

A Study on Clinical Profile of Neonatal Seizures

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ABSTRACT

Introduction: The neonatal period is limited to the first 28 days of life in a term or preterm infants. Neonates are at particular risk for the development of seizures because metabolic, toxic, structural and infectious diseases are more likely to be manifested during this time than during any other period of life. Study aimed to know the etiology, presentation and complications of neonatal seizures. To evaluate the clinical, CT scan Brain, EEG, Neurosonogram, metabolic profile and CSF analysis in these babies. To determine the response to antiepileptic drugs and outcome in these babies.

Material and methods: Study was done at Neonatal intensive care unit and nursery of a "Tertiary Care Teaching Hospital, Central Andhra Pradesh, South India". Study Group comprised of 108 neonates with neonatal seizures admitted over the period of one year were included in the study. Both term and preterm babies were included.

Results: Out of the 108 neonates in the study 58 were female 50 were male. 74 were born at term (39 male and 35 female). 34 babies were delivered prematurely. (18male, 16female). Out of 74 cases of term babies, normal outcome was observed in 30 cases (40.5%), sequelae have been observed in 26 cases (35.1%), 13 cases expired (17.6%).Out of 34 cases of preterm babies, 13 cases had normal outcome (38.2%), death occurred in 12 cases (35.3%), sequelae have been observed in 8 cases (23.5%).

Conclusion: Neonatal seizures are a common cause of neonatal morbidity and mortality. The most common cause of neonatal seizures are perinatal asphyxia and neonatal sepsis. CT Scan Brain and Neurosonogram are useful in early detection of cerebral edema, ischemic hypo densities and haemorrhages which have an important prognostic significance.

Keywords: Neonatal Seizures; HIE.

INTRODUCTION

The neonatal period is limited to the first 28 days of life in a term or preterm infants. Neonatal seizures occur mostly during early neonatal period for a few days and fewer than half of affected infants develop seizures later in life. Such neonatal seizures could be considered acute reactive (acute symptomatic), thus the term "neonatal epilepsy" is not used to describe neonatal seizures. Seizures in neonates are relatively common, with variable clinical manifestations. Their presence is often the first sign of neurological dysfunction and they are powerful predictors of long term cognitive and developmental impairment. Neonates are at particular risk for the development of seizures because metabolic, toxic, structural and infectious diseases are more likely to be manifested during this time than during any other period of life

Classification of Seizure Patterns^{1,2}

The usual well organized tonic clonic seizure patterns seen in older infants are not seen in the new-born because of the immaturity of the new-born brain. The arborization of axons and dendritic processes as well as myelination is incomplete in the neonatal brain. A seizure discharge cannot therefore be propagated throughout the neonatal brain to produce a generalized seizure. The predominance of oral and buccal phenomena such as chewing, lip smacking and sucking as well as gaze abnormalities and apnea may be related to the advanced development of the limbic structures and their connections to the brainstem and diencephalon in comparison with other forebrain structures.

1. Focal Clonic Seizures

The movements involve rhythmic, well localized, twitching or jerking of muscle groups, particularly those of extremities and face. They are not associated with loss of consciousness. They are most often provoked by metabolic disturbances, focal traumatic injury (e.g. cerebral contusion) subarachnoid hemorrhage, focal infarct and infections. The EEG is usually unifocally abnormal. Prognosis is generally good.

2. Multifocal Clonic Seizures: They are seen in full term infants. They are similar to focal clonic seizures but differ in that many muscle groups are involved, frequently several simultaneously. They are characterized by random clonic movements of limbs similar to those seen in normal infants less than 34 weeks of gestation. The EEG is multifocally abnormal. The movements migrate from one part of the body to another part in a non-ordered fashion. This non-Jacksonian migration is typical.

3. Tonic Seizures: The movements are focal or generalized and may resemble the decerebrate or decorticate posturing seen in older children, the movements are most often associated with eye deviation and occasionally with clonic movements or apnea. They are more often seen in premature babies and are most often associated with diffuse CNS disease

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or intraventricular hemorrhage. The prognosis is mixed but is generally poor. The EEG is multifocally abnormal, has a burst suppression pattern.

4. Myoclonic Seizures: The manifestations include synchronous single or multiple

slow jerks of the upper or lower limbs and are associated with diffuse CNS pathology. The prognosis is poor. EEG shows a burst suppression pattern or focal, sharp transient waves and may evolve into hypsarrhythmia.

5. Subtle Seizures: They constitute 50% of seizures in new born (both term and preterm) and most often occur in infants who manifest the other seizure types described above. These seizures may be sub cortical in origin and may not be ameliorated by anticonvulsant therapy. EEG may show normal records.

Subtle seizures may manifest as

- Tonic horizontal deviation, usually with jerking of eyes.
- Repetitive blinking or fluttering of eyelids.
- Oral and buccal movements, drooling, sucking,, yawning.
- Tonic posturing of a limb.
- Apnea: Apnea due to seizure most often has accelerated or normal heart rate when evaluated 20 sec after its onset. Apnea due to other causes is associated with bradycardia near the onset of the episode.
- Rhythmic fluctuation in vital signs and degree of oxygenation in pharmacologically paralyzed infants.
- Complex purposeless movements such as swimming, bicycling and pedaling movements.

The most common manifestations are ocular phenomena. In term infants the dominant ocular phenomena are horizontal deviation of eyes and in premature infant it is sustained eye opening with ocular fixation

Study aims and objectives were to study the etiology, presentation and complications of neonatal seizures, to evaluate the clinical, CT scan, EEG, neurosonogram, metabolic profile and CSF analysis in these babies and to determine the response to antiepileptic drugs and outcome in these babies.

MATERIAL AND METHODS

Study was done at Neonatal intensive care unit and nursery of a "Tertiary Care Teaching Hospital, Central Andhra Pradesh, South India". Study Group comprised of 108 neonates with neonatal seizures admitted over the period of one year were included in the study. Both term and preterm babies were included.

Methods: At admission detailed history of all the neonates was taken. The neonates were clinically assessed and careful physical and neurological examination was carried out. HIE staging was done using Sarnat classification. Gestational age was estimated using New Ballards scoring, modified Dubowitz scoring system.

- Blood samples were taken under strict aseptic conditions. Blood glucose, serum calcium and magnesium were done

by standard biochemical methods. Urine was estimated for reducing substances when ever required. Estimation of serum bilirubin was done whenever necessary.

CT Scan Brain was performed after stabilizing the baby. CT scan was done using IIIRD generation sub second, single slice, spiral CT machine, TOSHIBA ASTEON JAPAN. Slice thickness for posterior fossa structures was 5 mm. for rest of the brain was 10 mm. The smallest slice thickness in our CT machine was 0.67 mm. The whole procedure takes around 10 min

EEG was performed using 16 channel scan that is EEG IA 97 machine. The recording time was 40 min. Sedation was avoided as much as possible. Pedichloryl was used in some cases.

- Lumbar puncture was done under strict aseptic precautions. CSF was analyzed for total cell count, differential count, sugar, protein, globulin and chlorides. Culture and gram stain were performed.
- Neurosonogram was done as soon as the baby's condition was stabilized.
- X-ray chest, X-ray skull, thyroid profile was done whenever required.
- Depending up on the clinical condition the babies were treated with antiepileptic drugs, antibiotics, IV fluids and O₂ inhalation. Phototherapy was given whenever necessary.
- Outcome was assessed clinically and electrographically (EEG).

Criterion for meningitis: One of the following

- Positive DNA amplification test for N meningitidis performed on a normally sterile body fluid.
- Detection of N meningitidis antigen in CSF.
- Positive immunohistochemical staining for N meningitidis antigen on formalin - fixed tissue.

Criterion for sepsis:

Total cell count less than 5000 /mm³, Band cell to mature neutrophil ratio more than 0.2

C - reactive protein more than 10 mg/ml, Radiological evidence of pneumonia.

Isolation of pathogens either from blood or CSF by culture.

Criterion for hypoglycaemia: Blood glucose level less than 40 mg/dl.

Criterion for Hypocalcaemia: Serum calcium level less than 7 mg/dl

CT scan Brain Criteria: $\frac{\text{Frontal horn Diameter}}{\text{Biparietal Diameter}}$

Ventricular Size Index:

Normal: 0.3 cm Mild enlargement: 0.3-0.39 cm

Moderate enlargement: 0.4-0.46 cm Severe enlargement: more than 0.46 cm

EEG criteria: Electro encephalography provides a continuous recording of electrical activity between reference electrodes placed on the scalp.

- The waves are classified according to their frequency. Delta and theta waves are normally seen in neonates. Delta waves: 1-3/sec, Theta waves : 4-7/sec Alpha waves: 8-12/sec Beta Waves: 13-20/sec
- Low voltage waves, poly spikes, sharp waves, burst suppression and flat waves were considered as abnormalities

RESULTS

Out of the 108 neonates in the study 58 were female 50 were male. 74 were born at term (39 male and 35 female). 34 babies were delivery prematurely. (18male, 16 female).

Birth Weight Distribution of the babies was as follows.

>4000 Grams: 2, 3500-3999 Grams : 6, 3000-3499 Grams : 7, 2500-2999 Grams: 41, 2000-2499 Grams:18, 1500-1999 Grams: 21, <1500 Grams : 13 babies

52 babies had low birth weight, of which 18 were term, and 34 were preterm.

	Term	Preterm	Total
Day 1	25	13	38
Day 2	11	9	20
Day 3	10	4	14
Day 4	7	2	9
Day 5	5	1	6
Day 6	3	1	4
Day 7	4	2	6
2 nd Week	5	2	7
3 rd Week	3	0	3
4 th Week	1	0	1
Total	74	34	108

Table-1: Age at onset of seizures

	Total	Deaths	Normal Outcome
Subtle	43 (39.8%)	10 (23%)	13 cases (30.2%)
Multifocal Clonic	21 (19.4%)	2 (9.5%)	12 cases (57.1%)
Tonic	19 (17.66%)	7(36.8%)	6 cases (31.6%)
Focal Clonic	17 (15.7%)	1 (5.9%)	12 cases (70.6%)
Myoclonic	8 (7.42%)	5 (62.5%)	0

Table-2: Types of seizures

	HIE Stage II	HIE Stage III	Sepsis and Meningitis	Metabolic Conditions	Congenital Abnormalities
Focal spikes	7		5	2	1
Multifocal spikes	6	3	4	3	
Low voltage	3	2	2		
Flat Waves	-	-	-	-	-
Burst Suppression	-	-	-	-	-

Table-3: EEG findings

	Term	Preterm	Total Cases
Normal Outcome	30(40.5%)	13(38.2%)	43
Sequelae	26(35.1%)	8(23.5%)	34
Death	13(17.6%)	12(35.3%)	25
Lost to follow up	5(6.8%)	1(2.9%)	6

Table-4: Outcome depending on gestational maturity

seizures 30 cases (40.5%) followed by multifocal clonic seizures 17 cases (22.9%), Tonic seizures 13 cases (17.6%), focal clonic seizures 10 cases (13.5%). Least common type was myoclonic seizures 4 cases (5.4%).

In preterm babies most common type of seizures was subtle seizures 13 cases (38.2%) followed by focal clonic seizures 7 cases (20.62%), Tonic seizures 6 cases (17.6%). Least common types were myoclonic seizures and multifocal clonic seizures 4 cases each (11.76%).

EEG has been done in 61 cases. Focal spikes were observed in 7 cases in HIE stage II, 5 cases with sepsis and meningitis. 1 case each of hypoglycemia and hypocalcemia and congenital abnormality. Multifocal spikes were observed in 6 cases in HIE stage II, 3 cases in HIE stage III, 4 cases with sepsis and meningitis and in 3 cases metabolic abnormalities (2 cases of hypoglycemia 1 case in hypocalcemia). There were low voltages in 3 cases in HIE stage II, 2 cases in HIE stage III, 2 cases with meningitis.(Table-3)

CT scan brain

CT scan brain has been done in 59 babies with hypoxic ischemic encephalopathy and cases with sepsis and meningitis. Out of 59 cases the scan was abnormal in 47 (80%) cases. The scan was normal in 6 cases in HIE stage II and 6 cases with sepsis and meningitis. Hypo densities were observed in 13 cases in HIE stage II and 4 cases in HIE stage III and in 3 cases with meningitis. Cerebral edema was seen in 6 cases in HIE stage II, 2 cases in HIE stage III and 4 cases with Sepsis and meningitis. There was one case of subarachnoid hemorrhage and two cases of intra cerebral hemorrhage. The ventricular size was decreased (effacement of ventricles) in 4 cases in HIE stage II and 2 cases in HIE stage III. Hydrocephalus was seen in 5 cases with meningitis and one case of HIE stage II

CI Scan Brain in sepsis and meningitis

Normal: 6cases, Hypo Densities: 3cases, Edema: 4cases, Hydrocephalus: 5 cases

Neurosonogram

Neurosonogram has been done in 83 cases out of which coarse echo texture of cerebral parenchyma and hypoxic changes have been observed in 32 cases. Edema was observed in 7 and hemorrhage in 5 cases. There were exudates in 6 cases and hydrocephalus in one case. The scan was abnormal in 51 cases out of 83 (61.4%).

LP has been done in 81 cases under strict aseptic conditions. In majority of cases the total cell count was in between 0-10 cells, of which lymphocytes were predominant cells. Cell count was in between 10-20 cases in 6 cases. Cell count was in between 20-50 cells in 2 cases. Cell count was in between 50-100 in 3 cases, 2 cases in between 100-500 and in 2 cases cell count was above 500 cells (cells mostly netrophilic in nature). Globulins were positive in 11 cases. Protein mean value was 74 mg/dl and in 9 cases protein value in more than 100 mg/dl. Glucose mean value is 55 mg/dl. Glucose was less than 30mg/dl in 7 cases. Hemorrhagic tap was observed in 8 cases out of which 7 were due to traumatic tap. One was due to subarachnoid hemorrhage. Chloride mean value was

570 mg/dl. Gram stain and culture were negative in all cases.

Biochemical Analysis: Blood glucose was done in all cases. Hypoglycemia was observed in 22 cases (20.5%) of which 7 were in HIE and 8 were associated with sepsis and meningitis. Isolated hypoglycemia was observed in 7 cases of which 2 were babies of diabetic mother and remaining 5 cases of hypoglycemia were observed in premature and low birth weight babies. Serum calcium was done in all cases. Hypocalcaemia was observed in 13 cases (12%) of which, 7 were associated with HIE and 6 cases with sepsis and meningitis. Serum bilirubin levels were estimated where ever necessary. 22 babies had hyper bilirubinemia of which one baby was brought in kernicterus with total serum bilirubin 36 mg/dl (indirect 35.2 mg/dl direct 0.8 mg/dl). All babies of hyper bilirubinemia were treated with phototherapy and 2 cases with exchange transfusion. Investigations to rule out inborn errors of metabolism could not be done because of financial constraints.

Treatment: Airway, breathing, circulation were stabilized and seizures were first treated with Phenobarbitone with loading dose of 15-20 mg/kg and with maintenance dose of 5mg/kg. 50% of cases required second Loading dose of 10 mg/kg of Phenobarbitone. 40% of cases requires phenytoin with loading dose of 15-25 mg/kg. Maintenance dose of phenytoin was 4-8 mg/kg. 2 cases responded to midazolam. (0.1 mg/kg). 1 case responded to pyridoxine (dose was 100 mg). Hypoglycemia was treated with 10% dextrose in a dose of 2 ml/kg over one minute. Then followed by 8 mg/kg/min infusion. Hypocalcaemia was treated with 10% calcium gluconate in a dose of 2 ml/kg (18 mg of elemental calcium / kg) mixed equal volume of 5% dextrose given intravenously over 5 minutes. This was followed by maintenance therapy of calcium.

Prognosis and outcome

The total numbers of term babies were 74. Normal outcome was observed in 30 cases (40.5%) sequelae have been observed in 26 cases (35.1%). 13 cases expired (17.6%).5 Cases lost to follow up (6.8%).

Total number of preterm babies were 34. 13 cases had normal outcome (38.2%). Death occurred in 12 cases (35.3%). Sequelae have been observed in 8 cases (23.5%). One case lost to follow up (2.9%).(Table-4)

Prognosis and outcome based on gestational maturity and seizure pattern

In term babies out of 30 cases multifocal clonic seizures 11 cases had normal outcome (36.6%), 13 cases had sequelae (43.3%), whereas 6 cases expired (20%). In 10 cases of focal clonic seizures 6 had normal outcome (60%), 3 cases had developed sequelae (30%). Mortality was seen in 1 case (10%). In 13 cases of tonic seizures 4 had normal outcome (30.8%), 6 cases developed sequelae (46.2%), whereas 3 cases expired (23%). In 12 cases of subtle seizures 9 cases had normal outcome (75%) whereas sequelae have been observed in 2 cases (16.6%). One baby expired (8.3%). In 4 cases of myoclonic seizures normal outcome was not

observed, whereas sequelae have been in 2 cases (50%). 2 cases expired (50%).

In preterm babies out of 13 cases of multifocal clonic seizures normal outcome was seen in 2 cases (15.4%). 7 cases had sequelae (53.8%) death occurred in 4 cases (30.8%). In 6 cases of focal clonic seizures all 6 cases had normal outcome (100%), sequelae and death were not seen. In 6 cases of tonic seizures 2 cases had normal outcome (33.3%) and death occurred in 4 cases (66.6%). In 4 cases of subtle seizures 3 cases had normal outcome (75%) one case expired (25%). In 4 cases of myoclonic seizures normal outcome was not seen. Neurological sequelae have been seen in 1 case (25%). 3 cases expired (75%).

In HIE, out of 43 cases of HIE stage II, 5 cases expired (11.6%), sequelae were seen in 10 cases (23.2%) and normal outcome was observed in 28 cases (65.11%). In HIE stage III, out of 19 cases, 10 cases expired (52.63%) and neurological sequelae occurred in 9 cases (47.36%). Normal outcome was not seen in any case of HIE stage III.

There are 36 cases of sepsis and meningitis out of which 8 expired and sequelae were observed in 13 cases. 15 cases became normal. Hypoglycemia has been observed in 22 cases out of which 7 were due to isolated hypoglycemia of these 2 cases were born to diabetic mothers and other 5 cases of hypoglycemia were due to prematurity and low birth weight. All 7 cases of isolated hypoglycemia had normal outcome. 7 cases of hypoglycemia were associated with HIE whereas 8 cases were associated with sepsis and meningitis.

Hypocalcaemia was observed in 13 cases out of which 6 were associated with HIE, and 7 cases were associated with sepsis and meningitis. There was one case kernicterus (total serum bilirubin was 36 mg/dl indirect 35.2 mg/dl direct 0.8 mg/dl). The baby was treated with exchange transfusion and photo therapy. The baby expired.

There was one case of encephalocele and meningocele. Case of encephalocele was expired whereas meningocele was operated. Neurological sequelae were observed during follow up.

DISCUSSION

Seizure is the most frequent sign of neurological dysfunction in a neonate. Since seizure may be the only sign of the CNS disorder, their recognition is very important. They are powerful predictors of long term cognitive and developmental impairment. Seizures are not only more frequent during the neonatal period than at any other age but they are also more difficult to diagnose because of the subtle nature of the behavioural and EEG manifestations. This study attempts to define the most common causes, diagnosis, response to antiepileptic medication and prognosis of neonatal seizures. 108 cases of neonatal seizures admitted in Neonatal intensive care unit and nursery of a "Tertiary Care Teaching Hospital, Central Andhra Pradesh, South India" over the period of one year were taken up for the study. 53% were female (56 cases) and 47% were male (51 cases) showing no definite sexual predominance in correlation with earlier study of Sheth RD, Hobbs GR, Mullett M et al³. 37% of the Babies were

preterm (34 cases) 48% had low birth weight. Prematurity and low birth weights are the risk factors for factors for the birth asphyxia sepsis, and intra cranial bleeds, which are the common etiological factors for neonatal seizures. The average age at onset of seizure in term new born during first week of life was 2.83 days. While that in pre term was 2.5 days. 33% of term and 32% of pre-term had seizures on the first day of life. 86.5% term and 94% of pre term has seizures within the first week.

66% of babies were delivered vaginally. 31.5% accounted for home delivery. 13.9% were delivered by outlet forceps. High incidence of home deliveries is probable cause for birth asphyxia. Family History of seizures was observed in 4 cases.

Out of 59 CT Scans of Brain were done, 47 scans were abnormal. The most common abnormality found was hypodense lesions. The other abnormalities found were edema and hemorrhage (Hydrocephalus was observed in 6 cases mostly in sepsis and meningitis. 6 cases of decreased ventricular size have been seen mostly in HIE. There was one case of sub arachnoid hemorrhage and two cases of intra cerebral hemorrhage. The incidence of hemorrhage is lower when compared to earlier study of merchant et al⁴ in 1987. The prognosis of hemorrhage is comparable to that in the earlier studies.

EEG has been done in 61 cases. abnormalities were observed in 16 cases (26%). 74% had no EEG abnormalities. this is slightly higher than 19% of 243 analyzed seizures shown in a retrospective evaluation by weiener et al⁵. Most of the subtle seizures did not have an EEG correlate. This is in consonance with earlier study by Mizrahi and Kellaway⁶ in 1980. Hypoglycemia was observed in 22 cases (20.4%) out of which 7 were due to isolated hypoglycemia which had normal outcome. 7 were associated with HIE, while 8 cases were along with sepsis and meningitis. Hypocalcaemia was observed in 13 cases (12%) of which 6 were along with HIE and 7 with sepsis and meningitis. There were 11 cases of meningitis proven by CSF analysis. Lumbar puncture was done in all cases of suspected sepsis and meningitis.

Neurosonogram has been done in 83 cases out of which coarse echo texture of cerebral parenchyma and hypoxic changes have been observed in 32 cases. Edema was observed in 7 and hemorrhage in 5 cases. There were exudates in 6 cases and hydrocephalus in one case. The scan was abnormal in 51 cases out of 83 (61.4%).

The most common type of seizures in this study in both term and preterm babies were subtle seizures. Least common type in term babies was myoclonic seizures, whereas in preterm babies least common type of seizures was myoclonic and multifocal clonic seizures. The results correlate with the previous study of Moayedi AR, Zakeri S et al⁷. Term babies had a better outcome than preterm babies. Mortality was higher in preterm babies. In both term and preterm babies unifocal clonic seizures had best prognosis.

The most common causes of seizures in this study were HIE and neonatal sepsis. Out of all the cases of sepsis 25% were culture positive. In 30.5% of sepsis cases seizures

were due to metabolic abnormalities like hypoglycemia and hypocalcemia and one case of Kernicterus. In most of the cases there was a combination of etiological factors.

Phenobarbitone was effective in controlling seizures in 50% of the patients with a single loading dose. A second loading dose of phenobarbitone controlled the seizure activity in another 10% (total 60%). Put together phenobarbitone and phenytoin were effective in 75% of cases. This is slightly higher than the results obtained (60%) when both the drugs used together in earlier studies by Painter et al⁸, in 1999. Midazolam proved effective in 2 cases and seizures responded to pyridoxine in one case.

The mortality in neonatal seizures in this study was 23%. Hypoglycemia not associated with HIE, Sepsis and meningitis and HIE stage III had very poor outcome in both term and preterm babies. The other causes of mortality were kernicterus, Encephalocele. Deaths were associated with severe cerebral edema, multiple ischemic hypo densities, intra cerebral hemorrhage, and abnormal EEG records and poor response to anti epileptic drug therapy⁹.

Outcome: Neurological handicaps like spasticity, persistent seizures, persistent EEG abnormalities, abnormal neurological examination in 30% of the patients, when evaluated at a gap of 1, 2 and 3 months of discharge from the hospital. The results were in correlation with study of Tekgul H, Gauveau K, Soul JS et al¹⁰. They were associated with cerebral edema, ischemic hypo densities on CT scan, moderate hypoxic changes in neurosonogram and abnormal EEG records. Months of discharge from the hospital. 6 cases were lost to follow up. 41% of the infants were normal on neurological examination and did not have recurrent seizure activity on follow up. The absence of abnormalities on CT scan Brain and EEG correlated well with normal outcome¹¹. Death occurred in 25 cases (23.1%)

CONCLUSION

- Neonatal seizures are a common cause of neonatal morbidity and mortality.
- The most common cause of neonatal seizures are perinatal asphyxia and neonatal sepsis.
- CT Scan Brain and Neurosonogram are useful in early detection of cerebral edema, ischemic hypodensities and haemorrhages which have an important prognostic significance.
- EEG is also useful in early detection of electrographic seizure activity and babies with persistently abnormal EEG records have a uniformly bad prognosis.
- Treatment with anti epileptic drugs should be initiated in time and adequately and promptly treated babies have relatively good neurological outcome.
- Developmental assessment and neurological examination should be carried out during follow up for early detection of neurological handicaps.

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