Personal practice

Investigation and management of neonatal jaundice: a problem-orientated case record

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SUMMARY A problem-orientated case record was used for the investigation and management of neonatal jaundice. Investigation of babies requiring phototherapy rarely showed any abnormality but we consider that such routine investigations are worth retaining. There were problems in the interpretation of moderately low plasma concentrations of thyroxine in small, preterm babies. There was biochemical evidence of hepatitis in 3 babies; in all 3 the biochemical abnormality was mild and had disappeared 6 months later in 2 of them. It may be that mild episodes of the neonatal hepatitis syndrome are more common than have been thought and that such infants have a fairly good prognosis.

Jaundice is common in the newborn infant. It is generally of little clinical significance but occasionally it indicates an underlying illness. Such illness may be of immediate importance—such as an infection—or it may be one that does not become apparent for many months—such as hypothyroidism. Sometimes the investigation and management of a jaundiced baby are clear—for example, if septicaemia is strongly suspected. However, often there are no other clinical signs and it is difficult to decide if further investigation is indicated and, if so, how far it should be pursued. The path between unnecessary investigation and missed diagnosis is difficult to tread and there is a danger that the pattern of investigation may be influenced too much by the pressure of work and the amount of clinical experience.

With these problems in mind we set up a firm protocol for the investigation and management of jaundiced babies. This protocol has been used and analysed for a year and we now describe it.

The protocol

The protocol is shown in Table 1. It was designed mainly for babies who seemed reasonably well. It was not designed for very small babies or for very preterm ones (those less than 34 weeks' gestational age or below 1.5 kg birthweight), nor was it intended

for those with rhesus incompatibility, although with some modification it was often used as a guide in the management of such babies; for example, the small, preterm infant might start phototherapy at 200 rather than 250 $\mu\text{mol/l}$ as shown.

The reasoning behind the management and investigations will generally be clear but it may be useful to comment on some points. The action lines for extra water, phototherapy, and exchange transfusion are horizontal, although it might have been more sensible to climb upwards against time and to have had different sets of action lines according to gestational age. The single set of horizontal action lines are easily remembered by staff even if the protocol is not in front of them. We considered that simplicity over-rode the pathophysiological arguments for a series of sloping action lines. We realise that a bilirubin concentration $>250 \mu\text{mol/l}$ (14.6 mg/100 ml) in a healthy, term baby towards the end of the first week of life is far from dangerous. There are not many such babies however, and sometimes this late onset of jaundice is a sign of illness. We therefore prefer to keep this line even though it may later be decided to dispense with phototherapy in a particular child. There is evidence that higher volume milk feeds are associated with lower plasma bilirubin levels.^{1,2} Recent work has questioned whether water alone achieves the same result³ and after further evaluation it may be that

Table 1 Neonatal jaundice

Plot plasma bilirubin concentration on chart above. Investigate and treat according to protocol below. Put in date when investigation was sent off and record results in Table.

Zone	Suggested investigation	Management	Date
			Began/ended
Early jaundice	(H)	Watch carefully. Consider phototherapy if $> 175 \mu\text{mol/l}$. If Coombs's positive (ie blood group incompatibility) individual management required	
Extra water	Nil	Extra water (30% of normal feed volume) for one course of 4 days	
Phototherapy	(H) (U) (C)	Extra water as above. Phototherapy for 24-hour periods until end of 24-hour period in which bilirubin falls below $220 \mu\text{mol/l}$	
Prolonged	(H) (U) (T) (C)	Initially, investigate only	
Haematology (H)		Urine (U)	Conjugated bilirubin (C); estimate and plot; if greater than $50 \mu\text{mol/l}$ and bile present in urine proceed to investigations below
Mother	Clinitest:	Virus	IgM
Group	Clinistix:	Throat swab	α -1-Antitrypsin
Antibodies	Ictotest:	Urine	Toxoplasmosis
	Bacteriology		Cytomegalovirus
Baby			Rubella
Group		Other LFT	Wassermann reaction
Coombs	Thyroid function (T)	For example,	Australia antigen
Cord bilirubin		AST	
Hb	T4	ALT	
G6PD (in male immigrant)	T3 uptake	5 nucleotidase	
	TSH		
Other			

Table 2 Patients and their management

	Birthweight (g)						Total all weights
	>2500	2251–2500	2001–2250	1501–2000	1001–1500	Up to 1000	
Live births in this hospital	1786	93	47	37	17	8	1988
Babies admitted on SCBU							
Born in this hospital	229	50	47	37	17	8	388
Born elsewhere	3	0	8	23	12	5	51
Deaths	8	2	0	1	7	10	28
<i>Early jaundice sector</i>							
Number investigated	55	13	5	20	6	5	104
Results of investigation							
(H) Rhesus incompatibility*	2	0	0	0	0	0	2
Possible ABO incompatibility†	11	1	1	4	0	0	17
G6PD deficiency‡	0	0	0	0	0	0	0
Haemoglobin <14 g/dl	2	1	1	2	1	0	7
<i>Phototherapy sector</i>							
Number investigated and treated	58	11	8	13	3	0	93
Results of investigation							
(H) Rhesus incompatibility	1	0	0	0	0	0	1
Possible ABO incompatibility	12	0	2	2	0	0	16
G6PD deficiency	0	0	0	0	0	0	0
Haemoglobin <14 g/dl	3	1	0	1	1	0	6
(U) Clinitest positive	0	0	0	0	0	0	0
Bile positive	8	1	0	1	0	0	10
Urinary tract infection	1	1	0	0	0	0	2
(C) Conjugated bilirubin >50 µmol/l	1	2	0	1	0	0	4
<i>Prolonged jaundice sector</i>							
Number investigated	2	0	1	4	2	1	10
Results of investigation							
(H) Rhesus incompatibility	0	0	0	0	0	0	0
Possible ABO incompatibility	1	0	0	0	0	0	1
G6PD deficiency	0	0	0	0	0	0	0
Haemoglobin <12 g/dl at 1 week	0	0	0	1	1	1	3
(U) Clinitest positive	0	0	0	0	0	0	0
Bile positive	1	0	1	1	2	1	6
Urinary tract infection	0	0	0	0	0	0	0
(T) Thyroxine <100 nmol/l	2	1	1	5	3	1	13 ⁸⁸
Thyroxine <80 nmol/l	0	0	0	2	1	0	3
(C) Conjugated bilirubin >50 µmol/l	0	0	1	0	2	1	4
Total number investigated in all sectors	115	24	14	37	11	6	207
% of SBCU admissions	50	48	25	61	24	46	47
% of all babies in hospital	6	26	25	61	24	46	10

*Mother Rh-negative, baby Rh-positive, Coombs's positive; †mother O, baby A or B in all cases; ‡using Sigma decoloration—for example Cresyl blue spot test.

⁸⁸Three were investigated for hypothyroidism on indications other than prolonged jaundice.

our practice of giving extra water will have to be reviewed. We consider that extra water is necessary during phototherapy. Glucose-6-phosphate dehydrogenase (G6PD) deficiency can, of course, occur in Europeans and in girls (double hemizygote), but we thought this was too rare to concern us unless there was a strong family history of neonatal jaundice. On the other hand, although we realise that galactosaemia is unlikely to cause jaundice in an otherwise well baby, the Clinitest is easy to perform; we have some sympathy with the recommendation of the American Academy of Pediatrics that the urine of every baby should be tested for reducing sugars.⁴ Cytomegalovirus may result in unconjugated hyperbilirubinaemia only, but this and any other infection

if it causes jaundice, nearly always leads to a rise in conjugated bilirubin too.⁵ There is little point therefore, in pursuing the investigation (bottom right box) unless the conjugated bilirubin level is raised, and bile in the urine acts as an extra check on this. Plasma conjugated bilirubin and Ictotest on the urine were performed in each child who entered the phototherapy or the prolonged sector.

Patients and relevant aspects of neonatal management

In 1976, the year of the study, 1988 infants were born in the hospital and 388 (19%) of them were admitted to the Special Care Unit. A further 51 were admitted to the Special Care Unit from their homes or from another hospital. About half of the patients were

white and the remainder of South Asian families. The first three lines of Table 2 show birthweight distribution. Many infants were of low birthweight (10% compared with national incidence of 7%).

Our obstetric colleagues have a fairly conservative induction policy and about one-fifth of the mothers receive oxytocin. All babies born in the hospital receive intramuscular vitamin K (Konakion)—0.5 mg for babies of low birthweight, 1 mg for the others. In the postnatal wards only half of the mothers attempted breast feeding, and this was progressing satisfactorily in only 30% of them by the 6th day of life; the other babies received Ostermilk Complete. Babies requiring special care receive the following volumes of feed: if appropriate weight for gestational age 40 ml/kg in the first 24 hours, increasing by 20 ml a day to reach 150 ml/kg by day 7 in the term babies, and 200 ml/kg by day 9 in the preterm; if light for gestational age they receive 60 ml/kg in the first 24 hours increasing by 30 ml a day to reach 200 ml/kg by day 6. Pasteurised pooled expressed breast milk was generally given to any baby who was ill or to any baby weighing less than 1.5 kg; other babies received SMA Gold Cap. Only occasionally was a special care baby completely breast fed. Sulphonamides were not used but cloxacillin was, quite frequently.

Use of the protocol

The results of using the protocol throughout 1976 are shown (Table 2). Of the babies who were inpatients in 1976, 104 (5%) were investigated further because of early jaundice, 93 (5%) because the bilirubin concentration was above 250 $\mu\text{mol/l}$ (they were given phototherapy), and 10 (1%) because of prolonged jaundice.

Just under half the babies admitted to the Special Care Unit required further investigation of jaundice, but only 10% of all the babies in the hospital required investigation.

Haemolysis. There were 3 babies with rhesus incompatibility and 34 with possible ABO incompatibility. About half of them presented as early jaundice, half as requiring phototherapy, and only one as prolonged jaundice. Haemolysis was a possible factor in about one-fifth of the babies with early jaundice or in those requiring phototherapy. No instance of G6PD deficiency was found. During the last 4 years during which the number of live births has been similar, only 2 cases have been diagnosed and each presented as requiring phototherapy. Appreciable anaemia was found in the 3 babies with rhesus incompatibility, but of the 34 babies with possible ABO incompatibility only 10 were anaemic.

Three babies who presented with prolonged jaundice were also anaemic; perhaps they had unrecognised haemolysis but no obvious cause was found.

Infection. Unsuspected infection was rarely diagnosed after investigation of jaundice. Two (2%) of the 93 children requiring phototherapy were found to have infections of the urinary tract; during the same year a further 2 (1%) cases of urinary tract infection were diagnosed in the 210 other children admitted to the unit, but neither of them required phototherapy.

Hypothyroidism. The 3 babies with plasma thyroxine (T4) concentrations less than 80 nmol/l (6.2 $\mu\text{g}/100$ ml) were all preterm. T4 returned to normal levels between ages 3 and 4 weeks in 2 of them. In the third baby a low plasma thyroxine level (46 nmol/l; 3.5 $\mu\text{g}/100$ ml) was found and confirmed, so the baby was started on thyroxine, 50 μg daily. Subsequently the thyroid-stimulating hormone values on samples obtained before treatment were noted to be low. Pituitary hypothyroidism was considered but it seemed more likely that the low T4 reflected a low thyroid-binding globulin. At that time the thyroid-binding globulin was not being measured routinely in our laboratory. It was decided therefore, cautiously to stop thyroxine at age 101 days. The plasma T4 level dipped briefly but remained within normal limits. At age 10 months, plasma T4, thyroid-stimulating hormone, and psychomotor development were normal.

Conjugated hyperbilirubinaemia. Of the 8 children with conjugated hyperbilirubinaemia (>50 $\mu\text{mol/l}$; 2.9 mg/100 ml) 4 presented in the phototherapy sector. In 3 of them (1 ABO incompatibility and 2 preterm babies), the raised levels were only transient and had fallen to normal levels before age 3 weeks. The remaining infant was considered to have neonatal hepatitis and had persistently raised transaminases even at age 3 years. This baby had developmental retardation as well but all aetiological investigations had shown negative results. Four further children presented with prolonged conjugated hyperbilirubinaemia. Two of them had neonatal hepatitis which gradually resolved over some months. The 2 remaining children had chronic illnesses, one with persistent pulmonary syndrome of the newborn, probably Wilson-Mikity type. The other had propionic acidemia, only partially controlled by biotin and an exclusion diet, and the child died after an episode of pneumonia at age 4 months.

Discussion

Although the protocol was formidable it was easy to

use once it had been introduced. The chart was in effect a 'problem orientated case record'.⁶

The potential list of investigations was long but many investigations never had to be performed. In particular, the rule that intrauterine infection as a cause of jaundice should be sought only if the conjugated bilirubin level was raised, reduced the number considerably.

Were the phototherapy investigations worth while? No case of galactosaemia was diagnosed in 1976 and only one case has been seen since at another hospital; he presented as an ill acidotic baby at 48 hours, by which time he was in neither the early jaundice nor the phototherapy sector. Nevertheless, since the test is simple, we think it is worth while retaining it. Investigation showed one instance of rhesus incompatibility and 16 of possible ABO incompatibility. Six infants were anaemic and this would probably not have been detected had they not had phototherapy investigations. However, as none required transfusion, it was perhaps not necessary to know the haemoglobin concentration. Of the 4 with raised conjugated bilirubin levels, in 3 the levels were only transiently raised and the fourth with hepatitis would have been diagnosed in the prolonged sector. Nevertheless, since the next treatment after phototherapy is exchange transfusion, it seems reasonable to find out the unconjugated bilirubin concentration before a decision is taken. Urinary tract infection was diagnosed in 2% of babies receiving phototherapy and was present in a further 1% with other symptoms. Opinions on the prevalence of urinary tract infection in newborn babies vary from 0.1%⁷ to 1.4%⁸ so this 2% may be little more than in the general population. Nevertheless, it seems desirable to diagnose urinary tract infection. On balance therefore, we have decided to retain all of these phototherapy investigations.

Was the investigation for G6PD deficiency worth while? Only 2 cases of G6PD deficiency have been diagnosed in 4 years and none during this study year. Since this did not affect the immediate management and since the only long-term management is to issue a list of potentially dangerous drugs, we are doubtful about the value of the investigation. On the other hand, a study of the families of these patients led to other affected members so that preventive advice was able to be given to a number of people.

What is the significance of low T4 values (<80 nmol/l) in preterm infants? The frequency of congenital hypothyroidism may be as high as 1 in 2850,⁹ but thyroid investigation for prolonged jaundice should soon be unnecessary when screening all babies

becomes established. Our experience leading to the unnecessary 'treatment' of one baby illustrates some of the problems that will be encountered in interpreting results in individual very small babies; however, whether ill preterm babies with very low T4 levels require temporary cover with thyroxine is not known. Such babies will warrant a more detailed endocrine assessment probably including responses to thyroid-stimulating hormone and thyroid-releasing hormone before starting treatment. In 4 years (about 8000 births) 2 cases of hypothyroidism have been diagnosed in this hospital. One was diagnosed by following the protocol for prolonged jaundice, although the mother was breast feeding. The other was diagnosed at age 3 months; while in hospital she had entered the phototherapy sector but had not had prolonged jaundice.

What is the importance of conjugated hyperbilirubinaemia? It was rare, but when it occurred it was often of serious significance (serious in 3 out of the 8 children). We were nevertheless surprised that the majority did well subsequently. The poor prognosis attributed to conjugated hyperbilirubinaemia is because of its association with the neonatal hepatitis syndrome, including biliary atresia. It may be that milder episodes of the syndrome are more common than had been realised and that these have a fairly good prognosis.

References

- 1 Smallpiece V, Davies P A. Immediate feeding of premature infants with undiluted breast milk. *Lancet* 1964; ii: 1349-52.
- 2 Wharton B A, Bower B D. Immediate or later feeding for premature babies? A controlled trial. *Lancet* 1965; ii: 969-72.
- 3 De Carvalho M, Hall M, Harvey D. Effects of water supplementation on physiological jaundice in breast-fed babies. *Arch Dis Child* 1981; 56: 568-9.
- 4 Committee on Fetus and Newborn. Screening of newborn infants for metabolic disease. *Pediatrics* 1965; 35: 499-500.
- 5 Hanshaw J B, Betts R F, Simon G, Boynton R C. Acquired cytomegalovirus infection. *N Engl J Med* 1965; 272: 602-9.
- 6 Walker H K, Hurst J W, Woody M F, eds. *Applying the problem orientated system*. New York: Medicom Press, 1973: 14-6.
- 7 O'Brien N G, Carroll R, Donovan D E, Dundon S P. Bacteriuria and leucocyte excretion in the newborn. *J Irish Med Assoc* 1968; 61: 267-8.
- 8 Littlewood J M, Kite P, Kite B A. Incidence of neonatal urinary tract infection. *Arch Dis Child* 1969; 44: 617-20.
- 9 Illig R, Torresni T, Sobradillo B. Early detection of neonatal hypothyroidism by serial TSH determination in dried blood. *Helv Paediatr Acta* 1977; 32: 289-97.

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