Factors associated with preventable hypoxic ischemic encephalopathy in term neonates at Kacyiru hospital, Rwanda - a retrospective study

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ABSTRACT

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Introduction: Hypoxic-ischemic encephalopathy (HIE) is a type of brain injury that occurs when the brain doesn't receive enough oxygen or blood flow occurring during pregnancy, labor and delivery or in the postnatal period. This study aimed at determining factors associated with preventable HIE at Kacyiru Hospital in Rwanda.

Methods: This is a case control study using quantitative analysis of data from patients records of all neonates admitted into the neonatology ward for HIE and their respective mothers from 1st January 2016 to 31st March 2018.

Results: This study showed that APGAR scores less than 7 at 1, 5 and 10 min were found in cases 79.9%, 88.8% and 100% respectively. Convulsions were mostly observed in cases (94.6%) while sucking reflex ability was more detected in controls (93.8%). The presence of Moro reflexes was also different in cases and controls, 18.1 % and 81.9% respectively. Women with stained amniotic fluids were 6 times more likely to have babies with HIE. Women presenting abnormal fetal heart tracings on CTG during labor were 18 times more likely to have babies with HIE and women who attended 0 to 2 ANC visits were 2 times more at risk of delivering babies with HIE.

Conclusion: Preventable HIE in term neonates at Kacyiru Hospital was likely to be associated with meconium-stained amniotic fluid, abnormal fetal heart tracing, inappropriate ANC and male gender. Since HIE treatment is only limited to supportive care with no curative treatements, its prevention and case reduction is crucial.

INTRODUCTION

Hypoxic ischemic encephalopathy (HIE) is a type of brain injury that occurs when the brain doesn't receive enough oxygen or blood flow and may occur during pregnancy, labor and delivery or in the postnatal period [1,2]. Hypoxic ischemic encephalopathy remains a global concern especially in developing countries [3].

A retrospective study on the incidence and prediction of hypoxic-ischemic encephalopathy in Japan showed that potential risk factors predicting poor outcome include out-born birth, low Apgar score at 5 min and use of epinephrine. Laboratory abnormalities such as serum lactate, aspartate aminotransferase and alanine aminotransferase as well as abnormal brain MRI findings were also associated with poor

health outcomes [4]. Findings from Nepal also revealed that maternal infections, low socioeconomic status and multiple births were important risk factors for HIE mortality in low-resource settings [5].

In Saudi Arabia, several risk factors of HIE in newborns were identified and comprised being a prim gravida woman, lack of antenatal care, pregnancy-induced hypertension, antepartum hemorrhage and emergency C-section [6].

A few studies were also conducted in Sub Saharan African and revealed that poor fetal heart monitoring was indirectly associated with over 40% of perinatal death and was a major cause of avoidable hypoxic-ischemic encephalopathy in Tanzania [7]. Good obstetrical care and immediate resuscitation of newborns were found critical in reducing

cases of HIE and improving outcome on newborns. In Ethiopia, maternal illiteracy, low birth weight, preterm delivery and meconium-stained amniotic fluid were factors of HIE [8].

Rwanda, in particular, lacks evidence on HIE risk factors. It was previously observed that pregnant women in the country tend to delay their visits to professional medical staff and rather seek advice from traditional healers and take unspecified traditional medicines. Such practices have often been associated with abnormal fetal heart rate tracing during labor; risks factors traditionally believed to potentially affect neonates in Rwanda and in other developing countries. However, no scientific studies have this far been published on HIE even with the apparent / observed rise in HIE case in different hospitals in the country.

Based on knowledge gaps on actual risk factors associated with HIE, we believe this study will provide needed evidence to further strengthen maternal and child health promotion efforts across all health systems levels with the hope of reducing the case. Currently, since there is no known reversal HIE treatment available (treatment is only limited to supportive care, it is important for a health professional to maximise the reduction of HIE cases.

This study generally sought to determine factors associated with preventable hypoxic-ischemic encephalopathy. Specific objectives were:

i.   To describe clinical characteristics of cases of hypoxic-ischemic encephalopathy in term neonates at Kacyiru Hospital.

ii. To determine risk factors associated with preventable HIE cases at Kacyiru Hospital.

iii. To provide recommendations for effective preventable hypoxic-ischemic encephalopathy prevention.

METHODS

Study design
This study used an unmatched case control design to perform quantitative analysis of data extracted from patients' files.

Study Population
The study population included all neonates who were admitted in the neonatology ward for hypoxic-ischemic encephalopathy between 2016 and 2018 at Kacyiru district hospital. Mothers of all recruited neonates were also included in the study.

Selection criteria

• **Inclusion criteria**
- *Cases:* All term neonates and their mothers, admitted for HIE grade 2 and 3 in the neonatology- ward at Kacyiru hospital from 1st January 2016 to 31st March 2018.

- *Controls:* All term neonates and their mothers admitted without HIE in neonatology ward from 1st January 2016 to 31st March 2018.

• **Exclusion criteria**
Premature neonates with hypoxic-ischemic encephalopathy because prematurity itself is a risk factor for hypoxic-ischemic encephalopathy.

Study site

The study was conducted at Kacyiru hospital located in Gasabo district, City of Kigali. The hospital's monthly records report that out of 620 births, 40 ended up in neonatology and out of the 40 (6.5%) neonates, 7 neonates are admitted for HIE condition.

Study period

The study was conducted in 2018.
A sample size of 184 cases and 368 controls with a sample ratio of cases to controls 1:2 is needed to fit logistic regression of preventable hypoxic ischemic encephalopathy on different predictors to achieve 80% statistical power at a 5% significance level to detect a change in probability to preventable hypoxic ischemic encephalopathy from the baseline value of 0.30 to 0.42. This change corresponds to an odds ratio of 1.70.

The total number of study population becomes 1104.

Data collection methods

For both cases and controls, those meeting the inclusion criteria were recruited until the sample size was met.

A pre-designed questionnaire was used for both cases and controls using medical files of neonates and their respective mothers. Mothers' files were specifically checked to extract pregnancy and labour-related information.

All data were entered and stored in SPPS (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).

Variables

Independent variables: This study considered exposures of interests already reported in previous studies to potentially be associated with the risk of HIE in Neonates. [4]–[6], [8]

This included: the numbers of antenatal care visits, duration of the active phase of labor, fetal heart tracing pattern, amniotic fluid color, maternal history of infection, anemia and preeclampsia.

Dependent variable/Outcome

Hypoxic-ischemic encephalopathy

Statistical data analysis

Data were analyzed using STATA.13. Variables were summarized using frequency tables in univariate analysis.

Bivariate analyses were performed using chi-squared test to compare cases and controls.

All variables that showed a statistically significant association were included in multivariate logistic regression model to adjust for potential confounders.

A backward selection method was used. All variables showing statistical significant associations in bivariate analyses were fitted in a multivariate model. Adjusted ratios with their corresponding 95% CI and P-values were reported. The statistical test was interpreted at a significance level of 5%.

Ethical consideration

Standards for data security, privacy and confidentiality were considered based on scientific and ethics guidelines of Kacyiru research department and the Rwandan National Ethical Committee.

RESULTS

A total of 1028 subjects were recruited. This reflects a total of 294 cases (147 neonates with HIE and 147 mothers) and 734 controls (367 neonates and 367 mothers). Description of clinical characteristics of cases of hypoxic-ischemic encephalopathy in term neonates at Kacyiru Hospital.

Comparative description of cases and controls vis-à-vis neonatal clinical features showed that APGAR scores less than 7 at 1,5 and 10 min were found in cases (79.9%, 88.8% and 100%) respectively (table 1). Convulsions were mostly observed in cases (94.6%) while sucking reflex ability was more detected in controls (93.8%). 72.3% of cases required aspirations compared to only 27.7% in controls. The presence of Moro reflexes was also different in cases and controls at 18.1 % and 81.9% respectively. Cyanosis was more present in cases at 81.5% than in controls in 18.5%. The normal tone was less present in cases at 2% while it was more present in controls at 98%.

Table 1. *Descriptive Comparisons of clinical characteristics between HIE cases and Controls*

	Arm Control N	%	Case N	%	Total N	%	p-value
APGAR score at 1 min							
7 + (n=346)	332	96	14	4	346	100	0.000
1-6 (n=164)	33	20.1	131	79.9	164	100	
Total (n=510)	365	71.6	145	28.4	510	100	
APGAR score at 5 min							
7 + (n=412)	354	85.9	58	14.1	412	100	0.000
1-6 (n=98)	11	11.2	87	88.8	98	100	
Total (n=510)	365	71.6	145	28.4	510	100	
APGAR score at 10 min							
7 + (n=413)	364	88.1	49	11.9	413	100	0.000
1-6 (n=42)	0	0	42	100	42	100	
Total (n=455)	364	80	91	20	455	100	
Required aspiration after birth							
Yes (n=184)	51	27.7	133	72.3	184	100	0.000
No (n=315)	309	98.1	6	1.9	315	100	
Total (n=499)	360	72.1	139	27.9	499	100	
Length of hospital stay							
Less than 1 week (n=390)	339	86.9	51	13.1	390	100	0.000
2 week + or died in hospital (n=119)	25	21	94	79	119	100	
Total (n=509)	364	71.5	145	28.5	509	100	
Convulsions							
Yes (n=149)	8	5.4	141	94.6	149	100	0.000
No (n=362)	358	98.9	4	1.1	362	100	
Total (n=511)	366	71.6	145	28.4	511	100	
Sucking reflex							
Present (n=386)	362	93.8	24	6.2	386	100	0.000
Absent (n=126)	4	3.2	122	96.8	126	100	
Total (n=512)	366	71.5	146	28.5	512	100	
Moro reflex							
Present (n=442)	362	81.9	80	18.1	442	100	0.000
Absent (n=67)	3	4.5	64	95.5	67	100	
Total (n=509)	365	71.7	144	28.3	509	100	
Cyanosis							
Yes (n=27)	5	18.5	22	81.5	27	100	0.000
No (n=483)	361	74.7	122	25.3	483	100	
Total (n=510)	366	71.8	144	28.2	510	100	
Tone							
Normal (n=357)	350	98	7	2	357	100	0.000
Decreased or flaccid (n=150)	14	9.3	16	90.7	10	10	
Total (n=507)	364	71.8	143	28.2	507	100	

Identification of risk factors associated with preventable hypoxic ischemic encephalopathy in term neonates at Kacyiru Hospital.

Seven risk factors were found to be statistically associated with HIE condition (appendix 2).

The association was highly observed with amniotic fluid color, where women with stained amniotic fluids were 6 times more likely to have babies with HIE than those with clear fluids (aOR =6.39, CI: 8.23, 24.19, P<0,001). Women presenting abnormal fetal heart tracings on CTG during labor

were 18 times more likely to have babies with HIE than women with normal fetal heart tracing (aOR =18.6, CI: 8.30, 41.77, P<0,001).

Women who attended 0 to 2 ANC visits were 2 times more at risk of delivering babies with HIE compared to women who

attended 3 to 4 ANC visits (aOR=2.53, CI: 1.14, 5.65, P-value =0.023). Male neonates were more than 2 times more at risk of developing HIE compared to female neonates (aOR= 2.63, CI: 1.30, 5.29, P=0.007), (Table 2).

Table 2: *Multivariate analyses using Logistic Regression computing unadjusted and adjusted OR between exposures and the outcome of interest*

	Unadjusted OR			Adjusted OR		
	OR	95% CI	p-value	OR	95% CI	p-value
Sex						
Female (n=219)	1			1		
Male (n=295)	1.88	[1.25,2.81]	0.002	2.63	[1.30,5.29]	0.007
Amniotic fluid color						
Clear (n=409)	1			1		
Stained (n=90)	14.1	[8.23,24.19]	0.000	6.39	[2.88,14.20]	0.000
Abnormal fetal heart tracing						
No (n=278)	1			1		
Yes (n=194)	22.3	[12.66,39.44]	0.000	18.6	[8.30,41.77]	0.000
Duration of active phase of labor						
< 20 hours (n=366)	1			1		
20 - 30 hours (n=8)	18.6	[2.26,153.25]	0.007	27.0	[1.60,457.74]	0.022
ANC						
3-4 ANC (n=407)	1			1		
0-2 ANC (n=97)	3.09	[1.95,4.90]	0.000	2.53	[1.14,5.65]	0.023
Taken iron during pregnancy						
Yes (n=410)	1					
No (n=87)	2.04	[1.26,3.32]	0.004			
History of preeclampsia						
Yes (n=17)	1					
No (n=487)	6.26	[0.82,47.68]	0.076			

DISCUSSION

Neonates with HIE were most frequently found with APGAR scores less than 7 at all intervals of 1, 5 and 10 minutes. This is similar to findings from Aliyu et al. who found that all cases with Stage 3 HIE had a score lower than 7 (Fisher's exact test = 49.024; P = 0.00) [9]. Normally lower APGAR scores are an indication of possible poor labor monitoring or lack of timely resuscitation of a neonate.

Convulsions were found as a common clinical feature in neonates with HIE, similar findings in a study completed in India where abnormal neonatal reflex and convulsions were the most frequent clinical features in babies with HIE [10]. Similar results were also reported in Saudi Arabia and in Southern Nepal [5,11]. Such scenarios also imply potential deterioration of the brain and an urgent necessity to initiate resuscitation to save neonates. Weak Sucking, poor moro reflexes and decreased tone were predominantly present in neonates with HIE, which closely compares with the findings from Uganda revealing that weak sucking reflex, poor Moro reflex and hypotonia were the most common clinical features in neonates with HIE [12]. In a study exclusively involving neonates with HIE in Tanzania, weak/absent reflexes were also the most present accounted for 46.0% [3]. In this study, the majority of neonates with HIE stayed in a hospital for more than two weeks or even died in the hospital, which aligns with a study done in the United States of America revealing that average length of hospitalization was in a range of 6 to 36 days in neonates with HIE [13]. This means that neonates with HIE are critically ill and need urgent intervention to reduce long term complications.

Amniotic fluid color and the duration of the second stage of labor were significantly associated with HIE in this study. Similar to a study done in Indonesia and Pakistan [14,15]. This means that adequate labor monitoring would save many neonates from having hypoxic-ischemic encephalopathy. Improvement in the monitoring of mothers in labor and of the newborns with HIE should be strengthened.

Statistically significant associations were observed between abnormal fetal heart tracing during labor and hypoxic-ischemic encephalopathy group in our study. This shows a similarity to a case-control study conducted on intrapartum factors associated with neonatal hypoxic-ischemic encephalopathy in the United States of America that showed the presence of a category 3 fetal heart rate tracing in any of the four 15-min segments during the hour prior to delivery (28.0% versus 4.0%, p = 0.002) to be more common among hypoxic-ischemic encephalopathy cases [16]. This could be explained by limited skills on CTG interpretation or the insufficient number of CTG machines with regards to the demand during labor monitoring.

In this study, inadequate antenatal care (ANC) was found to be associated with a higher risk for HIE (Table 2). Similar to a study conducted in Pakistan, on risk factors of hypoxic-ischemic encephalopathy reporting that pregnant women who did not attend antenatal visits had high chances of hypoxic-ischemic encephalopathy due to a high likelihood of home and unattended delivery practices [16]. This already known information, thus health education programs to encourage women to attend at least 4ANC visits.

Male neonates were twice more likely at risk of developing HIE than females, though the results were not conclusive. This finding is compared with a study in Nepal where male gender was conclusively found as a risk factor for HIE [5]. However, Simiyu et al. found that the majority of severe HIE cases was composed of female neonates [3].

This aligns with findings of a preclinical study that showed that gender differences in anti-inflammatory response underlie the sex-specific chronic HIE outcomes, and enhanced neurogenesis in females contribute to the sex differences [17].

Evidence presented in this study cannot be generalized. Being a retrospective study, we largely relied on patients' files as the primary source of information and some patients's files had incomplete information recorded. This led to difficulties in assessing several known factors associated with preventable hypoxic-ischemic encephalopathy. Since effects reported in this study might therefore suffer the effect of potential confounders.

In conclusion, results in this study demonstrated that factors associated with preventable hypoxic-ischemic encephalopathy in term neonates at Kacyiru Hospital were meconium-stained amniotic fluid, abnormal fetal heart tracing, inappropriate ANC and male gender. Since HIE treatment is only limited to supportive care and no curative treatment is available, its prevention and case reduction is very important.

Health providers need to appropriately offer a full package of ANC services during pregnancies and encourage women to attend all recommended ANC visits. They must ensure that abnormal fetal heart tracings are timely handled during labor monitoring and introduce real-time monitoring system to check such difficulties that could lead to hypoxic-ischemic encephalopathy. We recommend studies in larger maternity hospitals in Rwanda to further validate our findings.

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