The Duffy Blood Group System in Transfusion Reactions: A Review of the Literature and Report of Four Cases

By Allan Compton and Jane M. Haber

THE DUFFY BLOOD GROUP factor (Fy^a) has been recognized for the past eight years as an occasional source of difficulty in blood transfusion. The present report is concerned with four new cases in which antibodies to this factor were detected and with methods for preventing transfusion reactions due to anti-Fy^a.

History

In 1950 Cutbush and Mollison[1,2] reported the detection of a new blood group factor in man which they encountered following a transfusion reaction in a hemophiliac who gave a history of several transfusions over a 20 year period. The donor's blood had been matched with the patient's blood by conventional technics (albumin medium, incubation at 37 C.) and appeared to be compatible. The blood, however, was found to be incompatible when the anti-human globulin (Coombs' serum) test was employed. Using serum obtained from their patient, they found that the antigen to which he had been sensitized was present in 64.9 per cent of 205 unrelated Englishmen. They named the system "Duffy" by permission of the patient, postulated the existence of an allele, and adopted the notation suggested in the previous year for the Lutheran and Lewis blood groups[3] as follows:

system	Duffy
genes	Fy^a, Fy^b
genotypes	Fy^aFy^a, Fy^aFy^b, Fy^bFy^b
phenotypes	Fy(a+), Fy(a−)
antibody	anti-Fy^a

In addition they showed that this antigen appeared to be inherited as a Mendelian dominant, not closely linked with ABO, Rh or other blood groups known at the time. Independence of ABO, Rh, MNSs, P, Lutheran, Kell, Lewis and Kidd blood groups was substantiated subsequently.[4-8]

Within the next two years there were seven reports of the detection of anti-Fy^a[4,9-14] that of Freiesleben[13] involving a fatal transfusion reaction. In 1951 Ikin et al.[15] reported the detection of the postulated anti-Fy^b in the serum of a woman who had a history of blood transfusion, following the birth of her third child. Blumenthal and Pettenkofer[16] substantiated the

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relationship of this antibody to anti-Fy^a. There has only been one further report of anti-Fy^b.[17] Recently, Shapiro[18] in a discussion of the general problems of blood transfusion mentioned two instances of transfusion reaction due to anti-Fy^a. One he attributed to the use of the "universal donor" without compatibility testing; the other was due to a very weak antibody overlooked by an "experienced technician."

The possible role of the Duffy system in hemolytic disease of the newborn suggested by Ikin's report has proven to be real although apparently rare. Baker et al.[19] in 1956 reported the case of a full-term baby girl who became jaundiced 12 hours after birth (with total serum bilirubin reaching a maximum of 22.8 mg. per cent at 14 hours) and had high reticulocyte and normoblast counts. The direct Coombs' test was weakly positive; the baby was group O, Rh-negative, Fy(a+). The father was found to be group O, Rh-negative, Fy(a+); the mother, who had received two transfusions five years previously, was group O, Rh negative, Fy(a−), with anti-Fy^a present in her serum in a titer of 1:8, and no other demonstrable antibodies. A second case of this disease due to anti-Fy^a, of lesser severity, was reported by Chown et al. in 1957.[20]

The frequency and distribution of the Duffy blood group antigens have been the subject of several studies since the initial observations of Cutbush and Mollison. The results of 6 studies indicate a frequency of just over 65 per cent for the factor Fy(a+) in England and Germany.[2,5,21-24] Anthropologic differences in the distribution of the Fy(a+) phenotype have been explored since Cutbush and Mollison reported that a high proportion of Pakistanis living in London were Fy(a+). Miller et al. reported that 99 out of 100 Chinese they studied were Fy(a+), and that the distribution in Negroes is about 25 per cent Fy(a+), 75 per cent Fy(a−).[25] Brazilian Indians have been reported to be almost 100 per cent Fy(a−).[26] More recently, Sanger, Race and Jack reported the existence of the phenotype Fy(a−b−) in New York City Negroes.[27]

Case Reports

Case 1.—F.L., NYH #783168, a 53 year old white male was admitted on November 26, 1957 because of gastrointestinal bleeding. He had received 3 transfusions in 1941 and 3 more in 1951 at other institutions. On admission his serum was found to contain an antibody which was not immediately identified, but 3 donor bloods appeared compatible by the Coombs' technic using an incubation period of 15 minutes at 37 C. He received the first transfusion uneventfully, but on the following day during the second transfusion he developed a shaking chill after receiving 150 ml. of blood. Dyspnea and wheezing occurred and an antihistaminic was given; his chest cleared within an hour. He then reported that he had experienced similar reactions to transfusions in 1951. Total serum bilirubin rose from 1.8 mg. per cent on 11/26/57 to 6.4 mg. per cent on 11/27/57. No free hemoglobin could be detected in the urine.

His blood was group O, Rh-negative. Postreaction serum was shown to contain anti-Fy^a in a titer of 1:16. The blood this patient received was rechecked for the Duffy (Fy^a) antigen. The first bottle was found to be Fy(a−); the second Fy(a+), compatible at 15 minutes incubation with the patient's serum but incompatible at 30 minutes. Subsequently he received nine bottles of Fy(a−) blood without reaction. He was discharged after surgery with a diagnosis of Osler-Weber-Rendu disease.

Case 2.—T.C., NYH #224355, a 51 year old white male, was admitted on November 27, 1957 because of black vomitus and tarry stools. He had received one blood transfusion in 1939 during a gastrectomy at this hospital. His serum contained an antibody and was incompatible with 6 out of 17 bloods tested. The antibody was identified as anti-Fy^a, present in a titer of 1:32. His blood was group A, Rh positive, and he received 4 bottles of group A, Rh positive, Fy(a−) blood without reaction. Discharge diagnosis was bleeding marginal ulcer.

Case 3.—M.E., NYH #783397, a 62 year old white female, was admitted on November 30, 1957 for relief of intestinal obstruction due to a redundant Meckel's diverticulum. She had received several transfusions during surgical procedures in the 8 weeks prior to admission here and possibly another transfusion 9 years previously, also during a surgical procedure. Her blood was group O, Rh-negative, and on admission her serum contained an antibody in a titer of 1:16. Anti-Fy^a and anti-Kell (K) were identified. She received three bottles of group O, Rh-negative, Fy(a−), Kell negative blood without reaction.

Case 4.—I.G., NYH #663880, a 33 year old white female was admitted on January 23, 1958 with advanced scleroderma. She had received one transfusion at another institution 2 years prior to her admission here. Her blood group was O, Rh-positive, and her serum contained an antibody in a titer of 1:32. Anti-Fy^a and anti- Lewis (Le^a) were identified. The patient was not transfused during this admission.

Discussion

The first example of anti-Fy^a detected at this institution, a case in which a serious hemolytic reaction occurred, was reported in 1952 by Hutcheson, Haber and Kellner.[14] In this report it was suggested that Fy^a is a relatively weak antigen; that in most cases sensitization probably occurs only after many transfusions; that there is a definite hazard if anti-Fy^a is present in the serum; and that incompatibilities due to anti-Fy^a can best be detected by use of the Coombs' test as part of the cross match.

Five years and approximately 50,000 blood transfusions separate that case from the 4 recent cases. This experience supports the observation that Fy^a is weakly antigenic. It may be estimated on the basis of the several studies quoted above that about two-thirds of the New York City population is Fy(a+), one-third Fy(a−). Certainly there have been many instances in the past five years in which Fy(a−) persons received two or more transfusions of Fy(a+) blood at this hospital, without either clinical or laboratory evidence of sensitization. However, it would appear that multiple transfusions are not necessary for the development of sensitization, at least in certain individuals. Two of the 4 patients reported here had only a single previous transfusion.

Although the likelihood of sensitization to anti-Fy^a is not great, the danger to the patient who has become sensitized is great. No essential difference has been suggested between transfusion reactions due to the Duffy factor and those due to Rh or ABO incompatibilities. An hemolytic reaction occurred in case 1, though fortunately, in this instance, the reaction was not of great severity. The hemolytic reaction reported by Freiesleben resulted in the death of his patient. It would seem to be important, therefore, to avoid transfusing persons who are sensitized to Fy^a with Fy(a+) blood.

Cutbush and Mollison originally described anti-Fy^a as demonstrable by the Coombs' serum method. This procedure was necessary for detection of the antibody in each of the other 7 early cases, and was also found to be necessary in the four cases reported here. Race, Sanger and Lehane have reported the existence of 2 unusual antisera which agglutinated Fy(a+) cells in saline, but these appear to be exceptions. The Coombs' serum method has been employed routinely at this institution in all compatibility tests since the serious reaction due to anti-Duffy occurred in 1952, and it is likely that this practice prevented transfusion reactions in three of the above cited patients.

Failure to detect incompatibility in the case of F. L. may very likely be attributed in this instance to the use of a 15 minute incubation period for the Coombs' compatibility test. A recent paper by N. A. F. Young suggests that incubation periods longer than 30 minutes do not increase the amount of agglutination in Coombs' compatibilities, and that a 15 minute incubation period is usually, though not always, adequate for detecting even weak sensitization.[28] French recently studied 69 examples of various "incomplete" antibodies and found that a 15 minute incubation period was adequate for the detection of 97 per cent of these by the Coombs' serum method. Notably, 8 of these antibodies were anti-Fy^a, 2 of which required more than a 15 minute incubation period.[29] In our case a transfusion reaction could have been prevented in spite of the 15 minute incubation period for the Coombs' compatibility if the antibody in the patient's serum had been specifically identified before transfusion. Specific identification, if possible, of any antibody detected in a patient's serum and transfusion only with donor blood in which the corresponding antigen cannot be demonstrated would seem to be indicated as a routine practice.

Finally, the Biologics Control Laboratory of the National Institutes of Health does not require that Coombs' serum be proved potent for the detection of anti-Fy^a. F. H. Allen points out that it is not easy to produce a Coombs' serum adequately potent in demonstrating anti-Fy^a, that it is probable that many Coombs' sera on the market are deficient in this respect, and that until the situation is remedied, each blood bank should check the serum it uses for potency against Fy^a.[30]

Summary and Conclusions

1. The literature on the incidence and inheritance of the "Duffy" blood group factors and their significance in blood transfusion and erythroblastosis fetalis is briefly reviewed.

2. Four new cases in which anti-Fy^a was detected are reported.

3. The necessity for the use of the Coombs' compatibility test with a potent Coombs' serum to prevent reactions due to anti-Fy^a is re-emphasized.

4. The inadequacy of a 15 minute incubation period for the Coombs' compatibility test in certain cases is noted.

5. The desirability of specific identification of an antibody detected in a patient's serum prior to transfusion whenever possible is suggested.

SUMMARIO IN INTERLINGUA

1. Es presentate un breve revista del litteratura relative al incidentia e al transmission hereditari del factores de gruppos de sanguine Duffy e al signification de ille factores in le transfusion de sanguine e le disveloppamento de erythroblastosis fetal.

2. Es reportate quatro nove casos in que anti-Fy^a esseva detegite.

3. Es signalate e sublineate de novo le necessitate del uso del test de compatibilitate secundo Coombs con un potente sero de Coombs pro prevenir reactiones causate per le presentia de anti-Fy^a.

4. Es notate le inadequatia de un periodo de incubation de 15 minutas pro le test de compatibilitate secundo Coombs in certe casos.

5. Es constatate le desirabilitate del identification specific de un anticorpore detegite in le sero de un patiente ante le transfusion.

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