DISSERTATION ON

CLINICAL OUTCOME OF NEONATAL SEIZURES

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CERTIFICATE

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CONTENTS

INTRODUCTION

Seizures are the most common manifestation of neurological disorder in the neonatal period and may be the only clinical indication of neurological dysfunction in this age group. Neonatal seizures is a clinical emergency which represent an age-specific seizure disorder, which is usually considered to be in a separate category from epilepsy. Neonatal seizures also have many other characteristics that are quite different from seizures in children and adults. Neonatal seizures are rarely idiopathic[10,11,32,35] and are the single most major predictors of adverse neurological outcome.

DEFINITION

The International League against Epilepsy classification adapted by WHO still considers neonatal seizures within an UNCLASSIFIED CATEGORY (commission 1981)[50]. Neonatal seizures[32,35,36] is defined as paroxysmal alterations in neurological function. This definition allow the inclusion of clinical seizures associated with EEG abnormality as well as paroxysmal clinical activities that involves motor, behavioural or autonomic functions that are not associated with EEG alterations.

BURDEN OF ILLNESS

Newborn babies are vulnerable to epileptogenic activity, thus have a high incidence of seizures[10,11,32,35,40,64] 1-2/1000 in term infants and up to 60/1000 in premature infants. Neonatal seizures are among the most common causes of morbidity and mortality among neonates.

The reported incidence of neonatal seizures varies widely across studies, that is primarily the result of inconsistent diagnostic criteria, subtle manifestation and their potential confusion with non-epileptic neonatal behaviours. Regardless of precise incidence, it is clear that seizures are more common in neonatal period and the tendency towards recurrent seizures and status epilepticus is far greater in newborn period.

PATHOPHYSIOLOGY [10,11,32,35]

The neurons within the CNS undergo depolarization as a result of inward migration of sodium and repolarization occurs via efflux of potassium. A seizure occurs when there is excessive depolarization, resulting in excessive synchronous electrical discharge. Volpe(2001)[3] proposed the following four possible reasons for excessive depolarization.

(1) Failure of the sodium-potassium pump because of a disturbance in energy production

(2) A relative excess of excitatory versus inhibitory neurotransmitter

(3) A relative deficiency of inhibitory versus excitatory neurotransmitter.

(4) Alteration in the neuronal membrane, causing inhibition of sodium movement.

However, the basic mechanisms of neonatal seizures are unknown.

The decreased seizure threshold in the newborn reflects the developmental events active in the immature brain. In essence, the newborn brain has a transient over development of excitatory systems compared to inhibitory systems. For example, the immature brain has a transient overexpression in the density of excitatory amino acid (primarily glutamate) receptors and a relative paucity of glutamate reuptake transporters. Together these features translate into more prolonged and intense contact of glutamate with postsynaptic receptors. Furthermore, these immature glutamate receptors are far more permissive of cationic influx, facilitating membrane depolarization and seizure activation, in contrast, inhibitory gamma-aminobutyric acid (GABA) ion channels are relatively underexpressed in the immature brain. In fact, in certain areas of the developing brain these immature GABA may be depolarizing rather than hyperpolarizing. In addition to these cellular factors, differential development of neural systems may enhance the excitatory state of the immature brain and predispose to seizures.

ETIOLOGY

A specific etiology for neonatal seizures can usually be identified in the majority of cases. In contrast to children who often develop idiopathic epilepsy without identified cause, it is relatively rare for an otherwise healthy baby to have epileptic seizures. In this respect, neonates more closely resemble older adults in that most new onset seizures among the elderly are also symptomatic, such as from a stroke, brain tumour or neurodegenerative disease. Infact because the neonatal nervous system has a relatively limited repertoire of behavior and symptoms, seizures are often the only neurological manifestation of a serious underlying neurological or systemic disease. Therefore if a neonate develops seizures and the etiology is not readily apparent an extensive diagnostic work-up is often warranted.

There are numerous causes of neonatal seizures, but relatively most common causes are as follows:

(1) CEREBRAL HYPOXIA AND ISCHAEMIA

It can be global or focal ischaemic injury

(a) **Global – Perinatal hypoxia:** It is a leading cause of neonatal seizures[2] which occurs in antenatal, intrapartum or neonatal period and account for 25-40% of neonatal seizures. Most post-asphyxial seizures occur within first 24hours after the insult, 50% or more occurring within twelve hours. The seizure onset is likely to be influenced by severity, duration and onset of intra-uterine asphyxia insult. It is likely that more

severe insults are followed by earlier onset seizure, but this is not firmly established. In premature infants seizure are of the generalized tonic type whereas in full term, multi-focal clonic type is common. Accompanying subtle seizures are usually present in both types.

(b) **Focal ischaemic injury:** It can be caused by arterial stroke or venous thrombosis. Seizures are the most common presentation of stroke in neonatal period and stroke is the second most common cause of neonatal seizures accounting 15-20%. Arterial strokes most commonly involves left middle cerebral artery and thus right clonic seizures are most common. Cerebral venous thrombosis usually occurs in large dural sinuses particularly in the posterior aspects of superior saggital sinus which usually presents as subtle seizures and lethargy. Mental status is relatively normal in arterial stroke whereas in venous thrombosis neonate is more encephalopathic.

(2) INTRACRANIAL HAEMARRHAGE

This is implicated in 10% of neonatal seizures and clinical features varies with gestational age. Term infants have sub-arachnoid hemorrhage in common and less often sub-dural hemorrhage. Sub-arachnoid hemorrhage usually results in focal or multifocal seizures from second day of life and have a good long-term outcome in 90% of cases. Sub-dural hemorrhage usually presents with seizures on first day of life.

Post-hemarrhagic seizures in premature infants have different features and more ominous prognosis. These seizures are usually

associated with severe intra-ventricular hemorrhage and peri-ventricular hemorrhagic infarct and usually present within first three days. The newborn is usually sick and have poor prognosis

(3) CNS INFECTION

Seizure can be caused by meningitis or encephalitis from variety of bacterial or viral agents or other organisms like cytomegalovirus and toxoplasmosis. It can also be caused due to cerebral abscess. The mechanism of seizures in this may be through direct cerebritis or vaso-occlusive injury with secondary seizures and usually develop in later part of first week or later.

(4) METABOLIC DISTURBANCE

It can be transient and rapidly correctable or persistent inherited causes. Transient causes include hypoglycemia, hypocalcemia, hypomagnesemia, hyponatremia and hypernatremia. It usually occurs in conjunction with other potentially epileptogenic conditions such as perinatal asphyxia. Most of the persistent inherited conditions are due to permanent enzyme defects and are largely incurable. However, their recognition is important for two reasons.

- Some metabolic disturbances have transient forms that resolve over time as some forms of non-ketotic hyperglycemia.
- Some are treatable as pyridoxine dependent seizures.

(5) CEREBRAL DYSGENESIS

Conditions most commonly associated with neonatal seizures are:

- Disorders of neuronal migration like heterotropias, lissencephaly, etc.
- Disorders of neuronal organization like polymicrogyria

These ectopic or disorganized collection of neurons are abnormally prone to hyperexcitability and burst of discharges leading to seizures.

(6) EPILEPTIC SYNDROMES IN NEONATES

There are two benign and three malignant epileptic syndromes presenting with seizures in neonate:

- Benign familial neonatal seizures and benign idiopathic seizures.
- Neonatal myoclonic encephalopathy, Ohtahara syndrome and Migrating partial seizures of infancy (Coppola syndrome)

These malignant encephalopathies are usually associated with poor prognosis.

(7) OTHERS

The drugs used in mother can cause drug withdrawal and drug toxicity resulting in seizures in infants. Inadvertent injection of local anesthetics into the fetus at the time of delivery may cause generalized seizures. Kernicterus and AICARDI syndrome are also rare causes.

The time of onset helps in determining the likely etiology[27]

AGE OF ONSET	*LIKELY ETIOLOGY*
<24 hrs	HIE, severe birth trauma, congenital anomalies of CNS, pyridoxine dependency, hypoglycemia, drugs.
24-48hrs	All the above + milder birth trauma, hypocalcemia, hypomagnesemia, infarcts, some IEM.
48-72hrs	All the above + dyselectrolytemia, sepsis, other encephalopathies.
72hrs-1wk	All the above + benign neonatal seizures
>1wk	Late hypocalcemia, sepsis, progressive hydrocephalus, cerebral dysgenesis, epileptic syndromes, herpes encephalitis, some IEM.

CLINICAL FEATURES

It is important to understand that seizures in the neonate are different from those in older children. The difference is perhaps due to the neuroanatomic and neurophysiologic developmental status of the neonate. In the neonatal brain glial proliferation, neuronal migration, establishment of axonal and dendritic contacts and myelin deposition are incomplete. The relatively underdeveloped organization of cortex and undermyelination of axons are likely to cause the disorganized convulsive activity and lack of orderly seizure propagation in neonate. For same reasons, primary generalized seizures are very rare in neonate (exception is Benign familial neonatal seizures).

Clinically seizures are categorized broadly into four groups – subtle, clonic, tonic and myoclonic. In many cases more than one type of seizures occurs in a neonate over time.

(1) **SUBTLE SEIZURES:**[13] It is most common and accounts for half of all seizures in full and premature neonates. Subtle seizures are rarely isolated and will almost always have other seizure types as well. It includes broad spectrum of behavioral phenomenon occurring in isolation or in combination.

- **Ocular:** Most common and it includes tonic eye deviation, roving nystagmoid eye movement and sudden sustained eye opening with apparent visual fixation.
- Oro-bucco-lingual: chewing, sucking and lip smacking. These are often associated with drooling.
- **Progressive movements:** pedaling, boxing, rowing and swimming.
- **Autonomic phenomenon:** sudden change in skin colour, tachycardia and apnoea

Most subtle seizures are not associated with EEG seizures. Based on their inconsistent association with EEG as well as their poor response to conventional anti-convulsant, many consider these seizures to be non-epileptic "brainstem release phenomenon".

(2) CLONIC SEIZURES: It is most common in full term infants and are commonly associated with EEG seizures. It is stereotypic and repetitive biphasic movements with a fast contraction phase and slow relaxation phase involving muscle groups of limbs, face and trunk. It can be unifocal, multifocal or generalized. Common causes are neonatal

stroke, focal traumatic contusions, sub-arachnoid hemorrhage or metabolic disturbances.

(3) TONIC SEIZURES: These are most common in premature infants. It is characterized by sustained period of muscle contractions without repetitive features. It can be focal or generalized. It is often associated with motor automatism or clonic seizures and infants are obtunded or lethargic between seizures. It is usually not associated with EEG seizures. The background EEG tends to have multifocal generalized voltage depression and undifferentiated frequencies. Diffuse neurological dysfunction and major intra-ventricular hemorrhage are major causes and prognosis is usually very poor.[21]

(4) MYOCLONIC SEIZURES: It occurs both in full term and premature infant. It is characterized by lightning fast contractions and non-rhythmic character. It can be focal, multifocal or generalized. Myoclonic seizures are associated with diffuse and usually serious brain dysfunction like perinatal asphyxia, IEM, cerebral dysgenesis and major brain trauma. The electroclinical association of these seizures is variable.

SEIZURE MIMICS:[29]

In newborn it may be difficult to distinguish between normal immature behavior like non-nutritive sucking and abnormal but non-epileptic behavior like jitteriness from true epileptic manifestations.

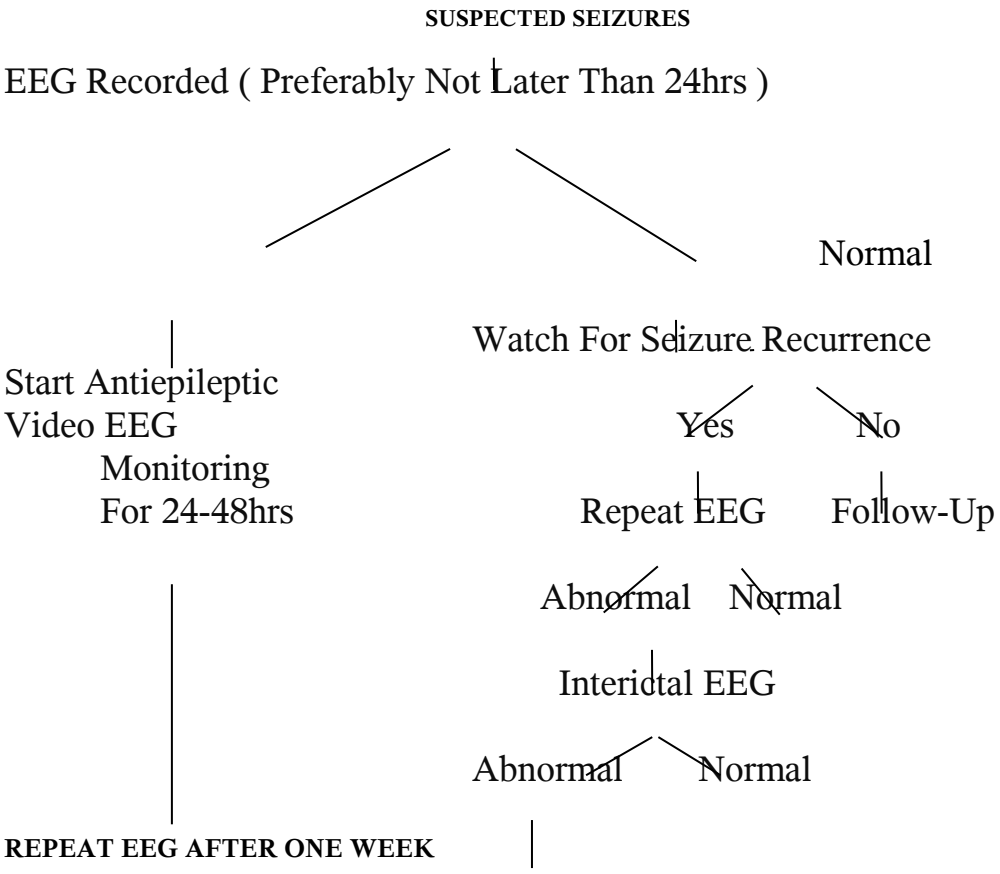
Non-epileptic phenomena can be distinguished clinically by:

- Can be provoked by stimulation
- Can be suppressed by gentle restraint
- Not accompanied by abnormal eye movements
- Not associated with autonomic changes (Tachycardia, increase BP, etc)
- Have rhythmic oscillatory quality. Do not have jerky fast and slow components.
- No EEG abnormality.

INVESTIGATIONS

- It is mandatory to do blood glucose, serum calcium, serum magnesium, blood urea, serum electrolytes and blood gas levels. They may reveal the abnormality causing the seizures.
- CSF analysis is essential because of consequence of delayed treatment or non-treatment are grave. Septic work up is mandatory including peripheral smear, blood and urine culture and CRP.
- Ultrasonography of head is available bedside diagnosis and is good to rule out intra-ventricular hemorrhage and peri-ventricular hemorrhage. It has more value in prognostication. In a study conducted by Levene et al, 20% of neonate with seizures were detected to have intracranial hemorrhage or infarction in middle cerebral artery by real time ultrasonography. So routine imaging technique was advised in all neonates with seizures.

- EEG[38] is indicated in all cases of seizures which is recurrent, resistant and those associated with abnormal neurological findings and where no definite etiology is forthcoming. By definition EEG seizures is a repetitive series of electrical discharges that evolves in frequency, amplitude and topographic field. The threshold criterion for diagnosis of EEG seizures has been set at 10secs or more of repetitive electrographic discharges. Gestational age has an important influence on EEG expression of seizures in neonate. EEG seizures are rare in babies with gestation age less than 34wks. Unlike the interictal EEG in older patients with seizures, the neonate EEG lacks interictal epileptiform pattern that reliably predict the risk for subsequent seizure. In fact, the development of EEG seizures in newborn has been described as an all or none phenomenon.



(PROGNOSTIC VALUE)

- CT/MRI is helpful in looking for evidence of infarction, hemorrhage, calcification and cerebral malformation. CT is good for hemorrhages and calcification whereas MRI provides better resolution of anatomy and details of function and perfusion with diffusion weighted MRI, MRS and MRA.

- **Others:** If suspected to have chromosomal abnormalities, karyotyping can be done. Urine examination for reducing substances and metabolic screening can be done. TORCH screening can be done. With family history of neonatal seizures or fetal loss, history and examination suggestive of IEM, blood ammonia, plasma and urine aminoacidogram, serum and CSF lactate:pyruvate ratio, blood and urine pH can be done.

MANAGEMENT

As a general rule, seizures in neonate are less responsive to conventional anticonvulsants than are seizures in older patients. A number of potentially deleterious effects on the systemic and cerebral systems support the treatment of neonatal seizures.[28] First, seizures may cause significant hemodynamic and respiratory disturbances, which in the sick newborn, may complicate management and potentially extend brain injury. Seizures disrupt cerebral pressure autoregulation and cause wide fluctuations in blood pressure, a combination with potentially serious consequences for the immature brain. Second, massive amounts of cerebral energy are consumed during the repeated neuronal depolarization-repolarization associated with seizures. Neonatal seizures

cause a rapid fall in cerebral glucose and rise in brain lactate, even with normal or elevated bold glucose levels. In the insulted brain, such energy depletion may seriously compromise recovery. Third, seizures release large amounts of glutamate, and in conditions of cerebral energy failure, seizures inhibit the reuptake of glutamate. Together these mechanisms result in the accumulation of extracellular glutamate to toxic levels that are potentially lethal to postsynaptic neurons and immature oligodendrocytes. Seizures may also disrupt protein and lipid metabolism of immature neurons and activate genes that stimulate axonal growth and new synapse formation. These sublethal insults may result in aberrant neuronal pathways and a long-term reduction in seizure threshold. Together, these mechanisms likely contribute to the epilepsy, motor and cognitive impairment seen in some survivors of neonatal seizures.

So, once a seizure is appreciated clinically in a neonate, it is taken as an emergency and warrants the following actions.

- Stabilisation of the neonate and treatment of the seizure.
- Detection and treatment of underlying cause.
- Long term planning and prognostication.

The repertoire of drugs used for neonatal seizures is relatively limited for several reasons. First, few drugs have been formally tested in the neonatal population. Second, oral preparations often cannot be used in neonates. Finally, the complicated metabolism and pharmacokinetics of neonates makes use of some drugs difficult.

Unresolved issues in treatment of seizures are

- Optimal maintenance doses of anticonvulsants.
- Importance of eliminating electrographic seizures.
- Optimal duration of anticonvulsant therapy.
- Whether anti-epileptic drugs or seizures adversely affect immature brain.

After recovery from neonatal seizures, the duration of treatment with anti-epileptic drugs beyond the neonatal period varies, depending most on the predicted prognosis for seizure recurrence. It mainly depends on etiology, neurological status and EEG. Early withdrawal of antiepileptics[58] is beneficial for the neurodevelopment outcome. Long term anti-convulsant may be considered in neonate with recurrent seizures with persistent neurological abnormality, EEG abnormality or family history of seizures.

PROGNOSIS

As a result of improved obstetric management and modern neonatal intensive care, the outcome of infants with seizures has improved with overall prognosis for survival around 85%. Unfortunately, the prognosis for long term neurodevelopmental outcome remains largely unchangeable. There are numerous studies done on outcome and prognosis of neonatal seizures. Most of them showed 10-50% mortality mostly during neonatal period and it has been decreasing nowadays(Volpe, 1995)[12] . 50% of them were found to have long term

neurological complications like epilepsy, mental retardation, cerebral palsy (25-35% - Neurological sequelae and 17% - seizures).

The prognosis depends on type of clinical seizure, etiology, associated problems, effect of intervention, EEG changes and severity of insult.

*ETIOLOGY: Hypocalcemia[20] and primary sub-arachnoid hemorrhage has best prognosis while cerebral dysgenesis[1,2,6] have worst prognosis. Hypoglycemia, infection and infarcts have a poor prognosis if extensive and prolonged duration. The outcome of intracranial hemorrhage depends on degree of parenchymal injury. If extensive diagnostic evaluation fails to identify an etiology, the outcome is likely to be favourable.

*Among seizure types,[21] focal clonic have invariably benign course while persistent tonic seizures and myoclonic seizures have poor outcome. Refractory seizures and seizures lasting for >30mts have poor prognosis.

*Infants with gestation age <32wks have high mortality rate of 80% and significantly higher risk of adverse neurological outcome among survivors.

*A better outcome may be expected when clinical and EEG seizures are consistently correlated whereas electrically silent clinical

seizures or clinically silent EEG seizures have worst prognosis. Interictal burst suppression pattern, isoelectric EEG, multifocal abnormal discharges in EEG[18,22,25] predict poor neurological outcome in >80% of cases. Unifocal diphasic spike and sharp wave pattern has good prognosis. Myoclonic seizures with spike burst pattern have worst prognosis.

* Neonatal neurological examination is also a good predictor of outcome in patients with neonatal seizures. With normal neurological examination being associated with good prognosis and abnormal predicts poor outcome.

* Response to first antiepileptic[41] is the most powerful predictor for good prognosis.

* Shorter the course of antiepileptic drugs, better is the outcome.[58]

REVIEW OF LITERATURE

Assessment of development status and long term outcome of child is gaining more importance especially of the at risk neonate. In this era of advanced health infrastructure and era of preventive medicine, many studies has been conducted to know the long term outcome of neonatal seizures.

IYPE et al,[1] from a medical college in Kerala, undertook a follow-up study in neonate with seizures with objective to determine the sequelae of neonatal seizures in a cohort of newborns recruited over a six month period. It was a prospective hospital based study performed in NICU of a tertiary care hospital. 135 babies were recruited of whom 10 died and 25 lost to follow-up, rest of the cases were followed up over four months. While analysing the results, 68% had normal outcome, 32% had abnormal neurological outcome and 7% had post natal epilepsy. Hypocalcemia was significantly associated with mortality [OR: 21.9, 95% CI: 1.2-391.2] and no risk factor could be identified for postnatal epilepsy. Presence of spike waves in EEG was significantly related to abnormal neurological outcome {OR: 3.5, CI: 1.2-10.8}. Thus the conclusion of the study was that majority of neonates with seizures have normal outcome with no developmental delay or neurological deficit and predominantly spike waves in EEG is predictor of abnormal neurological outcome.

TEKGUL et al,[2] conducted a study in children hospital in Boston, with 89 infants with clinical neonatal seizures. All these infants underwent neurological examination, EEG, neuroimaging and extensive diagnosis tests in neonatal period. After discharge, all infants underwent regular neurological evaluation at 12-18months and formal neurodevelopmental testing and prognostic value of seizure etiology, neurologic examination, EEG and neuroimaging were tested. In 77% of cases etiology was identified, Global and focal cerebral hypoxia-ischaemia and intracranial hemarrhage were most common. Mortality was around 7% and 28% had poor neurological outcome.

Association between seizure etiology and outcome was strong, with cerebral dysgenesis and global hypoxia-ischaemia being associated with poor outcome. Normal neonatal period or early infancy neurological examination was associated with uniformly favourable outcome at 12-18months. Abnormal neurological examination in prediciting poor outcome lack specificity. Normal or mildly abnormal EEG had favourable outcome, particularly if neuroimaging was normal. Moderate or severely abnormal EEG and multifocal diffuse cortical or primary deep grey matter lesions had worse outcome. Thus it was concluded that the mortality associated with neonatal seizures has declined although long term neurodevelopment morbidity remains unchanged. The powerful prognostic factors remained to be seizure etiology and background EEG. Diagnostic advancement have changed the etiological profile and

improved the accuracy of outcome prediction, however global cerebral hypoxia-ischaemia remains the most common etiology and is responsible for majority of infants with poor long term outcome.

GABRIEL M. RONEN et al,[6] in a population based study conducted in a health centre in Canada, assessed long term prognosis in children with neonatal seizures. The aim of the study was to examine the outcome and explore for prognostic markers in a cohort <10yrs following neonatal seizures. The study was conducted between 1990-1995 and children were followed up by specialised provincial health services. Follow-up data were collected on epilepsy, physical and cognitive impairment and other health issues. The data was available for 82 infants among 90 registered. Prognosis was better for term than preterm (p=0.003). Among the term infants, 45% had normal outcome while 16% died and 39% had impairment. Among the preterm, only 12% had normal outcome, 42% died and 46% had impairment. Of the survivors, 27% had epilepsy, 25% had cerebral palsy, 20% had mental retardation and learning disorder was present in 27% of them. Sarnat stage-III or equivalent severe encephalopathy, cerebral dysgenesis, complicated IVH, infection in preterm, abnormality in EEG and the need for multiple drugs were the variables associated with poor prognosis. Pure clonic seizures with focal involvement in term infants suggested favourable outcome whereas generalised myoclonic seizures in preterm was associated with increased mortality. It was concluded that poor

prognosis for preterm with seizures is reflected in high rates of subsequent long term disability and mortality. The severity and timing of pathologic process continue to be the major determinant for outcome.

A **CANADIAN**[44] population based outcome study of neonatal seizures with follow-up of >10yrs had 35% normal outcome and 34% postnatal epilepsy. Same cohort at the end of decade had only 12% normal outcome and had 48% postnatal epilepsy. Term babies had uniformly better outcome and short follow-up was associated with good outcome. Normal EEG with interictal epileptic discharge had poor outcome. Mild motor and cognitive deficits were also reported. Abnormal background activity was more correlative than interictal discharges for poor outcome. Hypocalcemia had high mortality, however they were small in number. So analysis showed wide confidence interval and make interpretation difficult.

A study done at **HARVARD MEDICAL SCHOOL, BOSTON**[48] correlated prenatal and perinatal events with outcome of neonatal seizures. The study included 277 neonates and it was a prospective cohort study. The mortality rate among the neonates was 34.8%. Among 181 survivors, 70% had normal outcome, cerebral palsy was present in 13% of the cases, 19% had mental retardation (IQ<70) and 20% had epilepsy. Low apgar score at birth, the requirement of resuscitation >5mts, low birth weight, early onset seizures and prolonged seizures were identified to be the prognostic factors.

GHERPELLI JL et al,[37] in a follow-up study done in a medical School in Brazil, looked for seizure recurrence in infants with neonatal convulsions. It was a prospective cohort study for 11months. 23 infants were followed up and all had a neurological examination, EEG , cranial USG performed at follow-up. Anti-convulsant was discontinued, if follow-up EEG and neurological examination were normal. Seven out of twenty three, ie, 30% had seizure recurrence. Abnormal EEG, neurological examination and Cranial ultrasonography were statistically correlated with seizure recurrence. They concluded that infants with neonatal seizures can remain free of anticonvulsant medication provided they have normal neurological examination, EEG and cranial USG.

ARTHUR L. ROSE et al,[60] conducted a study of clinical, pathological features in 137 full term babies with neonatal seizures with a follow-up of four years. The study was carried out in Neurology department, Children's Hospital Medical Centre, Boston. They followed 144 full term babies above 2.5kg who had seizures during their neonatal period. Seven subjects were lost in follow-up, leaving a total of 137. Clinical types were classified by observation. No etiological clues was present in 25% of babies and 75% had probable etiology. EEG in neonate period is helpful in prognostication. 86% of babies with normal EEG had normal development at end of 4yrs. Flat, periodic or multifocal EEG was associated with normal development only in 7% of babies. At the end of the study 50% had normal outcome, 30% had neurological deficit and 20% died.

JOSEPH J. VOLPE et al,[12] demonstrated in a study conducted in Washington School of Medicine, that certain clinical seizures in neonate are not consistently accompanied by seizure activity in EEG. Subtle seizures, most of the generalized tonic seizures and focal and multifocal myoclonic seizures are the seizures of that category. Myoclonic jerks were found to originate from several levels of nervous system like brainstem, spinal cord and cortex.

OUTCOME IN VARIOUS STUDIES

Character &Outcome	Iype et al (n=135)	Canadian study (n=90)	Harvard study (n=277)	Gherpelli et al (n=23)
Follow-up duration	1yr	10yrs	7yrs	11mo
Mortality	7%		34.8%	
Recurrence	7%	34%	20%	30%
Cerebral palsy	32%		13%	
Normal	68%	35%	70%	

One of studies done in 1999,[46] in rats, demonstrates that recurrent neonatal seizures result in changes of neuronal connectivity and alterations in seizure susceptibility, learning and memory. Degree of impairment following 50 seizures was modest, demonstrating that the immature brain is remarkably resistant to seizure induced damage.

Immature brain is more prone to seizure due to imbalance of excitatory and inhibitory neurotransmitters. This was reported in the

article of neuroscience, January 2002.[47] It was also stated in that article that neonatal seizures are also associated with a number of activity dependent changes in brain development including altered synaptogenesis and decreased neurogenesis. Functional abnormalities following seizures with impairment of visual-spatial memory and decreased seizure threshold were demonstrated. Thus the conclusion was that neonatal seizure was no more a benign event.

KELLAWAY AND MIZRAHI,[13] in their studies showed that subtle seizures are motor automatism which includes oral-buccal-lingual movements, ocular signs, limb and axial movements as swimming, stepping, pedalling and struggling movements of head and trunk. This was probably thought due to brainstem release phenomenon. They also said that clinical distinction of epileptic from non-epileptic activity at bed side can be made by sensitivity of movements or posturing to sensory stimulation, ability to suppress the movements by gentle restraint and accompanying autonomic phenomenon. Duration of antiepileptic treatment was decided based on neurological examination, cause of seizures and EEG. They also proposed that transient metabolic disturbances had no risk of recurrence.

HALLIOGLU O et al,[59] studied 57 full term neonates with hypoxic insult admitted in NICU of tertiary care centre and analysed occurrence of seizures during first 24hrs and cranial USG in first five days of life in relation to mortality and neurological status at 2 yrs. In this

study of 57, 10 were lost to follow-up. 20 out of 47 had severe adverse outcome. Among predictors occurrence of seizures was poor predictor but cranial USG had 100% sensitivity and 55% specificity in predicting the outcome.

RONALD W. COHEN et al,[61] did a study from Department of Pediatrics, University of California. Authors concluded that recent data derived from national collaborative perinatal project have been interpreted to show that 70% of infants with neonatal seizures had normal outcome at 7yrs.

In a dissertation submitted by **LUIS FERNANDO GARCIAS DA SILVA,**[38] in PORTO ALEGRE, the incidence-density of epilepsy in a population of neonate inpatients with neonatal seizures was studied. The objectives were also to describe possible etiological factors related to neonatal seizures as well as neurophysiological abnormalities observed and to relate clinical and neurophysiological variables that could influence post-natal epilepsy development. It was a retrospective and prospective study. 127 babies were analysed for a period from January 1987 to December 1997. All of them with clinically defined seizures, data of gestation, perinatal period and neonatal seizures were obtained retrospectively. Polygraphic recording (PR) were analysed by experts in neonatal EEG tracings. Detailed questionnaires were prospectively collected for all infants with neonatal seizures, after informed consent. The incidence-density of epilepsy in 12 and 36 follow-up months was

22% and 28.3% respectively. Metabolic disturbances and asphyxia were the most frequent etiological factors observed. Polygraphic recordings were obtained in 110 newborns and considered normal in14 (12.7%) and abnormal in 96 (87.3%). Ictal discharge patterns were observed in 10 PR, abnormal paroxysmal patterns with or without ictal correlations in 74 PR and background abnormalities or EEG dysmaturity in 47PR. Anticonvulsants during the neonatal period and CNS infection are associated to post-natal epilepsy. Inter-ictal normal neurological examination and normal polygraphic recordings as well, were related to good outcome in this study. The conclusions of the study were that the Incidence Density of epilepsy in newborns with neonatal seizures was elevated. Metabolic disturbances and asphyxia were the most frequent etiological factors. Normal inter-ictal neurological examinations as well as PR have shown good outcome. CNS infection and the need for anticonvulsant therapy during neonatal period led to negative follow-up in this cohort.

SPITTLE et al,[55] in his meta-analysis demonstrated that early developmental interventions post-hospital discharge for preterm infants have a significant impact on cognitive development at infant and preschool age. However, there is currently little evidence of an effect of early developmental interventions post-hospital discharge on motor development at infant age. At school age there have only been three studies that investigated the long term effects of intervention on cognitive

outcome and two that investigated the effect on motor outcome, none of which demonstrated any substantial difference in long term outcomes. Interventions that focus on the parent-infant relationship, along with infant development, have the greatest impact on cognitive development in the short to medium term. The heterogeneity between early developmental intervention programs in regard to content, focus and intensity limit the conclusions that can be drawn from this review.

KAREEM I, et al,[39] in their study done at Nigeria with 57 infants with neonatal seizures over a 3yr period showed perinatal asphyxia and hypoglycaemia as the principal etiologic factors in 47 and 19 per cent of the cases, respectively. Seizures were commoner in preterm, and among them outcome was also poorer. As regards etiological factors, outcome was poorest with perinatal asphyxia, with mean mental age of 72.5 (9.1) wks at a chronological age of 24months. Outcome in infants with seizures and coma was most favourably predicted by the absence of abnormal neurological signs, and the way the infant was feeding at 7-10 days, all infants who were clinically and neurologically normal and taking more than half their estimated requirements by mouth at 7 days were not handicapped. Thus at the end the overall incidence of neonatal seizures was 7.5/1000 live births and the mortality (19.3%) was closely related to the etiology. In view of the fact that the associated adverse perinatal events are largely preventable,

improved prenatal and perinatal health care delivery should lead to a decline in the frequency of neonatal seizures.

ELENJICKAL MG. et al,[45] did a study in Pushpagiri Institute, Kerala. This study was done during April 2004 – July 2005. 55 high-risk neonates were followed up. Growth was compared with 2000 CDC charts and development assessment was done with Trivandrum Development Screening Chart and Denver Development Screening Test. Statistical analysis was done using Kappa and chi-square tests. A highly significant association was observed between the risk score and the severity or developmental delay. Kappa statistics revealed the Trivandrum Developmental Screening Chart (TDSC) and Denver Development Screening Test (DDST) were in excellent agreement with each other, babies who received early intervention therapy came out with minimum impairment. Thus it was concluded that TDSC is equally good in detecting developmental delay compared to DDST and can be used as a rapid screening method by training paramedical staff.

ETIOLOGICAL PROFILE IN VARIOUS STUDIES

Etiology	Levene et al	Goldberg et al	Watanabe et al	Bergman et al
HIE	53%	16%	53%	30%
Intracranial **Hemarrhage**	17%			
Hypoglycaemia	3%	2%	3%	5%
Hypocalcemia				22%
Malformations		8%		4%
Fifth day fits		52%		
Meningitis	8%	3%	8%	7%
Idiopathic	8%			

GILMAN et al,[8] demonstrated seizure control with phenobabitone Alone in 77% of cases using rapid sequential method. With initial loading dose of 15-20 mg/kg and stepping 5-10mg/kg every 30mts if seizures were uncontrolled to a maximum of 40mg/kg this result was observed.

TEMPLE et al ,[19] in his study with 14 neonates with seizures conducted a follow up study. At the end of 4yrs he found that 11 of them had normal outcome. But when they were followed till adolescence, many of them had spelling and memory problems.

BERGMAN et al[24] conducted a study in University of Pittsberg, Pennsylvania. They found that 53% of HIE with or without intracranial hemarrhage had severe to moderate neurological impairment. Out of 18 of them who had seizures for >4days, 16 were severely impaired. 18 among 24 who required more than two antiepileptics were severely impaired. The unexpected late seizure recurrence within this group was 8% which led to the recommendation that anticonvulsant to be discontinued after two seizure free weeks in neonate.

A study carried out in Leichester University Medical School by M.I. LEVENE et al,[4] was with 61 neonates with gestational age of 35-42wks and time of convulsions of 2hrs-25days. The cause was evident in 92% of the infants. Commonest cause was perinatal asphyxia which accounted for 53%, 4% were due to infection, 5% due to metabolic disturbances and 3% was due to congenital malformations. Since 20% of cases was detected to have either intracranial hemarrhage or infarction or MCA territory by real time USG, routine imaging techniques was advised in all neonates with neonatal seizures.

STUDY JUSTIFICATION

Seizures during neonatal period are relatively common, occurring in approximately 1% of all neonates. While in children seizures often occur in the absence of another neurological disorder, neonatal seizures frequently are a non specific sign of underlying disease. The neonatal seizures are considered an acute manifestation of disturbance of neonatal brain. The technological advances in perinatal care have been promoting the survival of preterm and term newborns, morbidity however remains high determining serious neurological sequelae. Therefore, we aim at studying the outcome of neonatal seizures and prognostic factors influencing these outcome so that we can contribute to make a significant improvement in the management of neonatal seizures and long term outcome of these infants.

Different studies[1,2,4,6,37,44,48,60,61] done on neonatal seizures has given varied incidence with regard to etiology, mortality, seizure recurrence and neurodevelopment delay. These variations in other studies may be due to different study population, ethnic variations, pattern of referral and available investigations. Hence we want to have our own experience of the etiology and outcome of neonatal seizures in this large referral hospital serving the population in this part of the country.

STUDY OBJECTIVES

- To identify the etiological factors and to know clinical profile in neonates with seizures who were admitted in medical newborn unit of Institute of Child Health and Hospital for Children.
- To determine the incidence of normal development after neonatal seizures.
- To determine other clinical outcomes like seizure recurrence, neurological sequelae and others.
- To determine prognostic factors of neonatal seizures.
- To identify the means and methods to prevent or modify these factors.

SUBJECTS AND METHODS

STUDY PLACE

This study was conducted in department of neonatology and neurology at Institute of Child Health and Hospital for Children, a tertiary care children hospital, Egmore, Chennai.

STUDY PERIOD : November 2006 to October 2008.

STUDY DESIGN : Prospective Hospital Based Study

STUDY POPULATION : Newborns with seizures admitted in medical newborn unit in Institute of Child Health and Hospital for Children in first six months of the study period Were enrolled in the study.

♦ INCLUSION CRITERIA

All term neonates with clinically diagnosed seizures by observation

♦ EXCLUSION CRITERIA

-Readmission

-Gestational age <37wks [by modified Ballard scoring]

SAMPLE SIZE

All children with above inclusion criteria who presented during first six months of study period.

STATISTICAL ANALYSIS

Proportions of various outcomes measured using Pearson Chi-square test.

STUDY MANOEVURE

All term babies with seizures admitted in medical newborn ward of Institute of Child Health and Hospital for Children, who satisfied the inclusion Criteria during the first six months of study period, 1st November 2006 to 30th April 2007 were enrolled in the study and followed up for a minimum period of one year (20% of infants were followed up till one and half years). A prior approval from the institutional ethical committee and informed consent from parents were obtained.

After enrolling, a detailed history and thorough clinical examination was done for all babies on admission and data collected were entered in the proforma. Every infant was followed up daily during hospital stay. The biochemical parameters including blood sugar by Glucose oxidase-peroxidase method, serum calcium using

O-cresophthalein complexon method, serum sodium and potassium using flame photometry and serum bicarbonate using titration method were done for all babies enrolled. Urine for metabolic screening which included Benedict's test, Ferric chloride test, cetrimide test, Dinitro phenyl hydrazine test and cyanidenitroprusside test was done. Blood culture and capillary blood gas analysis were done for all babies on the day of admission. Lumbar puncture with CSF analysis and Ultrasonography of cranium were done for all babies after hemodynamic stabilization. For babies in whom lumbar puncture could not be done before death, post- mortem lumbar puncture was done. Cerebro-spinal fluid was examined for cells, biochemical parameters including protein and sugar and its culture and sensitivity was also done. If any biochemical parameters were abnormal, they were repeated before discharge.

The babies were treated according to the underlying illness and were discharged. At the time of discharge, the babies were examined for presence of abnormal neurological sign. The weight, height, head circumference and chest circumference were noted for every baby. The parents were counseled regarding the outcome of neonatal seizures and the necessity of follow-up. A CDC card with CDC register number was issued to every baby with details of follow-up dates.

The infants were followed up at 1,2,3,6,9 and 12 months of age at Child Development Clinic(CDC), which is a high-risk follow-up OP of Medical Newborn Unit. During each visit, babies were weighed first and

head circumference measured. Growth of the baby was assessed with WHO chart.

History of seizure recurrence was enquired about and noted in follow-up proforma. In case of recurrence, antiepileptic drug was advised and the drug was asked to be collected from Department of Neurology. For those babies with seizure recurrence, Electroencephalography and CT Brain was done.

Detailed neurological examination including Amiel Tison Angles[51] were Done for all babies during each follow-up visits. A neonate is considered to be neurologically normal if there is no paucity of movements, cry, tone and neonatal reflexes are normal. If any abnormality detected, Early stimulation was taught to parents. Neurodevelopmental assessment was done at each visit using Trivandrum Development Screening Chart (Annexure IV).[14,45,52]

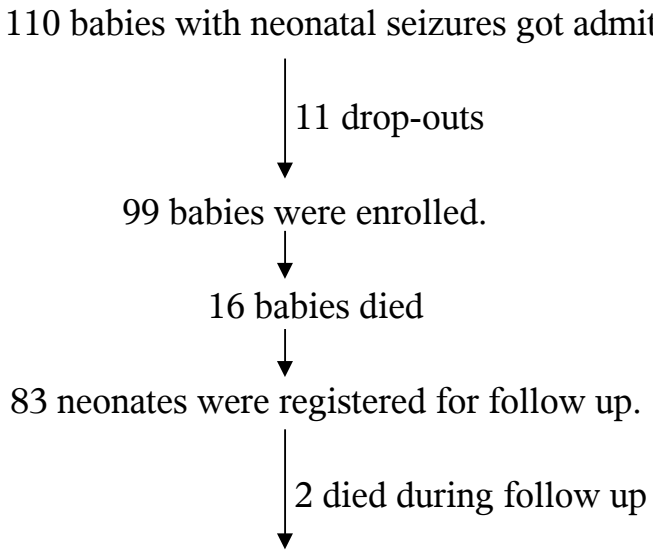
Babies with neurodevelopment delay and neurological sequelae were treated With physiotherapy and were given multidisciplinary care.

During each visit, parents were motivated for next visit and were advised regarding immunisation, weaning and nutrition of their babies.

Visual assessment[57] was done at three and six months by gross appearance of eyes, perception of light and following of bright objects, visual fixation on coloured objects, red reflex by ophthalmoscopy, eye movement and fundoscopy. Hearing assessment[57] was done at three and six months by behaviour observation audiometry or free field audiometry. BERA could not be done as the facilities were not available in our hospital. At the end of one year, various outcomes were analysed.

RESULTS AND ANALYSIS

For our study, the infants were enrolled from November 2006 to April 2007 and they were followed up for a minimum period of one year (to a maximum period of one and half years) from the date of enrollment. During enrollment, total number of admissions in newborn unit was 1913. Number of babies with seizures were 110, 5% of total newborn admissions. Among 110 babies, 11 babies were not enrolled because their parents were not willing. So remaining 99 neonates were enrolled in our study. Among the babies enrolled, 16(16%) died during hospital stay. Child Development Clinic (CDC) card and register number was issued to remaining 83 babies and were counseled for follow-up. However, during follow up, two babies died (both babies died due to sepsis, one of them at fifth month and the other at seventh month of follow up). At the end of study period, 81 babies had completed the follow up.



At the end of the study, the data was evaluated using Microsoft Excel Spreadsheet and the proportions of various outcomes were measured using Pearson Chi-square test. The data were analysed in the following headings:

I Baseline data.

II Etiological factors.

III Outcome measures.

IV Analysis of risk factors for outcome.

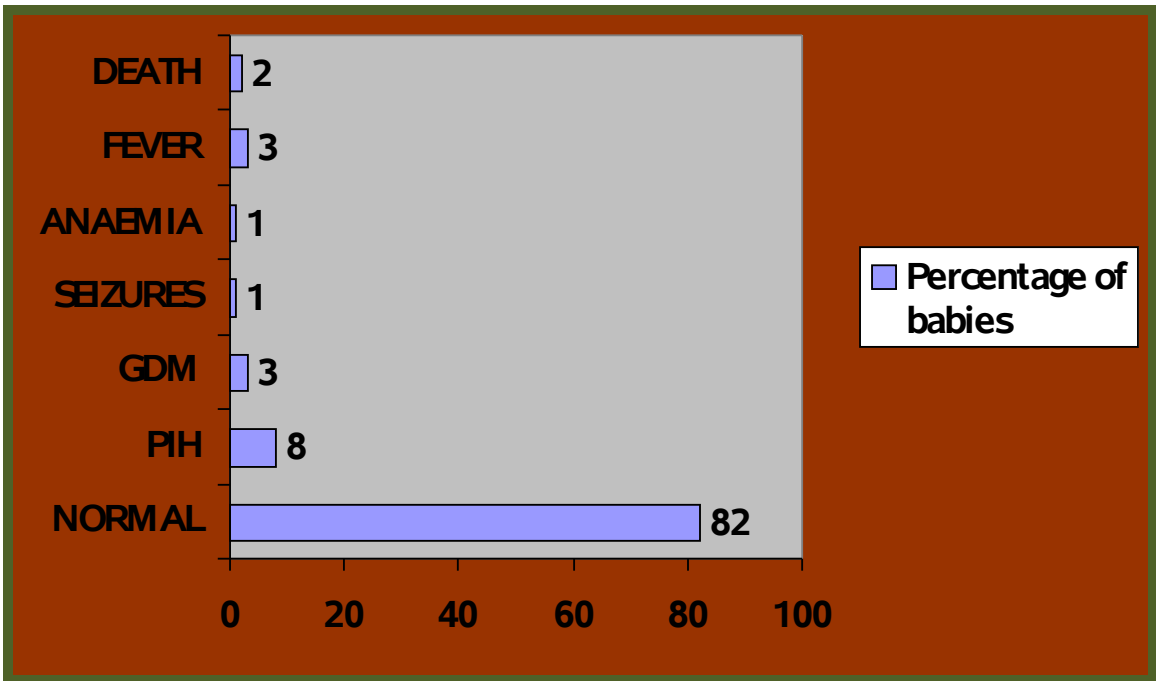
BASELINE DATA ANALYSIS

All babies recruited for the study had gestational age >37wks. No preterm (by modified Ballard scoring) was included in the study.

CHARACTERS		NUMBER OF BABIES (n=99)	
		n	**%**
SEX	Male	51	51
	Female	48	49
NUTRITIONAL STATUS	SGA	15	15
	AGA	84	85

Thus among the study group, males and females were almost equal. Small for gestation age babies (with birth weight <2.5kg) were 15(15%) of study population and among them, six of them were intrauterine growth retarded babies. 50% of newborns recruited for study was first born, 37% were second born and 12% of them were third born. The birth order of none of the babies were greater than three.

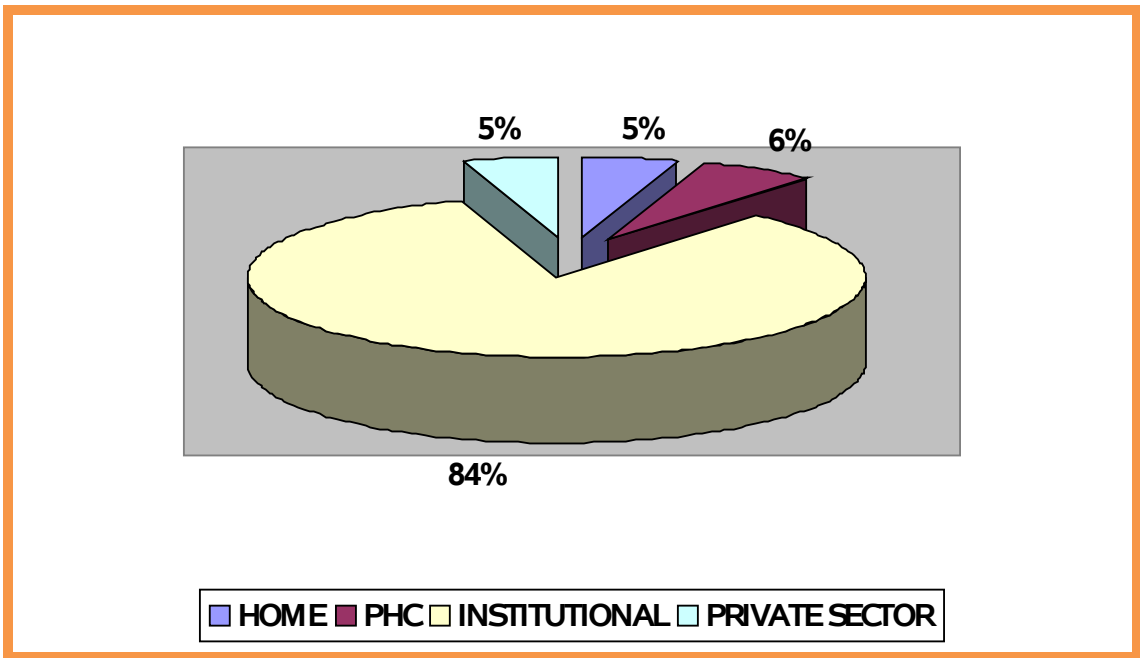
HIGH RISK PREGNANCY



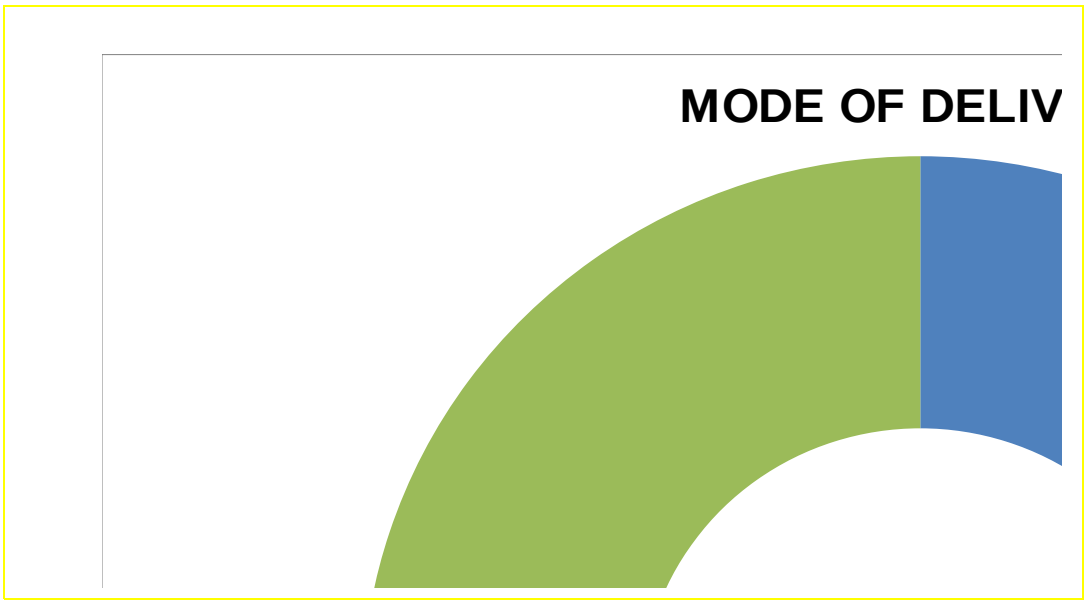
18% of the mothers had history of high risk pregnancy with Pregnancy Induced Hypertension predominating the list. Maternal deaths were observed among two babies (one of the maternal deaths in follow-up babies was due to Post-partum hemorrhage and the other was an unmarried pregnancy where the cause of death was not related to pregnancy). Family history of seizures was present in 5% of cases and history of sibling death was present in 4% of the babies.

While analyzing the maternal data, 81% of them were in the age group of 20-30yrs. Only 5% of them were between 30-35yrs and 14% of them were teen age pregnancy. About 95% of the mothers had at least primary schooling done and only 30% of the babies were born of consanguinous marriage. The awareness of importance of maternal and child health has increased which was shown in our study where 96% of the mothers had history of regular ante-natal checkups.

PLACE OF DELIVERY



On analyzing the birth history of all babies registered, the proportion of institutional deliveries has increased. Only 5% percent of the babies were delivered at home and one amongst all these home deliveries, was conducted by Untrained Dai. 84% of the babies were born under institutional care. 6% of babies born in primary health care were referred to our hospital for seizures.



73% of the babies were delivered by normal vaginal delivery while LSCS was the mode of delivery in 25% of the cases. 2% of babies however needed forceps delivery.

Perinatal factors were analysed and prolonged rupture of membranes for >24hrs were found in 2% of the cases and prolonged labor was found in 2% of the cases. History of meconium stained liquor was present in 11%, 1.2% had history of oligohydramnios and 2.5% had cephalo-pelvic disproportion. 12.5% of babies had history of cord around neck.

While analyzing the history for birth asphyxia, 35% had positive history. Among these babies, seven (9%) were severely asphyxiated and had history of bag and mask ventilation being used and they needed resuscitation for more than 20mts.

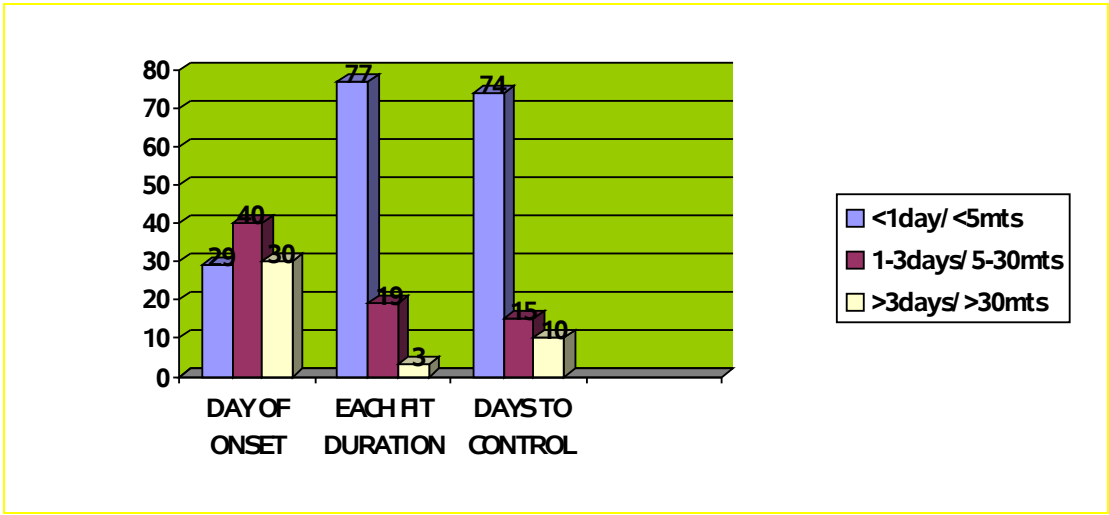
CO-MORBIDITIES

CO-MORBIDITIES	NUMBER OF CASES (n=99)	
	n	%
ICTERUS	36	36.4
CHD	3	3
SHOCK	17	17.2

NOTE: CHD – Congenital Heart Disease.

In the post-natal period 36 babies had icterus but none of them had serum bilirubin greater than 15mg/dl. History of bad child rearing practices was present in 25% of cases and 3% babies had congenital heart diseases. Shock was a common co-morbidity associated with seizures especially in those babies with history of hypoxia. Babies who had severe shock, were the ones who succumbed to death in our study. Among the neonates who presented with shock, two of them (12%) survived as against 15 babies (88%) who died. Icterus and shock were the two co morbidities which had statistically significant association with neonatal seizures.

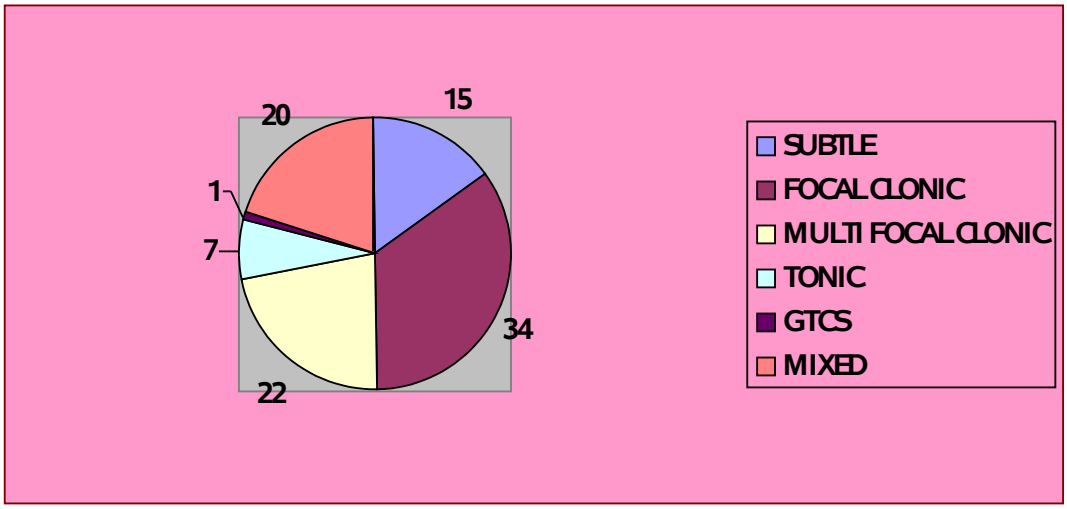
The day of onset of seizures, type of seizures, duration of seizures and the response of seizures to antiepileptic used were some of the important parameters considered to be important in a neonate presenting with neonatal seizures.



Most of the seizures had their onset on one to three days. It accounted for 40% of the seizures, 29% of the seizures occurred on day 1 of life and 21% had after third day. Only 10% of the babies presented with seizures after 14days.

Almost 77% of seizures (85% among the survived babies and 37.5% among the babies who died) lasted only for less than five mts. 19.5% had seizures lasting for 5-30mts and only 3.5% of the babies had seizures lasting for greater than 30mts. Ours being a tertiary care centre receiving referral cases, only 29% have been admitted with single episode seizures while 71% had multiple seizure episodes. However, 74% of seizures got controlled in one day, while 15% of seizures was brought under control in 1-3days. About 11% (7% among those who survived and 25% among those who died) of these babies had seizures controlled only after three days.

TYPES OF SEIZURES[21]



NOTE: GTCS: Generalized Tonic Clonic Seizures

The type of seizures was clinically determined by observation. 35% of the babies were found to have presented with focal clonic seizures while multifocal clonic seizures were observed in 22% of the cases. Only one case of Generalised Tonic Clonic seizures was observed in a case of hypoxia. Two cases had myoclonic seizures and 7% was observed to have tonic seizures. 15% neonates had subtle seizures, which included cycling, sucking, chewing, eyelid twitching, vacant stare, incessant cry, nystagmus and apnoea. Cycling, vacant stare and nystagmus were the commonest among them. Some of the babies (20%) presented with more than one seizure type. It was subtle seizures which occurred in combination with other seizure types. However, there were two babies who had myoclonic seizures with other seizure types. In our study,

myoclonic seizures never occurred isolated. Family history of seizures was present in 5% of the cases.

Among the babies recruited, 5% had microcephaly, abnormal neurological examination was present in 35% of the cases. The abnormality in the neurological examination included bilateral flaccid paralysis, bilateral spastic paralysis and depressed neonatal reflexes. However, none of them had unilateral flaccid weakness, unilateral spastic weakness or neurocutaneous markers which was looked for in all babies. Seven cases had congenital anomalies namely macule, polydactyly, and dysmorphic facies.

Seizure in the babies enrolled in our study was treated as per our hospital protocol. Nine babies did not require antiepileptics as their seizures got controlled with the treatment of their metabolic disturbances namely hypoglycemia or hypocalcemia. Phenobarbitone was the first line oantiepileptic drug used and it was observed that 72 (73%) babies got their seizure controlled with phenobarbitone. Remaining 18% of the babies needed more than one drug to control seizures.

CORRELATION BETWEEN SEIZURE TYPES AND DAYS TO CONTROL SEIZURES

TYPE OF SEIZURES (n=99)	DAYS TO CONTROL SEIZURES		
	<1day (n=74)	1-3days (n=15)	>3days (n=10)
GTCS(1)	1	-	-
Subtle (15)	14	-	1
Focal clonic(34)	29	5	-
MF clonic(22)	19	1	2
Tonic (7)	5	1	1
Mixed (20)	6	8	6

NOTE: GTCS: Generalised Tonic Clonic Seizures.
MF Clonic: Multifocal Clonic.

Focal clonic seizures were the commonest type of seizures and they were the seizures easy to control. 85% of focal clonic seizures got controlled in one day and none of them persisted after three days.

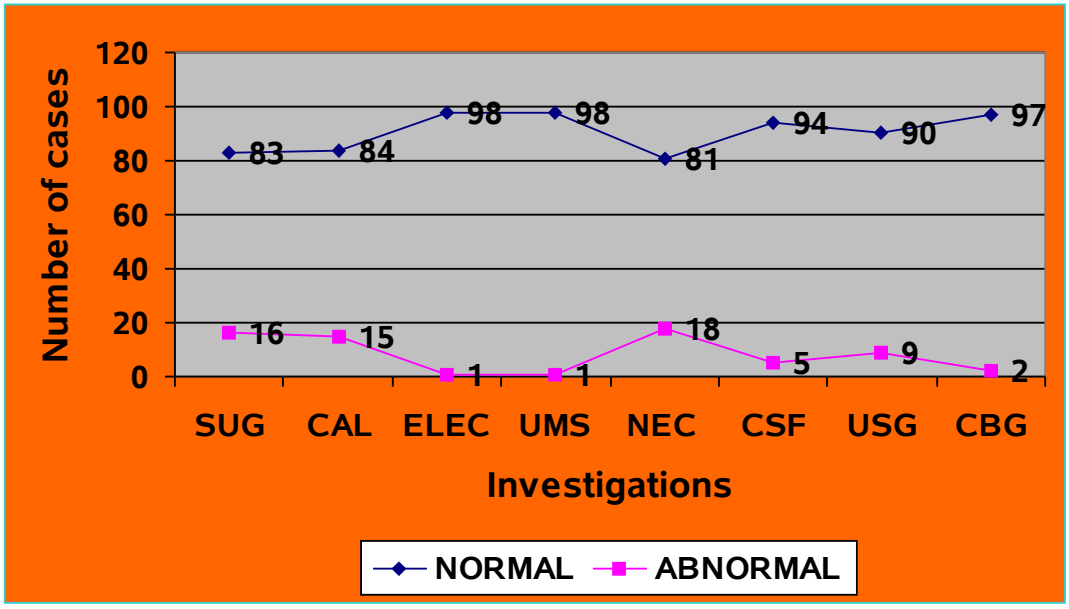
Multifocal clonic and Subtle seizures had the similar trend in days taken to control them. However, one baby with subtle seizures and two with Multifocal clonic seizures had their seizures uncontrolled till three days. 30% of the Mixed seizures was difficult to control and took more than to three days to control and 40% of them needed more than one day to control. Among Tonic seizures, 71% of the babies had their seizure control within one day. Thus in general, most of the seizures got controlled within one day irrespective of seizure type. However, the babies presenting with Mixed seizure type required more days to control seizures

INVESTIGATIONS

All the neonates included in the study underwent the panel of investigations and the results were:

INVESTIGATIONS	RESULTS (n=99)	
	Normal	Abnormal
Blood sugar	83	16
Serum calcium	84	15
Serum electrolytes	98	1
Urine for metabolic screening	98	1
Blood culture	81	18
CSF analysis	94	5
USG Cranium	90	9
CBG analysis	97	2

NOTE: CSF: Cerebro Spinal Fluid, USG: Ultrasonography
CBG: Capillary Blood Gas.

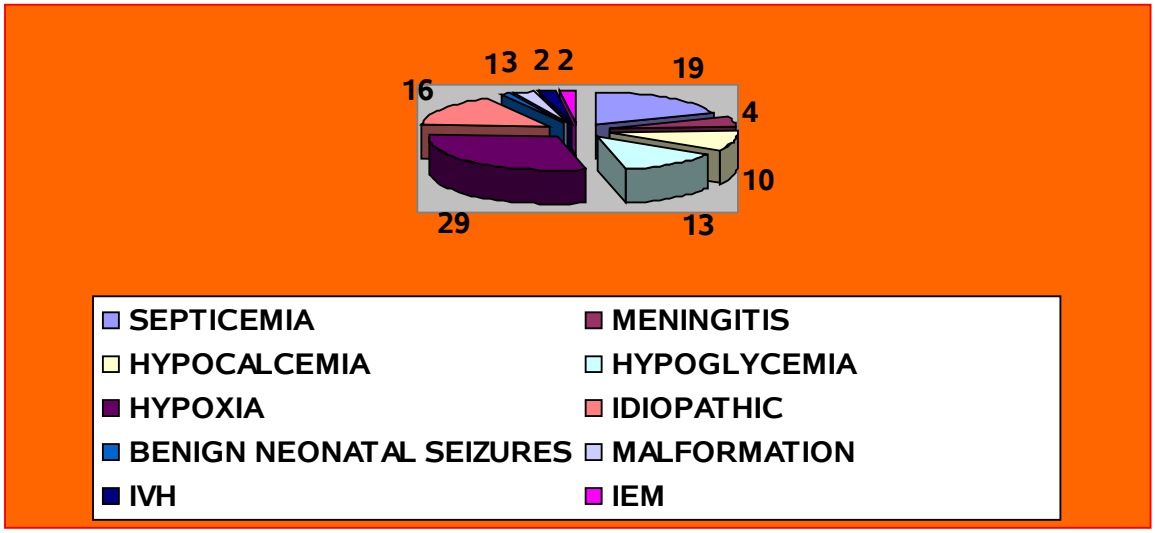


NOTE: SUG: Blood Sugar, CAL: Serum Calcium, ELEC: Serum Electrolytes, UMS:Urine for metabolic screening, NEC: Blood culture.

While investigating the babies, the blood sugar value less than 40mg/dl and total serum calcium less than 7mg/dl (ionized calcium <4mg/dl) were consideredhypoglycemia and hypocalcemia respectively. The analysis showed that 16% of babies had hypoglycemia and 15% had hypocalcemia. Only 1% had electrolyte abnormalities and that baby showed metabolic acidosis in capillary blood gas analysis. One neonate showed positivity in urine for metabolic screening for Alkaptanuria which was not clinically related. Abnormal USG findings included resolving intra-ventricular hemorrhage, CNS Malformation namely periventricular leukomalacia, agenesis of corpus callosum (present in two cases) and features of HIE. The ultrasonography findings of HIE[56] included cerebral edema, loss of gyral and sulcal pattern and parenchymal bleeds. Extradural fluid with dilated ventricles with turbid fluid was present in one baby. One of the newborns also had echogenic region in left frontal region in ultrasonography. Thus 9% of the babies had abnormal Ultrasound cranium. 18% had pathogenic growth in their blood culture and 5% had abnormal Cerebrospinal fluid analysis with increased protein andorganism grown in culture of CSF.

ETIOLOGY

Etiology, being the powerful prognostic indicator was analysed in our study.



On analysis of the etiological profile of the babies in our study, the bulk of the cases were due to hypoxic insult, infection and metabolic causes. Among 99 newborns enrolled, hypoxia[2] was found to cause seizure in 29 (30%) babies, septicemia in 19 (19%) and hypoglycemia[16] in 13 (13%) babies. Four babies had meningitis and ten babies had seizures because of hypocalcemia.

Benign neonatal seizures was diagnosed in one child and three babies had CNS malformations. Intra-ventricular hemorrhage and Inborn Error of Metabolism was found to be the etiology in 2% of the neonates included in the study. However the cause of the seizures could not be found in 16 babies(16%).

CORRELATION BETWEEN DIAGNOSIS AND TYPE OF SEIZURES

The etiology of the seizures and its association with type of seizures were analysed. The results are as follows:

DIAGNOSIS (n=99)	TYPES OF SEIZURES					
	Subtle (n=15)	**Tonic (n=7)**	**MFC (n=22)**	**F Clonic (n=34)**	**GTCS (n=1)**	**Mixed (n=20)**
Septicemia(19)	2	1	6	7		3
Meningitis(4)	-	-	1	2		1
Hypocalcemia(10)	2	2	1	3		2
Hypoglycemia(13)	7	1	3	2		-
Hypoxia(29)	1	2	3	12	1	10
Idiopathic(16)	2	1	4	6		3
BNS(1)	1	-	-	-		-
Malformations(3)			1	1		1
IVH(2)			1	1		-
IEM(2)			2			-

NOTE: MFC: Multifocal Clonic, F Clonic: Focal Clonic, GTCS: Generalised Tonic Clonic seizures, IVH: Intraventricular hemorrhage, IEM: Inborn Error of Metabolism, BNS: Benign Neonatal Seizures.

In babies with septicemia and meningitis clonic (both focal and multifocal) seizures were common. Among metabolic seizures, hypocalcemia presented as clonic seizures while in hypoglycemia, subtle seizures were common. Two cases of hypocalcemia had mixed seizures while none of the hypoglycemic seizures were of mixed type. Most of

the clonic seizures were of hypoxic etiology while tonic seizures were common in hypoxia and hypocalcemia. Benign neonatal seizures presented as subtle seizures. Generalized tonic clonic seizures occurred in one neonate who had hypoxic etiology. Clonic seizure was the type of seizure in Intraventricular hemorrhage and Inborn Errors of Metabolism and also contributed to the bulk of cases in whom etiology was not detectable. Mixed seizures were also observed among 20% of newborns. Hypoxia was the common etiology associated with mixed seizures. However, mixed seizures were also observed in septicemia, hypocalcemia, malformation and idiopathic seizures.

CORRELATION BETWEEN DIAGNOSIS AND DAY OF ONSET OF SEIZURES

DIAGNOSIS (n=99)	**DAY OF ONSET OF SEIZURES**			
	<1day (n=29)	**1-3days (n=40)**	**4-14days (n=20)**	**>14days (n=10)**
Septicemia(19)	1	7	6	5
Meningitis(4)	-	1	3	-
Hypoglycemia(13)	2	11	-	-
Hypocalcemia(10)	3	4	2	1
Hypoxia(29)	18	7	3	1
Idiopathic(16)	1	8	4	3
BNS(1)	-	-	1	-
Malformations(3)	2	1	-	-
IEM(2)	1	1	-	-
IVH(2)	1	-	1	-

NOTE: BNS: Benign Neonatal Seizures, IEM: Inborn Error of Metabolism, IVH : Intraventricular hemorrhage.

In the babies with hypoxia, 25(86%) babies had their seizure onset within three days [18 (62%) babies within one day]. Late onset seizures were more common in babies with Septicemia. Among hypocalcemia, 7(70%) babies had early onset hypocalcemia and remaining 30% had late onset hypocalcemia. All hypoglycemic seizures occurred within three days. About 85% of babies with hypoglycemia had seizures between 1-3days. Congenital malformations of brain presented with seizures within three days, about 66% within one day and similar trend was noted in Inborn Errors of Metabolism. Most of the late onset seizures were due to septicemia or idiopathic,

CORRELATION BETWEEN DIAGNOSIS AND DURATION OF SEIZURE CONTROL

DIAGNOSIS (n=99)	**DURATION OF SEIZURE CONTROL**		
	< 1day (n=74)	**1-3 days (n=15)**	**>3 days (n=10)**
Septicemia(19)	14	4	1
Meningitis(4)	4	-	-
Hypocalcemia(10)	8	2	-
Hypoglycemia(13)	10	2	1
Hypoxia(29)	23	4	2
Idiopathic(16)	13	2	1
Malformations(3)	-	1	2
IVH(2)	1	-	1
IEM(2)	-	-	2
BNS(1)	1	-	-

NOTE: IVH: Intraventricular hemorrhage, IEM: Inborn Error of Metabolism, BNS: Benign Neonatal Seizures.

Irrespective of etiology, 75% of infant had seizures controlled within one day. Only 10% of the seizures needed >3days for control. Seizures which took greater than three days to get controlled were caused by hypoglycemia, hypoxia, Inborn Error of Metabolism and Malformations of brain, with CNS Malformation topping the list. About 66% of babies with CNS Malformation had prolonged seizures.

OUTCOME MEASURES

Among 110 cases recruited, 11 cases dropped out as the parents were not willing. Thus 99 cases were enrolled. 16 (16%) cases among them succumbed to death during neonatal period.

RISK FACTORS FOR MORTALITY

RISK FACTORS		TOTAL (n=99)	NUMBER OF DEATHS (n=16)		p-value
			n	%	
Nutritional status	SGA	15	1	6.6	0.227
	AGA	84	15	17.8	
H/oBirth asphyxia	PRESENT	34	9	26.4	0.050
	ABSENT	65	7	10.7	

NOTE: SGA: Small for Gestation age,
AGA: Appropriate for gestation age.

In the neonates with history of birth asphyxiaand seizures, 26.4% died as compared to 10.7% among those who did not have history of birth asphyxia which also showed statistically significant association. However SGA did not show increased incidence of death. Thus nutritional status among babies with neonatal seizures is not a risk factor.

RISK FACTORS		TOTAL (n=99)	NUMBER OF DEATHS (n=16)		p-value
			n	%	
Day of onset of seizures	<1day	29	8	27.5	0.151
	1-3days	40	4	10	
	4-14days	20	2	10	
	>14days	10	2	20	
Type of seizures	Subtle	15	3	20	0.092
	Focal clonic	34	3	8.8	
	MF clonic	22	2	9	
	GTCS	1	-	-	
	Tonic	7	3	43	
	Mixed	20	5	25	
Days to control seizures	<1day	74	9	12	0.083
	1-3days	15	3	20	
	>3days	10	4	40	
Number of drugs used	Phenobarbitone	72	9	12.5	<0.001**
	+ phenytoin	5	-	-	
	+ midazolam	11	7	63.6	
	Others	2	-	-	
	No drugs used	9	-	-	

NOTE: ** denotes significant at 1% level
* denotes significant at 5% level.

Seizures and its character play a major role in determining the outcome in neonatal seizures. In our study, out of 10 babies whose seizure onset was greater than 14 days, 20% of them died as compared to 27.5% among those who had their onset within one day. The mortality

was lowest (10%) when seizure started between 1-14days. Both very early onset (<1day) and very late onset (>14days) were associated with poor prognosis. Even though subtle seizures were the commonest, it was the tonic seizure which had highest correlation with mortality. About 43% of neonates with tonic seizures died while 8.8% died among babies with focal clonic seizures. Greater the days taken to control seizures higher was the mortality though it did not reach statistical significance. Among 10 newborns who had prolonged seizures, 40% met with death whereas among 72 babies who got their seizure controlled in one day only 12% died. Among our study population, among those who responded to phenobarbitone therapy alone, 12.5% died. But others needed multiple drugs and 63.6% of them succumbed to death. Thus early and late onset seizures, seizure type, prolonged seizures and seizures which needed multiple drugs had highest risk of mortality. However, when analysed, number of drugs used was the only parameter which showed statistically significant association with mortality.

RISK FACTORS		TOTAL (n=99)	NUMBER OF DEATHS(n=16)		p-value
			n	%	
Co-morbidities (Shock)	Present	17	15	88.2	<0.001**
	Absent	82	1	1.2	
Neurological examination	Normal	65	2	3	<0.001**
	Abnormal	34	14	41.1	

Both comorbidities and neurological examination were found to have significant role in determining outcome especially mortality. Shock, which was the major comorbidity seen in neonatal seizures, was associated with a mortality of 88.2% while only 1.2% of the babies who did not have shock died. Neurological examination which is the simple tool to assess, on analysis showed that 41.1% of neonates with abnormal neurological examination died while only 3% of babies with normal neurological examination died. Both had significant p-value.

As 16 babies died during neonatal period, remaining 83 were followed up. However during follow-up, 2 babies died. Thus 81 babies completed follow-up for one year period and their clinical outcome was analysed at the end. Thus at the end of one year, 64% had normal outcome[(1)]. Among the remaining, seizure recurrence and neurological sequelae were two major outcomes measured which was present in 16% and 20% of infants respectively. Other adverse outcomes noted were developmental delay in 11%, microcephaly in 5%, isolated speech delay

in 3.5% and failure to thrive in 2% of infants. Vision and hearing assessment in all babies did not show any abnormality. The risk factor assessment for two major outcomes, seizure recurrence and neurological sequelae is as follows.

RISK FOR SEIZURE RECURRENCE

RISK FACTORS		TOTAL (n=81)	NUMBER OF SEIZURE RECURRENCE (n=13)		p-value
			n	%	
Nutritional status	SGA	15	2	13	0.751
	AGA	66	11	16	
History of birth asphyxia	Present	25	5	20	0.518
	Absent	56	8	14	

NOTE: SGA: Small for gestation age,
AGA: Appropriate for gestation age.

While analyzing the role of nutritional status and birth asphyxia as a risk factor for seizure recurrence, both did not show any significant correlation. 13% of SGA babies had seizure recurrence as compared to 16% among AGA babies and 20% of babies with asphyxia had recurrence while 14% of babies who did not have asphyxia had seizure recurrence.

RISK FACTORS		TOTAL (n=81)	NUMBER OF SEIZURE RECURRENCE (n=13)		p-value
			n	%	
Day of onset of seizures	<1day	19	8	42	0.005**
	1-4days	36	3	8	
	5-14days	18	1	5	
	>14days	8	1	12	
Days taken to Control seizures	<1day	63	8	12.6	0.251
	1-3days	12	3	25	
	>3days	6	2	33.3	
Family H/O seizures	Present	5	1	20	0.804
	Absent	76	12	15.7	
Type of seizures	Subtle	12	1	8	0.533
	F Clonic	30	3	10	
	Tonic	4	2	50	
	MF clonic	20	4	20	
	Mixed	15	3	20	

Among the babies who had the seizures onset on day1, 42% had seizure recurrence while those with seizure onset after 14 days 12% had seizure recurrence. Longer the days taken to control seizures, more was the seizure recurrence. 12.6% was the recurrence rate among the babies who had seizure controlled within one day. 33.3% babies were observed to have seizure recurrence among those whose seizures were not controlled even after three days. Among the babies who had their seizure controlled less than three days but longer than one day, 25% had seizure

recurrence. While correlating with family history of seizures, it was observed that 20% of those with positive family history had seizure recurrence after neonatal period while it was seen in 15.7% cases without family history. Seizure recurrence was also influenced by type of seizures. Tonic seizures topped the list of type of seizures with seizure recurrence. 50% with tonic seizures had seizures recurrence and 20% of mixed and multifocal clonic seizures had seizure recurrence. While analyzing babies who presented with subtle and focal clonic seizures, only 8% and 10% of babies respectively had seizure recurrence.

Thus among the characteristics of seizures, early onset seizures, refractoriness of the seizure and the type of seizure were more influencing on the outcome, especially seizure recurrence. Among these characteristics, Day of onset of seizures had a significant p-value.

RISK FACTORS		**TOTAL (n=81)**	**NUMBER OF SEIZURE RECURRENCE (n=13)**		**p-value**
			n	**%**	
Microcephaly	Present **Absent**	4 77	2 11	50 14.2	0.058
Neurological Examination	Normal Abnormal	61 20	10 3	16 15	0.883
USG Cranium	Normal Abnormal	72 9	8 5	11 55.5	<0.001**

NOTE: USG: Ultrasonography.

Among babies with microcephaly and neonatal seizures, 50% had seizure recurrence on follow-up. While neurological examination did not seem to predict the seizure recurrence, abnormality in ultrasonography was a good predictor. 15% of babies with abnormal neurological examination had seizure recurrence as compared to 16% in those whose neurological examination was normal. 55.5% of the newborn with Ultrasound abnormality had seizure recurrence while among those with normal Ultrasound only 11% had seizure recurrence. Significant p-value is obtained only for abnormal ultrasound.

RISK FACTORS FOR NEUROLOGICAL SEQUELAE

RISK FACTORS		**TOTAL (n=81)**	**NUMBER OF CASES WITH NS (n=17)**		**p-value**
			n	**%**	
Nutritional status	SGA AGA	15 66	4 13	26 20	0.549
History of birth asphyxia	Present Absent	25 56	9 8	36 14	0.027*
H/O prolonged labor	Present Absent	2 79	1 16	50 20	0.307

NOTE: NS: Neurological Sequelae, SGA: Small for gestation age,
AGA: Appropriate for gestation age.

36% of the babies with birth asphyxia developed neurological sequelae and 50% of babies with history of prolonged labor had neurological sequelae at the end of one year follow-up. Birth asphyxia has significant association with neurological sequelae (p-value <0.05).

However SGA babies were not found to have a significant role as evidenced by 26% of them developing neurological sequelae as compared to 20% among AGA babies.

RISK FACTORS		TOTAL (n=81)	NUMBER OF CASES WITH NS (n=17)		p-value
			n	%	
Day of onset of seizures	<1day	19	10	52	0.001**
	1-3days	36	5	14	
	4-14days	18	1	5	
	>14days	8	1	12	
Type of seizures	Subtle	12	1	8	0.21
	Foc. clonic	30	6	20	
	MF clonic	20	2	10	
	Tonic	4	3	75	
	Mixed	15	5	33	
Days taken to control seizures	<1day	63	9	14	0.015*
	1-3days	12	6	50	
	>3days	6	2	33.3	

NOTE: NS: Neurological Sequelae, Foc.: Focal, MF: Multifocal.

Among babies who had their seizure onset within one day, 52% had neurological sequelae while among those having onset after 14days only 12% had abnormal neurological outcome. Similar to the seizure recurrence, mixed and tonic seizures had increased incidence of neurological sequelae. 33% of babies with mixed seizures and 75% of tonic seizures had abnormal neurological outcome. 8% of neonates with subtle seizures and 20% of them with focal clonic seizures had

neurological sequelae. Prolonged seizures had more incidence of neurological sequelae. Thus early onset seizures, mixed seizures, tonic seizures and seizures resistant to treatment were commonly associated with neurological sequelae and statistically significant p-value was obtained for Day of onset of seizures and Days taken to control them.

RISK FACTORS		TOTAL (n=81)	NUMBER OF CASES WITH NS (n=17)		p-value
			n	%	
Neurological examination	Normal Abnormal	61 20	10 7	16 35	0.076
USG cranium	Normal Abnormal	72 9	11 6	15 66.6	<0.001**
Microcephaly	Present Absent	4 77	2 15	50 19	0.144

NOTE: NS: Neurological Sequelae, USG: Ultrasonography.

When the baby had abnormal neurological examination during neonatal period, abnormal ultrasonography or microcephaly then the risk of that newborn going for neurological sequelae is more. Among our study population, 35% of those with abnormal neurological examination as against 16% babies with normal neurological examination, 50% of those with microcephaly as against 15% babies with normal head circumference and 66.6% with abnormal ultrasonography compared to 19% among babies with normal ultrasound cranium had abnormal

neurological outcome at the end of one year. However, significant p-value was obtained only for abnormal ultrasonography cranium.

ETIOLOGY AND OUTCOME

Etiology	Total (n=99)	Number Of Seizure Recurrence (n=13) n(%)	Number Of Neurological Sequelae (n=17) n(%)	Number Of Death (n=16) n(%)
Septicemia	19	2(10.5)	-	4(21)
Meningitis	4	-	-	1(25)
Hypocalcemia	10	-	2(20)	2(20)
Hypoglycemia	13	-	2(15)	-
Hypoxia	29	5(17.2)	8(27.5)	7(24)
Idiopathic	16	3(18.75)	1(6)	-
BNS	1	-	-	-
Malformations	3	1(33.3)	3(100)	-
IVH	2	1(50)	1(50)	1(50)
IEM	2	1(50)	-	1(50)

NOTE: BNS: Benign neonatal seizures, IVH: Intraventricular hemorrhage, IEM: Inborn Error of Metabolism.

Among the study group, 10.5% of the babies with septicemia had seizure recurrence and 21% of them died. However none of the babies developed neurological sequelae. Among those who had meningitis, 25% babies died, but none of the survived babies developed any abnormal outcome during the study period. Metabolic disturbances like hypocalcemia and hypoglycemia were associated with neurological sequelae in 20% and 15% respectively and both of them were not associated with seizure recurrence. However, in babies with seizures and

hypocalcemia, 20% died. Hypoxia was the only etiology which was observed to cause all abnormal neurological outcome. 17.2% had seizure recurrence, 27.5% had neurological sequelae and 24% of babies succumbed to death among the neonates who had hypoxic insult. None of the newborns with unknown etiology died, there were less percentage of babies who developed seizures on follow-up and 6% ended up with neurological sequelae at the end of one year. Benign neonatal seizures was the only etiology which did not have any abnormal outcome, though there was only one case. Among the babies who had CNS malformation, none died but about 30% had seizure recurrence and 100% had neurological sequelae. While analyzing the babies with Intraventricular hemorrhage, seizure recurrence and neurological sequelae was observed in 50% of the cases while 50% died. Among the neonates who were diagnosed to have Inborn Error of Metabolism, 50% died and 50% had seizure recurrence but neurological sequelae was not observed in any of those babies. Hypoxia, malformations, Intraventricular hemorrhage and Inborn errors of metabolism were the most common etiologies which were associated with abnormal neurological outcome. However, etiology had a significant association (p-value=0.002) with neurological sequelae while not with seizure recurrence or death. But when analysed using Mantel-Haenszel test for linear association, both neurological sequelae and seizure recurrence had significant p-value of 0.009 and 0.019 respectively.

DISCUSSION

Seizures are relatively common in neonatal period and there have been numerous studies looking at clinical profile, outcome and prognosis of patients with neonatal seizures. Hence to have our own experience of the etiology and outcome of neonatal seizures in this large referral hospital this study was undertaken.

Our statistics of the neonates admitted with seizures in the medical newborn ward of our institute in the recruitment period of six months is as follows:

CHARACTERS	TOTAL NUMBER
Total admission in MNB ward	1913
Number of cases of neonatal seizures	110(5.7%)
Total deaths in MNB ward	350(18.2%)
No. of deaths among neonatal seizures	16(4.5% of ND)

NOTE: MNB: Medical New Born, ND: Neonatal Deaths.

We were not able to estimate the incidence of neonatal seizures in our study, because ours being a referral hospital without intramural facilities, many subtle seizures and single episode seizures which are usually not referred would be missed. Thus we would be underestimating the incidence of neonatal seizures.

While analyzing baseline characteristics, the incidence among male and female babies were almost equal. With improvement in perinatology, the incidence of teen-age pregnancy has decreased accounting for only 14%, in our study and the unbooked pregnancy was only 5%. Institutional deliveries have increased and only 5% had history of home delivery. 5% of the babies presented with microcephaly and 35% had abnormal neurological examination in form of bilateral spastic or flaccid weakness or depressed neonatal reflexes. Shock was present in 17% of the babies and it was associated with mortality in 88% of the cases.

69% of the seizures had their onset in first three days of life, however there were 10% of them who had seizure onset after 14 days. The most common seizure type was Focal and Multifocal clonic and Subtle seizures. GTCS was observed only in one case. Other seizure type observed in our study were myoclonic and tonic seizures which were rare but were difficult seizures to control. 20% of babies had mixed type of seizures. Babies with subtle seizures in our study had motor automatism including ocular, oro-bucco-lingual, progressive movements and autonomic features. However cycling movement, vacant stare and nystagmus predominated. Motor automatism observed in our study was similar to those monitored by **KELLAWAY and MIZRALI** in their study and also showed that focal clonic convulsions were the predominant seizure type.

Inspite of 71% of babies having multiple episodes of seizures, 77% of them lasted only for <5mts and 74% got controlled in one day. Seizures which were prolonged and refractory to treatment were present in less than 10% of the babies and 18% required more than one drugs to control seizures. Phenobarbitone[41] was the first line antiepileptic used which achieved seizure control in 73% of the babies. This result is similar to one reported by **GILMAN** et al where 77% of babies had seizure control with phenobarbitone.

ETIOLOGY OF SEIZURES

A specific etiology for neonatal seizures can usually be identified in the majority of cases. In our study also, the cause of neonatal seizures was not detectable only in 16% of the babies. Hypoxia[2] contributed to the bulk of cases. About 30% of the babies had HIE (43.75% among babies who died and 25% among who survived). Infection was the next common etiology. Metabolic disturbance like hypoglycemia and hypocalcemia and inborn errors of metabolism contributed to neonatal seizures in 13%, 10% and 2% of the cases respectively. CNS malformation and Intraventricular hemorrhage were also diagnosed in <5% of the cases.

In the study of **IYPE et al,** HIE, hypoglycemia and meningitis contributed to the bulk of cases. **TEKGUL** et al, in their study, found that etiology of neonatal seizures was identifiable in 77% of the cases and global or focal cerebral hypoxia-ischemia and intracranial hemorrhage were the commonest etiologies. **LEVENE** et al found that 53% of the neonatal seizures was due to HIE, 4% due to infection, metabolic and CNS malformation. 75% of the babies with neonatal seizures had their etiology identified in a study undertaken by **ARTHUR L. ROSE** et al and 25% were idiopathic. In the study of **KAREEM et al,** perinatal hypoxia and hypoglycemia were found to be the principle etiologic factors accounting for 47% and 19% of cases respectively.

Our study also showed that etiology was identifiable in 84% of the babies and etiological profile was similar to all other studies with hypoxia predominating the list followed by Infection and Metabolic disturbances.

OUTCOME MEASURES

Neonatal seizures in many studies, have been shown to have long term detrimental effects on behaviour, seizure susceptibility and brain development. On evaluating, the long term outcome in our study population, 16% succumbed to death during the neonatal period. Among the remaining babies who were followed up, 64% had normal outcome[1]. 17(20%) of the babies had neurological sequelae and 13 (16%) had seizure recurrence. The neurodevelopmental outcome in our study was monitored by Trivandrum Development Screening Chart(TDSC)[14,45]. TDSC is a simple developmental test designed and validated for children below two years of age. There are 17 test items in the chart chosen from the norms given in Bayley Scales of Infant Development. It does not require any special kit and takes only 5-7mts.

In the study of **IYPE** et al, 68% had normal outcome, 32% had abnormal neurological outcome and 7% had seizure recurrence. The follow-up period in this study was four months.

In a **Canadian study,** at 10yrs 35% had normal outcome and 34% had postneonatal epilepsy. The same cohort when followed up till end of decade showed that only 12% had normal outcome and seizure recurrence was present in 48% babies. Sample size was not mentioned in this study. It was concluded in this study that , short term follow-up usually shows better outcome. Similarly in **TEMPLE** et al study of 4yrs follow-up 11

out of 14 had normal outcome. However the same children followed up till adolescence showed spelling and memory problems. In the study of **ARTHUR** et al, 50% had normal outcome, 30% had neurological deficits and 20% died.

7% mortality and 28% poor neurological outcome were reported in the study by **TEKGUL** et al with a follow-up period of 12-18months. **GABRIEL** et al, in his study on neonatal seizures, followed up 82 babies and his results showed 45% normal outcome, 16% death and 39% impairment. **HARVARD** study showed 70% normal outcome, 13% cerebral palsy and 20% seizure recurrence. **RONALD** et al showed in his study that 70% had normal outcome at 7yrs following neonatal seizures as compared to 64% in our study.

Except for Canadian study which showed 34% seizure recurrence, the results of our study were almost similar to all other studies. Follow-up for longer period may have shown similar results to the Canadian study.

ANALYSIS OF RISK FACTORS FOR ADVERSE OUTCOME

Among the various risk factors analysed babies with early onset seizures (especially within one day) and seizures refractory to treatment (seizures which required more than one drug or took more than three days to get controlled) had increased incidence of mortality, seizure recurrence and neurological sequelae. Resistant seizures notably had increased risk of mortality. Small for gestational age babies had the same risk for the bad outcome as Appropriate for gestation age babies and the same results were obtained in the study of **IYPE et al.** The babies with birth asphyxia showed increased incidence of abnormal outcome. While evaluating type of seizures, tonic seizures followed by mixed seizures showed high incidence of abnormal outcome. During discharge, if the neonate was found to have abnormal neurological examination, on follow-up, the incidence of neurological sequelae was high (35% as compared to 16% in normal child). The mortality rate among them was 50%, however seizure recurrence was comparable to those who had normal neurological examination. The presence of co-morbidities especially shock determined the immediate outcome in neonatal seizures. About 88.2% of babies with shock died during neonatal period while the incidence of death among those who did not have shock was 1.2%. All babies recruited for study had ultrasonography cranium done. At the end of study, it was found that among babies with abnormal USG 55% had seizure recurrence and 66% of them developed neurological sequelae.

Etiological factors has been determined to be the most critical factor in determining outcome in many studies. In our study, the same was proved. 100% of infants with Malformations and 50% of them with Intraventricular hemorrhage had abnormal neurological outcome while

50% of Intraventricular hemorrhage and Inborn Error of Metabolism had seizure recurrence. Beside these hypoxia-ischaemia was found to be an important etiology which showed increased incidence of seizure recurrence and neurological sequelae. Hypoxia was the commonest etiology associated with mortality. Benign neonatal seizures and transient metabolic disturbances had normal outcome. The risk of abnormal neurological sequelae (6%) and seizure recurrence (18.75%) was much lower when the etiology of neonatal seizures could not be identified.

Thus early onset seizures, seizures difficult to treat, abnormal neurological examination, abnormal ultrasonography, presence of co-morbidities like shock, mixed and tonic seizures and identifiable etiology were found to be major risk factors determining the outcome in infants with neonatal seizures.

IYPE et al, could not identify any risk factors for seizure recurrence. They also proposed that hypocalcemia was significantly associated with mortality. In **HARVARD study,** Low Birth Weight, early onset sepsis and prolonged seizures were identified as prognostic factors. **KELLAWAY and MIZRAHI** proposed that 100% of cerebral dysgenesis and 30% Hypoxic Ischaemic Encephalopathy had risk of recurrence of seizure and none of transient metabolic disturbances had the risk of recurrence which was similar to our study.

TEKGUL et al, in their study showed a strong association between seizure etiology and outcome especially with cerebral dysgenesis, global

hypoxia-ischaemia and poor outcome. While analyzing neurological examination, they proposed that normal neurological findings had favourable outcome however abnormal neurological examination lacked specificity. The variables associated with poor prognosis, as determined by **GABRIEL** et al in their study were severe hypoxic encephalopathy, cerebral dysgenesis, complicated Intraventricular hemorrhage and the need for multiple drugs. They also showed that pure clonic seizures had favourable outcome whereas myoclonic seizures had increased mortality. **HALLIOGLU** et al in their study showed that cranial USG has 100% sensitivity and 55% specificity in predicting outcome.

GABRIEL et al, TEKGUL et al, KELLAWAY and MIZRAHI, ARTHUR et al, Canadian study and IYPE et al proved in their studies that Electroencephalography was the major determinant of long term prognosis. However, due to technical difficulties, we were not able to do Electroencephalography in our study. Other risk factors and their role in predicting long term outcome as determined in our study was similar to other studies.

During the follow-up period, if any baby was found to have any developmental delay, the parents were taught about Early Infant Stimulation. Early Infant Stimulation[52,53,54,55] is now a well established strategy for preventing or reducing disability resulting from early CNS damage. When there is neuronal damage during prenatal period and infancy, activating of the spared synapses and relocation of the activity of

the damaged neurons is possible if spared synapses could be saved by stimulation. Infant Stimulation can be provided by structuring the environment to facilitate sensory, motor stimulation and also through direct responsive interaction with the mother or the caregiver. Marked improvement in the performance, hearing and speech subscales as well as development quotient have been observed in one **Jamaican study.** In a meta analysis done by **SPITTLE AT et al,** the crucial importance of stimulation during the early periods of development is emphasised as the motor, social and cognitive skills developed during this period have strong implication for future life-long development.

SUMMARY AND CONCLUSIONS

- Among the neonatal admissions, 5% of newborn had seizures in this extramural newborn ward.
- Sex of the baby does not have significant association with neonatal seizures.[31]
- Focal and multifocal clonic were the commonest type of seizures.[21]
- The obvious cause for seizures was not detectable in 16% of the neonates and probably they were idiopathic.[1,2,6]
- Hypoxia[2] was the most common etiology and was found in 30% of the babies.
- Seizure control was achieved in one day in 74% of the babies.
- Treatment includes specific therapy for cause and antiepileptic drugs. The goals of treatment need to be tailored to specific situation.
- Phenobarbitone was used as first line antiepileptic drug and it achieved seizure control in 73% of the neonates.[28,41]
- Among the babies with neonatal seizures, 16% died. Birth asphyxia, seizures controlled with multiple drugs, presence of co-morbidities especially shock and abnormal neurological examination were the important risk factors for mortality.
- Among the babies followed up, 64%[1] had normal outcome. So aggressive treatment of seizures is suggested.

- Seizure recurrence was observed in 13 (16%) babies at the end of one year follow-up. Early onset seizures[21] and abnormal ultrasonography of cranium were the risk factors identified for seizure receurrence in neonates with seizures.

- Seventeen (20%) babies with neonatal seizures had neurological sequelae on follow-up of one year. The risk factors for abnormal neurological outcome were birth asphyxia, Early onset seizures, Seizures which took more days to control and Abnormal ultrasonography of cranium.

- Prognosis following neonatal seizures is extremely variable and depends mostly on the underlying etiology of seizures[1,2,6,63]. Etiology of seizures has significant association with neurological sequelae than with seizure recurrence or death.

- In general, long term prognostication of babies with neonatal seizures is guarded in early onset seizures, recurrent seizures, refractory seizures, mixed and tonic type seizures[21] , babies with abnormal neurological examination and those with abnormal ultrasonography.

- Neurological examination is the tool not requiring sophisticated technology and is ideally suited for outcome prediction in Indian setting[44] . If any abnormality detected, Early Infant Stimulation can be advised, which has shown promising role in improving neurological status of high-risk babies in many studies[52,53,54,55].

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