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St. Paul Hospital Millennium Medical College

Post Graduate Study Program

Assessment of early neurodevelopmental outcome of patients with moderate to severe hypoxic ischemic encephalopathy at 3 and 6 Months: A Multicenter Study in Addis Ababa.

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January, 2026

Addis Ababa, Ethiopia

Assessment of early neurodevelopmental outcome of patients with moderate to severe hypoxic ischemic encephalopathy: A Multicenter Study in Addis Ababa.

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Addis Ababa, Ethiopia

Name of the Investigator	Dr. Munira Mohamed
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Abbreviation And Acronym

BPD Bronchopulmonary Dysplasia

CI Confidence Interval

CNS Central Nervous System

CP Cerebral palsy

HIC High Income Countries

HIE Hypoxic Ischemic Encephalopathy

IVH Intraventricular hemorrhage

MRI Magnetic Resonance Image

NDI Neurodevelopmental Impairment

OR Odd Ratio

PPV Positive Predictive Value

PVL Periventricular Leukomalacia

TH Therapeutic Hypothermia

A. Abstract

Background: - Neonatal hypoxic ischemic encephalopathy is an important cause of permanent damage to central nervous system tissues that may result in neonatal death or manifest later as cerebral palsy or developmental delay or learning disability and epilepsy. Surviving neonates with severe birth asphyxia and hypoxic ischemic encephalopathy has variable neurodevelopmental outcomes. Despite advancements in neonatal intensive care, a significant proportion of neonates who survive moderate to severe HIE continue to face adverse outcomes, including cerebral palsy, developmental delays, and cognitive impairments.

Objective: - Assessment of early neurodevelopmental outcome of patients with moderate to severe hypoxic ischemic encephalopathy in Addis Ababa.

Methods: - hospital-based, prospective cohort study with descriptive longitudinal analysis was conducted from June, 2025, – February, 2026, G.C. The data were collected using a standard questionnaire using a pretested structured interviewed and chart review questionnaire. The sample size was calculated based on the primary binary outcome (normal vs abnormal HINE score at six months). Using a 95% confidence level (Z = 1.96) and an expected proportion of abnormal outcomes of 20% from previous high-risk infant cohorts, the required sample size to estimate this proportion with a margin of error of 10%. rounded to 62. To increase precision, 10% of dropout/no responders was added and a total of 70 infants were enrolled. All enrolled infants completed follow-up assessments, and there was no loss to follow-up.

Results: At three months, the median HINE score was 51.0 (; range 22–60), with 57% of infants demonstrating abnormal neurological findings, and 55% classified as having severe neurological impairment. At six months, the median HINE score increased slightly to 58.0 (range 19–69), with 61% of infants continuing to show abnormal findings, of whom 72% had severe impairment. Among infants with normal neurological performance at three months, 86.7% remained normal at six months, while 97.5% of those with abnormal findings at three months continued to demonstrate abnormal performance. Severity-based analysis revealed predominantly persistent outcomes, particularly among infants with severe impairment at baseline. After adjustment, neonatal seizures remained an independent predictor of poor outcome at six months (adjusted odds ratio 14.7; 95% CI: 10.55–49.62; $p < 0.001$).

Conclusion: Abnormal neurological findings are highly prevalent among infants with moderate to

severe HIE, particularly in those with stage III HIE and neonatal seizures. prolonged resuscitation also has poor outcome. Early identification, close follow-up, and timely neuroprotective interventions are essential to support neurological development and optimize outcomes in this high-risk population.

Key word: -encephalopathy, neurodevelopment, SPHMMC

1. Introduction

1.1 Background

Neonatal hypoxic ischemic encephalopathy (HIE) is the clinical syndrome of disturbed neonatal brain function caused by perinatal asphyxia in the term or near-term infant (1). HIE is an acute encephalopathy that manifests as convulsion, apnea, and abnormal muscle tone caused by perinatal hypoxia and ischemia (2). It has been reported to cause death in newborns, acute neurological damage in the early period, and permanent neurodevelopmental problems in motor, cognitive and behavioral areas after years (3).

The incidence and factors of HIE may vary depending on the geographic region and the level of healthcare available (4, 5). The condition is more common in low- and middle-income countries (1.8 per 1000) than in high-income countries (0.5 per 1000) (4, 6). According to the study done in Ethiopia, illiterate mothers, no ultrasound checkup, preterm or post-term birth, caesarean section, and prolonged labor were a statistically significant factor for HIE (7).

HIE is an important cause of permanent damage to central nervous system (CNS) tissues that may result in neonatal death or manifest later as cerebral palsy or developmental delay or learning disability and epilepsy (8). HIE occurs in 1.5 per1000 full term births. Approximately 15-20% of infants with HIE die in the neonatal period, and 25% of survivors are left with permanent neurodevelopmental abnormalities (9). A prospective cohort study conducted in Uganda that followed term infants with neonatal encephalopathy up to 27–30 months reported high mortality and neurodevelopmental impairment rates. By two years of age, approximately 40.3% of infants with neonatal encephalopathy had died compared to 3.8% of non-encephalopathic controls. Among survivors, only 41.6% were free of neurodevelopmental impairment, while 29.3% had significant impairment including cerebral palsy and global developmental delay. The severity of encephalopathy, neonatal seizures, abnormal cranial ultrasound findings, and feeding difficulties at discharge were associated with adverse outcomes (37). Surviving neonates with severe birth asphyxia and hypoxic ischemic encephalopathy has variable neurodevelopmental outcomes they may have microcephaly, intellectual disability, psychomotor retardation (Gross motor and coordination problem), disabling cerebral palsy, epilepsy, blindness and hearing impairment (10).

Therapeutic hypothermia (TH) is now an accepted intervention in managing neonates with moderate-to severe HIE, and has been shown to prevent neurological disability (11, 12). Many studies in high income countries (HIC) have shown that TH resulted in improvement in neurodevelopmental outcome at 18–24 months of age, with only 25–30% having moderate-to-severe disability (12, 13). In low- and middle-income countries (LMIC), however, the benefits of TH remain unclear (14). A study in South Africa demonstrated that TH is feasible and safe in a resource-limited setting, provided there is adequate monitoring and support (15).

In the neonatal period, male gender, low APGAR score, severe acidosis, abnormal cranial MRI findings are risk factors that determine the neurodevelopmental prognosis of newborns with HIE. Epilepsy, cerebral palsy, and speech disorders are the most common chronic period problems in newborns with HIE. Monitoring and supporting the development of HIE cases with risk factors from the first months of life is very important for improving long-term outcomes (16). Depending on neurological symptoms and clinical findings in the newborn infant, the condition is graded as mild, moderate or severe (17). Moderate and severe HIE are known to be closely associated with significant neurological morbidity, long-term disability and mortality (18). From a public health perspective, early identification of neurodevelopmental impairment among infants with hypoxic-ischemic encephalopathy is critical, particularly in low- and middle-income countries where access to specialized rehabilitation services is limited. Early neurological screening tools that can be implemented within routine follow-up clinics allow for timely referral, targeted intervention, and more efficient allocation of scarce health resources. Serial neurological assessment during early infancy also provides an opportunity to stratify risk, counsel families, and strengthen continuity of care within existing maternal and child health services.

1.2 Statement of the problem

HIE is a major cause of neonatal death and neurodevelopmental impairment (NDI) (19, 20). Because perinatal asphyxia is unpredictable and difficult to prevent, adequate and timely treatment of affected newborns is essential for neuroprotective management of neonatal HIE (12). Therapeutic hypothermia is the only proven treatment for neonatal HIE (21).

However, not all neonates with HIE are eligible for therapeutic hypothermia, and there are still cases of treatment failure. One of the most challenging aspects of the management of a baby with probable HIE is counselling the parents about the likely prognosis. While many investigations have been explored as predictors of poor outcome, probably still the best tested and most widely used parameter is the severity of the encephalopathy. This is usually classified according to the three grades first described by Sarnat and Sarnat (17). There is consistency in the literature that the outcome of babies with mild HIE (grade 1) is good (almost 100% of patients are normal at follow up) and also that the outcome for severe HIE (grade 3) is poor, with a rate of death or survival with disability close to 100%(22). The situation is more difficult for babies with moderate HIE (grade 2) where the rates of poor outcome reported in the literature are quite variable, ranging from 20 to 50% in different papers(23-26).

The developmental outcome of HIE ranges from motor delay to learning disability, cognitive impairment, neurodevelopmental disorders and visual and hearing impairment. Studies have shown that TH reduces the rates of moderate or severe cerebral palsy (CP) from 30% to 19%, visual impairment from 14% to 7% and hearing impairment from 6% to 4% (27).

Despite advancements in neonatal intensive care, a significant proportion of neonates who survive moderate to severe HIE continue to face adverse outcomes, including cerebral palsy, developmental delays, and cognitive impairments. Early identification and monitoring of neurodevelopmental outcomes are critical for initiating timely interventions and improving quality of life(15, 19). A cohort study conducted in Uganda demonstrated that by two years of age, approximately 40% of infants with neonatal encephalopathy had died and only about 41.6% of survivors were free of neurodevelopmental impairment. Nearly one-third of survivors developed significant disability, including cerebral palsy and global developmental delay. These findings highlight the substantial long-term burden of HIE in sub-Saharan Africa and underscore the importance of early neurological assessment and risk stratification in similar resource-limited

settings (37)

In Addis Ababa hospitals, there is a growing need for local data to understand the early neurodevelopmental outcomes in infants affected by HIE. However, few studies have systematically assessed these outcomes at critical developmental milestones such as 3 and 6 months of age.

This study was done to address this gap by evaluating the neurodevelopmental risk status of infants with moderate to severe HIE at three and six months using age-specific HINE assessment, providing vital information for clinicians, policymakers, and caregivers to inform clinical decision-making and improve neonatal care strategies.

1.3 Significance of the study

Understanding the early neurodevelopmental outcomes of infants with moderate to severe hypoxic-ischemic encephalopathy (HIE) is essential for improving neonatal care and guiding early interventions. This study provides healthcare providers with data to identify infants at increased neurodevelopmental risk during the first months of life and plan appropriate interventions. The findings can inform hospital protocols, structured follow-up programs, and national neonatal care policies, including rehabilitation services and neurodevelopmental screening strategies. Additionally, the study contributes to the limited body of local research on HIE in Ethiopia, serving as a reference for future studies and potentially adding to global data on HIE in low- and middle-income countries. By highlighting early challenges faced by affected infants and their families, the study can also help improve caregiver education and support mechanisms.

2. Literature review

A study done India in Aligarh university on Neurodevelopmental outcomes in newborns with birth asphyxia among a total of 150 eligible asphyxiated newborn enrolled in the study, 91 babies were discharged. 89% of the Stage I HIE discharged infant had HINE score of more than 70 at 6 months whereas score of more than 65 was seen in 96%, 81% and 35% in the three advancing stages of HIE respectively. All babies in stage I, 77% of stage II and 50% of stage III babies had normal ophthalmological examination. All babies with stage III had an abnormal hearing(28).

Study done in Beatrix children university of Netherlands on Neurodevelopmental Impairment in Two-Year-Old Preterm-Born found that the out of 224 children 61(27%) had abnormal ASQ3 scores and 10 (4.5%) had NDI, using original cut-off scores for BSIDIII at -2SDs (<70). Significantly more children with a gestational age of <28 weeks failed ASQ3. Children who were part of a multiple birth, or who had intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL) >grade 2, or bronchopulmonary dysplasia (BPD). There were 10 (4.5%) children with NDI at the original BSIDIII cut-off thresholds of <70, 12 (5.4%) with an adjusted threshold of <80, and 15 (7.0%) with an adjusted threshold of <85. The negative predictive value (NPV) was 100% and positive predictive value (PPV) 16%. The significant correlation between ASQ-total scores and combined BSID scores, with a relatively wide range (R-square is 0.43, $p<0.001$). A cut-off for the ASQ total score below 188 led to a sensitivity of 96% with a specificity of 90% to detect NDI with a BSIDIII threshold set at < 70, area under the curve in the ROC curve was 96% ($p<0.0001$). The ranges in total ASQ scores for children with NDI and those without NDI (No-NDI), $p<0.001$. Children who passed ASQ3 had significantly higher cognitive scores and composite motor scores than children who failed ASQ3 ($P<0.001$), and who failed the ASQ without NDI ($P<0.001$)(29).

The study done in Turky on evaluation and Neurodevelopmental Outcomes of Infants with Hypoxic Ischemic Encephalopathy Treated with Therapeutic Hypothermia found that according to the Sarnat stage, moderate HIE was found in 17 infants (73.9%) and severe HIE was found in 6 infants (26.1%). Patients with severe HIE were found to have lower APGAR scores, more resistant metabolic acidosis, longer ventilation time, and abnormal cranial MRI findings in the neonatal period ($p<0.05$). DII DST results were normal in 12 (52.2%) patients and abnormal in 11 (47.8%) patients. 90.9% of infants with abnormal Denver II DST results were male. Denver II

DST results were abnormal in 29.4% of patients with moderate encephalopathy and in all patients with severe encephalopathy. Speaking (83.3%) and fine motor (100%) problems were found most frequently in infants with severe HIE. Epilepsy (100%), cerebral palsy (83.3%), and swallowing problems (50%) were found more frequently in infants with severe HIE compared to infants with moderate HIE (p:0.019, p:0.035, p:0.011). All of the infants with severe HIE needed physiotherapy, 66.7% needed speech therapy, 50% needed rehabilitation, and 33.3% needed vision and auditory therapies. Physiotherapy requirement was more frequent in infants with severe HIE compared to infants with moderate HIE (p: 0.014). Eighty-seven percent (n: 20) of the patients had convulsions in the neonatal period, but 50% (n: 10) of these patients had abnormal findings in MRI and EEG, and 55% (n:11) of them had abnormal Denver II DST results. It was determined that 65% (n:13) of the patients who had convulsions in the neonatal period were receiving drug treatment for epilepsy (30).

A study done in university of California, USA on Predictors of Death or Severe Impairment in Neonates with Hypoxic-Ischemic Encephalopathy Among 424 neonates, 105 (24.7%) had severe encephalopathy at enrollment. Overall, 59 (13.9%) died and 46 (10.8%) had severe NDI. Validation model metrics were 97.9% (95% CI, 92.7%-99.8%) for internal specificity, with a PPV of 77.8%, and 97.6% for external specificity, with a PPV of 46.2%. Internal specificity in this model was 98.9%, with a PPV of 92.9%; external specificity was 98.6%, with a PPV of 83.3%(31).

The study done in medical collage of Udaipur, India found that the neurodevelopmental outcome of babies with moderate to severe birth asphyxia with hypoxic ischemic encephalopathy found that 70 neonates with birth asphyxia HIE II / III were included in the study, 35 in TH group and 35 in non-TH group. Out of 70 babies enrolled 46 (65.7%) were having normal development and 24 (34.3%) were having development delay. Out of 46 who were having development delay 6 (17.4%) were of TH group and 18 (51.4%) were of non-TH group. Most of the babies of TH group i.e., 30 (85.7%) were neurodevelopmentally normal and 5 (14.3%) were having some neurodevelopmental abnormality (32).

A study done in Syndy university of Australia on One-year neurodevelopmental outcome after moderate newborn hypoxic ischaemic encephalopathy found that fifty-three babies who survived probable moderate HIE. Forty-two of these were seen at 1 year of age. Of these, 22 (52%) had

normal development and neurological examination and four (9.5%) had mild developmental delay with normal neurological examination. Thirteen babies (31%) had cerebral palsy, 11 of whom also had developmental delay. Two infants (5%) who had been severely impaired at 6 months died before 1 year of age. Overall, 36% of survivors of the neonatal period had significant disability and or had died by 1 year of age. Duration of anticonvulsant treatment and length of hospital stay were significantly related to adverse outcome (33).

A study done in Inha university hospital, Korea on Erythropoietin Reduces Death and Neurodevelopmental Impairment in Neonatal Hypoxic-Ischemic Encephalopathy among all patients with HIE, death or NDI (21.1 % vs. 50.0%) and brain injury on imaging (42.1% vs. 83.3%) were significantly lower in the EPO group than in the control group. Among patients with moderate-to-severe HIE, brain injury on imaging (54.2% vs. 90.9%) was significantly lower in the EPO group than in the control group (34).

Another study done in Yonsei university college of medicine, Korea found that the prevalence of HIE was 2.4 per 1000 births without significant change during the period. TH was performed in approximately 6.7% of infants with HIE, and the annual variation ranged from 2.4 to 12.5%. The mortality among all term infants with HIE was 4.6%. The mortality rate among infants with HIE and TH significantly declined from 40 to 16.9% during the eight years. Infants with TH had higher mortality, increased use of inhaled nitric oxide, and more invasive ventilator use, indicating greater disease severity in the TH group. Infants with TH also showed significantly poorer outcomes, including delayed development, cerebral palsy, sensorineural hearing loss, and seizure, compared to infants without TH ($p< 0.0001$)(35).

A study done in university of Witwatersrand, south Africa on Neurodevelopmental outcome in neonates with hypoxic-ischaemic encephalopathy managed with therapeutic hypothermia found that of 178 neonates with HIE attending the clinic, there was information on TH for 155 (87.1%), 113 of whom (72.9%) received TH. HIE was moderate in 88% and severe in 10%. Twenty-seven (23.9%) and 16 (14.1%) were assessed at one time-point at 12 or 18–24 months, respectively, 40 (35.3%) at both time-points, and 30 (26.6%) were not assessed. At 18– 24 months, 32% had moderate-to-severe disability compared with 6% at 12 months, with the sensitivity and specificity of assessment at 12 months being 50% and 100%, respectively. The disability attrition rate at 18–24 months was 50%(36).

A study done in Uganda on early childhood outcomes after neonatal encephalopathy followed

term infants with neonatal encephalopathy up to 27–30 months of age. The study found that by two years of age, approximately 40.3% of infants with neonatal encephalopathy had died compared to 3.8% of non-encephalopathic controls. Among survivors, only about 41.6% were free of neurodevelopmental impairment. Approximately 29.3% of survivors had significant neurodevelopmental impairment, including cerebral palsy (19%) and global developmental delay without cerebral palsy (10.3%). The severity of encephalopathy, presence of neonatal seizures, abnormal cranial ultrasound findings, and feeding difficulties at discharge were associated with poor outcomes. Neurodevelopment was assessed using standardized tools including the Hammersmith Infant Neurological Examination (HINE), which showed predictive value for later motor outcomes (37).

A study done in Ethiopia on the determinants of HIE were Illiterate mothers [adjusted odds ratio (AOR) = 1.913, 95% CI: 1.177, 3.109], no ultrasound checkup (AOR = 1.859, 95% CI: 1.073, 3.221), preterm (AOR = 4.467, 95% CI: 1.993, 10.012) or post-term birth (AOR = 2.903, 95% CI: 1.325, 2.903), caesarean section (AOR = 7.569, 95% CI: 4.169, 13.741), and prolonged labour (AOR = 3.591, 95% CI: 2.067, 6.238) increased the incidence of HIE (7).

Conceptual framework

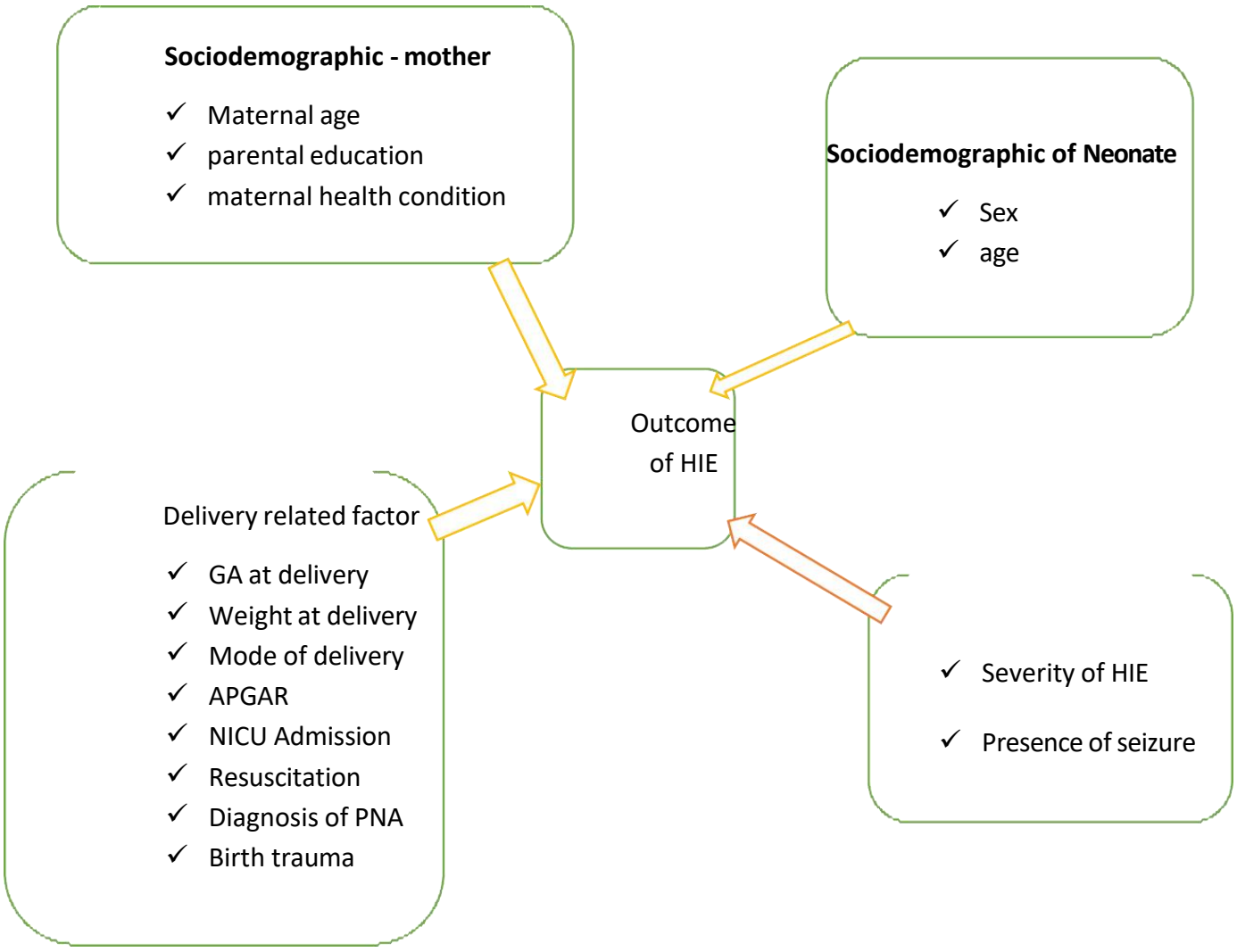


Figure 1. The literature review adopted from the literature by the authors

3. Objective

3.1 General objective

- To Assess early neurodevelopmental outcome of patients with moderate to severe hypoxic ischemic encephalopathy at three and six months of age in Addis Ababa.

3.2 Specific objective

- To determine proportion of infants with abnormal neurodevelopmental outcome at three and six months of age using the Hammersmith infant neurological Examination.
- To compare and evaluate changes in neurological status between three and six months of age among infants with moderate and severe HIE
- To identify neonatal and perinatal factors associated with adverse neurodevelopmental outcomes at six months of age.

4. Materials and Methods

4.1 Study Area

The study was conducted at Yekatit 12 Hospital Medical College, Zewditu Memorial Hospital, and St. Paul's Hospital Millennium Medical College (SPHMMC), all of which are major public tertiary and teaching hospitals located in Addis Ababa, Ethiopia. These hospitals provide comprehensive maternal, neonatal, and pediatric healthcare services and serve as referral centers for infants from Addis Ababa and other regions of the country. Due to their advanced neonatal units, they play a crucial role in the early identification and management of infants at risk of neurodevelopmental impairments. Infants attending these hospitals commonly include those with a history of perinatal complications such as prematurity, birth asphyxia, neonatal infections, hyperbilirubinemia, and low birth weight. Such conditions place infants at increased risk of neurological abnormalities, making early neurodevelopmental assessment essential. The study populations are pediatric aged visiting neuro-clinics at the given three and six month's period.

4.2 Study period

The study period were from June, 2025, – February, 2026, G.C

4.3 Study design

A hospital-based, prospective cohort study design with descriptive longitudinal analysis was employed.

4.4 Study population

Infants with moderate to severe HIE who are discharged from the NICU and attending care at pediatric HRIC and neuro clinics at the hospitals in the study.

4.4.1 Inclusion criteria

- ✓ Infants with moderate to severe hypoxic-ischemic encephalopathy (HIE) attending HRIC, neuro-clinics, or the Pediatrics outpatient department, aged 2–3 months at enrollment.
- ✓ Infants whose caregivers provided informed consent for participation.

4.4.2 Exclusion criteria

- ✓ Infants who had no complete data.
- ✓ Infants whose caregivers did not consent to participate.

4.5 Sample Size

The sample size was calculated based on the primary binary outcome (normal vs abnormal HINE score at six months). Using a 95% confidence level (Z = 1.96) and an expected proportion

of abnormal outcomes of 20% from previous high-risk infant cohorts, the required sample size to estimate this proportion with a margin of error of 10%.

n= (1.96)2×0.20×0.80 / (0.10)2 = 3.8416×0.16/ 0.01 ≈61.5 rounded to 62.

To increase precision, 10% of dropout/no responders was added and a total of 70 infants were enrolled. This sample size also ensured adequate events per predictor variable for logistic regression analysis. All enrolled infants completed follow-up assessments, and there was no loss to follow-up.

4.6 Sampling procedure

Participants were selected using convenience sampling until the maximum sample size.

4.7 Study variables

1. Independent variable

- ✓ Age
- ✓ Sex
- ✓ Severity of HIE
- ✓ Time to resuscitation
- ✓ Postnatal seizures
- ✓ Therapeutic hypothermia treatment
- ✓ Maternal health conditions
- ✓ Gestational age at delivery
- ✓ APGAR score at delivery
- ✓ Neonatal admission in NICU

- ✓ Perinatal asphyxia

2. Dependent variable

- ✓ Neurodevelopmental outcome of moderate to severe HIE.

4.8 Data collection instrument & technique

The questionnaire was adapted from relevant literature and pretested in a similar population. The questionnaire was initially developed in English and was translated into Amharic and back to English to maintain consistency. Data were collected through face-to-face interviews using a semi-structured questionnaire by trained general practitioners and residents data collectors who received training on HIE and associated factors, ethical considerations, interviewing techniques, sampling procedures, and neurological assessment methods.

Neurodevelopmental assessment was conducted using the Hammersmith Infant Neurological Examination, a standardized tool designed for the evaluation of infants aged 2 to 24 months, and assessments were conducted in accordance with established guidelines to ensure consistency across evaluators. The total HINE score ranges from 0 to 78 using the five domains of (cranial nerve, posture, movement, tone, and reflexes) with higher scores indicating better neurological function. Scores below certain thresholds at specific ages are associated with increased risk of motor impairments:

At 3 months, scores <57 were considered abnormal, while scores <40 indicated severe neurological impairment and a high risk of cerebral palsy..

At 6 months, scores <65 suggested abnormal neurological development, and scores <40 indicated severe neurological impairment.

HINE scores at 6 months:

- ❖ 40–60 indicates likely GMFCS I–II
- ❖ <40 indicates likely GMFCS III–V

Developmental Milestones Evaluated Indirectly Through HINE at Key Time Points:

At 3 Months:

- ✓ Posture & Tone: Assessment of symmetrical movements, head control.

✓ Cranial Nerves & Reflexes: Suck, Moro reflex, visual tracking, response to auditory stimuli.

At 6 Months:

✓ Motor Control: Improved tone and posture, spontaneous movements, head control.

✓ Functional Tasks: Visual orientation, reaching, grasping.

✓ Neurological Maturation: Diminishing primitive reflexes, emergence of postural reaction.

4.9 Data Processing and Analysis

.All Data were checked for completeness and consistency before being entered into EpiData version 4.1 and subsequently exported to SPSS for Windows version 25.0 for analysis. Descriptive statistics were used to summarize sociodemographic, clinical, and neurodevelopmental characteristics of the study participants.

HINE scores obtained at 3 and 6 months were categorized using age-specific cut-off values to classify infants as being at increased or lower risk for neurodevelopmental impairment. Bivariate logistic regression analysis was performed to assess the association between individual clinical and perinatal factors and neurodevelopmental risk status. Variables with a p-value <0.25 in the bivariate analysis were entered into a multivariable logistic regression model to identify independent determinants of neurodevelopmental outcome.

Adjusted odds ratios (AORs) with 95% confidence intervals were calculated, and a p-value <0.05 was considered statistically significant.

4.9 Operational definition

Moderate HIE (Stage 2): Babies may experience more noticeable signs of neurological dysfunction, such as lethargy, difficulty feeding, and some level of hypotonia or hypertonia (abnormally high muscle tone). In this stage, interventions like therapeutic hypothermia (cooling therapy) are often used to reduce brain damage (30).

Severe HIE (Stage 3): Severe brain injury, with signs such as coma, absent reflexes, seizures, and significant breathing and cardiac difficulties. Infants at this stage have a high risk of long-term neurological impairment, including cerebral palsy, developmental delay, and cognitive and motor deficits(30).

Abnormal HINE Score : A HINE total score below the age-specific optimality.

- <57 A cut-off was used for 3 months and considered abnormal neurological outcome with results <40 considered severely abnormal.
- <65 cut-off was used 6 months and considered abnormal neurological outcome with results <40 considered severely abnormal.

Normal HINE Score : HINE total score equal to or above the age-specific optimality cut-off at assessment were considered Normal Neurodevelopmental Outcome

4.10 Data Quality Control and Management

To assure the quality of data, structured data collection was used. Data collectors were trained by the investigator. Each day the data was checked for accuracy and completeness. The participant's names were not collected and the data were de-identified after the questionnaire is completed. The data were then stored in a secured location and only the investigator was having access to this location.

4.11 Ethical clearance

The ethical clearance was obtained from the hospital's institutional review board IRP (SPHMMC-ERC-238/25) of department of pediatric and child health then submitted to each hospital administration. And consent was obtained from the Hospital administrations, and confidentiality of the information was ensured using codes rather than names during registration data, informed and written consent was collected from the parents or caretakers.

VI. 5. Results

A. 5.1 The clinicals characteristics of the study participants

the infants were assessed at 3 months of age and at 6 months. Males constituted a higher proportion of cases (55.7%) compared with females (44.3%). Most infants had a birth weight between 2500 and 3999 g (87.1%), while 12.9% weighed ≥4000 g. The vast majority were born at term (37–41^{+6} weeks) accounting for 94.3%, whereas preterm births (<37 weeks) represented 4.3% and post-term births (≥42 weeks) 1.4%. All infants were from singleton pregnancies (100%). Regarding APGAR scores, 91.4% had a first-minute APGAR score of 1–4 and 8.6% scored 5. By the fifth minute, 38.6% still had APGAR scores of 1–4 and 61.% scored 5. Spontaneous vaginal delivery was the most common mode of delivery (59.3%), followed by emergency caesarean section (30%), vaginal operative delivery (9.3%), and elective caesarean section (1.4%). Among infants delivered by caesarean section, the most frequent indications were cephalopelvic disproportion and non-reassuring fetal heart beat pattern (each 27.3%), followed by GIIIMSAF with fetal bradycardia (13.6%), fetal distress (9%), placental abruption (9%), and smaller proportions due to repeat caesarean scar, breech presentation, and placenta previa (each 4.5%).

Table 1.The clinical characteristics of infants with moderate to severe hypoxic ischaemic encephalopathy at several hospitals in Addis Ababa

Variable	frequency	Percent
Sex		
Male	39	55.7
Female	31	44.3
Birth weight in gram		
2500-3999	61	87.1
>=4000	9	12.9
Gestational age at birth		
<37	3	4.3
37-41^{+6}	66	94.3
>=42	1	1.4
Types of pregnancy		
Single	70	100
First minute APGAR		
1-4	64	91.4
5	6	8.6
Fifth APGAR		
1-4	27	38.6
5	43	61.4
Mode of delivery		
SVD	43	61.4
Emergency CS	21	30

Elective CS	1	1.4
Vaginal operative delivery	5	7.1
Indication for CS (n=22)		
Scar opted for repeat	1	4.5
Breech	1	4.5
CPD	6	27.3
Fetal distress	2	9.1
GIIIMSAF with fetal bradycardia	3	13.6
NRFHBP	6	27.3
Placenta previa	2	9.1
Placenta abruption	1	4.5

B. 5.2 Neonatal period resuscitation related characteristic the infant

All infants required resuscitation at birth (100%). Positive pressure ventilation was the most commonly used intervention, administered to 98.6% of infants. Chest compression and adrenaline medication were each required in 20% of cases, while continuous positive airway pressure was used in 5.7% and inhaled oxygen in 1.4% of infants. Regarding the duration of resuscitation, more than half of the infants required resuscitation for 10–20 minutes (54.3%), followed by those resuscitated for less than 10 minutes (32.9%), and 12.9% who required resuscitation for more than 20 minutes. Perinatal asphyxia was present in all infants (100%). Based on Sarnat and sarnet staging of hypoxic-ischemic encephalopathy, the majority of infants were classified as Stage II (77.1%), while 22.9% were classified as Stage III.

Table 2.Neonatal period resuscitation related characteristic the infant.

Variable	frequency	Percent
Resuscitate at birth		
Yes	70	100
Specify types of resuscitation		
PPV	69	98.6
CPAP	4	5.7
INO2	1	1.4
Chest compression	14	20
Adrenaline medication	14	20
Duration of resuscitation in minute		
<10	23	32.9
10-20	38	54.3
>20	9	12.9
Presence of perinatal asphyxia		
Yes	70	100
HIE severity (Sarnat stage)		
Stage II (moderate)	54	77.1

Stage III (severe)	16	22.9

C. 5.3 Neonatal seizure related characteristics the infant

Seizures during the neonatal period were observed in 62.9% of the infants, while 37.1% did not experience seizures. Among infants who developed seizures, subtle seizures were the most common type (42%), followed by clonic seizures (28.4%) and tonic seizures (26.2%), whereas generalized tonic–clonic seizures were least frequent (3.4%). Antiepileptic treatment was administered to 60% of the infants, while 40% did not receive antiepileptic therapy. Regarding the duration of neonatal intensive care unit admission, the majority of infants stayed for 7–14 days (61.4%), followed by those admitted for 15 days or longer (25.7%), while a smaller proportion had a hospital stay of less than 7 days (12.9%).

Table 3. Neonatal seizure related characteristics the infant

Variable	Frequency	Percent
Seizures in neonatal period		
Yes	44	62.9
No	26	37.1
Types of seizure (n=44)		
Clonic	12	27.3
GTC	1	2.3
Subtle	19	43.2
Tonic	12	27.3
Antiepileptic treatment given		
Yes	43	61.4
No	27	38.6
Duration of NICU admission during neonatal period in days		
<7	9	12.9
7-14	42	60
>=15	19	27.1

5.4 Maternal and primary care giver related characteristics of the infant

Most mothers were aged 21–34 years at the time of delivery (88.6%), while 7.1% were younger than 20 years and 4.3% were aged 35 years or older. The majority of mothers had no reported health problems during pregnancy (92.1%), whereas 7.9% had hypertension. Regarding primary caregiving, more than half of the infants were primarily cared for by their mothers alone (54.3%). In 37.1% of cases, both the mother and father shared caregiving responsibilities, while 8.6% of infants were primarily cared for by grandparents.

Table 4. Maternal and primary care giver related characteristics of the infant

Variable	frequency	Percent
Maternal age during the delivery of the baby		
<20	10	7.1
21-34	124	88.6
>=35	6	4.3
Maternal health condition during pregnancy		
Have HTN	11	7.9
Normal	129	92.1
Primary caregiver of the baby		
Mother	76	54.3
Mother and father	52	37.1
Grandparents	12	8.6

D. 5.5 HINE score vales at 3months of age

The mean HINE total score was 48.3, with a median score of 51.00, indicating that half of the infants scored at or below this value. The scores ranged widely, with a minimum of 22 and a maximum of 60, demonstrating substantial variability in neurological status. Analysis of percentile distribution showed that 25% of infants had HINE scores of 30.75 or lower, 50% had scores of 51.00 or lower, and 75% had scores of 60 or lower.

Table 5. The level of HINE score at three months

Statistics		
HINE total score		
Mean		48.3
Median		51.00
Minimum		22
Maximum		69
Percentiles	25	30.75
	50	51.00
	75	60.00

E. 5.6 neurodevelopmental outcome of patients at three months

At three months of age, more than half of the infants, 57% (n = 40), were classified as having abnormal neurological findings based on HINE assessment, while 43% (n = 30) demonstrated normal neurological performance.

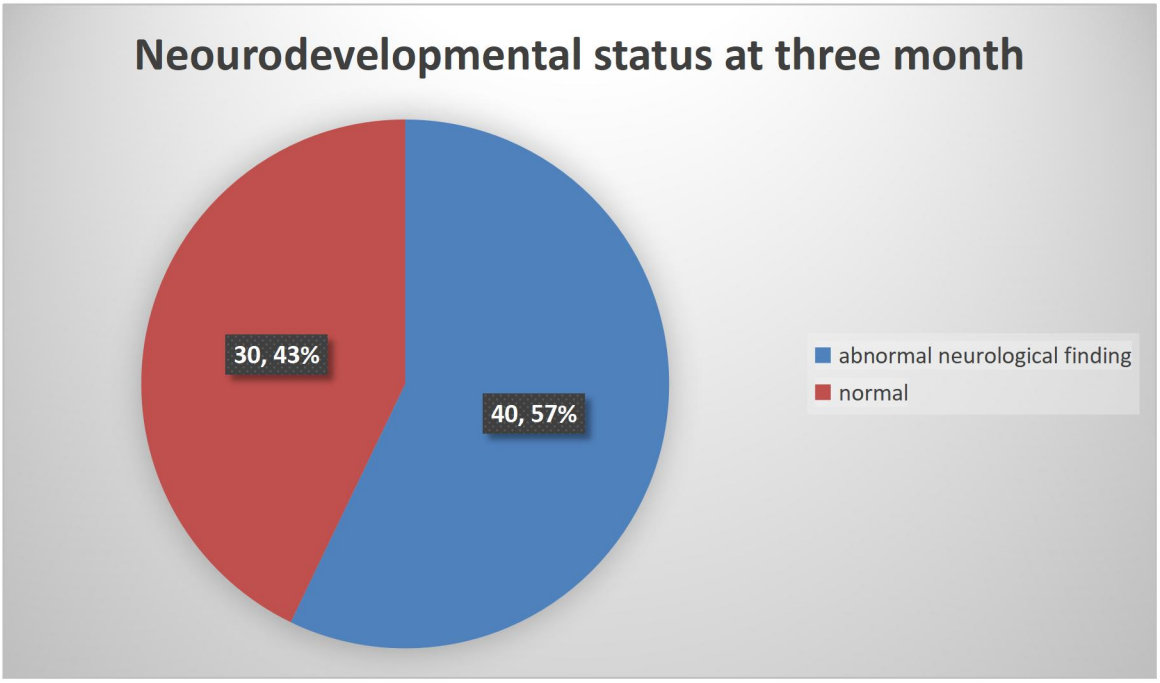


Figure 1.Neurodevelopmental outcome of patients with hypoxic ischemic encephalopathy.

F. 5.7 Neurological impairment severity at three-month age of the infant

At three months of age, HINE global scores were stratified into practical severity ranges used in published cohorts and clinical utility documents. 55% of the affected infants were classified as having severe neurological impairment based on HINE scores <40, representing the largest proportion of the cohort. neurological impairment above the cut point of 40 was observed in 45% of infants.

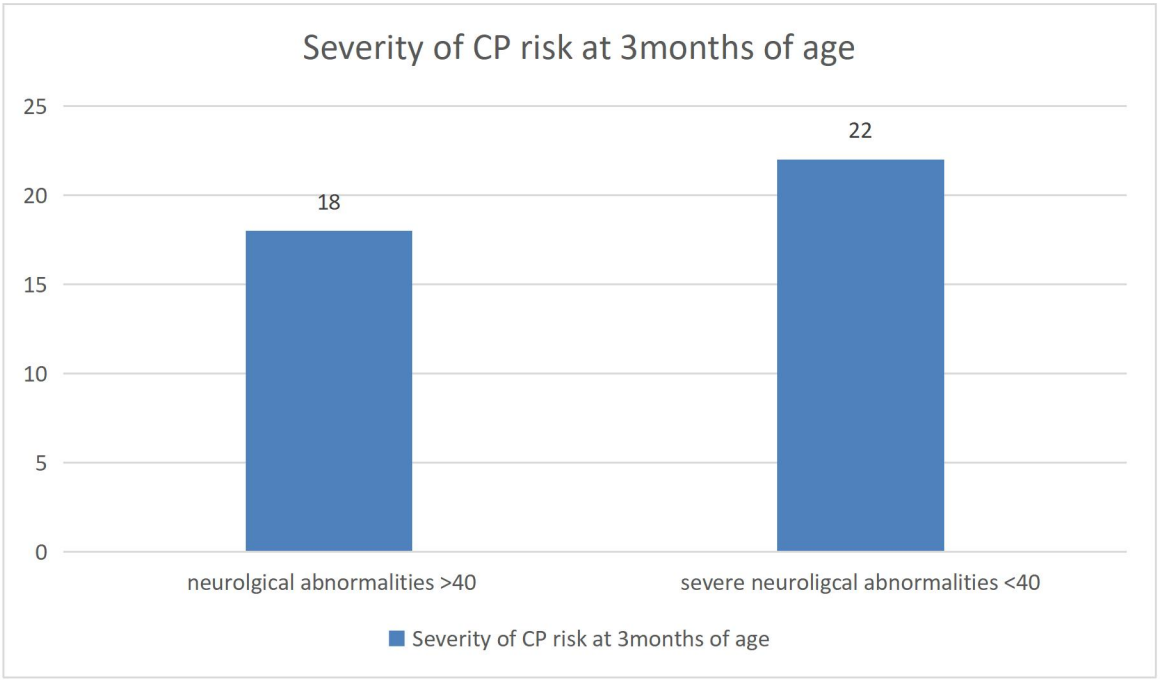


Figure 2. Neurological status of HIE infants at 3 months of age.

G. 5.7 HINE score at six months of age

The mean HINE total score was 50.3, with a median score of 58.00, indicating that half of the infants scored at or below this value. The scores ranged widely, with a minimum of 19 and a maximum of 76, demonstrating substantial variability in neurological status. Analysis of percentile distribution showed that 25% of infants had HINE scores of 27.5 or lower, 50% had scores of 58.00 or lower, and 75% had scores of 69 or lower.

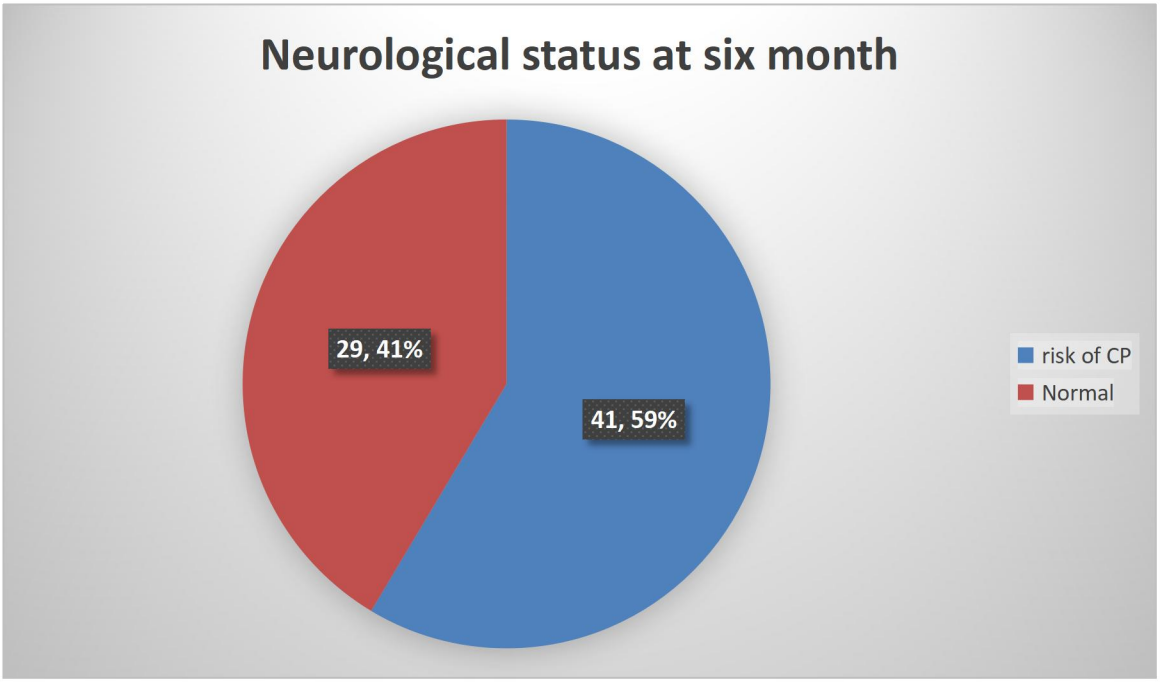
Table 6. The level of HINE score at six months

Statistics		
HINE total score		
Mean		50.3
Median		58.00
Minimum		19
Maximum		76
Percentiles	25	27.5
	50	58.00
	75	69.00

H. 5.8 Level of neurological status at six months

I.

At six months of age, 59% of infants were identified as being at risk of cerebral palsy, while 41% demonstrated a normal neurological status



At six months of age, 72% of infants were classified as having a severe neurological abnormality <40, while 28% exhibited a neurological abnormality above the cut point of 40.

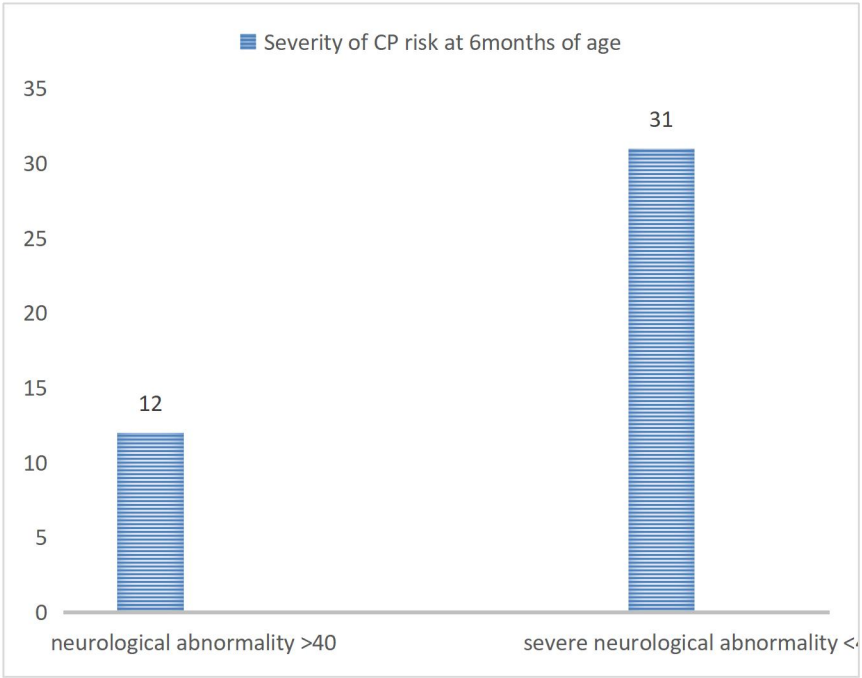


Figure 3. Neurological status among HIE infants at 6 months .

J. 5.8 Neurological status over time (3 to 6 months)

Tracking the neurological development of infants from three to six months revealed a clear pattern of persistence in early findings. Most infants who showed normal neurological performance at three months

continued to do so at six months, with 86.7% (26/30) maintaining their normal status. A small number, 10% (3/30), showed subtle signs of suboptimal neurological development and 1 patient (3%) showed significant deterioration.

Conversely, among infants who had abnormal neurological findings at three months, the majority—97.5% (39/40)—remained abnormal at six months, while a few, 3% (1/40), demonstrated improvement to normal neurological performance. These findings highlight that early neurological status often sets the trajectory for the following months, while also showing that some infants can exhibit neurological maturation which might unmask late-emerging deficits.

Table 7. The relation between three month and six month age of neurological outcome of HINE patients.

Neurological status at three months		Total	Neurological status at six months	
			Abnormal	normal
	Normal	30	4	26
	Abnormal	40	39	1
	Total	70	43	27

Based on the comparison of neurological status at three months and follow-up, the findings show that early neurological patterns were largely persistent, with only limited improvement and some instances of deterioration. Infants who had severe neurological abnormality at three months below the cut point of 40 all remained severely abnormal at follow-up, with 100% (22/22) showing no improvement.

Among infants with impairment above 40, outcomes were mixed: 50% (9/18) maintained the same level of impairment, 44.4% (8/18) worsened to severe impairment, while a small number improved, with 5.6% (1/18) reaching normal neurological performance.

In contrast, infants who were neurologically normal at three months largely maintained favorable outcomes, with 86.7% (26/30) remaining normal. Nevertheless, 13.3% (4/30) exhibited some decline, developing impairment.

These findings indicate that early neurological status strongly influences outcomes at six months, highlighting both the persistence of early impairment and the small but notable potential for improvement or deterioration.

Table 8. The relation of CP severity risk level between three month and six months age evaluation of HINE patients

Severity neurological status at three months follow up	Severity neurological status at six months follow-up			Total
	neurological abnormality >40	Severe neurological abnormality <40	Normal	
neurological abnormality >40	9	8	1	18
Severe neurological abnormality <40	0	22	0	22
Normal	3	1	26	30
Total	12	31	27	70

K. 5.7 The chi-square relation between independent variable and outcome

most baseline demographic factors, including sex, birth weight, gestational age, APGAR scores, and mode of delivery showed no statistically significant association with neurological status at either three or six month ($p > 0.05$). In contrast, clinical severity indicators related to perinatal insult and neonatal course demonstrated strong and consistent associations with neurological outcomes at both time points.

Markers of intensive resuscitation were among the strongest predictors of neurological outcomes. The need for CPAP, chest compressions, or adrenaline was significantly associated with persistent abnormal neurological findings at both three and six months ($p < 0.001$). Notably, all infants requiring chest compressions or adrenaline continued to show abnormal findings at follow-up.

Similarly, HIE severity, as classified by Sarnat staging, was highly associated with neurological outcomes at both time points ($p < 0.001$), with more severely affected infants showing persistent abnormal performance. This pattern was reinforced by the presence of neonatal seizures, which were strongly linked to adverse neurological status ($p < 0.001$). Infants without seizures largely maintained normal outcomes, while those with seizures predominantly continued to exhibit abnormal findings. The need for antiepileptic treatment reflected the same trend, showing a strong association with persistent abnormal neurological status at both three and six months ($p < 0.001$).

Table 9. The chi-square relation between independent variable and outcome variable at three and six month period.

Variable	Total (%)	Neurological status three month		Chi square(p-value)	Neurological status six month		Chi square(p-value)
		Risk of CP	Normal		Risk of CP	Normal	
Sex							
Male	39(55.7)	22(56.4)	17(43.9)	0.02(0.890)	22(56.4)	17(43.6)	0.17(0.681)
Female	31(44.3)	18(58.1)	13(41.9)		19(61.3)	12(38.7)	
Birth weight in gram							

2500-3999	61(87.1)	35(57.4)	26(42.6)	0.1(0.918)	37(60.7)	24(39.3)	0.85(0.357)
≥4000	9(12.9)	5(55.6)	4(44.4)		4(44.4)	5(55.6)	
Gestational age at birth							
<37	3(4.3)	0	3(100)		0	3(100)	
37-41+6	66(94.3)	40(60.6)	26(39.4)	5.67(0.059)	41(62.1)	25(37.9)	5.99(0.058)
≥42	1(1.4)	0	1(100)		0	1(100)	
Types of pregnancy							
Single	70(100)	40(57.1)	30(42.9)		41(58.6)	29(41.4)	
First minute APGAR							
1-4	64(91.4)	36(56.3)	28(43.8)	0.243(0.62	37(57.8)	27(42.2)	0.18(0.674)
5	6(8.6)	4(66.7)	2(33.3)	2)	4(66.7)	2(33.3)	
Fifth APGAR							
1-4	27(38.6)	17(63)	10(37)	0.55 (0.46)	17(63)	10(37)	0.35(0.84)
5	43(61.4)	23(53.5)	20(46.5)		24(55.8)	19(44.2)	
Mode of delivery							
SVD	43(61.2)	27(62.8)	16(37.2)	4.71(0.194)	27(62.8)	16(37.2)	2.1(0.559)
Emergency CS	21(30)	9(42.9)	12(57.1)		10(47.6)	11(52.4)	
Elective CS	1(1.4)	0	1(100)		1(100)	0	
Vaginal operative delivery	5(7.1)	4(80)	1(20)		3(60)	2(40)	
Resuscitate at birth							
Yes	70(100)	40(57.1)	30(42.9)		41(29)	2(29)	
Specify types of resuscitation							
PPV	69(98.6)	39(56.5)	30(43.5)	0.76(0.383)	41(59.4)	28(40.6)	1.4(0.231)
CPAP	4(5.7)	1(25)	3(75)	13.1(0.000)	2(50)	2(50)	0.13(0.720)
INO2	1(1.4)	1(100)	0	1.4(0.431)	0	1(100)	1.4(0.231)
Chest compression	14(20)	14(100)	0	12.4(0.000)	14(100)	0	12.4(0.000)
Adrenaline medication	14(20)	1)4(100)	0		14(100)	0	
Duration of resuscitation in minute							
<10	23(32.9)	11(47.8)	12(52.2)	1.33(0.515)	11(47.8)	12(52.2)	2.52(0.283)
10-20	38(54.3)	23(60.5)	15(39.5)		23(60.5)	15(39.5)	
>20	9(12.9)	6(66.7)	3(33.3)		7(77.8)	2(22.2)	
Presence of perinatal asphyxia							
yes	70(100)	40(57.1)	30(42.9)		41(58.6)	29(41.4)	
HIE severity (Sarnat stage)							
Stage II (moderate)	54(77.1)	24(44.4)	30(55.6)	15.6(0.000)	25(46.3)	29(53.7)	14.7(0.000)
Stage III (severe)	16(22.9)	16(100)	0		16(100)	0	
Seizures in neonatal period							
Yes	44(62.9)	37(84.1)	7(15.9)	35.2(0.000)	38(86.4)	6(13.6)	37.7(0.000)
No	26(37.1)	3(11.5)	23(8.5)		3(11.5)	23(88.5)	
Types of seizure (n=44)							

Clonic	12(27.3)	9(75)	3(25)		9(75)	3(25)	
GTC	1(2.3)	1(100)	0		1(100)	0	
Subtle	19(43.2)	16(84.2)	3(15.8)		17(89.7)	2(10.5)	
tonic	12(27.3)	11(91.7)	1(8.3)		11(91.7)	1(8.3)	
Antiepileptic treatment given							
Yes	43(61.4)	36(83.7)	7(16.3)	32.2(0.000)	37(86)	6(14)	34.6(0.000)
No	27(38.6)	4(14.8)	23(85.2)		4(14.8)	23(85.2)	
Duration of NICU admission during neonatal period in days							
<7	9(12.9)	1(11.1)	8(88.9)	9.16(0.000)	0	9(100)	14.6(0.001)
7-14	42(60)	26(61.9)	16(38.1)		28(66.7)	14(33.3)	
≥15	19(27.1)	13(68.4)	6(31.6)		13(68.4)	6(31.6)	

L. 5.9 The determinant factors of neurodevelopmental outcome among HIE infant

In the bivariate logistic regression analysis, the presence of neonatal seizures showed a very strong association with adverse neurological outcome in the bivariate analysis. In the multivariable logistic regression analysis, after adjusting for potential confounders, neonatal seizures remained an independent and robust predictor of poor neurodevelopmental outcome at six months. Infants with seizures had nearly 15 times higher odds of developing neurodevelopmental problems compared with those without seizures (AOR = 14.7; 95% CI: 10.55–49.62; $p < 0.001$). After adjustment, the association between duration of resuscitation and outcome was attenuated. Resuscitation for 10–20 minutes was not independently associated with neurodevelopmental problems (AOR = 1.3; 95% CI: 0.27–5.82; $p = 0.772$) and infants resuscitated for more than 20 minutes continued to demonstrate increased odds of adverse outcome (AOR = 2.8; 95% CI: 1.23–35.99).

Table 10.The bivariate and multivariable logistic regression of association between neurological outcome of six month HIE patient and independent variable

Variable	Neurodevelopmental problem		p-value	COR with 95%CI	P-value	AOR with 95%CI
	Yes	no				
Duration of resuscitation						
<10	11(47.8)	12(52.2)	1		1	
10-20	23(60.5)	15(39.5)	0.335	1.7(0.59, 4.76)	0.772	1.3(0.27, 5.82)
>20	7(77.8)	2(22.2)	0.138	3.8(0.65, 22.45)	0.009	2.8(1.23, 35.99)
Seizure in neonatal period						
Yes	38(86.4)	6(13.6)	0.000	14.5(8.06, 41.19)	0.000	14.7(10.55, 49.62)
No	3(11.5)	23(88.5)	1		1	

VII. 6.Discussion

This study assessed early neurodevelopmental outcomes among infants with hypoxic ischemic encephalopathy

(HIE) using the Hammersmith Infant Neurological Examination (HINE) at three and six months of age and explored clinical predictors of adverse neurological outcomes. The findings demonstrate a high prevalence of early abnormal neurological findings, limited neurological improvement over time, and a strong association between severity of neonatal insult and persistent neurodevelopmental impairment.

At three months of age, the mean HINE score was 48.3, with a median score of 51, and a wide range from 22 to 60, indicating marked heterogeneity in neurological function. More than half of the infants (57%) had abnormal neurological findings, and 55% were classified as having severe neurological impairment based on HINE scores. These findings suggest that neurological impairment manifests early and can be reliably detected within the first three months of life. By six months, although the mean HINE score increased slightly to 50.3 and the median to 58, a majority of infants (61%) continued to demonstrate abnormal neurological findings, and the proportion with severe impairment increased to 72%. This pattern likely reflects consolidation and clearer expression of the initial hypoxic-ischemic brain injury rather than ongoing neurological deterioration, as neurological maturation unmasks deficits in tone, posture, and motor control. Neonatal seizures, in particular, likely reflect more extensive brain injury and ongoing secondary damage, which helps explain their strong and independent association with poor outcomes. Taken together, these findings highlight the importance of early neurological assessment not only for identifying impairment but also for anticipating longer-term developmental challenges.

The observed HINE score distribution is broadly consistent with findings from the Indian study conducted at Aligarh University, where infants with Stage I HIE predominantly had HINE scores above 70 at six months, while progressively lower scores were observed with advancing HINE severity (28). In contrast, the lower median HINE scores in the present study suggest a greater burden of moderate-to-severe HIE, which may be related to lack of inclusion of stage I HIE in this study, delayed resuscitation, and limited access to neuroprotective strategies such as therapeutic hypothermia.

Longitudinal analysis in the present study demonstrated that neurological outcomes were largely persistent, particularly among infants with early severe impairment. Nearly all infants with abnormal neurological findings at three months (97.5%) continued to show abnormal findings at six months, and 100% of infants with severe impairment at three months below the cut point of 40 remained severely affected at follow-up. Only minimal improvement was observed among infants with impairment above the cut point of 40 with a substantial proportion showing progression to more severe impairment. These findings highlight the strong association between early neurological assessment and subsequent short-term outcomes, supporting previous reports that early neurodevelopmental testing reliably identifies infants at risk of persistent impairment (33,36).

Infants who were neurologically normal at three months largely maintained normal outcomes at six months (86.7%), although a small proportion showed some decline. This pattern mirrors findings from the South African study on infants with HIE treated with therapeutic hypothermia, which reported increasing rates of moderate-to-severe disability between 12 and 18–24 months, emphasizing that early normal findings do not completely exclude later emerging neurological deficits (36). The attrition and late-emerging disability observed in that cohort further underscore the need for prolonged follow-up beyond infancy.

Most baseline demographic and obstetric variables in the present study—such as sex, birth weight, gestational age, APGAR scores, and mode of delivery—did not show statistically significant associations with neurological outcomes at either three or six months. This finding is consistent with reports from high-income settings, including studies from the United States and the Netherlands, which emphasize that postnatal neurological injury severity outweighs demographic factors in determining outcome (29,31).

Markers of severe perinatal insult were among the strongest predictors of abnormal neurological findings in this study. The need for advanced resuscitation measures, including CPAP, chest compressions, and adrenaline, was significantly associated with persistent abnormal neurological performance at both follow-up points, with all infants requiring chest compressions or adrenaline continuing to demonstrate abnormal findings. These findings align with studies from Sydney and California, which identified prolonged resuscitation and intensive neonatal support as key predictors of death or severe neurodevelopmental impairment (31,33). Prolonged resuscitation likely reflects profound hypoxic ischemic injury with limited potential for neurological recovery.

HIE severity, as classified by Sarnat staging, emerged as a critical determinant of outcome. Infants with more severe HIE had significantly higher rates of persistent abnormal neurological findings at both three and six months. This finding is consistent across multiple studies, including those from India, Turkey, and the United States, which consistently report poorer neurodevelopmental outcomes, higher rates of motor, speech, and sensory impairments among infants with severe HIE (28,30,31). In the Turkish cohort, all infants with severe HIE demonstrated abnormal neurodevelopmental screening results, with particularly high rates of motor, speech, and swallowing difficulties (30).

The presence of neonatal seizures was one of the most powerful predictors of adverse outcome in the present study. Infants with seizures had nearly 15 times higher odds of abnormal neurological findings at six months, even after adjusting for confounders. This finding is consistent with previous reports from Uganda Turkey, Australia, and Korea, where neonatal seizures were strongly associated with abnormal neurodevelopment, epilepsy, and increased need for rehabilitative services (30,33,34,37). Seizures likely represent both the severity and extent of underlying brain injury, explaining their strong and independent association with poor outcome.

Similarly, the need for antiepileptic treatment was strongly associated with persistent abnormal neurological performance, further supporting seizures as a marker of severe neurological injury rather than a modifiable risk factor. Multivariable regression analysis also identified duration of NICU admission as an independent predictor of outcome. Infants admitted for 7–14 days and those admitted for ≥15 days had significantly higher odds of abnormal neurological findings compared with infants admitted for less than 7 days. These findings align with studies from Sydney and South Africa, where longer hospital stay and prolonged anticonvulsant use were significantly associated with persistent neurological impairment and late-emerging deficits (33,36).

VIII. 7. Strengths and Limitations

A. 7.1 Strengths

A major strength of this study is the prospective longitudinal design, which allowed for systematic neurological assessment of the infants at both three and six months of age and enabled evaluation of the persistence and evolution of early findings. The use of the Hammersmith Infant Neurological Examination (HINE), a standardized and validated neurological assessment tool, strengthened the reliability and comparability of the findings. Detailed characterization and neonatal factors permitted comprehensive analysis of potential predictors, and the multicenter nature of the study enhanced the representativeness of the findings. Complete follow-up of all enrolled infants minimized attrition bias and multivariable regression helped identify independent risk factors for persistent abnormal neurological findings.

B. 7.2 Limitations

Several limitations were encountered when interpreting the results. First, the follow-up period was limited to six months, which restricts conclusions about long-term neurodevelopment, as some impairments may only emerge later in infancy or early childhood. Secondly, while the sample size was sufficient to detect strong associations, it might have limited power to identify more subtle relationships, especially those with less frequent exposures.

Third, HIE diagnosis in this study was based on established clinical criteria, including Apgar scores, neurological examination, and Sarnat and sarnat staging. Brain MRI was performed in only 10 of 70 infants and was therefore not included in the analysis. While clinical diagnosis is the standard approach in many settings, the limited MRI data meant that correlations between imaging findings and neurological outcomes could not be explored, which might have provided additional anatomical context to support the clinical findings. Fourth, none of the infants in this cohort received therapeutic hypothermia or other neuroprotective interventions, so the outcomes observed reflect the natural course of moderate-to-severe HIE in the absence of such treatments.

Finally, as this study was conducted in multicenter urban hospitals in Addis Ababa, the findings may not be fully generalizable to rural settings or other regions with different levels of neonatal care and follow-up capacity.

IX. 8.Conclusion

Neurological impairment remained largely persistent between 3 and 6 months, with a modest increase in severity at follow-up showing that HINE can detect CP as early as 3 months in infants with etiologic risk factors for CP. Multivariable analysis showed that Severity of HIE and neonatal seizures were the strongest independent predictors of adverse neurodevelopmental outcomes. Infants with Stage 3 HIE all had abnormal neurological performance, underscoring that clinical severity remains a robust prognostic factor. Similarly, prolonged hospitalization and prolonged resuscitation times likely reflect more severe initial brain injury and associated complications, further increasing the risk of long-term neurodevelopmental challenges.

X. 9.Recommendations

- Promote early screening in infants with risk of cerebral palsy using HINE.
- Promote early intervention of the affected infants.
- Promote training programs for healthcare providers in advanced neonatal resuscitation and neuroprotective interventions, such as therapeutic hypothermia where feasible.
- Conduct longitudinal studies to track neurodevelopmental outcomes beyond 6 months, including cognitive, motor, and sensory domains.

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Neurodevelopmental Outcome Assessment Questionnaire

Consent Form

Study Title: Early Neurodevelopmental Outcome of Infants with Hypoxic Ischemic Encephalopathy

Purpose:
This study aims to assess the development of infants with HIE at 3 and 6 months using a neurological examination.

Your Participation:
Participation involves your infant undergoing a clinical assessment and answering some questions. The process is safe and confidential.

Voluntary:
Participation is voluntary. You can choose not to participate or withdraw at any time without affecting your infant's care.

Consent:
By signing below, you agree to allow your infant to participate in this study.

- Parent/Guardian Name: _____
- Signature: _____
- Date: ____/ ____/ _____

Section A: Demographic Information

- **Infant MRN number:** _____
- **Date of Assessment:** ____/ ____/ _____
- **Age of Infant at Assessment:** ☐ 3 months ☐ 6 months
- **Sex:** ☐ Male ☐ Female
- **Date of Birth:** ____/ ____/ _____
- **Birth Weight (grams):** _____
- **Gestational Age at Birth (weeks + days):** _____

- **Multiple Pregnancy:** ☐ Yes ☐ No

Section B: Perinatal Risk Factors

- **Apgar Score:**
  - At 1 minute: _____
  - At 5 minutes: _____
  - At 10 minutes (if applicable): _____
- **Mode of Delivery:** ☐ Spontaneous Vaginal ☐ Assisted Vaginal (forceps/vacuum) ☐ Elective Cesarean ☐ Emergency Cesarean
- **Indication for Cesarean (if applicable):** _____
- **Resuscitation at Birth:** ☐ Yes ☐ No
- **If Yes, specify method:**
  ☐ Positive Pressure Ventilation ☐ Intubation ☐ Chest Compressions ☐ Medications (e.g., adrenaline) ☐ Other: _____
- **Duration of Resuscitation (minutes):** _____
- **Presence of Perinatal Asphyxia:** ☐ Yes ☐ No
- **Therapeutic Hypothermia (cooling therapy):** ☐ Yes ☐ No
- **HIE Severity (Sarnat Stage):** ☐ Stage 1 (Mild) ☐ Stage 2 (Moderate) ☐ Stage 3 (Severe)
- **Seizures in Neonatal Period:** ☐ Yes ☐ No
- **Type of Seizures Observed:** _____
- **Antiepileptic Treatment Given:** ☐ Yes ☐ No
- **NICU Admission Duration (days):** _____
- **Other Relevant Medical Conditions:** _____

Section C: Social and Environmental Factors

- **Maternal Age at Delivery:** _____years
- **Maternal Health Conditions During Pregnancy:** (e.g., hypertension, diabetes)

  _____
- **Primary Caregiver:** ☐ Mother ☐ Father ☐ Grandparent ☐ Other:

Section D: Hammersmith Infant Neurological Examination (HINE)

HAMMERSMITH INFANT NEUROLOGICAL EXAMINATION

SUMMARY OF EXAMINATION
Global score (max 78)
Number of asymmetries
Behavioral score (not part of the optimality score)

Cranial nerve function	**score**	**(max 15)**
Posture	**score**	**(max 18)**
Movements	**score**	**(max 6)**
Tone	**score**	**(max 24)**
Reflexes and reactions	**score**	**(max 15)**

COMMENTS

(Throughout the exam, if a response is not optimal but not poor enough to score 1, give a score of 2)

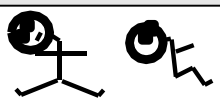
NEUROLOGICAL EXAMINATION

ASSESSMENT OF CRANIAL NERVE FUNCTION

	score 3	2	score 1	score 0	score	Asymmetry / Comments
Facial appearance (at rest and when crying or stimulated)	Smiles or reacts to stimuli by closing eyes and grimacing		Closes eyes but not tightly, poor facial expression	Expressionless, does not react to stimuli		
Eye movements	Normal conjugate eye movements		**Intermittent** Deviation of eyes or abnormal movements	**Continuous** Deviation of eyes or abnormal movements		
Visual response Test ability to follow a black/white target	Follows the target in a complete arc		Follows target in an incomplete or asymmetrical arc	Does not follow the target		

Auditory response Test the response to a rattle	Reacts to stimuli from both sides		Doubtful reaction to stimuli or asymmetry of response	No response		
Sucking/swallowing Watch infant suck on breast or bottle. If older, ask about feeding, assoc. cough, excessive dribbling	Good suck and swallowing		Poor suck and/or swallow	No sucking reflex, no swallowing		

ASSESSMENT OF POSTURE (note any asymmetries)

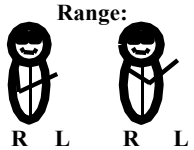
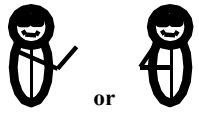
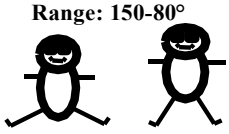
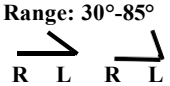
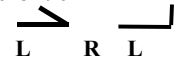
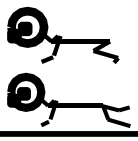
	score 3	score 2	score 1	score 0	sc	Asymmetry / comments
Head in sitting	 Straight; in midline		 Slightly to side *or* backward *or* forward	 Markedly to side *or* backward *or f*orward		
Trunk in sitting	 Straight		 Slightly curved or bent to side	 Very rounded rocketing back bent sideway		
Arms at rest	In a neutral position, central straight or slightly bent		**Slight** internal rotation *or* external rotation **Intermittent** dystonic posture	**Marked** internal rotation *or* external rotation or dystonic posture hemiplegic posture		
Hands	Hands open		**Intermittent** adducted thumb *or* fisting	**Persistent** adducted thumb *or* fisting		
Legs in sitting	Able to sit with a straight back and legs straight or slightly bent (long sitting) 		Sit with straight back but knees bent at 15-20 ° 	Unable to sit straight unless knees markedly bent (no long sitting) 		
in supine and in standing	Legs in neutral position straight *or* slightly bent	**Slight** internal rotation or external rotation	Internal rotation *or* external rotation at the hips	**Marked** internal rotation *or* external rotation *or* fixed extension or flexion or contractures at hips and knees		
Feet in supine and in standing	Central in neutral position Toes straight midway between flexion and extension		**Slight** internal rotation *or* external rotation **Intermittent** Tendency to stand on tiptoes or toes up or curling under	**Marked** internal rotation *or* external rotation at the ankle **Persistent** Tendency to stand on tiptoes *or* toes up or curling under		

ASSESSMENT OF MOVEMENTS

	Score 3	Score 2	Score 1	Score 0	score	Asymmetry / comments
Quantity Watch infant lying in supine	Normal		Excessive or sluggish	Minimal or none		

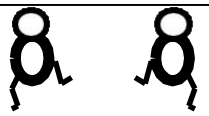
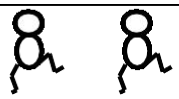
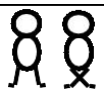
Quality Observe infant's spontaneous voluntary motor activity during the course of the assessment	Free, alternating, and smooth		Jerky Slight tremor	• Cramped & synchronous • Extensor spasms • Athetoid • Ataxic • Very tremulous • Myoclonic spasm • Dystonic movement		

ASSESSMENT OF TONE

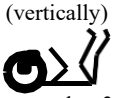
	Score 3	Score 2	Score 1	Score 0	sc	Asym/Co
Scarf sign Take the infant's hand and pull the arm across the chest until there is resistance. Note the position of the elbow in relation to the midline.	**Range:**  **R L R L**		 **R L**	 **or** **R L R L**		
Passive shoulder elevation Lift arm up alongside infant's head. Note resistance at shoulder and elbow.	Resistance overcomeable  **R L**	Resistance difficult to overcome **R L**	No resistance  **R L**	Resistance, not overcomeable  **R L**		
Pronation/supination Steady the upper arm while pronating and supinating forearm, note resistance	Full pronation and supination, no resistance		Resistance to full pronation / supination overcomeable	Full pronation and supination not possible, marked resistance		
Hip adductors With both the infant's legs extended, abduct them as far as possible. The angle formed by the legs is noted.	**Range: 150-80°**  **R L R L**	**150-160°**  **R L**	**>170°**  **R L**	**<80°**  **R L**		
Popliteal angle Keeping the infant's bottom on the bed, flex both hips onto the abdomen, then extend the knees until there is resistance. Note the angle between upper and lower leg.	**Range: 150°-100°**  **R L R L**	**150-160°**  **R L**	**~90° or > 170°**  **R L R L**	**<80°**  **R L**		
Ankle dorsiflexion With knee extended, dorsiflex the ankle. Note the angle between foot and leg.	**Range: 30°-85°**  **R L R L**	**20-30°**  **R L**	**<20°or 90°**  **R L R L**	**> 90°**  **R L**		
Pull to sit Pull infant to sit by the wrists. (support head if necessary)						
Ventral suspension Hold infant horizontally around trunk in ventral suspension; note position of back, limbs and head.						

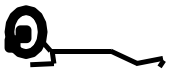
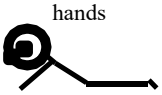
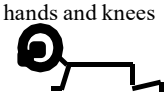
REFLEXES AND REACTIONS

	Score 3	Score 2	Score 1	Score 0	sc	Asym / Co
Arm protection Pull the infant by one arm from the supine position (steady the contralateral hip) and note the reaction of arm on opposite side.	 Arm & hand extend **R L**		 Arm semi-flexed **R L**	 Arm fully flexed **R L**		

Vertical suspension hold infant under axilla making sure legs do not touch any surface – you may "tickle" feet to stimulate kicking.	 Kicks symmetrically		 Kicks one leg more or poor kicking	 No kicking even if stimulated or scissoring		
Lateral tilting (describe side up). Hold infant up vertically near to hips and tilt sideways towards the horizontal. Note response of trunk, spine, limbs and head.	 R L	 L R	 R L	 R L		
Forward parachute Hold infant up vertically and quickly tilt forwards. Note reaction /symmetry of arm responses,	 (after 6 months)		 (after 6 months)			
Tendon Reflexes Have child relaxed, sitting or lying – use small hammer	Easily elicitable biceps knee ankle	Mildly brisk bicep knee ankle	Brisk biceps knee ankle	Clonus or absent biceps knee ankle		

SECTION 2 MOTOR MILESTONES (not scored; note asymmetry)

Head control	Unable to maintain head upright normal to 3m	Wobbles normal up to 4m	Maintained upright all the time normal from 5m			**Please note age at which maximum skill is achieved**
Sitting	Cannot sit	With support at hips  normal at 4m	Props  normal at 6m	Stable sit  normal at 7-8m	Pivots (rotates)  normal at 9m	Observed: Reported (age):
Voluntary grasp – note side	No grasp	Uses whole hand	Index finger and thumb but immature grasp	Pincer grasp		Observed: Reported (age):
Ability to kick in supine	No kicking	Kicks horizontally but legs do not lift	Upward (vertically)  normal at 3m	Touches leg  normal at 4-5m	Touches toes  normal at 5-6m	Observed: Reported (age):

Rolling **- note through which side(s)**	No rolling	Rolling to side normal at 4m	Prone to supine normal at 6 m	Supine to prone normal at 6 m		Observed: Reported (age):
Crawling **- note if bottom shuffling**	Does not lift head	On elbows  normal at 3m	On outstretched hands  normal at 4m	Crawling flat on abdomen  normal at 8m	Crawling on hands and knees  normal at 10m	Observed: Reported (age):
Standing	Does not support weight	Supports weight normal at 4m	Stands with support normal at 7m	Stands unaided normal at 12m		Observed: Reported (age):
Walking		Bouncing normal at 6m	Cruising (walks holding on) normal at 12m	Walking independently normal by 15m		Observed: Reported (age):

SECTION 3 BEHAVIOUR (not scored)

	1	2	3	4	5	6	Comment
Conscious state	Unrousable	Drowsy	Sleep but wakes easily	Awake but no interest	Loses interest	Maintains interest	
Emotional state	Irritable, not consolable	Irritable, carer can console	Irritable when approached	Neither happy or unhappy	Happy and smiling		
Social orientation	Avoiding, withdrawn	Hesitant	Accepts approach	Friendly			

Assurance of Principal Investigator

I the undersigned agree to accept all responsibilities for the scientific and ethical conduct of the research project. I will provide timely progress report to my advisor and seek the necessary advice and approval from my primary advisors in the course of the research. I will communicate timely to my advisors all stakeholders involved in the study including any source of funding for this research.

Name of the student: MUNIRA MOHAMED

Signature:_____Date: ___

Approval of the Primary Advisor

Name of the advisors:

Dr Meskerem Abatkun (Pediatrician,pediatric neurologist)

Signature: _____Date:_____

Dr Gesit Metaferia (MD, Pediatrics Neonatologist)

Signature: _____Date: _____