ISSN 2249-4847

Journal of Clinical Neonatology

www.jcnonweb.com

Vol 9 / Issue 2 / April-June 2020

The official Journal of Saudi Neonatology Society

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Original Article

Magnitude, Short-Term Outcomes and Risk Factors for Hypoxic Ischemic Encephalopathy at Abha Maternity and Children Hospital, Abha City, Saudi Arabia and Literature Review

Raja M. Thigha, Ahmad A. Alzoani, Mufareh H. M. Almazkary, Amal A. Khormi, Rania H. Albar

Department of Neonatology, Abha Maternity and Children Hospital, Abha, Saudia Arabia

Abstract

Background: When hypoxia is the cause for neonatal encephalopathy, a clinical syndrome has been described known as hypoxic–ischemic encephalopathy (HIE). **Aim of the Study:** This study aimed to determine the magnitude of HIE occurrence, its short-term outcomes, and associated risk factors. Literature review was included for comparing our reported findings with other published ones. **Methods:** A retrospective, case–control study was conducted at "Abha Maternity and Children Hospital" (AMCH) that included all inborn term and late-preterm newborns with the "admission diagnosis" of HIE during 2016–2017. Healthy newborn babies were taken as controls. Data were extracted from neonatal medical files for HIE cases and maternal medical files for the controls. **Results:** Of 15,790 livebirths, 124 cases had HIE (7.85/1000 livebirths), of whom 3.98/1000 and 3.86/1000 livebirths were staged as mild and moderate-to-severe HIE, respectively. Short-term outcomes for HIE were 14 deaths (11.3%) and 33 cases with seizures (26.6%), which occurred exclusively among moderate–severe HIE cases; 87 cases (70.2%) required positive pressure ventilation, and 45 cases (36.3%) required mechanical ventilation, with significantly higher rate among moderate–severe HIE than mild cases ($P < 0.001$). By the 7th day of admission, moderate-to-severe HIE cases showed significantly higher rates for both lack of nutritive sucking reflex and respiratory support than mild HIE ones ($P = 0.016$ and $P < 0.001$, respectively). Among HIE cases who required cooling, 96.2% were subjected to it within the "therapeutic window" of ≤6 h. Risk factors associated with HIE were urinary tract infection/vaginitis ($P = 0.001$), late preterm ($P = 0.002$), meconium stain ($P = 0.003$), abnormal cardiotocographic tracing ($P < 0.001$), prolonged second stage of labor ($P = 0.001$), assisted delivery ($P = 0.011$), sentinel events ($P = 0.027$), and low 1-min APGAR scores ($P < 0.001$). **Conclusions:** The burden of moderate-to-severe HIE at AMCH is high with an associated high mortality rate. Early identification of high-risk pregnancy with improved antepartum, intrapartum, and neonatal care can reduce occurrence of HIE.

Keywords: *Hypoxic–ischemic encephalopathy, newborns, retrospective case–control, risk factors, short-term outcomes*

Submitted: 03-Feb-2019
Revised: 07-Jun-2019
Accepted: 23-Mar-2020
Published: 21-Apr-2020

Introduction

Neonatal encephalopathy (NE) is a nonspecific term that describes a clinically defined syndrome of disordered brain function in term and late-preterm

Access this article online

Quick Response Code:

Website: www.jcnonweb.com

DOI: 10.4103/jcn.JCN_12_19

Address for correspondence: Dr. Raja M. Thigha, Dr. Hassan Albar Maternity and Children Hospital, Abha, KSA. E-mail: raja-thiqah@hotmail.com

How to cite this article: Thigha RM, Alzoani AA, Almazkary MH, Khormi AA, Albar RH. Magnitude, short-term outcomes and risk factors for hypoxic ischemic encephalopathy at Abha Maternity and children hospital, Abha city, Saudi Arabia and literature review. J Clin Neonatol 2020;9:98-110.

newborns within the first few days of life.[1] The term "NE" is simply a clinical description and does not imply assumptions about either pathogenesis. The etiology of NE disorder includes several conditions, e.g., hypoxia, congenital malformation, neurological/or metabolic causes, trauma, and infectivion.[2]

Antepartum or intrapartum hypoxic–ischemic events, e.g., perinatal asphyxia or birth asphyxia, refer to an insult accompanied by decreased oxygen delivery to the fetal brain before or during birth.[3] When hypoxia is the cause for NE and is followed by encephalopathy signs during the first few hours after birth, a clinical syndrome has been described known as hypoxic–ischemic encephalopathy (HIE), i.e., HIE is a subgroup of NE.[4]

Levels of cerebral oxygen are not directly measurable in humans (*in vivo*), although fetal venous scalp sample may be taken during labor when clinically indicated but not as a routine practice. This has led to the use of indirect clinical markers for hypoxic–ischemic events, such as low APGAR score (AS)[5-7] and low cord blood pH,[4,6,8,9] which if present either alone, or in combination with features of encephalopathy, are taken to imply the occurrence of HIE.[10,11]

There is a scarcity of national studies on HIE. Therefore, this study aimed to determine the magnitude of HIE occurrence, its short-term outcomes, and associated risk factors among newborns at Abha Maternity and Children Hospital (AMCH), Assir Region, Saudi Arabia, with detailed literature review for interpreting our HIE rate in relation to those of others, taking into consideration different study methodologies, which produced those figures rather than dealing with those figures as absolute values.

Methods

This study followed a retrospective, case–control research design. It is a hospital record-based review that covered the period from January 2016 to December 2017. The study was conducted at AMCH, which is a referral, tertiary care, and teaching hospital at the southwestern region of the Kingdom of Saudi Arabia.

The inclusion criteria of patients' data were inborn during the study period, term (gestational age [GA] ≥37 weeks) and late preterm (GA ≥34 0/7 up to 36 6/7 weeks) with "admission diagnosis" of HIE. Exclusion criteria were outborn and inborn with admission diagnoses other than HIE, GA <34 weeks, obvious congenital malformation, metabolic disorders, and initial positive blood culture. The rationale for outborn exclusion is to limit the issue of missing information and to improve, to some extent, accuracy of rate calculation.

The AMCH Statistics Department provided the total number of livebirths during the study period. Recruitment of HIE cases was based on the sequence at which HIE cases were identified, i.e., encephalopathy signs following perinatal depression or asphyxia events. To maximize the ascertainment of cases selection and minimize the risk of loss of cases, HIE cases were identified as follows:

- The "NICU admission log book" that belongs to the study period (from January 1, 2016, through December 31, 2017) was manually searched for the "initial diagnosis" of the following clinically related terminology: "birth asphyxia," "perinatal depression," or even HIE ± its staging. Neonates' medical file numbers were directly entered into a preformed Excel sheet (which was designed to include all variables of this study). The list was used to retrieve the medical files from the "Medical Records Department"
- As an added guide, those admitted neonates were subjected to neurological examination. Based on the neurological data, if the "admission diagnosis" was HIE secondary to hypoxia after exclusion of other causes of encephalopathy (such as major congenital malformation), HIE staging was assigned using Sarnat and Sarnat,[12] which was used to determine the legibility for "therapeutic hypothermia."

Variables related to HIE short-term outcomes included HIE severity, mortality, requirement for positive pressure ventilation at birth, mechanical ventilation, seizure (either clinical documentation or use of phenobarbitone as an antiepileptic medication used as an indicator of seizure occurrence), and therapeutic hypothermia for moderate and severe (clinically significant HIE); moreover, on the 7th day of admission, the "Neonatal ICU Flow Sheet" was reviewed for lack of nutritive suckling reflex and need for respiratory support of any form: supplemental oxygen and noninvasive or invasive respiratory support.

Among our NICU admission criteria is the admission of all newborns <34 weeks. Therefore, choosing the control group from the well-baby, facilitated GA matching between the HIE cases and their controls as both groups were ≥34 weeks. For each HIE case, two healthy babies who were delivered within the same study period were randomly selected, using the random number tables.

To assess the role of antepartum, intrapartum, and neonatal risk factors for HIE occurrence, a predesigned Excel sheet was used for HIE cases and for their controls as follows: For control group, the maternal medical files were reviewed to collect data related to HIE risk factors. For HIE cases, the neonatal medical files were reviewed

to collect data related to HIE risk factors, in addition to certain neonatal characteristics and short-term outcomes for HIE cases.

Variables were included in this study based on previous studies' findings. The following clinical data were retrospectively collected for both HIE cases and their controls:

- Antepartum-associated risk factors: Maternal age, nationality, gravidity, un-booked at AMCH, maternal comorbidity (diabetes, preeclampsia/hypertension, urinary tract infection (UTI)/vaginitis)
- Intrapartum-associated risk factors: GA, malpresentation, meconium-stained amniotic fluid, premature rupture of membranes (PROM), abnormal cardiotocographic (CTG) findings, labor augmentation, prolonged second stage of labor, placental abnormalities, mode of delivery, instrumental delivery, sentinel event (included antepartum hemorrhage, abruption placentae, ruptured uterus, shoulder dystocia, and cord prolapse)
- Neonate's data: Gender, birth weight, and AS. Based on our hospital's eligibility criteria for "therapeutic hypothermia," the following cutoff values were selected: pH ≤7, base deficit (BD) ≥16, and AS ≤5 at 10 min.

This study was approved by the Research and Ethics Committee at AMCH. Full confidentiality was maintained all throughout the study, and the collected data were exclusively used for research purposes. This study was self-funded by the researchers, and there was no conflict of interest.

Collected data were coded and entered directly into the preformed Excel sheet. Data analysis was carried out using the Statistical Package for the Social Sciences (SPSS, version 23, IBM Company, New York, USA). Descriptive statistics were calculated, (i.e., frequency and percentages for categorical data and mean and standard deviation for quantitative data). Odds ratio (OR), 95% confidence interval (CI), and tests of significance (e.g., χ^2 test and unpaired *t*-test) were applied. To control for confounders, multivariate binary logistic regression analysis was applied to identify risk factors for HIE. $P < 0.05$ was considered statistically significant.

Results

A total of 15,790 all live-born infants were delivered during the study period (2016–2017). Of those newborns, 140 were admitted with the initial diagnoses of "birth asphyxia," "perinatal depression," or "HIE of any stage." Only neonates with the "admission diagnosis" of HIE were included in the study, while others ($n = 7$) were excluded. Moreover, three cases were further excluded for being outborn in addition to six cases with GA <34 weeks. Therefore, the total number of HIE cases included in this study was 124, with an overall HIE rate of 7.84/1000 all livebirths, of whom 3.98/1000, and 3.86/1000 all livebirths were mild and moderate-to-severe HIE, respectively.

Characteristics of mild and moderate-to-severe HIE cases are shown in Table 1. The mean age at which HIE cases received therapeutic cooling was 3.1 ± 2.1 h. A total of 52 HIE cases (41.9%) received cooling, mostly within ≤6 h (50, 96.2%), while only two (3.8%) received it after 6 h of age.

Based on the "admission diagnosis," 49.2% of HIE cases had moderate-to-severe HIE. We studied evidence on diagnostic accuracy according to the following criteria: AS ≤5 at 10 min of birth, at birth pH ≤7, and BD ≥16 mEq/L for predicting moderate-to-severe HIE. Table 1 shows that their sensitivities were 36.1%, 55.7%, and 55.7%, respectively, and their specificities were 96.8%, 87.3%, and 88.9%, respectively, for predicting moderate–severe HIE, while their positive likelihood ratios (LR+) were 11.2, 4.4, and 5.0, respectively. The posttest probabilities of moderate-to-severe HIE would rise to 91.3, 80.4%, and 82.9%, respectively.

Table 2 shows that the details of short-term outcomes among HIE cases. The potential antepartum risk factors for HIE are listed in Table 3. Of these, young maternal age (<20 years), non-Saudi nationality, un-booking, and maternal morbidity (i.e., hypertension/PET and UTI or vaginitis) were statistically significant ($P = 0.041$, $P = 0.045$, $P < 0.0001$, $P < 0.0001$, and $P < 0.0001$, respectively).

Table 4 lists the potential intrapartum risk factors for HIE. Noncephalic presentation and delivery augmentation among HIE cases were more than the control ones but did not differ significantly (10.5% and 6.5%, respectively, $P = 0.175$, and 21% and 14.5%, respectively, $P = 0.117$). Other potential intrapartum factors occurred significantly more among HIE cases than the control group, i.e., late preterm babies, meconium-stained amniotic fluid, PROM, abnormal CTG tracings, prolonged second stage of labor, placental abnormalities; less normal vaginal deliveries and more instrumental deliveries occurred among HIE cases than the control group; sentinel events occurred more among HIE cases than the control group.

Table 5 shows no significant difference between HIE cases and control group according to neonatal gender.

Table 1: Characteristics of hypoxic-ischemic encephalopathy cases

HIE cases characteristics	Mild HIE HIE (*n*=63), *n* (%)	Moderate-to-severe HIE (*n*=61), *n* (%)	*P*
Mean age on admission (h)[§]	7.1±5.3	2.0±1.9	0.0001
Age on admission (h)			
>6	28 (44.4)	1 (1.6)	<0.0002
≤6	35 (55.6)	60 (98.4)	
Gender			
Male	41 (65.1)	33 (54.1)	0.213
Female	22 (34.9)	28 (45.9)	
Gestational age			
Late preterm (GA: 34 0/7 up to 36 6/7 weeks)	12 (19.0)	17 (27.9)	
Full term (GA ≥37 weeks)	51 (81.0)	44 (72.1)	0.248
Fitting for "therapeutic hypothermia" criteria?			
AS at 10 min			
Yes, if AS ≤5	2 (3.2)	22 (36.1)	
No, if AS >5	61 (96.8)	39 (63.9)	0.0002
Cord pH/or if not available, 1st h pH			
Yes, if pH ≤7	8 (12.7)	34 (55.7)	0.0001
No, if pH >7	55 (87.3)	27 (44.3)	
Cord base deficit (BD)/or if not available, 1st h BD			
Yes, if BD ≥16	7 (11.1)	34 (55.7)	0.0001
No, if BD <16	56 (88.9)	27 (44.3)	
Receiving therapeutic hypothermia			
Yes	2 (3.2)	50 (82.0)	
No	61 (96.8)	11 (18.0)	0.0001

[§]Quantitative variables, reported as mean±SD and *t*-test was applied to test for significance. GA – Gestational age; BD – Base deficit; SD – Standard deviation; HIE – Hypoxic–ischemic encephalopathy; AS – APGAR score

However, there were significantly more newborns in the HIE group than the control group with low birth weight (24.2% and 8.5%, respectively, $P < 0.0001$). Newborns in the HIE group had significantly lower APGAR scores ≤ 7 at 1 and 5 minutes ($P < 0.0001$ and 0.0004, respectively), while there was no significant difference between both groups regarding AS at 10 min.

After controlling for confounders by applying multivariate binary logistic regression analysis, the statistically significant risk factors for HIE were limited to UTI/vaginitis ($P = 0.001$), late preterm ($P = 0.002$), meconium-stained amniotic fluid ($P = 0.003$), abnormal CTG findings ($P < 0.001$), prolonged second stage of labor ($P = 0.001$), assisted delivery ($P = 0.011$), sentinel events ($P = 0.027$), and AS at 1 min ($P < 0.001$), as shown in Table 6.

Discussion

The HIE rate in our study, being 7.84/1000 all livebirths, varies widely when compared to the reported HIE incidence in the national and international studies [Table 7]. This figure is in relative accordance with other reported national figures in Saudi Arabia,[13,14] significantly lower than internationally cited studies from: Nepal,[15] Nigeria,[16] India,[17] Tanzania,[18] Uganda,[5]

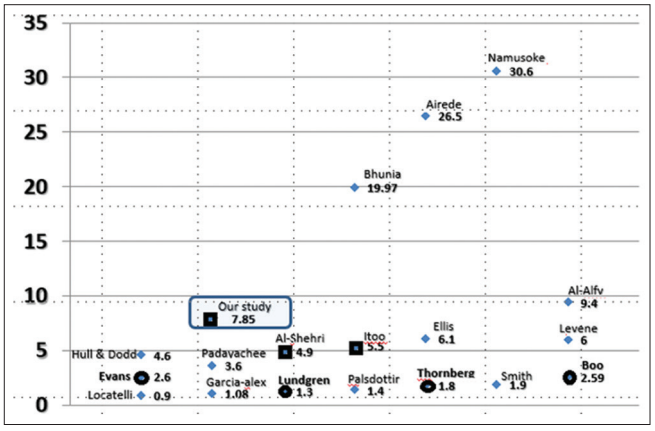

Figure 1: Hypoxic–ischemic encephalopathy rates (per 1000) as reported by local studies (■) and international population-based studies (●) and international hospital-based studies (♦) compared with our study

and significantly higher than other internationally cited studies from: Sweden,[5,19] London,[20,21] Malaysian,[22] Italy,[23] Iceland,[24] Spain,[25] and South Africa,[26] as shown in Table 7 and Figure 1.

We found it an opportunity to compare, over time,[21,27] our HIE rate of 7.84/1000 with the previously published study of AlShehri and Eid[14] of 4.9/1000 all livebirths. Both studies were carried out in Abha City, but the hospital setting itself was changed to a new one. The

Table 2: Short-term outcomes of hypoxic-ischemic encephalopathy newborns according to their hypoxic-ischemic encephalopathy staging at Abha Maternity and Children Hospital during 2016 and 2017 (*n*=124)

Short-term outcomes	Mild HIE HIE (*n*=63), *n* (%)	Moderate-to-severe HIE (*n*=61), *n* (%)	*P*
HIE outcome			
Discharged	59 (93.7)	46 (75.4)	<0.001
Died	0 (0.0)	14 (23.0)	
Left against medical advice	2 (3.2)	1 (1.6)	
Transferred to another hospital	2 (3.2)	0 (0.0)	
Length of hospital stay (days)§	4.8±3.8	15.5±16.1	<0.001
Length of hospital stay (days)			
≤7	52 (82.5)	10 (16.4)	0.0001
>7	11 (17.5)	51 (83.6)	
Seizure			
Yes	0 (0.0)	33 (54.1)	0.0005
No	63 (100.0)	28 (45.9)	
Received positive pressure ventilation			
Yes	33 (52.4)	54 (88.5)	0.0001
No	30 (47.6)	7 (11.5)	
Mechanical ventilation			
Yes	4 (6.3)	41 (67.2)	0.0001
No	59 (93.7)	20 (32.8)	
Lack of nutritive suckling on 7th day*			
Yes	10 (41.7)	38 (70.4)	0.0185
No	14 (58.3)	16 (29.6)	
Respiratory support¶ on 7th day*			
Yes	1 (4.5)	33 (61.1)	<0.001
No	21 (95.5)	21 (38.9)	

§Continuous variables, reported as mean±SD and *t*-rest used to test for significance, ¶Respiratory support of any form: supplemental oxygen, noninvasive or invasive respiratory support, *There were missing data for newborns on 7th day of admission. The main reason for those missing values were because those neonates were either discharged or died before day 7; only few were missing because of LAMA or transfer to other hospital. SD – Standard deviation, HIE – Hypoxic–ischemic encephalopathy; LAMA – Left against medical advice

comparison might be misleading in terms of concluding that the situation is getting worse over time, this unlikely to be so. It can be argued that the detection rate of HIE cases in the current setting is increased over time, considering the positive changes in our clinical setting, higher qualification of the current staff, mandating NRP for all neonatology staff, introduction of active cooling as a therapeutic modality which was not available during AlShehri and Eid[14] study. This contributed largely to the increase in both clinical awareness and scrutiny in examining those cases in more detail to determine their eligibility for cooling.

One might argue that developed countries are better in terms of HIE occurrence in comparison to our setting. This might be acceptable if published studies settings were comparable. By reviewing in detail cited literatures, variations were found in studies' set-up and design, HIE case definition, and HIE rate estimations. If this reviews' findings were taken into consideration while interpreting our HIE rate figure in relation to others, the comparison will be fair as it is taking into consideration the different study methodology which produced those figures rather than dealing with those figures as absolute values.

Variations in cited studies' setup

Study's setup was either population-based or, as our study, hospital-based ones [Table 7]. Hospital-based studies tend to be conducted in referral centers.[28] Therefore, due to referral bias, hospital-based incidence figures tend to be higher than population-based results. While our study excluded outborn newborns, referral bias is still likely to be present, to some extent, because of continued antenatal referrals of complicated pregnancies whose newborns are counted as inborn with the possibility of greater risk of HIE occurrence. Moreover, among hospital-based studies that reported HIE rate lower than ours, apart from the studies by García-Alix *et al.*[25] and Padayachee and Ballot,[26] most of them were before 2005 [Table 7].[20,21,23,24,27,33,37] There is again a possibility of increasing detection rate over time.

Variations in cited studies' design

As other cited studies,[13,14,23] our study is retrospective case–control one, where being retrospective might make

Table 3: Antepartum risk factors among hypoxic-ischemic encephalopathy cases in comparison to the control group

Antepartum risk factors	HIE group (*n*=124), *n* (%)	Control group (*n*=248), *n* (%)	OR (95% CI)	*P*
Maternal age (years)				
≤20	15 (12.1)	16 (6.5)	2.18 (1.03-4.61)	0.041
21-35‡	88 (71)	205 (82.7)	1	
>35	21 (16.9)	27 (10.9)	1,81 (0.97-2.98)	0.061
Nationality				
Non-Saudi	13 (10.5)	12 (4.8)	2.30 (1.02-5.21)	0.045
Saudi	111 (89.5)	236 (95.2)		
Gravidity				
Primigravida	47 (37.9)	74 (29.8)	1.58 (0.98-2.54)	0.058
Gravida‡ 2-5	59 (76.6)	147 (84.5)	1	
Gravida >5	18 (23.4)	27 (15.5)	1.66 (9.85-3.24)	0.137
Unbooked at AMCH*				
Yes	51 (41.1)	32 (12.9)	4.72 (2.82-7.90)	0.0001
No	73 (58.9)	216 (87.1)		
Hypertension/PET				
Yes	29 (23.4)	10 (4.0)	7.27 (3.41-15.49)	0.0001
No	95 (76.6)	238 (96.0)		
Maternal diabetes				
Yes	7 (5.6)	7 (2.8)	2.06 (0.71-6.01)	0.186
No	117 (94.4)	241 (97.2)		
UTI/or vaginitis				
Yes	35 (28.2)	4 (1.6)	23.99 (8.29-69.42)	0.0001
No	89 (71.8)	244 (98.4)		

*Unbooked at AMCH, i.e., the mother came only for delivery without previous antenatal care booking at AMCH, This does not mean lack of antenatal care as the mother might have attended antenatal care at another health care facility, ‡Baseline comparison group.
UTI – Urinary tract infection; AMCH – Abha Maternity and Children Hospital; HIE – Hypoxic–ischemic encephalopathy; OR – Odds radio; CI – Confidence interval; PET – Pre-eclamptic/toxemia

it prone to information bias. Other study designs were used [Table 7].

Variations in hypoxic–ischemic encephalopathy case definition

By reviewing all cited studies, it was found that no sets of two investigators used the same HIE case definition, i.e., there was lack of agreement on what hypoxia/asphyxia is. As shown in Table 7, cited studies used a single or different combination of clinical, laboratory, or perinatal events were used as a surrogate clinical marker for hypoxic-ischemic encephalopathy case definition.

Variation in hypoxic–ischemic encephalopathy rate estimations

There were difficulties in interpreting our HIE rate in comparison with other published rates. The first difficulty is related to the numerator and the other one is related to the denominator definitions. Regarding the numerator, most studies included term HIE newborns,[5,13,16-18,20,21,23,24,27,30] while few included both term and late preterm[19,22,25] [Table 7]. Our study addressed this gap in knowledge by including both term and late preterm HIE cases. Late preterm are at an increased risk of adverse outcome in comparison to the term ones; this might contribute to inflation in our numerator figure and consequently increases HIE rate. When it comes to the denominator, there is a concern regarding the selection of the correct denominator.[28] The correct denominator should include only those newborns at risk of being in the numerator (at risk of being a case), which by definition for HIE means that they should be all late-preterm and term newborns. In our study, it was difficult to get livebirths data by GA, so the denominator included all livebirths at AMCH. Most studies quoted HIE incidence per 1000 all livebirths,[5,15,18-22,25-27,29,31-34] and some quoted per 1000 term livebirths.[6,13,17,23,24,30,35-37]

The proportion of clinically significant (moderate–severe) HIE in the present study (49.1%) is comparable to some studies: Airede[16] (45.8%), Simiyu *et al.*[18] (49.2%), and al-Alfy *et al.*[36] (51%); lower than Namusoke *et al.*[30] (56.5%), Bhunia and Saharia[17] (56.9%), Mahar *et al.*[38] (60.5%), Ellis *et al.*[15] (63%), Alshehri and Eid[14] (63%), and Itoo *et al.*[13] (71%); and higher than Selvakumar *et al.*[43] (45%).

In our study, the overall HIE rate was 7.84/1000 livebirths, of whom 3.85/1000 showed moderate–severe

Table 4: Intrapartum risk factors among hypoxic-ischemic encephalopathy cases in comparison to the control group

Intrapartum risk factors	HIE group (*n*=124), *n* (%)	Control group (*n*=248), *n* (%)	OR (95% CI)	*P*
Gestational age				
Late preterm	29 (23.4)	9 (3.6)	23.99 (3.70-17.77)	0.0001
Full term ≥37	95 (76.6)	239 (96.4)		
Presenting part				
Noncephalic	13 (10.5)	16 (6.5)	1.70 (0.79-3.65)	0.171
Cephalic	111 (89.5)	232 (93.5)		
Meconium-stained AF				
Yes	55 (44.4)	26 (10.5)	6.81 (3.9711.67)	0.0001
No	69 (55.6)	222 (89.5)		
PROM				
Yes	30 (24.2)	10 (4.0)	7.60 (3.57-16.15)	0.0001
No	94 (75.8)	238 (96.0)		
Abnormal CTG[§]				
Yes	89 (74.8)	61 (29.2)	7.60 (4.67-12.39)	0.0001
No	30 (25.2)	148 (70.84)		
Augmented labor				
Yes	26 (21.0)	36 (14.5)	1.56 (0.89-2.73)	0.117
No	98 (79.0)	212 (85.5)		
Prolonged 2nd stage				
Yes	50 (40.3)	29 (11.7)	5.10 (3.01-8.65)	0.0001
No	74 (59.7)	219 (88.3)		
Placental abnormality				
Yes	17 (13.7)	6 (2.4)	6.41 (2.46-16.70)	0.0001
No	107 (86.3)	242 (97.6)		
Mode of delivery				
Cesarean section	58 (46.8)	86 (34.7)	1.66 (1.07-2.57)	0.024
Vaginal delivery	66 (53.2)	162 (65.3)		
Instrumental delivery				
Yes	19 (15.3)	19 (7.7)	2.18 (1.11-4.29)	0.024
No	105 (84.7)	229 (92.3)		
Sentinel events*				
Yes	18 (14.4)	5 (2.0)	8.25 (2.99-22.81)	0.0001
No	106 (85.5)	243 (98.0)		

*Sentinel event: Antepartum hemorrhage, abruption placentae, ruptured uterus, shoulder dystocia, cord prolapse, [§]5 HIE cases and 39 controls did not undergo CTG, AF – Amniotic fluid; CTG – Cardiotocography; PROM – Premature rupture of membrane; HIE – Hypoxic-ischemic encephalopathy; OR – Odds radio; CI – Confidence interval

HIE. Table 7 and Figure 2 show our moderate–severe HIE rate in comparison to other studies.

Apart from the risk factor chorioamnionitis (which was excluded), the issue of missing information for the predetermined risk factors assessment was not of a major concern.

The mortality rate in the present study (11.3%) was higher than those reported by Selvakumar *et al.*[43] (4.8%), Finer *et al.*[32] (7%), Badawi *et al.*[35] (9.1%), and Simiyu *et al.*[18] (9.1%) and lower than Shireen *et al.*[44] (16%), Itoo *et al.*[13] (17.1%), Babu *et al.*[34] (17.8%), Mahar *et al.*[38] (25%), Namusoke *et al.*[30] (26%), Bhunia and Saharia[17] (31%), and Ellis *et al.*[15] (44%).

Therapeutic hypothermia guidelines mandate early identification of clinically significant HIE cases to start

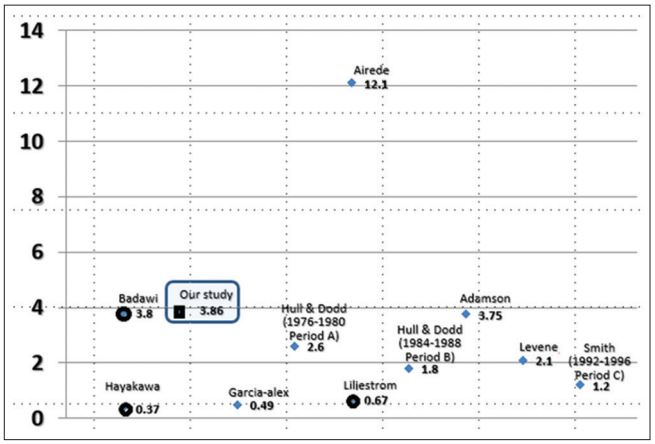

Figure 2: Moderate-to-severe hypoxic–ischemic encephalopathy rates (per 1000) as reported by international population-based studies (⭘) and international hospital-based studies (♦) compared with our study (□)

Table 5: Neonatal hypoxic-ischemic encephalopathy risk factors among hypoxic-ischemic encephalopathy cases compared with those in the control

Intrapartum risk factors	HIE group (*n*=124), *n* (%)	Control group (*n*=248), *n* (%)	OR (95% CI)	*P*
Gender				
Male‡	74 (59.7)	146 (58.9)	1.03 (0.67-1.60)	0.881
Female	50 (40.3)	102 (41.1)		
Birth weight (kg)				
Low (<2.5)‡	30 (24.2)	21 (8.5)	3.45 (1.88-6.33)	<0.0001
Normal (≥2.5)	94 (75.8)	227 (91.5)		
Apgar score at 1 min				
≤3‡	66 (53.2)	2 (0.8)	1	
4-7	58 (46.8)	234 (94.4)	133.14 (31.68-559.61)	0.0001
≥8	0 (0.0)	12 (4.8)	665.00 (30.08-14702.05)	<0.0001
Apgar score at 5 min				
≤3‡	12 (9.7)	0 (0.0)	1	
4-7	78 (62.9)	6 (2.4)	2.07 (0.11-39.07)	0.627
≥8	34 (27.4)	242 (97.6)	175.72 (10.17-3035.34)	=0.0004
Apgar score at 10 min				
≤3‡	1 (0.8)	0 (0.0)	1	
4-7	59 (47.6)	0 (0.0)	0.03 (0.00-1.75)	0.089
≥8	64 (51.6)	78 (100.0)	3.65 (0.15-91.16)	0.430

There are 170 controls with missing Apgar scores at 10 min, ‡Baseline comparison group; HIE – Hypoxic-ischemic encephalopathy; OR – Odds radio; CI – Confidence interval

Table 6: Binary logistic regression model for the association of potential antepartum/intrapartum/neonatal risk factors for the occurrence of hypoxic-ischemic encephalopathy at Abha Maternity and Children's Hospital

Antepartum/intrapartum/ neonatal risk factors	*B*	SE	*P*	Exp(B)	95% CI for Exp(B)	
					Lower	Upper
Birth weight	−0.084	0.617	0.892	0.920	0.274	3.083
Maternal age	−0.925	0.545	0.089	0.396	0.136	1.153
Gender	−0.677	0.505	0.180	0.508	0.189	1.367
Nationality	−0.510	0.960	0.595	0.600	0.091	3.943
Maternal diabetes mellitus	1.767	1.261	0.161	5.851	0.494	69.242
Hypertension/PET	1.291	0.747	0.084	3.637	0.842	15.717
UTI/vaginitis	2.601	0.776	0.001	13.484	2.945	61.731
Gravidity	−0.188	0.134	0.163	0.829	0.637	1.079
Gestational age (Late preterm)	2.293	0.750	0.002	9.90	2.283	43.478
Presenting part	0.744	0.824	0.367	2.104	0.419	10.568
Abnormal CTG	3.036	0.601	<0.001	20.83	6.36	66.67
Prolonged 2nd stage	2.284	0.666	0.001	9.813	2.661	36.192
Mode of delivery	−0.111	0.590	0.850	0.895	0.281	2.844
Assisted delivery	1.822	0.717	0.011	6.186	1.516	25.244
Sentinel events	2.369	1.070	0.027	10.684	1.311	87.044
PROM	0.567	0.699	0.417	1.764	0.448	6.936
Meconium-stained AF	1.680	0.569	0.003	5.367	1.759	16.370
Placental abnormalities	0.638	1.017	0.530	1.892	0.258	13.876
Cord abnormalities	−0.216	1.129	0.849	0.806	0.088	7.373
Augmented delivery	0.729	0.664	0.272	2.074	0.565	7.614
Apgar score at 1 min	−5.137	0.966	<0.001	0.006	0.001	0.039
Constant	7.392	2.369	0.002		1622.883	

AF – Amniotic fluid; Exp(B) – Exponential of B; CI – Confidence interval; PET – Pre-eclamptic/toxemia; PROM – Premature rupture of membranes; SE – Standard Error; UTI – Urinary tract infection; CTG – Cardiotocography

cooling within the "therapeutic window" of the 1st 6 h of life.[40-42] Our study reported the mean age at which cooling started was ≈3 h.

Among clinically significant HIE cases, AS ≤5 at 10 min reported moderate-to-large rise in posttest probability, while both pH ≤7 and BD ≥6 reported slight-to-moderate

Table 7: Case definition in cited studies and associated hypoxic-ischemic encephalopathy/birth asphyxia/perinatal asphyxia estimated rate

Author	Study type	Location year	HIE case definition	HIE/BA either per[§,¶] or %
Local hospital-based studies (KSA)				
Itoo *et al*.[13]	Case control	Madinah 1995-1996	Cases: FT, HIE ⇨ Sarnat and Sarnat staging[12] Exclusion: CM and outborn Control: 1:1, FT born next to the index case	HIE 5.5¶
AlShehri and Eid[14]	Case control	Abha 2005	Cases: FT, HIE ⇨ Sarnat and Sarnat staging[12] Control: 1:1, Normal newborns	HIE 4.9§
International population-based studies				
Thornberg *et al*.[5]	Retrospective cohort	Sweden 1985-1991	Cases: FT, data obtained from Swedish Medical Birth Record on: "Low AS group" <7 @ 5 min "Pure BA group" ⇨ [exclude cases with infection, CM, and opioid-induced respiratory depression "BA + HIE group" ⇨ [HIE staging, Fenichel[29]	Low AS 6.9§. Pure BA 5.4§. BA + HIE 1.8§
Evans *et al*.[20]	Cohort include 15/16 hospitals	London 1993-1995	Cases: FT or BW ≥2.5 kg, with ≥1 NE signs during the 1st 96 h after birth Exclusions: Down's syndrome	NE 2.62§
Badawi *et al*.[35]	Unmatched case-control	Australia 1993-1995	Cases: FT with criteria of moderate-severe HIE: either seizure alone or any of the following that last >24 h: Abnormal consciousness, tone, reflexes, respiratory difficulty, feeding difficulty Exclusion: Down' syndrome or neural tube defect	Mod-severe HIE 3.8¶
Hayakawa *et al*.[6]	Retrospective cohort	Japan 2008	Cases: FT with moderate-severe HIE caused by PA. Data were collected via nationwide surveys from 263 out of 290 responding hospitals Exclusion: NB with encephalopathy attributed to a cause other than PA	Mod-severe HIE 0.37¶
Liljestrom *et al*.[31]	Retrospective cohort	Swedish 2009-2015	Cases: GA ≥36 w. Therapeutic hypothermia served as surrogate marker of mod-severe HIE Data were from Swedish Medical Birth Register and Swedish Neonatal Quality Register were linked	Mod-severe HIE 0.67§
Lundgren *et al*.[19]	Retrospective Cohort 2009-2015	Swedish	Cases: GA ≥35, HIE newborns National HIE incidence: Obtained data from medical birth and/or national patient register Regional HIE incidence: Obtained data from 6 hospitals in the southeast region of Sweden	National HIE 1.3§ Regional HIE 1.7§
Boo and Cheah[22]	retrospective Cohort	MNNR, had a membership of 37 member NICUs 2012	Cases: GA ≥36 w, HIE was diagnosed if all of the following three criteria were met Any 3 features of NE sign within 1st 72 h of birth ≥3 of acute perinatal events: pH <7.00, AS <5 at 5 min, evidence of multi-organ dysfunction within 72 h of birth, evidence of fetal distress on antepartum monitoring, abnormal EEG, abnormal brain imaging within 7 days Absence of any underlying congenital cerebral infections/abnormalities, inborn errors of metabolism that could account for the NE	HIE 2.59§

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Table 7: Contd...

Author	Study type	Location year	HIE case definition	HIE/BA either per[§,¶] or %
International hospital-based studies				
Hull and Dodd[27]	Retrospective cohort	UK 1976-1980 (Period A) 1984-1988 (Period B)	Cases: Medical records of all infants ≥37 w and admitted to Derby City General Hospital Neonatal unit during period A, period B, and period C were studied. Records For infants with HIE features were identified. Grading used by Levene *et al*. Exclusion: Infants with encephalopathy clearly attributable to a cause other than asphyxia	All HIE 7.6[§] Mod-sev 2.6[§] All HIE 4.6[§] Mod-sev 1.8[§]
Case definition in cited studies and associated HIE/BA/PA estimated rate				
Smith *et al*.[21]		1992-1996 (Period C)		All HIE 1.9[§] Mod-sev 1.2[§]
al-Alfy *et al*.[36]	Prospective case control	Kuwait 1989 (3.5 m)	Cases: FT with asphyxial neurological syndrome preceded by an asphyxial event Criteria for an asphyxial syndrome: alterations in consciousness state and abnormal muscle tone Criteria for an asphyxial event: ≥1 of: FHR <80 bpm for 60 sec; late decelerations, AS <5 at 5 min, positive pressure ventilation needed for 2 min after delivery pH <7.1 within the 1st h of life Controls: 1st singleton FT born after each case	PAE 9.4[¶] M 49% Mo 23%, S 28%
Levene *et al*.[33]	Retrospective cohort	London UK 1980-1983	Cases: FT, Computer search for the diagnosis BA, or symptoms related to asphyxia (irritability, hypotonia, convulsions, poor feeding) Exclusion: No intrapartum asphyxia evidence	PAE 6[§] Severe PAE 2.1[§]
Airede[16]	Retrospective cohort	Nigeria 1987-1989	Cases: FT and admitted BA signs (irritability, hypotonia, convulsions, poor feeding) PAHIE severity grading used Fenichel criteria[38]	PAHIE 26.5[§] Severe PAHIE 12.1[§]
Adamson *et al*.[37]	Prospective matched case-control	Australia 5 hospitals 1992 (8 m)	Cases: Singleton, FT admitted to any of 5 study hospitals during 1st w with ≥1 of *NE signs Controls: with no NE signs	Mod-sev HIE 3.75[¶]
Locatelli *et al*.[23]	Retrospective Case-control 1993-2003	Italy	Cases: FT with NE ⇨ Sarnat and Sarnat criteria[37] Exclusion: metabolic disorders, major CM, chromosome abnormalities, and viral infections	NE ⇨ 0.9[¶]
Ellis *et al*.[20]	Prospective unmatched case control	Nepal 1995-1996	Cases: FT evidence of *NE signs at 6-24 h after birth. Staging based on Fenichel criteria[8] Exclusion: major CM; intrauterine infection; hypoglycemia correction normal neurology	HIE 6.1[§]
Palsdottir *et al*.[24]	Retrospective cohort	Iceland 1997-2001	Cases: FT with BA defined as AS ≤6 at 5 min	BA 9.4 [¶] HIE 1.4[¶]
García-Alix *et al*.[25] Non-English	Retrospective cohort	Spanish 2000-2008	Cases: GA ≥34 w with evidence of BA and HIE GA ≥34 w. Evidence of BA and HIE	All HIE 1.08[§] Mod-sev 0.49[§]
Padayachee and Ballot[26]	Retrospective cohort	South Africa 2006-2011	Cases: BW >1800 g PA ⇨ AS at 5 min <6 HIE ⇨ Sarnat and Sarnat staging[37]	PA 4.7[§] HIE 3.6[§]
Dalal and Bodar[46]	Descriptive Longitudinal	India 2007-2008	Cases: FT, AS <7 at 1 min Exclusion: Maternal sedation/maternal anesthesia, major CM as anencephaly, diaphragmatic hernia	BA 79.8% HIE among BA 32.5%
Babu *et al*.[34]	Cross section	India 2013-2014	Cases: FT, AS <7 at 1 min	BA 6.6%
Bhunia and Saharia[17]	Prospective cohort 2014-2015	India	Cases: FT, PA if the baby is gasping or no breathing at 1 min after birth HIE staging was based on Sarnat and Sarnat[37]	HIE 19.97[¶]

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Table 7: Contd...

Author	Study type	Location year	HIE case definition	HIE/BA either per[§,¶] or %
Case definition in cited studies and associated HIE/BA/PA estimated rate				
Simiyu *et al*.[18]	Prospective cohort	Tanzania 2014-2015	Cases: Median GA 38 w, median BW 2900 g BA ⇨ AS <7 at 5 min HIE ⇨ used Sarnat and Sarnat criteria[37]	BA 11.5% HIE 10.7%
Selvakumar[29]	Prospective	India 2017 (6 m)	Cases: GA ≥36 w, PA ⇨ AS <7 at 5 min PA cases ⇨ Sarnat and Sarnat staging[37]	PA 2.7% HIE: M 55%, Mo 36%, S19%
Namusoke *et al*.[30]	Prospective Cohort	Uganda October 2015-January 2016	Cases: FT, BW >2000g, intrapartum asphyxia: AS <7 at 5 min, or pH <7.0, or BD ≥12.0, *NE signs HIE ⇨ Sarnat and Sarnat[37]	HIE 30.6¶ M 43.5%, Mo 34.8%, S 21.7%

[§]Per 1000 all livebirth, ¶Per 1000 term livebirth, *NE signs: Neonatal Encephalopathy signs: abnormality in: consciousness level, muscle tone and reflexes, Moro and suckling reflexes, maintaining respiration, ± seizure. AS – APGAR score; BA – Birth asphyxia; BD – Base Deficit; bpm – Beats per minute; BW – Birth weight; CM – Congenital malformation; EEG – Electroencephalogram FT – Full term; FHR – Fetal heart rate; GA – Gestational age; LPT – Late preterm; Mod-sev – Moderate-to-severe; M – Mild; Mo – Moderate; NE – Neonatal Encephalopathy; S – Severe; w – Weeks; PA – Perinatal aphyxia; PAE – Postasphyxial encephalopathy; MNNR – Malaysian National Neonatal Registry; HIE – Hypoxic-ischemic encephalopathy; m – Months

Table 8: Reported antepartum, intrapartum, and neonatal risk factors for hypoxic-ischemic encephalopathy occurrence

Antepartum HIE Associated Risk Factors

Maternal age,[15,27] Ethnicity,[44] Consanguinity,[22] Unemployed/housewife mother[15]
Primiparity,[12,13,16,17,22,27,31-33,43-45] and Multiple births (twin).[27,39,44]
Maternal Height/Short stature (156 cm).[16,27]
Maternal weight/Overweight (BMI > 25 kg/m^2),[16,26]
Pregnancy-induced hypertension/Pre-eclampsia.[12,13,15,22,26,32,43,44]
Maternal morbidity: fever,[25,44] Anemia (<8 gm/dl),[27,39] Diabetes,[26] Hypothyroidism,[15,25-27]
Infertility treatment.[15]
Antepartum hemorrhage (APH).[12,13,15,32,39]
Lack of antenatal Care.[7,13,27,30,31,39,45]
Place of delivery.[30,39,44,45]

Intra-partum HIE Associated Risk Factors:

Malpresentation.[13,16,27,39,41,46]
Umbilical Cord complications (cord prolapse.[7] cord wrapped around neck).[28,45,]
Induction of labor with Oxytocin (augmentation).[25,27,32,43]
Prolonged 2nd stage of labor.[12,13,22,25,27,32,33,43]
PROM,[27,32,39,43,45] Chorioamnionitis[26]
Abnormal amniotic fluid,[26] Meconium-stained amniotic fluid.[18,25,27,28,30,31,39,45]
Occurrence of Sentinel event[¶] [47]
Abnormal CTG tracing.[17,25,26,28]
Instrumental deliveries [9,12,13,22,28,41]
Emergency Cesarean Section[12,41]/Previous cesarean section.[16,26]

Newborn HIE Associated Risk Factors:

Gender (Male).[7,12,30-32,42,43,47]
LBW,[16,31] IUGR[12,26]
Prematurity,[16,44] Postmaturity.[7,46, 47]
Out-born[6,18]
Out-born[6,18]

[¶]A sentinel obstetric event is "an event which is uncommon, is likely to lead to severe impairment of placental bed transfer, and offers on its own a plausible mechanism by which an infant might suffer hypoxic damage," e.g., of reported sentinel obstetric event: cord prolapse, shoulder dystocia, ruptured uterus. Definition of prolonged second stage of labor: For those without regional anesthesia, a second stage >2 h in a multiparous patient and >3 h in a primiparous. For those with regional anesthesia, a second stage >3 h in a multiparous patient and >4 h in a primiparous. PROM is defined as spontaneous rupture of fetal membranes <37 weeks of gestation at least 1 h before the onset of uterine contraction. HIE – Hypoxic–ischemic encephalopathy; APH – Antepartum hemorrhage; PROM – Prolonged rupture of membrane; CTG – Cardiotocography; LBW – Low birth weight; IUGR – Intrauterine growth restriction

rise in posttest probability, i.e., AS can be used as predictor of clinically significant HIE.

Although it was beyond the scope of the current study to review those retrieved medical files of the surviving and discharged HIE cases for long-term neurodevelopmental outcome as cerebral palsy,[16,20,32,33,44,45] our reporting, as in other studies,[5,30] for the following: presence of seizure, lack of sucking reflex, requirement for oxygen of any form, closely approximates short-term neurological outcome of HIE.

Some antepartum/intrapartum risk factors for HIE are probably universal, such as obstetric emergencies, whereas the contribution of others may vary among populations and over time. In the present study setting, the majority of HIE-associated risk factors were similarly reported in other studies [Table 8].

Conclusions

The rate for HIE at AMCH is 7.85/1000 livebirths. Reported HIE rates vary widely. These variations can be either genuine or due to differences in HIE case definition, studies' set up or design. However, HIE occurrence rate at AMCH is an area for improvement by identifying risk factors in order to understand the causal pathways and to enable the application of preventive strategies at both primary (reduce HIE incidence) and secondary (early HIE detection and timely management) levels. It is important to pay close attention to modifiable risk factors which if tackled appropriately might alter the natural course of HIE and modify the outcome favorably. This can be achieved by implementing long-term programs and team-based training that can optimize appropriate, timely recognition, and management of HIE risk factors; early communication between the caring obstetrician and neonatology staff in case risk factor(s) is/are identified; improve facility for antenatal care; maternal screening for pregnancy-associated morbidity; wise application of augmented and instrumental deliveries; early recognition of intrapartum adverse obstetrical events (such as: fetal distress manifested by abnormal CTG tracing, meconium-stained amniotic fluid, placental and cord abnormalities, and prolonged second stage of labor); early identification of HIE cases and its staging, so as to offer timely cooling of HIE cases within the therapeutic window.

Adding preterm to term HIE cases has important implications at different levels, in particular for the healthcare planner, in planning their strategies for minimizing HIE occurrence, and in identifying the accurate proportion of clinically significant HIE cases that are likely to benefit neurologically from cooling annually.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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