ORIGINAL ARTICLE

Risk Factors for Hypoxic Ischemic Encephalopathy in Children

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ABSTRACT

Objective: To determine underlying risk factors in neonates with hypoxic ischemic encephalopathy.
Study Design: Case-control study.
Place and Duration of Study: Neonatology Unit at the Children's Hospital and the Institute of Childhealth, Lahore, from March to July 2005.
Patients and Methods: All neonates (153) with the diagnosis of Hypoxic Ischemic Encephalopathy (HIE) were included in the study. Controls (187) were selected from admissions on the same day. Possible risk factors such as maternal age, parity, antenatal monitoring, place of delivery, prolonged second stage of labour, type of delivery, type of attendant at delivery and the gestational age were noted and compared.
Results: Sixty one (39.9%) mothers of asphyxiated babies reported no antenatal visits compared to 24.1% in the control group (OR 2.1, 95% CI 1.3-3.2; p=0.002). Only 6.5% of cases were born in government hospitals (teaching and district) in comparison to 20.9% of controls (OR 3.8, 95% CI 1.9-7.6; p=0.001). In 28.1% of cases, mothers had history of prolonged 2nd stage of labour in comparison to 5.9% of controls (OR 6.3, 95% CI 3.3-11.9; p<0.001). Fifty five cases (35.9%) were delivered by unskilled birth attendants compared to 28 (14.9%) controls (OR 3.2, 95% CI 1.9-5.3; p<0.001). No significant difference was found in maternal age, maternal parity, gestational age and the mode of delivery between the two groups.
Conclusion: Delivery by unskilled birth attendant, prolonged second stage of labour, birth in a non-government hospital setup and absence of antenatal care were significant risk factors for hypoxic ischemic encephalopathy in neonates. Improvement in antenatal and intrapartum care may be helpful in decreasing the frequency of this problem.

Key words: *Neonatal. Hypoxic ischemic encephalopathy. Risk factor. Birth attendant. Prolonged labour. Antenatal care.*

INTRODUCTION

Despite major advances in fetal monitoring and knowledge of fetal and neonatal pathologies, perinatal asphyxia or more appropriately, Hypoxic Ischemic Encephalopathy (HIE), remains a serious problem. Along with prematurity and infections, it is one of the three main causes of neonatal mortality.[1,2]

HIE is characterized by clinical and laboratory evidence of acute or sub-acute brain injury due to asphyxia leading to hypoxia and acidosis. Often, the underlying cause and the exact timing of brain injury remain uncertain. Various risk factors e.g. sub-optimal intrapartum obstetric care has been associated with the condition.[3] This is also an area of considerable medico-legal concern in the western world.[4] Frequency of HIE is reported to be high in developing countries although exact figures are not available. Global estimates of asphyxia related neonatal deaths vary from 0.7 to 1.2 million annually,[5] and as many children survive with long-term neurological sequelae. Severe HIE is associated with a mortality rate of 50-75%. Upto 80% of infants, who survive severe HIE, develop serious complications. Ten to twenty percent develop moderately severe disability.[6] Data from Pakistan has shown that it is one of the leading causes for admission in a neonatal unit.[7] It has also been shown that most causes of neonatal morbidity in Pakistan are preventable.[8] Birth asphyxia is clearly a problem where prevention should be the aim.

Any preventive strategy should be based on local facts and figures to be effective. It is, therefore, vital to collect local data about the problem and to use that information to formulate guidelines aimed at reducing the incidence of birth asphyxia.

The magnitude and impact (in terms of neonatal mortality and subsequent morbidity) of this preventable condition and the paucity of local data provided the impetus for this study. The aim of this study was to determine factors that may predispose a neonate to hypoxic insult at birth.

PATIENTS AND METHODS

This case control study was carried out in the Neonatal Unit of the Children's Hospital and the Institute of Child

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Health, Lahore. As there was no obstetric service within the hospital, all neonates were delivered elsewhere.

The study period was from March 2005 to July 2005. During this time, 153 cases were identified and included. A matched control group of 187 neonates was also included. Inclusion criterion was clinical diagnosis of hypoxic ischemic encephalopathy based on history of delayed cry, presence of thick meconium stained liquor, need for resuscitation, APGAR scores of less than 4 at one minute or less than 7 at 5 minutes of age and early onset of encephalopathy in the absence of other causes. History of at least two of the above with abnormal neurological examination (abnormalities in tone, posture, neonatal reflexes or conscious level) was taken as important.

Controls were selected from admissions on the same day. These included neonates with diagnoses other than HIE. Admissions immediately following the cases were selected. If more than one baby presented at the same time, both were included. Neonates with major congenital malformations and other causes of encephalopathy (infectious or metabolic) were excluded from both the groups.

The possible risk factors studied included maternal age (<18 years, 18-30 years, >30 years), parity (primigravida, 1-4 previous live births, 5 or more live births), history of antenatal care, place of delivery (home, private health facility, government hospital), history of prolonged (>30 minutes) second stage of labour, type of delivery (vaginal, caesarean section, instrumental), gestational age and the birth attendant at delivery. Birth attendants were divided into four groups: untrained person e.g. family member, traditional birth attendant with no formal training but practical experience in the field, lady health visitor/nurse with some formal training or a doctor. The two former groups were considered as unskilled while the latter two as skilled birth attendants. Antenatal care was determined by asking about antenatal visits and antenatal ultrasound scan performed at some stage in pregnancy. History of at least two antenatal visits to a health care provider and/or even a single antenatal ultrasound scan was considered as antenatal care. Gestational age was estimated either by date, by cranial ultrasound scan or by physical examination (Ballard scoring). All teaching and district hospitals and 'government centers' were included under the term of 'government hospitals'. Private health care facilities included 'private clinics' and 'private maternity centres'. Details of history and examination were noted on a structured proforma and information subsequently entered on a data base.

Statistical analysis was carried out using STATA version 9.2. All the variables were qualitative. Odd ratio (OR) and 95% confidence interval was calculated to determine significance of risk factors. If there were less than 5 cases in any cell of the table, they were pooled with the other relevant group. P-value was also calculated using chi-square or Fischer's exact test on SPSS 11 and value > 0.05 was considered significant.

RESULTS

A total of 340 neonates were included in the study (Table I). These included 153 cases and 187 controls. Male neonates numbered 126 (82.4% of cases and 67.4% of the controls) in both the groups. This difference was statistically significant (OR 2.3 95% CI 1.3-3.8; p=0.002).

Table I: Patient characteristics.

	Cases (n=153)		Controls (n=187)	
Sex	Number	Percentage	Number	Percentage
Males	126	82.4	126	67.4
Females	27	17.6	61	32.6
OR 2.3 (95% CI 1-3-3.8); p=0.002				
Gestational age				
< 37 weeks	17	11.1	31	16.6
37-42 weeks	136	88.9	155	82.9
> 42 weeks	0	0	1	0.5
OR 0.63 (95% CI 0.33-1.18); p=value > 0.05				
Age at admission				
<48 hours	102	66.7	36	19.2
2-7 days	36	23.5	70	37.4
>7 days	15	9.8	81	43.3
OR 8.3 (95% CI 5.2-13.4); p<0.001				

Term babies accounted for the majority in both the groups. There was no statistical difference in gestational age between the cases and controls (OR 0.6, 95% CI 0.3-1.2).

One hundred and two of the cases (66.7%) presented to our unit within 48 hours of life. Majority of babies (43.3%) in the control group were more than 7 days old at admission (Table I). Babies with HIE were statistically more likely to present in the first 48 hours of age as compared to controls (OR 8.3, 95% CI 5.2-13.4; p < 0.001).

Absence of antenatal care appeared to be a significant risk factor for HIE (OR 2.1, 95% CI 1.3-3.2; p=0.002). Almost 40% mothers of asphyxiated babies had no antenatal monitoring compared to 24.1% mothers from control group (Table II). Fifty-one women (33.3%) in the

Table II: Antenatal care in mothers.

	Cases (n=153)		Controls (n=187)	
Antenatal visit	Number	Percentage	Number	Percentage
Yes	92	60.1	142	75.9
No	61	39.9	45	24.1
OR 2.1 (95% CI 1.3 – 3.2); p=0.002				
Antenatal scan				
Yes	102	66.7	146	78.1
No	51	33.3	41	21.9
OR 1.8 (95% CI 1.1 – 2.9); p=0.018				

HIE group compared to 41 (21.9%) women in the control group reported not having any ultrasound scan during their pregnancy (OR 1.8, 95%CI 1.1-2.9; p=0.018).

Fifty-one babies in each group (33.3% cases, 27.3% controls) were born to primigravida mothers (OR 1.3, 95% CI 0.8-2.1) while majority of the babies in both groups were delivered to mothers with 1-4 previous live births (81/153; 54.2% cases; 119/187, 63.6% controls). Only 12.4% (19/153) cases and 9.1% (17/153) controls were born to mothers with 5 or more previous live births (OR 1.4, 95% CI 0.7-2.8). The parity of the mother was not significantly different between the two groups.

Spontaneous vaginal delivery was the commonest mode of delivery in both the groups (71.9% cases and 74.9% controls). This was followed by delivery by caesarean section (23.5% cases; 22.9% controls). Seven (4.6%) babies in the HIE group and 4 (2.1%) in the control group needed forceps extraction. Caesarean section and instrumental delivery did not appear to be major risk factors for HIE (OR 1.2, 95% CI 0.7-1.9).

Mothers of most babies in both the groups (86.9% cases; 85% controls) were between 18 and 30 years of age. Only 3.9% cases and 4.8% controls were born to women less than 18 years old (OR 0.8, 95% CI 0.3 -2.3). Remaining (9.1% cases and 10.2% controls) were born to mothers older than 30 years (OR 0.9, 95% CI 0.4-1.8). There was no statistically significant relationship between maternal age and the diagnosis of HIE in the neonates.

Majority of babies in both groups were delivered in a private health facility and fewer in government hospitals (Table III). However, significantly more babies with HIE were delivered in a non-government hospital setup than controls (OR 3.8, 95% CI 1.9-7.6; p=0.001).

The type of birth attendant at the time of delivery was also compared (Table III). Babies with HIE were more likely to be delivered by unskilled birth attendants compared to controls (OR 3.2, 95% CI 1.9-5.3; p<0.001). Likewise, history of prolonged second stage of labour was significantly more likely to be present in mothers of asphyxiated babies (OR 6.3, CI 3.3-11.9; p<0.001).

Table III: Intrapartum risk factors.

	Cases (n=153)		Controls (n=187)	
Place of delivery	Number	Percentage	Number	Percentage
Home	67	43.8	67	35.8
Private	76	49.7	81	43.3
Government Hospital	10	6.5	39	20.9
OR 3.8 (95% CI 1.9-7.6); p=0.001				
Type of attendant at delivery				
Doctor	80	52.3	116	62.0
Lady health visitor	18	11.8	43	23.0
Traditional birth attendant	51	33.3	27	14.4
Untrained	4	2.6	1	0.5
OR 3.2 (95% CI 1.9-5.3); p =value > 0.01				
Prolonged second stage labour				
Present	43	28.1	11	5.9
Absent	110	71.9	176	94.1
OR 6.2 (95% CI 3.5-11.9); p < 0.001				

DISCUSSION

Twenty three percent of all the newborn deaths are caused by birth asphyxia.[5] It is important to be aware of factors that may predispose a newborn to hypoxic insult at birth with the aim of formulating preventive strategies. These factors may be antepartum in origin in 50% of the cases, intrapartum in 40% and postpartum in remaining 10%.[9] Given the reduced availability of skilled care during delivery in developing countries, intrapartum causes may have greater contribution.[10]

Of the factors that we studied, absence of antenatal monitoring emerged as a significant risk factor. Sub-optimal fetal monitoring is well recognized as a common contributor to moderate or severe neonatal encephalopathy. It was seen as an antecedent event in 42% of cases of moderate to severe neonatal encephalopathy.[11] Failure to respond to signs of fetal distress has been found to be linked to cerebral palsy (OR 4.5, 95 %CI 2.4-8.4).[3] Similarly, non-accessibility to antenatal care is also a significant risk factor (OR 1.89) for hypoxic ischemic encephalopathy.[12] Same authors also reported prolonged second stage of labour as being significant risk factor (OR 6.67). In this study comparable possible association was found between prolonged second stage and HIE (OR 6.3, 95% CI 3.3-11.9). Improving awareness of the importance of antenatal monitoring with easy access to a health services at delivery may play a part in reducing the incidence of birth asphyxia.

A significant correlation between the person conducting delivery and HIE has also been observed. Infants with HIE were more likely to be delivered by unskilled birth attendant compared to babies in the control group (OR 3.2, 95% CI 1.9-5.3). A study in India showed that traditional birth attendants were able to recognize signs of asphyxia, but were mostly unable to deal with it.[13] Training programmes targeting at traditional birth attendants may be of benefit in decreasing birth asphyxia in our country where only 31% of deliveries are attended by skilled health personnel.[14]

Delivery in non-government hospital setting (home/ private health facility) emerged as a significant risk factor for HIE (OR 3.8). This may point to a better level of training in people working in government hospitals in comparison to the private sector. It may also mean that government hospitals being more capable of dealing with the problem themselves are less likely to refer asphyxiated babies elsewhere. Private health care facilities may vary widely in terms of quality of care that

they provide but there is no objective way of categorizing care as these facilities are not graded. A large majority of patients were from a socioeconomic group who had no access to the expensive private hospitals. The private facilities were mostly described by the patients as 'private clinics' or 'private centres'. No patient in either group was born in a privately managed teaching hospital. It is noteworthy that collectively in both the groups, 46.2% infants were delivered in private sector in comparison to 14.4% deliveries in government hospitals. Perhaps the private sector is more accessible to the general public. Taking measures to standardize and improve the level of health service in private sector may be of benefit to a large section of the population.

There were significantly more male babies amongst the cases (OR 2.3). Male gender as being a risk factor for HIE (OR 4.8) has also been reported by others.[15] The significance of this finding remains unclear. Same study also reported inappropriate antenatal care as a significant risk factor (OR 9.49).[15] Majority of the studied cases presented within 48 hours of life. Similar results were seen in a study on neonatal seizures. Infants with seizures due to HIE were more likely to be admitted within 48 hours of life.[16] This may show a tendency towards early referral to an experienced unit where there is suspicion of asphyxia at birth – a practice that should be encouraged and streamlined.

Maternal age at delivery did not appear to be significant. This was similar to the results reported from Sweden.[17] However, other researchers found that maternal age >35 years was a risk factor (OR 4.35) for neonatal encephalopathy.[18] A vast majority of present patient group came from a low income, illiterate segment of the population. Many women were unaware of their exact age and the age stated was an approximation with a tendency towards younger age. This may be a reason why very few mothers in both the groups were over 30 years of age. No correlation was found between maternal parity and HIE. In this study, the mode of delivery did not appear to be of significance. Vacuum extraction (OR 2.16) and caesarean section (OR 2.36) were found to be significantly associated with birth asphyxia in a study from Uganda.[19] Other researchers have reported an inverse relationship (OR 0.17) between neonatal encephalopathy and elective caesarean section. Operative vaginal delivery (OR 2.34) and emergency caesarean section (OR 2.17) were identified as risk factors in the same study.[20] The reason why instrumental and operative delivery was not associated with birth asphyxia in the present study group may be reflective of the fact that such deliveries would have been conducted by trained medical personnel in our study population, thus, conferring a benefit.

Gestational age of infants did not appear to be significant risk factor in this study. Premature infants are reported in literature as being more prone to ischemic injuries of the white matter.[21] These babies are more likely to have several other potentially fatal problems compared to term infants. Since all our patients were delivered elsewhere, it is quite possible that many preterm babies failed to make it to the unit. This may be the reason why preterm babies were underrepresented in this study. It is also true that neonatal brain injury is difficult to diagnose in premature infants because either obvious signs are absent or if present, are attributed to developmental immaturity.[22] Regional cortical volumes are significantly smaller in preterm brains.[23] This may lead to neurological findings, which may be difficult to differentiate from HIE and thus to missed diagnosis in this particular group of neonates.

CONCLUSION

In the group studied, lack of antenatal care in mothers, delivery by unskilled birth attendants either at home or a private health facility and prolonged labour emerged as significant risk factors for asphyxial insult at birth. These babies are likely to present to hospital within 2 days of life. Improving antenatal care of pregnant mothers and providing training to people who assist the process of labour and delivery are areas that should be targeted in the health structure.

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