

Prevalence of Bilirubin Encephalopathy in Calabar, South-South Nigeria: A Five-year Review Study

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ABSTRACT

Background: Bilirubin encephalopathy is a clinical syndrome, associated with bilirubin toxicity in the central nervous system, resulting in chronic and permanent sequelae. It has been estimated that approximately 60% and 80% of term and preterm newborns develop jaundice in the first week of life, respectively. In the present study, we aimed to determine the prevalence, morbidity, and mortality of bilirubin encephalopathy in the neonatal unit of the University of Calabar Teaching Hospital, Calabar, Nigeria.

Methods: In this retrospective, descriptive review, medical records of all newborns, diagnosed with bilirubin encephalopathy over the past five years (from January 2010 to December 2014), were studied. Information retrieved from the medical records included age, sex, presence of fever, duration of disease, place of delivery, causes of the disease, and selected treatments. Variables such as hospital discharge, discharge against medical advice, and mortality were also evaluated.

Results: Out of 2,820 newborns, 21 (0.74%) cases were admitted on account of bilirubin encephalopathy. Among these affected cases, 17 (81%) were male and 4 (19%) were female (male-to-female ratio of 5:1). Based on the findings, 18 newborns (85.7%) had pyrexia, while 8 (38.1%) and 6 (28.6%) cases were hypertonic and hypotonic, respectively upon admission. Only 33.3% of deliveries took place in healthcare facilities. The established factors responsible for jaundice included infection, i.e., septicemia (n=15, 71.4%), ABO incompatibility (n=4, 19.1%), and glucose-6-phosphate-dehydrogenase (G6PD) deficiency (n=2, 9.5%). The mean maximum total bilirubin level in subjects was 321.3 $\mu\text{mol/L}$ (range: 242.5–440.3 $\mu\text{mol/L}$). Also, mortality was reported in 4 (19%) out of 21 cases.

Conclusion: Based on the findings, neonatal septicemia is associated with bilirubin encephalopathy. Therefore, identification and prompt treatment are of utmost importance in preventing the associated morbidity and mortality.

Keywords: Bilirubin, Exchange blood transfusion, Infection, Kernicterus

Introduction

Bilirubin is the breakdown product of heme, which is a component of red blood cells. The rise in serum bilirubin level can result in jaundice, which is defined as the yellow discoloration of the skin and sclera. Neuronal damage or toxicity occurs as a result of increased concentration of unbound unconjugated bilirubin in blood. Unconjugated bilirubin crosses the blood-brain barrier as the bilirubin binding capacity is exceeded.

Bilirubin encephalopathy (BE) is a clinical syndrome, associated with bilirubin toxicity in the central nervous system, while kernicterus, which was first introduced by Schmorl in 1903, refers to a pathological or anatomic diagnosis at autopsy, resulting in chronic and permanent sequelae (1).

The causes of hyperbilirubinemia vary in different populations, with rhesus isoimmunisation

being more common in Europe (2, 3) and glucose-6-phosphate dehydrogenase (G6PD) deficiency predominating in the United States and Canada (4, 5).

Complications such as infection, prematurity, acidosis, asphyxia, and hypoalbuminemia may facilitate bilirubin penetration into brain tissues (4). It has been estimated that approximately 60% and 80% of term and preterm newborns develop jaundice in the first week of life, respectively, and nearly 10% of breastfed infants are icteric at one month of age (4).

Severe neonatal jaundice is 100 times more frequent in Nigeria than industrialized countries (2). A recent study in Ife and Ilesha, Nigeria reported that 30% of newborns with severe jaundice, who had already undergone exchange transfusion, had certain features of BE (6). According to previous research, the incidence of

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chronic BE is estimated at 1 per 100,000 population (2, 7), although a recent study in Canada revealed a higher incidence of 2.3 per 100,000 population.

In view of the aforementioned background, we aimed to determine the prevalence of BE in Calabar, Nigeria over the past five years to determine the burden of this condition.

Methods

This retrospective, descriptive study was conducted in the neonatal unit of the Department of Pediatrics, University of Calabar Teaching Hospital, situated in Southern Nigeria. These units, as previously described by Udo et al. (8), manage inborn and outborn infants, admitted to the hospital.

The medical records of newborns, diagnosed with BE over the past five years (from January 2010 to December 2014), were reviewed. It should be noted that a standard protocol on the diagnosis of BE and exchange blood transfusion (EBT) as the treatment method has been established in the neonatal unit of the hospital. This protocol included serum bilirubin level ≥ 20 mg/dL, rate of bilirubin increase ≥ 5 mg/dl/day, bilirubin $\geq 10\%$ of body weight (especially in preterm newborns), and clinical features suggestive of bilirubin-induced neurological deficit (BIND).

Phototherapy was conducted on all newborns with jaundice whose serum bilirubin level exceeded 10 mg/dL; also, prophylactic phototherapy was performed for plethoric infants. Information retrieved from the medical records included age, sex, presence of pyrexia, duration of disease, place of delivery, causes of disease, and selected treatments. The total number of hospital admissions during the specified period was obtained from the ward registry. All infants were managed by consultants and members of the medical team.

Variables including hospital discharge, discharge against medical advice, neurological sequelae, and mortality were extracted from the records. Data were analyzed, using SPSS version 20. For statistical analysis, descriptive statistics including mean and standard deviation were calculated. P-value less than 0.05 were considered statistically significant.

Results

A total of 2,820 newborns were admitted to the hospital during the study period. In total, 553 (19.6%) cases had neonatal jaundice, and 21 (3.8%) icteric infants had BE. The prevalence of BE was estimated at 0.74% among all

admitted newborns in the units. Among 21 newborns with BE, 17 (81%) cases were male, while 4 (19%) cases were female (male-to-female ratio of 5:1).

The mean age and weight of the newborns were 13 days (range: 2-28 days) and 2.88 kg (range: 1.2-4.2 kg), respectively. The mean duration of disease and treatment was three days (ranging from 8 hours to 14 days). All the newborns presenting with BE within the specified period were born out of the hospital. In total, 18 (85.7%) infants had pyrexia prior to admission, while 8 (38.1%) and 6 (28.6%) cases were hypertonic and hypotonic, respectively.

The mean duration of jaundice before admission was 3.2 days. Based on the findings, 17

Table 1. Sociodemographic characteristics of mothers of newborns with bilirubin encephalopathy (BE)

Variables	Frequency	Percentage (%)	P-value
Age group (years)			
18-25	5	23.9	0.048*
26-30	7	33.3	
31-35	7	33.3	
36-40	2	9.5	
>40	0	0	
Total	21	100	
Occupational status			
Housewife	5	23.9	0.090
Civil servant	4	19.0	
Business woman	2	9.5	
Petty trader	10	47.6	
Others	0	0	
Total	21	100	
Educational level			
None	4	19.0	0.011*
Primary	8	38.1	
Secondary	6	28.6	
Tertiary	3	14.3	
Total	21	100	
Parity			
1	3	28.5	0.025%
2	5	23.9	
3	7	33.3	
4	3	14.3	
>5	0	0	
Total	21	100	

*Statistically significant

(81%) mothers had antenatal care visits. The mean age of mothers was 28 years (range: 18-40 years). The highest prevalence of jaundice was reported in the age range of 26-35 years ($P=0.048$). The majority of mothers were petty traders (47.6%) and multiparous (33.3%) ($P=0.090$ and $P=0.025$, respectively); also, the majority had only primary education (38.1%) ($P=0.011$) (Table 1).

Based on the findings, 33.3% and 28.6% of newborns were delivered at hospital and home, respectively. Also, 28.6% of the infants were delivered by traditional birth attendants, and 9.5% were born at church facilities. In total, among patients with BE, 19 (90.5%) and 2 (9.5%) cases were born via spontaneous vaginal delivery and caesarean section, respectively. Based on the findings, 10 (47%) and 8 (38%) infants were born term and preterm, respectively ($\chi^2=1.285$ and $\chi^2=0.142$, respectively) (Table 1).

The established factors associated with BE included infection, i.e., septicemia ($n=15$, 71.4%), ABO incompatibility ($n=4$, 19.1%), and G6PD deficiency ($n=2$, 9.5%) (Figure 1). Among 15 infants with infection, only 5 (33.3%) cases were delivered at healthcare facilities. The mean duration of admission was estimated at 8.6 days. None of the dead newborns had documented evidence on the administration of herbal drugs, camphor, naphthalene balls, mentholatum, or other medicinal agents.

Term, preterm, and post-term infants accounted for 47.7%, 38%, and 14.3% of all newborns, respectively (Table 2). The mean serum bilirubin level of subjects was 321.3 $\mu\text{mol/L}$ (range: 242.5–440.3 $\mu\text{mol/L}$). According to the findings, EBT was performed on 17 (81%) infants. Four (19%) infants were discharged from the hospital against medical advice, while 7 (62%) infants were discharged home after treatment.

A total of 431 (15.3%) out of 2,820 newborns died during the study period. In total, 8 (38%) out of 21 newborns with BE died during the study. Among newborns admitted to the neurology clinic,

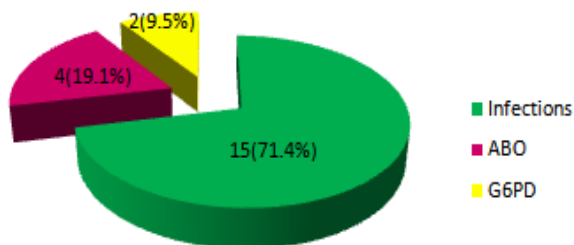


Figure 1. Risk factors for bilirubin encephalopathy (BE)

only two had regular clinic visits due to cerebral palsy and microcephaly as sequelae of BE; the rest of infants missed the follow-up sessions.

Discussion

The prevalence of BE in this study was estimated at 0.74% in all neonatal admissions. Ogunlesi et al. reported prevalence rates of 3.4% and 2.3% in two tertiary healthcare centers in Sagamu and Ilesha in Southwestern Nigeria, respectively (9). However, the prevalence of this condition was higher than the rate reported in Canadian children, i.e., 2.3 per 100,000 births (3).

In a study in Denmark, the incidence rate of BE was estimated at 0.6 per 100,000 births (5). Also, Brooks et al. recorded an incidence rate of 0.44 per 100,000 births among Californian children (4). The comparatively high prevalence of BE in this study could be due to the low socioeconomic status, literacy level, and high, which were significantly associated with BE.

In the present study, the majority of cases were term neonates, which is contradictory with previous studies indicating the higher number of preterm newborns presenting with kernicterus (10, 11). A study in Denmark did not identify any risk factors during pregnancy or delivery, associated with the subsequent development of kernicterus (12). Also, the majority of newborns in this study were born through spontaneous vaginal delivery in unorthodox places; hence, vertical transmission of infection might be the likely cause of septicemia.

In a systemic review and meta-analysis by Grace et al. (13), 17% of infants born to mothers with laboratory-confirmed infections had positive laboratory cultures for infection, while in mothers with clinical signs of infection, 20% of newborns had positive laboratory cultures for infection. This was in line with studies conducted in Abakaliki (14), Ife (15), and Benin (16), Nigeria, while in contrast with some studies in Canada (3), United Kingdom, and Ireland (8, 17).

Table 2. Maturity indices of newborns who died due to bilirubin encephalopathy (BE)

Delivery	Mortality rate (n=21)	χ^2
Preterm	8 (38%)	0.142
Term	10 (47.7%)	1.285
Post-term	3 (14.3%)	2.285

$\chi^2=3.71$; P -value=0.156; $DF=2$

In addition, poor personal hygiene, which is usually observed among mothers and care givers from a low socioeconomic status, may predispose newborns to infections. This finding was in line with a study by Ogunlesi et al. (18), who also found that the majority of mothers with a good level of knowledge and tertiary education showed good healthcare-seeking behaviors in terms of neonatal jaundice; consequently, their infants did not develop BE.

In line with the policy and protocol established in our hospital, EBT was performed for newborns with BE to avoid further damages, even though they reported signs of BIND (1). In fact, according to the US kernicterus registry, neurological sequelae can be reversed with early EBT (11, 19, 20). In the presents study, the low patient turnout after discharge may be attributed to parents' search for alternative therapies in unorthodox places or patient's death. Also, mortality might have resulted from cardiorespiratory failure due to profound encephalopathy.

Conclusion

BE still remains as a cause of death among neonates in Nigeria. This study emphasized the need for further attention to early identification and treatment of septicemia, considering its association with BE; also, early and timely EBT was shown to be effective for the patients. Therefore, educating mothers on specific preventive strategies for kernicterus is highly recommended.

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