NEONATAL JAUNDICE ASSOCIATED WITH FAMILIAL G6PD DEFICIENCY IN ISRAEL

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It is now well established that hyperbilirubinaemia and even kernicterus may occur in the newborn in association with glucose 6 phosphate dehydrogenase (G6PD) deficiency, in the absence of any of the other causes of neonatal jaundice (Panizon, 1960a; b; Doxiadis, Fessas, and Valaes, 1960; Doxiadis, Fessas, Valaes, and Mastrokalos, 1961; Fessas, Doxiadis, and Valaes, 1962; Smith and Vella, 1960; Weatherall, 1960; Flatz, Szingam, Premyothin, Penbharkkul, Ketsuingh, and Chulajata, 1963).

In Israel, in spite of the high incidence of G6PD deficiency in some communities, a retrospective survey of 42,000 births undertaken by Szeinberg, Oliver, Schmidt, Adam, and Sheba (1963), revealed only one case of severe neonatal jaundice that could possibly be ascribed to the enzyme deficiency. We wish to report here 8 cases of severe neonatal jaundice which occurred in G6PD-deficient infants in a Jerusalem hospital (Shaare Zedek), and to submit evidence suggesting that an antiseptic dye applied to the umbilicus was the precipitating haemolytic agent.

Material and Methods

Each newborn was examined daily, and in every case of moderate or severe jaundice the serum bilirubin was determined. If the result was over 18 mg./100 ml. a detailed history was taken of the mother including her country of origin, past and family history of anaemia, jaundice, or favism, and details of drugs taken in the perinatal period. Whenever Rh iso-immunization could be excluded, the blood of the infant and of the parents was examined for G6PD deficiency by the semi-quantitative method of Motulsky and Campbell as described by Doxiadis et al. (1961).

The test is based on the time taken to decolorize a solution of 'brilliant-cresyl-blue' (National Aniline Division) mixed with the blood to be examined. If decolorization occurred after 60 minutes enzyme deficiency was considered to be present, values between one and two hours suggesting heterozygosity.

For blood group studies clotted venous blood was used. The blood groups of the mothers and the babies were determined for the following red cell antigens: ABO, Rh (including C, c, D, e, E, e) MN, Kell, and Duffy. The direct Coombs test was performed on the blood of the infants. The serum of the mothers was screened against a panel of group O red cells for the presence of antibodies belonging to the following blood group systems: MNS, P, Lutheran, Rh, Kell, Duffy, Kidd, and Lewis. The red cell antigen typing of the panel cells was performed for us by Dr. A. G. Mourant of the Lister Institute, London. The screening techniques were performed using the panel cells suspended in saline, and also using the same cells treated with ficin. The saline tubes were incubated both at room temperature and at 37°C. and were followed by the indirect Coombs test. The ficinized cells were incubated at 37°C. Titres for complete and incomplete anti-A and/or anti-B were performed where indicated by the ABO groups of the mothers and babies. A dextran medium was used for the detection of the incomplete anti-A and anti-B (Mollison, 1961). The techniques used were the standard methods described by Race and Sanger (1954).

Description of Cases

The criterion of severe neonatal jaundice in this report is a total serum bilirubin level of 18 mg./100 ml. or above on one or more occasion. Exchange transfusion was performed in all but one of the cases here described. During the period July 1962 until February 1963 (incl.) there were 10 cases of severe neonatal jaundice: in 2 of these there was evidence of Rh incompatibility; G6PD deficiency was present in the other 8. The details are presented in Table 1. Most of the parents were Jewish immigrants from Kurdistan among whom the incidence, in males, of G6PD deficiency is 58-2%—the highest of any Jewish community in Israel (Sheba, Szeinberg, Ramot, Adam, and Ashkenazi, 1962). Kurdish infants constitute less than one-fifth of the infants born in this hospital. The sudden increase in the proportion of Kurdish infants requiring exchange transfusion during the period in question is shown in the Figure. ABO
incompatibility was present in Cases 6 and 8 as shown by the titres of complete and incomplete anti A and anti B antibody respectively. In Case 7, ABO incompatibility could not be excluded as insufficient blood was available. The direct Coombs test was negative in the 8 cases, and no incompatibility in the CDE, Kell, Duffy, and MN systems could be found. Irregular blood group antibodies in the mother's serum were not detected. Details of the delivery and of drugs administered are given in Tables 2 and 3. With the exception of mild analgesics, of whose administration no record is kept, no drug was given uniformly to all the mothers. The vitamins administered to the mothers consisted of a multiple preparation without vitamin K. Although Case 1 also had signs of systemic infection, these were not considered to be responsible for his jaundice since jaundice was marked within 24 hours, whereas signs of infection appeared only on the fifth day.

Triple dye was used in this hospital as prophylactic treatment against umbilical sepsis. This dye is applied
while the infant is still in the delivery room and thereafter daily in the nursery. The three premature infants received vitamin K in a dose of 1 mg., intramuscularly. Antibiotics were administered as shown in Tables 2 and 3. A history of severe neonatal jaundice in previous infants was obtained in only one family.

**Discussion**

In previous years between two to five exchange transfusions were performed yearly. A sudden increase in the need for exchange transfusion, such as here described, suggested the possibility of a laboratory error in the estimation of bilirubin. Such an error would not explain why the proportion of Kurdish infants requiring exchange transfusion should rise suddenly. Neither the total number of births nor the ethnic composition of the hospital population had changed in recent years. As the Kurdish community in Israel is unique in its particularly high incidence of G6PD deficiency, suspicion was immediately cast on this fact as being related to the jaundice. We could demonstrate this enzyme deficiency in all infants requiring exchange transfusion in the nine months under review, apart from two in whom Rh incompatibility was the obvious cause. Prematurity and ABO incompatibility were present in some cases but there was an associated G6PD deficiency. No exchange transfusions were required for the first two reasons alone during the period under review.

Hyperbilirubinemia in newborn infants may be due to increased cell destruction or to inhibition of the conjugating capacity of the liver. That increased haemolysis had occurred in our cases can be assumed by the early onset of jaundice in some cases and the low haemoglobin values on discharge. The sudden appearance of a comparatively large number of cases of jaundice of this type, which heretofore was almost non-existent in Israel (Szeinberg et al., 1963), led to a search for changes in treatment which might have given rise to haemolysis in enzyme-deficient infants.

As jaundice appeared within 24 hours in five infants, a hypothetical haemolytic agent in the breast milk could not have been the precipitating factor. None of the mothers ate beans at the time of delivery and the cases were not confined to the season in which favism occurs. It was suggested to us by Professor E. Goldschmidt that a likely cause was the antiseptic dye used in treating the umbilicus. The reason for implicating this substance is as follows: as jaundice due to enzyme deficiency was confined to our hospital, the provoking agent must be confined to that hospital. The other hospitals in this town use either 'brilliant green' alone or no dye at all, whereas in our hospital a 'triple dye' was used to prevent umbilical sepsis, as recommended in the control of staphylococcal infections in newborn nurseries (American Academy of Pediatrics, 1958). The B.P.C. preparation of 'triple dye' consists of a mixture of brilliant green, crystal violet, and proflavine hemisulphate, but instead of the last, the closely related ethacridine lactate ('Rivanol') was used. By April 1963 the evidence against this dye was strong enough to warrant using brilliant green alone, which was the practice in a neighbouring hospital where G6PD deficiency jaundice was not occurring in newborn infants. In the nine months following the discontinuation of its use, only one Kurdish infant had severe neonatal jaundice.

In order to test the potential haemolytic properties of our 'triple dye', it was incubated with enzyme-deficient red cells. There was no abnormal decrease of reduced glutathione and we, therefore, failed to confirm such a haemolytic effect in vitro (E. Heimann-Hollander and S. Freier, 1963, unpublished observations). This, however, does not exclude the possibility that one of the breakdown products of these dyes present in the patient's plasma may be responsible for haemolysis. The amount of substance that can be absorbed through the umbilicus is obviously very small, but cases of G6PD-deficient jaundice are on record where the offending substance was probably a comparably small amount of naphthalene present in clothes impregnated with this substance (Zinkham and Childs, 1958; Dawson, Thayer, and Desforges, 1958; Jim and Chu, 1963).

The evidence is, therefore, strongly in favour of an external factor being the cause of G6PD-deficient neonatal jaundice in Israel.

The rarity of severe neonatal jaundice due to G6PD deficiency in African infants in America and in infants of Oriental Jews in Israel as opposed to the
high incidence of such jaundice in Greece, Italy, and Singapore, has given rise to the suspicion that some, as yet unrecognized, toxic substance is responsible for increased haemolysis in those countries. Our findings support such a theory. On the other hand Fessas et al. (1962) have adduced evidence for a familial tendency for enzyme-deficient neonatal jaundice. They suggest that a second genetic factor inherited independently of G6PD deficiency may exist in these families. As deficiencies of other enzymes, namely acid phosphomonoesterase and catalase, are known to occur in the erythrocytes of some G6PD deficient subjects (Tarlov and Kellermeyer, 1961; Oski, Shahidi, and Diamond, 1963) this possibility must be seriously considered. The relative importance of hereditary as opposed to environmental factors in enzyme-deficient jaundice in newborn infants, therefore, awaits further evaluation.

Summary

Eight infants with severe neonatal jaundice associated with deficiency of G6PD were observed in a Jerusalem hospital. Incompatibility of the ABO groups of mother and infant possibly contributed to the jaundice in three cases. In spite of the high incidence of G6PD deficiency among Kurdish Jews in Israel, neonatal jaundice of this type is known to be uncommon in this country. An antiseptic preparation applied to the umbilicus was considered to be the most likely cause of the haemolysis in our cases.

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