ORIGINAL ARTICLE

The Incidence and Outcome of Bilirubin Encephalopathy in Nigeria: A Bi -Centre Study

***Ogunlesi T. A.** *FWACP,* **Dedeke I.O.F.** *FWACP,* ****Adekanmbi, A.F.** *FWCAP,*
***Fetuga M.B.** *FWCAP,* ***Ogunfowora O.B.** *(FWCAP)*

**Department of Paediatrics, Olabisi Onabanjo University, Sagamu, Nigeria. **Department of Paediatrics, Wesley Guild Hospital, Ilesa, Nigeria.*

Abstract

***Objective**: To determine the current trends in the incidence and outcome of bilirubin encephalopathy among Nigerian babies.*

***Methods**: A review of the hospital records of babies managed for bilirubin encephalopathy at the Wesley Guild Hospital (WGH), Ilesa and Olabisi Onabanjo University Teaching Hospital (OOUTH), Sagamu, both in southwest Nigeria between 2001 and 2005 was carried out. The age, sex, weight, body temperature on admission, place of delivery and outcome of hospitalization were studied. The fatal cases and the survivors were compared for risk factors for mortality.*

***Results**: Fifty eight (3.4%) and 57 (2.3%) babies had bilirubin encephalopathy out of 1706 and 2492 total neonatal admissions at OOUTH and WGH respectively. Of these 115 babies, 3 (2.6%), 84 (73.0%) and 28 (24.3%) were aged <3 days, 3-6 days and 7 days or more. Sixty eight (59.1%) babies were delivered in orthodox health facilities. Aside clinically suspected cases of G6PD deficiency, ABO incompatibility and septicaemia were commonly associated with bilirubin encephalopathy. Forty four (38.3%), 36 (31.3%) and 35 (30.4%) had Unconjugated bilirubin of <340µmol/ L, 341-425µmol/ L and >425µmol/ L respectively. Sixty eight (59.1%) were discharged, 42 (36.5%) died while 5 (4.7%) were discharged against medical advice. Prematurity, low birth weight, severe anaemia and inability to do Exchange Blood Transfusion were significant risk factors for mortality among babies with bilirubin encephalopathy. Cerebral palsy, seizure disorders and deafness were the leading neurological sequelae (86.4%, 40.9% and 36.4% respectively) among the 22 survivors who were followed up.*

***Conclusion**: Bilirubin encephalopathy remains a common clinical finding in Nigeria and the associated mortalities and neurological sequelae are significant.*

***Key words:** Bilirubin encephalopathy, Neonatal Jaundice, Nigeria*

Paper accepted for publication 5th September 2007

INTRODUCTION

Bilirubin encephalopathy or kernicterus is a public health problem because it is a preventable cause of childhood morbidity and mortality. In the developed world, bilirubin encephalopathy is regarded as a re-emerging disease, coming up on the heels of early hospital discharges, increased breastfeeding and less adherence to guidelines on the management of neonatal jaundice (NNJ).[1] On the other hand, it has persisted in most developing countries as a major clinical issue because most births take place outside the orthodox health facilities[2] where there is a lot of ignorance about NNJ and its potential dangers.

Studies in Nigeria had established the aetiologies of severe NNJ and bilirubin encephalopathy to include Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency, blood groups incompatibilities, prematurity and septicaemia.[3, 4] However, it is essential to know the trend of incidence of bilirubin encephalopathy as an index of the quality of neonatal care available in the country.

The Wesley Guild Hospital (WGH), Ilesa and the Olabisi Onabanjo University Teaching Hospital (OOUTH), Sagamu are tertiary health facilities strategically located in the south-western part of the country. Each of them serves about three different states in the country. NNJ is a common reason for neonatal admission in the two hospitals, particularly when the Total Serum Bilirubin (TSB) is above 170µmol/ L. Such babies are managed with phototherapy. Jaundiced babies with TSB close to or greater than 340µmol/ L were considered as severe cases of NNJ[4] and were routinely admitted for management with Exchange Blood Transfusion (EBT) and phototherapy. Babies with severe jaundice and tone abnormalities, abnormal cry and abnormal movements were diagnosed to have bilirubin encephalopathy. Even in the presence of features of bilirubin encephalopathy, EBT is still carried out to minimise the extent of neuronal damage.

Correspondence to: ***Dr T.A Ogunlesi*** *e-mail: tinuade_ogunlesi@yahoo.co.uk,togunlesi@hotmail.com*

This study is aimed at describing the current pattern of the incidence and outcome of bilirubin encephalopathy in southwest Nigeria from the perspective of two teaching hospitals.

MATERIALS AND METHODS

The records of all newborn infants admitted into the Special Care Baby Units of the WGH, Ilesa and the OOUTH, Sagamu, with the diagnoses of bilirubin encephalopathy between January 2001 and December, 2005 were retrospectively studied.

The following information were extracted from the individual case records of the babies: age and weight on admission (this was preferred since it may be difficult to know the birth weight of out-born babies), sex, maternal parity, place of delivery, medications administered prior to presentation, history of exposure to icterogenic substances (like naphthalene, menthol-containing cosmetic materials, herbs), results of laboratory investigations like blood groups (ABO and Rhesus), blood culture, G6PD deficiency screening (using Methaemoglobin Reduction method), Packed Cells Volume (PCV) and serum bilirubin concentrations as well as the outcome of the hospitalization. Post-mortem examinations to confirm the diagnosis of kernicterus were not performed due to cultural disapproval.

The subjects at both centres were compared for the incidence of important clinical and laboratory features. For the assessment of risk factors for mortality, babies who were discharged against medical advice were excluded and the survivors and the deaths at each centre were also compared using factors like gestational ages, prematurity and weight.

Statistical analysis of data was done by Chi-Square test using the SPSS version 11.0 software. Statistical significance was established with p values less than 0.05 in two-tailed tests. Odds Ratio was also calculated when p values of Chi Squares were significant.

RESULTS

General characteristics of the subjects

There were 1,706 and 2,492 total neonatal admissions at the OOUTH and WGH respectively. Three hundred and eighty four babies (15.4%) and 338 (19.8%) were admitted primarily for NNJ at WGH and OOUTH respectively during the same period. Bilirubin encephalopathy was diagnosed among 57 (14.8% of NNJ admissions and 2.3% of total neonatal admissions) at the WGH and among 58 (17.2% of NNJ admissions and 3.4% of total admissions) at the OOUTH.

These 115 babies with Bilirubin encephalopathy were aged 2 to 15 days on admission. The mean age was 5.6± 2.3 days. Three (2.6%), 84 (73.0%) and 28 (24.3%) were aged less than 3 days, between 3 and 6 days and between 7 and 15 days respectively. They comprised 88 males and 27 females (male: female ratio of 3.3: 1). Thirty eight (33.0%) weighed less than 2.5kg while the remaining 77 (66.9%) weighed $\geq$ 2.5kg. Eighteen (15.7%) were preterm babies (EGA 30 to 36 weeks) while 97 (84.3%) were term babies. In OOUTH, 4 (6.9%) babies were in-born while the remaining 54 (93.1%) were out-born babies unlike in WGH where all the kernicteric babies were out-born. The places of delivery included OOUTH, General Hospitals, Private Clinics, Primary Health Centres, Traditional Birth Homes, Churches and residential homes in 4(3.5%), 9(7.8%), 34(29.5%), 21(18.3%), 16 (13.9%), 14 (12.2%) and 17(14.8%) babies respectively.

The mean Unconjugated Serum Bilirubin (USB) was 348.4 ± 113.3 µmol/ L [range: 182 to 824µmol/ L], USB less than 340µmol/ L, 341 to 425µmol/ L and greater than 425µmol/ L were found among 15 (26.3%), 15 (26.3%), 27 (47.4%) babies respectively at the WGH. Similar distributions were found among 29 (50.0%), 21 (36.2%) and 8 (13.8%) babies respectively at the OOUTH. A significantly higher proportion of babies at the WGH has USB more than 340µmol/ L compared with OOUTH [42; 73.7% Vs 29; 50.0%; p = 0.009]. Conjugated Serum Bilirubin (CSB) greater than 20% of the TSB (Conjugated hyperbilirubinaemia) occurred among 24 (41.4%) and 23 (40.4%) babies at the OOUTH and WGH respectively.

Incidence and aetiology of Bilirubin encephalopathy and other clinical profiles

The overall incidence of Bilirubin encephalopathy at the OOUTH for the 2001 to 20005 period was 3.4% while it was 2.3 % at WGH. The incidence of Bilirubin encephalopathy ranged between 1.7 % and 3.1% at WGH and between 2.4% and 4.0% at OOUTH. The incidence of Bilirubin encephalopathy at the two centres did not show any consistent trend over the period studied.

The aetiology was not determined among 34 (29.6%) babies while G6PD deficiency was suspected among 40 (34.8%) babies with bilirubin encephalopathy. Twenty two (19.1%), 7 (6.1%), 12 (10.4%) and 18 (15.7%) babies had ABO incompatibility alone, Rhesus incompatibility alone, septicaemia alone and prematurity respectively. ABO and Rhesus

incompatibilities as well as ABO incompatibility with septicaemia were found among 2 (1.7%) and 4 (3.5%) babies respectively.

Table I: Comparative analyses of the clinical characteristics of kernicteric babies at the WGH and the OOUTH

	Characteristics	*WGH (n = 57)*	*OOUTH (n = 58)*	*p values*
1.	Age < 7 days	48 (84.2)	39 (67.2)	0.034
2.	Male sex	38 (66.7)	50 (86.2)	0.013
3.	Preterm gestation	10 (17.5)	8 (13.8)	NS
4.	Delivery*	19 (33.3)	28 (48.3)	NS
5.	Maternal Primiparity	23 (40.4)	24 (41.4)	NS
6.	Duration <3 days	36 (63.2)	30 (51.7)	NS
7.	Admission**	52 (91.2)	52 (89.7)	NS
8.	Use of home remedies	17 (29.8)	42 (72.4)	0.000005
9.	Exposure to icterogens	15 (26.3)	25 (43.1)	0.05
10.	Temperature $\geq 38^{O}C$	19 (33.3)	29 (50.0)	NS
11.	PCV < 30%	4 (7.0)	25 (43.1	0.000006
12.	EBT done	44(77.2)	43 (74.1)	NS

Keys: *Delivery outside orthodox health facilities
**Admitted with features of Bilirubin Encephalopathy
†Packed Cell Volume
††Exchange Blood Transfusion
NS- Not Significant
Figures in parentheses are percentages.

Table I shows that a significantly higher proportion of WGH subjects were younger than 7 days on admission (p = 0.034) while a significantly higher proportion of OOUTH subjects were males (p = 0.013). The two groups were similar in terms of maternal primiparity, predominance of term babies, delivery in non-orthodox health facilities and the incidence of body temperature greater than $38^{0}C$ on admission. While all the babies in the WGH group were out-born, 4 (6.9%) babies in the OOUTH group were in-born. The latter were re-admitted at age varying from 4 and 8 days with severe NNJ. Six (10.3%) and 5 (9.8%) babies at OOUTH and WGH respectively developed Bilirubin encephalopathy after hospitalization for reasons like lack of appropriate blood for EBT, delay in getting the consent of the parents (especially for religious and financial reasons), inability to provide phototherapy due to power outages and inability to cannulate the umbilical veins as a result of co-existing omphalitis.

Twenty five (43.1%) babies at OOUTH had contact with icterogens (particularly naphthalene balls and menthol-containing balms and powders) compared with 15 (26.3%) at WGH [$\chi^2 = 3.598$; p = 0.004]. Home remedies and medications (pawpaw leaf extract, glucose drinks and *Ampiclox*® drops) were administered on 59 (51.3%) of the subjects. For subjects aged less than 1 week, the proportion of babies with PCV less than 40% was higher in the OOUTH group than in the WGH group [32/39; 82.1% Vs 20/48; 41.7% (p = 0.00013]. PCV less than 30% was found among 5 (8.8%) babies at WGH compared with 25 (43.1%) at OOUTH (p = 0.00004).

The proportion of babies for whom EBT was not done was similarly low in both groups (p = 0.703). The major reason for not carrying out EBT in both groups was poor clinical state (recurrent apnea and cardio-pulmonary instability) of the babies.

OUTCOME OF HOSPITALIZATION

The outcomes of admissions at WGH were as follows: discharges (36; 63.2%), death (20; 35.1%) and discharge against medical advice [DAMA] (1; 1.8%). At OOUTH, the outcomes were as follows: discharges (32; 55.2%), death (22; 37.9%) and DAMA (4; 6.9%). The mortality among preterms was 9 (90.0%) and 7 (87.5%) at WGH and OOUTH respectively.

The exact pattern of post-bilirubin encephalopathy morbidities could not be fully determined due to high default rate from the Out-Patient Clinics. Only 22 (32.4%) survivors were seen at the Out-Patient Clinics with cerebral palsy (19; 86.4%), seizures (9; 40.9%), developmental delays (3; 13.6%), deafness (8; 36.4%), microcephaly (5; 22.7%) and strabismus (2; 9.1%). Some babies had multiple deficits.

The Case Fatality Rates (CFR) ranged between 25.0% and 45.5% at WGH and between 18.2% and 58.3% at OOUTH. The overall CFR for both groups were similar (p = 0.752). While the proportion of neonatal deaths accounted for by bilirubin encephalopathy ranged between 2.6% and 4.7% at WGH, the range at OOUTH was between 1.8% and 10.9%.

Table II: Risk factors for mortality in Bilirubin encephalopathy

	OOUTH			WGH		
Factors	*Survivors*	*Dead*	*p values*	*Survivors*	*Dead*	*p values*
	(n = 32)	*(n = 22)*		*(n = 36)*	*(n = 20)*	
Weight < 2.5kg	7	13	0.031	9	10	0.05
	(21.9)	(50.0)	(OR = 3.6)	(25.0)	(50.0)	(OR = 3.0)
Preterm	1	7	0.004	1	9	0.00007
	(3.1)	(31.8)	(OR = 14.5)	(2.8)	(45.0)	(OR = 28.6)
Temperature $\geq 38^{O}C$	14	14	NS	13	6	NS
	(43.8)	(63.6)		(36.1)	(30.0)	
TSB*	11	10	NS	26	14	NS
> 425ÿmol/L	(34.4)	(45.5)		(72.2)	(70.0)	
Presence of seizures	9	5	NS	8	9	NS
	(28.1)	(22.7)		(22.3)	(45.0)	
PCV** < 30%	12	13	NS	1	4	0.03
	(37.5)	(59.1)		(2.8)	(20.0)	(OR = 8.8)
EBT not done	1	15	0.0000002	1	11	0.000005
	(3.1)	(68.2)	(OR = 66.4)	(2.8)	(55.0)	(OR = 42.8)

Keys: *Total Serum Bilirubin
**Packed Cells Volume
†Exchange Blood Transfusion
OR Odds Ratio
NS Not Significant
Figures in parentheses are percentages.

Table II describes the risk factors for mortality at the two centres. Prematurity, low birth weight and inability to intervene with EBT were significantly associated with mortality while fever, seizures and TSB >425µmol/ L were not significant risk factors for mortality among babies with bilirubin encephalopathy.

DISCUSSION

With the resurgence of Bilirubin encephalopathy in the industrialized world,[1] it is imperative even in less-industrialized world to have updated knowledge about the incidence and burden of this preventable disease particularly for the purpose of planning, implementations and evaluation of control strategies. This study, which is a step in that direction, has shown that Bilirubin encephalopathy remains an important cause of childhood morbidity and mortality in Nigeria. The prevalence of Bilirubin encephalopathy among babies primarily admitted for NNJ were remarkably lower than 47% previously reported by Owa and co-workers[3] at Ibadan about two decades ago. This may be due to increased level of awareness about the disease and improved care-seeking behaviour of the parents over the years. Specifically, the overall incidence of Bilirubin encephalopathy was also relatively higher at OOUTH compared with WGH for unclear reasons.

The higher incidence within the first week of life was typical. This is presumably due to insufficient hepatic bilirubin conjugation predisposing to a high load of USB.[5] Thus, babies within this age group deserve meticulous examination and evaluation for NNJ. The mothers need to be taught the simple method of blanching the tip of the nose to detect jaundice. For this to be useful, the tradition of keeping newborn babies indoor and in poorly lit rooms need to change for better visualization of jaundice.

The fact that majority of our subjects were out-born agrees with previous reports. [4] The in-born babies appear to be relatively protected by virtue of the relatively longer duration of hospitalization and the opportunity for close monitoring by experienced personnel. The four in-born babies with bilirubin encephalopathy were re-admitted with severe NNJ. This highlights the role of early discharges from nurseries in the resurgence of Bilirubin encephalopathy in the developed world as well as its persistence in the developing world. While babies are prematurely discharged from nurseries in the developed world to prevent overcrowding and nosocomial infections, socioeconomic pressures are the major reasons for such in Nigeria.[6] Where this is inevitable, hour-specific nomograms which may detect babies at risk of severe hyperbilirubinaemia and re-hospitalization using transcutaneous bilirubin levels may be useful. [7]

Late presentation may plausibly explain the fact that most of the babies were kernicteric on admission. The high rate of administration of home remedies and medications may also contribute to this since these practices which are not helpful in the reduction of serum bilirubin gives a false sense of security, distracts and delays effective interventions.[8] Thus, with communication, information and education, efforts should be intensified on discouraging such harmful practices.

The wide range of USB among these babies made it extremely difficult, as it were, to predict the level of USB at which Bilirubin encephalopathy occurs. Although, the traditional practice of using 340µmol/ L TSB as the cut-off point for EBT still operates in many parts of the developing world,[9] there have been suggestions that abnormal findings from visual evoked potentials, electroencephalography, brainstem auditory evoked potentials and brain magnetic resonance imaging may be better predictors of the risk of bilirubin staining of the brain at TSB of between 405 and 825µmol/ L. [10] Laboratory tests that would reliably estimate the concentration of free (unbound) USB which is responsible for staining the brain are highly desirable. However, non-invasive methods of assessing the severity of NNJ like the Icterometer and the Jaundice meters which have been shown to be reliable, [11] may be very helpful in the screening of newborn babies delivered in places where serum bilirubin cannot be measured.

Health providers need to come to terms with the grave medical and socioeconomic implications of Bilirubin encephalopathy. Therefore, policies on the management of NNJ with emphasis on early detection and appropriate intervention are desirable. Health education, training and re-training of health workers [12] and improved provision of infrastructures in the existing health facilities would be helpful tools in this regard. The guidelines recommended by the American Academy of Paediatrics[13] for the management of NNJ may be adopted and adapted to neonatal care in the developing world. It may be appropriate to pursue this goal with the vigour with which the Baby Friendly Hospital Initiative was adopted and entrenched in the various national health policies.

ACKNOWLEDGEMENT

The assistance of Dr Alex Oyinlade (OOUTH, Sagamu), Dr (Mrs) Olubosede (WGH, Ilesa), Mr Femi Ajayi (Medical Records Department, Wesley Guild Hospital, Ilesa) as well as Mrs Omotayo and Alhaji Allison (Medical Records Department, OOUTH, Sagamu) is deeply appreciated. Dr JAO Okeniyi is also appreciated for his useful comments on the manuscript.

References

1. Bjerre JV, Ebbesen F. Recurrence of Bilirubin encephalopathy in term and near-term infants in Denmark. *Acta Paediatr*. 2000; **89**: 1213 7.
2. Ogunlesi TA. The pattern of utilization of prenatal and delivery services in Ilesa, Nigeria. *The Internet Journal of Epidemiology 2005 Volume 2 Number2.*
3. Owa JA, Dawodu AH, Familusi JB. Bilirubin encephalopathy in Nigerian Infants. *West Afr J Med*. 1987; **6**: 11 20.
4. Owa JA, Taiwo O, Adebiyi JAO, Dogunro SA. Neonatal Jaundice at Wesley Guild Hospital, Ilesa and Ife State Hospital, Ile Ife. *Nig J Paediatr*. 1989; **16**: 23 30.
5. Maisels MJ. Neonatal Hyperbilirubinaemia. In: Klaus MH and Fanaroff AA (Eds.). Care of the High Risk Neonate. 3rd Edition, WB Saunders Company, Philadelphia. 5th Edition. 2001: 324 - 62.
6. Oyedeji GA. Hospital discharges of children against Medical Advice. *Nig J Paediatr*. 1986; **13**: 1 5.
7. Sanpavat S, Nuchprayoon I, Smathakanee C, Hansuebsai R. Nonogram for prediction of the risk of neonatal hyperbilirubinaemia using transcutaneous bilirubin. *J Med Assoc Thai* 2005; **88**: 1187 93.
8. Ogunlesi TA. Managing Neonatal Jaundice at the General Practice and Primary Health Care Level: An Overview. *Nig J Paediatr*. 2004; **31**: 33 8.
9. Stanley IP, Joseph L, Mei C *et al.* Hyperbilirubinaemia and Bilirubin encephalopathy: 50 years later. *Pediatr*. 2004; **114**: 262 4.
10. Alotaibi SF, Blaser S, MacGregor DL. Neurological complications of Bilirubin encephalopathy. *Can J Neurol Sci*. 2005; **32**: 311 5.

11. Owa JA, Esimai VC, Olowu WA, Jegede OA. Correlation between Serum Bilirubin levels, Jaundice Meter and Icterometer Readings in Nigerian Neonates. *Nig J Peadiatr*. 1995; **22**: 24 30.
12. Ogunfowora OB, Daniel OJ. Neonatal Jaundice and its management: Knowledge, attitude and practice of Community Health Workers in Nigeria. *BMC* Public Health 2006; 6: 19 doi:10.1186/1471 2458-6-19.
13. American Academy of Pediatrics 's Subcommittee on Hyperbilirubinaemia. Management of hyperbilirubinaemia in the newborn infant 35 weeks or more weeks of gestation. *Pediatr.* 2004; **114**: 297 316.