ORIGINAL ARTICLE

HYPOXIC ISCHEMIC ENCEPHALOPATHY IN NEONATES

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Background: Birth anoxia remains an important cause of mortality and morbidity in neonates. Hypoxia/ischemia can lead to permanent brain damage and also affects other tissues of the body. It results from lack of oxygen before, during or after birth. The study was designed to assess the risk factors of birth asphyxia, common presentations and association of Apgar score with grades of hypoxic-ischemic encephalopathy. **Methods**: the study is descriptive, prospective and carried out in the Paediatric Department of Ayub Teaching Hospital, Abbottabad from September 2007 till September 2008. A total number of 181 neonates (144 males and 37 females) who showed the neurological signs of hypoxic-ischemic encephalopathy were included in the study. Maternal history was taken, Apgar scoring was done and neurological grading was done for the assessment of brain damage. **Results**: out of 181 neonates 77.9% were full term, 8.8% were premature, 5.2% were having intra uterine growth retardation and 6.1% were post mature. 38.7% were diagnosed as having grade-3, 38.7% as grade-2 and 22.6% as grade-1 encephalopathy. Mortality due to hypoxic ischemic encephalopathy in our unit was 16%. 52.5% of the mothers were primigravida, 50% of the multigravid mothers had history of perinatal deaths, and 6.1% had ante-natal examination. Antenatal factors like lack of antenatal examinations, toxaemia of pregnancy and prolonged labour were major contributors to the mortality of neonates. **Conclusion**: Primigravid mothers, maternal anaemia, lack of antenatal examination, toxaemia of pregnancy and prolonged labour were the major contributors to the hypoxic ischemic encephalopathy. Early recognition of the risk factors and public health awareness needs to be addressed. Improvements in maternal health and regular antenatal checkups should be emphasised.

Key words: Hypoxic ischemic encephalopathy, risk factors, birth asphyxia.

INTRODUCTION

Birth asphyxia refers to not crying at birth. This definition is inadequate as it includes the healthy premature neonates and does not include those who have suffered intrauterine asphyxia and brain damage. So a better terminology for birth asphyxia is perinatal asphyxia, as brain insult secondary to hypoxia may start even before delivery of the baby. Birth asphyxia, more appropriately called hypoxic ischemic encephalopathy (HIE) remains one of the major causes of mortality and morbidity in neonates. There is no gold standard test for HIE-foetal distress, acidemia, Apgar score and other clinical markers of possible intrapartum injury have low positive predictive value. Brain hypoxia and ischemia due to systemic hypoxemia, reduced cerebral blood flow (CBF), or both are the primary physiological processes that lead to hypoxic-ischemic encephalopathy.[1–3]

Epidemiological measurement of intrapartum injury has moved from the process-based (e.g., prolonged labour) and symptom-based (e.g., Apgar score) to multiple indicator outcomes particularly neonatal encephalopathy, which refers to an abnormal neuro-behavioural state in the first few days of life and is most commonly related to intra partum insult.[4] Sarnat and Sarnat proposed a staging system useful in classifying the encephalopathy associated with birth asphyxia.[5] According to the classification stages 1, 2, and 3 correlates with the description of mild, moderate, and severe encephalopathy, respectively.

Almost 40% of deaths in children under age 5 years occur in the neonatal period.[6] The recent advances in better understanding the neonatal physiology and pathology has created any difference remains unknown. Reduction in the mortality due to HIE seen in the developed countries could be due to improved neonatal care, the mortality and morbidity due to HIE in the developing countries remains high. Reported global totals of neonatal deaths due to non-specific conditions of HIE vary from 0.7 million[7] to 1.6 million per year.[8] The data input and methods for obtaining these estimates are not available. Ninety nine percent of the deaths occur in the middle-and low-income countries because half of these deliveries take place at home without a skilled attendant and minority have access to the hospitals. In severe hypoxic-ischemic encephalopathy, the mortality rate is reportedly 25–50%. Most deaths occur in the first week of life due to multiple organ failure or redirection of care. Some infants with severe neurologic disabilities die in their infancy from aspiration pneumonia or systemic infections.[9] Incidence of prenatal asphyxia is about 3.3% in Pakistan[10] and is usually related to gestational age and birth weight. It occurs in 9% of infants less than 36 weeks gestational age and is 0.5% of infants more than 36 weeks of gestational age accounting for 20% of perinatal deaths (or as high as 50% deaths if still births are included).

The study was carried out to assess the incidence of birth asphyxia as limited data is available, risk factors of birth asphyxia, common presentations and

association of Apgar score with grades of hypoxic-ischemic encephalopathy.

MATERIAL AND METHODS

This study was carried out in the neonatal unit of Ayub Teaching Hospital, Abbottabad from September 2007 till September 2008. All neonates showing the neorobehavioural signs of HIE were included. A total of 181 neonates meeting the criteria were enrolled in the study using a specially designed Performa which included the antenatal factors, Apgar scoring, grading of the HIE and cranial ultrasound examination. Clinically manifested fits were recorded. Mothers were interviewed in detail using the Performa. Special emphasis was given on number of siblings and previous siblings' death in the neonatal period. Maternal conditions like anaemia, hypertension, and premature rupture of membranes, difficult labour and antenatal examinations were recorded. Premature rupture of membranes for more than 12 hours was enrolled in the study. Instrumental, normal vaginal delivery and Caesarean section were also taken into account. Neonates with meconium staining and congenital malformations were also included in the study. Still births were not included. Sarnat and Sarnat classification was used for grading of the HIE (Table-1). Depending on the neurobehavioral signs neonates were divided in three stages 1, 2 and 3.

Table-1: Sarnat and Sarnat classification of HIE grading

	STAGE- 1	STAGE-2	STAGE-3
Level of Consciousness	**Hyper alert**	**Lethargic or obtunded**	**Stuporous**
Neuromuscular Control			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive	Decreased or absent
Segmental myoclonus	Present	Present	Absent
Complex Reflexes			
Suck	Weak	Weak or absent	Absent
Moro	Strong; low threshold	Weak; incomplete; high threshold	Absent
Oculovestibular	Normal	Overactive	Weak or absent
Tonic neck	Slight	Strong	Absent
Autonomic Function	Generalised sympathetic	Generalised parasympathetic	Both systems depressed
Pupils	Mydriasis	Miosis	Variable; often unequal; poor light reflex
Heart Rate	Tachycardia	Bradycardia	Variable
GI Motility	Normal or decreased	Increased; diarrhoea	Variable
Seizures	None	Common; focal or multi-focal	Uncommon (excluding decerebration)
EEG Findings	Normal (awake)	Early: low-voltage continuous delta and theta Later: periodic pattern (awake) Seizures: focal 1-Hz spike-and-wave	Early: periodic pattern with Isopotential phases Later: totally isopotential
Duration	1–3 days	2–14 days	Hours to weeks

RESULTS

A total of 181 neonates classified according to Sarnat and Sarnat classification were enrolled into the study out of which 144 (79.6%) were males and 37 (20.4%) were females (Table-2).

One hundred and forty-one (77.9%) were full term, 16 (8.8%) were premature, 13 (7.2%) were having intrauterine growth retardation and 11 (6.1%) were postmature neonates. Forty-one (22.7%) of the neonates were having Grade 1, 70 (38.7%) were having Grade 2 and 70 (38.7%) were having Grade 3 encephalopathy. During the stay in hospital 22 (12.2%) were fed orally, 103 (56.9%) were given nasogastric feeds where as 56 (30%) were kept nil by mouth. At discharge from neonatal unit 81 (44.8%) were orally fed, 65 (35.9%) were on nasogastric tube feeding and in 35 (19.3%) feeding could not be established.

Twenty-five (13.8%) had Apgar score less than 4, 143 (79.0%) had Apgar score 4 to 7 and 13 (7.2%) had Apgar score >7. One neonate (1.4%) with Grade-1 HIE developed fits. Thirty-eight (55.1%) with Grade-2 whereas 30 (43.5%) with Grade-3 developed fits. Eight (19.5%) with grade-1, 37 (52.9%) with grade-2 and 57 (81.4%) with grade-3 HIE had documented cerebral oedema by cranial ultrasonography (Table-2). Maternal factors contributing to the HIE were also taken into account. One hundred and seventy (93.9%) did not have any antenatal examination. Ninety-five (52.5%) of the mothers were primigravida, 43 (23.8%) of the mothers were hypertensive, anaemia in 29 (16%), premature rupture of membranes was present in 24 (13.3%), difficult labour in 19 (10.5%), antepartum haemorrhage in 9 (5%), mismanaged at home 9 (5%), forceps application in 8 (4.4%), vacuum delivery in 5 (2.8%)

pre-eclampsia in 7 (3.9%) and in 28 (15.5%) no maternal cause was found. Sixty-two (34.3%) were delivered by Caesarean section (Table-4).

Twenty-nine (16%) neonates expired due to HIE and its complications in our unit. None of the neonate expired due to grade 1 or grade 2 HIE whereas 29 (41.4%) expired with grade 3 HIE out of which 22 (75.9%) were full term, 5 (17.2%) were premature, 1 (3.4%) was having intrauterine growth retardation and 1 (3.4%) was postmature. Seventeen (24%) of the expired neonates had history of maternal hypertension, 3 (10.3%) had maternal anaemia, 1 (3.4%) had pre-eclampsia, 2 (6.9%) had antepartum haemorrhage, 3 (10.3%) had premature rupture of membranes, 2 (6.9%) had difficult labour, 1 (3.4%) were mismanaged at home, 28 (96.6%) were un-booked cases, 3 (10.3%) had prolonged labour and 14 (48.3%) of the mothers had Caesarean section.

Birth anoxia was more common in neonates delivered vaginally $p<0.05$ (95% CI 0.000–0.010) than the infants who were delivered by Caesarean section. Apgar score (symptom based scoring system) poorly predicted the mortality associated with HIE $p>0.05$ (95% CI 1.607–9.894). Mortality due to HIE was better predicted by the multifactor neurobehavioral based system, 29 (100%) expired with grade-3 HIE $p<0.05$ (95% CI 0.481–0.713).

Table-2: Gender distribution of HIE

Gender	HIE-grades.			Total
	1	2	3	
Male	33 (80.50%)	57 (81.40%)	54 (77.10%)	144 (79.60%)
Female	8 (19.50%)	13 (18.60%)	16 (22.90%)	37 (20.40%)
Total	41 (100%)	70 (100%)	70 (100%)	181 (100%)

Table-3: Features associated with HIE grades

	HIE-grades			Total
	1	2	3	
Bulging Fontanel	9 (11.4%)	27 (34.2%)	43 (54.4%)	79 (100%)
Fits	1 (1.4%)	38 (55.1%)	30 (43.5%)	69 (100%)
Comatose	1 (1.5%)	2 (3.1%)	62 (95.4%)	65 (100%)
Brain oedema	8 (7.8%)	37 (36.3%)	57 (55.9%)	102 (100%)

Table-4: Maternal factors contributing to HIE

	HIE grades			Total
	1	2	3	
Hypertension	9 (20.9%)	20 (46.5%)	14 (32.6%)	43 (100.0%)
Pre eclampsia	1 (14.3%)	4 (57.1%)	2 (28.6%)	7 (100.0%)
Anemia	4 (13.8%)	15 (51.7%)	10 (34.5%)	29 (100.0%)
APH[(a)]	3 (33.3%)	1 (11.1%)	5 (55.6%)	9 (100.0%)
PROM[(b)]	7 (29.2%)	6 (25.0%)	11 (45.8%)	24 (100.0%)
Mismanaged at home	0 (.0%)	6 (66.7%)	3 (33.3%)	9 (100%)
Vacuum	0 (.0%)	4 (80.0%)	1 (20.0%)	5 (100.0%)
Forceps	3 (37.5%)	3 (37.5%)	2 (25.0%)	8 (100%)
Prolonged labour	3 (17.6%)	4 (23.5%)	10 (58.8%)	17 (100.0%)
un-booked cases	38 (22.4%)	65 (38.2%)	67 (39.4%)	170 (100.0%)
C- section	17 (27.4%)	19 (30.6%)	26 (41.9%)	62 (100.0%)

[(a)]ante-partum haemorrhage, [(b)]premature rupture of membranes

Table-5: Maturity of neonate and associated mortality

Maturity of neonate	HIE- grades			Expired
	1	2	3	
Full term	33 (23.4%)	57 (40.4%)	51 (36.2%)	22 (75.8%)
Premature	3 (18.8%)	6 (37.5%)	7 (43.8%)	5 (17.2%)
IUGR	2 (15.4%)	3 (23.1%)	8 (61.5%)	1 (3.4%)
Post-mature	3 (27.3%)	4 (36.4%)	4 (36.4%)	1 (3.4%)

DISCUSSION

The clinical diagnosis of birth asphyxia, along with the closely related conditions of hypoxic ischemic encephalopathy and newborn encephalopathy, is recognized as an important cause of morbidity and mortality in newborn infants.[11–15] Birth asphyxia or HIE is a global issue especially in the developing countries like Pakistan. Mortality and morbidity due to HIE remains high despite the recent advances in better understanding of the pathophysiology of the newborn. A lot of work has been done but local data is unavailable. It is a treatable problem and early identification and intervention is necessary to prevent the long term sequelae of HIE.

Two recent hypothermia trials provided updated information on mortality and the incidence of abnormal neuro-developmental outcomes infants with moderate to severe hypoxic-ischemic encephalopathy.[16,17] In these trials, 23–27% of infants died prior to discharge from the neonatal ICU (NICU), whereas the mortality rate at follow-up 18–22 months later was 37–38%. Mortality in our unit was 16%. Actual mortality would be higher as the study does not include those infants who do not have the access to the advanced medical facilities and the still births. The difference noted in the mortality in our study as compared to other Pakistani studies could be due to Pakinsonian bias.

Although no gender predilection to birth anoxia is noted.[18] The study shows male preponderance with a 4:1 ratio. A number of antepartum risk factors are identified, IUGR, severe pre-eclampsia, post-dates, abnormal appearance of the placenta, maternal thyroid disease, pre-conceptual factors including maternal unemployment, family history of seizures or neurological disorder, and infertility treatment. Among antepartum risk factors, intrauterine growth restriction was the strongest (relative risk 38.2, 95% CI 9.4–154.8).[19] In a small hospital-based case-control study, intrauterine growth restriction was associated with a 17–20 fold increased risk of neonatal encephalopathy.[20] The major antenatal contributing factor leading to HIE was maternal hypertension in our study. Other factors like maternal anaemia, premature rupture of membranes and lack of antenatal examination also contributed significantly to the development of HIE. Earlier surgical

intervention for delivery was associated with reduced incidence of HIE.

Preterm infants can also suffer from hypoxic-ischemic encephalopathy, but the pathology and clinical manifestations are different. Most often, the condition is noted in infants who are term at birth. The symptoms of moderate-to-severe hypoxic-ischemic encephalopathy are almost always manifested at birth or within a few hours after birth.[18] Full terms were more prone to development of HIE in our study as compared to premature and postmatures, which could be attributed to lack of antenatal examinations and early identification of HIE.

The HIE correlates well with the neurological classification rather than the Apgar score. However fits were seen in one neonate with grade 1 HIE, these were due to hypocalcaemia. All the infants who expired were having grade 3 HIE, developed multiorgan complications.

CONCLUSION

Despite major emphasis on the mother and child health programme from the government, mortality and morbidity due to HIE remains high as compared to the developed nations. Proper training of the medics and paramedics especially working in peripheries is required for early identification of birth anoxia and appropriate intervention should be stressed in the mother and child health programmes. Public health awareness needs to be improved. Regular antenatal check-up and referral to appropriate centres should be encouraged. It should be ensured by the Executive Health Officers that health facilities where high risk infants are delivered, proper resuscitation facilities are available.

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