SPECTRUM OF NEONATAL HYPERBILIRUBINEMIA: AN ANALYSIS OF 454 CASES

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ABSTRACT

A prospective study of 454 newborn babies with pathological hyperbilirubinemia revealed that in about one-third of cases (34.6%), no cause could be identified despite detailed investigations. Nearly three-fifth of infants (62.5%) had hyperbilirubinemia due to hemolytic causes. On the basis of four variables, i.e., peak serum bilirubin level, age of attaining the peak level, age of starting phototherapy and total duration of phototherapy, the cases of hyperbilirubinemia can be categorized into three groups: (a) Group I (mild) included non-hemolytic hyperbilirubinemia, i.e., idiopathic, bacterial infections, intrauterine infections and others, (b) Group II (moderate) comprised of hemolytic as well as non-hemolytic hyperbilirubinemia due to prematurity, administration of oxytocin, bruising/cephalhematoma, and (c) Group III (severe) comprised of hyperbilirubinemia due to hemolysis as a result of blood group incompatibility between the mother and the neonate and G-6-PD deficiency. Sixty six babies required exchange blood transfusion (EBT) and a total of 100 EBTs were performed. Most of the babies (80.3%) requiring exchange blood transfusion belonged to Group III. The most common cause of hemolytic hyperbilirubinemia needing exchange blood transfusion was Rh isoimmunization followed by G-6-PD deficiency and ABO isoimmunization. There was no death attributable to the procedure of exchange blood transfusion.

Key words: *Hyperbilirubinemia, Clinical profile, Exchange blood transfusion.*

Jaundice is the commonest abnormal physical finding in the newborn babies and is mostly due to physiological handicaps. Non-physiological or pathological hyperbilirubinemia is known to occur in 4-8% of newborn babies. Its timely detection and optimal management are crucial to prevent brain damage and subsequent neuromotor retardation due to bilirubin encephalopathy(1-3). To prevent this, it is pertinent to diagnose and treat neonatal hyperbilirubinemia at the earliest which would be possible only if one is acquainted with its clinical profile and severity(2-4). The literature on these aspects is scarce in the developing countries(5). The present study was planned to assess the clinical profile of neonatal hyperbilirubinemia and to categorize it on the basis of various causes, severity and need for therapeutic intervention.

Material and Methods

Serum bilirubin determinations were performed in the clinically suspected hyperbilirubinemic neonates born at All India Institute of Medical Sciences Hospital, New Delhi, from 1st January, 1986 through 31st December 1989. The study population included both preterm and term healthy as well as sick babies. The various details of these newborns, *i.e.*, sex, weight, gestation, parity of the mother, h/o gestational or insulin dependent diabetes in the mother, h/o oxytocin administration during

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Received for publication April 11, 1991;
Accepted September 4, 1991

labor, *etc.* were prospectively recorded over a pretested proforma. Serum bilirubin was measured by a modified diazo method using an automatic clinical analyzer (Toyo Bilirubin analyzer BA-III). The serial measurements were done as per the requirements of individual case till serum bilirubin returned to the physiological range.

To identify the etiological spectrum, detailed investigations were carried out; ABO and Rh blood typing, direct Coombs test, reticulocyte count, hematocrit, total and differential leucocyte counts, micro ESR, blood culture, screening for G-6-PD deficiency, and total serum bilirubin concentrations. Specialized investigations like T3, T4 and TSH levels, direct-reacting bilirubin and liver functions tests, TORCH antibodies and metabolic screening were undertaken in selected cases.

Phototherapy and exchange blood transfusion were used to treat hyperbilirubinemic babies as per the standard recommendations(3,4). The course of events on phototherapy (*i.e.,* age of starting, duration, rate of fall of serum bilirubin, complications, *etc.*) and exchange transfusion (*i.e.,* number of exchange transfusions per neonate, complications, and mortality, *etc.*) were recorded.

The results were statistically analyzed by using λ^2 test and Student's 't' test.

Results

Of a total 7680 live births, 454 (5.9%) developed hyperbilirubinemia (serum bilirubin >12 mg/dl). Nearly half of the hyperbilirubinemic neonates (56.8%) were male. Prematurity as a cause of hyperbilirubinemia was observed in 76 neonates (16.7%). About one-fourth of the neonates (29.1%) were low birth weight. The most common cause of hyperbilirubinemia was idiopathic (34.6%) followed by prematurity and ABO isoimmunization (*Table I*). In nearly two third babies (65.6%), the nutritional requirements were met exclusively by breast milk. Non-hemolytic hyperbilirubinemia accounted for 63.2% of the total hyperbilirubinemic neonates. The various high risk factors aggravating neonatal jaundice were birth asphyxia (12.1%), infants of diabetic mothers (9.5%), hypoglycemia (9.3%), respiratory distress syndrome (6.4%) and polycythemia (5.7%) (*Table I*). Peak serum bilirubin levels in cases due to ABO isoimmunization, Rh isoimmunization and G-6-PD deficiency were significantly higher and were achieved at a significantly younger age when compared with infants in whom no cause of pathological jaundice was identified (*Table II*). Moreover, infants with ABO isoimmunization, Rh-isoimmunization and G-6-PD deficiency required phototherapy at a significantly earlier age and for a longer duration compared to infants with idiopathic hyperbilirubinemia (*Table III*). Of 66 hyperbilirubinemic neonates (14.5%) requiring exchange blood transfusion (EBT), 53 (80.3%) belonged to hemolytic hyperbilirubinemia. A total of 100 EBTs were performed in 66 babies (1.52 EBT/neonate) (*Table IV*). Forty five babies required only one exchange transfusion while 11, 7 and 3 babies needed 2, 3 and 4 exchange transfusions, respectively. The common early complications related to EBT were tachypnea (7 cases), bradycardia (5 cases), cardio-respiratory arrest (4 cases) and difficult cannulation of umbilical vein (3 cases). The delayed complications included anemia (17 cases), hypoglycemia (7 cases), septicemia (6 cases), acidosis (5 cases) and congestive heart failure (1 case). Of the total babies requiring exchange transfu-

TABLE I—*Causes and Factors Aggravating Pathologic Hyperbilirubinemia*

	No. of infants	Column %	Aggravating factors*				
			Birth asphyxia	IGDM/ IDM	RDS	Polycythemia	Total
Idiopathic**	156	34.4	35 (22.4)	26 (16.7)	14 (9.0)	15 (9.6)	90 (57.7)
Prematurity**	76	16.7	6 (7.9)	4 (9.3)	8 (10.5)	4 (9.3)	22 (28.9)
ABO isoimmunization	65	14.3	3 (4.6)	2 (3.1)	2 (3.1)	3 (4.6)	10 (15.4)
Oxytocin induced	45	9.9	4 (8.9)	5 (11.1)	4 (8.9)	2 (4.4)	15 (33.3)
Rh isoimmunization	37	8.1	3 (8.1)	3 (8.1)	1 (2.7)	1 (2.7)	8 (21.6)
Bacterial infections**	26	5.7	2 (7.7)	1 (3.8)	– –	– –	3 (11.5)
G-6-PD deficiency	23	5.1	2 (8.7)	1 (4.3)	–	1 (4.3)	4 (17.4)
Significant bruising/ Cephalhematoma**	13	2.9	–	–	–	–	–
Intrauterine infections**	6	1.3	–	1 (16.7)	–	–	1 (16.7)
Hypothyroidism**	3	0.7	–	–	–	–	–
Epidural anesthesia with Bupicaine**	3	0.7	–	–	–	–	–
Galactosemia**	1	0.2	–	–	–	–	–
Total	454	100.0	55 (12.1)	43 (9.5)	29 (6.4)	26 (5.7)	153 (33.7)

* Figures in parentheses indicate row percentage of total infants in each group.
** non-hemolytic hyperbilirubinemia.

sion, two died; one of them was a preterm (gestation, 28 weeks, birth weight 950 g) while the other was a term SFD (38 weeks, weight 1450 g) infant with severe meconium aspiration syndrome. There was no mortality directly attributable to the procedure of EBT.

Discussion

The incidence of pathologic hyperbilirubinemia of 5.9% is in accordance with other reports(3,5). In more than one-third of cases of hyperbilirubinemia, no cause could be identified. Various reports from our country have revealed that idiopathic hyperbilirubinemia ranges between 8.8 to 57.6%(3-12). In idiopathic group of hyperbilirubinemia, more than three-fourth babies (77.9%) were receiving exclusive breast feeding. Maisels and Gifford *et al.*(8) reported that 82.7% of the infants with no identifiable cause for hyperbilirubinemia, were breast fed. The high incidence of 23% of idiopathic hyperbilirubinemia in Asian women living in United

TABLE II—*Peak Serum Bilirubin Levels Achieved Due to Various Causes of Hyperbilirubinemia (Mean ± SD)*

	Cause of hyperbilirubinemia	Peak serum bilirubin (mg/dl)	Age of attaining peak serum bilirubin (h)
(*a*)	Idiopathic*	16.9 ±4.1	108 ± 29
(*b*)	Bacterial infections	17.6 ±4.1	96 ± 36
(*c*)	Intrauterine infections	17.4 ±4.8	101 ± 39
(*d*)	Others**	17.7 ±2.1	104 ± 33
(*e*)	Prematurity	18.7 ±3.6	117 ± 32
(*f*)	Oxytocin	17.2 ±4.3	58 ± 24
(*g*)	Significant bruising/ cephalhematoma	17.8 ±4.3	69 ± 28
(*h*)	ABO-isoimmunization	21.5 ±4.6	66 ± 21
(*i*)	Rh-isoimmunization	22.7 ±5.5	53 ± 38
(*j*)	G-6-PD deficiency	25.2 ±9.7	62 ± 23

* Idiopathic group served as controls.

** Included hypothyroidism, epidural anesthesia with bupicaine and galactosemia.

p value		
a *vs* b, c & d	NS	NS
a *vs* e	0.0007	NS
a *vs* f & g	NS	<10 (–6)
a*vs* h, i & j	<10 (–6)	<10 (–6)

States(6) was believed to be due to high frequency of breast feeding in that population. Breast feeding leads to substantial elevation of bilirubin levels during first few days of life due to physiologic inadequacy of lactation(6-8).

The contribution of prematurity, ABO isoimmunization and Rh-isoimmunization as a cause of hyperbilirubinemia was in accordance with other reports in the literature(3,9-12). A number of factors, *i.e.,* birth asphyxia, infants of gestational or insulin dependent diabetic mothers (IGDM/ IDM), RDS, polycythemia, *etc.* are associated with an increase in serum bilirubin levels(3-5). It is substantiated by the present study wherein these high risk factors were present in about one-third of hyperbilirubinemic cases. Again, more than half of the infants with idiopathic hyperbilirubinemia (57.7%) did have one or more of these risk factors. It is possible that breast feeding in the presence of one of these high risk factors may predispose some of the infants with physiologic hyperbilirubinemia to develop the so called idiopathic (pathologic) hyperbilirubinemia. The association, to be further substantiated, may explain at least some of the cases of idiopathic hyperbilirubinemia. Moreover, most investigations of neonatal hyperbilirubinemia are directed to identify hemolytic process while we have no reliable tests to assess the maturity of liver and severity of enterohepatic circulation.

The lowest peak serum bilirubin levels were observed in infants with idiopathic variety of hyperbilirubinemia while the

TABLE III—*Effect of Phototherapy on Hyperbilirubinemia Due to Various Causes (Mean ± SD)*

Causes	Age of starting phototherapy (h)	Total duration of phototherapy (h)	Rate of fall of serum bilirubin (mg/dl/day)
(*a*) Idiopathic*	86 ±34	52 ±33	2.5 ±1.8
(*b*) Bacterial infections	82 ±33	54 ±30	2.1 ±1.4
(*c*) Intrauterine infections	84 ±31	54 ±23	2.5 ±1.6
(*d*) Others**	83 ±27	51 ±19	2.3 ±1.4
(*e*) Prematurity	82 ±38	65 ±35	2.8 ±1.6
(*f*) Oxytocin	52 ±23	58 ±32	3.2 ±1.6
(*g*) Significant bruising/ cephalhematoma	59 ±25	67 ±32	2.9 ±1.7
(*h*) ABO-isoimmunization	46 ±31	98 ±48	2.1 ±1.4
(*i*) Rh-isoimmunization	55 ±21	72 ±28	3.4 ±2.4
(*j*) G-6-PD deficiency	52 ±23	77 ±32	2.4 ±1.4

* Idiopathic group served as controls.

** Included hypothyroidism, epidural anesthesia with bupicaine and galactosmia.

p value			
a *vs* b, c & d	NS	NS	NS
a *vs* e	NS	0.0073	NS
a *vs* f	<10 (–6)	NS	0.023
a *vs* g	<10 (–6)	NS	NS
a *vs* h	<10 (–6)	0.0002	NS
a *vs* i	<10 (–6)	<10 (–6)	NS
a *vs* j	<10 (–6)	0.0021	NS

TABLE IV—*Exchange Blood Transfusion (EBT) for Hyperbilirubinemia Due to Various Causes*

Causes	No. of neonates requiring EBT (% of total neonates in each group)	Total No. of EBTs	No. of EBTs/ neonate
Idiopathic	6 (3.8)	7	1.16
Bacterial infections	2 (7.7)	2	1.00
Intrauterine infections	–	–	–
Others*	–	–	–
Prematurity	5 (6.6)	5	1.00
Oxytocin	3 (6.7)	4	1.33
Significant bruising/ cephalhematoma	–	–	–
ABO-isoimmunization	18 (27.7)	27	1.50
Rh-isoimmunization	21 (56.8)	39	1.86
G-6-PD deficiency	11 (47.8)	16	1.45
Total	66 (14.5)	100	1.52

* Included hypothyroidism, epidural anesthesia with bupicaine and galactosemia.

highest peak values were seen in babies with G-6-PD deficiency. The peak serum bilirubin levels in infants with prematurity, ABO isoimmunization, Rh isioimmunization and G-6-PD deficiency were significantly higher as compared to idiopathic hyperbilirubinemia. A higher peak serum bilirubin level in these conditions is because of continuing hemolysis(3,4). In idiopathic variety, peak serum bilirubin level was achieved at a mean age of 108 hours while in ABO isoimmunization, oxytocin, Rh isoimmunization and G-6-PD deficiency, peak serum bilirubin levels were achieved at a significantly earlier age as compared to that of idiopathic variety. The achievement of early peak serum bilirubin levels is because of a hemolytic process which sets *in utero* or immediately after birth(3).

Early phototherapy has been suggested in cases of hyperbilirubinemia due to hemolytic process(3,5). It is in accordance to the observations of the present series, where it was started at a significantly earlier age in ABO isoimmunization, oxytocin, Rh isoimmunization, G-6-PD deficiency as compared to nonhemolytic (idiopathic) variety.

Premature babies as well as those with a continuing hemolytic process are predisposed to develop prolonged hyperbilirubinemia(4,5). It is substantiated by our study because phototherapy was required for a significantly longer duration in infants with prematurity, ABO isoimmunization, Rh isoimmunization and G-6-PD deficiency compared to babies with idiopathic hyperbilirubinemia. The rate of fall of serum bilirubin during phototherapy varied from 2.1 mg/dl to 3.2 mg/dl per day which is comparable to other reports(3-5).

The most common cause of hyperbilirubinemia requiring exchange transfusion, as revealed in the present series, was Rh isoimmunization followed by ABO isoimmunization and G-6-PD deficiency. In the series reported by Dikshit *et al.*(13), the commonest cause of neonatal hyperbilirubinemia requiring EBT was ABO isoimmunization followed by Rh isoimmunization, septicemia and G-6-PD deficiency. The immediate exchange transfusion related complications in the present study were cardiorespiratory arrest, bradycardia, tachypnea, *etc.* which is in accordance with the available literature(3,5,13). Post exchange anemia, septicemia, hypoglycemia and acidosis have been the most frequent late complications in different Indian studies(5,13) as well as in the present series. However, it needs to be emphasized that in the experienced hands, EBT is a relatively safe procedure and had no procedure related mortality in our series of 100 consecutive exchange blood transfusions.

Based on our observations, the neonatal hyperbilirubinemia can be broadly categorized into three groups (*a*) Group I (mild variety) constituted by idiopathic cases, bacterial infections, intrauterine infections and others like hypothroidism, galactosemia, *etc.* These cases presented with the lowest peak serum bilirubin levels, required phototherapy at a later age and for a minimum duration; (*b*) Group II (moderate) included cases due to oxytocin and significant bruising/cephalhematoma. These cases had peak serum bilirubin levels comparable to that of idiopathic variety but required phototherapy at a significantly earlier age. In hyperbilirubinemia due to prematurity, peak serum bilirubin levels were significantly higher and required phototherapy for a significantly longer duration as compared to Group I and they can also be considered in this group; (*c*) Group III

(severe) included cases due to ABO isoimmunization, Rh isoimmunization, and G-6-PD deficiency. These infants had a significantly higher peak serum bilirubin levels which were attained at a significantly earlier age and required phototherapy at a significantly younger age and for a longer duration as compared to Group I and Group II. This type of classification will help us to identify the serious causes of hyperbilirubinemia so that preventive and therapeutic measures can be instituted early in Group II and Group III cases to minimize the risk of brain damage and sequelae due to kernicterus.

REFERENCES

1. Singhal PK, Mathur GP, Mathur S, Singh YD. Neonatal morbidity and mortality in ICDS urban slums. Indian Pediatr 1990, 27: 485-488.
2. Singh M, Deorari AK, Khajuria RL, Paul VK. Spectrum of neonatal morbidity in a hospital: A four year study. Indian J Med Res (in press).
3. Maisels KJ. Neonatal jaundice. *In:* Neonatology-Pathophysiology and management of the newborn. 3rd edn. Ed Avery GB. Philadelphia, J.B. Lippincott Company, 1987, pp 534-608.
4. Cloherty JP. Neonatal hyperbilirubinemia. *In:* Manual of Neonatal 2nd edn. Eds Cloherty JP, Stark AR. Boston. Little, Brown and Company, 1985, pp 233-262.
5. Singh M. Care of the Newborn, 3rd edn. New Delhi, Sagar Publications, 1985, pp 204-231.
6. Newman TB, Easterling J, Goldman ES, Stevenson DK. Laboratory evaluation of jaundice in newborns. Am J Dis Children 1990, 144: 364-368.
7. Jeffares MJ. A multifactorial survey of neonatal jaundice. Br J Obstet Gynecol 1977, 84: 452-455.
8. Maisels KJ, Gifford K. Neonatal jaundice in full term infants: Role of breast feeding and other causes. Am J Dis Children 1983, 137: 561-562.
9. Anand VR, Magotra ML. Neonatal Jaundice: Its incidence and etiology. Indian Pediatr 1978, 15: 155-160.
10. Bajpai PC, Misra PK, Agarwal M, Engineer AD. An etiological study of neonatal hyperbilirubinemia. Indian J Pediatr 1971, 38: 424-429.
11. Merchant RH, Merchant SM, Babar ST. A study of 75 cases of neonatal jaundice. Indian Pediatr 1975, 12: 889-894.
12. Mohapatra SS, Menon PSN, Bhan MK, Dhar V. Cockington nomogram as a guide to phototherapy in the management of neonatal hyperbilirubinemia: Evaluation of Indian neonates. Indian Pediatr 1984, 21: 229-233.
13. Dikshit SK, Gupta PK. Exchange transfusion in neonatal hyperbilirubinemia. Indian Pediatr 1989, 26: 1139-1145.