NEURODEVELOPMENTAL OUTCOME IN NEONATES WITH HYPOXIC ISCHEMIC ENCEPHALOPATHY- ASSESSMENT BY MUNICH FUNCTIONAL DEVELOPMENTAL SCALE

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CERTIFICATE

Certified that this dissertation entitled **"NEURODEVELOPMENTAL OUTCOME IN NEONATES WITH HYPOXIC ISCHEMIC ENCEPHALOPATHY-ASSESSMENT BY MUNICH FUNCTIONAL DEVELOPMENT SCALE"** is the bonafide work done by **Dr. SAILEELA. R**, Post graduate, Institute of Child Health and Hospital for Children, Madras Medical College, Chennai, during the academic years 2005-2008.

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CONTENTS

INTRODUCTION

Advances in perinatal care and the establishment of neonatal nurseries have improved the survival chances of many neonates that would otherwise have succumbed. As more of these babies survive; the chances of childhood developmental delay, speech problems, behavioural problems, attention deficit hyperkinetic behaviour and scholastic backwardness increase. Very often their problems are identified quite late, may be at school age when only some rehabilitation measures can be taken, which does not necessarily bring out the best in the child. Such issues are of paramount importance to the average Indian parents, obviously because of ready acceptance of small family norm, resulting in a new thrust on quality of the child. Hence if we have special care/intensive care services in our hospital, it should be mandatory that we offer neonatal follow up and early stimulation services. It is true that there are many sophisticated, scientific methods for the assessment of development in children, but what we need is simple screening procedures which can be used in the community by field workers and can be propagated even among illiterate mothers.

Notwithstanding the huge advances in our understanding of the mechanisms that contribute to the injuries of the developing brain and many efforts at prevention, perinatal brain injury continues to be a major cause of neonatal mortality and is

associated with long term neurodevelopmental sequelae[1].It ranks as the second most important cause of neonatal death after infections, accounting for around 30% mortality worldwide[1]. Although many organ systems can be affected by hypoxia-ischemia, it is the nervous system that bears the brunt of perinatal asphyxia in the long run. The risk of developing cerebral palsy and other neurodevelopmental sequelae is more in the asphyxiated newborn than in the general population. So if these infants with Hypoxic Ischemic Encephalopathy are followed up for sufficient period of time and any deviation from normal neurodevelopment is detected early, appropriate interventional measures can be initiated early.

Table 1:Hospital statistics of ICH, Chennai

Hospital statistics	2004	2005	2006
Total no of admissions in the hospital	38608	36948	35885
Total no of admissions in newborn unit	3596	3807	3625
No of deaths in newborn unit	677	720	724
No of admissions with HIE	602	557	579
No of deaths among HIE	293	229	200

Our hospital is a tertiary referral centre for neonatal care for Corporation hospitals and Private hospitals within a radius of 100 kms. Roughly about 500 cases of birth asphyxia are admitted in this hospital each year.

High risk newborn follow up clinic is conducted daily in our hospital, where these babies who had HIE are followed up, neurodevelopmental assessment done, and appropriate rehabilitation initiated.

HYPOXIC ISCHEMIC ENCEPHALOPATHY

In spite of major advances in monitoring technology and knowledge of fetal and neonatal pathologies, perinatal asphyxia or, more appropriately, hypoxic-ischemic encephalopathy (HIE), remains a serious condition, causing significant mortality and long-term morbidity. HIE is characterized by clinical and laboratory evidence of acute or subacute brain injury due to asphyxia (i.e., hypoxia, acidosis).The exact time of brain injury often remains uncertain.

Definition

There is no unanimity or consensus regarding the definition of birth asphyxia and various workers have used different definitions making it difficult to ascertain the incidence of asphyxia. The National Neonatology Forum of India has defined asphyxia as "gasping or ineffective breathing or lack of breathing at one minute of life"[2].

The essential criteria for diagnosing perinatal asphyxia as outlined by American Academy of Paediatrics (AAP)[2] are

- Prolonged metabolic or mixed acidemia (pH <7.0 on cord arterial blood sample)
- Persistence of an Apgar score of <3 for 5 min or longer

- Clinical neurologic manifestation as seizures, hypotonia, coma or HIE in the immediate neonatal period
- Evidence of multi-organ system dysfunction in the immediate neonatal period

Amiel Tison has defined HIE as a condition with signs and symptoms of neurologic dysfunction and stereotypical evolution in the clinical course.

Pathophysiology

Brain hypoxia and ischemia due to systemic hypoxemia, reduced cerebral blood flow (CBF), or both are the primary physiological processes that trigger HIE. The initial compensatory adjustment to an asphyxial event is an increase in the CBF due to hypoxia and hypercapnia. This is accompanied by a redistribution of cardiac output such that the brain receives an increased proportion of the cardiac output. A borderline increase in the systemic blood pressure (BP) further enhances the compensatory response. The BP increase is due to increased release of epinephrine; these are classic early cardiovascular compensatory responses to asphyxia. In the fetus and newborn suffering from acute asphyxia, after the early compensatory adjustments fail, the CBF can become pressure-passive, at which time brain perfusion is dependent on systemic BP. As BP falls, CBF falls below critical levels, and the brain continues to suffer from diminished blood supply and a lack of sufficient oxygen to meet its needs. This leads to intracellular

energy failure. During the early phases of brain injury, brain temperature drops, and local release of the neurotransmitters, such as gamma aminobutyric acid transaminase (GABA), increase. These changes reduce cerebral oxygen demand, transiently minimizing the impact of asphyxia.

At the cellular level, neuronal injury in HIE is an evolving process. The magnitude of the final neuronal damage depends on both the severity of the initial insult and the damage due to reperfusion injury and apoptosis. Following the initial phase of energy failure from the asphyxial injury, cerebral metabolism may recover, only to deteriorate in the secondary phase, or reperfusion. This new phase of neuronal damage, starting at about 6-24 hours after the initial injury, is characterized by cerebral edema and apoptosis. This phase has been called the "delayed phase of neuronal injury." The duration of the delayed phase is not known precisely in the human fetus and newborn but appears to increase over the first 24-48 hours and then start to resolve thereafter.

At the biochemical level, a large cascade of events follow HIE injury. Both hypoxia and ischemia increase the release of excitatory amino acids (EAAs), such as glutamate and aspartate, in the cerebral cortex and basal ganglia. EAAs cause neuronal death through the activation of receptor subtypes such as kainate, N-methyl-D-aspartate (NMDA), and amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA). Activation of receptors, with associated opening of ion channels (e.g., NMDA), lead to increased

intracellular and subcellular calcium concentration and cell death. A second important mechanism for the destruction of ion pumps is the lipid peroxidation of cell membranes, in which enzyme systems, such as the Na+/K+-ATPase, reside; this can cause cerebral edema and neuronal death. The EAAs may also disrupt the factors that control apoptosis, increasing the pace and extent of programmed cell death.

Histologic Findings

The neuropathology of neonatal HIE varies considerably. Brain maturity at the time of the insult is an important factor in the evolution of neuropathology. In the preterm infant, the damage is at the germinal matrix area, leading to hemorrhage in the subependymal region, the germinal matrix, or the intraventricular region. In the full-term infant, the pathology is mainly in the cerebral cortex and in the basal ganglia. Selective neuronal necrosis is the most common neuropathology. Major sites of necrosis are the cerebral cortex, diencephalon, basal ganglia, brain stem, and cerebellum..

- Selective neuronal necrosis: This injury occurs at specific sites to specific cell types (neurons > glia).The damage selectively involves hippocampus, lateral geniculate body, thalamus, caudate nucleus, putamen, globus pallidus, motor nuclei of the fifth and seventh cranial nerves and dorsal vagal nuclei.

- Parasagittal cerebral necrosis: This lesion is bilateral, usually symmetrical, and occurs in the cerebral cortex and the subcortical white matter, especially in the

parietooccipital regions. These regions represent the border zones of perfusion from major cerebral arteries.

- Status marmoratus: In this lesion, the basal ganglia, especially the caudate nucleus, putamen, and thalamus, demonstrate neuronal loss, gliosis, and hypermyelination, leading to a marble white discoloration of these regions. This is the least common type of neuropathology, and its full evolution may take months to years.

- Focal and multifocal ischemic brain necrosis: These lesions are relatively large, localized areas of necrosis of cerebral parenchyma, cortex, and subcortical white matter. The most frequently affected region is the zone perfused by the middle cerebral artery.

- Periventricular leukomalacia: This lesion is characterized by necrosis of white matter, which is seen grossly as white spots adjacent to the external angle of the lateral ventricles. These sites are the border zones between penetrating branches of major cerebral arteries. These lesions are more common in preterm than in term infants.

Clinical Features

The symptoms of moderate-to-severe HIE are almost always manifested at birth or

within a few hours after birth. Clinical manifestations and course vary depending on HIE severity.

- Mild HIE
    - Muscle tone may be increased slightly and deep tendon reflexes may be brisk during the first few days.
    - Transient behavioural abnormalities, such as poor feeding, irritability, or excessive crying or sleepiness, may be observed.
    - By 3-4 days of life, the CNS examination findings become normal.
- Moderately severe HIE
    - The infant is lethargic, with significant hypotonia and diminished deep tendon reflexes.
    - The grasping, Moro, and sucking reflexes may be sluggish or absent.
    - The infant may experience occasional periods of apnea.
    - Seizures may occur within the first 24 hours of life.
    - Full recovery within 1-2 weeks is possible and is associated with a better long-term outcome.

- An initial period of well-being or mild HIE may be followed by sudden deterioration, suggesting ongoing brain cell dysfunction, injury, and death; during this period, seizure intensity might increase.

- Severe HIE
  - Stupor or coma is typical. The infant may not respond to any physical stimulus.
  - Breathing may be irregular, and the infant often requires ventilatory support.
  - Generalized hypotonia and depressed deep tendon reflexes are common.
  - Neonatal reflexes (e.g., sucking, swallowing, grasping, Moro) are absent.
  - Disturbances of ocular motion, such as a skewed deviation of the eyes, nystagmus, bobbing, and loss of "doll's eye" (i.e., conjugate) movements may be revealed by cranial nerve examination.
  - Pupils may be dilated, fixed, or poorly reactive to light.
  - Seizures occur early and often and may be initially resistant to conventional treatments. The seizures are usually generalized, and their frequency may increase during the 24-48 hours after onset, correlating with the phase of reperfusion injury. As the injury progresses, seizures subside and the EEG

becomes isoelectric or shows a burst suppression pattern. At that time, wakefulness may deteriorate further, and the fontanelle may bulge, suggesting increasing cerebral edema.

  - Irregularities of heart rate and BP are common during the period of reperfusion injury, as is death from cardiorespiratory failure.

- Involvement of multiple organs besides the brain is a hallmark of HIE. Reduced myocardial contractility, severe hypotension, severe pulmonary hypertension requiring assisted ventilation, renal failure may occur in the first few days of life.

The staging system proposed by Sarnat and Sarnat in 1976 is often useful in classifying the degree of encephalopathy. Stages I, II, and III correlate with the descriptions of mild, moderate, and severe encephalopathy described above.

Lab Studies

No specific test can always confirm or exclude a diagnosis of HIE, since a diagnosis of HIE is made based on the history and physical and neurological examinations. Routine imaging studies may or may not consistently reveal abnormal findings. Therefore, a normal cranial imaging study does not rule out HIE.

Cranial Ultrasonography

Sonography may be useful as the initial neuroimaging study in the examination of term infants with suspected brain injury. However, as many as 50% of neurosonograms in neonates with HIE are normal. Ultrasonography is most useful for the detection of PVL. Selective neuronal injury and parasagittal or watershed lesions are frequently missed on sonography. Ultrasonography has poor specificity in differentiating increased echogenicity due to ischemic or hemorrhagic lesions. Focal and multifocal ischemic lesions, especially small cortical infarcts, may be missed on sonography but detected on CT or MRI. Early, large ischemic infarcts (e.g., large infarct of the middle cerebral artery) may be observed on ultrasonography before it is apparent on CT.

Computed tomography

CT depicts focal, multifocal, and generalized ischemic lesions. In the first few days after a severe hypoxic-ischemic insult, bilateral hypoattenuations are seen and probably reflect both neuronal injury and edema. Diffuse cortical injury is not initially detected on CT. After days to weeks, diffuse hypoattenuation may appear, with loss of the gray matter–white matter differentiation. Diffuse cerebral atrophy with ex vacuo ventricular dilatation due to severe hypoxemic insult may take several weeks to develop. A CT scan demonstrating generalized, diffuse hypoattenuation after a hypoxic-ischemic event is predictive of both neonatal death and long-term severe disability, whereas normal CT findings are predictive of mild disability or a normal outcome. Interpretation of normal results should be done with caution because hypoattenuation may take a few

weeks to develop.

Magnetic Resonance Imaging

MRI is the imaging modality of choice in the assessment of HIE, and it is sensitive in detecting focal and multifocal ischemic lesions. Changes on DWI are correlated with clinical outcomes and have been reported within 6-8 hours of life in neonates who had presumed HIE.

In the premature infant, an acute PVL lesion can be demonstrated on MRI. This pattern has been correlated with spastic diplegia in formerly premature infants with a history of PVL, but it is also frequently observed in term infants after HIE.Abnormalities of the basal ganglia, thalamus, and internal capsule have been correlated with motor dysfunction on the first 3 years of life. The watershed or parasagittal pattern of insult is associated with late cognitive impairment.

Magnetic resonance spectroscopy may reveal indirect evidence of neuronal damage by showing a decreased ratio of *N*-acetylaspartate (NAA) to choline and by showing elevated lactate peaks. These findings are somewhat correlated with subsequent neurologic deficits. High lactate-to-choline ratios with basal ganglial and thalamic abnormalities appear to be correlated with poor neurologic function after the neonatal period.

Table 2: Summary of MRI and MRS Findings in HIE

Time	Finding
24 h	Increased lactate peak
24-72 h	Increased NAA-to-choline ratio and DWI signal intensity
>72 h	Increased T2-weighted signal intensity
1-3 wk	Generalized atrophy (ex vacuo hydrocephalus), cystic changes (polycystic encephalomata)

Electroencephalograph

EEG allows for the diagnosis of neonatal seizures and helps in determining the prognosis for infants with HIE. EEG studies of neonates with HIE showed that low-voltage (5- to 15-mV) activity, electrocerebral inactivity (voltage, <5 mV), and burst-suppression patterns are predictive of a poor outcome on follow-up neurodevelopmental examination. One pattern that portends a poor prognosis is the burst-suppression pattern.

Mortality/Morbidity

In severe HIE, the mortality rate has been reported to be 50-75%. Most deaths (55%) occur in the first month, due to multiple organ failure or termination of care.

The incidence of long-term complications depends on the severity of HIE. Up to 80% of infants who survive severe HIE develop serious complications, 10-20% develop moderately serious disabilities. Among the infants who survive moderately severe HIE, 30-50% may suffer from serious long-term complications, and 10-20% with minor neurological morbidities. Infants with mild HIE tend to be free from serious CNS complications. Even in the absence of obvious neurologic deficits in the newborn period, long-term functional impairments may be present.

DEVELOPMENTAL ASSESSMENT

Developmental screening is a brief testing procedure designed to identify children who should receive more intensive diagnosis or assessment[3]. The goal of screening is to identify, as early as possible, developmental disabilities in children at high risk so that a treatment or remediation can be initiated at an early age when it is most effective. Early screening does not merely mean the administration of a single test

at one point of time; rather it is a set of processes and procedures used over a period of time. There is a need to distinguish developmental screening from developmental assessment and developmental surveillance. Developmental assessment refers to a more detailed investigation of developmental delay and is diagnostic in scope. On the other hand, developmental surveillance is a continuous, flexible and comprehensive process which includes all activities related to the detection of developmental problems and the promotion of development during primary child health care visits. Developmental surveillance includes identification of parental concerns, child observations, screening, immunization and anticipatory guidance[4].

Developmental Screening Tests

Several developmental screening tests are available for use in infants and children.It is recommended that screening test should be simple, brief, convenient to use, cover all areas of development, have adequate construct validity, be applicable to a wide age range, and have referral criteria that are both specific and sensitive[5]. Good developmental screening tests have sensitivities and specificities of 70% to 80% largely because of the nature and complexity of measuring the continuous process of child development[6].

One of the earliest assessment that has been used right in the NICU itself is the Brazelton Neonatal Behavioural Assessment Scale[7]. As this is time consuming this has not become very popular.By far the most commonly used screening test is the Denver

Development Screening Test (DDST)- first described by Frankenburg and Dodds in 1967[3,8]. The DDST is used to screen children from two weeks through 6 years of age in four developmental domains; gross motor, fine motor adaptive, personal social and language skills. The test consists of 105 items but only those items are administered which are appropriate to the child's age. Each item is scored pass or fail. Scores are interpreted as "abnormal", "questionable", or "normal" in each sector. The main usefulness of the test is that it is easy to administer and score and does not require extensive training or experience in testing. Concerns about the inadequate psychometric properties of the DDST prompted a major revision of the test and led to the development of Denver II. The major differences between the DDST and Denver II are an increase in the language items, inclusion of articulation items, a new age scale, a new category of identifying milder delays, and a behavior rating scale. However, this test too has been criticized for its limited specificity and has not been extensively used in the Indian setting. The DDST is most useful in identifying children with moderate to severe motor or cognitive deficit. However its usefulness is limited in detecting more subtle delays[9].

Trivandrum Developmental Screening Chart[10] is a simple developmental test designed and validated for children below 2 years of age. There are 17 test items in the chart chosen from the norms given in the Bayley Scales of Infant Development (BSID).It does not require any special kit and takes only 5-7 minutes.

Vojta’s neurokinesiological examination is based on 7 postural reactions for early

diagnosis of abnormal motor function. These reactions include traction reaction, Landau reaction, axillar hanging reaction, lateral tilt reaction, Collis horizontalis reaction, Peiper Isbert reaction and Collis verticalis reaction[11].

Amiel Tison has incorporated a relatively simple method of detecting abnormal neurodevelopmental status using various angles. This is a pure neuromotor test and does not take into consideration the mental development of the child[12].

Baroda Developmental Screening Test (BDST) based on the Baroda norms on BSID was proposed by Dr.Phatak[13]. This is standardized for Indian children and is widely used. This contains 54 items and tests both motor (22 items) and mental (32 items) development in the age group of 0-3 years. The items are arranged sequentially according to the 97% pass age-placements. They are grouped age-wise: one monthly for the first 12 months, three monthly for the next 6 months and six monthly for the next 12 months. A sensitivity and specificity of 65%-95% has been reported.

Munich Functional Diagnostic Scale was designed by Thedor Hellbrugge and his colleagues at the German Academy for Developmental Rehabilitation. It is based on the state of development in different functional areas. Unlike most other tests, this scale does not calculate a global developmental age or a developmental quotient. The individual results of the seven subtests are used in planning the therapeutic starting points. The early intervention strategies can be directed to the specific functional area at which the child is deficient.

Early interventional therapy

Early stimulation is now well established strategy for preventing or reducing disability resulting from early CNS damage. When there is neuronal damage during prenatal period and infancy, pruning of the spared synapses and relocation of the activity of the damaged neurons is possible if the spared synapses could be saved by stimulation[14]. Early intervention improves the neurodevelopmental outcome by preventing active inhibition of the central nervous system pathways due to inappropriate input, and supporting the use of modulating pathways during a highly sensitive period of brain development. Developmentally supportive care may be associated with improved cortical and specifically frontal lobe development from early on. This explains the positive lasting effects into school age.

REVIEW OF LITERATURE

Assessment of the developmental status of the child is gaining more importance, especially of the at risk neonates, in this era of advanced health infrastructure. The studies on the neurodevelopmental assessment of infants were started by Arnold Gessel[15] who started his studies on the development of infants as early as 1920. Dr. Juli Richmond described the last two decades as 'Era of child development and prevention in pediatrics'. Research and research techniques in child development have burgeoned.

In a study by Jaimin M Patel et al[16] at a tertiary care centre in Jamnagar, 36 neonates with HIE II and HIE III were followed up for a period of 1 year. Neurological examination was done on day 3, day 7 and every 3 monthly for the 1st year by Amiel Tison method. Trivandrum Developmental Screening Chart was carried out separately. 34% of HIE II children and 44% of HIE III children developed moderate to major deficit. Neurological examination at day 7 had a statistically significant association with abnormal neurological examination at 1 year. TDSC had a sensitivity of 92.31% in screening moderate and major deficit but only 68% in detecting minor deficit.

A prospective study was conducted by Samatha and Maiya[11] at the Neonatal Intensive Care Unit of M.S. Ramaiah Medical Teaching Hospital, Bangalore, between October 1994 and January 1997. There were 167 babies with HIE who were discharged alive and were enrolled for the follow-up. However, only 91 infants completed the follow-up till 1 year of age and only these infants were used for the final analysis. There were 28 in HIE Stage I, 37 in HIE Stage II and 26 in HIE Stage III. At one year normal development was seen in 94.6% of HIE Stage I, 62.2% of HIE Stage II and 23% of HIE Stage III. The proportion of infants with significant abnormal Vojta reactions (>3) increased significantly with increasing HIE staging. The sensitivity, specificity, positive and negative predictive values were 100% when >3 abnormal Vojta reactions of 3 months were used to detect one year neurodevelopmental outcome.

Healingly O et al[17] studied fifty seven full-term newborn infants with a diagnosis of HIE consecutively admitted to the neonatal intensive care unit in a tertiary care centre. Occurrences of seizures during the first 24 hours, cranial ultrasonography (US) findings within the first 5 days of life, and Denver developmental screening test II (DDST II) at 6 months of age, were analyzed in relation to mortality and neurological status at 2 years of age. Of the 57 infants, 10 were lost to follow-up. Twenty of the remaining 47 infants had a severe adverse outcome. Among the predictors of severe adverse outcome, occurrence of seizures was found to have a poor predictive accuracy. Cranial US had 100% sensitivity, however with a rather low specificity (55%). However, DDST II at 6 months of age, yielded a very high predictive accuracy

(sensitivity=100%, specificity=95%). It was concluded that DDST II at 6 months of age could be used in predicting severe neurological outcome in infants with HIE.

Deorari AK et al[18] studied 36 neonates with severe birth asphyxia, 32 with moderate birth asphyxia and 35 controls matched for weight and gestation. They were followed up prospectively for neurodevelopmental outcome. 6 neonates with severe birth asphyxia had abnormal neurological signs such as delayed sucking, hypo or hypertonia, apneic spell or seizures. Of these only 2 had delayed developmental milestones. The study highlights the fact that a majority of survivors of birth asphyxia enjoy good quality of life thus emphasising the need for vigorous management of asphyxiated babies at birth.

In a study by Robertson C et al[19], a total of 167 term neonates with a diagnosis of hypoxic-ischemic encephalopathy had detailed neurodevelopmental follow-up at 3.5 years of age. All 66 children with mild HIE were free from handicap; all seven with severe HIE were severely handicapped; and of the 94 with moderate HIE at birth, 21.3 per cent were handicapped. Mean IQ was significantly related to the category of HIE. Within the moderate HIE category; the neurological examination at discharge from the Neonatal Intensive Care Unit was more useful than the presence of neonatal convulsions in identifying children with subsequent developmental delay. Although neonatal convulsions were associated with an increased number of handicapped children, they did not significantly affect most other developmental outcome measures. In term infants

with documented HIE at birth, major neurodevelopmental dysfunction at 3.5 years depended more on prospectively established category of HIE than on other perinatal or social factors.

Finer NN[20] and his colleagues followed up forty nine term infants shown to have HIE. All infants survived the neonatal period, and all but two infants (seen at 12 months) were followed up to at least 27 months of age. Factors that significantly correlated with outcome included the Sarnat encephalopathy stage and the occurrence of intractable seizures. There was no association between the one- or five-minute Apgar score, the need for early ventilation, the EEG, the occurrence of seizures, and the subsequent outcome.

Misra et al[21] studied 64 term infants with APGAR <6 at 5 minutes and 90 controls. 40 cases and 48 controls turned out for complete follow up. Mortality and poor neurodevelopmental outcome correlated inversely with the Apgar scores at 5 and 10 minutes. The outcome of babies with low 5 minute Apgar was significantly better than those with same scores at 10 minutes. Symptomatic neonates with same Apgar showed significantly poorer outcome.

In a prospective study, Mejaski-Bosnjak et al[22] correlated USG and neurodevelopmental handicap in 10 infants with severe HIE. The early USG findings found in the study were cerebral edema in 9 and intraventricular hemorrhage in 2 of them. In all 10 of them, the late USG finding was severe cerebral atrophy,

predominantly in cortico-subcortical area. All of them were followed up for a period of 3 years. Six out of the ten babies developed multiple disabilities. All of them developed microcephaly. It was concluded that USG was very useful in the diagnosis of hypoxic ischemic brain damage in term neonates as well as in predicting neurodevelopmental outcome.

STUDY JUSTIFICATION

In developing countries like India, though malnutrition and communicable diseases are still the major health hazards, there has been a welcome shift towards better care of neonates both in routine care and care of high risk neonates. Risk factors like birth asphyxia, jaundice, sepsis play an important role in deciding the future development of the child.

Approximately 500 babies with HIE are admitted every year in our newborn unit. The development of health infrastructure and effective tertiary level care has decreased the mortality rates, thus shifting the emphasis to morbidity pattern. Available data regarding HIE in term babies and associated multiple risk factors are still confusing and conflicting. This issue is the focal point of this study.

This study is expected to provide insight into the pathophysiology and the course of illness of HIE. Risk factors that have an impact on the outcome, when identified will

help us to plan appropriate intervention. Early detection and intervention program to be planned for childhood disabilities can be based on the outcome of this study.

OBJECTIVES OF THE STUDY

1. To assess the neurodevelopmental outcome in neonates with HIE using Munich Functional Developmental Scale.

2. To determine the association between staging of HIE (according to Sarnat and Sarnat staging[23]) in the newborn period and neurodevelopmental outcome at the age of one year.

3. To identify the factors which have an impact on the neurodevelopmental outcome in neonates with HIE.

4. To compare the neurodevelopmental outcome assessed by Munich Functional Developmental Scale with that assessed by Baroda Developmental Screening Test (Abbreviated Bayley Scale of Infant Development).

STUDY METHODOLOGY

Study design

This study was done as a Cohort study.

Setting

This study was conducted at the Institute of Child Health and Hospital for Children, Madras Medical College, a Tertiary care Children's hospital in Chennai.

Study period

It was done during the period from November 2005 to April 2007.

Study Population

Neonates with Hypoxic Ischemic Encephalopathy admitted in the Medical Newborn Unit at the Institute of Child Health and Hospital for Children, Chennai were enrolled in the study.

Inclusion Criteria

All term neonates with history suggestive of Perinatal Asphyxia and clinically diagnosed to have HIE by Sarnat and Sarnat staging.

Exclusion Criteria

- Infants with sepsis (positive blood/CSF cultures).
- Neonates with birth weight <2.5 kgs.
- Severely dysmorphic infants with at least one major congenital anomaly.
- Any congenital brain anomaly on Cranial Ultrasonogram.
- Infants with hepatosplenomegaly and cataracts indicative of intrauterine infection.
- Presence of other identifiable causes of seizures like Hypoglycemia and Hypocalcemia.
- Babies with suspected neuromuscular disorders.

Sample Size

Based on previous studies, the incidence of neurodevelopmental outcome in neonates with HIE was expected to be about 40%. With 10% precision and alpha error of 5%, the required sample size was 92.

Manoeuvre

The study was conducted at the Medical Newborn Unit and Child Development Clinic of Institute of Child Health and Hospital for Children between the period of November 2005 and April 2007. The neonates were enrolled during the first six months of the study period and followed up for a period of one year.

All neonates included in the study were staged by Sarnat and Sarnat staging[23] (except EEG) at admission and periodically every 12th hourly till day 3 of life. The age of the baby at admission and the sex was recorded in the proforma. The details regarding the presence of antenatal illnesses, place of delivery, mode of presentation, duration of second stage of labour and mode of delivery were obtained by interviewing the mothers and from the discharge notes of the referring hospital. As this study was conducted in an extramural newborn unit, reliable data regarding Apgar scores could not be obtained in most neonates. Every enrolled child was followed up during the hospital stay for the presence of seizures, onset of seizures if any, and the need for ventilatory support. The biochemical parameters of the neonates were analysed for detecting conditions like hypoglycemia and hypocalcemia. A Cranial Ultrasonogram was performed on every child to look for features suggestive of HIE and to exclude any congenital anomaly of the brain.

At the time of discharge, the children were examined for the presence of abnormal neurological signs. The weight, length, head circumference and chest circumference

were noted for every child. The parents were counselled regarding the outcome of HIE and the need for follow up and periodic development assessment. A Child Development Clinic (CDC) card was issued to every child, with details of follow up dates.

The infants were followed up at 1, 3, 6, 9, and 12 months of age. At each visit, the child's weight, length, head circumference and chest circumference were noted. The child's development was assessed by Munich Functional Developmental Scale and Abbreviated Bayley Scales of Infant Development (Baroda Developmental Screening Chart).

In Munich Functional Developmental Scale, the infants were assessed in seven functional areas namely Crawling age, Sitting age, Walking age, Grasping age, Perception age, Speech age and Social age.

There are 13 items in each area. A particular area of development was completely clarified only when the child had correctly executed at least 3 items. After the last positively rated item, three consecutive difficult items were clarified which the child could not execute. The items performed by the child were plotted on the graph.

In BDST, the performance of the child was noted by plotting the total number of items passed by him/her (score) against the chronological age. The intersection of the horizontal level of this score with the 50% level curve indicated the developmental age of the child, i.e., the age at which 50% normal children are expected to have the same scale. The developmental quotient was calculated as follows:

$$\frac{\text{Developmental age}}{\text{Chronological age}} \times 100$$

If the child's developmental quotient was 77.5 (-1.5 SD) or less, the child was considered to have delayed development[13].

Visual assessment was done at 3 months and 6 months by

- Gross appearance of the eyes
- Perception and following of a bright object
- Visual fixation on coloured objects
- Red reflex by ophthalmoscopy
- Eye movements
- Fundoscopy
- Retinoscopy for refractive error

Auditory evaluation was done at 6 months and one year by Behaviour Observation Audiometry[24]. BERA could not be done as the facilities were not available in our hospital.

At the end of one year, the correlation between the HIE stages and the final neurodevelopmental outcome was analysed. The results are as follows.

RESULTS

The infants were enrolled from November 2005 to April 2006 and they were followed up for a period of one year from the date of enrollment. During the enrollment period, the total number of admissions in the newborn unit was 1800. Number of babies with HIE were 292, constituting 16.22% of total admissions. Among them, 103 babies died during the hospital stay contributing to 24.81% of total number of deaths in the newborn unit. Among the 189 who survived, 42 neonates were excluded after applying the exclusion criteria. The remaining 147 neonates were followed up. Their parents were counselled and CDC cards were issued at the time of discharge. 25 of them were lost to follow up. 2 infants died after discharge. At the end of the study period, 120 of them had completed the follow up. The data from those 120 newborns were analysed using SPSS for windows version 11.0.

The observations were analysed under the following headings:

I. Baseline data

II. Profile of HIE

III. Analysis of neurodevelopmental outcome

IV. Analysis of the risk factors for outcome

I. Baseline data

The demographic details of the study population were analysed in the following

ways:

(i) Sex distribution among HIE neonates

Table 3: Sex distribution among HIE neonates

Sex	n	%
Males	51	42.50
Females	69	57.50

Among the 120 babies with HIE who were followed up, 42.5% were males and 57.5% were females.

(ii) Antenatal illnesses among mother with HIE babies.

Table 4: Antenatal illnesses among mother with HIE babies.

Antenatal Illnesses	n	%
Anemia	29	24.16
PIH	24	20
GDM	5	4.16
Antepartum Hemorrhage	6	5.0
Obstructed Labour	3	2.5
Infections	3	2.5
Nil	50	41.66

Among the mothers with HIE babies, 41.66% had normal antenatal period; 24.2% of them had anemia,20% of them had PIH, 4.16% had GDM, 5% had antepartum hemorrhage, 2.5% had obstructed labour and 2.5% had medical illnesses like infections (2 cases of UTI and 1 case of LRI), heart disease etc..

(iii) Place of Delivery

Table 5: Place of Delivery

Place of Delivery	n	%
Medical College Hospital/Tertiary Hospital	7	5.83
Corporation Hospital /District Hospital	37	30.83
Primary Health center / Subcentre	38	31.66
Private Nursing Home	32	26.66
Home / Transit	6	5.0

Among the 120 babies included in the study, 95% had institutional deliveries.

(iv) Mode of Presentation

Table 6: Mode of Presentation

Mode of Presentation	n	%
Vertex	113	94.16

Breech	6	5
Others	1	0.8

Among the babies included in the study, 94% had vertex presentation and 5% had breech presentation.

(v) Duration of Second Stage of Labour

As the study was conducted in an extramural unit, history regarding duration of second stage of labour could not be obtained in many cases and thus could not be analysed. Among the 40 cases in whom the history could be obtained, 26 of them had prolonged second stage of labour.

(vi) Apgar score

As this study was conducted in an extramural newborn unit, reliable data regarding Apgar scores could not be obtained in most neonates.

(vii) Mode of Delivery

Table 7: Mode of Delivery:

Mode of delivery	n	%
Normal Vaginal	78	65
LSCS	37	30.83
Vacuum / Forceps	5	4.16

65% of babies were delivered by normal vaginal delivery, 30.83% by caesarian section and 4.16% by forceps delivery

(viii) Age at Admission

Table 8: Age at Admission

Age at admission in Hrs)	N	%
<12	68	56.66
13-24	32	26.66
25-36	9	7.5
37-48	11	9.1

Among the babies included in the study, 56.6% of them were referred to the hospital within 12 hours.

II. Profile of HIE

(i) Stages of HIE

Table 9: Stages of HIE

Stage of HIE	n	%
HIE – I	30	25
HIE – II	64	53.33
HIE – III	26	21.66

Among the 120 babies, 25.0% belonged to HIE Stage I, 53.33% to HIE Stage II and 21.66% to HIE Stage III.

(ii) Incidence of Seizures among HIE babies

Table 10: Incidence of Seizures among HIE babies

HIE	**Incidence of Seizures**		**p-value**
Stage	**n**	**%**	
I (n=30)	-	-	
II (n=64)	58	90.6	0.00*
III (n=26)	12	46.2	
TOTAL (n=120)	70	58.33	

Overall, seizures occurred in 58.33% of babies with HIE. Seizures occurred in none of the HIE I babies, 90.6% of HIE Stage II and 46.2% of HIE Stage III. Incidence of seizures was highest in HIE II and it was statistically significant.

(iii) Onset of Seizures

Table 11: Onset of Seizures

Stage of HIE	Onset of seizures in HIE						p-value
	<6 hrs		6 – 24 hrs		> 24 hrs		
	n	%	n	%	n	%	
I (n=0)	-	-	-	-	-	-	0.02*
II (n=58)	21	36.2	29	50.0	8	13.8	
III (n=12)	8	66.7	4	33.3	-	-	
Total (n=70)	29	41.42	33	47.14	9	12.85	

Among HIE Stage II babies with seizures, 36.20% developed seizures within 6 hrs of life, 50% at 6-24 hrs and 13.7% after 24 hrs of life. Among HIE Stage III babies with seizures, 66.66% developed seizures within 6 hrs of life and 33.33% at 6-24hrs.Onset of seizures was found to be earlier as the HIE stage increased and it was statistically significant.

(iv) Need for Ventilatory Support

Table 12: Need for Ventilatory Support:

HIE Stage	Need for ventilatory support		p-value
	n	%	
I (n=30)	-	-	0.00*
II (n=64)	6	9.37	
III (n=26)	15	57.69	
Total (n=120)	21	17.5	

None of the HIE I required ventilatory support. 9.37% of HIE II & 57.69% of HIE

III needed ventilatory support .Need for ventilatory support significantly increased as the stage of HIE increased.

(v) Cranial Ultra Sonogram in HIE Babies

Table 13: Cranial Ultra Sonogram in HIE Babies

Stages of HIE	Ultrasound findings in HIE				p-value
	Normal		Abnormal		
	n	%	n	%	
I (n=30)	20	100.0	-	-	0.00*
II (n=64)	51	79.7	13	20.3	
III (n=26)	11	42.3	15	57.7	
Total (n=120)	92	76.7	28	23.3	

More than 50% of HIE III babies had abnormal USG and none of the HIE I babies had abnormal USG .The difference was statistically significant. Loss of sulci gyri echodistinction, presence of ischemic changes, hemorrhages, PVL and edema (midline shift, ventricular compression) were the abnormal USG findings.

(vi) Duration of hospital stay

Table 14: Duration of hospital stay

Stages of HIE	Duration of hospital stay				p-value
	< 1 week		< 1 week		
	n	%	n	%	
I (n=30)	28	93.3	2	6.7	0.00*
II(n=64)	26	40.6	38	59.4	
III (n=26)	-	-	26	100.0	
Total (n=120)	54	45.0	66	55.0	

The hospital stay increased as the HIE stage increased and all babies with HIE III stayed in the hospital for more than one week. The difference was found to be statistically significant.

(vii) Neurological status at Discharge

Table 15: Neurological status at Discharge

Stages of HIE	Neurological status at discharge				p-value
	Normal		Abnormal		
	n	%	n	%	
I (n=30)	30	100.0	-	-	0.00*
II (n=64)	44	68.8	20	31.3	
III (n=26)	-	-	26	100.0	
Total (n=120)	74	61.7	46	38.3	

All the HIE I babies were neurologically normal at discharge and all HIE III babies were neurologically abnormal at discharge. One third of the HIE II babies were abnormal at discharge.

III. Analysis of Neurodevelopmental Outcome

A. Assessment by Munich Functional Developmental Scale

(i) Neurodevelopmental Outcome in HIE by Munich Functional Developmental Diagnostic Scale

Table 16:

Neurodevelopmental Outcome in HIE by Munich Functional Developmental Diagnostic Scale

HIE Stage	Incidence of Developmental Delay		p-value
	n	%	
I (n=30)	2	6.66	0.00*
II (n=64)	29	45.31	
III (n=26)	26	100	
Total (n=120)	57	47.5	

According to Munich Functional Developmental Diagnostic scale, 47.5% of babies with HIE had adverse neurodevelopmental outcome at 1 year of age. 6.6% of HIE Stage I babies, 45.31% of HIE Stage II babies and all HIE Stage III babies had developmental delay at 1 year of age.

(ii) Profile of delay in specific developmental areas – assessment by Munich Functional Developmental Diagnostic Scale.

Table 17:
Profile of delay in specific developmental areas – assessment by Munich Functional Developmental Diagnostic Scale

Developmental Areas	Babies with Delay					
	HIE I (n=2)		HIE II (n=29)		HIE (n=26)	
	n	%	n	%	n	%
Crawling Age	-	-	19	65.51	21	80.76
Sitting Age	-	-	20	68.96	20	80.76
Walking Age	1	50	19	65.51	22	84.61
Grasping Age	2	100	23	79.31	24	92.30
Perception Age	-	-	18	62.06	19	73.07
Speech Age	1	50	20	68.96	24	92.30
Social Age	-	-	18	62.06	20	76.92

When the developmental domains were assessed, it was found that no specific area was more commonly affected than the rest. However for a given child, the delay was not necessarily global.

(iii) Predictability of neurodevelopmental outcome at 1 year by Munich Functional Developmental assessment at 3 months.

Table 18:

Predictability of neurodevelopmental outcome at 1 year by Munich Functional Developmental assessment at 3 months.

Neurodevelopmental Outcome at 3 months	**Neurodevelopmental outcome at 1 year**	
	Abnormal	**Normal**
Abnormal (n=59)	56	3
Normal (n=61)	1	60
Total	57	63

Kappa statistic- 0.93 (p-value 0.00)

Sensitivity of 3rd month assessment in predicting development at 1 year was 98.24%, specificity was 95.23%, positive predictive value was 94.91% and negative predictive value was 98.36%.

B. Assessment by Baroda Developmental Screening Test.

(i) Incidence of developmental delay in HIE- Assessed by Baroda Developmental Screening Test.

Table 19:

Incidence of developmental delay in HIE- Assessed by Baroda Developmental Screening Test.

HIE Stage	**Incidence of Developmental Delay**		**p-value**
	n	**%**	0.00*
I(n=30)	2	6.6	
II(n=64)	26	40.62	
III(n=26)	25	96.15	
Total(n=120)	53	44.16	

According to Baroda Development Screening Test, 44.16% of HIE babies had adverse neurodevelopmental outcome at 1 year of age. 6.6% of HIE I babies, 40.62% of HIE II Babies and 96.15% of HIE III babies had delayed development at 1 year of age.

(ii) Developmental Quotient in HIE Babies – Assessed by Baroda Development Screening Test.

a. Among all babies

Table 20:

Developmental Quotient in HIE Babies

Stage of HIE	Mean	SD	p-value*
I	94	12	0.00
II	75	25	
III	36	20	
Total	72	29	

*ANOVA test

b. Among babies with developmental delay

Table 21:

Developmental Quotient in HIE Babies with developmental delay

Stage of HIE	Mean	SD	p-value*
I	69	4	0.002
II	53	19	
III	36	20	
Total	46	21	

*ANOVA test

The mean developmental quotient among HIE I was 94, HIE II was 75, and HIE III was 36.The mean developmental quotient among those with developmental delay was as follows- 69 in HIE I, 53 in HIE II and 36 in HIE III. The difference in the mean DQ among the different stages of HIE was statistically significant.

C. Comparison of Munich Functional Developmental Diagnostic scale (MFDS)

and Baroda Developmental Screening Test (BDST).

Table 22:
Comparison of Munich Functional Developmental Diagnostic scale (MFDS) and Baroda Developmental Screening Test

Developmental delay by MFDS	Developmental delay by BDST		Total
	Yes	No	
Yes	53	4	57
No	0	63	63
Total	53	67	

Kappa statistic 0.93 (p-value 0.00)

MFDS had a sensitivity of 100%, specificity of 94.02%, positive predictive value of 92.98% and negative predictive value of 100% in predicting the developmental delay among HIE babies as assessed by BDST.

D. Co-Morbidity among Babies with Developmental Delay.

(i) Visual Disturbance:

Table 23:

Visual Disturbance among Babies with Developmental Delay.

HIE Stage	Cortical Blindness		p-value
	n	%	0.14
I (n=2)	-	-	
II (n=29)	1	3.44	
III (n=26)	5	19.23	
Total (n=57)	6	10.52	

10.52 % of those with developmental delay had cortical blindness which amounted to 5% of total HIE babies .Other ophthalmic problems like strabismus & nystagmus were found in 9 babies, 15.78% of those with developmental delay.

(ii) Hearing Impairment:

Table 24:
Hearing Impairment among Babies with
Developmental Delay.

HIE Stage	Hearing Impairment		p-value
	n	%	0.08
I(n=2)	-	-	
II(n=29)	1	3.44	
III (n=26)	6	23.07	
Total(n=57)	7	12.28	

12.28% of those with developmental delay (5.87% of all HIE babies) had hearing impairment. The incidence of hearing impairment was not significantly higher in HIE III.

(iii)**Presence of Seizures at 1 year of age among those with developmental delay.**

Table 25:
Presence of Seizures at 1 year of age among those with developmental delay.

HIE Stage	Prevalence of Seizures		p-value
	n	%	0.02
I (n=2)	-	-	
II (n=29)	4	13.79	
III (n=26)	12	46.15	
Total (n=57)	16	28.07	

28.07% of those with adverse neurodevelopmental outcome continued to have seizures at 1 year of age (46.15% among HIE III and 13.79% among HIE II, None of HIE I had seizures at 1 year).Persistence of seizures at 1 year was significantly high in HIE III.

(iv) Microcephaly among those with developmental delay

Table 26: Microcephaly among those with developmental delay

HIE Stage	Microcephaly at 1 year		p value
	n	%	
I(n=2)	-	-	0.01
II(n=29)	3	10.3	
III(n=26)	12	46.15	
Total(n=57)	15	26.3	

None of the HIE babies studied were microcephalic at birth. Among babies with adverse outcome, 10.3% of HIE II and 46.15% of HIE III babies had microcephaly at 1 year. None of the HIE I babies developed microcephaly.

73.68% of those with developmental delay did not have microcephaly. Microcephaly was significantly higher in HIE III.

IV. Analysis of the risk factors for outcome

(i) Predictors of neurodevelopmental outcome among HIE babies

Table 27: Predictors of neurodevelopmental outcome among HIE babies

Risk Factors	Developmental delay		No developmental delay		p-value*
	n	%	n	%	
Sex					
Male	25	49.0	26	51.0	0.85
Female	32	46.4	37	53.6	
Antenatal illnesses					
Anemia	13	44.8	16	55.2	
PIH	9	37.5	15	62.5	
GDM	1	20.0	4	80.0	
APH	4	66.7	2	33.3	
Obstructed labour	2	66.7	1	33.3	0.58
Infections	2	66.7	1	33.3	
Nil	26	52.0	24	48.0	
Place of delivery					
Medical college/tertiary hospital	2	28.6	5	71.4	
Corporation hospital/district hospital	16	43.2	21	56.8	
Primary health centre/sub centre	18	47.4	20	52.6	0.69
Private hospital	18	56.3	14	43.8	
Home	3	50.0	3	50.0	
Mode of presentation					
Vertex	53	46.9	60	53.1	0.57
Breech	3	50.0	3	50.0	
Others	1	100.0	-	-	
Mode of delivery					
Normal/vaginal	35	44.9	43	55.1	0.69
LSCS	3	60.0	2	40.0	
Vacuum/forceps	19	51.4	18	48.6	
Stages of HIE					
I	2	6.7	28	93.3	
II	29	45.3	35	54.7	0.00
III	26	100.0	-	-	

*C

hi-

square test

The sex of the neonate, antenatal illnesses, place of delivery, mode of delivery, mode of presentation and age at admission did not have statistically significant association with neurodevelopmental outcome. The following had statistically significant association with neurodevelopmental outcome- HIE stage, presence of seizures, need for ventilatory support, abnormal cranial ultrasonogram, abnormal neurological status at discharge and a hospital stay of more than one week.

(ii) Onset of seizures as a predictor of neurodevelopmental outcome among those with seizures

Table 28:

Onset of seizures as a predictor of neurodevelopmental outcome among those with seizures

Onset of seizures	Developmental delay				p-value
	Yes		No		
	n	%	n	%	
< 6 hrs	23	79.3	6	20.7	0.02
6-24 hrs	15	45.5	18	54.5	
> 24 hrs	4	44.4	5	55.6	

Earlier onset of seizures was significantly associated with adverse neurodevelopmental outcome.

(iii) Univariate Logistic Regression – Risk Factors for Neurodevelopmental Outcome

Table 29: Univariate Logistic Regression – Risk Factors for Neurodevelopmental Outcome

Risk Factors	O.R.	95% C.I.	p-value
Presence of seizures	3.3	1.5, 7.1	0.002
Need for Ventilatory support	33.4	4.3, 259.1	0.001
Abnormal Cranial Ultrasound	25.6	5.7, 114.8	0.00
Hospital stay ≥ 1 week	13.3	5.4, 32.7	0.00
Abnormal Neurological Status at discharge	22.3	8.1, 61.7	0.00

As all neonates with HIE stage III had developmental delay, an Odds ratio could not be calculated for the same. Presence of seizures in the early neonatal period was significantly associated with adverse neurodevelopmental outcome with an Odds ratio of 3.3. Developmental delay was more common in those who needed ventilatory support. This was statistically significant with an Odds ratio of 33.4. A child with an abnormal cranial ultrasound was 25 times at higher risk of developing delayed milestones when compared to those with normal ultrasonogram. Similarly those who were neurologically abnormal at discharge were more likely to have developmental delay (Odds ratio 22.3). Hospital stay of ≥ 1 week had a statistically significant association with an adverse neurodevelopmental outcome with an Odds ratio of 13.3. The same variables were

subjected to Multivariate Logistic Regression

(iv) Multiple Logistic Regression- Risk Factors for Neurodevelopmental Outcome

Table 30: Multiple Logistic Regression- Risk Factors for Neurodevelopmental Outcome

Risk Factors	O.R.	95% C.I.	p-value
Presence of seizures	3.2	1.0 , 10.1	0.04
Need for Ventilatory support	5.7	0.5 , 59.7	0.15
Abnormal Cranial Ultrasound	11.1	2.2 , 56.5	0.004
Abnormal Neurological Status at discharge	8.7	2.6 , 29.8	0.001
Hospital stay ≥ 1 week	1.2	0.3, 4.9	0.78

When the same variables were subjected to multivariate analysis, it was found that the need for ventilatory support and a hospital stay of more than one week were not predictive of developmental delay in HIE.

Presence of seizures, an abnormal cranial ultrasonogram and abnormal neurological signs at the time of discharge had a statistically significant association with delayed neurodevelopment with a p value of <0.05.

SUMMARY

Analysis of the results showed that seizures were more common in HIE II when compared to HIE III. The possibility of detecting an abnormal finding in the cranial ultrasound increased as the HIE stage increased. Similarly abnormal neurological findings at the time of discharge were more common in HIE III when compared to other stages.

The incidence of developmental delay correlated with the HIE stages. The incidence increased with increase in the stage. There was no predilection for involvement of any specific area when assessed by Munich Functional Developmental Scale. The developmental delay detected at 3rd month of life was a sensitive predictor of neurodevelopmental delay at 1 year. The results obtained by Munich Functional Developmental Scale agreed with those of Baroda Developmental Screening Test.

Analysis of risk factors for an adverse neurodevelopmental outcome showed that the maternal or perinatal factors were not predictive of the long term outcome. The predictors of delayed development were HIE stage, occurrence of seizures in the neonatal period, earlier onset of seizures, abnormal neurological status at discharge and abnormal cranial ultrasonogram.

DISCUSSION

The incidence of birth asphyxia is reported to be much higher in developing countries, and presents a formidable challenge to health professionals from the point of view of preventive as well as therapeutic interventions. In our study, HIE constituted 16.22% of the total newborn admissions which correlated exactly with the national statistics (16.0%) as reported in National Neonatal Perinatal Database (NNPD) 2002-2003[25]. HIE contributed to 24.8% of total neonatal deaths in our newborn unit, which was slightly higher than the national reports[25] (19.0%). In a study done by Jaimin et al[16], HIE accounted for 22.25% of total NICU deaths which was similar to our study.

Longitudinal studies are time consuming and have high fall out rate, as shown in the study by Bhargava et al[26] from Delhi, where, of the 572 Low Birth Weight babies with birth weight <2000 grams, only 1/3 of the sample was available at 6 yrs. In another study[27] from Goa on early intervention of LBW, it was noted that, only half of the babies could be followed up till 1 year of age. In our study, we were able to follow up 80 % of the babies till one year of age.

Occurrence of seizures was more common in HIE II than in HIE III which correlated with the results of Sarnat and Sarnat[23]. It is important to closely follow the neurodevelopment of neonates with HIE as they carry a high risk of developing neurological abnormalities. The incidence of developmental delay in HIE was 47.5% in

the present study. It was comparable with the studies done by Samatha et al[13] (49.45%), Rajadurai et al[28] (42.85%), Hallioglu O et al[17] (42.55%) and Thomson et al[29] (42%). Jaimin et al[16] reported a higher incidence of 69.44% but their study had included only HIE II and HIE III, excluding HIE I babies who are expected to have better outcomes.

Our observations also confirm with Sarnat and Sarnat[23] in that, there is a demonstrable relationship between severity of HIE and neurodevelopmental outcome. The incidence of developmental delay was 6.6% in HIE I and 40.62% in HIE II in the present study. It was similar to the observations of Samatha et al[13] (5.4% and 37.8% in HIE I and HIE II respectively). All the HIE III babies in our study had a delayed development which correlated with the observations of Sarnat and Sarnat[23]. According to their study, one half of HIE III babies don't survive and the other half are left with neurological sequelae. However Samatha et al[13] reported only 77% incidence of delay in HIE III. Early diagnosis in these infants is imperative as the handicap can be reduced to a great extent by early intervention.

In the present study, the developmental assessment was done by Munich Functional Developmental Diagnostic Scale. To the best of our knowledge, there are no articles published in English literature regarding the early diagnosis by Munich Functional Developmental Diagnostic Scale and therefore we were unable to compare our results with similar studies. In this study, it was found that no specific developmental area was more commonly affected than the rest when analysed as a

whole. But when analysed on an individual child basis, most children had delay in few specific areas and only few infants with severe delay were affected globally. The early intervention programs can be directed towards those specific functional areas in which there is a delay. This therapeutic approach is the prime feature of Munich Functional Diagnostic Scale.

This study has also assessed the predictive value of Munich developmental assessment at 3 months of age as a screening test to predict neurodevelopmental outcome in babies with HIE at one year of age. The 3rd month assessment had a sensitivity of 98.24%, specificity of 95.23%, positive predictive value of 94.91% and negative predictive value of 98.36%. Thus Munich Functional Diagnostic Scale is a sensitive screening tool as early as 3 months of age. . Based on this early diagnosis the child can be referred for early intervention in order to prevent a lifelong handicap. These results are similar to the observations of Samatha et al[13] who had employed the Vojta's system of kinesiological diagnosis. In their study, the sensitivity, specificity, positive and negative predictive values were 100% when >3 abnormal Vojta reactions of 3 months were used to detect neuro-developmental outcome at one year of age. However Chaudhari et al[30] reported only 26.6% prediction using abnormal Amiel Tison test at 3 months of age. The differences are due to the varying sensitivities of the different scales used in the studies.

In our study, we had compared the results of Munich Functional Developmental

Scale with those of Baroda Developmental Screening Test which is standardised for Indian children. MFDS had a sensitivity of 100%, specificity of 94.02%, positive predictive value of 92.98% and negative predictive value of 100% in predicting the developmental delay among HIE babies as assessed by BDST. MFDS agreed with BDST with a Kappa statistic of 0.93. Thus MFDS was found to be valid for Indian children. However it needs more extensive studies to confirm it. There are no previous studies comparing these two scales. Thus we couldn't compare our results with similar studies.

In our study, the mean developmental quotient (DQ) was lower as the HIE stage increased. The difference in the mean DQ among the HIE stages was statistically significant. Similar observation was made in a study by Robertson et al[19], where the mean DQ correlated significantly with the HIE stage.

Hearing impairment was found in 7 cases (5.87% of all HIE babies) in our study. As BERA could not be done, it was difficult to test the objectivity, but the findings correlated with other studies[31] in which the incidence of permanent hearing loss of 4% was observed at 3 months of age with BERA. Cortical blindness was found in 5% of HIE babies. Incidence of cortical blindness in HIE is not reported in any other study. Jaimin et al[16] had reported 22% incidence of ophthalmic problems like strabismus and nystagmus. It was 15.78% in our study. Microcephaly occurred in 12.5% of our study population (26.32% of those with developmental delay). Microcephaly was present in

48% of the infants with HIE, compared with 3% of the controls in a study done by Eugenio Mercuria[32] and his colleagues. The significantly different results between the two studies were probably because of the different standards used for defining microcephaly. WHO standards for head circumference was used in the present study while charts[33] designed by the Child Growth Foundation 1996 was used in their study.

In the present study, on analysing the risk factors for delayed development, it was found that the maternal or perinatal factors did not predict the outcome. This was supported by Robertson C et al[19] in their study. The stage of HIE correlated well with the outcome in our study as stated by Sarnat and Sarnat[23]. The same was observed in studies by Robertson C et al[18], Rajadurai et al[28] and Finer NN et al[20].

Presence of seizures in the early neonatal period was a predictor of outcome in the present study which was supported by Finer NN et al[20]. Our study states that earlier onset of seizures predicted an adverse neurodevelopment.

Mejaski-Bosnjak et al[22] correlated USG and neurodevelopmental handicap in infants with HIE. All of them were followed up for a period of 3 years. It was concluded that USG was very useful in the diagnosis of hypoxic ischemic brain damage in term neonates as well as in predicting neurodevelopmental outcome. Hallioglu et al[17] too concluded that abnormal cranial ultrasound had a high accuracy in predicting the developmental outcome in HIE. In our study too, abnormal ultrasound predicted adverse neurodevelopment in HIE with an odds ratio of 11.1.

According to this present study, if an infant has abnormal neurological signs at the time of discharge, he/she has a significantly higher risk of manifesting neurological deficits during follow up at one year (Odds ratio 8.7). A similar study by Jaimin et al[16] demonstrated that abnormal Examination at Day 7 has significant association with abnormal neurological status at the end of 1 year as assessed by Amiel Tison Method ($P < 0.01$, Positive predictive value of 91%). Supporting the same, Robertson et al[19] had stated that the neurological examination at discharge from the Neonatal Intensive Care Unit was more useful than the presence of neonatal convulsions in identifying children with subsequent developmental delay. The need for ventilation and duration of hospital stay did not predict the outcome in our study as analysed by multiple logistic regression. Finer NN et al[20] also had shown that there was no association between the need for early ventilation and subsequent outcome.

CONCLUSION

- About one half of the neonates with HIE have delayed development at one year of age as assessed by Munich Functional Developmental Scale.
- The neurodevelopmental outcome worsens as the severity of encephalopathy increases.
- Severe degrees of encephalopathy, presence of seizures, abnormal ultrasonogram and abnormal neurological signs at the time of discharge predict adverse neurodevelopmental outcome.
- Munich Functional Developmental Scale is comparable to Baroda Developmental Screening Test in the developmental assessment of Indian children.
- The third month developmental assessment by Munich Functional Developmental Scale is predictive of the neurodevelopment at one year and can be employed as an effective screening tool.

Neonatal care is incomplete without adequate follow up, which is mandatory for early prediction of outcome and selection of infants who would benefit from early interventions. Successful early identification of delayed development requires that the pediatricians be skilled in the use of screening tests and be aware of the strengths as well as the limitations of developmental screening.

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ANNEXURE – I

SARNAT AND SARNAT'S CLINICAL STAGES OF HIE

	Stage 1	Stage 2	Stage 3
Level of Consciousness	Hyperalert	Lethargic or obtunded	Stuporous
Neuromuscular Control			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive	Decreased or absent
Segmental myoclonus	Present	Present	Absent
Complex Reflexes			
Suck	Weak	Weak or absent	Absent

Moro	Strong; low threshold	Weak; incomplete; high threshold	Absent
Oculovestibular	Normal	Overactive	Weak or absent
Tonic neck	Slight	Strong	Absent
Autonomic Function	Generalized sympathetic	Generalized parasympathetic	Both systems depressed
Pupils	Mydriasis	Miosis	Variable; often unequal; poor light reflex
Heart Rate	Tachycardia	Bradycardia	Variable
Bronchial and Salivary Secretions	Sparse	Profuse	Variable
Gastrointestinal Motility	Normal or decreased	Increased; diarrhea	Variable
Seizures	None	Common; focal or multifocal	Uncommon (excluding decerebration)
Electroencephalogram Findings	Normal (awake)	Early: low-voltage continuous delta and theta Later: periodic pattern (awake) Seizures: focal 1-to 1-Hz spike-and-wave	Early: periodic pattern with Isopotential phases Later: totally isopotential
Duration	<24 hours	2-14 days	Hours to weeks

ANNEXURE – II

DATA COLLECTION FORM

CDC FOLLOW UP NO:

NAME :

SEX :

ADDRESS :

DOB :

DOA :

DOD :

HISTORY

ANTENATAL HISTORY

Booked / Unbooked

Medical Illness	:	Anemia / DM/Heart Disease/TORCH infections
Obstetric Complications	:	PIH/GDM/APH/Obstructed Labour
Presentation	:	Vertex / Breech / Others

NATAL HISTORY

Place of Delivery	:	Med. College hospital / GH / Dist.

		Hospital / PHC / SC/ Private MC / NH/ Home / Others
Mode of Delivery	:	Normal Vaginal / LSCS / Vacuum / Forceps
Birth Weight	:	
Apgar (If Available)	:	
Resuscitation	:	Initial Steps / Tactile Stimulation, O2 Suction / BMV / Intubation / Drugs / Not Known

HIE STAGE: I II III

No. of Seizure Episodes :

Onset of Seizures :

Co-Morbidity :

Investigations: Biochemical parameters;

Cranial Ultrasonogram:

Treatment in NICU :

No of Days of Hospital Stay:

Condition at Discharge: Neurologically Normal / Abnormal

Clinical Examination at Admission:

Weight :

Length :

HC :

CC :

Others :

DATA COLLECTION FORM

(During Follow Up)

History :

Persistence of Seizures after discharge : Yes / No

ANTHROPOMETRY

	1 Month	3 Months	6 Months	9 Months	12 Months
Weight					
Length					
HC					
CC					
Others					

DEVELOPMENTAL ASSESSMENT:

Baroda Developmental Screening Test

BDST	1 Month	3 Months	6 Months	9 Months	12 Months
Score					

Developmental Quotient at 1 year -

MUNICH FUNCTIONAL DEVELOPMENTAL DIAGNOSTIC TEST

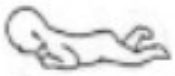
ronologica l Age	**Crawling Age**	**Sitting Age**	**Walking Age**	**Grasping Age**	**Perception Age**	**Speech Age**	**Social A**
12							
11							
10							
9							
8							
7							
6							
5							
4							
3							
2							
1							

ANNEXURE – III

MUNICH FUNCTIONAL DEVELOPMENTAL SCALE

CRAWING AGE

End of 12th Month	Safe Crawling	
End of 11th Month	Cross-Coordinated crawling with hands and knees	
End of 10th Month	(a) Swinging on hand and knees. (b) Uncoordinated crawling. (c) Able to come to sit with flexion of hip and rotation of trunk.	
End of 9th Month	Commando Crawling	
End of 8th Month	Transition Stage	
End of 7th Month	(a) One arm lifted from the ground for 3 seconds. (b) Parachute reaction.	
End of 6th Month	(a) Support with extended arm on half or full opened hands. (b) When foundation is lifted from one side arms and legs of the higher side will be abducted (balance reaction).	
End of 5th	Interrupted elbow support by lifting the arm in co-	

Month	ordination with repeated extension of lifted legs (swimming).	
End of 4th Month	Using safe elbow support	
End of 3rd Month	(a) Raising head between 45 and 90º (b) raising head for one minute minimum (c) Beginning of elbow support (d) Hips mostly in loose extension	
End of 2nd Month	(a) Raising head 45º minimum (b) Raising head 10 seconds minimum	
End of 1st Month	Raising head for 3 Seconds minimum	
Newborn	(a) Turns head from middle position to one side. (b) Upper and Lower limbs in total flexion (c) Reflex Creeping	

SITTING AGE

End of 11th and 12th Month	Safe balance in long-sit Position	
End of 10th Month	(a) Coming to, sit from supine position only using furniture as support. (b) Long-sit- free sitting with extended back and loosely extended legs.	
End of 9th Month	Able to sit without support atleast one minute.	
End of 8th Month	(a) Begins to pull up actively from the supine position if you offer finger as support. (b) Sitting atleast five seconds independent with hand forward support.	
End of 7th Month	(a) Turning over from supine to prone position actively. (b) Playing with the feet in supine position (hand feet co-ordination).	
		

End of 6th Month	(a) During traction-reaction both arms in beginning of flexion. ((b) In sitting position the head is well controlled, if trunk is inclined to all four directions.	
End of 5th Month	(a) During traction-reaction head is lifted in lengthening of spine. (b) Head in straight position even if trunk is inclined aside passively.	
End of 4th Month	During traction-reaction head and loosely flexed legs are rising.	
End of 3rd Month	(a) In sitting position head is held straight for about half a minute. (b) In horizontal floating position head is not falling backwards.	
End of 2nd month	In sitting position head is in straight position at least five seconds.	
End of 1st Month	In supine position head is kept in middle position at least five seconds.	
Newborn	(a) Head kept aside without preferring one side. (b) Struggling without preferring one side. (c) Head lifted from forward in sitting position several times for one second.	

PERCEPTION AGE

End of 12th Month	(a) Pulling a rope to get a desired toy (toy with rope). (b) Let fall coins into the small box.	
End of 11th and 10th Month	(a) is throwing away toys with intention. (b) Touching details with the fore finger (touching the eyes, nose etc. of the doll).	
End of the 9th Month	Recognizing cubes inside a box and grasping it.	

End of 8th and 7th Month	Tries to reach a toy which only can be got by changing the position.	
End of 6th Month	Is following a fallen down toy with it's eyes.	
End of 5th Month	Is looking towards resulted noise	
End of 4th Month	Watching a toy in his hand.	
End of 3rd and 2nd Month	(a) is following a red rattle from one corner of the eye to the other. (b) is watching a ringing bell by stopping its movements and fixing the eyes for a short moment.	
End of 1st Month	Is following a red rattle with the eyes to the both sides about 45º	
Newborn	Reacting unwilling to extreme light and noise effect.	

GRASPING AGE

End of 12th and 11th Month	Grasping small things with flexed fore finger and opponent thumb (forceps-grip).	
End of 10th Month	(a) Grasping small things with extended fore finger and opponent thumb. (Pincer- grip).	
End of 9th Month	Lets thing fall down with intention.	

End of 8th and 7th Month	(a) Grasping with both hands ever one cube and is holding them a short moment. (b) Take a coin between two fingers and extended thumb without touching the palmar hand.	
End of 6th Month	(a)Is Grasping offered toys directly. (b) Palmar grasping: with the whole palmar side of hand and extended thumb.	
End of 5th Month	Brings hands to the toy and touching it	
End of 4th Month	(a) Hands mostly half opened (b) hand-hand co-ordination (hands playing together) (c) Put toys into the mouth (hand-mouth-coordination).	
End of 3rd Month	Moves half opened hands in direction of an offered red toy.	
End of 2nd Month	Transition stage:-hands mostly light opened.	
Newborn	(a) Hands mostly fisted (b) Strong hand grasping reflexes.	

WALKING AGE

End of 12th Month	(a) Side-step waling along furniture. (b) Steps forward, hold on one hand.	
End of 11th Month	(a) Pulls up to stand using furniture as support. (b) Making steps on one place and aside. (c) Stepping forward with support on both hands.	
End of 10th Month	Standing with holding on furniture.	

End of 9th Month	Standing with support and holding the own weight for half a minute.	
End of 8th Month	Transition stage	
End of 7th Month	Bouncing with support	
End of 6th Month	(a) Extension in knees and hip so that the baby can hold its weight atleast 2 seconds. (b) In between touching floor with the whole sole of feet.	
End of 5th month	Tip-Toe position	
End of 4th Month	When touching the floor repeated interruption of flexion of legs by light extension of knee and ankle joint.	
End of 3rd Month	Touching ground with flexed legs.	
End of 2nd Month	Transition stage: Legs – support reaction and walking – automatism slowly wears off.	
End of 1st Month	Like newborn.	
Newborn	(a) Primitive leg support reaction: Extension of hip and knees when placed on the floor. (b) Walking automatically when weight is shifted from one leg to another.	

SPEECH AGE

End of 12th Month	First Meaningful syllables.
End of 11th Month	Imitate sounds (produced by lip vibrations)

End of 10th Month	Dialogue correctly imitate familiar syllables
End of 9th Month	Distinct double syllables
End of 8th Month	Whispering
End of 7th Month & 6th Month	Babbles continuously and pronounces clearly difference syllables with varying volumes and pitch
End of 5th Month	Rhythmic coins of syllables
End of 4th Month	Fricative sounds (w,f) Labial sounds (m,b)
End of 3rd Month	r-r-r- chains
End of 2nd Month	Guttural sounds e-eche, eh-che, e-rrhe
End of 1st Month	Vowel: sounds between ‘a’, ‘an’, ‘ae’, often connected with ‘h’.
New born	(a) cries if not in the mood (b) strange sucking reflex

SOCIAL AGE

End of 12th Month	When requested, in words or with gestures, gives one object to familiar person
End of 11th Month	Can refuse a request by protesting
End of 10th and 9th Month	Will resist an attempt however, careful to take away a toy.
End of 8th Month	React happily to hide – and seek – games.
End of 7th Month	Observes intensely the activities of the familiar person.
End of 6th Month	Behave differently with familiar and unfamiliar persons.

End of 5th Month and 4th Month	Laughs loudly when it is teased
End of 3rd Month	Social smile (2nd month)
End of 2nd Month	Stares at the face and follows its movements.
End of 1st Month	Stops its movement for a second on seeing a face
New born	Is pacified, when baby carried around

ANNEXURE – IV

BARODA DEVELOPMENTAL SCREENING TEST

BARODA DEVELOPMENTAL SCREENING TEST

Screening Test items with Serial Numbering and Age Grouping: The Corresponding Number on the Motor (*) and Mental (without asterick) Scales of BSID and the 50% and 97% Age Placements are also Presented.

Age Group(mon)	S.No. Items	BSID No.	Age Placements (mon) 50%	90%
1	1. Arms and legs thrust in play. 2. Momentary regard. 3. Lateral head movement (prone)	*3,4 1 *5	0.5 0.5 0.6	1.0 1.0 1.1
2.	4. Responds to sound. 5. Follows moving person 6. Free inspection of surrounding	5,7,8 10 12	0.6 0.7 0.8	1.1 1.6 1.9
3.	7. Social smile/vocalises 8. Eye co-ordination 9. Head erect and steady	19,20 13,14,15,18 *10	1.4 1.4 1.5	2.9 3.0 3.1
4.	10. Holds head steady 11. Recognises mother 12. Elevates on arms	*14 28 *13	2.2 2.3 1.9	3.7 3.8 3.9

5.	13. Play with rattle / hand play 14. Reaches for dangling ring 15. Sits with slight support	37,38 36 *16	2.9 2.8 2.8	4.7 4.9 4.9
6.	16. Turns head to sound 17. Turns from back to side 18. Exploitive paper play	46,47 *18 52	3.9 3.4 4.4	5.7 5.8 5.9
7.	19. Discriminates strangers 20. Pulls to sit	59 *22	4.9 4.9	6.9 6.9
8.	21. Bangs in play 22. Sits alone steadily	69 *30	5.6 6.2	7.0 7.9
9.	23. Retains two things in two hands 24.Pulls to stand 25. Playful response to mirror image 26. Sits with good co-ordination	75 *29 76 *31	6.1 6.1 6.3 6.5	8.6 9.0 9.2 9.2
10.	27. Pulls string – secures toy 28. Co-operates in play 29. Crawling (pre-walking)	81 79 *35	7.1 6.9 6.9	9.4 9.9 10.0
11.	30. Rings bells purposefully 31. Fine prehension 32. Raises to sit 33. Stands by furniture	85 *41 *37 *40	7.7 8.6 8.2 8.5	10.7 10.9 11.0 11.0
12.	34. Adjusts to words 35.Says da-da	85 88	8.3 9.0	11.7 11.9
13 to 15	36. Inhibits on command 37. Midline skills 38. Walks with help 39. Turns pages	90 *42 *43 100	9.7 9.4 9.7 11.0	12.6 12.7 13.0 13.9
16 to 18	40. Imitates words 41. Stands alone 42. Spontaneous scribble 43. Throws Ball 44. Aufstein I	103 *45 108 *48 *46	11.9 10.8 13.1 12.6 12.3	15.7 15.9 16.5 16.7 17.3

	45. Walks alone 46. Gestures for wants	*47 112	12.5 13.7	17.4 18.3
19 to 24	47. Shows shoes, etc 48. Two words 49. Walks up and down stairs with help 50. Words for wants	115 114 *53,54 124	14.1 14.1 16.5 17.5	18.8 19.1 24.5 24.8
25 to 30	51. Two word sentences 52. Names three objects 53. Stands on one foot 54. Walks up and down stairs without help	134 144 *60,61 *57, 58	21.2 24.1 26.6 24.4	28.8 29.0 29.0 29.6