

Clinical Characteristics and Risk Factors of Neonatal Hypoxic-Ischaemic Encephalopathy and Its Associated Neurodevelopmental Outcomes During the First Two Years of Life: A Retrospective Study in Saudi Arabia

Mohammed AlMuqbil¹⁻³, Jawaher Alanazi², Nada Alsaif¹, Duaa Baarmah², Waleed Altwajiri^{1,2}, Ahmad Alrumayyan^{1,2}, Muhammad Talal Alrifai^{1,2}, Fatmah Othman^{3,4}, Hassan Al-shehri⁵, Saif Alsaif^{1,3}

¹College of Medicine, King Saud bin Abdulaziz University for Health Sciences (KSAU-HS), Riyadh, Saudi Arabia; ²Division of Pediatric Neurology, King Abdullah Specialist Children's Hospital (KASCH), National Guard Health Affairs (NGHA), Riyadh, Saudi Arabia; ³King Abdullah International Medical Research Center (KAIMRC), Ministry of National Guard, Riyadh, Saudi Arabia; ⁴Department of Epidemiology and Biostatistics, College of Public Health and Health Informatics, King Saud bin Abdulaziz University for Health-Science, Riyadh, Saudi Arabia; ⁵Department of Pediatrics, College of Medicine, Imam Mohammad Ibn Saud Islamic University, Riyadh, Saudi Arabia

Correspondence: Mohammed AlMuqbil, College of Medicine, King Saud bin Abdulaziz University for Health Sciences (KSAU-HS), Riyadh, 11481, Saudi Arabia, Tel +966 50533 7752, Email almuqbilmo@mngha.med.sa

Objective: This study aimed to determine the clinical characteristics and factors associated with neonatal hypoxic-ischaemic encephalopathy (HIE) and its neurodevelopmental outcomes.

Methods: We conducted retrospective case-control research to investigate the clinical and labour-related risk factors for HIE. In addition, a single-centre cohort study was conducted on infants with HIE to describe their neurodevelopment from birth to 24 months. For this investigation, cases with a diagnosis of HIE who were born at King Abdullah Children's Specialist Hospital (KASCH), Riyadh, Saudi Arabia, between 2015 and 2019 were identified and matched with controls from the same facility (1:4). Each case's clinical information was extracted using electronic medical records. In addition, 24-month follow-up HIE cases were included in a cohort study to describe their neurodevelopmental outcomes.

Results: The sample includes 60 infants diagnosed with HIE and 234 infants serving as controls, with a mean gestational age of 38.8 weeks (SD 1.6) and a predominance of males (56.4%). Around one-third of the HIE cases (36.6%) had moderate HIE (stage 2), whereas 35.1% of infants had severe HIE (stage 3), according to Sarnat staging. Compared to the control group, children with HIE were twice as likely to be born to mothers with maternal comorbidities and more likely to have prepartum and intrapartum complications. A 24-month follow-up of neurodevelopmental outcomes for HIE babies revealed that approximately 24% exhibited delays in gross motor skill development, 22% in fine motor skill development, 33% in language skill development, and 22% in social skill development.

Conclusion: In the HIE group, maternal comorbidities and prepartum or intrapartum complications were more common. The severity grade of HIE can be used to predict neurodevelopmental consequences. Enhancing patient care and rehabilitation requires a minimum of 24 months of neurodevelopmental follow-up.

Keywords: hypoxic-ischaemic encephalopathy, seizure, perinatal asphyxia

Introduction

Hypoxic-ischaemic encephalopathy (HIE) is a combination of clinical and biochemical signs of immediate or subacute brain injury in term or near-term newborns associated with asphyxia.^{1,2} HIE affects approximately one to eight per 1000 live newborns worldwide.³ It is regarded as one of the most prevalent causes of persistent injury to the central nervous system, leading to newborn mortality or neurodevelopmental impairment.⁴ Infants with moderate HIE have a 10% chance of death, while those who

survive have a 30% chance of developing impairments.⁵ Infants with severe HIE have a 60% chance of death, and nearly all survivors suffer from epilepsy and neurodevelopmental damage, such as cerebral palsy and intellectual incapacity.⁶

The conventional treatment for newborns of ≥ 36 weeks' gestational age (GA) with moderate to severe HIE is therapeutic hypothermia.^{7–10} The first injury generally creates reactive oxygen species, neurotransmitters, inflammatory mediators, and apoptosis.¹¹ Hypothermia mitigates this toxicity. Erythropoietin has also been provided to newborns with prenatal HIE to minimise the risk of brain injury, cerebral palsy, and cognitive impairment; however, there is limited evidence to support its role as an adjuvant to hypothermia.^{1,12}

Numerous studies have been undertaken to investigate the risk factors associated with HIE and its consequences.^{13–16} Although these studies have identified peripartum monitoring patterns and acute obstetric emergency events associated with neonatal HIE morbidity and mortality,^{13–15} they have not identified risk factors for HIE in the absence of a sentinel event, other than nulliparity and infection (not identified before delivery), with comparable morbidity and mortality between cases of unexplained HIE and those with a sentinel event. Most commonly reported risk factors for HIE included meconium-stained amniotic fluid, a prolonged second stage of labour, the occurrence of a sentinel or acute event, signs indicated by electronic fetal monitoring such as an indeterminate baseline heart rate, bradycardia, low variability, rupture of a previous uterine caesarean scar and placental abruption, nulliparity, infection, clinical chorioamnionitis, a maternal age of ≥ 35 years, and a urinary tract infection during pregnancy.^{13–16}

Given the significance of sentinel events, research continues to emphasise the significance of developing improved mechanisms for prediction and prevention, with a focus on reducing other complications, such as clinical chorioamnionitis and/or maternal pyrexia, to improve the ability to prevent HIE.¹⁵

Few local studies have sought to investigate the characteristics of HIE in Saudi Arabia. Al-Shehri et al described the risk factors for the development of HIE in 57 cases and a comparable number of controls.¹⁷ Identified HIE risk variables included a non-cephalic presentation, antepartum haemorrhage, instrumental delivery, and a prolonged second stage of labour.¹⁷

Although previous research has examined the epidemiological characteristics of newborns with HIE, there is limited evidence regarding the neurodevelopmental outcomes of these children. Using clinical and imaging biomarkers, this research aimed to identify predictors of HIE and neurodevelopmental outcomes in newborns. This research may facilitate the identification of novel risk factors for HIE among newborns in Saudi Arabia, as well as the identification of important elements to predict potential severe neurodevelopmental consequences, hence facilitating the use of HIE severity as a predictive tool.

Methods

Study Type and Population

We conducted a retrospective case-control study to identify clinical and labour-related HIE risk factors. In addition, a retrospective cohort study was undertaken on infants with HIE to describe their neurodevelopmental outcomes over their first two years. Initially, the study group comprised all live-born newborns at KACSH, Riyadh, Saudi Arabia, between 2015 and 2019. Then, for the case-control study, the study case group comprised newborns who had been admitted to the neonatal intensive care unit (NICU – Level IV) with a final diagnosis of HIE, either as a primary diagnosis or a secondary diagnosis attributed to other causes of encephalopathy, such as major congenital anomalies or metabolic disorders. The diagnosis of HIE was confirmed based on the operational definition outlined in the hospital's developmental policies and procedures (DPP 7610–2009) as a clinical syndrome characterised by abnormal consciousness, tone, reflexes, feeding, and respiration (and occasionally seizures) in full-term or near-term newborns. This syndrome is a subtype of neonatal encephalopathy, which can occur for a variety of reasons, including HIE,¹⁸ and is characterised by significant oxygen and blood flow restriction near the time of delivery. As it was difficult to follow their neurodevelopmental-outcome data, we excluded neonates who were born in other facilities or who had been moved to another hospital after birth. For each case of HIE, up to four controls were selected at random from all hospital deliveries during the same calendar year and matched to the HIE cases in terms of gestational age (± 2 weeks) and maternal age (± 5 years).

Study Variables for HIE Cases and Control

Clinical data for each HIE case and control were extracted from the hospital's electronic medical record (ie, maternal obstetric history and delivery details). The following data were extracted: antepartum-associated risk factors, intrapartum-associated

risk factors, and infant characteristics. The antepartum-associated risk factors included maternal age at delivery, maternal comorbidities (eg, gestational diabetes, hypertension, thyroid disease), and maternal mortality during the delivery. For the intrapartum-associated risk factors, we collected data on the gestational age, mode of delivery (vaginal or C-section), and intrapartum complications and events, including malpresentation, abnormal cardiotocographic findings, the presence of peripartum decelerations, positive screening for a group B streptococcus test (GBS), meconium-stained amniotic fluid, abruption placentae, uterine rupture, and abnormality of amniotic fluid. For the neonatal data, the following variables were collected: sex, birth weight, Apgar score (at 1, 5, and 10 minutes), the need for and method of resuscitation (including the use of non-invasive or invasive ventilation), the presence of congenital anomalies, and the length of stay in NICU for those admitted to NICU.

Classification of HIE Cases and Description of Their Clinical Variables

Clinical and radiological investigation information was extracted from the HIE patients' medical records. This was performed exclusively for HIE cases to offer a descriptive analysis of this group of patients. Thus, information regarding the severity of HIE, mortality, abnormalities in imaging modalities, documentation of neonatal seizures, cerebral palsy, and intellectual and learning deficits were retrieved. A trained neonatology expert evaluated the severity of HIE as normal, mild (stage 1), moderate (stage 2), and severe (stage 3) based on the modified Sarnat Staging System.¹⁹ In addition, information was collected on the treatment and utilisation of therapeutic hypothermia for mild and severe HIE. Data on various clinical investigations conducted on HIE cases, such as audiology tests, autism spectrum disorder, attention deficit hyperactivity, diagnosis of epilepsy, and EEG information, were obtained. The hospital followed a set of diagnostic criteria and a precise definition for diagnosing these conditions.

Neurodevelopmental Outcomes of the HIE Cases

Only the HIE cases were monitored retrospectively for 24 months using medical records to describe the neurodevelopmental outcomes of this cohort concerning gross motor, fine motor, language, and social skills development. Thus, the HIE case's medical records were reviewed up to 24 months following delivery. Those who were lost to follow-up within this time frame were excluded. The neurodevelopmental assessment was standardised using the third edition of the Baily Scales of Infant and Toddler Development.²⁰ For infants and toddlers younger than five years of age, the Baily scales were used, whereas neuropsychology was utilised for older children. The neurodevelopment testing was standardised following the hospital policy that governs healthcare delivery and service management in terms of clinical visits, referrals, follow-up tests, and evaluation procedures.

Statistical Analysis

In the case-control study, the baseline characteristics of HIE cases and controls were reported as numbers and percentages for categorical variables and as mean and standard deviation (SD) for normally distributed continuous variables. Histogram and the Shapiro–Wilk test were employed to determine the data's normality. Using a Chi-square or Fisher's exact test for categorical variables and two-sample t-tests for continuous variables, we compared the maternal intrapartum factors and the neonatal features of the HIE patients (case group) with the control group. The risk factors of interest were estimated using conditional logistic regression models, the odds ratio (OR), a 95% confidence interval (CI), and p-values. We divided the characteristics that were substantially linked with HIE into three categories: maternal comorbidities, prepartum, and intrapartum. If $p < 0.05$, the variable was maintained in the final multivariable model.

For the cohort study analysis of HIE patients, we described the clinical outcome 24 months after birth for those patients who survived and for those whose clinical follow-up data were available. This included intellectual and learning disabilities, cerebral palsy, epilepsy, radiological findings, and treatment received. Using the Chi-square test or Fisher's exact test for categorical data, the difference between the proportion of patients stratified by HIE stage and their neurodevelopmental outcomes was analysed. The p-value threshold for statistical significance was set at $0 < 0.05$. The statistical analyses were conducted using version 15 of the STATA[®] software (StataCorp, College Station, TX, USA).

Results

Description of the Cases and Control

Initially, 79 infants with HIE were identified; however, after analysing the medical records of these infants, 19 infants were excluded from the case group (incomplete data), leaving 60 infants with an HIE diagnosis for analysis (which formed the study cases group). Of these cases, 234 infants (the control group) were matched, bringing the total number of infants included in the final case-control analysis to 294 (Figure 1). Then, the case group was retrospectively followed through their medical records for the neurodevelopmental outcome, which was available for 55 HIE cases, and these were included in the cohort analysis. Table 1 displays the maternal and labour characteristics of the HIE cases analysed and the control cases. The average maternal age for the study sample was 30.6 (5.6) years. The average maternal age was comparable across children with and without HIE ($p \geq 0.05$). The proportion of women with gestational diabetes was considerably greater among children with HIE compared to the control group (26.9% vs 13.6%) (p -value = 0.010), and the occurrence of polyhydramnios was significantly higher among HIE cases compared to controls (3.1% vs 0.4%) (p -value = 0.041). The prevalence of peripartum distress during childbirth was considerably greater among children with HIE (case group) compared to infants in the control group compared to the case group (1.2% vs 78.3%) (p -value < 0.001).

The majority of HIE patients and controls were male (56.4%), with a mean gestational age of 38.8 weeks (SD = 1.6) (Table 2). Children with HIE were much more likely to be born to mothers who suffered maternal uterine rupture, and showed considerably higher rates of meconium-stained amniotic fluid and nuchal cord compared to controls (Table 2). Similarly, the Apgar scores for 1, 5, and 10 minutes were significantly lower among HIE cases than among controls, with HIE cases significantly more likely to have 5- and 10-min Apgar scores below 7 on average. Of the HIE patients that required resuscitation, 77.0% were intubated. In addition, congenital abnormalities were more prevalent among HIE cases than among the control group; (p -value < 0.001).

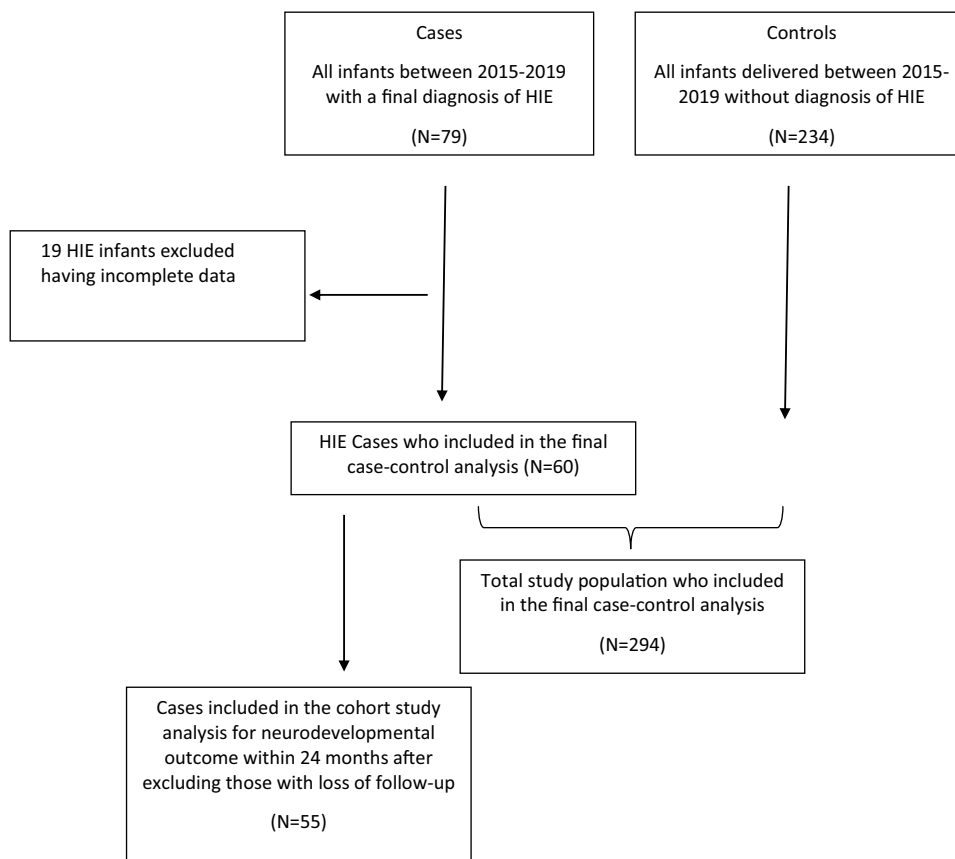


Figure 1 Flow chart describing the enrollment of the hypoxic-ischemic encephalopathy (HIE) cases and controls.

Table 1 Maternal and Labor Characteristics for the Hypoxic-Ischemic Encephalopathy Cases and Their Matched Controls

Characteristics	All Patients (n = 294)	Control (n = 234; 80%)	Cases (n = 60; 20%)	P-value*
Maternal age (mean± SD)	30.6±5.6	30.3±5.4	31.6±6.4	0.130
Maternal comorbidity				
Thyroid disease	18 (6.1)	12 (5.1)	6 (10.0)	0.163
Gestational diabetes	48 (16.3)	32 (13.6)	16 (26.9)	0.010
Hypertension	6 (2.1)	4 (1.7)	2 (3.1)	0.420
Prepartum complications and events				
Presence of fetal deceleration	50 (17.0)	3 (1.2)	47 (78.3)	< 0.001
Positive screening for GBS	39 (13.2)	32 (13.6)	7 (11.1)	0.683
Breech presentation	9 (3.1)	6 (2.5)	3 (5.0)	0.320
Polyhydramnios	3 (1.0)	1 (0.4)	2 (3.1)	0.041
Oligohydramnios	4 (1.3)	2 (0.8)	2 (3.1)	0.137
Mode of delivery				< 0.001
Vaginal (spontaneous or induced)	218 (73.8)	198 (84.6)	20 (33.3)	
Caesarean section (emergency or elective)	76 (25.8)	36 (15.3)	40 (66.6)	

Notes: *Chi square or Fisher's exact test was used for the categorical variables and the two-sample t-tests for the age. Cutoff point of 0.05 was used for significant level.

Abbreviations: SD, standard deviation; GBS, positive screening for a group B streptococcus test.

Table 2 Intrapartum-, Postpartum-, and Neonatal-Related Characteristics for the Hypoxic-Ischemic Encephalopathy Cases and Their Matched Controls

Characteristics	All Patients (n = 294)	Control (n = 234; 80%)	Cases (n = 60; 20%)	P-value
Gestational age at delivery; mean (SD)	38.8±1.6	38.9±1.5	38.4±1.9	0.113
Infant characteristics				
Male	166 (56.4)	125 (53.4)	41 (68.2)	0.032
Birth weight (kg); mean (SD)	3.13±0.1	3.17±0.47	2.93 (0.61)	0.004
Head circumference (cm); mean (SD)*	34.3±2.5	34.4(1.4)	33.7 (4.9)	0.060
Placenta abruption	10 (3.4)	1 (0.4)	9 (15.0)	< 0.001
Uterine rupture	3 (1.0)	0	3 (3.3)	0.005
Meconium staining	42 (14.0)	22 (9.4)	21 (33.3)	< 0.001
Meconium aspiration	10 (3.4)	0	11 (17.4)	< 0.001
Nuchal cord	29 (9.8)	18 (7.6)	11 (17.4)	0.014
Apgar score; mean (SD)				
At 1 minutes	7.4±2.7	8.6±0.7	2.2±1.6	< 0.001
At 5 minutes	8.1±1.7	8.9±0.34	5.1±2.1	< 0.001
At 10 minutes	8.5±1.3	9±1	6.1±1.9	< 0.001
Arterial cord pH; mean (SD)	7.07±0.1	7.2±0.06	7.01±0.15	< 0.001
Resuscitation				
Bag valve mask ventilation	60 (20)	0	60 (95.2)	< 0.001
Positive-pressure ventilation	61 (20)	4 (1.7)	57 (95)	< 0.001
Cardiac massage	9 (3.1)	0	9 (15.8)	< 0.01
Bicarbonate given	3 (1.0)	0	3 (4.7)	0.001
Epinephrine	2 (0.6)	0	2 (4.7)	0.005
Intubation	47 (15)	0	47 (77)	< 0.001
Neurological examination abnormality after delivery	27 (9.1)	0	27 (54)	< 0.001
Presence of congenital abnormality (congenital heart diseases, central nervous system diseases, congenital hypothyroidism, and bilateral hydronephrosis)	19 (6.4)	8 (3.4)	11 (17.4)	< 0.001
Dysmorphism	8 (2.7)	0	8 (13.3)	< 0.001

Notes: *Chi square or Fisher's exact test was used for the categorical variables and the two-sample t-tests for the age.

Abbreviations: SD, standard deviation; GBS, positive screening for a group B streptococcus test.

Factors Associated with HIE Cases Compared to Controls

Table 3 presents the results of a univariate logistic regression study of clinical and labour characteristics linked with HIE. Compared to infants in the control group, infants with HIE were twice as likely to be born to mothers with maternal comorbidities (OR 2.68, 95% CI 1.45–4.96, $p \leq 0.05$), and this remained unchanged after controlling for other variables. Similarly, infants with HIE were more likely than infants in the control group to experience prepartum and intrapartum complications ($p \leq 0.05$).

Description of the Clinical Characteristics of HIE Cases

The clinical outcomes and complications of HIE patients are detailed in Table 4. Sixty infants with HIE (case group) were included in this investigation. Of these, 28.3% had mild HIE (ie, stage 1), 36.6% had moderate HIE (ie, stage 2), and 35.1% of infants had severe HIE (ie, stage 3). Table 4 presents the clinical outcomes and neurological complications of the HIE cases,

Table 3 Clinical and Labor Characteristics and Factors Associated with Hypoxic-Ischemic Encephalopathy Cases Compared to Control Cases

Characteristic	Univariate Analysis Unadjusted OR (95% CI)	Multivariable Analysis Adjusted
Maternal comorbidity disease	2.68 (1.45–4.96)	2.73 (1.11–0.03)
Prepartum complication	25.1 (11.5–55.0)	30.2 (11.8–77.2)
Intrapartum complication	9.82 (5.17–18.6)	13.5 (5.37–34.09)

Notes: The significant risk factors were lumped in three categories maternal comorbidity, prepartum, and intrapartum complications. Reference group were those who do not have those factors.

Abbreviations: CI, confidence interval; OR, odds ratio.

Table 4 Clinical Outcomes and Complication of the Patients with Hypoxic-Ischemic Encephalopathy

	Total Population n = 60 (%)	Staging According to Sarnat			P-value*
		Stage 1 17 (28.3%)	Stage 2 22 (36.6%)	Stage 3 21 (35.1%)	
Muscle tone					
Normal	18 (29.3)	13 (71.3)	2 (10.0)	3 (14.2)	< 0.001
Hypotonia	36 (60.0)	4 (23.5)	19 (86.3)	13 (62.1)	<0.001
Hypertonia	6 (10.0)	0	1 (4.5)	5 (23.8)	< 0.001
Treatment					
Therapeutic hypothermia	45 (75)	8 (47.1)	20 (90.9)	17 (89.4)	< 0.001
Erythropoietin	41(68.3)	9 (52.9)	16 (72.7)	16 (84.2)	0.011
Imaging modularity					
Abnormal CT	6 (10)	1 (5.2)	1 (4.5)	3 (15)	0.172
MRI abnormality finding	36 (61)	5 (29.4)	13 (59.1)	17 (98)	0.001
Basal ganglia or thalamus lesion	17 (28.3)	3 (17.6)	6 (27.2)	7 (36.8)	0.081
Watershed predominant	26 (43.3)	4 (23.5)	8 (36.3)	13 (68.4)	0.031
White-matter predominant	21 (35)	2 (11.7)	7 (31.8)	11 (57.8)	0.050
Global	22 (36)	3 (17.6)	9 (40.9)	10 (52.6)	0.021
Outcome among those who survived					
Intraventricular hemorrhage	10 (15.8)	2 (10.5)	3 (13.6)	5 (25)	0.624
Delayed myelination	2 (3.1)	1 (5.2)	0	1 (5)	0.562
Hypoglycemia encephalopathy	1 (1.5)	0	1 (4.5)	0	0.900
Intellectual disability	2 (3.1)	1 (5)	0	1 (5)	0.800
Learning disability	1 (1.5)	0	0	1 (5)	0.660
Cerebral palsy	4 (6.3)	0	0	4 (20)	0.021
Epilepsy	5 (7.9)	0	0	5 (25)	

Note: *Chi square test was used for the categorical variables.

Abbreviations: CT, computerized tomography scan; MRI, Magnetic resonance imaging.

stratified by HIE severity stage, for all HIE cases. The most prevalent characteristic among HIE cases was hypotonia (60%), followed by normal muscular tone (29.3%) and hypertonia (10%). Seventy-five percent of all HIE cases and 89% of HIE stage 2 cases were treated with therapeutic hypothermia. Only patients with moderate to severe HIE are administered therapeutic hypothermia, per centre policy. Imaging abnormalities on magnetic resonance imaging (MRI) were more common in HIE stage 3 patients than in HIE stages 2 or 1. Around 44.8% of HIE cases had neonatal seizures, of which 82% had simple seizures (defined as seizures in which the patient maintains consciousness) and 17% were intractable. At hospital discharge following the diagnosis of HIE, phenobarbital was the most commonly recommended drug for 37 cases (62%). In eight patients (13.3%) with HIE, audiology tests were abnormal, autism spectrum disorder was present in two patients (3.3%), and attention deficit hyperactivity disorder was present in two individuals (3.3%).

Epilepsy was identified in 6.6% of HIE cases, and of those with epilepsy, three (75%) patients had uncomplicated epilepsy (two patients received levetiracetam and the other received valproic acid) and one patient had intractable epilepsy (and therefore received levetiracetam and topiramate). Around 28% of HIE patients had first EEG background information in their medical file; of these, 56% had a normal first EEG background and 40% had an abnormal one. Nine (30%) of these individuals showed epileptiform activity on their initial EEG, while five (16%) had a burst suppression pattern. Seven individuals (41%) exhibited a final EEG pattern, of which four (23%) exhibited aberrant epileptiform activity and none exhibited a burst suppression pattern.

Neurodevelopmental Outcome of HIE Cases During 24 Months After Delivery

A total of 55 HIE infants out of the original 60 HIE infant cases were included in the study and had a complete follow-up over 24 months. Table 5 displays the neurodevelopmental outcomes at 24 months for the 55 HIE infants whose records were complete. In total, 42 infants (76.3%) had no delay in gross motor skills development, whereas 3.5%, 9.1%, and 10.9% had mild, moderate, or severe delays in gross motor skills development, respectively. The majority of individuals with a moderate

Table 5 Neurodevelopmental Outcome After 24-Months Follow-Up According to the HIE Staging

	Study Population n = 55 (%) Total (%)	Staging According to Sarnat			P-value
		Stage 1 16 (29.1%)	Stage 2 19 (34.5%)	Stage 3 20 (36.3%)	
Neurodevelopmental outcome after 24 month follow-up					
Gross motor skills development					0.035
No delay	42 (76.3)	14 (87.5)	19 (100)	9 (45.0)	
Mild	2 (3.5)	0	0	2 (10.5)	
Moderate	5 (9.1)	2 (12.5)	0	3 (15.7)	
Severe	6 (10.9)	0	0	6 (30.0)	
Fine motor skills development					0.011
No delay	43 (78.1)	14 (87.5)	19 (100)	10 (50.0)	
Mild	2 (3.6)	0	0	2 (10.0)	
Moderate	3 (5.4)	2 (12.5)	0	1 (5.6)	
Severe	7 (12.7)	0	0	7 (35.0)	
Language skills development					0.009
No delay	37 (67.6)	11 (68.7)	16 (72.7)	10 (48)	
Mild	5 (9.0)	2 (12.5)	2 (9.1)	1 (5)	
Moderate	6 (10.9)	3 (18.7)	1 (4.5)	2 (10.5)	
Severe	7 (12.7)	0	0	7 (36.8)	
Social skills development					0.012
No delay	43 (78.1)	13 (81.2)	19 (100)	11 (55.0)	
Mild	1 (1.8)	0	0	1 (5.0)	
Moderate	3 (5.4)	3 (18.7)	0	0	
Severe	8 (14.5)	0	0	8 (40.0)	

Note: Fisher's exact test was used for the categorical variables.

to severe delay in gross motor development had HIE stage 3. Similarly, 78.1% of the 55 infants with HIE had no delay in the development of their fine motor skills, whereas 12.7% had a severe delay in the development of their fine motor skills, and all of them had HIE stage 3. A total of 67.6% of all HIE cases exhibited no delay in language skills, while 9% exhibited mild delay, 10.9% exhibited moderate delay, and 12.7% exhibited a severe delay. Around 78.1% of HIE cases exhibited no delay in the development of social skills, while 1.8% and 5.4% of cases exhibited mild and moderately severe delays, respectively. Approximately 14.5% of individuals exhibited severe social developmental deficits, and 40% had HIE stage 3 (Table 5).

Discussion

The objectives of this study were to identify risk factors for HIE and to describe the clinical and neurological characteristics of infants diagnosed with HIE. Intrapartum risk factors, such as placenta abruption, uterine rupture, meconium-stained amniotic fluid, and nuchal cord, were substantially more prevalent among HIE cases. Two-thirds of the HIE cases exhibited a mild delay in gross motor skills development at the age of 24 months, but the majority had no delay in fine motor, language, or social skills development, respectively.

Previous studies have investigated the maternal and neonatal factors associated with an elevated risk of HIE.^{3,13–15,21} Consistent with previous research, maternal comorbidities such as gestational diabetes were prevalent in our study among mothers who had a child with HIE compared to the control group. Newborns whose mothers had comorbidities were twice as likely to have HIE compared to infants whose mothers did not have comorbidities.²¹ Previous research indicated maternal hypertension as a frequent risk factor for HIE; however, our study failed to reveal a significant link ($p = 0.42$).¹

Compared to the control group, the HIE cases were shown to have a considerable risk for the prepartum complication/event of peripartum distress during labour (78% vs 1.2%), such as polyhydramnios (3.1% vs 0.4%). Regarding other prenatal complications/events, such as GBS screening positivity, breech presentation, and oligohydramnios, the HIE cases did not demonstrate statistical significance ($p > 0.05$) when compared to the controls. Surprisingly, our analysis found no connection between non-cephalic presentation and the incidence of HIE (5% vs 2.5%). This contradicts the conclusions of the Abha City (southwest Saudi Arabia) study conducted in 2005.¹⁷ Multiple factors could have contributed to the difference between the two studies' findings. High-risk pregnancies, including obesity, the presence of diabetes mellitus, high blood pressure, intrauterine growth restriction, multiple pregnancy (twins, triplets, or more), the presence of autoimmune disorders, smoking status, maternal age (a mother who is under 20 or over 35) and a history of complications in previous pregnancies are important factors that might have increased the risk of HIE and may account for the differences between our current study and the previous study in Abha.²² Unfortunately, however, we did not have information on these variables to explore the difference in the maternal profiles between the two studies.

The majority of HIE cases were male, which was substantially different from the control group ($p=0.03$), and the incidence of acute intrapartum events was likewise higher in HIE cases than in controls. The incidence of placenta abruption, uterine rupture, meconium-stained amniotic fluid, and nuchal cord was substantially higher among HIE cases ($p \leq 0.05$). Similarly, the Apgar ratings for 1, 5, and 10 minutes were considerably lower for HIE cases than for controls. Significantly more HIE cases had average 5- and 10-minute Apgar scores below 7 than non-HIE cases. These findings are comparable to those of a 2005 local study that identified the following risk variables as significant: mode of delivery, antepartum haemorrhage, low Apgar score, and low birth weight.²³ In the HIE group, congenital abnormalities and dysmorphism were more prevalent than in the control group ($p < 0.001$): 17% vs 3.4% and 13% vs 0%, respectively. This confirms the findings of previous studies that identified HIE risk factors, which defined meconium-stained amniotic fluid as a risk factor that increases the risk of HIE by 12-fold.¹⁶ Both antepartum and intrapartum conditions are considered to be potential risk factors for the development of HIE. Antepartum factors, including gestation above 41 weeks, and intrapartum factors, including prolonged membrane rupture, thick meconium, abnormal cardiotocography, sentinel event, shoulder dystocia, tight nuchal cord, and failed suction, are significant risk factors for HIE.²⁴

Around 77% of all HIE patients who had resuscitation were intubated; 95% required bag valve mask ventilation and positive pressure breathing; only nine individuals had a cardiac massage, and two patients were administered epinephrine.

Magnetic resonance imaging (MRI) is the most sensitive and specific imaging method for assessing infants suspected of having hypoxic-ischaemic brain injury.^{25,26} Brain MRI was categorised as the final HIE-recommended pattern in this study.²⁷ MRI abnormalities were more prevalent in cases of severe HIE (stage 3) than in cases of moderate and mild HIE (stages 2

and 1). Watershed prominent lesions were the most numerous, followed by global, white matter, and basal ganglia or thalamus lesions ($p < 0.001$). Although HIE cases were more likely to have abnormal brain CT scans than controls, we were unable to demonstrate a significant link ($p = 0.17$). Imaging plays a crucial role in the diagnosis and treatment of HIE, guiding case management in the acute setting and providing significant prognostic information for the long term.²⁸ To make an accurate radiologic diagnosis of HIE, one must be conversant with the numerous imaging symptoms of this injury. Brain maturity, the duration and severity of the injury, and the type and timing of imaging examinations all influence the findings in HIE.²⁸ Severe hypoxia-ischaemia preferentially affects the deep grey matter in both preterm and term infants, with periorlandic involvement being detected more commonly in the latter age group. Less severe injuries cause periventricular white matter injury and intraventricular haemorrhages in preterm infants, and infarcts in the parasagittal watershed territory in term neonates. In the neonatal period, acute injuries result in diffuse damage to grey matter, but the periorlandic cortex and structures supplied by the posterior circulation are mostly spared.²⁸

In our study, around 75% of all HIE cases and 89% of severe HIE (stage 3) cases were treated with therapeutic hypothermia. In the majority of these patients, erythropoietin was also administered. This includes 84% of patients with severe HIE (stage 3) and 72% of patients with moderate HIE (stage 2). In a non-human animal model of prenatal hypoxia, a previous study found that therapy with erythropoietin and hypothermia decreased cerebral palsy. In addition, the efficacy of combining moderate hypothermia and erythropoietin for the treatment of neonatal HIE was promising.²⁹

Neurodevelopmental outcomes are more prevalent in cases of severe HIE (stage 3) than in mild and moderate cases (stages 1 and 2). These include intellectual disability, learning disabilities, autism spectrum disorder, attention deficit hyperactivity disorder, cerebral palsy, and epilepsy. Cerebral palsy and epilepsy were significantly associated with severe HIE (stage 3) ($p < 0.02$). Cerebral palsy cases accounted for 6.3% of all severe HIE (grade 3) cases, with the majority being quadriplegia, one case being diplegia, and other forms (hemiplegia or monoplegia) not noted in any patients. A total of 42 newborns with HIE had abnormal muscle tone, with the majority (60%) having hypotonia. At the 24-month follow-up, concerning the neurodevelopmental outcomes, which comprise gross motor, fine motor, language, and social skills, only 24% of HIE cases exhibited gross motor skills development delays, while 22%, 33%, and 22% had delays in fine motor, language, and social skills, respectively. The majority of severe HIE (stage 3) cases exhibited substantial delays in all four neurodevelopmental-outcome domains, with language skills development being notably affected ($p < 0.05$). However, all developmental skills indicated a significant connection with the severity of HIE. The previous literature reported that the spectrum of developmental outcomes associated with HIE includes motor delays, learning difficulties, cognitive impairment, neurodevelopmental disorders, and visual and hearing impairments.³⁰

In over half of the HIE cases, a neonatal seizure was identified, with the majority being a simple seizure that was most frequently treated with phenobarbital. Around 38% of HIE patients with neonatal seizures were discharged without antiepileptic therapy. In 6.6% of HIE cases, epilepsy was identified, with the majority having uncomplicated seizures that required only one drug. In HIE cases with epilepsy, levetiracetam was the most frequently prescribed medicine, followed by valproic acid. An electroencephalogram (EEG) was performed in only 28% of HIE cases, and aberrant background was frequently noted in the initial EEG. In addition, in the initial EEG, epileptiform activity was detected in nine patients, although the burst suppression pattern (shown in [Figure 2](#)) was detected in only five individuals. In the previous EEG, only 23% of patients had aberrant results, which included abnormal epileptiform activity. In the 2005 study conducted in Abha City (southwest Saudi Arabia),¹⁷ moderate or severe HIE occurred in approximately 63% of all HIE cases, with seizures occurring in 67% of these cases. Seizures are common in infants with hypoxic-ischaemic encephalopathy and are strongly associated with neurodevelopmental outcomes that are detrimental. Preclinical research suggests that the majority of anticonvulsants are associated with detrimental effects on the developing brain.³¹ Levetiracetam appears to have fewer possible neurotoxic effects than other anticonvulsants; yet, it may not be more effective. Small clinical trials suggest that prophylactic administration of phenobarbital may improve neurodevelopmental outcomes in comparison to delayed treatment; however, additional, high-quality research is needed to validate this.³¹

This study was able to uncover prenatal/antenatal and perinatal variables related to HIE that were more thorough and precise than those discovered in other Western Asian studies, particularly local studies conducted in Saudi Arabia. This study had limitations. First, the data were gathered from a single centre, limiting the generalisability of this study's findings and emphasising the need for a nationwide register of HIE cases. By identifying risk variables and analysing the

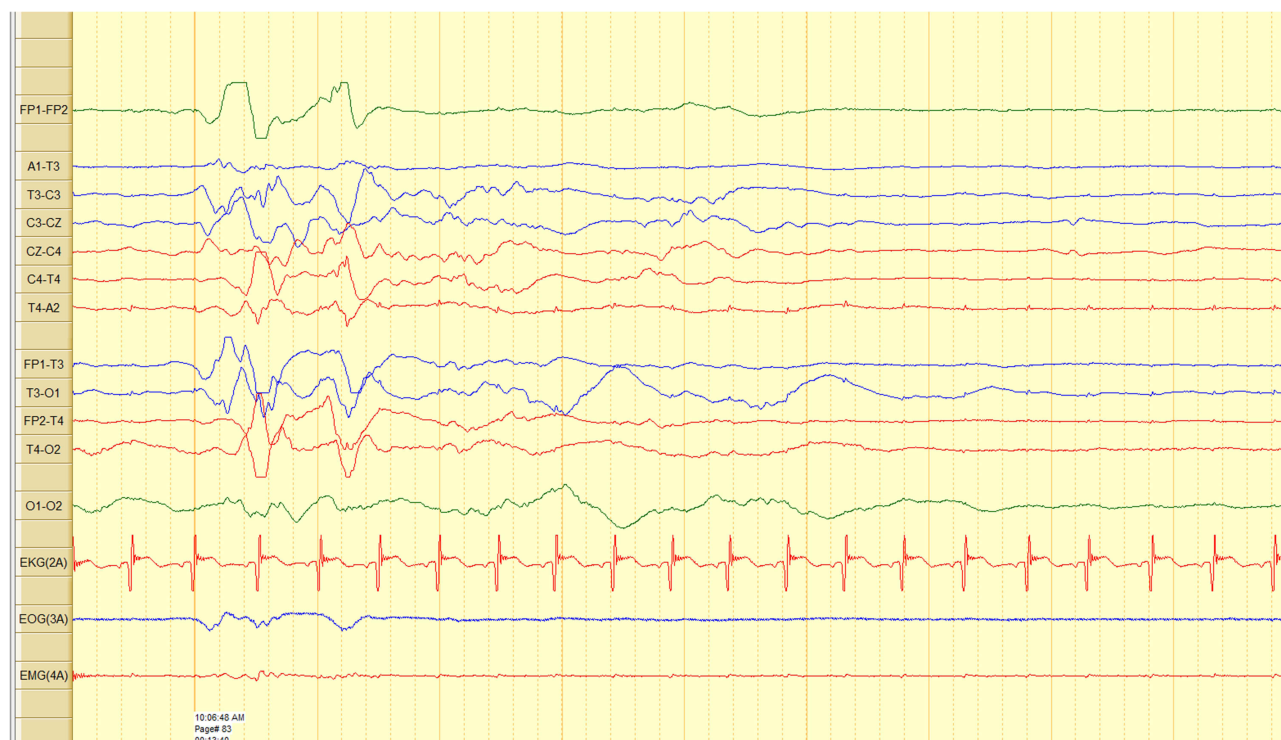


Figure 2 EEG in neonate with Hypoxic ischemic encephalopathy showing burst suppression pattern.

most effective management strategies, such a registry would greatly assist the care of newborns with HIE by identifying risk factors and assessing the most effective management plans. The second limitation of this investigation was the potential effect of the presence of unmeasured or uncollected confounders between cases and controls, which could either underestimate or overstate the associated risk. Our study sample size was relatively small and additional research with a larger sample size is necessary to improve the accuracy of our estimates. Lastly, the completeness of the obstetric, neonatal, and neurologists' records from which the study data were retrieved or obtained may have an impact on the validity of the findings. In light of these limitations, it is recommended to interpret the results with caution.

Conclusion

In neonates diagnosed with HIE, maternal comorbidities such as gestational diabetes, fetal deceleration, and polyhydramnios were more prevalent. These results demonstrate the need to implement stringent preventative measures, especially for high-risk pregnancies. The severity grade of HIE can be utilised as a predictor of neurodevelopmental outcomes, particularly gross motor skills. A minimum of 24 months of neurodevelopmental follow-up is required to improve the care and rehabilitation of patients. Further research is needed to explore the role of HIE severity in predicting infants' neurodevelopmental outcomes.

Abbreviations

HIE, hypoxic-ischemic encephalopathy; GA, gestational age; NICU, neonatal intensive care unit; DPP, developmental policies and procedures; GBS, group B streptococcus test; OR, odds ratio; CI, confidence interval; MRI, magnetic resonance imaging; EEG, electroencephalography.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval

This study has been approved by research ethics committee, Institutional Review Board (IRB), King Abdullah International Medical Research Centre (KAIMRC), Riyadh, Saudi Arabia (reference number RC19/302/R). All methods were carried out in accordance with relevant guidelines and regulations or declaration of Helsinki. The need for informed consent was waived by the ethics committee/Institutional Review Board of King Abdullah International Medical Research Center (KAIMRC), because of the retrospective nature of the study and based on the fact that patients gave their consent upon admission to hospital. All patients' data were kept anonymized in a password secured external driver by the primary investigator.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that there are no conflicts of interests.

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