</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

* Relatives to each other.

**Serologic Analysis**

Typing for the several blood factors was carried out by direct agglutination
tests, but tests with anti-Kell (Ortho Research Foundation and Certified Blood
Donor Service, N. Y.) were made using the antiglobulin method. The blood
groups of the patient, her family, and all but one donor are shown in table 1.

Since the patient and the donor whose blood caused the severe reaction had
the factors B, M, Rh_1Rh, differential agglutination could be carried out only by
the antiglobulin technic with known anti-Kell serum. The donor whose blood
causd the hemolytic reaction was Kell positive and the patient's red cells
tested one day after the hemolytic reaction were Kell negative. Apparently all
of the donor's red cells were rapidly destroyed. Parallel tests with a standard
anti-Kell and the antibody in the patient's serum gave identical results on the
ten bloods shown in table 1.

As to the source of the sensitization, pregnancies could be excluded since the
husband, the patient, and their four children were all Kell negative. Fortunately,
it was possible to locate three of the four individuals who had donated blood in
1929, and two of them, related to each other, who had given three transfusions
were Kell positive. Thus, the anti-Kell antibody, resulting from transfusions
performed in 1929 had persisted so that the readmission of Kell positive blood twenty-three years later resulted in a severe hemolytic reaction with anuria.

The patient's serum tested one day after the transfusion reaction agglutinated the red cells of the Kell positive donors suspended either in compatible serum or in 20 per cent bovine albumin. The reactions were strongest at 37 C. with titters of 1:4 to 1:8 after one hour incubation. The serum which failed to react with saline suspended cells gave a titer of 1:16 in the antiglobulin test.

The incidence of positive reactions of the antibody in the patient's serum was determined in tests of one hundred and eighty-two random individuals living in São Paulo, mainly of Italian and Portuguese origin. Aside from a few group O and B individuals tested with the patient's untreated serum, the vast majority of the tests were made with the serum to which pig stomach extract (pH7) and group AB serum were added. Of the one hundred and eighty-two bloods tested, fourteen gave positive reactions, i.e. 7.7 per cent—an incidence which is characteristic of the Kell factor in caucasoids.* The presence of antibodies for other factors of low incidence such as rh", Le", or Lu were excluded in tests of the patient's serum with a panel of red cells of known antigenic structure.

COMMENT

The Kell factor is one of the more antigenic factors among those discovered recently, but it is not quite as significant as the Rh0 factor. It was pointed out by Wiener and Sonn-Gordon that the probability that a Kell negative patient will receive Kell positive blood is about 1:10, and the probability of three consecutive transfusions of Kell positive bloods is 1:1000. It is generally assumed that in 40 per cent of recipients, two transfusions of the antigen will stimulate antibody production so that the third injection of sensitive blood would incite a hemolytic reaction. Taking into account the varying incidence of positive and negative reactions for Kell and Rh0, Mollison showed that the Kell factor is 100 times less antigenic than Rh0. This value is derived from the following calculation:

\[
\text{Kell: } 0.90 \times 0.10^3 \times 0.40 = \text{about } 0.0004 \\
\text{Rh0: } 0.17 \times 0.83^3 \times 0.40 = \text{about } 0.04
\]

The danger of isoimmunization by the Kell and other recently discovered blood factors is considerably greater than indicated because in the past ten years it has become routine practice to select Rh negative donors for Rh negative patients. As for the other factors, similar preventive measures, i.e. selection of donors of antigenic structure identical with that of the patient, are neither feasible nor practical. If, in the course of pregnancies or transfusions, isoimmunization does occur, the only safeguard is the routine application of a suitable compatibility test to detect unusual antibodies demonstrable either with albumin.

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* Racial differences in the Kell factor are discussed by Miller, Rosenfield, Vogel, and Shapiro. The genetic relation of the Kell-Cellano (K-k) factors was described by Levine, et al.
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suspended cells or by the antiglobulin test. Once an antibody is found, its identification must be established to facilitate the selection of compatible blood.

In his recent analysis, Van Loghem showed that of 60,000 blood transfusions in the Netherlands in one year, sensitization was discovered in thirty-one patients. In twenty-eight of these, anti-Rh was found, most frequently with no other antibodies, but in two instances with anti-Kell. In other words, Rh would seem to be only 14 times more dangerous than anti-Kell. However, these figures, large as they are, are not sufficient to establish the importance of the Kell factor in transfusions or pregnancies, because many cases of Kell sensitization will be found if special efforts are made to detect anti-Kell. At any rate, transfusion reactions due to anti-Rh will probably continue to decrease while under present conditions those due to anti-Kell or other blood factors should continue at the same rate.

The rules for preventing sensitization to those factors are well established but frequently not respected. No blood ought to be transfused without strict indication or without previous Rh typing and compatibility tests which must be particularly accurate in cases of multiparous women and repeated transfusions. Should sensitization occur, the cross-matching or direct compatibility testing should be sufficiently sensitive to detect antibodies demonstrable more readily by the antiglobulin test as for anti-Fy and many cases of anti-Kell. In the reports on transfusion reactions due to anti-Kell the direct compatibility test was either omitted or it was improperly performed. In the present case the test was positive one day after the hemolytic reaction, and it must have been present before the transfusion was performed.

SUMMARY

A woman of type B, M, Rh, Rh was transfused with blood of the same blood groups, but no direct compatibility tests were made. The patient developed a violent hemolytic reaction, became anuric, and subsequently received four compatible transfusions. The clinical course seemed satisfactory but after a week she died suddenly from a cerebrovascular accident. The donor was Kell positive and the patient Kell negative; the donor’s Kell positive cells had disappeared from her blood one day after the transfusion and her serum contained incomplete Kell antibody.

The patient’s husband and four children were Kell negative, but she had received twenty-three years previously, five transfusions from four donors. Three of these donors were located, two of whom were Kell positive. In tests of the patient’s serum with one hundred and eighty-two random bloods there were fourteen or 7.7 per cent positive reactions, an incidence which is characteristic of anti-Kell in caucasoids.

REFERENCES

15 Chown, B.: Personal communication, 1953.
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