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## Risk factors for development of hypoxic-ischemic encephalopathy in Abha City - Southwestern Saudi Arabia

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### Summary

Hypoxic ischaemic encephalopathy (HIE) is an important cause of permanent damage to central nervous system, which may result in neonatal death or manifest as cerebral palsy or mental deficiency. A matched-case control study of neonatal encephalopathy was conducted in Abha General Hospital, Abha City, Saudi Arabia to determine some possible risk factors for HIE. A total of 57 term infants with clinical evidence of HIE at birth were recruited over a period of 3 years, and compared with the same number of a control group of normal newborns. The cumulative incidence of HIE was 4.9 per 1000 live births (95% CI: 3.1 to 6.3). Moderate or severe encephalopathy occurred in about 63% of all infants, with seizures in 67% of these. All the 57 (100%) infants with encephalopathy required one or more of resuscitation measures compared with only 8 (14%) of the control. Significant antepartum risk factors for HIE include: primiparity (OR=3.13), nonaccessibility to antenatal care (OR=1.89), and pregnancy-induced hypertension (OR=2.13). Significant possible labour and delivery risk factors include: noncephalic presentation (OR=2.76), antepartum haemorrhage (OR=4.32), instrumental delivery (OR=7.91), and prolonged second stage of labour (OR=6.67). In conclusion, both antepartum and intrapartum factors are important in the causation of HIE in Abha city. Improvement of both antenatal care and care during delivery is a necessity.

**Keywords:** *Hypoxic ischaemic encephalopathy, delivery, neonate, antepartum risk factors, Saudi Arabia*

### Resume

L'encéphalopathie hypoxique-ischémique (EH) est une cause importante des dommages permanents du système central cerveau, qui peut aboutir à la mort néonatale ou se manifester comme dans la paralysie agitante ou la déficience mentale. Une étude du cas assorti de l'encéphalopathie néonatale a été menée à l'hôpital Général Abha à Abha-city en Arabie Saoudite pour déterminer quelques facteurs de risque possible du EHI. Un total de 57 enfants à termes avec un test en laboratoire d'EHI pendant l'accouchement ont été recrutés pendant une période de 3 ans, et comparés avec le même nombre d'un groupe témoin de nouveaux-nés normaux. Le taux cumulative d'EHI était 4,9 par 100 naissances (95% CI; 3,1 à 6,3). L'encéphalo-

pathie modérée et grave s'est produit chez à peu près 63% de tous les enfants, avec des crises dans 67% de tous les enfants, avec des crises dans 67% de ces cas. Tous les 57 enfants (100%) souffrant de l'encéphalopathie ont requis une ou plus de mesures de ressuscitation comparé à seulement 8 (14%) du contrôle. Les facteurs de risque antepartum considérable d'EHI inclus: La primiparité (OR=3.13), la non-accessibilité aux soins prénataux (OR=2.13). Les facteurs de risque possible qui sont considérables pendant les contractions et l'accouchement inclus: la présentation non-cephalique (OR=2.76), l'hémorragie antepartum (OR=4.32), l'accouchement à l'aide d'instruments (OR=7.91), et prolongé second stage of labour (OR=6.67). En conclusion, les facteurs sont importants dans la causalité d'EHI dans la ville. L'amélioration des soins prénataux et des soins pendant l'accouchement est une nécessité.

### Introduction

Asphyxia usually refers to an insult accompanied by decreased oxygen delivery to all parts of the body including brain, heart, gut, adrenal and kidneys. The incidence of HIE is significantly higher in developing countries. Nearly 4 million newborns suffer moderate to severe HIE, with at least 800,000 dying and at least an equal number developing sequelae such as epilepsy, mental retardation, cerebral palsy and learning disabilities [1-3]. HIE contributes to 10%-20% of cerebral palsy. Perinatal hypoxic ischaemic cerebral injury is an extremely important medico legal problem as well [4].

In developing countries, HIE may present as social problems with tremendous economic costs [1,5]. It presents a particular burden for women in terms of caring for handicapped children and if affected infant dies, the traditional spacing mechanism of breast feeding and abstinence are halted and this increases the exposure to risk of another pregnancy with a short birth interval [6-8].

In Abha General Hospital, Abha City, Southwestern Saudi Arabia we carried out follow-up of many cases of neonatal encephalopathy secondary to birth asphyxia and we observed the social burden as well as economic cost to families with handicapped children. We assume in our locality that most of handicapped children are sequelae of HIE which is secondary to perinatal asphyxia, though unfortunately we do not have scientific data to substantiate this. Hence, this study was undertaken to: (1) determine the avoidable risk factors of HIE, especially intrapartum and maternal factors, (2) estimate the cumulative incidence, and (3) identify the early outcome associated with HIE.



### Materials and methods

Abha, the capital city of Asir province with population of 1,200,000 in southwestern Saudi Arabia; it lies about 2250 km from the northern borders of the Republic of Yemen. Because of the abundance of water and the fertile soil, agriculture is the main occupation in the region of Abha. Industrial activity in the region includes the production of construction materials, timber processing, maintenance workshops and other secondary industries.

The inhabitants enjoy many modern facilities but retain the dietary and social habits of rural communities. Meat, chicken and rice constitute the major dietary items. Health services are provided by Primary Health Care Centres (PHCCs). Abha General Hospital is located in the middle belt region of the city and it is the only Maternity Hospital in Abha City. It has active obstetric and neonatal services. The Neonatal Special Care Unit has over 3500 live births annually. It has twenty five beds for intensive care.

This is a retrospective matched-case control study, all infants delivered at Abha General Hospital, over three year periods from December 2000 to December 2003, who were full term (37-42 completed weeks of gestation), with clinical evidence of neonatal encephalopathy at birth were included in this study. Preterm infants (less than 37 weeks), and infants with major birth defects or evidence of congenital or early neonatal infection were excluded to avoid these confounding factors. The controls were the first singleton term infant born after each asphyxiated patient, provided that the infant met the criteria of well newborn baby and did not have any features of HIE.

HIE in this study was defined as the presence of an asphyxial neurological syndrome preceded by an asphyxial event [7,8]. Minimal criteria for an asphyxial syndrome were alterations in the baby's state of consciousness and abnormalities of muscle tone. Criteria for an asphyxial event were the presence of one or more of the following: fetal bradycardia of less than 80 beats per minute for at least 60 min.; late deceleration as seen by continuous fetal heart monitoring; Apgar score of less than 6 at 5min. after delivery; need for positive pressure ventilation (bag and mask or endotracheal tube) for at least two minutes after delivery; a pH of less than 7.20 within the 1st hour of life.

The severity of encephalopathy was graded based on a modification of the system set forth by Fenichel<sup>7</sup> as follows: infants with mild (grade I) were irritable or hyper alert, with either mild hypotonia or poor sucking; infants with moderate (grade II) had seizures, marked abnormalities of tone, and requiring tube feeding; and infants with severe (grade III) encephalopathy had prolonged and persistent seizures, severe hypotonia and failure to maintain spontaneous respiration.

Data from mother's and infant's charts were recorded in standard forms, and these include, details of prenatal history and the possible risk factors for HIE, such as maternal age, parity, presence or absence of ante-

natal care, maternal hypertension, antenatal bleeding, diseases related to pregnancy and other chronic illnesses. Gestational age was calculated from the mother's menstrual date and uterine size, and confirmed by postnatal assessment of infants. Amount of amniotic fluid, placental abruption or praevia, and augmentation of labour with prostaglandin, length of labour, artificial or premature rupture of membranes, mode of delivery, presentation, presence of meconium, or blood stained amniotic fluid, fetal heart rate monitored by cardiotocogram (CTG) and any complications occurring during delivery and Apgar score at 1 and 5 minutes, umbilical arterial pH, and information regarding presence of umbilical cord prolapse were recorded. The infant's sex, date of birth, and birth weight (g) and associated neonatal complications and mortality were also obtained.

### Data analysis

The data was analyzed on the Statistical Package for Social Sciences (SPSS) Version 10 and Epi-Info (version 6.02) softwares, on IBM computer of the College of Medicine, King Khalid University, Family and Community Medicine Department. The Student's t-test was used to assess significance between two means of the continuous variables of age, length of labour, birth weight and Apgar scores. Chi-squared test with or without Yates' correction as well as Fisher's exact tests were used as appropriate for the difference between two proportions to ascertain the significance between the rates of two categorical variables. Multivariate logistic regression analysis, was used to model the presence of birth asphyxia as a function of some risk factors. The odd ratios for occurrence of the disease in association with one variable in the simultaneous presence of other variables were computed. Less than 5% level was chosen as the level of significance.

### Results

There were 11,746 live births at Abha General Hospital between December 2000 and December 2003. Of these, 57 infants had hypoxic ischaemic encephalopathy. The cumulative incidence of neonatal encephalopathy was 4.9 per 1000 live births (95% CI : 3.1 to 6.3). Table 1 gives grading of HIE in these encephalopathic infants. Moderate or severe encephalopathy occurred in about 63% of all infants, with seizures in 67%. Overall, 12 encephalopathic infants died before hospital discharge, giving an estimated

**Table 1:** Grading of HIE in 57 newborns with HIE

Variable	No. (%)
Grade of encephalopathy	
Grade I	21 (36.8)
Grade II	23 (40.4)
Grade III	13 (22.8)



early neonatal case fatality of 21%. Persisting clinical abnormalities of tone, suck, or conscious level were evident in 73% of survivors at discharge (table 2).

**Table 2:** Outcome in 57 newborns with hypoxic ischaemic encephalopathy (HIE)

Variable	No. (%)
Death before discharge	
Yes	12 (21.1)
No.	45 (78.9)
Neurologic condition of survivors*	
Normal	12 (26.7)
Abnormal tone	16 (35.5)
Poor sucking reflexes	5 (11.1)
Abnormal tone, suck, and conscious level	12 (26.7)

**Table 3:** Host-related risk factors of HIE

Features	Study group n (%)	Control group n (%)	P value
<i>Resuscitation</i>			
None	-	49 (86)	
Oxygen	12 (21)	5 (9)	
Ambu bag	20 (35)	3 (5)	<0.001
Intubations	10 (18)	-	
Cardiopulmonary resuscitation	15 (26)	-	
<i>Apgar score at 1 min.</i>			
0-3	46 (81)	4 (7)	
4-6	11 (19)	47 (82)	<0.001
7-10	-	69 (11)	
<i>Apgar score at 5 min.</i>			
0-3	29 (81)	-	
4-6	28 (49)	7 (12)	<0.001
7-10	-	50 (88)	
Birthweight (gram)	3322 (436)*	3390 (502)*	0.65
Gender			
Male	31	28	0.50
Female	26	29	0.43

\*Birth weight mean and standard deviation

Table 3 shows some possible infant-related risk factors of encephalopathy. Over all 46 of the encephalopathic infants had low (three or less) Apgar score at one minute and all had low (six or less) five minutes scores. All of the 57 (100%) of the infants with encephalopathy required one or more of the resuscitation measures compared with 8 (14%) of the control. This difference is statistically significant. Association between encephalopathy and both birth weight and sex was not significant.

Table 4 shows some possible antenatal risk factors of encephalopathy. Primiparity and nonaccessibility to antenatal care were significant risk factors of HIE by bivariate analysis, and this association remained significant even after adjustment for other confounding factors. Infants with encephalopathy were three times more likely to result from primiparous woman (OR=3.13, 95% CI: 1.40-5.66), and two times more likely to result from lack of antenatal care (OR=1.89, 95% CI: 1.15-3.44). Pregnancy-induced hypertension was a significant risk factor before and after adjustment. Infants with encephalopathy were two times more likely to be delivered from women suffering from pregnancy-induced hypertension (OR=2.13, 95% CI: 1.25-4.33). On the other hand, maternal age was not a significant risk factor of encephalopathy.

Table 5 shows some possible labour and delivery risk factors of encephalopathy. Noncephalic presentation ( $P<0.04$ ), antepartum haemorrhage ( $P<0.002$ ), mode of delivery ( $P<0.001$ ), and prolonged second stage of labour ( $P<0.001$ ), were all significantly associated with encephalopathy. Even after adjustment, they remained significant predictors of encephalopathy. Encephalopathic infants were three times more likely to be associated with noncephalic presentation, four times with antepartum haemorrhage, and seven times more likely to be associated with prolonged second stage of labour, as compared to normal infants. Forceps and emergency cesarean section deliveries had a significantly higher risk of getting an encephalopathic infant (OR=7.91, 95% CI: 4.57-12.78) and (OR=10.34, 95% CI: 6.52-14.29), respectively. Prolonged rupture of membranes was not significantly associated with encephalopathy ( $P=0.17$ ).

## Discussion

In less developed countries more information is needed about the nature and timing of events leading to HIE, and about risk factors that are potentially preventable. The cumulative incidence of severe HIE in the present study was 4.9/1000 livebirths. This figure is lower than that reported in Kuwait (9.4/1000), [9] but higher than estimates from some developed countries over the last 20 years [10]. However, the fact that HIE is defined differently by various investigators [11] makes comparison difficult.

HIE has a major contribution to neonatal mortality and the present study shows that mortality from HIE was 21%. This figure is lower than that of 31% in Nepal [12]. Most of deaths in the present study occurred in infants with grade II and grade III encephalopathy. About two thirds of infants with birth asphyxia had abnormal neurological findings at the time of discharge, although our findings are not based on long term follow up, other authors found the evaluation at 10 days closely approximates the eventual outcome of asphyxiated deliveries [13].

Pregnancy induced hypertension was a major risk factor for HIE in the present study [10]. Infants with HIE were five times more liable to be a result of delivery of hypertensive mothers as compared to non-



**Table 4:** Antenatal risk factors for neonatal encephalopathy

Variable	Study group N=57	Control group N=57	P value	cOR (95%CI)	aOR (95%CI)
Parity					
0	21	11	<0.04	2.44 (1.04-5.71)	3.13 (1.40-5.66)
>1	36	46			
ANC					
Yes	24	9	<0.004	3.88 (1.60-9.40)	1.89 (1.15-3.44)
No	33	48			
PIH					
Yes	12	3	<0.03	4.80 (1.28-18.07)	2.13 (1.25-4.33)
No	45	54			
Maternal age (years)					
Mean $\pm$ SD	25.06 $\pm$ 3.8	25.22 $\pm$ 4.7	0.82	-	-

cOR - crude odds ratio aOR - adjusted odds ratio (adjusted for effects of all other variables in the table).

ANC = Ante-Natal Care PIH = Pregnancy-Induced Hypertension

**Table 5:** Delivery risk factors for neonatal encephalopathy

Factor	Study group	Control group	P value	cOR (95%CI)	aOR (95%CI)
Presentation					
Noncephalic	45	53	<0.04	3.53 (1.06-11.72)	2.76 (1.11-3.16)
Cephalic	12	4			
Prolonged 2nd stage of labour					
Yes	28	3	<0.001	17.38 (4.86-62.09)	6.67 (3.89-9.57)
No	29	54			
APH					
Yes	15	2	<0.002	9.82 (2.13-45.32)	4.32 (2.36-5.79)
No	42	55			
PROM					
Yes	16	18	0.17	0.83 (0.38-1.89)	1.02 (0.25-2.34)
No	41	39			
Mode of delivery					
SVD	22	50	<0.001	11.36 (4.38-29.50)	2.10 (1.20-4.21)
Forceps	15	1	<0.001	14.64 (6.45-31.56)	7.91 (4.57-12.78)
C/S:					
Emergency	18	1	<0.001	22.63 (14.26-32.72)	10.34 (6.52-14.29)
Elective	2	5	<0.01	4.11 (2.63-7.81)	2.18 (1.27-4.35)

cOR - crude odds ratio aOR - adjusted odds ratio (adjusted for effects of all other variables in the table).

APH = Antepartum hemorrhage PROM = Prolonged rupture of membranes C/S = Cesarean Section

encephalopathic ones. Even after adjustment for other antenatal factors, this association remained significant. The association of HIE with maternal hypertension suggests a possible aetiology for the asphyxiated encephalopathy in hypertensive group. Recent work involving prostaglandin metabolism indicates that hypertensive pregnant women, particularly those who are primigravida, have highly abnormal levels of these vaso-active substances,

which are also present in the umbilical cords of their infants [12,14-16]. Thromboxane A2 concentration is disproportionately elevated [10,12,15-17]. This biologically active agent possesses vigorous vaso-constrictive properties which may adversely affect the fetus or infants and cause greater susceptibility to the effect of asphyxia. Prostacyclin, a vasodilator, is simultaneously decreased [10,12,15-17]. The infants would therefore be at greater



risk of developing asphyxia and its consequences during labour and delivery.

Primiparity was significantly associated with asphyxia. Asphyxiated infant was three times more likely to be of a primiparous woman. The significantly higher number of primigravida mothers in the study group has also been found in other studies [9,12,14,17].

The vertex presentation was associated with less risk of birth asphyxia as compared to non-cephalic presentation. Infants with asphyxia were about three times more likely to present with non-cephalic presentation. This finding was in agreement with the findings of Nepal study [12].

Antepartum hemorrhage was associated with increased incidence of HIE. Infants with HIE were four times more likely to be associated with antepartum hemorrhage. There was a significant association between one minute and five minutes Apgar scores and outcome, where the majority (81%) of infants with asphyxia were scored 0-3 at one minute and all of them were scored 6 or less at five minutes. This is in keeping with the initial observation of Drage et al. [18] Nelson and Ellinberg [19] found that an Apgar score of 0-3 at five minutes was an ominous findings with 44% of patients dying, 5% of all surviving infants showing evidence of disabling motor deficits, and the relative risk for cerebral palsy in such infants being 21 times normal.

We found a significantly higher rate of prolonged second stage of labour in the study group. This finding is the same like that of other authors [17,20,21]. Other intrapartum factors were significantly associated with HIE, these are forceps deliveries and emergency caesarian sections with adjusted odd ratios of 7.91 and 10.34 respectively.

Regarding neonatal findings, the sex distribution was not significant as opposed to other study [9]. All infants were full terms, and there was no significant difference in the birth weight. Our study was limited by the fact that, there is, as yet no widely agreed definition for perinatal hypoxic encephalopathy [22]. We chose the term hypoxic ischaemic encephalopathy so as to enable comparison with prevalence studies of hypoxic ischemic encephalopathy in other setting [23]. It is possible that a small number of mildly encephalopathy infants escaped our attention, but moderate or severe encephalopathy is not a subtle syndrome and presents within 24 hours of birth [7].

### Conclusion and recommendations:

HIE in Abha city was significantly associated with some antepartum risk factors such as primiparity, nonaccessibility to antenatal care, and pregnancy-induced hypertension; in addition to some intrapartum factors such as noncephalic presentation, antepartum haemorrhage, mode of delivery, and prolonged second stage of labour. The avoidance of HIE in term neonates must be amongst the highest priori-

ties in perinatology, especially in the developing world. If the recent recommendation by the committee on Fetus and Newborn, American Academy of Pediatrics and Committee on Obstetric Practice, American College of Obstetrician and Gynecologist [24] is followed, this will help in decreasing the incidence of HIE. Some improvement can be gained by closer monitoring of high-risk groups, such as the hypertensive primigravida. More fruitful prospects may lie in an experimental or interventional [25] approach in this high-risk groups. Lastly, improved recognition and more aggressive therapy of HIE postnatally may reduce the mortality and morbidity of the condition [2].

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