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Review Article

Neonatal Seizure: An Update

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Introduction

Neonatal seizures continue to be a diagnostic and therapeutic challenge to the clinicians. Seizures can permanently disrupt neuronal development, induce synaptic reorganisation, reduce neurogenesis, alter plasticity and prime the brain to increased seizures later in life[1]. The prevalence of seizures is 2-3 /1000 live births in term and 10-15 /1000 in preterm deliveries[2]. Diagnostic and therapeutic interventions should thus be established promptly, for which proper classification and etiologic workup are pre-requisite.

Definition: A seizure is defined clinically as a paroxysmal alteration in neurological function i.e., motor, behaviour and/or autonomic function.

Classification

A. According to clinical presentations[3]:

a) Subtle seizures: Occurs both in term and preterm infants. Subtle means the clinical manifestations are mild and frequently missed. They constitute 50% of all seizures. Examples:

   i. Ocular: Tonic horizontal deviation of eyes or sustained eye opening with ocular fixation or cycled fluttering.

   ii. Oral-facial-lingual movements (chewing, tongue thrusting, lip smacking)

   iii. Limb movements (cycling, paddling, boxing-jabs)

   iv. Autonomic phenomena (tachycardia or bradycardia)

   v. Apnea with accelerated or normal heart rate when evaluated 20 seconds after onset.

b) Clonic Seizures: Characterized by rhythmic movements of muscle groups, most commonly associated with abnormal EEG changes, seen primarily in term babies.

c) Tonic seizures: They are seen in preterm infants. They are sustained flexion or extension of axial or appendicular muscle groups, may be focal or generalized. EEG changes in generalized tonic seizures are usually absent.

d) Myoclonic Seizures: They are single or multiple jerks of the upper or lower limbs. EEG changes include burst suppression pattern, focal sharp waves and hypsarrhythmia.

B. According to clinical features and EEG changes[3]:

a. "Electroclinical": clinical phenomena are associated with corresponding seizure activity on electroencephalography (EEG), e.g., clonic seizures.

b. "Electrographic only" (sub-clinical/occult seizure): EEG abnormalities are not associated with any definite clinical seizure activity.

The above two categories respond to antiepileptic drugs (AED) and are often associated with autonomic changes such as tachycardia and mild elevation of blood pressure.

c. "Clinical only": Abnormal clinical events are not associated with EEG changes. Occur spontaneously or after stimulation and can often be suppressed or altered by restraining or repositioning the baby. There is no autonomic phenomenon, do not respond to AED.

Causes of Neonatal Seizures [3-7]

i. Hypoxic-ischemic encephalopathy (HIE): HIE secondary to perinatal asphyxia is the commonest cause of seizure in neonates, especially in developing countries, constituting 50-65% of all seizures. Most seizures (50-65%) due to HIE start within 12 hrs, remaining have an onset within 24-48 hours.

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ii. Metabolic causes: They include hypoglycemia (blood glucose level <2.6mmol/L), hypocalcaemia (serum calcium level <1.75mmol/L), hypomagnesaemia (Mg level <1.5mEq/L or<0.70mmol/L), hyponatremia, hypernatremia and rarely pyridoxine deficiency, pyridoxine dependency, amino acid, organic acid and urea cycle disorders, mitochondrial and peroxisomal disorders and other inborn errors.

iii. Infections: Meningitis (E.coli, Group B Streptococci, Listeria), viral encephalitis (Herpes simplex, Enterovirus), secondary to intrauterine infections (TORCH group, HIV, syphilis).

iv. Intracranial hemorrhage: Sub-arachnoid, intra-parenchymal or sub dural hemorrhage occur more often in term babies and intraventricular hemorrhage (IVH) occur in preterms, occur between 2-7 days.

v. Cerebral infarcts: Both arterial and venous strokes.

vi. Developmental brain defects: Cerebral dysgenesis and neuronal migration disorders are rare causes of seizures in the neonatal period.

vii. Neonatal epileptic syndrome

ix. Neonatal abstinence syndrome

x. Miscellaneous: Causes are polycythemia, maternal narcotic withdrawal, drug toxicity (theophylline), accidental local anesthetic injection into scalp and phacomatosis like tuberous sclerosis and incontinentia pigmentii.

Pathophysiology[3]

The neurons within the CNS undergo depolarization as a result of inward migration of sodium. Repolarization occurs via efflux of potassium. A seizure occurs when there is excessive depolarization, resulting in excessive synchronous electrical discharge. There are 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.

Management

History related to neonatal seizure[1-3]:

i. Seizure History: A complete description of seizure should be obtained from the attendant. The day of onset of seizure may provide an important clue to its diagnosis. Seizures occurring on day 0-3 may be related to perinatal asphyxia, intracranial hemorrhage, metabolic and developmental defects. Seizures occurring on day 4-7 may be due to sepsis, meningitis, metabolic causes and developmental defects.

ii. Antenatal History: History suggestive of intra-uterine infection, maternal diabetes and narcotic addiction should be taken. A history of sudden increase in fetal movements may be suggestive of intra-uterine convulsions.

iii. Perinatal History: History of fetal distress, decreased fetal movements, instrumentation delivery, need for resuscitation in labor room, low Apgar scores (<3 at 1m) should be obtained.

iv. Feeding History: Lethargy, poor activity, drowsiness and vomiting after initiation of breast-feeding may be suggestive of inborn errors of metabolism. Late onset hypocalcemia should be considered in the presence of top feeding with cows' milk.

v. Family History: History of consanguinity in parents, family history of seizures or mental retardation and early fetal/neonatal deaths would be suggestive of inborn errors of metabolism.

Investigations [3-7]:

Important investigations include blood sugar, hematocrit, serum electrolytes (Na, Ca, Mg), arterial blood gas, anion gap, cerebrospinal fluid (CSF) examination (if indicated), ultrasound (USG) examination of the head and electroencephalography (EEG). CSF study is very important as meningitis can coexist with another etiology and seizure may be the first sign of meningitis. But lumber puncture may be withheld temporarily in severe cardio-respiratory compromise or in cases with severe birth asphyxia. USG is useful to pickup intraventricular hemorrhage, ventricular dilatation but is unable to detect sub-arachnoid hemorrhage and sub-dural hemorrhage.

EEG[3-7] has both diagnostic and prognostic role in seizures. It should be done as soon as the neonate

is stable enough to be transported for EEG, preferably within the first week. EEG can confirm a paroxysmal event as a seizure.

However, all seizures do not have abnormal EEG pattern, because of immaturity of the brain and inter ictal scalp recording may fail to pickup seizure activity. There is often poor correlation between the electrographic and clinical manifestations of neonatal seizures[7]. Digital continuous EEG monitoring is an essential tool to detect seizures. Continuous video EEG recording further increases the yield of positive EEG finding.

EEG is also helpful in prognosis of birth asphyxia & neuromotor outcome. The risk of recurrence increases in the presence of persistent EEG abnormality or slowly resolving EEG. Electrical seizure activity in neonatal period is rare before 34 to 35 weeks. Seizure discharges of the depressed brain are typically low in voltage, long in duration & highly localized. Alpha seizure activity indicates severe encephalopathy. Burst suppression pattern is suggestive of severe epileptic encephalopathy.

Some other investigations[3-7] are considered in neonates who do not respond to anticonvulsant or earlier in neonates with specific features. Neuroimaging can detect neonatal strokes, structural abnormalities and neuronal migration defect. A CT scan should be done in all term infants where an etiology is not available after the first line investigations and is diagnostic in sub-arachnoid hemorrhage. An MRI scan is usually not required and done only if investigations do not reveal any etiology and seizures are resistant to usual anti-epileptic therapy. It can be diagnostic in cerebral dysgenesis, lissencephaly and other neuronal migration disorders.

A TORCH screening and VDRL test is indicated in the presence of hepato- splenomegaly, thrombocytopenia, growth retardation, small for gestational age and chorioretinitis.

Metabolic screen[3]: Include blood and urine pH, urinary reducing substances, blood ammonia, anion gap, urine and serum aminoacidogram, and serum and CSF lactate/pyruvate ratio. Neurometabolic screening is now available in Bangladesh, which helps early identification & management of inborn metabolic errors causing seizures.

Modern investigations reveal the causes in more cases than before. Investigation needs to be individualized depending upon clinical presentation, perinatal history and physical examination.

Diagnosis[3]:

The first step would be to exclude non-epileptic event like jitteriness, benign sleep myoclonus and to differentiate between benign neonatal seizure groups from malignant epileptic syndromes.

Non-epileptic seizure events during neonatal period[1-8]:

i. Jitteriness is due to cerebral excitability and usually mimics clonic seizure.

Causes: Physiological, idiopathic, perinatal asphyxia, hypoglycaemia, hypocalcaemia, polycythaemia, drug withdrawal etc.

Symmetrical tremors of extremities which are stopped by grasping the hand or passive flexion of limbs, aggravates by touching.

Rate of tremor is identical in either direction (whereas in clonic seizures there is a rapid alteration of fast and slow phase of movement).

Eye movements are normal (staring, blinking, nystagmoid jerks or tonic horizontal eye deviation occurs during seizure but absent in jitteriness).

ii. Benign neonatal sleep myoclonus: The mechanism for such nonepileptiform myoclonus is unclear but may be related to a transient dysmaturity of the brainstem reticular-activating system. Presents in the first week of life. Always occur during sleep, rapidly abolished by arousal, never occur during wakefulness.

Precipitated by gentle rhythmic rocking or tactile stimuli. Preictal, ictal and post-ictal EEG is normal. Anticonvulsants are not indicated, rather benzodiazepam exacerbate myoclonic jerks.Resolves spontaneously over weeks to months. Long-term outcome is good and epilepsy does not develop later.

The benign neonatal seizure group includes benign familial neonatal convulsion and benign neonatal convulsion (Table-I).

The malignant group includes early infantile epileptic encephalopathy (Ohtahara's syndrome) and early myoclonic encephalopathy. Both these groups are differentiated from commonly occurring neonatal seizure by their characteristic clinical features and EEG changes (Table-II).

Table-I

Difference between two common benign neonatal seizures

	Benign neonatal familial convulsion	Benign neonatal convulsion
Seizure	Clonic or apnoeic	Clonic or apnoeic
Appearance	2nd / 3rd day (3rd day fit)	5th day (5th day fit)
Disappearance	1-6 months of life	15th day of life
EEG	Normal	Normal
Outcome	14% develop epilepsy later on	Normal
Inheritance	Autosomal dominant	None, Idiopathic

Table-II

Difference between two malignant seizures

	Early myoclonic encephalopathy	Early infantile epileptic encephalopathy (Ohtahara's syndrome)
Onset	Neonatal	1-3 months of life
Seizure	Myoclonic	Tonic spasm
Etiology	IEM	Anoxia, cerebral dysgenesis
Supression burst on EEG	Only in sleep	Both in awake and sleep
Evolution	West syndrome	West syndrome, LGS
Treatment	Benzodiazepines	ACTH, benzodiazepines, pyridoxine
Outcome	Refractory to Rx	Refractory to Rx

Treatment:

The decision to initiate antiepileptic drug therapy should be based on consideration of several factors like etiology and nature of seizure. Usually all abnormal paroxysmal clinical events in the newborn are considered as seizures and therefore neonatal seizures are over treated in an attempt to abolish all evidence of seizure activity[5]. But only epileptic seizures are to be treated. Epileptic seizures in addition to their classical presentations are associated with EEG changes and autonomic disturbances like alterations in heart rate, blood pressure, respiration, salivation, flushing, pupillary dilatations etc[1-3]. When epileptic seizures are of long durations (longer than one minute) and occur frequently (more than two in one hour) should be treated vigorously with antiepileptic drugs[4,5].

Electroclinical dissociation (state where clinical seizures disappears but EEG evidence persists after treatment) is common in neonatal seizure and the persistence of such electrographic seizure adversely affect subsequent developmental outcome[9,10]. To overcome this problem continuous digital video EEG monitoring has been advocated for management of such electrographic seizure. This facility is not available in most developing countries, keeping this view in mind, treatment strategies are outlined here.

Aetiologic search for acute symptomatic neonatal seizure should be done simultaneously with the treatment. Upon identification of common metabolic derangements like hypoglycaemia, hypocalcaemia, hypomagnesemia, they are treated as per following protocol. To correct hypoglycemia 10% glucose in water 2 ml/kg bolus is followed by continuous infusion at up to 8 mg/kg/min. To treat hypocalcemia IV calcium gluconate 10% 2ml/kg over 10 minutes with cardiac rhythm monitoring and 8 ml /kg/day is given as maintenance therapy. Hypomagnesemia is treated with 50% solution of magnesium in a dose of 0.2 ml/kg. The rest of the symptomatic seizures (non-metabolic) are treated with phenobarbitone (PB). If seizures failed to respond or recurs after PB therapy, phenytoin (PHT) should be given[10,11] (Fig.-1).

If seizures are still intractable (not responding to maximum loading doses of PB and PHT, continuous intravenous drip of either lidocaine or midazolam has been suggested. A trend for lidocaine to be more effective in reducing seizure burden was noted compared to midazolam[11]. Lidocaine has been extensively used in Europe whereas midazolam has been practiced in USA and UK.PB and PHT are equally effective in controlling seizure in less than 50% cases. The efficacy is increased to 60% when PHT was added to PB[4]. Lidocaine drip can be started with a loading dose of 2 mg/Kg given over 20 minutes followed by 4-6 mg/kg/hr in continuous drips. Midazolam can be started with an infusion rate 60-200 μg/kg/hr but very high doses up to 1000 μg/kg/hr had been used to control drug resistant neonatal seizure[11,12].

Diazepam (0.25-0.35 mg/kg IV or 0.5 mg/kg/rectal) has a very long half-life in babies (approximately 30-75 hours); because of the respiratory depressant effect diazepam is not suitable for prolonged infusions. Experience with lorazepam in newborn is limited[1]. Clonazepam causes increased salivation and bronchial secretion. Other agents given orally to control medically refractory seizures include carbamazepine, valproate, vigabatrin and lamotrigine; but their use in neonates is very much rare. Topiramate is also found to be effective and of less toxic but still are not in common practice[1,2].

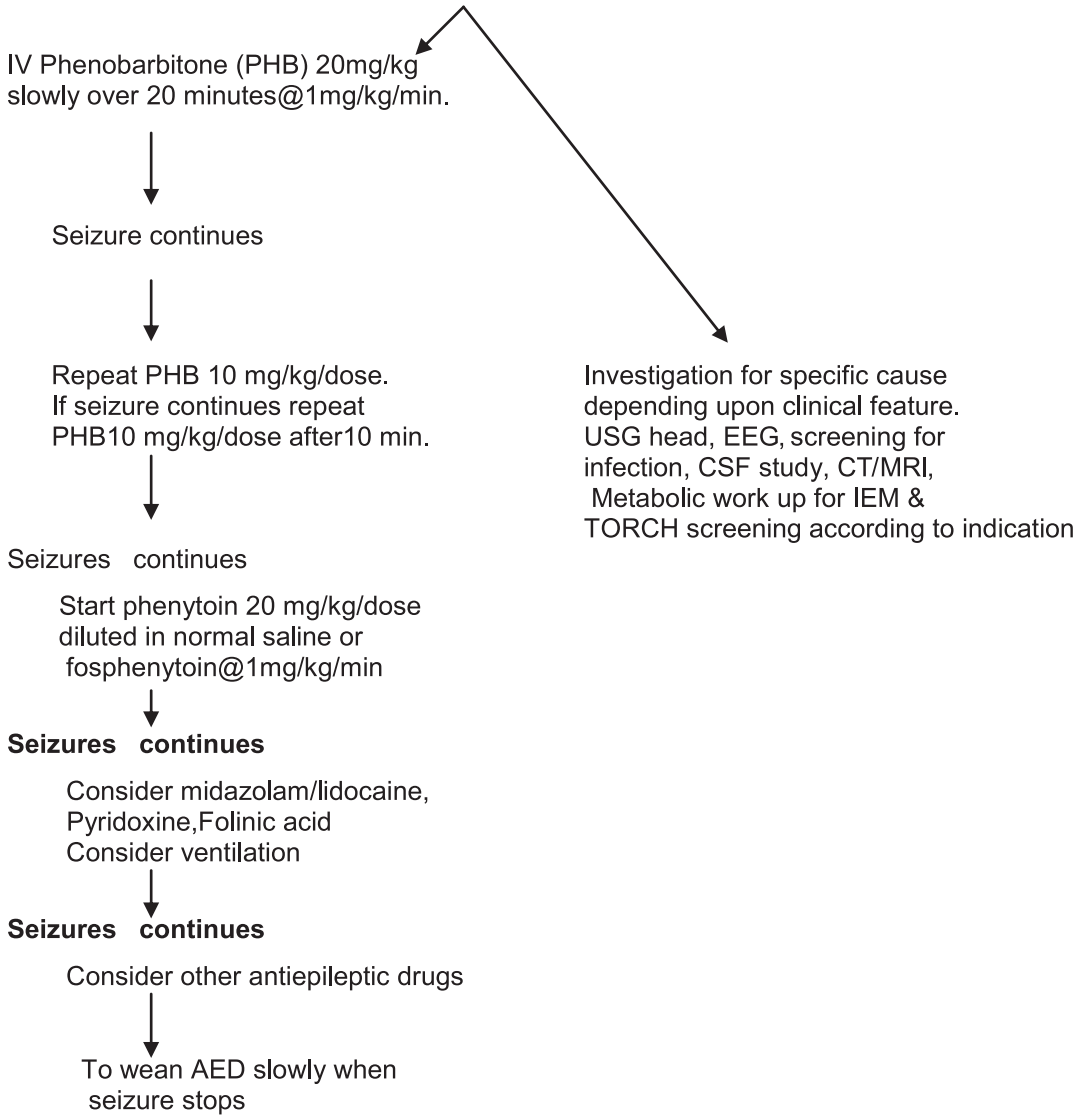
Once seizure control become difficult with above regimen, appropriate aetiological search should be made which commonly includes exclusion of pyridoxine related seizures(a therapeutic trial of iv 50-100 mg of pyridoxine followed by remission of seizures and normalization of EEG), folinic acid deficiency (a course of folinic acid 2.5 mg twice a day, increasing the dose up to 8 mg/kg/day may be required) and rare metabolic disorders[1,12] (Fig-1).

Maintenance therapy: The use of long-term antiepileptic drug (AED) as maintenance therapy for neonates after the acute seizures have been controlled, is not well standardized. There is no consensus guideline regarding optimum duration of long term treatment and type of AED[11,14-22]. Elimenation rates are particularly slow in asphyxiated infants where there is hepatic and renal involvement. However, elimination rates do increase with duration of therapy and dose may increase during maintenance therapy.

The maintenance is begun 12 hours after the loading dose. Phenobarbitone can be given IV/IM or per oral in two divided doses (12 hourly). Drug accumulation results within 5-10 days with a maintenance dose of 5 mg/kg/day. This effect may depress the infant significantly and relates to slow increase. Recent studies have shown increased apoptotic neurodegeneration in the developing rat brain after exposure to phenobarbitone, phenytoin and benzodizepines[16,17,19,23]. As phenobarbitone causes apoptosis, inhibits brain growth, impairs cognition and behviour, it should be used for the shortest time possible[24, 25].

Phenytoin should be given only by intravenous route. Intramuscular administration of phenytion can cause muscle necrosis. But fosphenytoin can be given IM or IV[1,2]. Oral administration of phenytoin is less reliable because of poor absorption. Maintenance administration of phenytoin in newborn is particularly difficult because of nonlinear kinetics and rapid decrease in elimination rates in the first weeks of life. Careful attention to levels is especially necessary when this drug is used for maintenance[18,19,22].

Fig.-1. *Flow diagram of management of neonatal seizure (To take blood glucose and calcium - to correct if abnormal)*

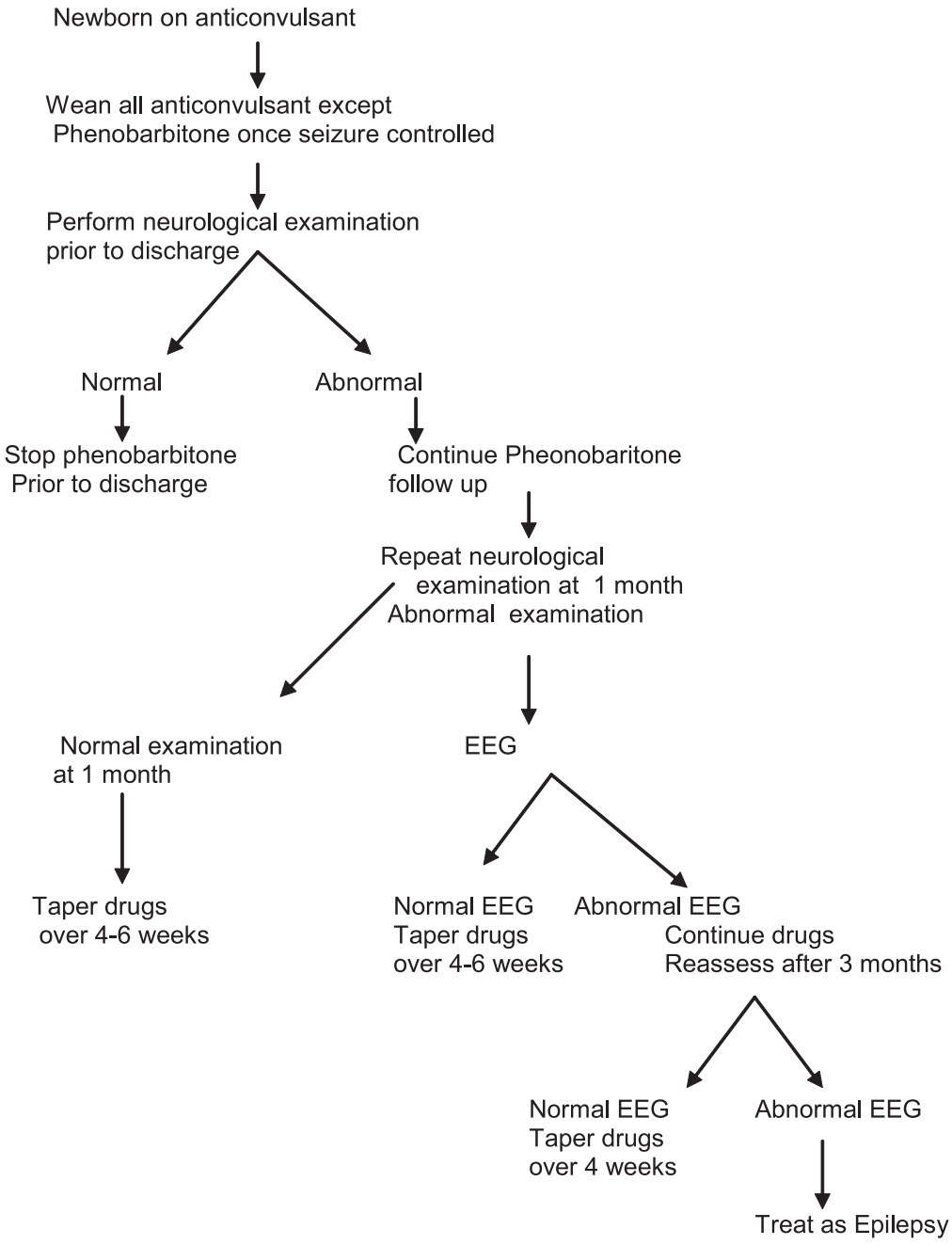


Duration of Therapy: Optimal duration of therapy is determined by underlying aetiology, recurrence rate, neurological status and EEG changes[18,19]. As the recurrence rate is relatively small and the potential toxicities are high on developing brain, the good practice is to stop anticonvulsant as early as possible. The common practice is to withdraw anticonvulsants before discharge home if the baby is neurologically normal on examination. Babies who are discharged home on anticonvulsant treatment, withdrawal is undertaken at the earliest opportunity when clinical neurological recovery occurs. In persistently neurologically abnormal infants, anticonvulsants may be continued for upto six months but an attempt should be made to withdraw phenobarbitone by that time, and, if seizure recurs, other appropriate anticonvulsant such as carbamazepine, topiramate and levetiracetam should be introduced.If a child receives AED for longer time, it should be tapered off gradually over 6 weeks[1-3,18,19] (Fig-2) .

Prognosis

Neonatal seizures have an adverse effect on neurodevelopmental outcome and predispose to cognitive, behavioral, or epileptic complications in later life[18,19]. Outcome of neonatal seizures varies

Fig.-2. *Flow Diagram on Weaning and Duration of Anticonvulsant Therapy*



with etiology; seizures due to sub arachnoid haemorrhage and late onset hypocalcaemia carry a relatively good prognosis than seizures due to hypoglycemia, cerebral malformations and meningitis [1-3]. The overall incidence of subsequent epilepsy is around 10- 20% and two thirds of the recurrences occur within first six months of life[18,19,25,] .

Conclusion

Immature brain of neonates is more epileptogenic than mature brain and seizure-induced injury to developing brain may lead to serious and significant problem[20]. So proper care is crucial. Controversies regarding drug choice have emerged. Electroencephalography remains the most useful investigation for diagnosis and prognosis. The search

for an effective antiepileptic treatment remains a challenge.

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