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Hypoxic Ischemic Encephalopathy: Think Outside the Box

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ABSTRACT

There are some factors that leads to hypoxic ischemic encephalopathy, like maternal age ≥ 35 years, social factors, family history of seizures or neurologic disease, infertility treatment, previous neonatal death, severe preeclampsia, multiple gestation, intrauterine growth restriction, trauma, breech presentation and antepartum hemorrhage. The aim of current study was to identify the associated risk factors which can lead to hypoxic ischemic encephalopathy. A descriptive cross-sectional study was conducted at Paediatrics Ward Unit-II of Civil Hospital, Karachi. All laboratory tests were done from the central laboratory of the civil hospital. The presence of hypoxic ischemic encephalopathy was staged using the Sarnat criteria at the time of admission. Data was collected on predesigned proforma consisting of demographic variables and the risk factors leading to HIE. Data was entered and analyzed in Statistical Package for Social Science (SPSS) version 20. The mean ± SD age of mother of neonates enrolled in this study was 27.41 ± 5.44 years. Mean ± SD gestational age was 34.63 ± 3.87 weeks. Risk factors for hypoxic ischemic encephalopathy include inadequate antenatal care (33.8%), maternal anemia (35.9%), history of hypertension (35.2%), prolonged second stage of labor (29%), vacuum extraction (23.4%), premature delivery (25.5%) and intrauterine growth retardation (16.6%). Overall, 95.2% neonates were identified to have one or more of these contributing factors. Stratified analysis showed that over all neonates of female gender were associated with having more frequency of HIE. Maternal anemia was found to be significantly associated with the occurrence of HIE. The frequency of HIE risk increased with increasing maternal age. Lowest the serum pH level, highest was the frequency of HIE risk factors. Prolonged 2nd stage of labor was significantly associated with lower neonatal weight, overall, very low and very high birth weight neonates were having higher frequency of HIE risk. To conclude the risk factors like insufficient antenatal care, high rates of maternal anemia, other maternal comorbid like history of hypertension, complications of delivery process and its management, prolonged second stage labor, vacuum extraction and fetus related factors like premature delivery and IUGR are quite common which prone the neonates to develop HIE.

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GM designed the study. JM and NI performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. SMT and MK managed the analyses of the study. LF managed the literature searches. All authors read and approved the final manuscript.

Key words
Hypoxic ischemic encephalopathy, Birth asphyxia, Neonatal mortality, Neurological complications, Risk factors

INTRODUCTION

Hypoxic Ischemic Encephalopathy (HIE) is the abnormal neurologic behavior in the neonatal period arising as a result of a hypoxia (Shankaran, 2010). It is commonly known as birth asphyxia. Hypoxia-ischemia can lead to neurologic injuries, seizures, and death. Neonates are particularly vulnerable to this condition (Delivoria-Papadopoulos and Marro, 2010). In term newborns, asphyxia can occur in utero and during labor and delivery as a result of impaired placental gas exchange (Futrakul *et al*., 2006). The exact cause is not always identified, antecedents include cord prolapse, uterine rupture, placental abruption, placenta previa, maternal hypotension, breech presentation, or shoulder dystonia. The manifestations of perinatal HIE in early postnatal life include abnormal fetal heart rate tracings, poor umbilical cord gases (pH < 7.0 or base deficit ≥ 12 mmol/L), low Apgar scores (de Vries and Cowan, 2009), presence of meconium stained fluid or the need for respiratory support

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within the first several min of postnatal life (Horn *et al*., 2009; Shalak and Perlman, 2004).

Newborn HIE is an important clinical problem associated with considerable morbidity and mortality (Higgins, 2005). It is an important cause of admission to neonatal intensive care units (NICU) with multi-organ dysfunction (Shah *et al*., 2004). Moreover, asphyxia has been shown to be the third most common cause of neonatal death (23%) after preterm birth (28%) and severe infections (26%) (Lawn *et al*., 2005). HIE is estimated to occur in about 2-9 per 1,000 live births. Roughly 10-60% of affected infants die in the newborn period and at least 25% of those that survive have significant brain damage and long-term neurodevelopmental impairments in developing countries (Graham *et al*., 2008; Martin *et al*., 2011). In Pakistan, perinatal events observed in a community based study in Lahore, showed that it affected 2.16% cases with case mortality of 65% (Zulfiqar, 2007).

Factors leading to birth asphyxia HIE can be antenatal or intranatal. These can be fetal or maternal. Pre-conception risk factors for asphyxia are maternal age ≥ 35 years, social factors, family history of seizures or neurologic disease, infertility treatment, previous neonatal death etc. Antepartum risk factors include maternal prothrombotic disorders and pro-inflammatory states, maternal thyroid disease, severe preeclampsia, multiple gestation, chromosomal/ genetic abnormalities, congenital malformations, intrauterine growth restriction, trauma, breech presentation and antepartum hemorrhage (Palsdottir *et al*., 2007; Futrakul *et al*., 2006; Wood *et al*., 2021). Numerous intrapartum risk factors for asphyxia are recognized, including abnormal fetal heart rate during labor, chorioamnionitis/maternal fever, thick meconium, operative vaginal delivery, general anesthesia, emergency cesarean delivery, placental abruption, umbilical cord prolapse, uterine rupture, maternal cardiac arrest, and fetal exsanguination (Palsdottir *et al*., 2007; Wood *et al*., 2021). Despite of being common issue, data on factors leading to HIE among population is limited. Upon thorough search only few studies were found at local level on magnitude of burden of risk factors which lead to neonatal mortality in HIE. So, the aim of current study was to identify the associated risk factors which can lead to HIE.

MATERIALS AND METHODS

A descriptive cross-sectional study was conducted at Paediatrics Ward Unit-II of Civil Hospital, Karachi from 07 March 2020 to 06 September 2020. Taking the prevalence of maternal anemia as risk of HIE at 10.3% (Qureshi *et al*., 2010), level of significance as 95%, margin of error at 5%, the sample size calculated was 142 ~ 145. The non-probability sampling technique was used**.** The inclusion crieteria of the study was (1) Age of patient's mother between 18-40 years, (2) parity 0-2 children, (3) gestational age between 28-42 weeks on clinical history and ultrasonology, (4) history of fetal distress as reported by obstetrics record, (5) birth history of delayed cry >5 min, limpness, cyanosis, apnea for > 20 seconds, (6) APGAR score 0-3 for longer than 5 min. The neonates with major systemic malformations like patent ductus arteriosus, ventral septal defect, cleft lip and cleft palate, down syndrome, spina bifida, exomphalos and tracheoesophageal fistula were excluded from the study.

After getting the approval from Research Evaluation Unit of CPSP, Karachi followed by permission from the ethical review committee of Civil Hospital the data collection was started. Neonate patients presenting to paediatrics emergency, who were eligible as per selection criteria and had picture of birth asphyxia/ HIE were enrolled after taking valid written assent from their parents. All laboratory tests like blood pH, was done from the central laboratory of the civil hospital. The presence of HIE was staged using the Sarnat criteria at the time of admission. Neonates were observed daily, using Sarnat criteria till their discharge. Data was collected on predesigned proforma consisting of two parts, the first part was for demographic variables including maternal age, gestational age, parity and APGAR score while the second part was for risk factors leading to HIE like antenatal care, maternal haemoglobin level, history of hypertension, prolonged second stage labour, vacuum extraction delivery, premature delivery, IUGR.

Data was entered and analyzed in Statistical Package for Social Science (SPSS) version 20. The continuous variables like maternal age, neonatal weight, gestational age, parity, duration of second stage labour, APGAR score and maternal haemoglobin level were expressed in mean and standard deviation (Mean±SD). Categorical variables like presence of HIE risk factors including antenatal care, history of hypertension, mode of delivery, premature rupture of membranes and intrauterine growth restriction (IUGR) were expressed in frequencies and percentages. To evaluate the effect modification, the maternal age, gestational age, parity, APGAR score, neonatal weight and gender of neonate were stratified followed by application of t-test and chi-square with a p value ≤0.05 taken as significant.

RESULTS

The mean ± SD age of mother of neonates enrolled in this study was 27.41 ± 5.44 years, gestational age was 34.63 ± 3.87 weeks, number of children was 1.28 ± 0.63

children. The mean ± SD of serum pH, APGAR score at 5 min and neonatal weight was 5.87 ± 0.82, 1.43 ± 0.91 and 2425.521 ± 427.31g, respectively (Table I).

Table I. Descriptive statistics on continuous demographic variables.

Demographical variables	Mean ± SD
Age of the mother (years)	27.41 ± 5.44
Gestational age (in weeks)	34.63 ± 3.87
Number of children	1.28 ± 0.63
Serum pH	5.87 ± 0.62
Apgar score at 5 min	1.43 ± 0.91
Neonatal weight (gm)	2425.521 ± 427.31

Table II. Frequency of different risk factors of HIE as found positive in patients.

Risk factors of HIE	Frequency (%)
Antenatal care	49 (33.8)
Maternal anemia	52 (35.9)
History of hypertension	51 (35.2)
Prolonged second stage labour	42 (29)
Vacuum extraction	34 (23.4)
Premature delivery	37 (25.5)
IUGR	24 (16.6)

Looking over the frequency of factors leading to hypoxic ischemic encephalopathy among neonates, the inadequate antenatal care was among 33.8% cases, maternal anemia 35.9%, history of hypertension 35.2% and prolonged second stage of labor was among 29% of the cases. While others less common factors included vacuum extraction 23.4%, premature delivery 25.5% and IUGR 16.6% as presented in Table II. Overall, 95.2% (n = 138) neonates were identified to have one or more of these contributing factors.

Stratified analysis showed that over all neonates of female gender were associated with having more frequency of HIE than male gender but the result was non-significant. Maternal anemia was found to be significantly associated with the occurrence of HIE as shown in Table III. Regarding maternal age relationship with HIE risk factors it was noted that the frequency of HIE risk factors including antenatal care, maternal anemia and history of hypertension were slightly increased with increasing maternal age but this finding was not significant. On the other hand, some risk factors like prolonged 2nd stage, vacuum extraction, premature delivery and IUGR decreased with decreasing maternal age as presented in Table III.

Frequency of maternal anemia, premature delivery and IUGR were the factors which persistently decreased with decreasing gestational age (P values = 0.223, 0.008 and 0.152, respectively) while antenatal care, history of hypertension and vacuum extraction slightly decreased with increasing gestational age but again increased in post-term neonates (≥41 weeks) associated with statistical significance (P values = 0.054, 0.036 and 0.001 respectively) as presented in Table III. Nulliparity was associated with higher frequency of HIE risk factors but the association was not significant as shown in Table III.

The stratified analysis revealed that lowest the serum pH level, highest was the frequency of HIE risk factors especially, antenatal care, maternal anemia, history of hypertension and premature delivery with non-significant p value as reported in Table III.

Prolonged 2nd stage of labor was significantly associated (P value = 0.011) with lower neonatal weight. Rest of the HIE risk factors were non-significantly associated with lower neonatal weight. It was also noted that overall, very low and very high birth weight neonates were having higher frequency of HIE risk factors as shown in Table III.

It was noted that few factors like antenatal care, history of hypertension, prolonged 2nd stage and IUGR were having high frequency of low APGAR score (1-2 or 3) but the finding was statistically non-significant as mentioned in Table III.

DISCUSSION

Newborn baby is at exposure of multiple disease conditions in very new environment. One of such is the perinatal asphyxia which is an important cause of acquired neonatal brain injury in term neonates leading to HIE. Hypoxia ischemia in the perinatal period is a major cause of neonatal death and long term disability (Gunn *et al*., 2005; Shah *et al*., 2007).

It is very important to identify potential risk factors for HIE and provide prophylactic/ preventive care. The current study identifies the most common risk factors including absence of regular antenatal check-up, anemia of mothers of the neonates, presence of hypertensive disorders among mothers and prolonged second stage labor. Apart from these other factors which this study found positive among nearly a quarter of HIE cases were use of vacuum extraction for delivery, premature delivery and intrauterine growth restriction of fetus. However; there were about 5% cases in whom no any factor was detected. A study conducted by Futrakul *et al*. (2006) favored current

Table III. Effect of neonatal gender on frequency of HIE risk factors.

Gender of neonate	Risk factors							
	Antenatal care	**Maternal anemia**	**History of hypertension**	**Prolonged 2nd stage**	**Vacuum Extraction**	**Premature delivery**	**IUGR**	**Presence of factor of HIE**
Male (n=55)	35(63.6)	14(25.5)	21(38.2)	17(30.9)	15(27.3)	12(21.8)	9(16.4)	52(94.5)
Female (n=90)	61(67.8)	38(42.2)	30(33.3)	25(27.8)	19(21.1)	25(27.8)	15(16.7)	86(95.6)
Total (n = 145)	96(66.2)	52(35.9)	51(35.2)	42(29.0)	34(23.4)	37(25.5)	24(16.6)	138(95.2)
P value	0.609	0.041	0.553	0.687	0.395	0.494	0.962	0.783
Maternal age categories								
18-20 years (n=16)	9(56.2)	2(12.5)	4(25.0)	7(43.8)	4(25.0)	4(25.0)	4(25.0)	15(93.8)
21-30 years (n=88)	59(67.0)	32(36.4)	33(37.5)	22(25.0)	21(23.9)	24(27.3)	11(12.5)	84(95.5)
31-40 years (n=41)	28(68.3)	18(43.9)	14(34.1)	13(31.7)	9(22.0)	9(22.0)	9(22.0)	39(95.1)
P value	0.665	0.084	0.621	0.283	0.960	0.811	0.254	0.958
Gestational age categories (Weeks)								
28-32 (n=45)	29(64.4)	21(46.7)	16(35.6)	12(26.7)	14(31.1)	19(42.2)	7(15.6)	43(95.6)
33-36(n=54)	37(68.51)	19(35.2)	24(44.4)	15(27.8)	6(11.1)	7(13.0)	13(24.1)	53(98.1)
37-40 (n=33)	20(60.6)	8(24.2)	5(15.2)	10(30.3)	8(24.2)	9(27.3)	4(12.1)	29(87.9)
> 41 (n=13)	10(76.9)	4(30.8)	6(46.2)	5(38.5)	6(46.2)	2(15.4)	0(0.0)	13(100.0)
P value	0.054	0.223	0.036	0.861	0.001	0.008	0.152	0.137
Number of children (Parity)								
Nulliparity (n=14)	9(64.3)	2(14.3)	7(50.0)	5(35.7)	6(42.9)	1(7.1)	2(14.3)	14(100.0)
1-2 (n=131)	87(66.4)	50(38.2)	44(33.6)	37(28.2)	28(21.4)	36(27.5)	22(16.8)	124(94.7)
P value	0.873	0.077	0.222	0.588	0.071	0.097	0.810	0.375
Serum pH level								
Upto 5.00 (n=15)	11(73.3)	6(40.0)	5(33.3)	5(33.3)	3(20.0)	5(33.3)	3(20.0)	14(93.3)
5.01 to 6.00 (n=63)	45(71.4)	23(36.5)	17(27.0)	12(19.0)	15(23.8)	12(19.0)	10(15.9)	61(96.8)
6.01 to 6.99 (n=67)	40(59.7)	23(34.3)	29(43.3)	25(37.3)	16(23.9)	20(29.9)	11(16.4)	63(94.0)
P value	0.305	0.909	0.149	0.067	0.946	0.282	0.927	0.713
Neonatal weight (g)								
Upto 2000 (n=08)	7(87.5)	3(37.5)	4(50.0)	0(0.0)	3(37.5)	4(50.0)	1(12.5)	8(100.0)
2001-3000 (n=122)	80(65.6)	41(33.6)	40(32.8)	42(34.4)	30(24.6)	28(23.0)	18(14.8)	116(95.1)
3001-4000 (n=14)	9(64.3)	7(50.0)	6(42.9)	0(0.0)	1(7.1)	4(28.6)	5(35.7)	13(92.9)
>4001 (n=01)	0(0.0)	1(100.0)	1(100.0)	0(0.0)	0(0.0)	1(100.0)	0(0.0)	1(100.0)
P value	0.305	0.350	0.350	0.011	0.341	0.115	0.231	0.891
Apgar score at 5 min								
Zero (n=21)	14(66.7)	8(38.1)	6(28.6)	6(28.6)	7(33.3)	6(28.6)	2(9.5)	20(95.2)
1-2 (n=103)	70(68.0)	37(35.9)	36(35.0)	27(26.2)	21(20.4)	26(25.2%)	19(18.4)	99(96.1)
3 (n=21)	12(57.1)	7(33.3)	9(42.9)	9(42.9)	6(28.6)	5(23.8)	3(14.3)	19(90.5)
P value	0.633	0.949	0.623	0.309	0.370	0.933	0.578	0.547

finding by reporting lack of antenatal visits among 55% cases of HIE, 28% was prolonged labor and other delivery complications, 37% was nulliparity, 27% elder age mothers and 15% was reasons of maternal morbidity like history of hypertension (Futrakul *et al*., 2006). Butt T, *et al*., have reported that highest prevalent factor of HIE was having delivery in private hospitals followed by lack of antenatal pregnancy care, nulliparity, prolongation of the

second stage labor which were 93.5%, 40%, 33.3% and 28.1%, respectively (Butt *et al*., 2008).

Study by Futrakul *et al*. (2006) has identified the neonatal risk factors for HIE, these including male gender, post-term neonates, low birth weight, very high birth weight (macrosomia) and APGAR < 3 at 5 min. The current study found similar results except the difference of gender. In current study it was found that female gender was more affected with HIE as compared to males. Kharoshankaya *et al*. (2016) also contradicted current finding by reporting higher prevalence of HIE among male neonates as compared to female. The reason for this variation may be difference in population or merely coincidence of sampled cases. However; other variables are same as that of current study like the maternal age of 3rd decade and beyond, nulliparous women, gestational age of less than 36 weeks or beyond 40th week and history of maternal hypertension had elevated risk of HIE. Qureshi *et al*. (2010), found in their study that among all HIE affected neonates there 8.8% premature, 7.2% having intrauterine growth retardation while 6% were post-mature neonates. Current study found that 31% premature, 16.6% having IUGR while 9% were post-mature neonates.

The current study with all its limitations like small size sample size, shorter duration of study and snap shot design, has come up with important and core evidence that there are many maternal and fetal factors associated with birth asphyxia. Prevention by early identification of the HIE risk factors and prophylactic care is the only way to save the neonates from life-long complications.

CONCLUSION

It can be concluded that some of the risk factors like insufficient antenatal care, high rates of maternal anemia, other maternal comorbid like history of hypertension, complications of delivery process and its management, prolonged second stage labor, vacuum extraction and fetus related factors like premature delivery and IUGR are quite common which prone the neonates to develop HIE.

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IRB approval

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Ethical statement

Study got ethical approval from the concerned institute.

Statement of conflict of interest

The authors have declared no conflict of interest.

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