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ARTICLE

Patterns of acute bilirubin encephalopathy in Nigeria: a multicenter pre-intervention study

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Abstract

Background Acute bilirubin encephalopathy (ABE) is an important cause of neonatal morbidity in Nigeria, accounting for 5–14% of neonatal deaths. Most newborns with severe ABE have irreversible damage before receiving treatment emphasizing the need for timely pre-admission monitoring and referral. There is limited evidence that educational interventions targeting mothers and health care providers will reduce delayed care.

Objective To provide baseline data on the incidence of ABE and associated pre-admission risk factors in five centers of Nigeria in order to evaluate the effect of subsequent educational interventions on outcome.

Study design The incidence of ABE among newborns treated for hyperbilirubinemia was documented prospectively. Bivariate analysis and multivariate logistic regression were used to evaluate risk factors for acute bilirubin encephalopathy and reasons for regional differences in its occurrence.

Results Of 1040 infants, 159 treated for hyperbilirubinemia (15.3%) had mild to severe bilirubin encephalopathy (including 35 deaths), but the incidence ranged from 7 to 22% between centers. Logistic regression identified four common predictors: total serum bilirubin (odds ratio 1.007 per mg/dl rise), out-of-hospital births (OR 2.6), non-alloimmune hemolytic anemia (OR 2.8), and delayed care seeking (OR 4.3).

Conclusion The high occurrence of bilirubin encephalopathy in Nigeria is due in large part to a delay in seeking care. A planned intervention strategy will target conditions leading to severe hyperbilirubinemia and delay.

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Background

Acute bilirubin encephalopathy (ABE) is a major cause of mortality and morbidity in Nigeria, reported to occur in 2.2–3.4% of special care nursery admissions [1–3], and account for 5–14% or more of neonatal deaths [4–7]. For every newborn that dies, 2–3 will have lifelong neurological deficits ranging from auditory neuropathy spectrum disorder to severe cerebral palsy [8–10]. In Nigeria, chronic bilirubin encephalopathy is a leading cause of cerebral palsy [11–13].

Most neonates with severe ABE have irreversible brain injury before being admitted to treatment centers [14–16]. Thus, avoiding behaviors that promote hyperbilirubinemia and delayed care seeking are critical. Educating health providers and parents about dangers of jaundice and the need for early evaluation has been recommended by several investigators [17–22], but evidence that jaundice instruction actually prevents ABE is limited. To that end, investigators from five centers in Nigeria developed consensus programs

for training physicians, nurses, midwives, clinical health extension workers (CHEWs), traditional birth attendants (TBAs), and mothers (during antenatal and postpartum clinic visits) about risks for and management of neonatal jaundice. This report provides base-line data on the incidence of severe hyperbilirubinemia and ABE among newborns treated for jaundice at each participating center and examines demographic, behavioral and medical risk factors that contribute to regional differences in ABE occurrence.

Methods

Study sites

The study involved nine major hospitals in five cosmopolitan cities in Nigeria representing varied urban densities, ethnicity, language, culture and religious backgrounds. Urban populations ranged from 174,000 in Asaba to over 13 million inhabitants in Lagos (Supplement Table 1). Asaba and Lagos are located in Southern Nigeria, Jos in Central and Zaria and Kano in Northern Nigeria. Yoruba and Igbo were predominant ethnic groups in the south and Hausa in the north. All participants were treated with phototherapy and exchange transfusion when indicated. Intensive phototherapy (irradiance ≥30 μW/cm^2) was not available at most study sites. Unfortunately, the study was interrupted by strikes at federal and state funded hospitals for several months limiting the total observation period from a planned 13 months (65 center-months) to approximately 43 center-months.

Subject recruitment

A total of 1106 newborns were treated for jaundice between February 2014 and June 2015 of which 1040 were eligible for inclusion into the study after excluding patients with undocumented outcomes, deaths from unrelated causes, or weighing <1000 g (averaging ~26 cases per center-month).

Study design

This was a pre-intervention prospective longitudinal hospital-based observational study documenting the incidence of ABE and associated risk factors among patients treated for hyperbilirubinemia in participating centers. The primary outcome was the presence of ABE, subdivided into mild (often reversible), moderate/severe ABE, death from ABE, or ABE/suspect sepsis (usually lethal). Signs indicative of mild ABE were lethargy, poor feeding, mild hypotonia/hypertonia or high-pitched cry. Moderate/severe ABE required the presence of opisthotonus, retrocollis, paralysis of upward gaze, rigidity or flaccidity, apnea, seizures, or "kernicteric facies" [23–26]. A diagnosis of ABE/suspected sepsis required signs consistent with both sepsis and ABE including fever/and or shock. An experienced attending physician confirmed all diagnoses of ABE. Secondary outcomes were the number of patients admitted with a total serum bilirubin (TSB) ≥20 mg/dL (342 μmol/L), a historic threshold for intervention [27], and TSB ≥30 mg/dL (513 μmol/L), a threshold associated with high risk for ABE and kernicterus [8, 28]. A delay in seeking/receiving care was defined as an admisssion TSB ≥18 mg/dL in patients admitted at 2 or more days of age; this represents a TSB greater than the 95th percentile at any age during the first week of life [29].

Laboratory data

TSB was measured in hospital laboratories or contract private laboratories by colorimetric methods. ABO and Rh typing was performed for 830/1029 (81%) mother/infant pairs. Although planned, we G6PD screening was not obtained due to lack of funding and availability in participating centers. A diagnosis of severe hemolytic disease (SHD) was defined arbitrarily as a TSB level ≥20 mg/dl in a patient with a hematocrit ≤35%.

Data collection

Demographic and behavioral information was obtained from mothers at admission, to which were added laboratory data and outcome observations (supplement Table 2).

Ethical considerations

Ethics Review Boards of each participating hospital approved the study. Verbal consent was obtained from mothers during admission interview. Patient identifiers were erased from data files following quality review and prior to final analysis. The study is registered with ClinicalTrials.gov, number NCT02713464.

Statistical analysis

Nominal data were compared using odds ratios and Pearson χ^2 test. Statistical significance was defined as 0.05. Ordinal data (TSB, age at admission, weight, mother's age) were bifurcated for paired analysis except in the logistic regression model. Model selection for logistic regression was performed using a weighted sum logistic regression of all variables and elastic net regulariazation [30] using an R package general logistic model, GLMNET. This combines rigid regularization [31] and the Lasso estimator [32] to discover the most important predictors as well as correlation between groups of predictors of ABE. We then fit a

standard multiple logistic regression using the selected variables.

Results

Subject characteristics

A total of 1040 patients were studied. Median admission weight was 2700 g; 133 newborns weighed less than 2 kg. The median admission age was 5 days; 132 patients were admitted at birth or within 24 h of age and 82 were admitted at an age ≥10 days. The male/female ratio was 1.47.

Incidence of ABE and associated demographic/behavioral risk factors

159 cases of ABE were diagnosed among 1040 patients admitted for treatment of jaundice (15.3%; Table 1). There were 35 ABE-related deaths yielding a case fatality rate of 22%. The average monthly occurrence was ~3.7 ABE cases/center/month. A total of 176 patients were either inborn or admitted <2 days of age, and eight developed ABE (4.7%; two with ABE/sepsis, five weighed ≤2 kg, and 3/8 were outborn). Excluding these patients, the incidence of ABE among babies admitted for treatment when ≥2 days of age increased from 15.3 to 17.3%. Eighty-three admissions (8%) were 10 days of age or older; the median TSB was 17.3 mg/dL, eight had TSB >30 mg/dL, and 8/83 had ABE (9.6%).

Paired analyses of covariates associated with ABE, reflecting the collective experience of all participating centers, are summarized in Table 2. Out-of-hospital births (home plus clinic), births not attended by skilled worker (physician or midwife), failure to have more than one antenatal clinic visit, self-referral for care (compared with health provider referral) and delayed care seeking were highly correlated with ABE.

The most common behavior associated with ABE, irrespective of birth site or underlying pathology, was a delay in seeking/receiving care (TSB > 95th percentile for age) until severe hyperbilirubinemia or clinical signs of ABE appeared. The most common reason offered for delayed care seeking was a failure to recognize the severity of jaundice (316/379 cases; 83%). Other reasons included advice from family members and health care workers (e.g., sun exposure, failed herbal trials) and transportation problems.

ABE trended higher with low birth weight, but the magnitude of effect was surprisingly small and not significant ($P = .07$). Male/female admission ratio was 1.5, but ABE rates per admission were identical. Compared with babies born to primigravid mothers, those born to multigravida mothers were more likely to be born outside of hospitals (OR 1.97; 95% CI 1.44–2.67), have unskilled birth attendants and have a higher incidence of non-alloimmune hemolytic anemia (OR 3.9; CI 1.73–8.70). However, despite these risks, delayed care seeking was only slightly higher among experienced mothers (OR 1.37; CI 1.01–1.88; $P = 0.044$), and the higher incidence of ABE (OR 1.48; CI 0.996–2.21) was not statistically significant.

Medical/laboratory associations with ABE

A total of 831/1040 infants (80%) had complete blood typing. Of these, 570/831 patients (69%) had no blood incompatibility, 64 of who had non-alloimmune SHD. TSB ≥30 mg/dl, ABO incompatibility, and SHD were highly associated with ABE ($P < 0.0001$; Table 3). ABE occurred in 55 of 190 (29%) newborns with TSB ranging 20–29.9 mg/dL and in 61% of 107 infants with TSB ≥30 mg/dL. A surprising 24% of patients with ABE had measured TSB values <20 mg/dL. Twenty seven of the 35 patients with low bilirubin ABE had one or more risk factors: weight ≤2.5 kg (23; 11 weighed <2 kg), sepsis (2) and/or age at admission ≥7 days of age (5). No known exposure to bilirubin displacing agents was identified (e.g., salicylates) but was not consistently asked.

SHD occurred in 99 patients including 5 of 38 patients with Rh incompatibility, 24/226 infants with ABO incompatibility, 63/577 babies with no maternal-infant blood type incompatibility or sepsis, 5/204 with incomplete blood type information and 2 newborns with ABE/sepsis. ABE occurred in 9 of 24 infants with SHD associated with ABO incompatibility (38%), 36 of 63 infants (57%) with no maternal/infant blood type compatibility and 2 of 5 infants with incomplete blood typing; G6PDd was suspected in non-alloimmune cases, but enzyme activity was not measured.

Table 1 Summary of major outcomes

Outcome	*N*	% ABE
Total patients studied	1029	
Normal at discharge	872	
Total ABE	157	15.3%
Mild ABE	51	5.0%
Survived with ABE	71	6.9%
Died from ABE	23	2.2%
Died from ABE/sepsis	12	1.2%
TSB ≥ 30 mg/dL–512 µmol/L (# ABE)	107 (65)[a]	6.4%
TSB ≥ 20–29.9 mg/dL (# ABE)	190 (55)	5.4%
TSB < 20 mg/dL–342 µmol/L (# ABE)	721 (35)	3.4%

[a]TSB was measured in 1018 patients. 2/11 without TSB had ABE

Table 2 Demographic/behavioral correlates with ABE: bivariate analysis

Pair	Total	ABE	No ABE	Odds	OR	95% CI	χ^2	*P* value
Home birth	213	59	154	0.383	3.471	2.348–5.131	42.14	<0.0001
Hospital birth	684	68	616	0.110				
Clinic birth	118	28	90	0.311	2.818	1.722–4.612	18.15	<0.0001
Hospital birth	684	68	616	0.110				
Out of hospital	332	87	245	0.355	3.217	2.267–4.565	45.73	<0.0001
Hospital birth	684	68	616	0.110				
Missing data	12	2	10					
Delayed care[a]	379	132	247	0.534	16.17	9.275–28.21	146	<0.0001
No delay	469	15	454	0.033				
Missing data	10	2	8					
171 patients were admitted <2 days of age—8 developed ABE								
Antenatal care								
<2 clinic visits	101	30	71	0.423	2.754	1.720–4.410	18.97	<0.0001
≥ 2 clinic visits	842	112	730	0.153				
Missing data	85	15	70					
Birth attendant								
Unskilled	229	60	169	0.355	2.572	1.785–3.705	26.95	<0.0001
MD/midwife	775	94	681	0.138				
Missing data	25	3	22					
Gravida 2+	662	108	554	0.195	1.406	0.945–2.091	2.84	0.09
Gravida 1	312	38	274	0.139				
Missing data	55	11	44					
Self referral	427	78	349	0.224	2.874	1.582–5.218	12.91	<.001
Provider ref	194	14	180	0.078				
Clinic ref	*341*	*55*	*286*	*0.192*	*2.473*	*1.336–4.576*	*8.74*	*0.003*
Missing data	67	10	57			(versus provider)		
Male	610	90	520	0.173	0.946	0.668–1.340	0.1	0.75
Female	414	64	350	0.183				
Missing data	5	3	2					
Wt ≤ 2500 g	381	70	311	0.225	1.437	1.015–2.035	4.21	0.040
Wt > 2500 g	613	83	530	0.157				
Missing data	35	4	31					

CI confidence interval, *ABE* acute bilirubin encephalopathy, *OR* unadjusted odds ratio ref referral, *wt* weight on admission

[a] Delayed care defined as presenting at care center with TSB ≥ 18 mg/dL after day 2 of life

Table 3 Potential hematologic causes of hyperbilirubinemia and ABE

Etiology	Cases	ABE	TSB ≥ 30 mg/dL
ABO incompatible	224	44 (20%)	31 (13.8%)
Rhesus incompatible	37	1 (2.7%)	4 (10.8%)
Non-alloimune SHD[a]	64	38 (59%)	32 (50%)
No blood incompatibility	506	54 (10.7%)	28 (5.5%)

Disease (hematocrit ≤ 35% in presence of severe hyperbilirubinemia (TSB ≥ 20 mg/dL)

ABE acute bilirubin encephalopathy, *TSB* total serum bilirubin, *SHD* severe hemolytic

[a] 1/64 had ABE/sepsis

Logistic regression

Out of hospital delivery, non-alloimmune SHD, delay in seeking care, and TSB level dominated all other risk conditions (Table 4, model A). Some highly correlated risk factors in bivariate analysis were reduced or disappeared in logistic regression because of the high interdependence of many social/demographic variables. For example, the skill of a birth attendant was not significant in any model that included birth site. However, with home birth excluded, unskilled birth attendants emerged as critical factors (Table 4, model B), consistent with bivariate analysis; care provided by TBAs was associated with four times the risk

Table 4 Demographic/ behavioral correlates with ABE: logistic regression

A. Logistic regression model including birth site			
Variable	Odds ratio	95% Confidence interval	*P*
≤1 antenatal clinic visit	2.0	(1.1, 3.6)	0.02
TSB (per mg/dL increase)	1.07	(1.04, 1.1)	1.0e-6
Non-alloimune hemolysis	2.8	(1.5, 5.3)	1.5e-3
Delay in receiving care[a]	4.3	(2.3, 8.1)	6.8e-6
Out of hospital birth	2.6	(1.7, 4.0)	2.1e-5
B. Logistic regression model including birth attendant			
Variable	Odds ratio	95% confidence interval	*P*
≤1 antenatal clinic visit	2.3	(1.2, 4.3)	0.02
TSB (per mg/dL increase)	1.07	(1.04, 1.1)	1.0e-6
Non-alloimune hemolysis	2.9	(1.5, 5.3)	1.0e-3
Delay in receiving care[a]	4.5	(2.3, 8.5)	4.8e-6
[b]Birth attendant: Midwife	1.7	(0.97, 3.0)	0.06
Birth attendant: TBA	4.2	(1.9, 9.5)	4.6e-4
Birth attendant: CHEW	3.8	(1.7, 8.3)	1.0e-3
Birth attendant family/none	1.7	(0.7, 4.2)	0.24

TBA traditional birth attendant, *CHEW* community health extension worker

[a] Presenting at care center with TSB ≥ 18 mg/dL after day 2 of life

[b] Compared with physician attended delivery

of developing ABE compared to physician attendance. Receiver Operating Characteristic analysis of ABE predictive models A and B had areas under the curve of 0.859 and 0.865 respectively (Figure 1, supplement).

Differences in incidence of ABE and hyperbilirubinemia among centers

Participating centers had significant asymmetries in demographic, social, and medical conditions as well as outcomes (Table 3, supplement). The incidence of ABE per admission ranged from 7 to 22%. Major contributors to these differences were the rates of out-of-hospital births, non-alloimmune hemolytic disease, antenatal care, and delay in seeking or receiving care. The percentage of out-of-hospital births ranged from 3.7% in Asaba to 58% in Kano. Kano and Lagos had higher incidences of ABE and out-of-hospital births, and fewer referrals from health providers than other centers ($P < 0.001$). Lagos had more cases of non-alloimmune SHD (40/63 total cases ($P < 0.001$). Among 33 babies with unexplained SHD and TSB ≥30 mg/dL, 18 were from Lagos. In comparison with Kano and Lagos, Jos had lower rates of delayed care seeking, TSB >30 mg/dL, and lack of antenatal clinic attendance ($P < 0.001$).

Discussion

This study confirms the high rate of ABE in Nigeria, with a incidence of nearly five cases per month in two of five collaborating centers in this study. In the vast majority of cases, babies with advanced ABE were affected before being admitted for care, in agreement with published observations [14–16]. Four major risk factors for ABE were identified in the population studied: severe hyperbilirubinemia, hemolytic anemia, out-of-hospital birth, and delay in seeking/receiving care.

The relationship between elevated TSB and ABE is well established and occurred in 61% of newborns with TSB ≥30 mg/dL. Studies from both Egypt [8] and United States [28] indicate that ABE and kernicterus is rare in term/near term infants at TSB <30 mg/dL. Thus, the high number of ABE cases occurring at TSB levels below 20 mg/dL was surprising but consistent with other reports from Nigeria. In a retrospective study (2001–2006), Ogunlesi et al. [2], reported that ABE occurred at TSB <20 mg/dL in 44 of 115 affected newborns (38%), some of whom also had sepsis and/or prematurity. About half of affected babies with low TSB ABE in this study had either low birth weight, sepsis, or were admitted at >7 days age (suggesting that peak TSB was missed) [33]. The finding of ABE at low TSB in the absence of known risk factors raises the question of a genetic predisposition to ABE or exposure to unknown substances affecting bilirubin binding and emphasizes the need for more detailed evaluation of those diagnosed with low TSB ABE. Because of uncertainty about risk for low TSB ABE, access to care, accurate rapid laboratory support, and guaranteed power supply for phototherapy, some have promoted lower TSB thresholds for initiating phototherapy in low-middle income countries (LMICs) where ABE is prevalent [34].

SHD (hematocrit ≤35% and TSB ≥20 mg/dL) was a major contributor to ABE. It is likely that the majority of cases with non-alloimmune SHD represent G6PDd hemolytic crises. G6PDd is the most common cause of hyperbilirubinemia reported in Nigeria [35–37]. Between 5 and 26% of male infants have G6PDd in Nigeria, depending on tribal genetic heritage [36]. The overall incidence of G6PDd is estimated to be 16.9% (IQR 14–20) [37]. In Nigeria, exposure to hemolytic triggers, e.g., decorative henna, mentholated balms or naphthalene ("camphor") is very common [38–40]. Massey Street Children's Hospital in Lagos had a disproportionately large number of newborns with non-alloimmune and presumably G6PDd SHD, but exposure to hemolytic triggers was not consistently documented. A World Health Organization study group on G6PDd recommended newborn screening be conducted in regions where there is a high incidence of G6PDd [41], but the cost of rapid screening is prohibitive for many individuals (as in this study) and currently impractical to administer for most home births. In the absence of universal screening in LMICs with high incidence of G6PDd, it would be prudent to consider all newborns to be at risk and instruct all mothers to avoid exposing their infants to hemolytic triggers [42].

Birth site per se should have little if any effect on serum bilirubin levels, but out-of-hospital births are associated with poor parental knowledge about jaundice and behaviors that influence the response to jaundice [16–18]. In this study, mothers giving birth at home had fewer antenatal clinic visits, higher rates of delayed care seeking, and were attended by TBAs, CHEWs or family members. Births attended by TBAs and CHEWs were 2–4 times more likely to develop ABE than those born in clinics or hospitals and attended by physicians. Birth attendants may be the only source for monitoring newborns and educating mothers about jaundice in home births, and a recent study identified CHEWs as the primary source of jaundice information for mothers [22],

Unskilled birth attendants and home births were highly interdependent risk factors for ABE having similar AUC results with ROC analysis, but in planning an intervention strategy it will likely be easier to train birth attendants than to eliminate home births.

Irrespective of etiology, a delay in treating severe hyperbilirubinemia was a critical factor contributing to the high rate of ABE in this study. Only a small number of patients were monitored and referred by health providers. The majority of admissions were self referrals. In Kano and Lagos, centers with highest ABE rates, provider monitoring and referral was less than 3.5%, compared with 28–40% in other centers. Hospital and clinic referrals (41% and 66%, respectively) were greater than other centers (17 to 29%), presumably because parents had first sought care at facilities unable to administer phototherapy or exchange transfusion, but the contribution of intermediate care facility evaluation to delay was not well documented. The most frequent behavioral reason for delay, here and in other studies [2, 6, 14–17, 23], was a failure to recognize the severity of jaundice or early signs of neurotoxicity (83%), again more common in out-of-hospital births [1, 17, 18, 23]. Failed trials of sun exposure, antibiotics or traditional medicines, and bad advice from health providers or family, economic and transportation issues have been cited in other reports [14, 19] but were minor contributors to delayed admission in this study population.

A common denominator to most of these harmful behaviors was a lack of basic understanding about jaundice by both parents and healthcare providers [17–22, 43]. Low maternal education (not assessed in this study) is associated with higher risks for delayed care seeking and lack of knowledge about jaundice [17, 18, 22]. Unfortunately, even when mothers are equipped with this information, traditional practices and social pressures often obstruct translating knowledge into appropriate behavior [14, 18, 44]. While many have addressed the need to instruct providers and parents about the risks of jaundice and need for early assessment, there is little evidence that these interventions change behaviors or, more importantly, prevent severe hyperbilirubinemia and ABE.

Limitations

The population served in this study may not be representative of the general population of states in which the centers are located. This was primarily an urban study and the incidence of ABE is likely to be higher in rural areas where quality of health care and percentage of home births is higher than we observed. An estimated 37% of births in Nigeria occur in hospitals [45] whereas 66% of cases in this study were delivered in hospitals. National estimates of unskilled birth attendants for Plateau, Kaduna, and Kano States ranged from 69 to 87% [46] compared with 4.7 to 34% in centers serving the same regions in this study. In contrast, unskilled providers delivered 74% of newborns referred to Massey Street Children's Hospital while delivering only 17% of newborns in the entire Lagos State [46].

The considerable variation in ABE rates between participating centers helped to identify risk factors that were unique to centers and common to all. However, we did not measure or document several previously shown contributors to ABE including G6PD activity, exposure to hemolytic triggers, maternal education, or prior awareness about jaundice and its risks. The study focused on pre-admission events rather than quality of treatment ABE. Other than monitoring and correcting irradiance during the study, no

attempt was made to document or evaluate the duration of treatment of phototherapy or the number of exchange transfusions and complications. Blood cultures were not obtained in suspect sepsis. The reported association of suspected sepsis with ABE in LMICs varies widely from a low of 8% (in this study) to over 50% [47], but confirmation by blood culture in most studies was often not obtained.

Intervention strategy

Creating an effective monitoring system for newborns by trained community health workers during week one of life, as recommended by the World Health Organization [48], will require substantial enhancement of post delivery care. Until community health care structures are in place, empowering parents to participate more fully in managing jaundice might decrease dangerous behaviors and improve timely care seeking. We are currently evaluating whether public awareness efforts, health provider and maternal education programs, and introduction of a point-of-care bilirubin assay [49] will decrease the incidence of extreme hyperbilirubinemia and ABE in centers participating in this study. This pre-intervention study, identifying major conditions underpinning the occurrence of ABE in Nigeria, provides a critical database for testing these interventions.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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