Hypoxic ischemic encephalopathy

Incidence and risk factors in North Western Saudi Arabia

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ABSTRACT

Objectives: To find the incidence, early outcome and the associated risk factors of hypoxic ischemic encephalopathy (HIE) in Madina Al-Munawara, Kingdom of Saudi Arabia (KSA) and compare it with other centers. Also, to find out whether any of these risk factors are preventable.

Methods: We conducted a case controlled study of HIE in Madina Maternity and Children's Hospital, Madina Al-Munawara, KSA over a one-year-period, from June 1995 to May 1996. All the inborn term babies without major congenital malformations that developed HIE were included in the study. A term baby born next to the index case was taken as a control for each case. Data was collected for possible risk factors. The incidence of risk factors in the 2 groups was analyzed and compared statistically.

Results: A total of 70 cases of HIE were recorded in the study period giving an incidence of 5.5 cases per 1000 term births. This incidence is lower compared to many developing countries and comparable to other centers. Among the maternal factors, being a primigravida, with no antenatal care, presence of pregnancy induced hypertension, and complications of pregnancy were significantly higher in the study population. Similarly, the frequency of prolonged 2nd stage of labor, antepartum hemorrhage, delivery by emergency cesarean section (CS) or the use of instruments was significantly higher in the study group. Babies suffering from intrauterine growth retardation and male sex were also at significantly higher risk. The average hospital stay of the cases was 12 days. Twelve cases of severe HIE died before discharge from the hospital giving an overall mortality rate of 17.1%.

Conclusion: The incidence of HIE and birth asphyxia reported in different studies varies widely. The incidence in our hospital is much lower than reported in many studies from developing countries. The important associated risk factors includes being a primigravida mother, lack of antenatal care, pregnancy induced hypertension, prolonged 2nd stage of labor, delivery by use of instruments or emergency CS and intrauterine growth retardation. Improvement in antenatal care and intra-partum monitoring can decrease the incidence of HIE. The threshold for intervention in cases with fetal distress needs to be lower.

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Hypoxic ischemic encephalopathy (HIE) is an important cause of permanent damage to central nervous system cells, which may result in neonatal death or manifest as cerebral palsy or mental deficiency. Fifteen to 20% of the infants with HIE die in the neonatal period and 25-30% of survivors develop permanent neurodevelopmental abnormalities. Death and disability may sometimes be prevented through

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symptomatic treatment with oxygen or artificial respiration and the correction of associated multiorgan system dysfunction.[1] Asphyxia usually refers to an insult accompanied by decreased oxygen delivery to the fetal or neonatal brain. Postnatal insults account for only 10% of cases.[2] In the developing world, the reported incidence of perinatal asphyxia and HIE is high, and it continues to be a major cause for neonatal morbidity and mortality.[3] In Britain, approximately one full term baby per thousand births dies or is severely disabled as the result of birth asphyxia.[4] Hypoxic ischemic encephalopathy contributes to 10-20% of cerebral palsy.[5] Perinatal hypoxic ischemic cerebral injury is an extremely important medicolegal problem as well.[6] Perinatal HIE can be divided into 3 stages of severity that have a predictable outcome.[7] Unfortunately, the stage of HIE can be assigned only when the HIE is established and no intervention can change the outcome appreciably. Early therapeutic intervention in the asphyxiated babies may be important to decrease cerebral injury and prevent complications. Therefore, there remains a need to have early markers of asphyxia such as features of fetal hypoxia, depressed Apgar scores, delay in establishing respirations or evidence of significant metabolic acidosis on samples of umbilical cord blood. To our knowledge, there is no published study on HIE from the Kingdom of Saudi Arabia (KSA) and the incidence in this country is unknown. One study reported that 1.4 per 1000 births die due to perinatal asphyxia in KSA.[8] We come across cases of HIE frequently. This gave us an impression that the incidence of HIE was high in our hospital and prompted us to conduct the present study with the aim: 1. To find the incidence and early outcome of HIE in our hospital and compare it with other centers. 2. To find the risk factors associated with HIE and 3. To study if any of these risk factors could be prevented.

Methods. We conducted a case controlled study of patients with different stages of HIE in Madina Maternity and Children's Hospital (MMCH), Madina-Al-Manawara, KSA. This is the only Maternity and Children's Hospital in the region of Madina-Al-Munawara. The hospital has 15,000-16,000 deliveries a year. The study spanned over a period of one year from June 1995 to May 1996. Babies with a gestational age of 37 weeks or more that were admitted with the clinical picture of HIE at birth on the basis of changes in the level of consciousness, muscle tone, neonatal and deep tendon reflexes and development of seizures was included. The cases were assessed and followed closely to assign a stage of HIE according to the criteria of Sarnat and Sarnat[7] without electroencephalogram. Babies with major congenital malformations and those born outside our hospital were excluded from the study. All the cases were subjected to the standard management of perinatal asphyxia. For the control group, a term singleton baby without major malformations born next to the index case was taken for each patient. Information was collected for the possible risk factors for HIE such as maternal age, parity, presence or absence of antenatal care, maternal hypertension, antenatal bleeding, diseases related to pregnancy and other chronic illnesses. Data was also collected on the mode of delivery, presence of meconium or blood stained amniotic fluid, prolonged 2nd stage of labor, fetal heart rate monitoring by auscultation and cardiotocogram (CTG), any complications occurring during delivery and Apgar score at 1, 5, and 10 minutes. Information regarding umbilical arterial pH and other organ system involvement was also recorded if available. The gestational age was recorded from the last menstrual period and confirmed by clinical assessment by the New Ballard score.[9] Babies weighing less than 10th centile for age were labeled small for gestational age and those weighing more than 90th centile were labeled large for gestational age. Similar information was collected regarding the controls by reviewing the maternal files and interviewing the mother. The incidence of risk factors between the 2 groups was compared statistically. Proportions were compared by Chi square test and Fisher Exact test if needed. The continuous normally distributed variables were compared by Student's t-test.

Results. Out of 15,005 births 12,730 babies were born at 37 weeks or more of gestational age. During the same period 70 term babies with the diagnosis of HIE fulfilling our inclusion criteria were admitted to the neonatal intensive care unit (NICU) giving an incidence of 5.5 cases per 1000 term births. The number of cases with mild HIE was 20 (29%), those with moderate HIE 18 (26%) and 32 (45%) babies had severe HIE.

Maternal risk factors (Tables 1 & 2). The mean age of mothers in the study group and that in the control group was comparable. The overall mean parity of the mothers in the HIE group was 2.98 and that in the control group was 3.9. When the mothers were grouped into primigravidas, gravida 2-5 and gravida >5 the differences in parity were evident. Twenty five (36%) in in the study group and 13 (19%) in the control group did not have antenatal care during the present pregnancy. Presence of maternal hypertension (diastolic blood pressure more than 85 mm Hg) was seen in 13 (19%) mothers in the study group as compared to 5 (7%) in the control in the group group. Saudi nationals were 91% in the study group and 76% in the control group.

Labor and delivery (Tables 3 & 4). Sixty (86%) cases in the study group and 67 (96%) in the control group had vertex presentation. This difference is statistically significant. When applied to the sub groups the difference was significant in the severe HIE group only. The incidence of breech presentation was significantly higher in the study group. Twenty-eight of the cases had meconium stained amniotic fluid as compared to only 8 in the control group. Twelve mothers in the study group had antepartum hemorrhage: 4 from placenta previa and 8 from abruptio placentae. Seven of these cases belonged to the severely

Table 1 - Maternal risk factors of all babies as a single group.

Variable	Study group N=70 n (%)	Control Group N=70 n (%)	p-value
Age (yrs) mean (SD)	26.05 (6.9)	26.33 (6.1)	0.799*
Parity mean (SD)	2.98 (3.4)	3.9 (2.5)	0.920*
Primigravida	23 (33)	10 (14)	<0.01†
Gravida 2-5	26 (37)	39 (56)	<0.05†
Gravida >5	21 (30)	21 (30)	<1*
No antenatal care	25 (36)	13 (19)	<0.025†
Pregnancy induced hypertension	13 (19)	5 (7)	<0.05†
Multiple pregnancy	2 (3)	1 (1)	<1.0*
Complications of pregnancy	11 (16)	6 (9)	<0.05*
Saudi	64 (91)	53 (76)	<0.025†

* - non significant, † - significant, yrs - years

Table 2 - Maternal risk factors according to stage of hypoxic ischemic encephalopathy.

Variable	Stage I HIE N=20 n (%)	Stage II HIE N=18 n (%)	Stage III HIE N=32 n (%)	Control group N=70 n (%)
Age (yrs) mean (SD)	26.2 (6.3)*	26.5 (7)*	25.5 (7.3)*	26.33 (6.2)
Parity mean (SD)	2.6 (6.3)*	3.16 (3.6)*	3.187 (3.5)*	3.9 (2.5)
Primigravida (%)	6 (30)*	7 (39)†	10 (31)†	10 (14)
Gravida 2-5 (%)	9 (45)*	3 (17)†	14 (44)*	39 (56)
Gravida >5 (%)	5 (25)*	8 (44)†	8 (25)*	21 (30)
No antenatal care (%)	4 (20)*	8 (44)*	13 (41)†	13 (19)
Pregnancy induced hypertension (%)	3 (15)*	4 (22)*	6 (19)*	5 (7)
Multiple pregnancy (%)	1 (5)*	0 (0)	1 (3)*	1 (1)
Complications of pregnancy (%)	4 (20)*	3 (17)*	4 (13)*	6 (9)

* - not significant, † - significant, yrs - years,
HIE - hypoxic ischemic encephalopathy

Table 3 - Labor and delivery factors of the study and control groups.

Variable	Study group N=70 n (%)	Control Group N=70 n (%)	P-value
Presenting part			
Vertex	60 (86)	67 (96)	<0.05†
Breech	9 (13)	3 (4)	<0.05†
Brow	1 (1)	-	-
MSAF	28 (40)	8 (11)	<0.001†
Fetal bradycardia	49 (70)	14 (20)	<0.001†
Abnormal fetal heart rate pattern	38/44 (86)	11/23 (48)	<0.001†
Prolonged 2nd stage	32 (46)	4 (6)	<0.0001†
Antepartum hemorrhage	12 (17)	4 (6)	<0.035
Cord prolapse	3 (4)	2 (3)	0.317*
Mode of delivery			
Normal	28 (40)	58 (83)	<0.001†
Breech	6 (9)	1 (1)	0.051*
Instrumental	21 (30)	3 (4)	<0.001†
Emergency CS	15 (21)	6 (9)	<0.05
Elective CS	-	4 (6)	-

* - not significant, † - significant, MASF - meconium stained amniotic fluid, CS - cesarean section

Table 4 - Factors related to labor and delivery according to the stage of hypoxic ischemic encephalopathy.

Variable	Stage I HIE N=20 n (%)	Stage II HIE N=18 n (%)	Stage III HIE N=32 n (%)	Control group N=70 n (%)
Presenting part				
Vertex	17 (85)*	16 (89)*	27 (84)†	67 (96)
Breech	3 (15)*	2 (11)*	4 (13)*	3 (4)
Brow	-	-	1 (3)	-
MSAF	7 (35)†	8 (44)†	13 (41)	8 (11)
Fetal bradycardia	13 (65)†	13 (72)†	23 (72)	14 (20)
Abnormal fetal heart rate pattern	14/16 (88)†	10/12 (83)†	14/16 (88)	11/23 (48)
Prolonged 2nd stage	6 (30)†	7 (39)†	19 (59)†	11/23 (48)
Antepartum hemorrhage	2 (10)*	3 (17)*	7 (22)†	4 (6)
Cord prolapse	1 (5)*	1 (6)*	1 (3)*	2 (3)
Mode of delivery				
Normal	9 (45)†	8 (44)†	11 (34)†	58 (83)
Breech	3 (15)†	1 (6)*	2 (6)*	1 (1)
Instrumental	4 (20)*	6 (33)†	11 (34)†	3 (4)
Emergency CS	4 (20)*	3 (17)*	8 (25)	6 (9)
Elective CS	-	-	-	4 (6)

* - not significant, † - significant, MASF - meconium stained amniotic fluid, CS - cesarean section, HIE - hypoxic ischemic encephalopathy

Table 5 - Comparative incidence of perinatal asphyxia and hypoxic ischemic encephalopathy.

Country	Year of publication	Incidence	Criteria for diagnosis
Nepal[3]	1992	36.3/1000 live births	-
India[10]	1997	22.5/1000 live births*	Encephalopathy and history of asphyxial episode
Nigeria[11]	1991	26.5/1000 live births	Encephalopathy
USA[13]	1980	5.19/1000 term deliveries	Encephalopathy
Kuwait[20]	1990	9.4/1000 term deliveries	Encephalopathy and history of asphyxial episode
Western Australia[21]	1998	3.8/1000 term deliveries†	Encephalopathy
Nepal[23]	2000	6.1/1000 live births	Encephalopathy
Present study	2002	5.5/1000 term deliveries	Encephalopathy

* - included still births only, † - only moderate and severe cases of hypoxic ischemic encephalopathy were included

asphyxiated group. Fetal bradycardia was noted in 49 (70%) cases as compared to only 14 (20%) in the control group. Monitoring by cardiotocography (CTG) was available only in 44 (63%) cases with 38 (86%) abnormal. Of these, 30 (68%) showed fetal bradycardia, 17 (39%) showed delayed deceleration, 9 (20%) had decreased beat to beat variability and only 6 (13%) were normal. Only 23 of the control deliveries had CTG available and 11 (48%) of them were abnormal. Prolonged 2nd stage of labor was seen in 32 (46%), associated birth trauma in 13 (19%), cord prolapse in 3 (4%), rupture uterus in one and cord around neck in one patient. The first most common mode of delivery was normal spontaneous vaginal deliveries but instrumental deliveries and emergency CS had a higher rate in the study group. Fifty-one (73%) deliveries were conducted by the physicians and 19 (27%) were conducted by midwives mainly because these were not recognized to be high risk before delivery or the physician was not available. The mean Apgar score at 5 minutes for the babies with mild HIE was 4.4, for babies with moderate HIE 3.7 while for those with severe HIE was 2.69 compared to 8.78 in the control group. Mean umbilical cord pH (available in 47 cases only) was 7.05 in the study group and 7.25 in the control group.

Neonatal factors. Forty-five of the cases were males and 25 were females giving a male to female ratio of 1.8 to one. The mean gestational age of the cases was 39.1 weeks and that for the control group was 39.2 weeks. The birth weight ranged from 1600-3950 gms. With a mean birth weight of 2947 gms. Eight (11%) babies in the study group and 2 (3%) in the control group were small for gestational age. Convulsions occurred in 10 (56%) babies with moderate HIE and in 21 (66%) babies with severe HIE. Associated morbidity such as meconium aspiration syndrome (13), birth trauma (13) and sepsis occurred in many cases in the study population. Acute renal failure occurred in 17 (53%) of cases with severe HIE but in only 4 (22 %) of cases with moderate degree of HIE and none of those with mild HIE. Hemorrhagic manifestation occurred in 13 (41%) cases with severe HIE but in only 2 cases with mild and moderated HIE. Out of 32 cases with severe HIE, 11 (34%) developed persistent pulmonary hypertension of newborn. There was no death in mild and moderate HIE groups, however, 12 out of 32 (37.5 %) cases with severe HIE died before discharge from the hospital. Eight of the deaths occurred at less than 7 days of age. Fourteen (20%) cases with severe and moderate HIE had abnormal neurological findings at the time of discharge in the form of impaired consciousness, abnormal muscle tone, inability to suck and swallow and paralysis of one or more limbs. The range of hospital stay was 1-85 days with a mean of 12.3 (standard deviation 13.77) days. In other words, 2.5 (5%) of the NICU beds were occupied by cases of HIE on any particular day.

Discussion. The reported incidence of perinatal asphyxia and HIE in the developing world is varied and high **(Table 5)**. However, some of these studies that recorded a high incidence of HIE included all the live born babies in their study while we included only term or post term babies.[3,10,11] The use of different criteria makes the comparison between different studies difficult.[7,10,12-16] The high incidence of perinatal asphyxia may present heavy social and economic cost. It presents a particular burden for women both in terms of caring for the handicapped child and early next pregnancy after the death of a baby.[17] The recent recommendation by the committee on Fetus and Newborn, American Academy of Paediatrics and Committee on Obstetric Practice, American College of Obstetricians and Gynecologist that "an infant who has had asphyxia proximate to

delivery that is severe enough to result in acute neurological injury should demonstrate umbilical arterial pH of <7, Apgar score of 0-3 at or beyond 5 minutes, evidence of multiorgan failure and encephalopathy.[18] This recommendation if followed is going to help in making the criteria for diagnosis of birth asphyxia uniform and comparison between different studies easier but many of the cases with clinical picture of HIE may not fulfill these criteria.[19] Our incidence of 5.5 cases per 1000 term births is less than the incidence reported from other developing countries **(Table 5)**. From Kuwait a study in 1990[20] reported an overall incidence of 9.4 per 1000 term births which, though higher than our study, the incidence of stage III HIE was similar to our study namely 2.6 per 1000 births. A recent study from Western Australia[21] reported an incidence of 3.8 cases of moderate and severe HIE per 1000 term births. If cases with mild HIE are excluded our incidence is similar. The high incidence of perinatal asphyxia and HIE reported over the years is mainly due to the less than optimal obstetric care available in the developing and underdeveloped nations and loose criteria used to diagnose asphyxia. Many of our cases were referred high risk mothers from other hospitals and this could lead to a relatively high incidence of HIE in our hospital. The average maternal age of 26.05 years did not differ significantly from the control group. This excludes the role of teenage pregnancy as a cause of HIE, at least in full term births in our community. Similar observations were made by others.[20,22] The significantly higher number of primigravida mothers in the study group has also been found by other authors.[20,21,23,24] Since the first delivery is more difficult than the subsequent one. This points to the importance of intrapartum factors in the causation of HIE. Gravida 2-5 were significantly less in our study population. This indicates the relatively less risk of asphyxia in this group. Mothers >5 gravida were significantly higher in the subgroup with moderate HIE only. Decreasing risk with increasing parity was also noticed by other authors.[21] Mothers without antenatal care were significantly higher in the study population. When applied to subgroups it was significant only in cases with severe HIE. Similar observations have been made by others.[23] Vertex presentation was significantly low, and breech presentation was significantly higher in our cases.

The number of normal deliveries was significantly less (40%) in the cases as compared to controls (83%). Instrumental deliveries and delivery by emergency cesarean section (CS) were significantly higher than the control group. None of the babies in the study group was delivered by an elective CS. This indicates that CS were carried out only when the initially chosen method of delivery failed. Similar observations were made by others as well.[21,23] In a retrospective review, Badawi et al[22] observed that if the similar antepartum indications were applied the rate of elective CS was significantly low in the mothers whose babies developed neonatal encephalopathy. However, the high incidence of emergency CS in our patients could be also due to other reasons like lack of antenatal care, delayed referral, failure to identify the risk to the infant earlier and refusal of CS by the family at an earlier stage. Although the overall rate of cesarean delivery was higher in the study group it was still lower than that reported by others.[21] The observation that emergency CS was more common in the HIE group does not mean a causal relation. In fact the CS was carried out most often for fetal distress which in itself may mean ongoing asphyxia. Other authors also found high incidence of perinatal asphyxia if the CS was carried out for a high risk indication.[13] Breech deliveries were not significantly high. Fewer number of breech deliveries compared to breech presentations was due to the fact that the others were delivered by emergency CS. We found a significantly higher rate of prolonged 2nd stage of labor in 32 (46%) cases much like other authors.[10,24,25] The high incidence of meconium stained amniotic fluid in the study population may be an indication of an ongoing asphyxial process in the fetus and should alert the obstetrician to assess the baby by other tests and intervene appropriately. Fetal bradycardia as recorded by clinical auscultation was significantly higher in the study group. This does emphasize the importance, sensitivity and the need for clinically monitoring the fetal heart rate during labour. Fetal heart rate pattern by cardiotocography was available in only 44 (63%) of cases and 23 (33%) controls. Most (86%) of the CTG's in the HIE group and 48% in the control group were abnormal and the difference was highly significant. This indicates that CTG although very sensitive is a less specific indicator of fetal distress but in combination with other risk factors could be a useful predictor of asphyxia. Many of our cases occurred as surprises at delivery with no recorded features of fetal distress. This also contributed to a high proportion of deliveries (27%) being conducted by midwives. Such observations have been made by other authors as well.[16] It has been seen that the reduction of asphyxia, morbidity and mortality in this group would require increased monitoring during labor and delivery but at a high cost.[16] The mortality was low in our study compared to many other studies. It could be as we offered aggressive support to all our cases while some others did not.[20]

In conclusion, HIE continues to be an important cause of morbidity and mortality in MMCH, KSA. The incidence is lower than many other developing and neighboring countries and is comparable to some advanced centers. The mortality is relatively low. There is a definite need to follow uniform criteria for diagnosis and identical terminology that can make comparison between different studies possible. Among the maternal factors being a primigravida, having hypertension and having no antenatal care are high risk factors for HIE. Similarly antepartum hemorrhage, prolonged 2nd stage of labor, meconium stained amniotic fluid, abnormal fetal heart rate pattern, delivery by emergency CS, and

instrumental deliveries have a high association with HIE. Similarly, babies with intrauterine growth retardation are more likely to suffer HIE. The incidence of HIE can be decreased by improving the antenatal care and monitoring of mothers in labor. Carrying our early CS on mothers with fetal distress may decrease the incidence of HIE. There is need for research into new medications and treatment modalities to decrease the morbidity and mortality from HIE.

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