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Risk factors for mortality in neonatal seizure in a Nigerian newborn unit

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Objective. To determine the risk factors for mortality in neonatal seizures.

Methods and design. A prospective study of consecutive newborn babies with seizures admitted to a Nigerian hospital between January and December 2006. Multiple regression analysis was used to determine the risk factors for mortality among consecutive neonates admitted with seizures.

Results. Seventy-eight babies were studied. Thirty-six of these (46.1%) had seizures within the first 24 hours of life. The mean age at onset of seizure was 85.4 ± 106.1 hours. The leading aetiologies included hypocalcaemia (65.4%), hypoxic-ischaemic encephalopathy (HIE) (60.3%) and hypoglycaemia (50.0%). Severe anaemia occurred in 56.4% of babies. Most (85.9%) had multiple aetiologies while no aetiology was identified in 5.1%.The mortality rate was 43.6%. Significant risk factors for mortality included duration of seizure longer than 24 hours (p = 0.019), hypoglycaemia (p = 0.001) and severe anaemia (p = 0.004). The co-existence of HIE with hypoglycaemia and hypocalcaemia was also more significantly associated with mortality (p = 0.03) than each of hypoglycaemia and hypocalcaemia co-existing with HIE separately.

Conclusion. The prevention of fatal neonatal seizures should start with good intrapartum care, prompt detection and correction of hypoglycaemia and anaemia and early control of seizures.

Neonatal seizures are commonly encountered in clinical practice. Their significance lies in the magnitude of associated morbidities and mortalities. The developing brain has an increased susceptibility to seizure activity because of its immaturity. Therefore, neonatal seizures may adversely affect cerebral functions and may cause significantly more damage among neonates than in older children.[1] Therefore, in clinical practice neonatal seizures are regarded as dire emergencies.

Several studies have established the causes of neonatal seizures as well as the determinants of outcome among survivors. Specifically, early onset of seizures, seizure type (especially subtle and generalised clonic seizures) and an abnormal electroencephalogram (EEG) may predict poor neurodevelopmental outcome.[2-5] Effective rehabilitative measures are available to further improve the outcome of such adversely affected survivors.

However, with various global attempts at reducing neonatal deaths, it is imperative to examine ways of reducing mortalities associated with neonatal seizures, a common problem in neonatal practice. Therefore, this study was aimed at determining the risk factors for mortality in babies with seizures.

Patients and methods

This prospective analytical study was done at the Special Care Baby Unit of the Olabisi Onabanjo University Teaching Hospital, Sagamu, Nigeria between January and December 2006.

All consecutive babies aged 0 - 28 days who presented with or who developed seizures (tonic, focal and multifocal clonic, myoclonic and subtle) on admission were studied. Using clinical evidence, seizures were differentiated from jitteriness or sleep-related muscular activities. For the purpose of this study, seizures occurring in the first 24 hours of life were regarded as early-onset seizures, while those recurring for more than 24 hours after hospitalisation were regarded as prolonged seizures.

Data obtained included age, weight, gestational age, place of birth, primary diagnosis, blood glucose, serum calcium and haematocrit as well as the outcome of hospitalisation. Hypoxic-ischaemic encephalopathy (HIE) was diagnosed based on APGAR scores less than 4 at 1 minute, co-existing with neurological deficits. Hypoglycaemia was defined as a blood glucose less than 40 mg/dl, hypocalcaemia as serum calcium less than 8.0 mg/dl and low cerebrospinal fluid (CSF) glucose as the ratio of CSF to blood glucose less than 0.5. A haematocrit of less than 0.40 within the first week of life and 0.35 after the first week of life was regarded as severe anaemia. Imaging studies were not routinely done but lumbar taps were done to exclude both meningitis and gross intracranial bleeding.

In addition to correction of glucose and calcium deficits and anaemia, seizures were routinely managed with a loading dose of intravenous phenobarbitone 20 mg/kg, followed by phenobarbitone 5 mg/kg/day in two divided doses. Other supportive measures such as intravenous fluid and oxygen therapies were usually given according to the primary diagnoses.

Data analysis was done using Epi Info 6.0. Using the risk ratio (RR) and its 95% confidence intervals (CIs), the fatalities and survivors were compared with regard to important demographic and clinical variables. Multiple regression analysis was used to determine the contribution of these

variables to mortality. Statistical significance was established when CIs did not include unity, or p-values were ≤ 0.05 in two-tailed tests.

Results

General characteristics

Out of a total of 292 babies admitted, 81 (27.7%) had convulsions. However, 3 of them (3.7%) were prematurely discharged from hospital and were excluded from further study. The remaining 78 babies comprised 51 males (65.4%) and 27 females (34.6%), giving a male-to-female ratio of 1.9:1. Seventy-three (93.6%) were referred and 5 (6.4%) were delivered in our hospital. The gestational ages ranged between 36 and 43 weeks.

The age at entering the study ranged between 1 hour and 672 hours, with a mean ± SD of 36.6 ± 76.8 hours. The distribution of the babies by age shows that on admission 36 (46.1%), 20 (25.7%), 13 (16.7%) and 9 (11.5%) of the subjects were aged 0 - 24 hours, 25 - 72 hours, 73 - 168 hours, and more than 168 hours, respectively. The body weight on admission ranged between 1.95 kg and 4 kg, with a mean of 2.7 ± 0.75 kg.

The age at onset of seizures ranged between 1 hour and 504 hours, with a mean of 25.4 ± 60.1 hours. Seizure was noticed within the first 24 hours of life in 24 out of the 36 babies (66.7%) admitted within the first 24 hours of life. The remaining 12 babies (33.3%) who were admitted within the first 24 hours of life developed seizures later.

Aetiologies

The identified aetiologies were as follows: hypocalcaemia (51; 65.4%), HIE (47; 60.3%), hypoglycaemia (39; 50.0%), kernicterus (10; 12.8%) and meningitis (3; 3.8%). Only 1 case of recurrent hypoglycaemia was recorded, which was suspected to be due to classic galactosaemia. No other likely case of in-born error of metabolism was found although we lacked the facilities for routine screening. No case of polycythaemia was found but severe anaemia occurred in 44 babies (56.4%). Most of the babies (67; 85.9%) had multiple aetiologies whereas no aetiology was identified in 4 babies (5.1%).

Out of the 47 babies with HIE, 21 (44.7%) also had hypoglycaemia and hypocalcaemia, 15 (31.9%) had only hypocalcaemia while 4 (8.5%) had only hypoglycaemia. The remaining 7 babies with HIE (14.9%) had neither hypoglycaemia nor hypocalcaemia.

Outcome

Forty-four babies (56.4%) were discharged alive while 34 died, giving a mortality rate of 43.6%. The case fatality rates for kernicterus, hypoglycaemia, hypocalcaemia, anaemia, HIE and meningitis were 70.0%, 64.1%, 54.9%, 52.3%, 40.4% and 33.3%, respectively. Table I shows that a higher proportion of babies who died had been born prematurely, and had hypocalcaemia, hypoglycaemia, severe anaemia, kernicterus and prolonged seizures.

Determinants of mortality

Table II shows the contributions of specific variables to mortality in neonatal convulsions. Significant risk factors for mortality included duration of seizures longer than 24 hours (p = 0.019), hypoglycaemia (p = 0.001) and severe anaemia (p = 0.004). On the contrary, HIE, hypocalcaemia, early onset of seizure, and presence of multiple aetiologies had no significant contributions to mortality. Using multistage regression analysis, neither hypoglycaemia nor hypocalcaemia coexisting with HIE separately was significantly related to the risk of death, whereas the coexistence of both hypoglycaemia and hypocalcaemia with HIE was strongly associated with mortality (p = 0.03) (Table III).

Duration of hospitalisation

The duration of hospitalisation of babies with seizures who survived ranged from 144 hours to 21 days (504 hours), with a mean ± SD of 168.79 ± 261.4 hours. For babies with seizures who died, the duration of hospitalisation ranged from 5 hours to 96 hours, with a mean ± SD of 43.28 ± 67.4 hours. The difference was statistically significant (t = 2.73; p = 0.008).

Discussion

The prevalence of neonatal seizure among the 78 babies studied was 27.7%, while the leading causes of seizures were hypocalcaemia, HIE and hypoglycaemia. The mortality recorded in this study was 43.6%, with significant risk factors including prolonged seizures, hypoglycaemia and severe anaemia.

A prevalence of 27.7% for neonatal seizures was recorded in this study; it is therefore a common occurrence in clinical practice – highly justifying the study. The likely aetiologies identified were similar to those in previous reports.[2,4,6] HIE and hypoglycaemia were widely known to be leading aetiological factors in neonatal seizure, but hypocalcaemia stood out as the most common aetiological factor in this study. Although the study did not set out to evaluate the role of hypocalcaemia in neonatal seizure, the findings may agree with previous suggestions that widespread maternal hypocalcaemia puts the newborn at risk of hypocalcaemia.[7]

The mortality of 43.6% recorded in this study was comparable to that of 40% previously reported in a Spanish study (between 1991 and 1993),[6] but higher than 20.8% reported in another Spanish study (between 1992 and 1998)[4] and 30% reported in Connecticut, USA.[3] The difference in mortality rates is best attributed to the ready availability of intensive care and advanced life-support facilities in the developed parts of the world. However, the range of causes identified in the studies did not differ significantly between Nigeria and the more developed countries.

We acknowledge the limitation we had in terms of neurodiagnostic imaging techniques. However, probable aetiological factors were identified in about 94.9% of our subjects compared with 99% reported in Faisalabad, Pakistan.[8] One baby had repeated hypoglycaemia and glycosuria, prompting our suspicion of galactosaemia, but this diagnosis was not confirmed as the assays of galactose-1-phosphate uridyltransferase could not be done. All the others remained normoglycaemic after the initial correction. Similarly, the facilities for diagnosing other in-born errors of metabolism were lacking and suggestive clinical features were not obvious.

The lack of a significant contribution of hypocalcaemia to mortality may reflect the common background of these babies in terms of the previously suggested 'endemic' materno-neonatal hypocalcaemia in the population.[7] Similarly, HIE is commonly associated with seizures as part of the syndrome of neonatal depression.[9] The high prevalence of perinatal

TABLE I. COMPARATIVE ANALYSIS OF CLINICAL PARAMETERS OF SURVIVORS AND FATALITIES

Parameters	Survivors (*N* = 44) N	%	Fatalities (*N* = 34) N	%	Statistics
Age at onset < 24 h	13	36.4	16	38.2	RR = 1.05; CI = 0.62 - 1.75
Male sex	31	70.4	20	58.8	RR = 0.76; CI = 0.46 - 1.25
Duration*	17	38.6	24	70.6	RR = 2.17; CI = 1.20 - 3.90
HIE	27	61.4	19	55.8	RR = 0.88; CI = 0.53 - 1.40
Anaemia	17	38.6	27	79.4	RR = 2.98; CI = 1.48 - 6.01
Kernicterus	3	6.8	7	20.6	RR = 1.76; CI = 1.07 - 2.91
Hypocalcaemia	24	54.5	27	79.4	RR = 2.04; CI = 1.03 - 4.06
Hypoglycaemia	14	31.8	25	73.5	RR = 2.78; CI = 1.50 - 5.16
Multiple†	16	36.4	16	47.1	RR = 1.28; CI = 0.78 - 2.11

* Duration of seizure longer than 24 hours.
† Presence of multiple aetiologies.
HIE = hypoxic-ischaemic encephalopathy; RR = risk ratio; CI = confidence interval.

TABLE II. MULTIPLE REGRESSIONS OF THE RISK FACTORS FOR MORTALITY IN NEONATAL SEIZURES

Risk factors	SE	Coefficient	*t*	*p*-values	95% confidence interval Lower	Upper
Prematurity	0.112	0.155	1.643	0.105	-0.039	0.406
Presence of HIE	0.122	0.092	0.770	0.444	-0.149	0.337
Early-onset seizure	0.100	-0.104	-1.115	0.269	-0.312	0.088
Prolonged	0.96	0.231	2.409	0.019	0.040	0.421
Presence of hypocalcaemia	0.108	0.394	3.637	0.001	0.177	0.607
Presence of hypoglycaemia	0.106	0.057	0.564	0.575	-0.152	0.271
Presence of severe anaemia	0.109	0.326	2.989	0.004	0.109	0.545
Presence of multiple aetiologies	0.164	-0.098	-0.752	0.455	-0.450	0.204
(Constant)	0.118		-1.241	0.219	-0.382	0.089

SE = standard errors; coefficient = standardised coefficient (beta); HIE = hypoxic-ischaemic encephalopathy.

TABLE III. MULTIPLE REGRESSIONS OF ASPHYXIA AND COEXISTENT METABOLIC DERANGEMENTS AS RISK FACTORS FOR MORTALITY IN NEONATAL SEIZURES

Risk factors	SE	Coefficient	*t*	*p*-values	95% confidence interval Lower	Upper
HIE coexisting with hypoglycaemia	0.277	-0.389	-1.574	0.120	-0.988	0.116
HIE coexisting with hypocalcaemia	0.132	-0.214	-1.622	0.109	-0.476	0.049
HIE coexisting with hypoglycaemia and hypocalcaemia	0.317	0.840	3.128	0.03	0.360	1.623
(Constant)	0.74		5.889	0.000	0.288	0.583

SE = standard errors; coefficient = standardised coefficient (beta); HIE = hypoxic-ischaemic encephalopathy.

asphyxia[10] and consequent HIE may explain its lack of significant contribution to death in neonatal seizure. Interestingly, the coexistence of HIE with hypoglycaemia and hypocalcaemia emerged as a significant risk factor for death in neonatal seizure. This may be a reflection of significant neuronal damage resulting from the cumulative effects of those aetiological factors. Since hypocalcaemia and hypoglycaemia typically occur during perinatal asphyxia, newborns who are depressed because of the effects of asphyxia risk death when they develop seizures. Therefore, prompt detection and correction of hypoglycaemia and hypocalcaemia should be incorporated into the management of severely asphyxiated infants.[11] Empirical treatment of hypoglycaemia and hypocalcaemia may be advised in the developing world where laboratory facilities may not be readily available. This may prevent delay in diagnosis and treatment of the metabolic derangements and may improve the outcome of such babies with seizures.

Haematocrit must be routinely estimated in babies with seizures.

The significant contribution of anaemia to the death of neonates with seizures reflects the vital role hypoxia plays in neuronal damage. Hypoxia is the consequence of abnormally low oxygen-carrying capacity of blood and may cause neuronal damage. This effect may be worsened in the presence of co-existing seizure activities. Therefore, haematocrit must be routinely estimated in babies with seizures, and oxygen therapy with blood transfusion must also be considered in neonates with severe anaemia co-existing with seizures. Prolonged duration of seizures, by catalysing neuronal exhaustion, may increase the extent of neuronal damage and consequently the risk of death. Although phenobarbitone is recommended as the drug of choice for managing initial neonatal seizures,[1] there are suggestions that the benzodiazepines and lamotrigine should be substituted for the third and subsequent seizures.[12-14] Pyridoxines may also be added to the management in spite of the rare case of pyridoxine dependency, which may cause refractory seizures.[12]

In conclusion, the risk of mortality in neonatal seizures is significantly increased by prolongation of seizures beyond 24 hours, hypoglycaemia, severe anaemia and coexistence of HIE with hypoglycaemia and hypocalcaemia. Therefore, efforts should be made to improve intrapartum care, promptly detect and correct hypoglycaemia, hypocalcaemia and severe anaemia in asphyxiated infants, and review the drug treatment of seizures in refractory cases.

The house officers who worked in the Special Care Baby Unit of the Olabisi Onabanjo University Teaching Hospital, Sagamu, Nigeria during the period of study are hereby acknowledged for diligently completing the seizure register.

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