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Perinatal asphyxia and jaundice in newborn infants*

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The serum bilirubin concentration was studied in 114 full term and 199 preterm babies suffering from either perinatal asphyxia or idiopathic indirect hyperbilirubinaemia, in order to establish the effect of asphyxia on the serum bilirubin level. Infants with any other disease causing non-physiologic jaundice were excluded. It was found that perinatal asphyxia *per se* does not exaggerate hyperbilirubinaemia either in full term or in preterm babies. Weight loss correlated significantly with the peak bilirubin concentration in all groups of patients. This would suggest the possible role of feeding and hydration in the genesis of hyperbilirubinaemia.

The role of perinatal asphyxia (hypoxaemia, hypercarbia and acidosis) has well been established in increasing the liability to bilirubin encephalopathy via various mechanisms [1, 2, 4, 5, 10]. This means that newborn infants suffering from asphyctic insults are at greater risk of kernicterus at similar or even lower serum bilirubin concentrations than those with no asphyxia [3, 9, 12]. The situation is worse and more complicated if neonatal diseases due to, or associated with, perinatal asphyxia *per se* increase the hyperbilirubinaemia. This has been stressed on clinical grounds [9, 11] but some theoretical considerations also seem to provide a basis for the assumption. Destruction of erythrocytes in haematomas, the effect of delayed oral feeding and partial starvation [13], disturbances of hepatic circulation due to asphyxia and the prolonged persistence of fetal circulation can all be causative factors in hyperbilirubinaemia of newborn babies with perinatal asphyxia [6, 7, 8].

In the present paper changes of serum bilirubin concentration in full term and preterm infants suffering from disorders of cardiorespiratory adaptation due to asphyxia were compared with that of babies with idiopathic indirect hyperbilirubinaemia without asphyxia. The purpose of the comparison was to study the effect of asphyxia on the time course of bilirubin concentration. In principle, jaundice of infants with perinatal asphyxia should have been compared with that of infants without asphyxia. As perinatal asphyxia is not necessarily associated with

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non-physiological jaundice, it seemed reasonable to use as a control newborn infants with non-physiologic icterus but without asphyxia.

Patients and Methods

The clinical course in newborn infants with "non-physiologic" jaundice was studied retrospectively, over a period of three years (1972—1974). Jaundice was considered physiologic if serum bilirubin concentration did not exceed 12 mg/dl in full term and 15 mg/dl in preterm infants, furthermore if it dropped below 7 mg/dl by the postnatal age of one week in full term and two weeks in preterm babies. A further selection was made according to whether they had had perinatal asphyxia or had only developed jaundice the cause of which could not be detected. Patients with haemolytic disease due to blood group incompatibility, perinatal infection, cephalhaematoma and/or multiplex skin bruises, and congenital malformations were excluded. Perinatal asphyxia was assumed to have occurred if hyaline membrane disease, type II respiratory distress syndrome or postasphyctic syndrome could be diagnosed on admission on the basis of physical examination, X-rays, and blood pH status.

A total of 199 preterm and 114 full term babies were selected; 22 full term and 89 preterm infants had perinatal asphyxia, the rest in both groups had jaundice of unknown origin. Sex distribution of the patients and their relevant clinical data are shown in Tables I and II.

Serum bilirubin estimations were done by the Jendrassik—Grof method when it was needed on clinical grounds. The first estimation was usually performed at the appearance of jaundice and subsequent determinations were then decided upon depending on the bilirubin concentration measured and the clinical course and signs. If two or more estimations were performed on a day, the higher value was taken into

Table I

Number, sex distribution, data of obstetric history of newborn infants and number of exchange transfusions performed

	Perinatal asphyxia		Idiopathic neonatal hyperbilirubinaemia	
	Full term	Preterm	Full term	Preterm
Number of infants	22	89	92	110
males	12	62	52	51
females	10	27	40	59
Pregnancy				
normal	11	40	67	84
pathological	11	49	25	26
Delivery				
spontaneous	16	71	77	98
Caesarean section	3	7	8	3
breech presentation	3	11	7	9
Exchange transfusion	4	30	19	25

TABLE II

Clinical data of the infants studied

	No.	Mean	SD	SE	Range
Maternal age (year)					
FT–PA	22	24.8	5.5	1.1	18–36
FT–INIH	88	24.7	6.0	0.6	17–43
PR–PA	89	26.1	5.5	0.5	17–44
PR–INIH	101	24.0	4.9	0.4	17–40
Pregnancy					
FT–PA	22	2.2	1.9	0.4	1– 8
FT–INIH	92	2.6	1.6	0.1	1– 7
PR–PA	89	3.6	2.7	0.2	1–14
PR–INIH	106	3.0	2.8	0.2	1–17
Delivery					
FT–PA	22	1.5	0.8	0.1	1– 3
FT–INIH	92	1.9	1.2	0.1	1– 7
PR–PA	89	2.1	1.3	0.1	1– 7
PR–INIH	106	2.0	1.6	0.1	1– 9
Birth weight (g)					
FT–PA	22	2846	459	97	1850–3700
FT–INIH	92	2972	460	62	1700–4250
PR–PA	89	1830	543	57	810–3100
PR–INIH	110	1977	512	49	1000–3050
Gestational age (week)					
FT–PA	22	38.5	1.5	0.3	37–42
FT–INIH	92	39.1	1.7	0.1	37–44
PR–PA	89	32.2	2.4	0.2	27–36
PR–INIH	110	33.2	1.9	0.1	27–36

Abbreviations: FT = full term infants; PR = preterm infants; PA = perinatal asphyxia; INIH = idiopathic neonatal indirect hyperbilirubinaemia.

account. The total number of patients and of bilirubin estimations performed in each group are shown in Table III. Averaged bilirubin curves were then plotted and compared. Correlation analysis was done between the following parameter-pairs within each group of infants: (1) gestational age—maximum serum bilirubin concentration; (2) gestational age—postnatal age at the time of peak bilirubin concentration; (3) gestational age—rate of increase in bilirubin level; (4) birth weight—maximum serum bilirubin concentration; (5) birth weight—postnatal age at the time of maximum bilirubin concentration; (6) birth weight—rate of increase in bilirubin level; (7) maximum bilirubin concentration—weight deficit in percentage of birth weight; (8) maximum bilirubin concentration—rate of increase in bilirubin concentration. In addition, in 24 preterm infants with perinatal as-

TABLE III

Plasma bilirubin concentration (mg/dl) of full term and preterm infants with perinatal asphyxia or idiopathic indirect hyperbilirubnaemia

Postnatal age	No.	Mean	SD	SE	Range
0—2 days					
FT–PA	18	8.2	2.3	0.5	3.8—12.9
FT–INIH	40	9.3	3.8	0.6	2.4—15.3
PR–PA	79	9.1	3.1	0.3	2.5—17.1
PR–INIH	48	8.5	2.8	0.4	2.3—13.8
3 days					
FT–PA	18	12.2	2.9	0.6	5.8—17.5
FT–INIH	43	14.4	4.3	0.6	5.8—24.6
PR–PA	74	14.3	3.5	0.4	8.6—24.5
PR–INIH	64	13.0	3.7	0.4	6.4—26.9
4 days					
FT–PA	17	15.7	4.7	1.1	8.5—28.0
FT–INIH	52	16.5	4.0	0.5	7.6—25.0
PR–PA	71	15.8	3.6	0.4	9.9—26.0
PR–INIH	84	15.2	3.5	0.3	6.4—25.2
5 days					
FT–PA	17	14.7	4.5	1.1	4.8—24.0
FT–INIH	52	16.7	4.7	0.6	7.3—28.5
PR–PA	45	16.2	2.6	0.3	11.4—23.9
PR–INIH	81	16.8	3.5	0.3	10.0—26.0
6 days					
FT–PA	14	13.1	5.8	1.5	7.5—25.0
FT–INIH	47	16.2	4.9	0.7	5.7—27.9
PR–PA	33	15.0	3.9	0.6	5.4—22.1
PR–INIH	67	15.5	3.1	0.3	10.0—24.7
7—8 days					
FT–PA	19	14.1	4.1	0.9	8.6—21.3
FT–INIH	39	13.8	4.4	0.7	2.4—20.8
PR–PA	47	15.6	3.8	0.5	9.9—26.2
PR–INIH	57	14.8	3.9	0.5	5.9—20.6
9—10 days					
FT–PA	12	7.1	3.3	0.9	1.3—10.5
FT–INIH	23	10.0	4.2	0.8	2.2—17.8
PR–PA	20	10.5	4.1	0.9	2.9—18.2
PR–INIH	17	13.5	3.9	0.9	5.1—18.5

TABLE III (cont.)

Postnatal age	No.	Mean	SD	SE	Range
11—14 days					
FT–PA	9	4.9	3.1	1.0	1.6— 9.4
FT–INIH	34	7.7	3.4	0.5	1.0—12.2
PR–PA	38	6.4	2.9	0.4	1.5—12.5
PR–INIH	42	7.0	3.6	0.5	1.2—16.7
15—21 days					
FT–PA	10	1.8	0.8	0.2	0.9— 3.4
FT–INIH	22	5.2	3.2	0.7	0.8—11.4
PR–PA	22	4.5	2.3	0.5	1.7— 8.9
PR–INIH	26	4.3	2.9	0.5	0.9—12.7

Abbreviations: FT = full term infants; PR = preterm infants; PA = perinatal asphyxia; INIH = idiopathic neonatal indirect hyperbilirubinaemia.

phyxia correlation analysis could be done between arterial pH, base excess and pCO_2 measured within two hours after birth and maximum serum bilirubin concentration observed later.

In all babies, prevention and treatment of jaundice were done according to generally accepted principles. Newborn infants who needed exchange transfusion were excluded from further study after the procedure. Full term infants received formula feeding while preterm babies were fed human milk. Oral or tube feeding was initiated as soon as possible. Patients with perinatal asphyxia could be fed orally considerably later than those with no asphyxia. No reliable data on prepartal and *sub partu* drug treatment of mothers could be obtained in most of the cases. Many patiens were admitted at various postnatal ages from various district hospitals.

Of the 89 preterm infants with perinatal asphyxia, 25 died. Necropsy revealed hyaline membrane disease in 13, and primary atelectasis in 7 cases. Pulmonary changes were associated with intraventricular haemorrhage in 10 patients. In 5 infants the only postmortem finding was intracerebral haemorrhage without pulmonary disorders. All full term infants survived and so did the preterm babies with idiopathic jaundice.

RESULTS

The changes in serum bilirubin concentration were closely similar in full term infants either with perinatal asphyxia or idiopathic indirect hyperbilirubinaemia during the first postnatal week (Fig. 1, Table III). After that time in babies with perinatal asphyxia a more precipitated fall in bilirubin concentration could be observed and the level remained significantly lower ($p < 0.05—0.01$) later on, too. No statistically significant difference was found in the peak bilirubin concentration between full term infants suffering from perinatal asphyxia and those with idiopathic jaundice. In both groups the bilirubin peak occurred on the fifth

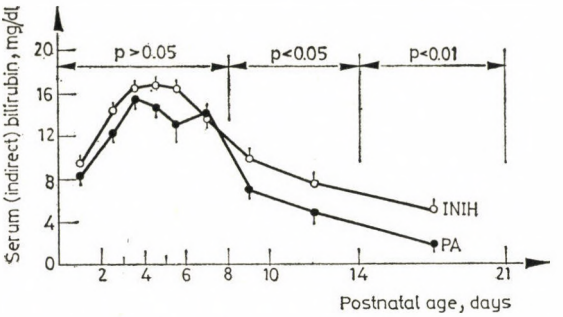

FIG. 1. Serum bilirubin concentration in full term infants suffering from perinatal asphyxia (●—●) or idiopathic indirect hyperbilirubinaemia (○—○)

TABLE IV

Maximum serum bilirubin concentration, postnatal age, weight loss and rate of bilirubin concentration in the infants studied

	No.	Mean	SD	SE	Range
Maximal serum bilirubin concentration (mg/dl)					
FT–PA	22	17.5	4.3	0.9	13.3 – 28.0
FT–INIH	92	18.0	4.2	0.4	12.7 – 28.5
PR–PA	89	17.9	3.0	0.3	12.2 – 26.6
PR–INIH	110	18.1	3.4	0.3	11.7 – 26.0
Postnatal age (days)					
FT–PA	22	4.9	1.4	0.3	3 – 7
FT–INIH	92	4.5	1.3	0.1	2 – 9
PR–PA	89	4.3	1.2	0.1	3 – 7
PR–INIH	110	5.1	1.3	0.1	3 – 10
Weight loss (in percentage of birth weight)					
FT–PA	22	4.5	2.6	0.5	0.0 – 10.9
FT–INIH	92	3.7	2.5	0.2	0.0 – 12.1
PR–PA	89	4.1	2.7	0.2	0.0 – 10.2
PR–INIH	110	4.5	2.3	0.2	0.0 – 10.6
Rate of increase (mg/dl 24 hours)					
FT–PA	13	2.1	1.6	0.4	0.5 – 6.5
FT–INIH	39	2.4	1.6	0.2	0.5 – 6.2
PR–PA	60	2.2	2.1	0.2	0.9 – 9.3
PR–INIH	59	2.4	1.3	0.1	0.5 – 5.1

Abbreviations: FT = full term infants; PR = preterm infants; PA = perinatal asphyxia; INIH = idiopathic neonatal indirect hyperbilirubinaemia.

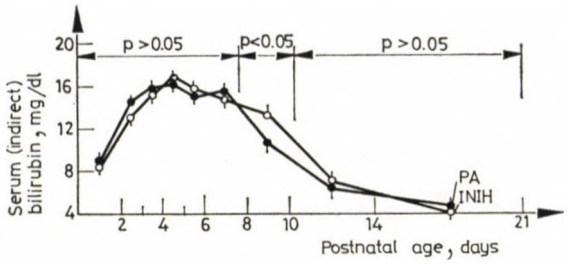

FIG. 2. Serum bilirubin concentration in preterm infants suffering from perinatal asphyxia (●—●) or idiopathic indirect hyperbilirubinaemia (○—○)

postnatal day, when the weight deficit was similar and no difference was observed in the rate of increase in bilirubin concentration either (Table IV).

Averaged bilirubin curves of preterm infants with perinatal asphyxia or idiopathic icterus are shown in Fig. 2. The only difference between the two groups was that in babies with perinatal asphyxia bilirubin concentration was significantly ($p < 0.05$) lower on the 9th and 10th postnatal days but not before or after that time. Maximum serum bilirubin concentration, postnatal age and weight loss at the time of highest bilirubin level, furthermore the rate of increase in bilirubin level were all practically the same in the preterm infants with perinatal asphyxia and those with idiopathic hyperbilirubinaemia (Table IV). To find out if asphyxia was more serious when associated with more pronounced hyperbilirubinaemia, we compared the peak bilirubin concentrations observed in preterm infants who had died, with that of the survivors (Table V). Despite the fact that gestational age and birth weight of those who died were considerably lower than of the survivors (30.6 *vs* 32.8 weeks and 1405 *vs* 1995 g) no difference in peak bilirubin concentration was detected. Postnatal age at the time of the peak bilirubin level was, however, similar in the two groups, and death occurred on the sixth (5.4 ± 0.5) day of life on the average. The assumption that no relationship exists between the severity of asphyxia and hyperbilirubinaemia was further supported by the finding that no significant correlation could be found between peak bilirubin concentration and arterial pH, base excess and pCO_2 measured within two hours after birth in 24 preterm infants. On the other hand, a significantly positive correlation was found between the peak serum bilirubin concentration and weight loss in both groups of full term (perinatal asphyxia: $r = 0.682$, $p < 0.001$; idiopathic jaundice: $r = 0.227$, $p < 0.05$) and preterm infants (perinatal asphyxia: $r = 0.3600$, $p < 0.01$; idiopathic jaundice: $r = 0.293$, $p < 0.01$). In full term and preterm infants with idiopathic hyperbilirubinaemia a significantly positive correlation

TABLE V

Gestational age, birth weight, maximum serum bilirubin concentration, postnatal age at time of bilirubin peak and weight loss (in percentage of birth weight) of preterm infants who died and of survivors

	No.	Mean	SD	SE	Range
Gestational age, week					
died	25	30.6	2.5	0.5	27—35
survived	64	32.8	2.1	0.2	27—36
all	89	32.2	2.4	0.2	27—36
Birth weight, g					
died	25	1405	489	97	780—2900
survived	64	1995	535	66	810—3100
all	89	1830	543	57	780—3100
Maximum serum bilirubin, mg/dl					
died	25	17.2	3.1	0.6	12.5—26.0
survived	64	18.2	2.9	0.3	13.3—26.6
all	89	17.9	3.0	0.3	12.5—26.6
Postnatal age, days					
died	25	4.1	1.2	0.2	2—7
survived	64	4.4	1.2	0.1	2—7
all	89	4.3	1.2	0.1	3—7
Weight loss, per cent					
died	25	4.2	2.7	0.5	0.0—11.0
survived	64	4.1	2.6	0.3	0.0—11.8
all	89	4.1	2.7	0.2	0.0—11.8

was found between the peak bilirubin concentration and the rate of increase in bilirubin level ($r = 0.428$, $p < 0.01$ and $r = 0.458$, $p < 0.001$, respectively). Gestational age and birth weight correlated significantly with the peak bilirubin concentration in preterm babies with perinatal asphyxia ($r = 0.214$, $p < 0.05$ and $r = = 0.335$, $p < 0.01$). No statistically significant correlations were found in any of the other parameter-pairs tested.

DISCUSSION

Kernicterus is known to threaten hypoxaemic and acidotic newborn infants at a considerably lower bilirubin concentration than babies of similar gestational age, birth weight, postnatal age and bilirubin concentration but with normal blood gas and pH status. As an additional risk factor, an exaggerated increase of bilirubinaemia has also been suggested [6, 7, 8, 9, 11, 13].

The present results, however, contradict that assumption. Figs 1 and 2 show that the time course of jaundice was remarkably similar in full term babies with perinatal asphyxia or idiopathic hyperbilirubinaemia just like in preterm infants with perinatal asphyxia or idiopathic icterus at least during the first postnatal week. After that time the bilirubin level fell more rapidly in full term babies with perinatal asphyxia than in the controls and remained at a significantly lower level. Changes in bilirubin concentration differed much less in preterm infants of the two groups. The only difference was that in babies with perinatal asphyxia the bilirubin level was significantly lower at the age of 9—10 days, but not before or after that time.

The natural course of the bilirubin concentration could not be observed and followed in the patients studied. Since many of the therapeutic measures applied may have influenced the bilirubin concentration, conclusions should be drawn with extreme caution. All what can be said is that the hyperbilirubinaemia of full term and preterm infants with perinatal asphyxia was not more severe as regards both its peak and duration than that of control babies.

It is known that like "physiologic" jaundice, hyperbilirubinaemia of newborn infants with perinatal asphyxia develops unpredictably. Data in Table III show that the severity of jaundice varies widely in asphyctic newborn infants. Furthermore, no correlation was found between peak bilirubin concentration and arterial pH, base excess and pCO_2 measured within two hours after birth in 24 preterm infants. For all these reasons infants with indirect hyperbilirubinaemia of unknown aetiology but without asphyxia have been selected for control instead of babies with perinatal asphyxia but without jaundice.

The cause of hyperbilirubinaemia of newborn infants either with perinatal asphyxia or idiopathic indirect hyperbilirubinaemia is still an enigma. The role of numerous factors has been assumed, some of which may well be common. The finding that weight loss correlated significantly with peak bilirubin concentration in both groups of full term and preterm infants suggests the possible role of nutrition, feeding and hydration. A mass of evidence has accumulated in the relevant literature proving the partial role of these factors in the genesis of neonatal hyperbilirubinaemia, but some more explanations are needed to settle the problem. The positive correlation between gestational age, birth weight and peak bilirubin concentration in preterm infants with asphyxia reflects very likely the therapeutic principle that the tolerance of a high bilirubin concentration increases with the advance of maturity.

In conclusion, it is suggested that hyperbilirubinaemia of newborn infants with perinatal asphyxia varies widely once it has developed. The similar time course of hyperbilirubinaemia in asphyctic babies and in those without asphyxia but with jaundice

of unknown aetiology suggests at least in part a common mechanism independent of the pathophysiological changes due to asphyxia. In consequence, if hyperbilirubinaemia develops, all efforts should be made to clarify its aetiology just like in any other case of non-physiologic jaundice. Since weight loss and dehydration seem to contribute to the increased bilirubin level, they should be prevented by any means.

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