HK J Paediatr (new series) 2000;**5**:76-84

Postgraduate Column

Neonatal Jaundice - the Hong Kong Data

DKK **NG**

Abstract Neonatal jaundice (NNJ) was a common disorder in the past in Hong Kong with its dreaded complication of kernicterus. With the improvement in socio-economic situation, better public education and readily available high standard medical service, kernicterus is now a highly unusual disease. A lot of research works have been published from different Hong Kong workers in this area. This review was attempted to put together most of the published works in NNJ to give an overall Hong Kong picture.

Key words Neonate; Jaundice; Chinese

Introduction

Neonatal jaundice (NNJ) is the commonest problem in Hong Kong neonates.[1] It is most likely to be unconjugated hyperbilirubinemia. Dramatic change was observed in last three decades with a sharp drop in incidence of kernicterus. This improvement was achieved through the concerted effort of the community, neonatologists, community medical practitioners, health nurses. Significant effort was put in by Hong Kong doctors to shed light on this problem as evidenced by the large number of publications in NNJ. This review was based on the published works of these doctors. Neonatal cholestasis would not be discussed.

Epidemiology

Yeung[1] found that neonatal jaundice accounted for 14.5% of admissions to the hospital paediatric department in 1971. By 1983, this condition only accounted for 7.8% of paediatric admissions.[2] This dropped to only 5% of admission in 1996.[3] Similar downward trends are observed in China, Taiwan and Singapore (personal communication). Degree of jaundice was found to be lower in higher socio-economic group[3] (Table 1). Poor hygiene, over-crowding, increased herbal consumption, less access to proper medical treatment were suggested to be responsible. The rate of kernicterus dropped from 1.8% of NNJ in 1966 to 0% in 1992-96.[3]

Clinical Features

Li and Chau[4] studied 131 jaundiced infants in 1967 and this group included 57 with indirect hyperbilirubinemia. Haemolysis and haematoma accounted for 46. Eighteen developed kernicterus. Amongst them, 14 were glucose-6-phosphate dehydrogenase (G6PD) deficient. 14 were kernicteric on admission and all but one died in this group. Yeung[1] reported a series of 1,811 infants with NNJ in 1973. No specific causes were found in 57.9% of this group of patients. The commonest known etiology for NNJ was ABO incompatibility, which was found in 22.9% of patients. However, overt features of haemolysis were present in only less than a third of those who developed moderately severe jaundice.[4] G-6-PD deficiency was found in 13.4%.

Li et al[5] studied the relationship between early immunization and jaundice in 200 full-term Chinese newborns with birth weight over 2,500 grams in 70/71. Those with G-6-PD deficiency, significant cephalhematoma, significant bacterial infections were excluded. They found no significant difference between control group, BCG vaccination group, smallpox vaccination group, polio vaccination group and the group that received all three vaccines. They also assessed if occurrence of jaundice was associated with occult intrauterine infections. They used cord blood IgM level of 20 mg/100 ml and above as indicative of occult

Department of Paediatrics, Kwong Wah Hospital, 25 Waterloo Road, Hong Kong, China

DKK **NG** *MB, BS(HK), M Med Sc(HK), FHKAM (Paed), FRCP(Edin, Glas)*

Correspondence to: Dr DKK **NG**

Received April 29, 1999

Table 1 Effect of socio-economic environment on frequency of neonatal jaundice in Hong Kong

Hospital	Socio-economic class	Number of infants	SB>171 μmol/L	SB>256.5 μmol/L
A	Lower	198	78.8%	12.6%
B	Higher	100	32%	5%

intrauterine infections. They found no significant difference in SB level between the group with IgM >= 20 mg/dL and the group with IgM < 20 mg/dL. Li et al[5] found SB level to be over 205 umol/l in 54% of their study population of 200 full-term Chinese neonates and 1% to have SB level over 342 umol/l. SB level was noted to peak on day 4 and day 5 of life.

Fok et al[6] studied a group of healthy Chinese term babies (N= 1,238) in 1983/84 (Table 2). Clinical jaundice was detected in 89%. Moderate/severe jaundice, ie SB>204 umol/l, was found in 23.9% of babies not associated with G6PD deficiency nor ABO blood group incompatibility with mothers. Subgroup analysis showed higher percentage in infants with ABO blood groups incompatible with that of the mother and infants with G6PD deficiency, 95.2% and 95.8% respectively. The mean age of peak serum bilirubin was 83 hours for 'physiological' jaundice, 81 hours for those with ABO blood group incompatible with that of the mother and 87 hours for those with G6PD deficiency.

Factors that were found to be associated with a higher peak SB level in the 'physiological' jaundice group included male sex, elder siblings who had a history of neonatal jaundice, breast-fed infants with or without supplementation with formula feed.

Pathogenesis

Lau et. al.[7] reported in a letter that they found evidence of increased bilirubin production in Chinese babies with 'physiological' jaundice. They analysed pulmonary carbon monoxide excretion rate (VeCO) which reflected total bilirubin production. In 20 infants with 'physiological' jaundice, mean VeCo was 15.7 ± 4.2 uL/kg/h in contrast to the mean VeCO 11.4 ± 1.7 uL/kg/h found in 18 infants with no jaundice; P<0.01. Increased bilirubin production is likely to be responsible for the high incidence of NNJ in Hong Kong Chinese.

Law et al[8] examined cord blood in 111 infants who were admitted to the neonatal unit before day 3 after birth. They were admitted for NNJ or for observation because of prolonged leakage of liquor, birth trauma or high birth weight (>4.0 kg). None had polycythemia, sepsis, G6PD deficiency or other blood group incompatibilities. The cord blood were retrieved for analysis of alpha-fetoprotein (cAFP), AFP variant that is nonreactive to concanavalin (CNAFP), bilirubin (cBIL), albumin (cALB), glutamyltransferase (cGGT) and transferrin (cTRF). SB was checked from day 3 to day 6 by heel prick. A serum bilirubin concentration of 200 umol/L was used as the cutoff value to distinguish the nonhyperbilirubinemic from the hyperbilirubinemic infants. Only cAFP, cCNAFP, cCNAFP/cAFP ratio and cBIL were found to be significantly higher in hyperbilirubinemic group than nonhyperbilirubinemic group. cAFP and cCNAFP were found to have a high correlation coefficient; r=0.9415, P<0.001. Hence, cCNAFP were excluded from further statistical analysis. Stepwise multiple regression affirmed that cAFP and cBIL contributed to post-partum peak serum bilirubin concentration, r=0.504, P<0.0001. No significant correlation existed between cBIL and cAFP. The authors

Table 2 Distribution of peak SB levels and incidence of phototherapy among the infant groups

	Distribution of peak SB level (mmol/l)											
Group		Clinical Jaundice	Absent or minimal <120		Mild 120-204		Moderate / severe >204		Phototherapy		Peak SB level (μmol/l)	
	n	%*	N	%*	n	%*	N	%*	n	%*	X	s.d.
1	1004	87.3	228	22.7	536	53.4	240	23.9	85	8.5	157	107
2	143	95.2	14	9.8	68	47.5	61	42.7^{+}	24	16.8^{+}	201	87^{+}
3	91	95.8	9	9.9	37	40.7	45	49.4^{++}	25	27.5^{++}	216	78^{++}

Group 1: non-specific jaundice, Group 2: ABO incompatibility, Group 3: G6PD deficiency

*Percentage of total number in each group

$^{+}$ P<0.01 when compared with Group 1

$^{++}$P<0.01 when compared with Group 1 and male infants in Group 1

concluded that a combination of cAFP and cBIL can be used to predict development of 'physiological' jaundice and the results suggested that both liver immaturity and increased bilirubin production were associated with development of 'physiological' jaundice. The question why Hong Kong Chinese have more bilirubin production and more immature liver than Caucasian remained unanswered. *The fact that liver immaturity played a role in 'physiological' jaundice would support the use of phenobarbitone in treatment of 'physiological' jaundice.*

Sung et al[9] studied glucaric acid excretion in 122 full-term Chinese babies with 'physiological' jaundice. One hundred were born by caesarean section and 22 were born by normal vaginal delivery. D-glucaric acid was shown to be a sensitive index of hepatic microsomal enzyme induction in adults and children. They measured urine D-glucaric acid / creatinine ratio daily for first 5 days of life. They found statistically significant higher ratio of D-glucaric acid / creatinine on Day 1 & 2 in those that developed jaundice. This result raised doubt about the hypothesis that liver immaturity play a role in physiological jaundice. However, this result may not negate the hypothesis that babies with 'physiological' jaundice had immature liver function because D-glucaric acid excretion may not be useful in assessing liver maturity in the newborn.

Kernicterus

Yeung reported the incidence of kernicterus to be 8.6% (156/1811) in term infants admitted for jaundice into two major hospitals, Queen Mary Hospital (1968-1970) and Queen Elizabeth Hospital (1970-1971).[1] The serum bilirubin of the infants with kernicterus ranged between 381 umol/l (22.3 mg/dl) and 855 umol/l (50 mg/dl) with an average 605.3 umol/l (35.4 mg/dl) in this series. Twenty-nine of the kernicterus infants died and most of them did not receive exchange transfusion. With the improvement of socio-economic condition in Hong Kong as well as a better educated public, the percentage of kernicterus dropped to 0.63% in 1981-82.[2] In the '90s, only 1 to 2 cases were seen every 3 to 4 years in Queen Mary Hospital.[10] The rate of brain toxicity from serum bilirubin above 20 mg/dl (342 umol/L) were 26.5% and 5.5% for 1971 series and 1981/82 series respectively. Of the three patients that developed kernicterus in 1981-82, two were associated with G6PD deficiency and there was no demonstrable cause in one infant and her bilirubin level was only 398 umol/l (23.3 mg/dl). The last patient illustrated the point that it would be dangerous not to do exchange transfusion for severe hyperbilirubinaemia not associated with haemolysis in this part of the world. *This patient re-confirmed the rationale of using SB level above 20 mg/dl as the cut-off point for ET in Hong Kong.* It can be seen from (Table 3) 12 cases of kernicterus occurred in the group with non-specific cause. This group may otherwise be labelled as physiological jaundice which is obviously a misnormer. It was suggested by Yeung to adopt the term 'non-specific jaundice' to describe raised SB level with no known causes rather than using the misleading term 'physiologic jaundice'.[3]

Herbs

Yeung[3] reported use of herbs in a survey of 125 pregnant women in 1982. Forty-five percent of them took herbs, '12 Tai Pau' being the most popular. He also found 75% of neonates were given some herbs, Chuen Lin and Ngau Huang being most popular in a survey of 250 cases in 1972. Similar survey found a lower incidence of 38% in 1982 (Table 4).

Fok et al[11] found 54% of expectant mothers took some Chinese herbs, eg Angelica Sinensis, Panax Ginseng, Radix Glycyrrhiza and Nelumbo Nucifera, after conception in their study of NNJ in Tsan Yuk Hospital in 1983/84. They found no significant association between

Table 3 Kericterus in hyperbilirubinaemic Chinese infants[2,3]

Associated condition	Infants		
	Number		Kernicterus deaths
	1969-71	1980-82	1969-71
ABO incompatible	51/157	2/29	3/157
G6PD deficient	58/130	4/26	13/130
Cephalhaematoma	3/12	0/12	1/12
Non-specific	40/275	1/26	12/275
Total n	152*/574	7/83	29/574
%#	26.5	8.4	5.1

*Average serum bilirubin=35.4 mg/dl (range=22.3-50), 605.3 µmol/l (range 381-855) for 1969-71 and 1981-82 respectively. # percentage of kernicterus among those with serum bilirubin >=342 µmol/L

Table 4 Chinese herbs commonly used in neonatal period[2]

Herbs	1972(%)	1983(%)
' Chuan-Lien'	50.9	28
' Nga-Huang'	35.9	23.2
' Leh-Mei-Hua'	30	14
Others	25	32
None	25	62.4
Infants Surveyed (n)	220	125

maternal herb consumption and the mean peak SB levels. This was attributed to the fact that none of the mothers took herbs during the third trimester and no one took Chuan-Lien, Nga-Huang, Leh-Mei-Hua.

Yeung et al[12] reported the in-vitro effect of a popular Chinese herb, 'Yin-chen' (Artemisia scoparia). This herb was manufactured in intravenous form and it was suggested to be given for treatment of jaundice. The dosage was 25-50 ml of the extract to be diluted with saline and to be infused over 15-20 minutes. The extract was incubated with pooled cord serum at different concentrations. Free bilirubin was assayed by the horseradish peroxidase method. They found that Yin-chen produced a significant increase in free bilirubin level compared with control for a given bilirubin/albumin molar ratio. Similar study was performed with 'Chuen-lin' (Coptis chinensus/japonicum).[13] Similar results of raised free bilirubin by displacing bound bilirubin were obtained. Subsequently, Yeung[3] summarized the effect of Chuen-lin, Ngau Huang and Yin-chen. He performed in-vitro study of effect of Chuen-lin and Yin-chen on bilirubin-protein binding in cord blood sample as well as in-vivo test of effect of Ngau-huang on bilirubin-protein binding. He found all three herbs were highly effective in displacing bilirubin from its albumin binding. Both Chuen-lin and Yin-chen were found to have a strong dose-response relationship. This result showed that these herbs were effective to decrease the SB level by displacing bilirubin from serum. This unbound bilirubin would be deposited in the brain and other organs. This of course would be more harmful than bilirubin in the serum. *Use of herbs is still common among the new immigrant population in Hong Kong. It is generally believed by the lay public that herbs are natural and free of any side effects. Hence it is important for obstetricians, neonatologists to reiterate the harmful effects of Chuen-lin, Yin-chen, Ngau Huang to expectant mothers lest we forget the painful lesson of the past.*

Indomethacin and Bilirubin-albumin Binding

Lam et al[14] reported an in vitro experiment studying the effect of indomethacin on bilirubin-albumin binding. Lyophilised indomethacin powder was added to 2 ml aliquots of pooled cord blood serum to make up concentrations of 1500 ug/l, 3000 ug/l and 4500 ug/l. The blood concentration of indomethacin after an oral dose of 0.2 mg/kg was shown to be 27-1500 ug/l. Free bilirubin was measured by using horseradish peroxidase. The concentration of free bilirubin was determined from the initial rate of bilirubin oxidation measured by direct spectrophotometry of the incubated mixtured after a timed exposure to peroxidase and hydrogen peroxide. The bilirubin to protein titration curve was compared with a normal serum control containing no indomethacin. No difference was found with the amounts of free bilirubin between the indomethacin treated serum and normal serum. It was suggested by the authors that the lack of competition between bilirubin and indomethacin for albumin binding may be due to presence of different binding sites for these two chemicals under usual therapeutic conditions. However, the authors cautioned that the in vitro study was conducted in physiological pH whereas ill-preterm infants were often acidotic and hypoxaemic.

Transcutaneous Bilirubinometer

Fok et al[15] compared the Airshield-Minolta transcutaneous bilirubinometer's readings (TcB readings) with serum bilirubin (SB) level as measured by the AO Unistat bilirubinometer. 259 full-term neonates with jaundice were recruited. 202 neonates were not treated before the measurement whilst 57 were receiving phototherapy during the measurement. The transcutaneous readings were obtained from both the forehead and mid-sternum.

TcB readings from the stemum were consistently lower than the forehead readings for the same SB level. Sternum reading correlation with SB was also slightly better than forehead readings ($r = 0.91$; $P<0.001$ versus $r = 0.86$; $P< 0.001$). Exposure to photolight significantly reduced the correlation between TcB indices and SB levels. The correlation coefficient dropped to 0.26 for TcB readings from the sternum and to 0.79 for those from the shaded area of the forehead. This rendered TcB index unreliable in those given phototherapy. This study showed that using forehead TcB index of >=22 would include all neonates with SB level >=255 umol/l (15 mg/dl), ie sensitivity=100% and specificity was 66%. They also found that haematocrit level contributed little to the regression formula.

Sung et al[16] studied 63 clinical jaundiced term babies who presented to the Kwun Tong MCH clinic in the first two weeks of life between June and September 1983. They found good correlation ($r=0.847$) between TcB index and SB level. TcB index was the mean reading of the duplicate TcB readings over glabella in this study. Using TcB index of >=21 to detect SB level >221, they found 100% sensitivity and 88% specificity.

Leung et al[17] studied 66 Chinese term babies who presented with jaundice after being delivered in their hospital between March and April, 1982. TcB index was taken as the mean of two readings. TcB index was obtained

at four sites: forehead, stemum, abdomen and right thigh. They found correlation between TcB index and SB level to be 0.89 (forehead), 0.92 (sternum), 0.84 (abdomen), 0.87 (thigh). They also found a highly reproducible results with coefficient of variation less than 3.5% after obtaining five consecutive readings in each of four patients.

As a direct result of these studies, transcutaneous bilirubinometer is now routinely used in the mother and child health clinics in Hong Kong. Those with high readings would be referred to hospitals for further management.

Phototherapy

Phototherapy was first used in Hong Kong in 1969. Lau et al[18] studied efficacy of continuous versus intermittent phototherapy in 34 full term normal birthweight babies with 'physiological' jaundice that required treatment, i.e. SB between 190 umol/l and 205 umol/l. The babies were divided into 3 groups- group A (n=13) underwent continuous phototherapy, group B (n=9) received four hours of phototherapy followed by four hours off, group C (n=12) underwent one hour of phototherapy and three hours off. Irradiance was checked regularly and was maintained at 350 uW/cm^2 ± 5%. SB level were determined every 6 to 8 hourly. The three groups had comparable birthweight, gestational age and initial SB level. The change in SB level with time was represented by a bilirubin growth curve which was constructed by the least square method. A polynomial of third degree ($SB = a+bxT+cxT^2+dxT^3$ where SB= interpolated serum bilirubin level; a,b,c,d=coefficients of the polynomial equation; and T=time) was found to be a satisfactory mathematical model. No significant difference was found in peak SB level, rate of decline of SB level amongst the three groups. Significant difference ($p<0.001$) was found in total hours of irradiation in these three groups. The mean hours of irradiation for group A, B and C were 89.9 hours, 43.4 hours and 25.0 hours respectively. This result supported the hypothesis that the rate-limiting step in photodegradation of bilirubin in vivo was the migration of photoproducts out of the skin. The time required for this step has been estimated to be one to three hours. This intermittent phototherapy regime allowed saving of energy, better bonding with mothers.

Chung et al[19] studied stool frequency in 68 jaundiced babies who received phototherapy. The mean daily stool frequency during and after phototherapy were 4.34 and 3.53 respectively. The difference was neither clinical nor statistically significant. They also examined for evidence of lactase deficiency by looking at the change of capillary blood glucose level after a dose of lactose, 2 gm/kg. In all 10 patients, the rise in blood glucose was above 20 mg/dl before, during and after phototherapy. They concluded that no evidence of lactase deficiency existed during or after light treatment.

This author conducted a study[20] to compare the effectiveness of Bilibed™ (phototherapy unit underneath the patient) with conventional overhead phototherapy. Bilibed does not require use of incubator nor use of eyepatch. Chinese term infants aged less than 2 weeks with normal hemoglobin were included if SB level was greater than 220 umol/l in first 2 days of life or greater than 240 umol/l after 48 hours of life. 20 term babies were recruited. Nine were randomized to Bilibed group and eleven in conventional group. The two groups had comparable birth weight, gestational age, initial SB level. Phototherapy was stopped when SB level dropped below 220 umol/l. The conventional treatment group had statistically significant lower bilirubin at end of therapy, 181.3 umol/l vs. 200.2 umol/l. However, there was no difference in total phototherapy time, total drop in bilirubin, rate of bilirubin drop, bilirubin rebound after stoppage. Nursing time for preparation was significantly shorter with Bilibed, 6.7 minutes vs. 20.5 minutes. Parents were asked to state their preference before discharge. 14 preferred Bilibed and 6 preferred conventional phototherapy. The average daily cost for conventional phototherapy was $43.9, $42.6 for nursing time and $1.32 for equipment. The cost for Bilibed was $38.1, $13.9 for nursing time and $24.2 for equipment. The authors concluded that Bilibed™ was as effective as conventional phototherapy and Bilibed was cheaper and more acceptable to parents.

Currently, continuous overhead phototherapy remained the standard treatment of NNJ in Hong Kong. Concerted effort would be required to effect changes based on the research findings. These changes would also help minimize disruption of breast feeding and maternal bonding.

Phenobarbitone Therapy

Yeung and Field[21] studied use of phenobarbitone in 93 Chinese neonates with SB level between 10-20 mg/dL in first two weeks of life. 117 cases were recruited as control. Treatment group received phenobarbitone syrup orally at a dose of 5 mg eight hourly for normal birth-weight and 6 mg/kg/day for low birth-weight until SB level dropped below 10 mg/dL. 45% of control cases required exchange transfusion (ET) whilst only 4% of treated cases required ET ($p<0.001$). This led to subsequent study of prophylactic phenobarbiton by Yeung et al[22] involving 133 term infants. Primigravida mothers of blood group O and Rh+ve with no complications of pregnancy were allocated

consecutively in turn to one of three study groups - group 1: control, group 2: mothers given phenobarbitone 30 mg every night commencing at 38 weeks' pregnancy and continuing until delivery, group 3: infants were given syrup phenobarbitone 5 mg 8 hourly from 6 to 8 hours after birth for 3 to 5 days until the serum bilirubin showed a tendency to fall to levels below 10 mg/100 ml. Those with G6PD deficiency, pyruvate kinase deficiency, cephalohematoma were excluded. In infants without ABO incompatibility, SB level in the phenobarbitone treated infants was significantly lower than control from the third day onward. In those with ABO incompatibility, the SB level was significantly lower in the pheonobarbitone treated infants than the control group by the second day. SB level of the treated infants were significantly lower than those of the infants of treated mothers from day 4 for Group O infants and from day 6 in those with ABO incompatibility. Comparing control group and 'treated mother' group, the treated group had significantly lower SB level by day 3 for group O infants but no significant difference was observed for those with ABO incompatibility. SB level remained significantly lower for two more days after cessation of treatment. Phenobarbitone prophylaxis is an effective method to prevent kernicterus in areas where phototherapy is not readily available.

Yeung and Yu[23] studied the bromsulphalein(BSP) clearance in NNJ that were treated with phenobarbitone. 40 full-term newborns were studied during the first 2 weeks of life. All were without clinical manifestation of other diseases or evidence of acute haemolysis. 20 were assigned to treatment group who received phenobarbitone syrup orally in the dosage of 5 mg 8-hourly. The 20 infants not receiving the drug served as controls. BSP tests were performed on admission and repeated 24 hours later. They found that BSP clearance of the first phase, which was related to uptake by liver; and second phase, which was related to liver excretion, was increased significantly, comparing 1st and 2nd day ($p<0.025$). Similar increase was seen in the control group but the increase was not significant ($p = 0.2$ to 0.49). The result suggested that phenobarbitone improved both hepatic uptake and excretion of BSP. Similar mechanisms might account for its effect on bilirubin level.

Yeung[24] reported a study looking at effect of phenobarbitone, which was given as therapy for NNJ, on blood glucose level for NNJ. 46 babies were recruited into the study. All were full-term normal birthweight first-born blood group O infants born to mothers with similar blood group. Those with G6PD deficiency or sepsis were excluded. Treatment group received syrup phenobarbitone 5 mg 8 hourly for 3 days starting 6 to 8 hours after birth for 3 days whereas control group received no medication. In the control group, a significant inverse correlation was found between the blood sugar and the serum bilirubin level. Similar inverse correlation was observed in the treatment group but the correlation did not reach statistical significance. Treatment group had statistical significant decrease in serum bilirubin level starting from day 3 as well as statistical significant increase in blood sugar level starting from day 3. It was postulated by the author that phenobarbitone raised blood sugar level through enzyme induction or enhancement of liver function which was also responsible for lowering the serum bilirubin level. Liberal use of oral phenobarbitone prophylaxis from 1970 to 1986 by the local maternal and child health centres was noted to be important to decrease the incidence of severe NNJ that require ET.[3]

Advent of phototherapy spelled the end of phenobarbitone treatment of NNJ. In retrospect, randomized controlled trial comparing the two methods in terms of effect on SB level and parental preference should have been performed in early '80s. This would provide evidence so badly needed for informed choice. It is the author's hope that someone would take up the challenge despite the fact that phototherapy is now the norm.

Exchange Transfusion (ET)

ET was first performed by Dr. SC Wu in Tsan Yuk Hospital, Hong Kong in 1960 for hyperbilirubinemia (Personal communication). Tsao & Yu[25] studied the effects of giving albumin before and during ET and compared them with controls. They found that the reserve dye-binding capacity was immediately increased but early priming decreased the efficiency of ET due to expansion of plasma volume. They concluded that ET should be performed as soon as possible after giving albumin. Ngai and Yeung[26] reported an in vitro study looking at cell survival: 1) at different times of exposure to bilirubin; 2) the effect of adding albumin to increase binding capacity; 3) effect of removing free bilirubin. They found that adding albumin was much better than simple removal of free bilirubin in improving cell survival. The reason is probably albumin helps remove bilirubin bound to cell surface whereas removing free bilirubin would do nothing to the membrane-bound bilirubin. This beneficial effect was greater when intervention occurred in first hours demonstrating that bilirubin toxicity occurs in two phases. The initial phase of toxicity, probably at the membrane level, could be reversed. The second phase was irreversible when bilirubin entered intracellular compartment. The requirement for ET dropped dramatically in last 30 years.[3] It was not uncommon to perform five ET on one

'call day' in the 70s. Now ET is hardly done more than once a month in any particular department.

Fok et al[27] reviewed their experience in using peripheral vessels for exchange transfusion from 1984 to 1989. 87 neonates underwent ET for severe NNJ and 127 for polycythaemia. The technique employed cannulation of radial artery with a 24 gauge Angiocath (Deseret Pharm.) and a peripheral vein with a 22 or 24 gauge Angiocath. Simultaneous withdrawal and replacement of blood or plasma were carried out at a rate of 5-10 ml/min They successfully performed exchange in 201 infants (95% success rate). Minor complications occurred in 8 infants, blocked or dislodged catheters in 6 and subcutaneous extravasation in 2. No adverse cardiorespiratory events occurred and no ischaemia of the limbs were observed. This study showed that peripheral exchange transfusion was a definite alternative to exchange transfusion through umbilical venous catheter. For all its advantages, the main deterrent to peripheral exchange transfusion is probably the perceived difficulty of cannulating the radial artery. With supervision and encouragement from the attending neonatologist, this reluctance could be overcome.

Glucose-6-phosphate Dehydrogenase (G6PD) Deficiency

G6PD catalyzes the entry step of G6P into the pentose phosphate shunt for production of NADPH which is important in protecting red cell membrane. In the Chinese, about five G6PD variants account for the majority of the enzymes characterised.[28] The G6PD gene, located on chromosome Xq28 region, is 18 Kb long consisting of 13 exons transcribed to a 2.269 Kb messenger RNA with 1.545 Kb of coding regions.[29] The commonest variant in South China, G6PD Canton, was found to be due to a G to T substitution in nucleotide position 1376 leading to mutation in amino acid position 459, arginine to leucine.[30] Routine screening for G6PD deficiency has been adopted in Hong Kong. G6PD deficiency was found to be high in South China and Indochina (Table 5).

Yeung and Lee reported the use of a semi-automated method to assay red cell G6PD activities.[31] Only 20 µl packed cells are required and 21 tests can be done at once in 20 minutes. They compared it with the WHO-37° manual method and found a highly significant correlation ($r=0.98$; $p<0.005$). They also found highly reproducible result (coefficient of variation = 1.4% to 2.6%). They examined 2,723 fresh cord blood samples from Chinese infants, 1379 boys and 1344 girls. Amongst the boys, the enzyme level separated into two groups. A small group of 61 (4.42%) infants had level less than 3 IU/g Hb and were obviously deficient. The other large group showed enzyme level to be distributed along a normal bell shaped curve (mean ± SD = 15.4 ± 2.7 IU). Using 3 SD as cut-off value for normal, enzyme level below 7.3 IU/g Hb would be classified as deficient state. 6 infant girls were found to have enzyme level less than 3 IU suggesting they were homozygous deficient subjects. This represented an incidence of 0.45% (6/1344). Eighteen girls had enzyme levels between 3.1 and 7.3 IU/g HB suggesting they were heterzygous deficient. Fluorescent spot test showed suspicious result in 6 of these 18 girls and normal result in the other 12 girls. However, fluorescent spot test showed complete correlation with this new test in those with enzyme level < 3 IU/g Hb and those with enzyme level > 7.3 IU/g Hb.

Lam et al[32] reported the results of the neonatal screening programme in Hong Kong in 1986. It was started in 3/84 to screen for congenital hypothyroidism and G6PD deficiency. It covered all newborns delivered in the 23 government maternity homes, three obstetric units in two major government regional hospitals and eight government subvented hospitals. Cord blood was collected from the placental side and 2.5 ml blood was put in EDTA bottles for G6PD screening. All male neonates were screened while females were screened on a selective basis. A total of 23,304 male were screened from 3/84 to 6/85. 1,041 were found to be deficient in fluorescent spot test. Thus, the incidence of G6PD deficiency in male newborns is 4.47%.

Yeung[33] reported 11.4% of infants (80/704) who developed bilirubinaemia above 10 mg/dl were associated with erythrocyte G6PD deficiency. G6PD deficiency was associated with higher incidence of severe hyperbilirubinemia compared to other causes. Two of the four infants who developed kernicterus were also from the G6PD deficient group. They tended to run a more prolonged course of jaundice and acute haemolysis often occurred beyond the first week of birth. Infection, herb exposure and inhalation of naphthalein vapour were associated with significantly higher incidence of severe hyperbilirubinaemia necessitating exchange transfusion among G6PD deficient infants. Among infants with low haemoglobin levels suggestive of haemolysis very little abnormality could be detected from the peripheral blood smear besides a fairly high number showing evidence of thrombocytosis and occasional Heinz bodies.

Chan et al[34] studied haemolysis in G6PD deficient patients who suffered from typhoid fever. They injected G6PD deficient cells into normal subjects in the early stage of typhoid fever. They found that it was typhoid fever that caused haemolysis and not chloramphenicol. Chan observed similar phenomenon in those with viral hepatitis.[30]

In G6PD deficient individuals, their tissue G6PD

Table 5 G6PD deficiency in South East Asia (male)[29]

Population groups	Number tested	G6PD deficient	%
Taiwan			
Mainland Chinese	282	5	1.77
Taiwanese Chinese	343	1	0.29
Hakka Chinese	1535	84	5.47
Hong Kong			
Adult Chinese	200	11	5.50
Newborn Chinese	1379	61	4.42
Kwangtung (Quangdong)			
Adult Chinese	1048	90	8.60
Malaya			
Aborigines	607	103	17.00
Chinese	747	28	3.80
Malays	550	14	2.60
Indonesia	446	5	1.10
Thailand			
Various Provinces	1577	189	11.98
Filipinos	1205	86	7.10

enzyme levels are also lower than normal in the leucocytes, platelets, liver, kidneys and adrenals.[30] Since there are alternative pathways for the generation of NADPH in nucleated cells, most of these subjects do not suffer from any other cellular dysfunction. Chan[30] tested the production of cortisol by the adrenals and the metabolism of cortisol as well as the bromsulphalein excretion by the liver and found these to be normal.

In some variants of G6PD deficiency with leucocyte G6PD level less than 2%, proneness to infection similar to chronic granulomatous disease was observed. Neutrophils did not kill non-hydrogen peroxide producing bacteria, eg S. aureus. Patients with leucocyte G6PD level which are 25% of normal or greater have been shown to have no increased susceptibility to infection or decreased bactericidal activity.[35,36] Lau et al[37] reported an 11-year-old boy with recurrent skin abscesses and lung abscess with methicillin sensitive Staphylococcus aureus. They found G6PD level to be 0.5 IU/gm Hb in rbc and around 9% of normal in wbc. Detailed investigations of his neutrophil function did not reveal any significant abnormality. Serum Ig level were all normal. They suggested that wbc G6PD activity between 9% and 25 % is probably the minimal level for normal neutrophil function.

Conclusion

We have experienced tremendous progress in the management of neonatal jaundice during the last decades in Hong Kong. Health education of a better-educated public, ready access to medical care provided by the Mother & Child Health Center, use of oral phenobarbitone, availability of phototherapy, steady blood supply for exchange transfusion are the important elements that will continue to play a vital part in the future. G6PD deficiency is a fine model of success of scientific medicine. It illustrated the path from disease, i.e. hemolysis, to identification of enzyme defect, i.e. G6PD, to gene defect, i.e. G to T substitution in G6PD Canton to pilot screening program showing it to be a common disease in Southern Chinese to adoption of universal screening program in the whole territory. It is a superb example of collaboration between clinicians, scientists and government. It serves as an example of successful screening program. A further refinement in the provision of phothotherapy to allow better mother-baby bonding will be needed. Adoption of intermittent phothotherapy instead of continuous phototherapy should be seriously considered. A clinical trial comparing pheonobarbitone, phototherapy or even tin-meso-protoporphyrin in terms of cost-effectivness, parents' preference would be a challenging but worthwhile project. The advent of univeristy-based Chinese traditional medicine should encourage further research into use of herbal medicine in neonatal jaundice.

Acknowledgement

The author would like to thank Prof. CY Yeung for his valuable advice during preparation of this manuscript.

References

1. Yeung CY. Neonatal hyperbilirubinaemia in Chinese. Trop Geogr Med 1973;25:151-7.
2. Yeung CY. Kernicterus in term infants. Aust Paediatr J 1995; 21:273-4.
3. Yeung CY. Changing pattern of neonatal jaundice and kernicterus in Chinese neonates. Clin Med J 1997;110:448-54.
4. Li AMC, Chau AS. Jaundice in Chinese infants. Far East Med J 1967;3:45-8.
5. Li AMC, Yeung CY, Chang WK, Soo HN. Epidemiology aspects of neonatal jaundice in Chinese infants. Trop Georg Med 1979;31:537-46.
6. Fok TF, Lau SP, Hui CW. Neonatal jaundice: Its prevalance in Chinese babies and associated factors. Aust Paediatr J 1986; 22:215-9.
7. Lau SP, Fung KP, Fok TF. Epidemiology of neonatal hyperbilirubinemia. Pediatrics 1985;76:1017.
8. Law LK, Pang CP, Cheung KL, Fok TF. Cord blood biochemistry and idiopathic neonatal jaundice. Clin Chem 1996;42:1716-7.
9. Sung RYT, Pang CP, Lyon A, Loong PL, Davies DP. Urinary D-Glucaric acid excretion in idiopathic neonatal jaundice. Chin Med J 1996;109:201-5.
10. Yeung CY. The changing pattern of neonatal jaundice in Chinese - a Hong Kong experience. Journal of Paediatrics, Obstetrics and Gynaecology 1996;Jul/Aug:5-12
11. Fok TF, Lau SP, Hui CW. Neonatal jaundice in Chinese infants in Hong Kong: an epidemiological study. HK J Paediatr 1985; 90-1.
12. Yeung CY, Leung CS, Chen YZ. An old traditional herbal remedy for neonatal jaundice with a newly identified risk. J Paediatr Child Health 1993;29:292-4.
13. Yeung CY, Lee FT, Wong HN. Effect of a popular Chinese herb on neonatal bilirubin protein binding. Biol Neonate 1990; 58:98-103.
14. Lam BCC, Wong HN, Yeung CY. Effect of indomethacin on binding of bilirubin to albumin. Arch Dis Child 1990;65:690-1.
15. Fok TF, Lau SP, Hui CW, et al. Transcutaneous bilirubinometer: Its use in Chinese term infants and the effect of haematocrit and phototherapy on the TcB index. Aust Paediatr J 1986;22:107-9.
16. Sung RYT, Davies DP, Simon MPT. Transcutaneous bilirubinometry: a valuable screening method for neonatal jaundice. HK J Paediatr 1985;2:14-8.
17. Leung NK, Auyeung CL, Chan KY. Transcutaneous bilirubinometry: a non-invasive method of evaluating jaundice in Chinese term infants. HK J Paediatr 1985;2:32-6.
18. Lau SP, Fung KP. Serum bilirubin kinetics in intermittent phototherapy of physiological jaundice. Arch Dis Child 1984; 59:892-4.
19. Chung CM, Kong YF. No evidence of lactase deficiency related to phototherapy of jaundiced infants. N Engl J Med 1976;295:1483.
20. Choi MS, Ng DK, Ho CS, Yuen KN. Comparison of conventional overhead and new underneath phototherapy in the treatment of neonatal jaundice. HK J Paediatr (new series) 1997;2:179-80.
21. Yeung CY, Field CE. Phenobarbitone therapy in neonatal hyperbilirubinemia. Lancet 1969;135-9.
22. Yeung CY, Tam LS, Chan A, Lee KH. Phenobarbitone prophylaxis for neonatal hyperbilirubinemia. Pediatrics 1971; 48:372-6.
23. Yeung CY, Yu VYH. Phenobarbitone enhancement of bromsulphalein clearance in neonatal hyperbilirubinemia. Pediatrics 1971;48:556-61.
24. Yeung CY. Blood sugar changes in neonatal hyperbilirubinaemia and phenobarbitone therapy. Arch Dis Child 1972;47:246-9.
25. Tsao YC, Yu VYH. Albumin in management of neonatal hyperbilirubinemia. Arch Dis Child 1972;47:250-6.
26. Ngai KC, Yeung CY. Biphasic bilirubin cytotoxicity. Proceedings of Chinese Paediatric Forum, 1996.
27. Fok TF, So LY, Leung KW, Wong W, Feng CS, Tsang SS. Use of peripheral vessels for exchange transfusion. Arch Dis Child 1990;65:676-8.
28. Chan TK, Todd D. Characteristics and distribution of G6PD deficient variants in South China. Am J Hum Genet 1972;24: 475-84.
29. Chan TK. Glucose-6-phosphate dehydrogenase deficiency : a review. HK J Paediatr (new series) 1996;1:23-30.
30. Stevens DJ, Wanachiwanawin W, Mason PJ, Vulliamy TJ, Luzzatto L. G6PD Canton: a common deficient variant in South East Asis caused by a 459 Arg to Leu mutation. Nucleic Acids Res 1990;18:7190.
31. Yeung CY, Lee FT. Erythrocyte glucose-6-phosphate dehydrogenase assay on Chinese newborn infants with an automated method. HK J Paediatr 1985;2:46-55.
32. Lam STS, Yuen MLM, Mak WP, Chau AS. Neonatal screening for congenital hypothyroidism and G6PD deficiency in Hong Kong. HK J Paediatar 1986;3:26-33.
33. Yeung CY. Erythrocyte glucose-6-phosphage dehydrogenase deficiency and neonatal hyperbilirubinemia. In Child Health in the Tropics, Sixth Nutricia Symposium 1985;281-5.
34. Chan TK, Chesterman CJ, McFadzean AJS, Todd D. The survival of G6PD deficient erythrocytes in patients with typhoid fever on chloramphenicol therapy. J Lab Clin Med 1971;77: 177-84.
35. Rodley GE, Jacob HS, Holmes B, et al. Leucocyte G6PD levels and bactericidal activity. Lancet 1970;1:355-6.
36. Schiliro G, Russo A, Mauro L, et al. Leucocyte function and characterization of leucocyte G6PD in Sicilian mutants. Pediatr Res 1976;10:739-42.
37. Lau YL, Samuda GM, Yeung CY, Lawton JWM. Recurrent infections associated with G6PD deficiency. JHKMA 1990;42: 231-3.