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Neonatal indirect hyperbilirubinaemia in twins

By

M. FEKETE and Maria KARDOS

Department of Paediatrics, University Medical School, Pécs

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Neonatal indirect hyperbilirubinaemia in 21 pairs of twins was compared and studied during the first postnatal week. Peak bilirubin concentration and the persistence of icterus was similar in the two sets of twins, but considerable individual inter-twin differences could be observed. Various postnatal parameters and inter-twin differences in these parameters were correlated with differences in hyperbilirubinaemia. It has been concluded that physiologic or idiopathic hyperbilirubinaemia is closely similar in twins, probably due to the similar functional maturity of bilirubin clearance mechanisms. Individual variations were related to differences in caloric intake: the higher the caloric supply the lower was the maximum bilirubin concentration.

Neonatal indirect hyperbilirubinaemia is basically a syndrome of multiple or quite frequently unknown aetiology. Despite various definitions in use, distinction between physiologic and nonphysiologic icterus can be difficult, as the severity of icterus does not necessarily reflect its pathogenesis. On the other hand, it is widely appreciated that the development of kernicterus depends only partly on the serum bilirubin concentration, especially in low birthweight newborn infants. Due to all these uncertainties, the management of jaundiced newborns still presents problems.

Neonatal indirect hyperbilirubinaemia may be caused by increased bilirubin production, decreased bilirubin transport, hepatic uptake and/or conjugation or exaggerated enterohepatic recirculation. These final mechanisms exert their effect mostly in combination. Apart from the maturity of the neonate, the predominance of one of the mechanisms is determined by intrauterine, subpartum or postnatal events. It is feasible to assume that causative mechanisms of hyperbilirubinaemia act with closely similar effectiveness in twins, especially those determined by functional maturity, for instance survival time of erythrocytes, hepatic uptake and conjugation of bilirubin. If this assumption is correct, comparative evaluation of hyperbilirubinaemia of twin neonates provides a useful model for studying the effects on neonatal hyperbilirubinaemia of various perinatal parameters independent of maturity.

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Patients and Methods

Hyperbilirubinaemia of 21 pairs of twins was compared and studied during the first postnatal week. Of the pairs, 13 and 2 were dizygotic and monozygotic, respectively, while in the rest zygosity was uncertain. Gestational age and birth weight ranged between 30—35 weeks and 1050—2360 g, though in 6 pairs the former was unknown. Of the 42 newborn infants, 7 died. The main postmortem finding was intraventricular haemorrhage in four babies, necrotic enterocolitis, massive pulmonary haemorrhage and hyaline membrane disease in the three others. Postnatal history was uneventful in 8 pairs of twins. Both twins of 6 pairs and one twin of 5 pairs suffered from various perinatal conditions such as perinatal infection, hypoxia, respiratory distress syndrome, etc.

On the 21 pairs of twins a total of 211 serum bilirubin estimations were performed by the Jendrassik—Gróf method. Bilirubin concentration was determined first on the second or third postnatal day and was then repeated daily simultaneously until the peak value had been reached and a consistent fall in bilirubin level was observed. Beside determining the maximum bilirubin concentration, an attempt was made to express the severity and duration of hyperbilirubinaemia by calculating the mean bilirubin concentration on the 3rd to 6th postnatal days. Furthermore, haemoglobin concentration, packed cell volume and pH status were also measured within six hours of birth, provided the babies were admitted in due time. Retrospectively, mean oral and parenteral fluid (ml/kg/24 hr) and caloric intake (kcal/kg/24 hr) was calculated for the period of the first postnatal week in every case as well as the maximum weight loss, expressed in percentage of birth weight.

All babies were fed on human milk during the observation period. None of them suffered from haemolytic disease due to blood group incompatibility or any other disease obligatorily associated with hyperbilirubinaemia. Measures to prevent jaundice were always the same.

Inter-pair differences in the parameters detailed above were studied in the twins. The correlation between maximum bilirubin concentration and birth weight, haemoglobin, haematocrit, actual pH, base excess, pCO_2, fluid and caloric intake and weight loss was investigated as also the correlation between these parameters and the severity and duration of icterus in the total population of twin babies. Inter-twin differences in each parameter were correlated in order to seek for significant association between them.

For statistical analysis, standard mathematical tests were used.

Results

The mean values for all the parameters studied in the two sets of twins were remarkably similar. Table I shows that no statistically significant difference was found in this respect, but notable individual variations could be observed.

In the total population of twin babies, a significant positive correlation was found between postnatal haemoglobin and peak bilirubin concentration ($r = 0.3554$, $p < 0.05$, $n = 34$). Maximum bilirubin concentration correlated significantly with the duration and/or severity of hyperbilirubinaemia ($r = 0.9192$, $p < 0.001$, $n = 27$). It is seen in Figs 1 and 2 that a highly significant negative correlation existed between caloric intake and maximum bilirubin concentration ($r = -0.8354$, $p < 0.001$, $n = 32$) and between the former and the duration of hyperbilirubinaemia ($r = -0.5925$, $p < 0.001$, $n = 27$).

TABLE I

Parameters studied and compared in the two sets of twins

	No.	Mean	SD	SE	Range	p
Birth weight, g						
twins I	21	1712	269.8	58.9	1050–2100	
twins II	21	1693	311.6	68.0	1050–2360	ns
Haemoglobin, g/dl						
twins I	21	17.3	2.3	0.5	13.8–21.2	
twins II	21	17.8	2.6	0.5	11.2–22.8	ns
Haematocrit per cent						
twins I	21	54.2	6.6	1.4	43.0–68.0	
twins II	21	56.4	7.1	1.5	41.0–67.0	ns
Arterial pH						
twins I	17	7.33	0.06	0.01	7.20–7.47	
twins II	17	7.29	0.01	0.00	7.09–7.43	ns
Base excess, mE/l						
twins I	15	−7.19	4.30	1.11	−16.5–(+0.6)	
twins II	15	−9.21	5.30	1.36	−18.2–0.0	ns
pCO_2 mm/Hg						
twins I	15	35.6	9.9	2.5	22.0–60.0	
twins II	15	35.3	9.5	2.4	18.0–52.0	ns
Maximum bilirubin level mg/dl						
twins I	15	13.2	1.5	0.3	11.0–17.7	
twins II	15	13.7	3.1	0.8	7.4–17.7	ns
Severity of icterus, mg/dl						
twins I	14	11.6	1.3	0.3	9.8–13.9	
twins II	14	13.0	2.9	0.7	9.1–17.6	ns
Fluid intake, ml/kg/24 hr						
twins I	20	108.4	24.3	5.4	62.0–184.0	
twins II	20	111.7	23.3	5.2	66.0–150.0	ns
Caloric intake, kcal/kg/24 hr						
twins I	18	72.9	11.6	2.7	56.0–96.0	
twins II	18	67.3	20.0	4.7	28.0–102.0	ns
Weight loss per cent						
twins I	21	5.1	3.5	0.7	0.0–15.4	
twins II	21	5.3	4.6	1.0	0.0–17.8	ns

None of the other parameter-pairs tested showed significant correlations ($r = -0.2039 - 0.4146$, $n = 19 - 34$).

The importance of caloric intake in regard of hyperbilirubinaemia was further supported by the finding of a significant positive correlation between inter-twin differences in caloric intake and maximum bilirubin concentration ($r = 0.7724$, $p < 0.01$, $n = 14$) and the severity and duration of icterus ($r = 0.5342$, $p < 0.05$, $n = 13$). No differences in any other parameters seemed to be related with the individually variable hyperbilirubinaemia of twin babies ($r = -0.5830 - 0.2314$, $n = 9 - 15$).

A correlation analysis was made between weight loss and fluid intake, fluid intake and caloric intake, and caloric intake and weight loss. Weight loss correlated significantly with caloric intake ($r = -0.3607$, $p < 0.05$, $n = 36$) while no significant correlation was found between weight loss and fluid intake ($r = -0.0404$) furthermore fluid and caloric intake ($r = 0.3130$).

Discussion

The present results demonstrated that hyperbilirubinaemia of the two sets of twins was remarkably similar as regards the peak bilirubin concentration and the persistence of icterus. Evaluation of individual bilirubin concentrations revealed, however, differences in bilirubin level sufficient to have clinical importance. This would suggest that the development and severity of hyperbilirubinaemia is not only determined by the functional maturity of bilirubin metabolism in newborn infants.

More information could be obtained by the correlation analyses. The direct correlation found between postnatal haemoglobin concentration and the degree of hyperbilirubinaemia indicates the role of erythrocyte destruction and bilirubin load. Inter-twin differences in haemoglobin and bilirubin concentration did not, however, correlate significantly. This might have been due to the small number of pairs studied but may also argue against the primary importance of overloaded bilirubin clearance capacity due to the increased haemoglobin mass.

In the 42 twin newborns, neither birth weight, nor arterial pH, base excess or pCO_2 seemed to be related to the hyperbilirubinaemia, nor did differences in these parameters between the two sets of twins correlate with differences in hyperbilirubinaemia. Birth weight truly reflects the functional maturity of the newborn but this is not necessarily the case with twin babies and even less if twin partners are compared. An intertwin difference in birth weight means a difference in the nutritional state and body composition rather than a difference in maturity.

The relation of perinatal asphyxia and hyperbilirubinaemia is controversial. It has been suggested that perinatal asphyxia per se causes and/or exaggerates hyperbilirubinaemia [7, 8, 9, 11] though our results contra-

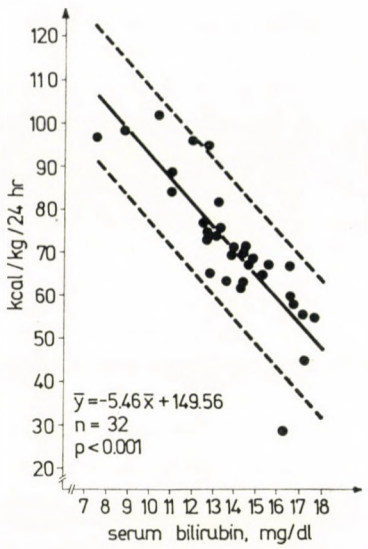

FIG. 1. Correlation between maximum bilirubin concentration and caloric intake, in 32 twin babies

dicted the assumption [3]. The acid-base status measured within six hours of birth offers reliable information concerning a previous asphyctic insult. A single estimation of the pH status reflects only the actual acid-base distortion but its prognostic value is limited as regards the consequences and further complications. Therefore, no correlation exists between the postnatal acid-base status and the severity of hyperbilirubinaemia developing during the first postnatal week.

An interesting finding was the highly significant inverse correlation between caloric intake and hyperbilirubinaemia (Figs 1 and 2). The fact that among the parameters studied only the different caloric intake of twins correlated significantly with intertwin differences in hyperbilirubinaemia provides good evidence of the important role of nutrition and caloric supply in the genesis of "non-pathologic" hyperbilirubinaemia. This observation confirms suggestions made by previous workers [1, 6, 10, 12, 13]. It should, however, be noted that these authors studied the effect on hyperbilirubinaemia of early versus late feeding and not that of the total caloric intake during the first postnatal week, but reasonable connections between the two types of approach are obvious. Considering the beneficial effect of early feeding on hyperbilirubinaemia, the question remains open whether the lower bilirubin level is due to the increased fluid or caloric supply. The present results proved the importance of the latter. The total fluid intake of the neonates studied represents both breast milk and parenterally administered fluids of various composition

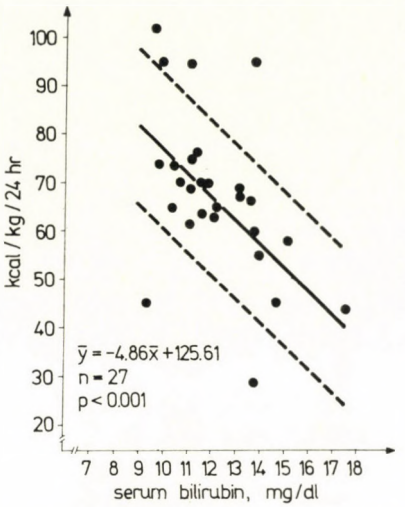

FIG. 2. Correlation between mean bilirubin concentration on postnatal days 3 to 6 and caloric intake, in 27 twin babies

and caloric value. The changing amounts of the two components explains the lack of correlation between fluid and caloric intake. At the same time this finding provides evidence that the caloric and not the fluid supply is causally related to mitigated hyperbilirubinaemia.

The question why early feeding or increased caloric supply reduces hyperbilirubinaemia remains open. As to the reasonable possibilities, it is well known that glucose is a precursor for glucuronic acid synthesis. It has also been pointed out that ketosis and a rise in the free fatty acid level characteristic of starvation may well depress bilirubin transport and hepatic uptake of bilirubin by competition for binding sites on plasma albumin and hepatic Z protein molecules [2, 4, 5].

All our twins received either phototherapy or phenobarbital for the prevention of jaundice and this must have influenced the "natural" course of their hyperbilirubinaemia. In spite of this, inter-pair differences in bilirubin concentration could reliably be evaluated because both twins received preventive therapy similar in quality and quantity.

In summary, physiologic or "idiopathic" hyperbilirubinaemia in pairs of twins is usually closely similar, probably because of the identical functional maturity of the bilirubin clearance mechanisms. Individual variations in the course of hyperbilirubinaemia during the first week of life are related to differences in caloric intake.

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M. Fekete, M.D.
Gyermekklinika
H-7623 Pécs, Hungary