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Neonatal Seizures

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1. Introduction

A seizure is defined as paroxysmal disturbances in neurological function of neurons which manifested clinically as alteration in motor, behavioral and/or autonomic functions. No period carry the danger of seizures to the individual person like the first four weeks of life because of immaturity of brain cell which render it more vulnerable to injury and because of wide range of problem that might cause seizures operate in this period. Neonatal seizures tend to be brief, because immature neurons are unable to sustain repetitive activity for long period of time and to be focal or multifocal. It requires immediate evaluation because of the variable conditions that might insult developing and vulnerable neurons of neonate, some of which might endanger the life of neonate. Some time seizures might be the first and probably the only manifestations of underlying significant dysfunction of CNS of newborn infant. Furthermore, these seizures are sometime difficult to be diagnosed clinically resulting in delaying treatment and worsening short and long term prognosis. There is still a great debate about pathophysiology, clinical classification, EEG significance and treatment of neonatal seizures.

2. Incidence

Neonatal seizures are common: and the incidence is variable according to age and maturity of the neonate, weight and the severity of the underlying condition. The real incidence has not been established clearly, although it had been estimated that the incidence rate of clinical seizures varies from 1.1 to 8.6 per 1000 live births [1 - 3]. Preterm newborn exhibits higher risk for neonatal seizures than term newborn and both lower birth weight and gestational age confers increased risk [2, 4, 5]. In term infant the incidence range from 0.7 to 2.7 per 1000 live births and from 57.5 to 132 per 1000 live births in preterm infants [6,7]. In those weighing less than 1,500 g, the incidence ranges from 19 to 57.5 per 1,000 live births, While in infants who's weight more than 2,500 g, the incidence is as low as 2.8 per 1,000 live births [3]. Scher and colleagues reported that seizures occurred in 3.9% of neonates of less than 30 weeks' conceptional age and 1.5% in neonates older than 30 weeks [8, 9]. Additionally, seizures may account for up to 3.4 % of all admission to neonatal intensive care unit [7].

3. Pathophysiology

A clinical seizure results from excessive synchronized depolarization of the neurons within the central nervous system resulting in excessive synchronous electrical discharge. Why this

excessive depolarization of the neurons might occur remains unknown. Theories were suggested include the following:

1. Imbalance between excitatory and inhibitory neurotransmitter like excessive excitatory amino acid (e.g. glutamate) or deficient inhibitory neurotransmitter (e.g. Gama Amino Butyric Acid, GABA) [10].
2. Failure of energy production due to disruption of ATP dependent resting membrane potentials resulting in failure of sodium potassium pump which in turn leading to movement of sodium into the neuron and potassium out of the neuron.[11,12]
3. Neuronal hyper excitability state in the neonatal period, as evidenced by the extremely low threshold to seizures in general and that this is the period of highest incidence of seizures across the life span [13, 14]. Among the factors that cause increase excitability are incomplete myelination and neuropeptides particularly corticotrophin releasing hormone (CRH) [15, 16].
4. Experimental and clinical evidence exists for early microglial activation and inflammatory cytokine production in the developing brain in both hypoxia/ischemia [17,18] and inflammation [19,20] Importantly, microglia have been shown to be highly expressed in immature white matter in rodents and humans during cortical development [21].
5. Genetic predisposition as most of the cases of Benign Familial Neonatal Seizures (BFNS) are due to mutations in two genes, *KCNQ2* and *KCNQ3*, which encode subunits of a type of voltage-gated potassium ion (Kv) channel. Of about 70 BFNS families so far studied genetically, 60% have mutations in *KCNQ2*, and 5% have mutations in *KCNQ3*. The cause in the remaining cases is unknown. Some are likely due to mutations in portions of the *KCNQ2* and *KCNQ3* genes that do not encode amino acids but may affect channel expression (e.g., enhancers, promoters, introns). It is possible that one or more additional BFNS genes remain undiscovered [22].
6. Idiopathic as in the cases of Benign Non Familial Neonatal Seizures (BNFNS), also called fifth day disease were the pathophysiology remains unknown [23, 24].

4. Causes

The causes of neonatal seizures are divers and voluminous. It covers the entire spectrum of neurological disorders of the newborn. In practice, knowing the cause is vital for neonatologist regarding therapeutic and prognostic issues. For example, neonatal seizures due to transient metabolic disorders of newborn like hypocalcemia and hypoglycemia are easily to be treated by correction of metabolic derangement and are usually associated with favorable outcome regarding neurodevelopment and future epilepsy risk. In contrast, neonatal seizures caused by structural abnormalities of the brain are difficult to control and associated with poor outcome. The causes of neonatal seizures can be grouped under the following heading (table 1):

1.	**Brain insults**
a.	Hypoxic ischemic encephalopathy
b.	Intracranial infections
c.	Intracranial hemorrhage

	d. Cerebrovascular infarction
	e. Structural malformation of brain
2.	**Metabolic disorders**
	a. Hypocalcemia
	b. Hypoglycemia
	c. Hyponatremia
	d. Hypernatremia
	e. Pyridoxine deficiency
3.	**Inborn error of metabolism**
	a. Urea cycle disorder
	b. Aminoacidopathies
	c. Biotinidase deficiency
	d. Mitochondrial disorder
	e. Defects in beta oxidation
	f. Glucose transporter deficiency
	g. Peroxisomal disorder
	h. Pyridoxine deficiency
	i. Non ketotic hyperglycinemia
4.	**Neonatal epileptic syndrome**
	a. Benign idiopathic neonatal seizures
	b. Benign familial neonatal seizures
	c. Ohtahara's syndrome
	d. Early myoclonic encephalopathy
5.	**Miscellaneous**
	a. Polycythemia
	b. Accidental local anesthetic drug injection
	c. Withdrawal syndrome
	d. Drug toxicity

Table 1. Causes of neonatal seizures

1. **Brain insults**: *hypoxic ischemic encephalopathy* is the most common cause of neonatal seizures accounting for about two third of all cases [25, 26]. The seizures are usually begin within the first 24 hours after birth and are associated with obtundation [27, 28, and 29]. In one study, 60% of these neonates developed seizures within the first 12 hours [30]. The frequency and the severity of seizures are usually parallel to the severity of the encephalopathy and about one third of them will be epileptic in the future [25]. The seizures types include subtle (the most common), focal and multifocal clonic and myoclonic. *Intracranial infection* account for 5 to 10 % of seizures [31]. Could be acquired prenatally or postnatally and it is more common in developing countries. Bacterial meningitis usually causes seizures later in the first post natal week (late onset) [32], the most common bacterial pathogens are group B streptococci, listeria, Escherichia coli and other gram negative bacteria. Congenital infection caused by such pathogen as toxoplasmosis, rubella and CMV virus may cause seizures which may be the sole manifestation but it usually tend to occur later in the neonatal period or early infancy. Encephalitis caused by various viruses such as herpes simplex virus (HSV) and enteroviruses may cause seizures. Some of these viruses acquired from birth canal during labor and other from the environment. HSV encephalitis is one of the most

important viruses causing encephalitides in the neonatal period. Seizures tend to occur in 57% of neonate who have CNS disease and 22% of neonate who have the disseminated form of the disease but rarely in the skin eye mouth disease form [33]. The neonatal form of HSV encephalitis is caused more often by type 2 HSV that the newborn acquires during delivery from maternal genital lesions. Fetal scalp monitoring may be a risk factor for acquiring the virus. Neuroimaging studies in neonatal HSV encephalitis often show diffuse brain abnormalities [25]. Because of the severity of the condition and poor outcome, any patient with neonatal seizure and suspected to have neonatal HSV, appropriate diagnostic tests should be obtained and the empirical acyclovir therapy should be initiated immediately. *Intracranial hemorrhage* account for about 10% of all cases of neonatal seizures [27]. In preterm infants, small intraventricular hemorrhage limited to the germinal matrix do not result in seizures, usually they present with poor activity and feeding with unexplained drop of hematocrit. When the hemorrhage is extensive, the seizures are a common correlates and may account for 45% of preterm infants who had EEG documented seizures [28]. Persistent tonic seizures are the most typical but subtle seizures can also occur. They commonly occurs between 3-7 days of age [32]. In full term neonates, subarachnoid, subdural and intraparenchymal hemorrhage are common causes. Subarachnoid hemorrhage tends to occur in healthy looking full term infant delivered vaginally. Classically seizures occur in the second day and have been named as well –baby with seizures [34]. They resolve rapidly with good prognosis. On the other hand, subdural hematomas are usually results from trauma and commonly associated with cerebral contusion. Focal rather than multifocal seizures are common and they tend to occur in the first two post natal days. Subdural hematoma after the second day of life in a neonate who was discharged from hospital should raise the possibility of non accidental injury. *Cerebrovascular infarction* is another cause of neonatal seizures and it can results from both arterial and venous occlusion. Arterial occlusion causes infarction of area supplied by a single artery. The middle cerebral artery is most frequently involved. Risk factors include trauma, congenital heart disease, coagulopathy and metabolic disturbances. Arterial occlusion leads to porencephalic cyst which in cases of multiple vascular involvement can leads to encephalomalacia and hydraencephaly. Focal neurological seizures are common and the neonate has abnormal neurological examination. The severity and localization of seizures are variable according to the location and the extent of infarction. On the other hand, cerebral venous thrombosis might result in seizures in 68% [35]. The occlusions usually occur in the superior saggital sinus, sigmoid/transverse sinus or multiple venous sinuses [25]. Polycythemia, dehydration, persistent pulmonary hypertension, infections, thrombophilic disorders and Extracorporeal membrane oxygenation [36, 37] are among the documented risk factors for venous thrombosis. *Structural malformation of the brain* is another cause for neonatal seizures. In one study they account for 1.8% of studied cases [38]. Fifty percent of patients with holoprosencephaly (failure of complete separation of cerebral hemispheres and deep gray nuclei) have neonatal seizures [39]. Lissencephaly (malformation of the brain in which the cortical surface is smooth or contain thick broad gyri) is commonly associated with seizures which are usually refractory to treatment [40]. Cerebral dysgenesis and neuronal migration disorders are rare causes of seizures in the neonatal period, they may be caused by a specific inborn error of metabolism that disturbs early fetal development. For example, nonketotic hyperglycinemia, pyruvate dehydrogenase deficiency, and maternal hyperglycinemia frequently are associated with corpus callosal dysgenesis while peroxisomal disorders

and fatty acid oxidation defects have been associated with migration abnormalities [25, 41]. Neurocutaneous syndromes like tuberous sclerosis and Sturge Weber syndrome might also present neonatal seizures.

2. **Metabolic disorders:** can also cause neonatal seizures. The severity of neurological symptoms is directly correlated with the duration of metabolic disturbances (42). Hypocalcemia nowadays account for about 3% of all cases of neonatal seizures, mostly are focal and occurs in the first 72 hours of life (29, 43). Most common causes are low birth weight especially those associated with intrauterine growth retardation, infants of diabetic mothers, and hypoxic ischemic encephalopathy. The incidence of hypocalcemia is inversely proportional to gestational age and birth weight. Other causes of hypocalcemia include maternal hypercalcemia, primary hypoparathyroidism, X linked hypoparathyroidism and DiGeorge syndrome (43). Hypomagnesaemia often associated with hypocalcemia, but it does not seem to cause seizures in isolation without hypocalcemia (25). One study shows that approximately 50% of cases being associated with congenital cardiac defects which if present should raise the possibility of particular causes of hypocalcemia such as DiGeorge syndrome (44). Hypoglycemia is another cause of neonatal seizures; common causes include intrauterine growth retardation, prematurity, infant of diabetic mothers, birth asphyxia, intracranial hemorrhage and infection. The most common symptoms of hypoglycemia in intrauterine growth retardation, in addition to seizures, are jitteriness, hypotonia, stupor and coma (45). Seizures and other neurological symptoms are rapidly relieved by correction of hypoglycemia. Failure of relieving seizures and hypoglycemia after adequate correction should raise the possibility of underlying metabolic or endocrine problems. Hyponatremia, hypernatremia and pyridoxine deficiency can also produce neonatal seizures but are less common.
3. **Inborn errors of metabolism:** are relatively rare causes of neonatal seizures. They should be suspected in any healthy neonate who deteriorates and develop encephalopathy and seizures after initiation of feedings. Metabolic disorders that can cause neonatal seizures include *urea cycle disorder, aminoacidopathies, biotinidase deficiency, mitochondrial disorders, defects in beta oxidation, glucose transporter deficiency and peroxisomal disorder*. Disturbances of amino acid or organic acid metabolism are often the most common inborn errors of metabolism that present with neonatal seizures [42]. Some of these disorders are treatable and some are not. *Pyridoxine dependency* is a rare disorder of pyridoxine metabolism , that produces sever seizures in the first few days of life and are resistant to antiepileptic drugs but can controlled with high dose of intravenous pyridoxine [46-50]. On the other hand neonatal *non-ketotic hyperglycinemia* (glycine encephalopathy) is a rare non treatable cause of neonatal seizures due to a defect in cleavage of the excitatory amino acid glycine. It usually present with myoclonic seizures in the second or third day of life associated with static encephalopathy [51].
4. **Neonatal epileptic syndromes:** these includes *benign idiopathic neonatal convulsions* or called fifth day fits which was first described by Dehan and colleagues in 1977 [52]. They may account for as many as 5% of seizures in the full term neonates [42]. It usually appears in otherwise healthy full term infants in the first week of life (mostly 4-6 days) and resolve within 24 to 48 hours after onset. The seizures are usually brief (1 to 3 minutes) but rarely prolong and might end with status epilepticus. They are mostly focal clonic and rarely focal tonic, fluctuating between right and left, and the infant is normal between the attacks. History and examination of neonate is normal, family

history is negative and they have no subsequent increase risk of epilepsy but some studies report increased risk of minor neurological impairment [53,54]. The etiology remain unknown, many theories had been postulated including zinc deficiency [55], rotavirus infection [56] and mutations in the neuronal potassium channels KCNQ2 [57], but none were confirmed. The interictal EEG shows a theta pointu alternant pattern. The EEG background consists of predominantly sharply contoured theta (4 to 7 Hz) activity that is discontinuous and intermixed with other sharp activity [25]. The diagnosis is that of exclusion and the treatment with anticonvulsant is controversial. *Benign familial neonatal convulsions* are rare disorder of autosomal dominant inheritance with incomplete penetrance, usually occurs in the first week of life after an initial seizure – free period. The neonate is otherwise healthy but with family history of neonatal seizures [58-60]. The seizures are focal clonic or focal tonic, sometimes associated with apnoeic spells or eye deviation to one side. The interictal EEGs can be normal, but ictal findings typically consist of an initial electrodecremental event (flattening of the EEG) followed by bilateral spike and slow wave discharges, often accompanied by rhythmic clonic activity [59]. Two chromosomal loci were implicated: one on chromosome 20q13[61] and one on chromosome 8q[62-64] and the Genes responsible for this disorder are potassium channel genes, referred to as KCNQ2 for the chromosome 20q gene [65,66] and KCNQ3 for the chromosome 8q gene[64]. There is no consensus on the treatment, some use phenobarbital to control acute seizures and continued for the first 3 months [22]. Two sever catastrophic epileptic syndromes have also been identified in the neonatal period namely Ohtahara's syndrome and early myoclonic encephalopathy. Both can present with seizures shortly after birth usually in the first 10 days. The infants with these two encephalopathies have sever neurological disease, with developmental delay and intractable seizures [42]. Seizures in *Ohtahara's syndrome* characterized by frequent tonic spasms (100-300 per day) often in clusters[67]and the EEG characterized by burst suppression pattern, both in sleep and waking. The etiology is usually related to malformation of cortical development like Aicardi syndrome or porencephaly. The seizures are resistant to treatment and the prognosis is poor and they may evolve into infantile spasms. On the other hand, seizures in *early myoclonic encephalopathy* characterized initially by fragmentary myoclonic jerk which replaced later by partial seizures, massive erratic myoclonus and infrequently tonic seizures [25]. The EEG characterized by burst suppression pattern, with periods of suppression (4-12 sec) that are seen during sleep [68]. The etiology may be related to inborn error of metabolism especially propionic academia, non ketotic hyperglycinemia and D-glyceric acidemia [68-70]. The seizures are resistant to treatment, the infants are severely neurologically abnormal and they may die early in the first year of life.

5. **Miscellaneous:** cause include polycythemia, accidental local anesthetic drug injection in the scalp, withdrawal syndromes associated with maternal drug use, and the drug toxicity like theophylline. Recently, neonatal seizures provoked by electrolyte abnormalities secondary to dehydration and renal failure from intestinal obstruction secondary to congenital duodenal atresia had been reported [71].

5. Clinical manifestations and classification

Clinically neonatal seizures are different in manifestations and classification when compared with older infants, children and adult. The reasons for this difference are related to difference in mechanisms causing seizures in immature brain and incomplete myelination

of neurons. Most seizures are subtle, difficult to be recognized and can easily be mistaken for common normal rhythmic and jerky neonatal behaviors. It might be fragmented, disorganized with abnormal spread leading to a multi focal appearance. Generalized tonic clonic seizures are very rare if ever occur in neonatal period because the arborization of axons and dendritic processes as well as myelination is incomplete in the neonatal brain. A seizures discharge, therefore, cannot readily be propagated throughout the neonatal brain to produce a generalized seizure [72]. The five clinical types of neonatal seizures adopted by Volpe [73] are the most widely accepted classification, these include;

Subtle: are the most common type in both term and preterm neonates, constitute about 50% of all neonatal seizures. Usually they manifest as mild paroxysmal alteration in behavioral, motor or autonomic function that are not clonic, tonic or autonomic and they are commonly missed or mistaken for normal neonatal behavior. They are often originated in subcortical area and have no EEG correlate. The most common manifestations are:

- *Ocular*: are the most common clinical findings in both term and preterm neonates. They are usually consisting of staring, horizontal or vertical sustained deviation of the eyes or eye blinking.
- *Oral:* can manifest as swallowing movement, tongue thrust, lip smacking or chewing movement.
- *Limb*: manifest as bicycling of legs, boxing or swimming movement of the arms or other stereotypic limb movement.
- *Autonomic*: include alteration in blood pressure and/or heart rate, excessive salivation, pupillary dilatation and central apnea associated with tachycardia.
- *Apnea*: is a rare manifestation of neonatal seizures, commonly associated with normal or exaggerated heart rate when evaluated within 20 second after the onset. It is more common in term infant and usually associated with eye signs. Apnea alone in preterm neonate should raise the possibility of other underlying problem than neonatal seizures.

Most of subtle seizures occurs in combination and prolong video EEG monitoring failed to demonstrate any associated abnormal electrographic discharge [27, 74].

Clonic: are more common in term than preterm neonates and usually associated with electrographic seizures. They involve abnormal slow rhythmic movement of group of muscles of face, neck, limbs or trunk involving one side of body or both sides simultaneously in a non synchronous manner.

Multifocal clonic: are clonic seizures occurring in several parts of the body. Also they are seen primarily in term neonates figure 1.

Clonic and multifocal clonic are easily to be diagnosed clinically but sometime they may be difficult to be differentiated from non epileptic movement s like jitteriness.

Tonic: they involve sustained flexion or extension of axial or appendicular muscles groups. It could be focal or generalized. The generalized tonic seizures can result in a posture resemble that of decerbrate (tonic extension of all limbs) or decorticate (tonic flexion of upper limbs and tonic extension of lower limbs). The generalized tonic seizures are usually associated with normal EEG tracing. On the other hand, focal seizures are characterized by sustained posturing of single limb or sustained a symmetrical posturing of the trunk or eyes usually accompanied by apnea, flushing or cyanosis. Usually the EEG is abnormal in focal tonic seizures [75].

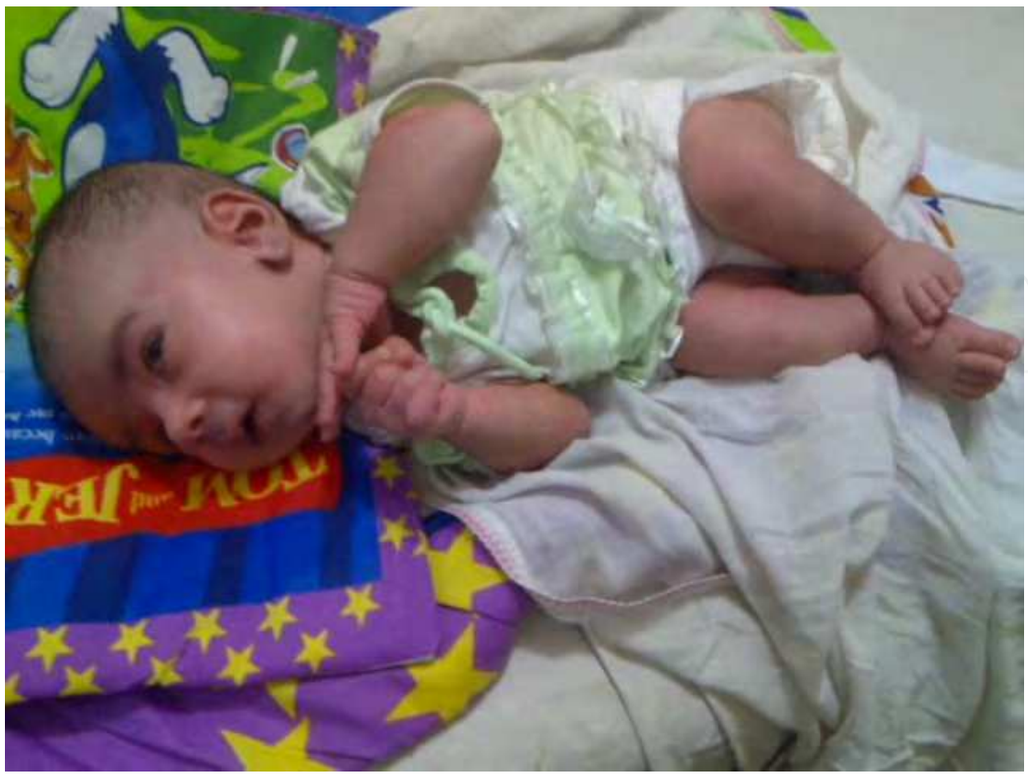

Fig. 1. Multifocal clonic fit with involvement of muscle of face, neck, trunk and limbs. Written informed consent was obtained from parents.

Myoclonic: these manifests as random single rapid contraction of groups of muscle the limbs, face, or trunk. It might be generalized, focal or fragmentary [75]. Occurrence at more rapid speed and predilection for flexor group of muscles can distinguish it from clonic seizures. EEG might be normal or shows changes including burst suppression pattern, focal sharp wave and hypsarrhythmia. If the myoclonus is related to sleep or hypoxic ischemic injury, the EEG shows no abnormal changes [27, 30, 76]. Myoclonic neonatal seizures carry the worst prognosis regarding the neurodevelopmental out come and some of it might progress to infantile spasm.

These clinical types of neonatal seizures should be differentiated from the more common repetitive, rhythmic and jerky movement made by normal newborn. Provoking by stimulation, elimination by passive flexion or soothing touch and presence of normal heart rate of value in differentiation.

Other classification of neonatal seizures depends on correlation between clinical events and occurrence of electrical seizures activity on EEG trace

- Electroclinical: when the clinical events overlaps in time with electrographic seizures activity.
- Clinical only: when the clinical events occurs in the absence of any EEG seizures activity. It's significant is not clear.
- Electrographic only: EEG shows electrical seizures without any coincidental clinical seizures activity. There is evidence that they have a similar impact on long term outcome as electroclinical seizures [77.78].

6. Investigations

Neonatal seizures are one of the neonatal emergencies that are required urgent treatment and evaluation. Because of the wide range of differential diagnosis, investigations should be guided by history and clinical examination but some investigations should be obtained in nearly all neonates with seizures. These investigations include basic biochemistry test, CSF, neuroimaging and EEG. Other tests might not be needed routinely and are suggested by history and clinical examination such as screening for TORCH, inborn error of metabolism and intoxications. The goal of determining the cause of neonatal seizures is to treat and prevent cases and to determine the prognosis. The investigations can be grouped under the following heading:

- **Septic screen**: because infections are common and readily treatable cause of neonatal seizures, investigations such as blood culture, urine culture and CSF analysis should urgently obtained when we suspect such cases as meningitis, ventricullitis and brain abscess. In such cases, empirical antibiotics should be started pending the results of investigations. When viral encephalitis is suspected especially herpes simplex virus, investigations including PCR and viral culture for HSV should be obtained while the neonate is empirically treated with antiviral agent such as acyclovir.
- **TORCH screening:** should be considered in any neonate with seizures and stigmata of congenital infection as micro or hydrocephaly, hepatosplenomegaly, skin rash, small for gestational age, thrombocytopenia and chorioretinitis.
- **Metabolic screen:** including serum electrolyte (Na, Ca, and Mg), blood sugar, arterial blood gas, anion gap, urine pH and reducing substances, blood ammonia for urea cycle abnormalities, urine and serum aminoacidogram, serum and CSF lactate/ pyruvate ratio and screening test for various inborn error of metabolism. A persistent metabolic acidosis suggests an organic acidemia.
- **Neuroimaging:** these investigations can detect neonatal strokes, structural abnormalities, intraventricular hemorrhage and neuronal migration defects. It includes skull X ray, ultrasound, CT scan and MRI. The choice of neuroimaging is frequently debated [25]. *Skull X ray* is of limited value but can shows intracranial classification in suspected TORCH infection. *Cranial ultrasound* is the test of choice when the patient is in critical condition and he or she suspected to have intracranial pathology. The advantages are that it is readily available in most centers, can be done at bedside and in most of the time there is no need for anesthesia but it is limited by its low resolution and its ability to assess cerebral cortex. *CT scan* is very helpful to exclude intracranial hemorrhage, infarction, structural abnormalities of the brain and hydrocephaly. *MRI* is indicated when other tests not revealed the underlying pathology and the seizures is refectory to antiepileptic drugs. It can be diagnostic in Lissencephaly, cerebral dysgenesis, neuronal migration defects and it's the study of choice for pattern of hypoxic ischemic brain injury [25]. For symptomatic seizures cause by HIE, abnormal T2, fluid attenuated inversion recovery, and diffusion signals can be used to pinpoint regional injury and severity [79]. Some studies revealed that magnetic resonance spectroscopy can be used to predict the severity and prognosis in those patients [80, 81].
- **Electroencephalography:** It should be done in all neonates with seizures requiring anticonvulsant therapy. It has both diagnostic and prognostic value. The EEG definitions vary, but paroxysms are considered to be seizures if they last more than 10 seconds [82]. The typical duration of the electrographic neonatal seizures is 2-3 minutes [83] but many seizures is shorter particularly in preterm infants [84]. Although focal sharp

waves may be present interictally in the neonatal EEG, they are not considered epileptiform. Some focal sharp waves are normal features of the neonatal EEG, such as frontal sharp transients and some temporal sharp waves [85]. On the other hand, not all neonatal seizures have abnormal EEG pattern, because of immaturity of the brain and interictal scalp recording may fail to pickup seizures activity especially those originated at subcortical level and are not propagated to surface electrodes [86] or some subtle and tonic seizures might not be epileptic but are primitive brain stem and spinal motor phenomena [76]. There is often poor correlation between the electrographic and clinical manifestations of neonatal seizures [87]. The background EEG activity can provide information concerning degree of associated central nervous system dysfunction, potential risk of seizures and prognosis. The degree of abnormality of the interictal background activity may suggest the extent and type of CNS dysfunction associated with seizures. The nature of the interictal background activity may also indicate the potential risk the individual infants have in experiencing a seizure [85, 88]. Video EEG monitoring has proved to be a powerful tool in diagnosis and management of neonatal seizures and as well as in clinical research. It is now becoming more available at many centers for routine use and more widely employed in neonatal intensive care units [85].

7. Diagnosis

Diagnostic evaluation for neonates with seizures should be performed in a stepwise manner starting with exclusion of conditions that might simulate seizures. *Jitteriness* is the most common neonatal movement that might mistaken for seizures. It is due to cerebral excitability and usually mimics clonic seizures. Common causes include hypocalcemia, hypoglycemia, hypoxic ischemic encephalopathy; infant of diabetic mother, polycythemia, drug withdrawal or idiopathic were no cause can be identified. It consist of fast tremor of one or more extremities that can be easily differentiated from seizures by the facts that it can be provocated by stimulation of the infant or stretching of a joint, terminated by holding or passive flexion of the limb, absence of eye signs, absence of autonomic changes especially tachycardia and finely by absence of EEG correlate. *Benign neonatal sleep myoclonus* is more commonly occur in preterm. The mechanism is unknown but might be related to a transient dysmaturity of the brain stem reticular activating system [87]. It present in the first week of life, always in sleep during rapid transmission from wakefulness to REM sleep or from REM to quite sleep. It might be induced by stimulation associated, commonly associated with sucking or stretching activities and can be rapidly abolished by arousal. The EEG is normal. *Apnea* especially if occur alone in preterm infant might be due to causes other than neonatal seizures. It usually associated with bradycardia in contrast with seizures where tachycardia is common. *Opisthotonos* consist of prolong arching of the back, might be mistaken for tonic seizures but absence of abnormal eye movement is useful for differentiation. Common causes include meningitis, intracranial hemorrhage and kernicterus. *Neonatal hyperekplexia* also known as startle disease, hyperekplexia is a rare disorder characterized by generalized muscle rigidity in the neonate, nocturnal myoclonus and an exaggerated startle reaction to auditory, tactile and visual stimuli. The startle reaction is a normal response to stimuli that consists of facial grimace and blinking followed by flexion of the trunk. The startle response is exaggerated when it interferes with normal activities, and causes apnea and frequent falls [89].

8. Treatment

The most important factor in determining the treatment in neonatal seizures is the recognition of underlying cause of the seizure. Some cases require only correction of the associated metabolic disturbances like hypocalcemia or hypoglycemia without the need for anticonvulsant drugs. On the other hand, some refractory cases require multiple anticonvulsant therapy in combination. Some causes of neonatal seizures may have more than one mechanism in producing seizures as in cases of hypoxic ischemic encephalopathy were brain injury and metabolic disturbance might play a role in producing seizures. This fact should be taken in consideration while managing a neonate with seizure.

There is a great debate whether a clinical – electrographic correlation is necessary to start vigorous treatment with anticonvulsant medication. Animal data indicate that both clinical and electrographic seizures may have long term behavioral and cognitive consequences on the immature brain. This may indicate aggressive anticonvulsant treatment for all seizures. Treatment of newborn with seizure involves:

1. **General supportive measures**: basic medical emergency principles should be applied to establish airway and breathing and to maintain circulation. Oxygen should be given if the seizures are prolonged and an intravenous line access should be secured for administrations of drugs and drawing blood for baseline investigations.
2. **Treatment of associated metabolic disturbances**:

2.1 **Hypocalcemia**: should be treated by slow intravenous infusion of 2ml/kg of 10% Ca gluconate at a rate of 1 ml/minute under strict monitoring heart rate. The dose can be repeated in 10 minutes if no response occurs. If ionized calcium level is suggestive of hypocalcemia, the Ca gluconate should continue for 3 days at a rate of 8 ml/kg/day. If despite of correction of serum calcium the neonate continue to have seizures, 0.2 ml/kg of 50% magnesium sulphate (50 mg/kg) should be given intramuscularly. The dose can be repeated every 12 hours until normalization of serum magnesium is achieved.

2.2 **Hypoglycemia:** animal studies revealed that glucose administration just before seizures prevents the decrease in brain glucose level that occurs with status epilepticus and markedly decrease mortality and neuronal cell loss [90]. Blood glucose should be obtained immediately and if there is hypoglycemia, 2 ml/kg bolus of 10% glucose in water should be given followed by continuous infusion of glucose at a rate of 6-8 mg/kg/minute. It is important to avoid hyperglycemia by frequent checking of blood glucose.

2.3 **Pyridoxine dependency:** dramatic response to intravenous 100 mg of pyridoxine used empirically in refractory seizures is highly suggestive of pyridoxine dependency this can be confirmed by continuous EEG monitoring.

2.4 **Anticonvulsant:** if the seizures persist or are recurrent, anticonvulsant drugs should be started. The most widely used drug for neonatal seizures is phenobarbitone which together with benzodiazepines (diazepam and lorazepam) and phenytoin (or Fosphenytoin) regarded as first line therapy (table 2).

Phenobarbitone: is the drug of choice for neonatal seizures by most centers. It is given as initial intravenous loading dose of 20 mg/ kg. If the seizure is persist after completions the loading dose, repeated doses of 5-10 mg/ kg every 20-30 minute until a clinical response or maximum dose of 40 mg / kg has been given. The highest therapeutic serum level of 180 μmol/L should not be exceeded. The maintenance dose is 3 – 5 mg/kg/day in 1-2 divided doses, started 12 hours after the loading dose. Careful monitoring of cardiac and respiratory

function is necessary. Some studies, using continuous video EEG monitoring reveals a clinical control in only 30-40% [91, 92]. The reminder might experienced a reduction in the electro-clinical seizures but increased the number of electrographic seizures [92, 93]. The use of phenobarbitone as prophylactic for neonatal seizures in birth asphyxia is debatable. One study reveals a better neurodevelopmental outcome at 3 years of age after 40 mg/kg phenobarbitone used as prophylactic in a term neonates with perinatal asphyxia [94]. Another study revealed immediate adverse effects to phenobarbital used as prophylactic therapy in term newborn with perinatal asphyxia at a dose of 10 mg/kg [95]. The phenobarbitone should be used for the shortest possible period of time because of the possibility of phenobarbital induced neurodegeneration, inhibition of brain growth and impaired cognition and behavior [96, 97].

Drug	Rout	Dose
First line drugs		
• Phenobarbitone	IV	Loading 20 mg/kg Maintenance 3 – 5 mg/kg/day
• Phenytoin	IV infusion	Loading 20 mg/kg Maintenance 2 – 3 mg kg/day
• Benzodiazepines Diazepam	IV injection , infusion or rectal	0.3 mg /kg bolus followed by o.3 mg/kg/hour infusion 0.5 mg/kg rectally
Lorazepam	IV injection	0.05 – 1 mg/kg
midazolam	IV injection and infusion	Loading 0.15 mg/kg followed by infusion 0.1 – 1.4 mg/kg/hour
Second line drugs		
• Lidocaine	IV infusion	Loading 2 mg/kg followed by 4 – 6 mg/kg/hour
• Levetiracetam	Oral Intravenous	Initial dose 10 mg/kg increased to 30 mg/kg
• Carbamazepine	Oral	10 mg/kg initially followed by 15 – 20 mg/kg/day
• Valproic acid	intravenous , rectal	Loading 20 – 25 mg/kg/day followed by 5 – 10 mg/kg/12 hourly
• Vigabatrin	Oral	50 mg /kg/day

Table 2. Anticonvulsant drugs used in neonatal period.

Phenytoin: is the second most commonly used drug as first line therapy for neonatal seizures. It is given as a loading dose of 20 mg/kg by slow intravenous infusion, not more than 1 mg / kg / minute followed by maintenance dose of 2-3 mg/kg/day intravenously in 2-4 divided doses. The drug should not be dissolved in dextrose as it precipitated in it and the intravenous line should be washed with normal saline before given the medication if the neonate receiving glucose water. There should be a close monitoring of the cardiovascular system for arrhythmia and hypotension. One study compared the effectiveness of phenytoin and phenobarbitone in controlling neonatal seizures found no significant difference between

the two drugs [98]. Another double blind prospective study shows phenytoin as effective in controlling neonatal seizures in 43% when use alone as first line drug and the efficacy is increased to 63% when combined with phenobarbitone [92]. Furthermore, another study revealed that 30% of neonates continued to have electrographic seizures despite full loading doses of both phenytoin and phenobarbitone [99]. Fosphenytoin is a prodrug of phenytoin has the advantages higher water solubility and lower pH, which, in addition to the lack of toxic vehicles required for its formulation, reduce local irritation of skin and blood vessel at the site of infusion, this will also avoid purple glove syndrome which represent the soft tissue necrosis and injury which occur with highly alkaline poorly soluble intravenous phenytoin [100]. Fosphenytoin is converted to phenytoin by plasma phosphatase enzyme and it does not cause cardiac arrhythmia and hypotension to the same degree as phenytoin. Dose is calculated as equivalent to phenytoin and 1.5 mg/kg of Fosphenytoin is equal to 1 mg/ kg of phenytoin.

Benzodiazepines: some centers use acute administration of repeated doses of short acting benzodiazepines (diazepam, lorazepam and midazolam) as first line anticonvulsant therapy in a neonates with seizures because of their rapid onset of action but most centers use it as second or third line therapy because of their short half life, narrow therapeutic index and immediate cardiac respiratory and central nervous system depressive effect. These drugs are given intravenously (or rectally in case of diazepam) and diazepam and midazolam are more effective when given by continuous intravenous infusion at which time the neonate should be monitored closely for cardio respiratory and CNS depression. Lorazepam is preferred over diazepam because of its longer duration of action and wider therapeutic index. Dose of diazepam is 0.3 mg/kg intravenously and 0.3 mg /kg/hour infusion rate when used by continuous infusion. Rectal rout might be used in a dose of 0.5 mg/kg. lorazepam is given by intravenous injection at a dose of 0.05 – 1 mg/kg over 2 – 5 minute while midazolam given as an initial loading dose of 0.15 mg/kg followed by continuous intravenous infusion at a rate of 0.1 – 1.4 mg/kg/hour.

Alternative anticonvulsant therapy for refractory seizures: the majority of neonatal seizures will respond to the above mention drugs. Less than 10% are refractory to treatment and another group of anticonvulsant drugs are needed. *Lidocaine* may be effective in refractory seizures but its use is hampered by potential cardiac toxicity [101]. Lidocaine drip given in an initial loading dose of 2 mg/kg given over 10 – 20 minutes followed by 4 – 6 mg /kg/hour in continuous drip. The drug has narrow therapeutic range and adverse effects include arrhythmia, hypotension and seizures if given in high doses. One study reports 4.8% incidence of cardiac arrhythmia, all of which is respond to Lidocaine discontinuation [102]. *Levetiracetam* may also be effective in controlling neonatal seizures but there is little pediatric experience on its use in neonatal period, although a recent survey among pediatric neurologist suggests quite widespread off label use of Levetiracetam for refractory neonatal seizures despite lack of evidence on the safety, pharmacokinetics and efficacy of its use in neonates [103]. Recent study use mean initial dose is 16 ± 6 mg/kg and the mean maximum dose is 45 ± 19 mg/kg/day. No respiratory or cardiovascular adverse effects were reported or detected. Levetiracetam was associated with a greater than 50% seizure reduction in 35% [104].

Other drugs that have been used orally as an adjunctive anticonvulsant therapy for controlling seizures in refractory cases include *carbamazepine* in a dose of 10 mg/kg initially

followed by 15 – 20 mg/kg/day. Also *valproic acid* can be used per rectally for acute condition and orally for maintenance therapy. Intravenous preparation of valproic acid is recently available. The dose is 20 -25 mg/kg/day followed by 5 – 10 mg/kg 12 hourly. The major risk of hepatotoxicity is more common in this age group which might occur at a rate of 1/500[42]. Other drugs include *primidone*, *felbamate*, *lamotrigine* and *vigabatrin*. The efficacies of the above mention drugs can be difficult to assess since they are seldomly used as sole therapy for neonatal seizures and are usually given in conjunction with other anticonvulsant drugs. One study shows significant reduction in mean seizures duration and frequency following treatment of intractable multifocal neonatal seizures with the diuretic *bumetainde* with no associated clinical side effect or metabolic imbalance [105]. Another study found bumetainde to enhance the anticonvulsant action of phenobarbitone in immature brain by alteration of Cl- transport. Seizures were abolished in 70% and significantly reduced the frequency, duration and power of seizures in the remaining 30% when both drugs used in conjunction [106].

Maintenance therapy: there are no consensuses guideline exist regarding the duration of keeping an infant on anticonvulsant therapy after a neonatal seizures [107, 108, 109]. The principle is to keep the infant for the shortest possible time on anticonvulsant therapy. The duration is variable according to the underlying etiology, neurological examination and EEG changes. The most widely accepted drug for maintenance therapy is phenobarbitone in a dose of 3 – 5 mg/kg/day in one or two divided doses with monitoring serum level. Phenytoin is an alternative therapy. Volpe [110] adopt a protocol recommend discontinuation of all medication at discharge if the neonate is neurologically normal, regardless the etiology and EEG findings. If the neurological examination is abnormal on discharge, the neonate kept on anticonvulsant therapy and reassessed at one month age. At the age of one month, if the neurological examination is normal and the infant has no further seizures, the phenobarbitone is weaned over two weeks. If the neurological assessment is abnormal, an EEG is obtained. If the EEG is normal, the drug is tapered and stopped but if the EEG is abnormal, the infant continue on his anticonvulsant and reassess every 3 months till the age of one year in the same manner. Another protocol recommends drug withdrawal 2 weeks after the infant last seizures [111] after doing EEG to exclude subclinical seizures.

9. Prognosis

Seizures in early life may results in permanent anatomical and functional alteration and enhance epileptogenicity [112, 113]. The long term outcome of neonatal seizures is determined by many factors including the underlying etiology of the seizure, seizure type and duration and the EEG findings. Hypocalcemia and benign familial neonatal seizures are associated with excellent prognosis regarding survival and long term sequel in contrast to symptomatic hypoglycemia, intracranial hemorrhage, meningitis and hypoxic ischemic encephalopathy which are associated with high mortality rate and high incidence of long term complication as epilepsy, mental retardation, and various neurological disorders. Short lived, easily controlled seizures are associated with favorable outcome probably because they may reflect transient benign CNS disorder while sustained refractory seizures, on the other hand, reflects more severe brain disorder. Focal clonic and focal tonic seizures where associated with a relatively good outcome, while generalized tonic posturing and motor automatisms where associated with a poor out come. This probably reflects the underlying etiology and the extent of brain dysfunction [85, 114]. A relationship has been shown in infants with neonatal seizures, associated with perinatal asphyxia, between a great amount of

electrographic seizures activity and subsequent relative increased morbidity and mortality [115, 116]. Many studies shows a mortality rate ranging from 7 to 30% , variable percentage of mental retardation and neurological abnormalities of different severity and post neonatal epilepsies in up to 56% in infants with severe brain injury[116-120]. In a population based study by Ronen between 1990 and 1994, a 62 term and 26 preterm newborn with neonatal seizures where followed comprehensively. Only 35% were a live and without disability. Twenty four percent of children died and of the survival, 41% had one of epilepsy, mental retardation, cerebral palsy or learning disability [121]. A scoring system to predict the neurological outcome at the onset of neonatal seizures was tested on 106 newborn with neonatal seizures between 1999 and 2004. This system used 6 variables including birth weight, Apgar score at one minute, neurological examination at the onset of the seizures, cerebral ultrasound, efficacy of anticonvulsant therapy and the presence of neonatal status epilepticus. This system found to be an easy, rapid and reliable prognostic indicator of neurological outcome after the onset of neonatal seizures [122].

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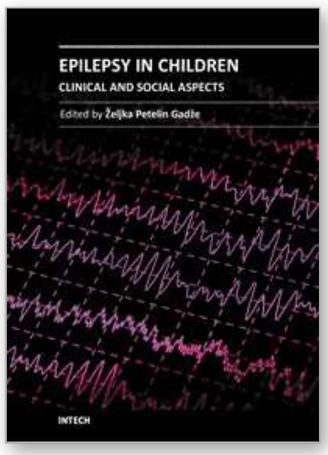

Epilepsy in Children - Clinical and Social Aspects

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Epilepsy is a neurological condition that accompanies mankind probably since its inception. About 400 years before Christ, the disease was already known by Hippocrates, who wrote the book â€œOn The Sacred Diseaseâ€. Classically, epilepsy has been defined as a chronic condition characterized by an enduring propensity to generate seizures, which are paroxysmal occurring episodes of abnormal excessive or synchronous neuronal activity in the brain. Out of all brain disorders, epilepsy is the one that offers a unique opportunity to understand normal brain functions as derived from excessive dysfunction of neuronal circuits, because the symptoms of epileptic seizures are not the result of usual loss of function that accompanies many disease that affect the brain. I am therefore extremely honoured to present this book. The 15 very interesting chapters of the book cover various fields in epileptology â€“ they encompass the etiology and pathogenesis of the disease, clinical presentation with special attention to the epileptic syndromes of childhood, principles of medical management, surgical approaches, as well as social aspects of the disease.

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