Introduction

Neonatal seizures: It is a paroxysmal spell of altered neurological function (behaviour, motor or autonomic functions) occurring during the first 28 days in term infants or 44weeks gestational age in pre-term infants. **(Joseph, 2008).**

Neonatal fits are a common condition in newborns. Incidence being 0.2-2.7/1000live births in term babies and 57.5-132/1000 live births in preterm babies. There is a long list of the causes for the neonatal fits so it is very important to investigate and treat it. **(Joseph, 2008).**

Neonatal seizures are a risk factor that markedly increases rate of long term morbidity and neonatal mortality and the presence of neonatal seizures is the predictor of long term physical and cognitive deficits. ***(Raj et al., 2008)***

The overall prognosis for survival in neonatal seizures is around 85% a significant improvement from earlier decades , Unfortunately , the prognosis for long-term neurodevelopmental outcome remains largely unchanged . Specifically , an adverse outcome occurs in approximately 50% of cases , with sequelae such as mental retardation , motor dysfunction and seizures . The range of long-term outcome being (i) the underlying etiology ,(ii) electrographic features , and (iii) gestational age . Other useful predictors include the neonatal neurologic examination and neuroimaging findings. ***(Adre, 2008)***

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The optimal treatment strategy for neonatal seizures remains controversial and there is little data regarding current treatment of neonatal seizures there is variation in practice. ***(Dimitri, 2009)***

Aim of the work

This work was done to evaluate the clinical aspects of seizures in the neonatal intensive care units as regard the incidence, the clinical types, etiology and time of onset of seizure .

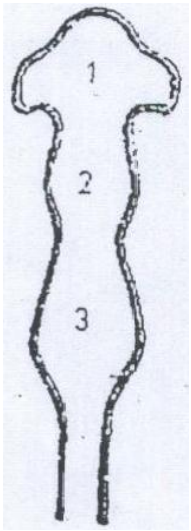
Embryology and Anatomy of CNS

At the third week, a thickening of the ectoderm appears known as the neural plate, which will form the neural groove which has two elevated edges called the neural folds.

The neural tube cranial to the fourth pair of somites develops into the brain. Fusion of the neural folds in the cranial region and closure of the rostral neuropore forms three primary brain vesicles from which the brain develops, the three primary brain vesicles form the:

- Forebrain (prosencephalon).
- Midbrain (mesencephalon).
- Hindbrain (rhombencephalon).

Figure (1): Neural tube**(Gray, 1997).**



1. Prosencephalon.
2. Mesencephalon.
3. Rhombencephalon.

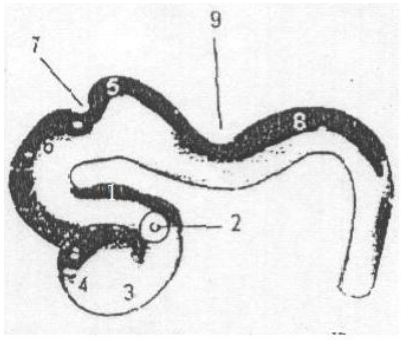


Figure (2): Brain vesicles, 6thweek**(Gray, 1997).**

1. Diencephalon.
2. Optic cup.
3. Telencephalon.
4. Primitive cerebral hemisphere.
5. Metencephalon.
6. Mesencephalon.
7. Rhombencephalic isthmus.
8. Myelencephalon.
9. Pontine flexure.

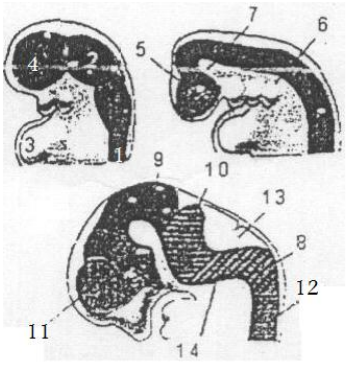


Figure (3): Early development of the brain**(Gray, 1997).**

1. Rhombencephalon (hindbrain).
2. Diencephalon.
3. Heart.
4. Prosencephalon (forebrain).
5. Optic outgrowth.
6. Cervical flexure.
7. Midbrain flexure.
8. Myelencephalon.
9. Mesencephalon (midbrain).
10. Metencephalon.
11. Telencephalon.
12. Spinal cord.
13. 4 th ventricle.
14. Pontine flexure.

During the fourth week, the embryonic brain grows rapidly and bends ventrally with the head fold. This produces the midbrain flexure in the midbrain region and the cervical flexure at the junction of the hindbrain and spinal cord. Later, unequal growth of the brain between these flexures produces the pontine flexure in the opposite direction. This flexure results in thinning of the roof of the hindbrain. Initially, the primordial brain has the same basic structure as the developing spinal cord **(Gray, 1997).**

However, the brain flexures produce considerable variation in the outline of transverse sections at different levels of the brain and in the position of the gray and white matter. The sulcus limitans extends cranially to the junction of the midbrain and forebrain, and the alar and basal plates are recognizable only in the midbrain and hindbrain (**Gray,1997)**

Hindbrain:

The cervical flexure demarcates the hindbrain from the spinal cord. Later, this junction is arbitrarily defined as the level of the superior rootlet of the first cervical nerve which is located roughly at the foramen magnum. The pontine flexure, located in the future pontine region divides the hindbrain into caudal (myelencephalon) and rostral (metencephalon) parts. The myelencephalon becomes the medulla oblongata and the metencephalon, the pons and cerebellum. The cavity of the hindbrain ., becomes the fourth ventricle and the central canal in the caudal part of the medulla **(Eldera et al., 2000).**

Myelencephalon:

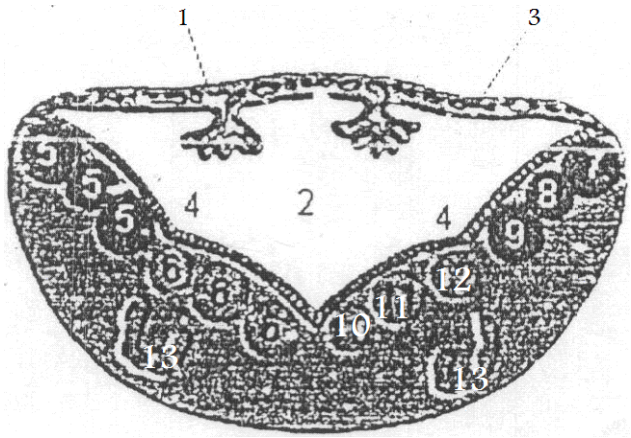
The caudal part of the myelencephalon (closed part of the medulla oblongata) resembles the spinal cord both developmentally and structurally. The neural canal of the neural tube forms a small central canal. Unlike those of the spinal cord, neuroblasts from the alar plate in the myelencephalon migrate into the marginal zone and form isolated area of grey matter (the gracile nuclei medially and the cuneate nuclei laterally).

The rostral part of the myelencephalon is wide and rather flat especially opposite the pointing flexure. The pointing flexures cause the lateral wall of the medulla to move laterally. It also causes the roof plate to become stretched and greatly thinned. In addition, the cavity of this part of the myelencephalon becomes rhomboidal. As the walls of the medulla move laterally, the alar plates come to lie lateral to the basal

plates. As the position of the plates changes, the motor nuclei generally develop medially to the sensory nuclei. Neuroblasts in the basal plates of the medulla develop into motor neurons. In the medulla, the neuroblasts form nuclei and organize into three columns on each side.

Neuroblasts of the alar plate form neurons that are arranged in four columns on each side.

Some neuroblasts from the alar plates migrate ventrally and form the neurons in the olivary nuclei **(Craig, 1992).**



Figure(4): Development of the medulla oblongata**(Gray, 1997).**
1. Choroid plexus.
2. 4th ventricle.
3. Tela choroidea.
4. Sulcus limitans.
5. Alar plate.
6. Basal plate.
7. Somatic afferent group.
8. Special visceral afferent group.
9. General visceral afferent group.
10. Somatic efferent group.
11. Special visceral efferent group.
12. General visceral efferent group.
13. Olivary nucleus.

Metencephalon:

The walls of the metencephalon form the pons and cerebellum and its cavity forms the superior part of the fourth ventricle. As in the rostral part of the myelencephalon, the pontine flexure causes divergence of the lateral walls of the pons, which spread the gray matter in the floor of the fourth ventricle. As in myelencephalon, neuroblasts in each basal plate develop into motor nuclei and organize into three columns on each side.

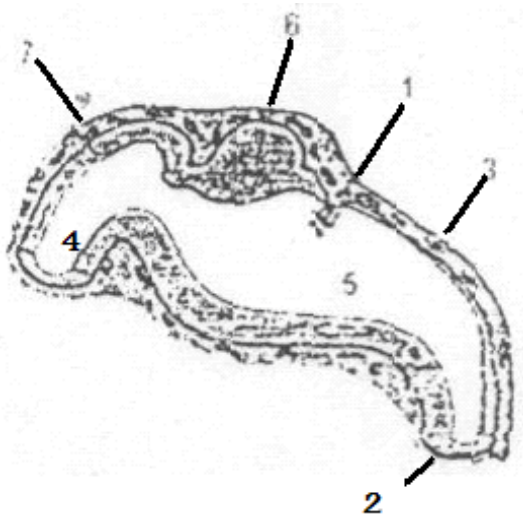


Figure (5): Development of the pons and cerebellum**(Gray, 1997).**

1. Choroid plexus.
2. Medulla.
3. Tela choroidea.
4. Pons.
5.4th ventricle.
6. Developing anterior lobe of cerebellum.
7. Midbrain.

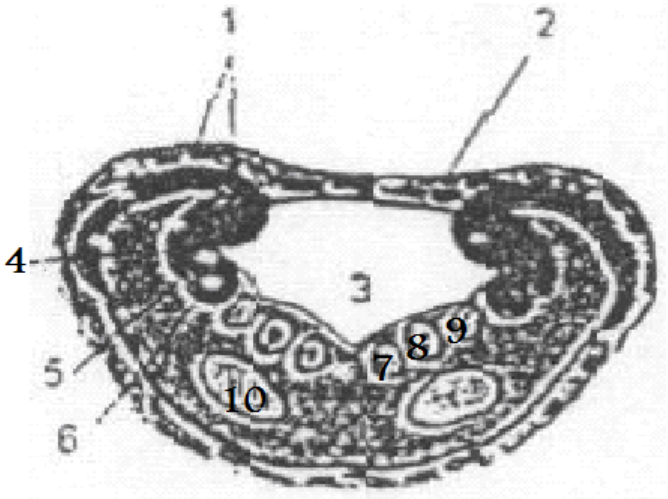


Figure (6): Development of the pons and cerebellum**(Gray, 1997).**

1. Developing cerebellum,
2. Tela choroidea.
3.4th ventricle. . ,
4. Somatic afferent group.
5. Special visceral afferent group.
6. General visceral afferent group.
7. Somatic efferent group. ,
8. Special visceral efferent group.
9. General visceral efferent group.
10. Pontine nuclei. .

The cerebellum develops from the thickenings dorsal part of the alar plates, initially the cerebellar swellings project into the fourth ventricle. As the swelling enlarge and fuse in the medial plane, they overgrow the rostral part of the fourth ventricle and overlap the pons and medulla. Some neuroblasts in the intermediate zone of the alar plates migrate to the marginal zone and differentiate into the neurons of the cerebral cortex. Other neuroblasts from these plates give rise to the central nuclei, the largest of which is the dentate nucleus. Cells from the alar plates also give rise to the pontine nuclei, the cochlear and vestibular nuclei and the sensory nuclei of the trigeminal nerve.

The structure of the cerebellum reflects the phylogenetic development:

- The archicerebellum (flocculonodular lobe) has connections with the Vestibular apparatus

- The paleocerebellum (vermis and anterior lobe) is associated with sensory data from the limbs.

- The neocerebellum (posterior lobe) is concerned with selective control of limb movements. **(Catherine, 1993).**

Midbrain:

The neural canal narrows and becomes the cerebral aqueduct, neuroblasts migrate from the alar plate of the midbrain into the tectum and aggregate to form four large groups of neurons, the paired superior and inferior colliculi which are concerned with visual and auditory reflexes respectively. Neuroblasts from the basal plates may give rise to groups of neuron in the tegmentum (red nuclei, nuclei of the fourth and third cranial nerves, and the reticular nuclei)the substantia nigra may also differentiate from the basal plate.

The substantia nigra may also differentiate from the basal plate. Fibers growing from the cerebrum form the cerebral peduncles anteriorly. The cerebral peduncles become progressively more prominent as more descending fiber groups (corticopontine, corticobulbar and corticospinal) pass through the developing midbrain on their way to the brainstem and spinal cord **(Catherine, 1993).**

Forebrain:

As closure of the rostral neuropore occurs, two lateral outgrowths optic vesicles appear one on each side of the forebrain. The optic vesicles are the primordial of the retina and optic nerves. A second pair of diverticula soon arises more dorsally and rostrally; these are the telencephalic vesicles. They are the primordia of the cerebral hemispheres is the telencephalon and the caudal or posterior part of the forebrain is the diencephalons. The cavities of the telencephalon and diencephalons contribute to the formation of the third ventricle, although the cavity of the diencephalons contributes more **(Craig, 1992).**

Diencephalon:

Three swellings develop in the lateral walls of the third ventricle, which later become the epithalamus, thalamus, and hypothalamus.

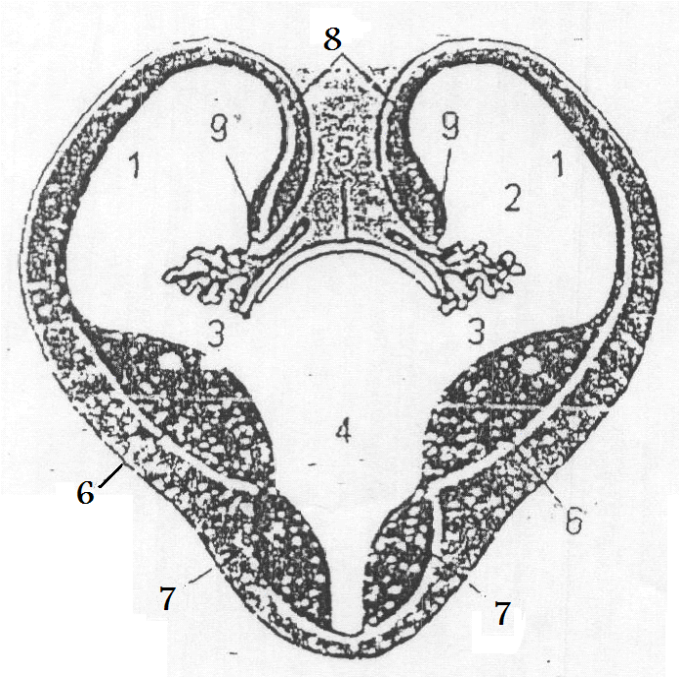


Figure (7): Diencephalon and telencephalon**(Gray, 1997).**
1. Lateral ventricle.
2. Choroid plexus.
3. Foramen of Monro.
4. 3rd ventricle.
5. Ependymal roof of the 3rd ventricle,
6. Corpus striatum.
7. Hypothalamus.
8. Neopallium.
9. Hippocampus.

Telencephalon:

The telencephalon consists of a median part and two lateral diverticula, the cerebral vesicles. These diverlicula are the primordia of the cerebral hemispheres. The cavity of the median portion of the telencephalon forms the extreme anterior part of the third ventricle.

At first, the cerebral hemispheres are in wide communication with the cavity of the third ventricle through the interventricular foramina. Along a line, the choroid fissure part of the medial wall of the developing cerebral hemispheres becomes very thin. Initially, this thin ependymal

portion lies in the roof of the hemisphere and is continuous with the ependymal roof of the third ventricle. The hemispheres meet each other in

the midline, the mesenchyme trapped in the longitudinal fissure between them give rise to the cerebral falx. The corpus striatum appears during the sixth week as a swelling in the floor of each cerebral hemisphere.

As the cerebral cortex differentiates, fibers passing to and from it pass through the corpus striatum and divide it into caudate and lentiform nuclei. This fiber pathway-the internal capsule-becomes C-shaped as the hemisphere assumes this form **(Gray, 1997).**

Cerebral commissures:

As the cerebral cortex develops groups of fibers-commissures-connect corresponding areas of the cerebral hemisphere with one another.

The most important of this commissures cross in the lamina terminalis, the first commissures to form are, the anterior commissure (which connects the olfactory bulb and related areas of one hemisphere with those of the opposite side) and hippocampal commissure (which connect the hippocampal formation). The largest cerebral commissure is the corpus callosum connecting neocortical areas.

Initially, the surface of the hemisphere is smooth however as growth proceeds sulci and gyri develop **(Moore and persaud, 2003).**

Brain malformations:

Neurologists practicing critical care neurology within the neonatal intensive care unit must recognize the importance of the developmental

process in the genesis of brain disorders with or without the expression of neonatal seizures. This developmental process begins before conception and subsequently encompasses embryonic, fetal and perinatal periods **(Scher, 2006).**

Trimester-specific stages in brain development will influence the response to and expression of a disease process resulting in brain injury expressed as neonatal seizures and later epileptic disorders. Profound malformations including neurulation, differentiation, proliferation and widespread migration of neuronal elements occur during the first half of pregnancy. Disruptions in synaptogenesis, dendritic arborization, myelination and neurotransmitter development underscore widespread or region-specific alterations during the second half of pregnancy. Fetal and neonatal responses to diseases must therefore be framed within the context of experience-dependent neural development throughout gestation and early life **(Scher, 2006).**

Specific neurocortical regions vary with respect to the dynamics of prenatal and postnatal maturational processes, reflecting activity (i.e. experience)-dependent development **(Casey et al., 2005).**

Disease processes will therefore promote region-specific changes in brain structure and function, timed to the specific stages and regions during the developmental process. Mechanisms of injury and repair-must be considered within these critical or with inherited traits.

Classification of brain malformations are traditionally sensitive periods of brain development during which a disease process or stress is introduced **(Johnson, 2005).**

Classification of brain malformations for example is traditionally defined during prenatal stages of brain development as largely genetically expressed disorders of neurulation, differentiation, proliferation and migration. However, genetic variability of expression also exists for even severe malformations as reflected in variable phenotypic expressions of the same genetic disorder, as described for trisomy 21, neurofibromatosis and tuberous sclerosis **(Casey et al., 2005).**

Pleomorphisms within a genetic sequence can define a general disease entity with variable patterns of malformation and/or injury expressed throughout the developmental process after environmental stresses **(Scher, 2006).**

Different brain lesions reflect both the stage of neural development as well as the vulnerability of specific brain regions to injury. Alterations

in the genetic expression for specific molecular properties of cells, synapses and neurotransmitters will later contribute to the expression of neonatal seizures with or without encephalopathic signs, and later epilepsy during childhood **(Redmond et al., 2003**).

Sites of injury reflect when the fetal brain during maturation was injured. This has implications for specific brain rescue and neural protection protocols introduced either during pregnancy, or in proximity to and including parturition. The following two examples stress the importance of assigning temporal relevance to etiology-specific disease states associated with asphyxia and inflammation.

Alteration of both white and gray matter development has been detected as early as term-age neonates exposed to disease at fetal or neonatal ages by advanced MRI techniques **(Inder et al., 2003).**

Marin-Padilla eloquently described subtle neuropathological abnormalities in developing neocortex adjacent to white matter gliosis. He postulated that focal cortical dysplasias result from altered neurocircuitry after sensory differentiation and/or anatomy. This pathologic study underscores the important role that post-injury reorganization in the neocortex plays in contributing to neurological sequelae during childhood after neonatal seizures with or without encephalopathy. Disease states from lung disease, sepsis or trauma can introduce new or additional stresses to the preterm brain from asphyxia, infectious or traumatic mechanisms of injury **(Scher, 2006).**

Brain reorganization may then result, for example, from brain injuries after the vascular insults of intraventricular hemorrhage and/or effects of white matter gliosis**(Palmini and Luders, 2002).**

Postnatal pathophysiological mechanisms of disease therefore compound prenatal brain injury resulting in a continuum of aberrant cortical reorganization **(Palmini and Luders, 2002).**

Pathophysiology of seizures

Seizures are defined as an excessive and repetitive electrical discharge in the Central Nervous System (CNS). Seizures are not a disease, but represent underlying disease proceses that result in disturbance within the brain **(Volpe, 2001**).

Some newborns with Nervous System (NS) fit the definition of epilepsy as "a condition with recurrent, unprovoked, ictal phenomenology because of a more or less chronically altered seizure threshold within an area or a neuronal system of the brain" **(Watanabe et al., 1999).**

A number of seizure classification systems have been proposed and the taxonomy modified many times **(Mizrahi and Keliaway, 2002**).

One classification focuses on the presence or absence of EEG correlates to categorize the episodes as epileptic or non-epileptic in origin **(Mizrahi, 2001).**

Whereas others focus on the clinical manifestation/behaviors of the seizure to label the event **(Volpe, 2001).**

In more recent literature, there seems to be a blending of these classifications into one that examines the clinical features of the seizure, and relates these to the likelihood of EEG correlates. In general, any abnormal, abrupt, repetitive behavior that cannot be controlled with containment or repositioning should be investigated as a possible seizure **(Granelli and McGrath, 2004).**

Non-epileptic events must also be recognized as distinct functional entities, similar to childhood movement disorders **(Sanger, 2003).**

For example, neonatal hypertonic states include spasticity, rigidity and dystonic motor patterns which require distinct diagnostic and therapeutic considerations independent to seizure states. Similarly, rhythmic movement disorders expressed as tremors and myclonus represent pathologic non-epileptic events with specific considerations for diagnosis and management **(Scher, 2002).**

Continuous long-term synchronised video-EEG monitoring is the appropriate bedside tool to document behavioral and electrographic expressions of seizures to be distinguished from non-epileptic events **(Scher, 2006).**

Some seizure behaviors/activities in newborns may not have EEG correlates. Conversely, seizure activity can occur without clinical manifestations **(Rennie and Boylan, 2003).**

These unique manifestations in the neonate may be related to the subcortical initiation of seizures (EEGs monitor for only cortical activity) **(Scher, 2003).**

Or the immature cortical organization of the newborn's brain, which results in failure to propagate or sustain epileptiform activity **(Rennie and Boylan, 2003).**

The mechanisms of seizures in newborns are complex and not well-understood as a result; theories of epileptogenesis are rapidly evolving **(Granelli and McGrath, 2004).**

Basic neurophysiology and neurochemistry governing excitability:

Given that the basic mechanism of neuronal excitability is the action potential, a hyperexctiable state can result from increased excitatory synaptic neurotransmission, decreased inhibitory neurotransmission, an alteration in voltage-gated ion channels, or an alteration of intra- or extracellular ion concentrations in favor of membrane depolarization. A hyperexcitable state can also result when several synchronous subthreshold excitatory stimuli occur, allowing their temporal summation in the postsynaptic neurons. Action potentials occur due to depolarization of the neuronal membrane, with membrane depolarization propagating down the axon to induce neurotransmitter release at the axon terminal**(Kandel et al., 2000).**.

The action potential occurs in an all-or-non fashion as a result of local changes in membrane potential brought about by net positive inward ion fluxes. Membrane potential thus varies with activation of ligand-gated channels, whose conductance is affected by binding to neurotransmitters; or with activation of voltage-gated channels, whose conductance is affected by changes in transmembrane potential; or with changes in intracellular ion compartmentalization **(Kandel et al., 2000).**

Neurotransmitters are substances that are released by the presynaptic nerve terminal at a synapse and subsequently bind to specific postsynaptic receptors. The major neurotransmitters in the brain are glutamate, Gamma-Amino-Butyric Acid (GABA), Acetylcholine (Ach),norepinehprine, dopamine, serotonin, and histamine. Other

molecules,such as neuropeptides and hormones, play modulatory roles that modify neurotransmission over longer time periods **(Takumi et al., 1998).**

The major excitatory neuro transmitter is the amino acid glutamate. There are several subtypes of glutamate receptors. Glutamate receptors can be found postsynaptically on excitatory principal cells as well as on inhibitory interneurons, and have been demonstrated on certain types of glial cells. The ionotropic subclasses are the Alpha-amino-2, 3-dihydro-5-Methyl-3-oxo-4-isoxazolepropanoic Acid (AMPA), kainite receptors, and N-methyl-D-Aspartate (NMDA); these allow ion influx upon activation by glutamate **(American Epilepsy Society, 2004).**

They are differentiated from one another by cation permeability as well as differential sensitivity to pharmacological agonists/antagonists. All ionotropic glutamate receptors are permeable to Na+ and K+, and it is the influx of Na+ and outflow of K+ through these channels that contribute to membrane depolarization and generation of the action potential. The NMDA receptor also has a Ca++channel that is blocked by Mg++ ions in the resting state, but under conditions of local membrane depolarization, Mg++is displaced and the channel becomes permeable lo Ca++; influx of Ca++tends to further depolarize the cell, and is thought also to contribute lo Ca++ mediated neuronal injury under conditions of excessive neuronal activation (such as status epilepticus and ischemia), potentially leading to cell death, a process termed excitotoxicity. **(American Epilepsy Society, 2004).**

The other major type of glutamate receptor is the metabotropic receptor, which functions by means of receptor-activated signal transduction involving membrane-associated G-proteins. There are at least 3 subyptes of metabotropic receptors, based on differential agonist potency, mechanism of signal transduction, and pre- versus post-synaptic localization **(American Epilepsy Society, 2004).**

The major inhibitory neurotransmitter, GABA, interacts with 2 major subtypes of receptor: GABAA and GABAB receptors. GABAA receptors are found postsynaptically, while GABAB receptors are found presynaptically, and can thereby modulate synaptic release. In the adult brain, GABAA receptors are permeable to Cl- ions; upon.activation, Cl- influx hyperpolarizes the membrane and inhibits action potentials. GABAB receptors are associated with second messenger systems rather than Cl- channels, and lead to attenuation of transmitter release due to their presynaptic location. The second messenger systems often result in

opening of K+ channels, leading to a hyperpolarizing current **(Acharya, 2002).**

Ion channelopathies:

More recently, the molecular genetic basis of a number of very rare idiopathic epilepsies and non-epileptic paroxysmal disorders presenting in the newborn period has been shown to be mutations in genes encoding ion channels and related proteins. These ion channelopathies include disorders of voltage-gated ion channels selective for sodium or potassium, and the ligand-gated GABA and glycine receptors **(Gardiner, 2006).**

1.Ligand-gated-receptors:

A) Ligand-gated GABA receptors:

Gamma-Aminobutyric Acid (GABA) receptors are classified into the ionotropic GABAA and GABAC receptors and metabotropic GABAB receptors. They are the major inhibitory neurotransmitter receptor in the vertebrate brain. In early infancy, it is excitatory rather than inhibitory **(Gardiner, 2006).**

During development, activation of Cl (chloride)-permeable GABA Receptor (GABA-R) excites neurons as a result of elevated intracellular Cl- levels and a depolarized Cl- Equilibrium potential (Ep_1). Chloride transport is a function of two membrane pumps with different time courses of expression. Early in development (roughly P_3-P_{15} in the rat), the Na+, K+, 2Cl- Cotransporter ($NKCC_1$) imports large amounts of Cl- into the neuron (along with Na+ and Cl- to maintain electroneutrality). This pump_sets_the Chloride Equilibrium potential (Ep_1) positive to the resting potential, so that when the GABAA receptor is activated, Cl- flows out of the neuron, depolarizing it. Over time, $NKCC_1$ expression diminishes, and another Cl- transporter, KCC_2 ,is expressed. KCC_2 has the opposite effect-it extrudes Cl- out of the neuron, placing the EC_1 more negative than the resting potential so that GABAA receptor activation allows extracellular Cl- to flow into the neuron, hyperpolarizing it and endowing GABA with an inhibitory action(**Dzhala et al., 2005).**

This developmental "switch" in Cl- homeostasis might influence the seizure susceptibility of the neonatal brain. The additional depolarization that is due to GABAA receptor activation would add to the excitation initiated by glutamate.

Neurotransmission and shift the excitation/inhibition balance toward excessive excitation and thus toward seizure activity. In the early postnatal period (weeks in rats and months in humans), $NKCC_1$ rises to a peak then declines to adult levels; while over the same time period, KCC_2 expression gradually rises to adult levels (**Dzhala et al., 2005).**

In the first postnatal week, GABAA receptor activation causes membrane depolarization rather than hyperpolarization as seen in the mature brain. With regard to GABAB receptors, activation of the presynaptic receptors, which decrease GABA release, occurs earlier in development than activation of polysynaptic receptors that mediate long-lasting hyperpolarization. The net result is increased excitability **(Acharya, 2002).**

B) Ligand-gated glycine receptors:

Glycine receptors are ligand-gated chloride channels mediating inhibition by post-synaptic hyperpolarization in the brainstem and spinal cord. Mutations in glycine receptor is associated with hypereplexia **(Gardiner, 2006).**

Hypereplexia (also known as_a startle disease or congenital Stiff baby syndrome) is usually familial with autosomal dominant inheritance but sporadic cases occur. It may present in the first days or weeks of life with a variety of manifestations. These may include a hyper-alert gaze and exaggerated startle response to auditory, visual or somatosensory stimuli. There may be prolonged tonic spasms, mimicking generalized tonic epileptic seizures, which may even lead to apnea and death. The clinical_hallmark is a consistent generalized flexor spasm in response to gentle tapping of the nasal bridge which does not habituate or diminish with repeated taps. There may be a history of abnormal intrauterine movements. The ictal EEG is usually normal but may show fast spikes

Initially during tonic spasms. The EMG shows a characteristic almost permanent muscle activity interspersed with quiet periods **(Gardiner, 2006).**

2. Voltage-gated channels:

A) Voltage-gated potassium channelopathies:

Potassium channels are a diverse group encoded by over 80 genes in the human genome. Mutation in at least 13 potassium channel genes causes human disease and four of these belong to KCNQ family of voltage-gated KV channels. Benign Familial Neonatal Seizures (BFNS) is a potassium channelopathy caused by mutations in $KCNQ_2$ or $KCNQ_3$ **(Gardiner, 2006).**

B) Voltage-gated sodium channelopathies:

It includes: Generalized Epilepsy with Febrile Seizures plus(GEFS+) ,Sever Myoclonic Epilepsy of Infancy(SEMI).Benign Familial Neonatal Infantile Seizures (BFN/IS), Infantile Spasm (IS) (there has been one case of infantile spasms associated with a SCN1A mutation in the C-terminus), Intractable Childhood Epilepsy with Tonic-Clonic Seizures (ICEGTCS). Its onset is during infnancy.

In contrast to the large number of genes encoding potassium channels, there are only nine genes encoding human sodium channel alpha subunits **(Gardiner, 2006).**

Development of glutamate receptors:

From animal studies, it appears that the early postnatal period represents a developmental window with ongoing synaptogenesis and increased neuronal plasticity as compared to adults **(Swann, 1999).**

There is an overshoot of synaptic density before it is pruned to adult levels. This is associated with a parallel overexpression of glutamate receptors, which is required for these normal developmental processes.

NMDA, AMPA and kainite receptors increase over the first few weeks of life, resulting in certain brain regions being more susceptible to the epileptogenic and excitotoxic effects of glutamate-receptor-agonists during this period. The expression of the NR2B NMDA receptor subunit, which is associated with increased duration of NMDA A receptor-mediated excitation and increased Ca^{++} influx, is higher during the postnatal period **(Monyer , 2000).**

Due to the relative underexpression of the $GluR_2$(B) subunit, a larger proportion of AMPA and kainite receptors show permeability to Ca^{++} in the immature brain as compared with the mature brain. The

development of metabolotropic glutamate receptors also favours a hyperexcitable state since the activity of post-synaptic receptors that promote increased intrinsic neuronal excitability predominates over that of receptors that presynaptically inhibit glutamate release. Finally, a relatively lower activity of some glutamate transporters could contribute to a greater susceptibility to seizures **(Meldrum et al., 2001).**

Maturational differences also occur in other neuromodulatory substances. For instance, Corticotropin-Releasing Hormone (CRH) is highly epileptogenic and particularly important in triggering seizures by fever or hypoxia in the immature brain. CRH receptor expression has been estimated to be twice the adult level in immature rat amygdala in the second postnatal week **(Acharya, 2002).**

The developmental patterns of voltage-gated ion channels promote increased intrinsic membrane excitability during early postnatal development because this is necessary for normal development. Changes in presynaptic Ca channels that mediate neurotransmitter release may particularly important in determining seizure susceptibility **(Sanchez and Jensen,2001).**

Inlracellular Ca homeostasis is also developmentally regulated. The calcium-binding protein calbindin D28K is not expressed in immature hippocampal granule cells. The major neuronal Na^+/K^+ ATPase also is less abundant in the immature brain so that a moderate increase in neuronal activity could cause extracellular K^+ to rise to epileptogenic levels **(Lieberman and Mody, 2002).**

Role of GABA in neonatal seizures:

In addition to excitatory connections, reduction of inhibition is necessary for synchronization of bursts. GABA-mediated inhibition normally holds the membrane potential below the action potential threshold and prevents recruitment of bursts. It also prevents synchronization of intrinsic burst discharges in pyramidal neurons by decreasing the connectivity of their divergent, polysynaptic excitatory pathways **(Acharya, 2002).**

Another aspect of the changing perspective on GABA concerns the key role it plays in the development of neuronal circuits. It is a major excitatory neurotransmitter in the immature brain at a time when glutamatergic synaptic connections are beginning to mature. In the early postnatal period in rats, the pairing of depolarizing GABA-mediated responses with glutamate release at immature excitatory synapses that

contain only N-Methyl-D-Aspartate (NMDA) receptors relieves their voltage-dependent block by magnesium ions. The resulting NMDA receptor-mediated calcium influx provides the signal required for insertion of AMPA-type glutamate receptors into the postsynaptic membrane and, therefore, leads to their maturation into active synapses. **(Khalilov et al., 2005).**

Given this crucial role in the development of excitatory synapses, it is likely that the depolarizing action of GABA contributes to the particular vulnerability of neonates to seizures and epilepsy. This developmental process appears to be analogous to the insertion of AMPA receptors that occurs during induction of long-term potentiation in more mature brain circuits, when glutamate provides the depolarizing signal. Considering the importance of long-term potentation in learning and memory functions, disruption of these analogous signaling patterns by seizures may have long-lasting consequences in patients at a vulnerable age **(Khalilov et al., 2005).**

The role of substantia nigra pars reticulata:

In humans, the incidence of epilepsy is higher in the neonates and population studies have shown that males have a higher incidence of seizures than females. These epidemiological data strengthen the need to understand mechanisms underlying the sex-dependent differentiation of the CNS, especially in relation to structures involved in seizure control. Understanding of how the sex hormones can modulate seizure-controlling substrates during development is important for the identification of, possible targets for prevention or treatments of seizure disorders **(Giorgi et al., 2007).**

The Substantia Nigra pars Reticulata (SNR), a midbrain structure populated largely by GABAergic neurons, serves as a main output of the basal ganglia. The SNR is involved in the control of seizures in an age- and sex-specific fashion **(Veliskova and Moshe, 2006).**

Immature rats [Postnatal day (PN)-15], localized bilateral SNR micro- infusions of muscimol, an agonist at GABA receptors, have proconvulsant effects on fluroethyl-induced tonic seizures in males but not in females **(Veliskova and Moshe, 2001).**

Additionally, in vitro gramicidin patch clamp recordings in slices from PN-14-17 males and females show sex-specific responses of the SNR GABAergic neurons to bath application of muscimol

(Galanopoulou et al., 2003) and to synaptically released GABA **(Kyrozis et al., 2006).**

In males, both have depolarizing effects on the membrane potential of the SNR GABAergic neurons, while in females the response is hyperpolarizing.Clinical evidence shows gender- and age-related expression in many seizure syndromes **(Christensen et al., 2005).**

As the SNR is part of a seizure controlling system, understanding the sex differences and the role of sex hormones in modulation of this system should offer significant insights in the pathophysiology and treatment of seizures **(Giorgi et al., 2007)**

Factors predisposing to the development of seizures:

Newborns are more susceptible to the development of seizures than older children or adults. This predisposition may be explained through several factors that are characteristic of the neonatal period:

1. The neonatal period is characterized by the fast growth and development of the Central Nervous System (CNS). The ontogenetic process of maturation of the CNS probably makes newborns more vulnerable to exogenous insults;

2. There is a predominance of excitatory systems over the inhibitory ones, thus facilitating convulsive manifestation, in addition to the extracellular accumulation of potassium, which results in hyperexcitability;

3. Neurotransmitters with inhibitory activity on the CNS have excitatory activity on the immature CNS.

4. The dissemination of the epileptogenic activity is more easily present in the immature brain due to the absence of restrictive inhibitory factors.

5. Subcortical structures such as the substantia nigra increase the epileptogenic activity of the immature CNS.

(Costa et al., 2001).

Genetics:

Determination of the biochemical and pathophysiological mechanisms that translate ion channel gene mutations into seizure disorders is challenging because of the large number of diverse functions that might be affected at any given level of analysis **(Burgess, 2005).**

It is unrealistic to assume that most epilepsy-associated ion channel mutations result in a simple loss of protein function and that this, in turn, causes seizures by a predictable increase in cell excitation or decrease in cell inhibition, depending on the normal membrane function of the protein. Even at the most basic levels of mutant gene function, potential defects might include such things as**:**

(i) Promoter/enhancer alterations that increase or decrease mRNA transcription, and thus the amount of protein produced, without altering the amino acid structure of that protein;

(ii) Promoter/enhancer alterations that do not alter baseline mRNA expression levels, but which increase or decrease the ability of that gene to respond to feedback regulation such as that mediated by activity-dependent Ca^{2+} concentrations, hormonal signaling, etc...;

(iii)Alterations in local chromatin structure that might alter the expression or regulation of multiple nearby genes in addition to that of a candidate ion channel gene;

(iv) Mutations in transcribed pre-mRNA splice sites that lead to altered splicing and subsequent abnormal protein structure;

(v)Mutations in mRNA untranslated regions that increase or decrease

mRNA stability, subcellular localization, or rate of translation; and

(vi) Mutations in mRNA translated regions that directly alter the amino

acid sequence of the resulting protein, with a large variety of potential consequences**(Burgess, 2005)**.

Risk Factors:

The following factors were reported to be significant for seizures occurring in term infants within the first 48 hours of birth: nulliparity, hydramnios, post-term pregnancy, oxytocin augmentation, of labor, fetal distress, prolonged second stage of labor, emergency cesarean section, assisted vaginal delivery, low Apgar score, resuscitation at delivery, and subsequent ventilator support **(Saliba et al., 2001).**

It is common knowledge that etiology and the degree of brain injury are the most important determinants of outcome. However, this is only partially true. Not all newboms with symptomatic or cryptogenic seizures are epileptic newborns **(Mastrangelo et al., 2005).**

Table(1): Classification of neonatal seizures based on electroclinical finding

Clinical seizures with coincident electrocortical signature (pathophysiology: Epileptic)
Focal clonic
Unifocal
Multifocal
Hemiconvulsive
Axial
Focal tonic
Asymmetric truncal posturing
Limb posturing
Sustained eye deviation
Myoclonic
Generalized
Focal
Spasms
Flexor
Extensor
Mixed extensor/flexor

Clinical seizures without a consistent electrocortical signature (pathophysiology: Non-epileptic)

Myoclonic

Generalized

Focal

Fragmentary

Generalized tonic

Flexor

Extensor

Mixed extensor/flexor

Motor automatisms

Oral-buccal-lingual movements

Ocular signs

Progression movements

Complex purposeless movements

Electrical seizures without clinical seizure activity

(Fanaroff et al., 2006).

NEONATAL SEIZURES

Definition: A seizure is defined clinically as a paroxysmal alteration in neurologic function (ie, behavioral, motor, or autonomic function) **(Blume et al., 2009)**

DIAGNOSIS OF NEONATAL SEIZURES.

The clinical manifestations of neonatal seizures differ in many ways from those in older patients. The behavioral features of seizures in the newborn may be very subtle, in some cases confined to autonomic and subtle motor phenomena. In addition, the motor manifestations are often disorganized, and an orderly homunculus-based progression of convulsive activity (i.e., "Jacksonian march") is very uncommon. Furthermore, continuous video-EEG monitoring has shown an often inconsistent temporal association between clinical and electrographic seizures. **(Adre, 2008).**

The peculiar clinical characteristics of seizures in the newborn infant likely reflect the immature state of brain development. In late gestation and early postnatal life, active but incomplete developmental processes include cortical organization, axonal and dendritic branching, and the development of synaptic connections. Myelination commences around term but at this stage is largely confined to the deep subcortical regions of the brain**(Adre,2008).**

The relatively underdeveloped organization of the cortex and undermyelination of axons likely underlies the disorganized convulsive activity and lack of orderly seizure propagation in the newborn. For the same reasons, primary generalized seizures are very rare in the newborn. In accordance with the caudal-to-rostral gradient of brain development, the cortical development of the deep limbic system, including its connections to the diencephalic and brainstem structures, is relatively advanced compared to the more rostral neocortex. This fact may underlie the prevalence of behaviors referable to the limbic system, diencephalon, and brainstem, such as the sucking and chewing oromotor automatisms, excessive drooling, oculomotor activity, and respiratory irregularities seen in subtle seizures. **(Adre,2008).**

A.Clinical diagnosis of neonatal seizures (Blume et al., 2009)

a)History:

Although it is often difficult to obtain a thorough history in infants transported to tertiary-care facilities from other hospitals, the physician must take a concerted effort to elicit pertinent historical data.

1. Family history: A positive family history of neonatal seizures is usually obtained in cases of metabolic errors and benign familial neonatal convulsions.

2. Maternal drug history: is critical in cases of narcotic withdrawal syndrome.

3. Delivery: Details of the delivery provide information regarding maternal analgesia, the mode and nature of delivery, the fetal intrapartum status, and the resuscitative measures used. Information regarding maternal infections during pregnancy points toward an infectious basis for seizures in an infant **(Blume et al., 2009)**.

b) Physical examination:

1. A thorough general physical examination should precede a well-planned neurologic examination. Determine the following:

a. Geslational age.

b. Blood pressure.

c. Presence of skin lesions.

d. Presence of hepatosplenomegaly.

2. Neurologic evaluation should include assessment of the level of alertness, cranial nerves, motor function, primary neonatal reflexes, and sensory function. Some of the specific features to look for are the size and "feel" of the fontanelle, retinal hemorrhages, chorioretinitis, pupillary size and reaction to light, extraocular movements, changes in muscle tone, and status of primary reflexes.

3. Notation of the seizure pattern. When seizures are noted, they should be described in detail. Including the site of onset, spread, nature, duration, and level of consciousness. Recognition of subtle seizures requires special attention **(Blume et al., 2009)**.

c) Laboratory studies:

In selecting and prioritizing laboratory tests, use the information obtained by history taking and physical examination and look for common and treatable causes.

1. CBC and differential. To rule out infection and polycythemia.

2. Serum chemistries. Estimations of serum glucose, calcium, sodium, blood urea nitrogen, and magnesium and blood gas levels must be performed. They may reveal the abnormality causing the seizures.

3. Spinal fluid examination. Evaluation of the cerebrospinal fluid (CSF) is essential because the consequences of delayed treatment or nontreatment of bacterial meningitis are grave. CSF PCR for herpes simplex virus if suspected.

4. Metabolic disorders. With a family history of neonatal convulsions, a peculiar odor about the infant, milk intolerance, acidosis, alkalosis, or seizures not responsive to anticonvulsants, other metabolic causes should be investigated.

a. Blood ammonia levels should be checked.

b. Amino acids should be measured in urine and plasma. The urine should be tested for reducing substances.

i. Urea cycle disorders.Respiratory alkalosis is seen as a result of direct stimulation of the respiratory center by ammonia.

ii. Maple syrup urine disease. With 2, 4-dinitrophenylhydiazine (2, 4-DNPH) testing of urine, a fluffy yellow precipitate is seen in cases of maple syrup urine disease **(Blume et al., 2009)**.

d) Radiologic studies:

1. Ultrasonography of the head is performed to rule out intraventricular hemorrhage (IVH) or periventricular hemorrhage.

2. Computed tomography (CT) scanning of the head provides detailed information regarding intracranial disease. CT scanning is helpful in looking for evidence of Infarction, hemorrhage, calcification, and cerebral malformations. Experience with this technique suggests that

valuable information is obtained in term infants with seizures, especially when seizures are asymmetric.

3. Magnetic resonance imaging (MRI). A cranial MRI is the most sensitive test to determine the etiology of seizures in the neonate. It is difficult to do in an unstable infant and is a test that requires a lot of time **(Blume et al ., 2009)**.

1. Clinical seizure subtypes:

It is important to understand that seizures in the neonate are different from those seen in older children.The differences are perhaps due to the neuroanatomic and neurophysiologic developmental status of the newborn infant.In the neonatal brain, glial proliferation, neuronal migration, establishment of axonal and dendritic contacts, and myelin deposition are incomplete Four types of seizures, based on clinical presentation,are recognized: subtle, clonic, tonic, and myoclonic **(Blume et al., 2009) .**

Continuous video-EEG monitoring has demonstrated a number of important facts about seizures in the newborn. First, nonepileptic mimics of clinical seizures are common in the newborn. These seizure-like behavior patterns may occur in the normal newborn (e.g., non-nutritive sucking) and nonepileptic paroxysmal clinical changes are common in encephalopathic newborns **(Adre, 2008).**

a.Subtle seizures:

They are characterized by paroxysmal alterations in neonatal behavior and motor or autonomic function that are not clearly clonic, tonic, or myoclonic **(Volpe, 2001).**

Subtle seizures are the most common subtype, comprising about half of all seizures in term and premature newborns. Subtle seizures are rarely isolated and infants with subtle seizures will almost always have other seizure types as well. Subtle seizures include a broad spectrum of behavioral phenomena, occurring in isolation or in combination **(Adre, 2008).**

Ocular phenomena are common and include tonic eye deviation, roving "nystagmoid" eye movements, and sudden sustained eye opening with apparent visual fixation. Tonic eye deviation is sometimes classified as a form of tonic seizure. Oro-bucco-lingual movements include

chewing, sucking, or lip-smacking movements, and are often associated with a sudden increase in drooling. Various alternating limb movements ("progression movements") have been described, including pedaling, boxing, rowing, or swimming movements. Autonomic phenomena, including sudden changes in skin color and capillary size, may occur alone or in combination with various motor manifestations. Such autonomic paroxysms are usually associated with initial tachycardia, and if sustained, with later bradycardia and possibly apnea **(Adre, 2008).**

Uncommonly, and unlike clonic seizures, some cases of subtle seizures may be provoked or intensified by stimulation.Available information from studies using EEG simultaneously with video recording or direct observation suggest that subtle seizures are more common in premature than in full-term infants and, some subtle clinical phenomena in full-term are not consistently associated with EEG seizure activity **(Mizrahi, 2001 and Biagioni et al., 2002)**

Radvanyi-Bouvet et al. indicated that common ictal clinical manifestations, confirmed by "simultaneous abnormal (EEG) discharges in a group of preature infants of 26 to 32 week gestation **(Radvanyi et al., 2000).**

Based on their inconsistent association with EEG seizures, as well as their poor response to conventional anticonvulsants, many consider these subtle seizures to be nonepileptic "brainstem release phenomena." **(Adre, 2008).**

Although these seizures are classified by some as non-epileptic in origin, one must keep in mind that these behaviors are mostly controlled by subcortical structures, and thus the cortical tracings of an EEG may not detect them (**Granelli and McGrath, 2004).**

b.Clonic seizures:

Are stereotypic and repetitive biphasic movements with a fast contraction phase and a slower relaxation phase. The rhythm of clonic seizures tends to be slower in the newborn than in older patients. Clonic seizures may be unifocal, multifocal, or generalized. Clonic seizures that remain unifocal are usually not associated with loss of consciousness. The most common cause for clonic seizures that remain unifocal Is neonatal stroke. Other causes of unifocal seizures include focal traumatic contusions, subarachnoid hemorrhage, or metabolic disturbances. In the newborn, multifocal clonic seizures rarely follow a "Jacksonian march;"

even when these multifocal seizures are sequential, they are rarely ordered in their progression. **(Adre,2008).**

Multifocal clonic seizures are migratory in nature. There can be a rapid migration of clonic movements from side to side or limb to limb, or prolonged focal tonic movements in one limb before progressing to another. Clonic seizures are usually associated with focal rhythmic sharp-wave EEG discharges **(Granelli and McGrath, 2004)**

Primary generalized clonic seizures are extremely rare in the newborn, probably because of the inability of the immature brain to propagate highly synchronized discharges simultaneously to the entire brain. (One exception to this is benign familial neonatal seizures. **(Adre, 2008).**

c. Tonic seizures:

Tonic seizures have a sustained period (seconds) of muscle contraction without repetitive features. Tonic seizures may be generalized or focal. **(Adre, 2008)**

A) Focal tonic seizures are associated consistently with EEG seizure discharges.

B)Generalized tonic seizures are characterized most commonly by tonic extension of both upper and lower extremities (mimicking "decerebrate" posturing) also by tonic flexion of upper extremities with extension of lower extremities (mimicking "decorticate" posturing).

The possibility that such clinical seizures usually represent posturing and not epileptic seizure was raised previously because of the frequent association with severe intraventricular hemorrhage and the often-poor response to anticonvulsant therapy **(Volpe, 2001).**

Tonic Seizures are most common in premature Infants with diffuse neurologic dysfunction or major intraventricular hemorrhage (IVH). Generalized tonic seizures are often associated with other motor automatisms or with clonic seizures, as well. Typically, infants are lethargic or obtunded between these seizures. Certain features suggest that these seizures may be nonepileptic in origin. Specifically, they may be precipitated by tactile or other stimuli, suggesting reflex discharges, and may be abolished by repositioning or light restraint. Finally, the

clinical events are typically not associated with electrographic seizure patterns. The background EEG pattern tends to have multifocal or generalized voltage depression and undifferentiated frequencies, and, in some cases, a markedly abnormal burst suppression pattern. Overall, the prognosis of tonic seizures is very poor, except in some cases of postasphyxial seizures where an outcome may be less grim. **(Adre, 2008).**

d. Myoclonic seizures:

Myoclonic seizures are distinguished from clonic seizures by their lightning-fast contractions and nonrhythmic character. These seizures may occur in a multifocal or generalized pattern. Even when repetitive, myoclonic seizures tend to be irregular or erratic in nature. In some cases, myoclonic seizures may be elicited by tactile or auditory stimulation or suppressed by restraint. The electroclinical association of myoclonic seizures is variable, and when present, the myoclonic contraction is usually associated with a single high-voltage spike and followed by a slow-wave complex **(Adre, 2008).**

Conversely, myoclonic movements in stimulus-sensitive myoclonic seizures or in those with chaotic fragmentary movement patterns are usually not associated with electrographic seizure activity. The EEG background activity tends to be low-voltage, slow-wave activity or a burst suppression pattern with focal sharp waves. These patterns may later evolve to a high-voltage, chaotic hypsarrhythmic pattern. Typically, myoclonic seizures are associated with diffuse and usually serious brain dysfunction resulting from etiologies such as perinatal asphyxia, inborn errors of metabolism, cerebral dysgenesis, or major brain trauma. Myoclonic seizures are usually associated with a poor long-term outcome. **(Adre , 2008).**

2. Seizure mimics:

In the newborn it may be difficult to distinguish between normal immature behaviors (e.g., non-nutritive sucking), abnormal but nonepileptic behaviors (e.g., "jitteriness"), and true epileptic manifestations. The following clinical guidelines may help distinguish true epileptic seizures from seizure mimics. These guidelines are most reliable with suspected clonic seizures but even then are not infallible.

First, true epileptic seizures are rarely stimulus-sensitive. **Second,** epileptic seizures cannot be abolished by passive restraint or repositioning of the infant. **Third,** epileptic seizures are often associated with

autonomic changes or ocular phenomena. "Jitteriness" (tremor) may be distinguished from clonic seizures by the equal amplitude and faster equiphasic rhythm, compared to the slower, fast-and-slow components of clonic seizures. Generally, normal nonepileptic behaviors are associated with a normal interictal examination. Conversely, abnormal but nonepileptic repetitive behaviors often occur in encephalopathic infants with an abnormal interictal exam **(Adre, 2008).**

A temporal association between repetitive clinical events and simultaneous repetitive EEG changes is the strongest supportive evidence for true epileptic seizures. However, using electrographic monitoring to confirm the epileptic nature of suspicious clinical events is more complicated and controversial in the newborn. This is particularly true when clinical seizure events are not accompanied by EEG changes, a situation most often seen with subtle seizures and generalized tonic seizures. **(Adre, 2008).**

There are two opposing views regarding electrically silent clinical "seizures," based on different interpretations of the same fundamental assumptions. In both views, cerebral hemispheric dysfunction results in "disconnection" between higher cortical regions and deeper brainstem areas, thereby causing the electroclinical dissociation in these "spells." On the one hand, these behavioral paroxysms are considered nonepileptic seizure mimics. In this model, the paroxysmal movements are considered to arise from "central pattern generators" in the brainstem. Normally, these brainstem centers are under tonic descending inhibitory input from higher cortical centers. However, injury to the more rostral hemispheric regions disconnects the inhibitory input to the brainstem, "releasing" the primitive reflex movement patterns. These released movements may include relatively complex progression movements, or simple tonic posturing that originates from the brainstem reticulospinal nuclei. Several features support the theory that these spells are disinhibited reflex movements. **First,** they can often be elicited by external stimuli (spontaneous events may be the result of endogenous stimuli). **Second,** there is often a temporal and spatial summation of these movements to stimulation, with repeated stimuli eliciting movements that radiate or spread to sites distant from the point of stimulation. **(Adre, 2008).**

In contrast to this "reflex release" concept of electrically silent clinical seizures, others consider these events to have a true epileptic origin. According to this model, seizure discharges originating in the inferomedial cortex are transmitted to deep brainstem centers where they elicit paroxysmal behavioral phenomena. However, these deep discharges cannot be transmitted through the injured and dysfunctional hemispheric

pathways to higher cortical regions, and therefore remain undetected by conventional EEG montages. Support for this model includes the fact that these clinical events with no EEG changes may at other times be coupled to EEG discharges in the same patient. To date, these difficult issues remain unresolved. **(Adre, 2008)**.

a.Epileptic apnea in the newborn:

The issue of apnea as a seizure manifestation in newborn deserves special consideration, because apnea has been demonstrated as a seizure manifestation in the premature newborn **(Dunati et al., 2001)**

The vast majority of apneic episodes in the premature infant are not epileptic in origin **(Eichenwald et al., 1997).**

Apnea is not uncommon during neonatal seizures, but is rarely the only manifestation. Most infants with epileptic apnea will at some point in their course develop other seizure manifestations. Epileptic apnea may be difficult to distinguish from apnea due to other causes, such as neurologic depression, prematurity, sedative medications, and respiratory illness. However, there are several helpful distinguishing features. Neonatal epileptic apnea rarely lasts longer than 10 to 20 seconds. Brady-cardia is often an early accompaniment of nonepileptic apnea, whereas in epileptic apnea, an initial tachycardia is more common, only followed in more prolonged seizures by later bradycardia **(Adre, 2008).**

The EEG discharges that accompany epileptic apnea are often monorhythmic (most commonly frequency); in addition, they are usually focal over the temporal regions, suggesting an epileptogenic focus in the limbic system. Conversely, nonepileptic apnea is not accompanied by EEG changes except for amplitude suppression that may develop during prolonged apnea. **(Adre, 2008).**

However, apnea has been documented with electrical seizure activity more commonly in the full-term newborn **(Helmers et al., 1999)**

b- Benign neonatal sleep myoclonus:

It is relatively common and sometimes dramatic nonepileptic form of myoclonus. This condition presents in the first week of life, and resolves spontaneously (i.e., without treatment) over weeks to months. The convulsive activity emerges during quiet non rapid eye movement (non-REM) sleep and is rapidly abolished by arousal. Myoclonic activity often builds up dramatically in both intensity and distribution over a period of minutes. Unlike other nonepileptic behaviors, this form of

myoclonu may be precipitated in some cases by gentle rhythmic rocking or tactile stimuli, and gentle restraint may actually increase rather than abolish the myoclonus. These events never occur during wakefulness and the neurologic examination is normal. Immediately before and during the episodes, the EEG shows features of quiet sleep (sometimes open-eye sleep) with no ictal changes. The interictal EEG is unremarkable. The mechanism is unclear but may be related to a transient dysmaturity of the brainstem reticular-activating system. Anticonvulsants are not indicated, and, in fact, benzodiazepines may exacerbate the myoclonic jerks. The long-term outcome is normal and later epilepsy does not develop **(Adre, 2008).**

B. EEG diagnosis of neonatal seizures.

By definition, an electrographic seizure is a repetitive series of electrical discharges that evolves in frequency, amplitude and topographic field.

As with the clinical manifestations, the electrographic features of neonatal seizures differ in a number of ways from those in more mature patients. Unlike older patients, focal-onset seizures are the rule in the newborn, and primary generalized seizures are exceptionally rare. In addition, there are rhythmic EEG patterns that are normal at specific gestational ages. Abnormal but nonepileptic rhythmic changes may occur on abnormal EEG background in encephalopathic infants. Somewhat arbitrarily, the threshold criterion for the diagnosis of an electrographic seizure has been set at 10 seconds or more of repetitive electrographic discharges. Gestational age has an important influence on the electrographic expression of seizures in the newborn. Such EEG seizures are rare before 34 weeks of gestation; with increasing maturation, the frequency and duration of electrographic seizures increase. **(Adre, 2008).**

Although the amplitude and frequency of an electrographic seizure tend to evolve as the focal seizure unfolds, the topographic field of seizure spread remains relatively circumscribed in the newborn. Even when several focal seizures develop in different brain regions at the same time, each seizure appears independent in frequency, amplitude, and morphology. Finally, unlike the interictal EEG in older patients with seizures, the neonatal EEG lacks interictal epileptiform patterns that reliably predict the risk for subsequent seizures; in fact, the development of electrographic seizures in the newborn has been described as an all-or-none phenomenon. **(Adre, 2008).**

1. The role and timing of EEG studies in the newborn with suspected seizures. Electroencephalograms (EEGs) obtained during a seizure are abnormal. Interictal EEGs may be normal. However, an order to obtain an ictal EEG should not delay other diagnostic and therapeutic steps. The diagnostic value of an EEG is greater when it is obtained in the first few days because diagnostic patterns indicative of unfavorable prognosis disappear thereafter. Electroencephalography is valuable in confirming the presence of seizures when manifestations are subtle or when neuromuscular paralyzing agents have been given. EEGs are of prognostic significance in full-term infants with recognized seizures. For proper interpretation of EEGs it is important to know the clinical status of the infant (including the sleep state) and any medications given **(Blume et al., 2009).**

Ideally an EEG study should be recorded as soon as a seizure is first suspected, and preferably not later than 24 hours after. If such an EEG is normal, particularly if a suspected clinical event is captured during the EEG recording, then subsequent EEGs are only indicated if the clinical spells keep recurring. Whenever possible, several suspect events should be captured on EEG to confirm the true epileptic nature of the events **(Adre, 2008).**

The absence of EEG changes during several clinical events, especially when the interictal EEG background is normal, is suggestive of a nonepileptic process. If the initial EEG captures the features of seizure activity and antiepileptic drugs are started, a period of continuous video-EEG monitoring is recommended because anticonvulsant medications may abolish only the clinical manifestations, allowing ongoing and undetected EEG seizures to persist. Ideally, EEG monitoring should continue for 24 to 48 hours after the last recorded electrographic seizure. A repeat EEG after 1 week may have particular prognostic value. The need for subsequent EEG studies as a guide to discontinuation of anticonvulsant medications is controversial. **(Adre, 2008).**

C. Etiologic diagnosis of neonatal seizures.

At the first suspicion of neonatal seizures, the immediate focus should be the exclusion of rapidly correctable and potentially injurious processes, including hypoglycemia, hypocalcemia, and Hypomagnesemia, among others. After seizures are confirmed and management has commenced, the etiology should be pursued through a rational and orderly approach, with a stepwise interpretation of the facts, and refocusing of the diagnostic plan. Using an orderly and rational

approach, most neonatal seizure etiologies should be identifiable. **(Adre, 2008).**

1. Specific etiologies

a. Hypoxic-Ischemic encephalopathy.

Most common cause of neonatal seizures in both preterm and term infant. Characteristically seizures occur in the first 24 hours of life.

Present with subtle seizures; multifocal clonic or focal clonic seizures. Focal clonic seizures may indicate associated focal cerebral infarction. **(Cloherty et al., 2004)**

Cerebral hypoxia-ischemia, may occur in the antenatal, intrapartum, or neonatal periods. Perinatal asphyxia is implicated in 25% to 40% of neonatal seizures. However, there is substantial variability in the reported incidence of this etiology, primarily because of the inconsistency of diagnostic criteria used in different reports. The advent of more sophisticated imaging techniques such as MRI and magnetic resonance (MR) spectroscopy have allowed the more precise in vivo diagnosis and timing of hypoxic-ischemic lesions. With such imaging, earlier (i.e., antepartum) hypoxic-ischemic lesions are diagnosed, even in cases without significant neonatal encephalopathy. **(Adre, 2008).**

Postasphyxial seizures occur in infants with moderate-to-severe grades of encephalopathy, that is, with obtundation, stupor, or coma. In addition, these infants tend to have muscle hypotonia, altered deep tendon reflexes and, in severe cases, brainstem abnormalities. Intrapartum asphyxia should never be a diagnosis of exclusion, and should satisfy certain criteria, including evidence of significant fetal distress, immediate postnatal "depression" at birth, and subsequent altered mental status **(Adre, 2008).**

Significant fetal distress manifests with evidence of certain specific abnormal fetal heart rate patterns (e.g., loss of variability plus late decelerations; sustained bradycardia) and/or evidence of "significant" fetal metabolic acidosis. Although the absolute criteria for significant metabolic acidosis remain controversial, most agree that an umbilical artery pH <7.0 with a base deficit of >12 mEq reflects fetal asphyxia capable of causing neonatal encephalopathy and seizures. Commonly

accepted criteria for immediate neonatal depression include an Apgar score of <5 at 5 minutes of life. In cases where there is a prolonged latency between a fetal asphyxial insult (e.g., an antepartum or early intrapartum insult) and delivery, the criteria in the preceding text may not be satisfied. In these cases, specialized MRI studies have demonstrated characteristic features of hypoxic-ischemic brain injury despite the absence of significant acidosis or immediate neonatal depression. Most postasphyxial seizures in the newborn occur within the first 24 hours after the insult, 50% or more occurring within 12 hours of birth. The seizure onset in each case is likely influenced by the severity, duration, and onset of the intrauterine asphyxial insult. It is likely that more severe insults are followed by earlier onset seizures, but this is not firmly established **(Adre, 2008).**

b.Focal ischemic injury

i. Neonatal arterial stroke:

It occurs in around 1 in 4,000 live births. In most cases, the etiology of neonatal strokes remains unknown; however, certain risk factors have been identified. Seizures are the most common presentation of stroke in the newborn period, and stroke is the second most common cause of neonatal seizures, accounting for 15% to 20% of cases. The onset of clinical seizures is variable and may be missed, because most strokes occur in otherwise well term infants, without previously known risk factors. These infants usually appear normal immediately before and after seizures. In fact, in the absence of identified seizures, the diagnosis of neonatal stroke may be delayed until the onset of infant hand use around 4 to 5 months when motor asymmetries become evident. These seizures are typically unifocal, with minimal spread. Because neonatal arterial stroke most commonly involves the left middle cerebral artery (MCA), right-sided clonic seizures are the most common clinical presentation. The clonic activity is generally slower than that in older patients. Poststroke seizures usually have a very good association between clinical and electrographic manifestations **(Adre, 2008).**

ii. Cerebral vein thrombosis:

It usually occurs in the large dural sinuses, particularly the posterior aspects of the superior sagittal sinus. Although the presentation of cerebral vein thrombosis may be subtle, with lethargy often the only feature, approximately 60% of cases develop neonatal seizures. Unlike the relatively normal mental status of infants with arterial stroke and seizures, infants with cerebral vein thrombosis and seizures are more

encephalopathic, with depressed mental status before and between seizures. **(Adre, 2008).**

iii. Cerebral infarction:

It has been described in neonates with seizures and can result from events during the antepartum, intrapartum or neonatal period; it may occure during the postnatal period from asphyxia, polycythemia, dehydration or coagulopathy. Cerebral infarction in the venous distribution of the brain may also lead to neonatal seizures **(Taeusch et al., 2005).**

c.Intracranial hemorrhage:

Intracranial hemorrhage is implicated in approximately 10% of neonatal seizures. The location of hemorrhage and the clinical features of the seizures vary with gestational age. With term infants, posthemorrhagic seizures are most commonly associated with primary subarachnoid hemorrhage and less often with subdural hemorrhage (SDH). Primary subarachnoid hemorrhage occurs more frequently after difficult prolonged or traumatic labor, including forceps and vacuum deliveries. However, primary subarachnoid hemorrhage may occur after apparently uncomplicated labor (i.e., so-called parturitional hemorrhage). Such primary parturitional subarachnoid hemorrhage results in focal or multifocal seizures, usually starting on the second day of life; in infants who appear relatively well between seizures. These seizures often have good clinical and electrical association **(Adre, 2008).**

Infants with seizures associated with primary subarachnoid hemorrhage have a good long-term outcome in 90% of cases. About half of all subdural hemorrhages (SDH) diagnosed in the newborn are complicated by seizures, usually presenting in the first days of life. Neonatal SDH usually occurs in large babies, breech delivery, or difficult instrumented delivery, because of sheering forces and tears of the tentorium, falx, or cortical bridging veins. Infratentorial SDHs in the limited posterior fossa space demand urgent evaluation because potentially fatal brainstem dysfunction may evolve rapidly posthemorrhagic seizures in the preterm infant have different features and a more ominous prognosis. **(Adre, 2008).**

Hemorrhages are principally General Matrix-Intraventricular (GM-IVH), often with Periventricular Hemorrhagic (PVH) infarction in the premature infant.Premature infants with severe GM-IVH; onset of seizures in first 3 days, usually generalized tonic type with subtle

seizures.Those with associated PVH usually develop seizures after 3 days of life. **(Cloherty et al., 2004)**

These seizures are usually associated with severe IVH, or its parenchymal complication, periventricular hemorrhagic infarction (PVHI). Seizures following severe IVH usually present within the first 3 days of life in sick, very premature infants. The seizures are usually generalized tonic seizures with poor electroclinical association. They form part of a critical illness, which often evolves to coma and death in the acute phase. Seizures associated with PVHI tend to occur after the third day of life. **(Adre, 2008).**

d.Central nervous system infections:

Central nervous system infections from a variety of agents, including viral, bacterial, or other organisms such as toxoplasmosis, may have neonatal seizures as a prominent part of their presentation. These infections may originate in the fetus, for example, congenital encephalitis due to cytomegalovirus (CMV) and toxoplasmosis. When CMV encephalitis occurs in earlier gestation it may cause cerebral dysgenetic lesions, which may further increase the risk of seizures. Intrauterine infections with toxoplasmosis or CMV that are severe enough to cause neonatal seizures usually do so within the first 3 days of life **(Adre, 2008).**

Other viral infections of importance are herpes simplex virus (HSV) infections that may become symptomatic in the first days of life after intrapartum infection [usually HSV type 2] or have a more delayed presentation (usually postnatal acquisition of HSV type 1). The development of bacterial meningitis, most commonly Group B streptococcal meningitis, may also have a biphasic appearance with early and late forms. The mechanism of seizures in central nervous system infections may be through direct cerebritis or vaso-occlusive injury with secondary seizures. The onset of infection-related seizures obviously depends on the various organisms and onset of infection. Of the bacterial infections, meningitis due to Group B streptococcus and Escherichia coli are the most common, and in these cases, seizures usually develop in the latter part of the first week or later**. (Adre, 2008).**

e.Metabolic disturbances :

Two types of metabolic disturbances may result in neonatal seizures: (i) transient and rapidly correctable disturbances, and (ii) inherited and usually persistent causes.

i. Transient metabolic disturbances include disturbances of blood glucose and electrolyte disturbances such as hypoglycemia, hypocalcemia and hypomagnesemia. These conditions frequently occur in conjunction with other potentially epileptogenic conditions such as perinatal asphyxia. **(Adre, 2008).**

a) Hypoglycemia. I. Early definitions of normal neonatal glucose levels were derived by measuring glucose levels in populations of infants, some of whom were not being fed or given other sources of glucose. The statistical definition of normal, values that are within two standard deviations of the mean, resulted in the acceptance of glucose levels in the range of 20 to 30 mg/dL.This definition was affected by clinical practice at the time, and did not define "optimal" glucose level in newborns. This definition is no longer generally accepted.

b. Clinical definition (Whipple triad) requires the following;

I. Reliable measurement of a low glucose level.

II. Signs and symptoms consistent with hypoglycemia. Development of

clinical signs or symptoms may be a late sign of hypoglycemia.

III. Resolution of signs and symptoms after blood-glucose level is restored to normal range **(Richard, 2009)**

Hypoglycemia is especially common in infants with intrauterine growth retardation, diabetic mothers, or perinatal asphyxia. Less commonly, hypoglycemia may be a prominent feature of certain inborn errors of metabolism (e.g., galactosemia, glycogen storage diseases) or hyperinsulinemic conditions (e.g., Beck-with-Wiedeman syndrome, nesidioblastosis). Glucose transporter deficiency is a more recently described condition in which blood glucose levels are normal but CSF glucose levels are low. . **(Adre, 2008).**

Occurrence of neurological symptoms is determined by the duration of hypoglycemia. This is more common in SGA infants compared to IDM.

Neurological symptoms include jitteriness, stupor, hypotonia, apnea and seizures.Often to establish that hypoglycemia is the cause of seizures because of frequently associated perinatal asphyxia, hypocalcaemia and hemorrhage **(Taeusch et al., 2005)**

The timing of seizures in neonatal hypoglycemia is usually on the second day of life, but the primary link between hypoglycemia and seizures may be difficult to establish. Because seizures usually develop after sustained hypoglycemia, these infants often have a poor outcome. **(Adre, 2008).**

b) Hypocalcemia. Definition: Neonatal hypocalcemia is defined as a total serum calcium concentration of <7 mg/dL or an ionized calcium concentration of <4 mg/dL (1 mmoI/L). In very low birth weight (VLBW) infants, ionized calcium values of 0.8 to 1 mmol/L are common and not usually associated with clinical symptoms. In larger infants, and in infants of >32 weeks gestation, symptoms may more readily occur with an ionized calcium concentration of <1 mmol/L. **(Steven, 2008).**

Hypocalcaemia has 2 major peaks of incidences:

1st peak in first 2 to 3 days of life, usually in low birth weight infants, IDM and infants with HIE of perinatal asphyxia. A therapeutic response to intravenous calcium is helpful in determining low serum calcium as a cause of the seizures. It is much more common for early hypocalcaemia to be an association of early seizures rather than a cause.

Later-onset of hypocalcaemia are associated with endocrinopathy (maternal hypoparathyroidism and neonatal hypoparathyroidism) and heart disease (with or without Differences George syndrome), rarely with nutritional type (cow's milk and high phosphorus synthetic milk). **(Taeusch et al., 2005).**

c) Hypomagnesemia: low serum magnesium level of < 1.6 mg/dll suggest Hypomagnesemia **(steven, 2008).**

Hypomagnesemia is a frequent accompaniment or indeed may be present without hypocalcemia. The neurological syndrome is consistent and distinctive, consisting, primarily of hyperactive tendon reflexes; knee, ankle, and jaw clonus; jitterness; and seizures. The convulsive phenomena are often focal, both clinically and

electroencephalographically. Later, onset hypocalcemic seizures are associated more commonly with endocrinopathy (maternal hypoparathyroidism and neonatal hypoparathyroidism) or with congenital Heart disease (with or without DiGeorge syndrome). Onset of seizures is most commonly between 2 and 6 weeks of age **(Volpe, 2001).**

d) Hyponatremia occurs most commonly with inappropriate antidiuretic hormone secretion, after severe trauma, infection, or asphyxia **(Fanaroff et al., 2006)**or excessive intake of water (with an unexperienced mother administering diluted formula, water only, or both **(Volpe, 2001)**perinatal asphyxia, and inadvertent water intoxication **(Adre, 2008).**

e) Hypernatremia:

It is a rare cause of seizures, usually associated with congenital adrenal abnormalities or iatrogenic disturbance of serum sodium balance, from the use of intravenous.fluids with high concentrations of sodium **(Taeusch et al., 2005**).

ii. Inborn errors of metabolism: are uncommon causes of neonatal seizures; nevertheless, neonatal seizures have been described in a long list of such conditions (see partial list in Table 2). **(Adre, 2008).**

Table 2: Some of the Inborn Errors of Metabolism Presenting with Neonatal Seizures

Pyridoxine dependency
Nonketotic hyperglycinemia
Urea cycle defects
Sulfite oxidase deficiency
Glutaric aciduria type II
Maple syrup urine disease
Menkes disease
Molybdenum cofactor deficiency
Propionic aciduria
Methylmalonic aciduria
Mitochondrial diseases
Glucose transporter deficiency

Certain of these conditions are more likely to be associated with seizures, including nonketotic hyperglycinemia, pyridoxine dependency, sulfate oxidase deficiency, glutaric aciduria type II, and urea cycle

defects. The most common diagnostic abnormalities associated with these conditions include metabolic acidosis, hyperammonemia, hypoglycemia and ketosis. Most of these conditions are due to permanent enzyme defects, and are largely incurable. However, their recognition is important for two reasons. **First,** some metabolic disturbances have transient forms that resolve over time (e.g., nonketotic hyperglycinemia). **Second,** some of these conditions are treatable (e.g., pyridoxine dependency). In both these situations, early diagnosis and treatment may prevent or limit brain injury. **(Adre, 2008).**

a) Pyridoxine dependency Pyridoxine dependent seizures are a rare but treatable subgroup of neonatal seizures, which can begin during the intrauterine life. Generalized clonic seizures are resistant to conventional Antiepileptic Drugs (AEDs) **(Taeusch et al., 2005).**

It results from impaired binding of the active form of pyridoxine to the enzyme glutamic acid decarboxylase (GAD). This enzyme is responsible for the conversion of the excitatory amino acid neurotransmitter, glutamate, to the inhibitory neurotransmitter, GABA. Therefore, impaired GAD activity causes a marked increase in excitatory versus inhibitory neurotransmitter levels. Not only does this elevated excitatory state precipitate seizures, but high glutamate levels may be lethal to both neurons and oligodendroglia. Seizures in pyridoxine dependency often present early, that is, within the first hours of life or even in the fetus. The diagnosis is usually made by a therapeutic trial of intravenous pyridoxine with simultaneous EEG monitoring. Seizures cease after appropriate doses of pyridoxine and recur after it is withdrawn. Ongoing seizures after adequate dosing exclude the diagnosis. In addition, affected infants have low GABA levels and high glutamate levels in the CSF. **(Adre, 2008).**

b) Glycine encephalopathy (nonketotic hyperglycinemia) is an autosomal recessive condition in which a deficiency in the glycine cleavage system results in very high levels of glycine in the brain and CSF. Glycine is a coagonist at the excitatory cerebral N-methyl-D-aspartate (NMDA) glutamate receptor, but is inhibitory in the brainstem and spinal cord. The marked elevation of glycine levels results in refractory myoclonic seizures (due to excitation of cortical NMDA receptors), stupor, respiratory disturbances, and hypotonia (due to brainstem inhibition). **(Adre, 2008).**

Myoclonus elicjted by tactile and painfui stimuli on the second or third day of life **(Scher et al., 2003).**

The diagnosis is made by demonstrating markedly elevated glycine levels In the CSF, and may be missed if only serum or urine levels are measured because these may be normal or mildly elevated. The EEG background pattern typically shows burst suppression. Most infants with nonketotic hyperglycinemia die by 1 year of age, but a transient and potentially benign form may present with seizures in early neonatal life. Consequently, aggressive support is indicated until such a transient form is excluded. Antenatal diagnosis is possible by chorionic villus sampling. **(Adre, 2008).**

c) Folinic acid-responsive seizures may present in the neonatal period, often within the first few hours as a severe neonatal epileptic encephalopathy with myoclonic, clonic, or apneic spells. Between seizures the infant may be irritable, jittery or comatose. The EEG may be discontinuous with multifocal discharges. Neuroimaging is normal at onset, but later shows white matter abnormalities and cerebral atrophy. The CSF shows an as yet unidentified compound; the true pathophysiology of this condition remains unknown. On occasion these seizures may respond initially to Phenobarbital (PB) or pyridoxine but eventually breakthrough seizures occur. Neonatal seizures of unknown etiology that persist after an adequate trial of anticonvulsant drugs and pyridoxine warrant a 24- to 48-hour trial of enteral folinic acid. Seizures usually cease within 24 hours of treatment. **(Adre, 2008).**

d) **Others:** Organic acidopathy, hyperammonemia (often associated with acidopathies), mitochondrial disturbance (pyruvate dehydrogenase, cytochrome-c oxidase) and peroxisomal disturbance (Zellweger syndrome and neonatal adrenal leukodystrophy) **(Taeusch et al., 2005)**

Drug withdrawal:

Newborns born to mothers with a history of prenatal substance abuse may be at increased risk for neonatal seizures. Exposure to barbiturates,

alcohol, heroin, cocaine or methadone commonly results in neurologic abnormalities that include tremors and irritability. Withdrawal symptoms in addition to seizures, may occur as long as 4 to 6 weeks alter birth. Electroencephalographic studies are useful to corroborate such movements with coincident electrographic seizures. Certain drugs such as short-acting barbiturates may be associated with seizures within the first few days of life. Seizures may occur directly after substance withdrawal or may be associated with longer-standing uteroplacental insufficiency,

promoted by chronic substance use and poor prenatal health maintenance by the mother. Inadvertent fetal injection with a local anesthetic agent during delivery may induce intoxication, which is rare cause of seizures **(Taeusch ct al., 2005)**

f.Cerebral dysgenesis: A number of dysgenetic cerebral lesions may be associated with neonatal seizures. In many, but not all, cases these lesions can be demonstrated in vivo by computed tomography (CT) or MRI scan. Conditions most commonly associated with neonatal seizures are disorders of neuronal migration (e.g., heterotopias, lissencephalies) or disorders of neuronal organization (e.g., polymicrogyria). These ectopic or disorganized collections of neurons are abnormally prone to hyperexcitability and bursts of discharges leading to seizures. The genetic lesions causing these disorders are being uncovered. Occasionally cerebral dysgenesis may be associated with and possibly caused by inborn metabolic disturbances, such as 7-dehydrocholesterol deficiency in certain holoprosencephalies, and carbohydrate-deficient glycoprotein syndrome and nonketotic hyperglycinemia in some cases of agenesis of the corpus callosum. Infants with cerebral dysgenesis and fluctuating consciousness, vomiting, and apparent regression, should be evaluated for metabolic conditions that may cause ongoing neurodegeneration. **(Adre, 2008).**

g.Epileptic syndromes in the newborn infant:

i. There are two benign and three malignant epileptic syndromes presenting with seizures in the newborn infant. **(Adre, 2008).**

a) Benign familial neonatal seizures Benign familiar neonatal convulsions constitute a rare disorder with autosomal dominant inheritance. Seizures occur mostly on the second or third day and may recur for days to weeks before gradually resolving. The interictal neurologic examination is normal **(Cloherty et al., 2004).**

And most cases have a normal long-term neurodevelopmental outcome. Less than 10% of cases later develop epilepsy, usually in adulthood. Neither the number of neonatal seizures, nor their treatment, appears related to the long-term outcome. These features have suggested that aggressive anticonvulsant therapy may not be indicated in this condition.

Benign familial neonatal seizures are a rare form of primary genaralized seizures in the newborn. The clinical phenomena are variable but include a brief initial phase of apnea, tachycardia, and tonic posturing

(with abduction or adduction of the arms, flexion of the hips, and extension of the knees) followed by a phase of clonic activity. As such this condition is one of the rare instances in which tonic-clonic seizures occur in the newborn. These seizures tend to occur mainly during active sleep and may be preceded by brief arousal. The ictal EEG features consist of a sudden brief period of generalized voltage attenuation (during the apneic and tonic phase) followed by a longer generalized discharge of repetitive spike and/or sharp waves (during the clonic phase). Rarely do benign familial neonatal seizures have a consistent EEG focus or a postictal phase. The interictal EEG is either normal or has occasional bursts of alternating 0-rhythmic activity (theta pointu alternant). All laboratory and imaging studies aimed at identifying an etiology are normal. Two separate genetic loci have been identified **(Adre, 2008).**

Most families have a locus at chromosome 20ql3.3, which encodes for a potassium channel, suggesting an impairment of potassium-dependent neuronal repolarization as the basis for the seizures. In other families, the locus is at chromosome 8q24**(Adre,2008).**

b) Benign idiopathic neonatal seizures make up approximately 5% of seizures in term infants. Certain diagnostic criteria have been proposed, including: (i) birth after 39 weeks' gestational age; (ii) normal pregnancy and delivery; (iii) Apgar scores >8; (iv) normal neonatal course before the seizures; (v) seizure onset between days 4 and 6 of life; (vi) normal neurologic state before and between seizures; (vii) clonic and/or apneic (never tonic) seizures; (viii) normal diagnostic testing; (ix) an ictal EEG showing brief (1-3 minute) seizures (never a frequency) in the rolandic regions; and (x) a normal interictal EEG except for theta pointu alternant pattern (in 60% cases) **(Adre,2008).**

The cause of these seizures remains unknown, but may be related transient zinc deficiency since CSF zinc level may be decreased **(Cloherty et al., 2004).**

Several features distinguish these idiopathic seizures from benign familial seizures; these include:

(i) absence of a family history; (ii) later seizure onset, around day 5 of life; (iii) convulsions that are clonic and/or apneic, but never tonic; (iv) multifocal clonic seizures that are never primary generalized; and (v) lack of the initial voltage attenuation on the ictal EEG. Instead, the ictal EEG shows lateralized or secondarily generalized rhythmic spikes and slow waves. The period of seizure activity is usually brief but intense, with frequent or serial seizures, and even status epilepticus. This phase is

followed by gradual resolution, with seizures seldom persisting longer than 2 weeks. The long-term outcome is invariably favorable and later epilepsy does not occur **(Adre, 2008).**

ii. There are three early epileptic encephalopathies with associated with a poor prognosis. **(Adre, 2008).**

a)Neonatal myoclonic encephalopathy (NME) presents with erratic and fragmentary partial seizures and massive myoclonus. These seizures typically start as focal motor seizures, and later evolve into typical infantile spasms. The most common etiologies associated with this condition are metabolic disorders (especially nonketotic hyperglycinemia). The ictal EEG shows high-amplitude EEG bursts coinciding with the massive myoclonic seizures. The interictal pattern shows a burst suppression pattern with complex bursts and sharp waves alternating with periods of low-amplitude quiescence. The long-term outcome is universally poor, with a high mortality in the first year and severe retardation in all survivors **(Adre, 2008).**

b) Ohtahara syndrome usually presents within the first 10 days of life but may present as late as 3 months. The seizures are typically numerous brief tonic spasms (and not clonic or fragmentary myoclonic). In contrast to the metabolic causes of NME, the causes of Ohtahara syndrome tend to be structural, with most being dysgenetic or, occasionally, destructive, such as hypoxic-ischemic injury. The interictal EEG is usually an invariant burst suppression pattern, with no sleep-wake cycling. Unlike the ictal EEG of NME, the tonic spasms tend to occur with a period of EEG suppression and not with the bursts. As in NME, the prognosis of Ohtahara syndrome is universally grim, with early death or, among survivors, severe handicap and frequently infantile spasms **(Adre, 2008).**

c) Migrating partial seizures of infancy (Coppola syndrome): It is an early onset epileptic encephalopathy starting between birth and 6 months of age, with no currently identifiable etiology and normal neuroimaging studies at the onset. The clinical seizures are partial clonic seizures often alternating between the two sides of the body. The seizures are typically multifocal on EEG and migrate independently and sequentially over both hemispheres. They are refractory to conventional antiepileptic medications and in most (but not all) cases develop marked hypotonia, severe neurodevelopmental retardation and cerebral atrophy over time. To date, extensive etiologic studies have not revealed a cause **(Adre, 2008).**

Differential diagnosis of etiology of seizure movements:

Table (3): differential diagnosis of neonatal seizures by peak time of onset (Grenelli and Mcgrath, 2004):

24 hours

1- Bacterial meningitis and sepsis.
2- Direct drug effects.
3- Hypoxic-ischemic encephalopathy.
4- Intrauterine infection.
5- Intraventricular hemorrhage at term.
6- Laceration of tentorium or falx.
7- Pyridoxine dependency.
8- Subarachnoid hemorrhage.

24 to 72 hours :

1- Bacterial meningitis and sepsis.
2- Cerebral contusion with subdural hemorrhage
3- Cerebral dysgenesis.
4- Cerebral infarction.
5- Drug withdrawal.
6- Glycine encephalopathy.
7- Glycogen synthase deficiency.
8- Hypoparathyroidism hypocalcemia.
9- Incontinentia pigmenti.
10- Intracerebral hemorrhage.
11- Intraventricular hemorrhage in premature newborns.
12- Pyridoxine dependency.
13- Subarachnoid hemorrhage.
14- Tuberous sclerosis.
15- Urea-cycle disturbances.

72 hours to one week :

1- Familial neonatal seizures.
2- Cerebral dysgenesis.

3- Cerebral infarction.
4- Hypoparathyroidism.
5- Intracerebral hemorrhage.
6- Kernicterus.
7- Methylmalonic acidemia.
8- Nutritional hypocalcemia.
9- Proprionic acidemia.
10- Tuberous sclerosis.
11- Urea-cycle disturbances.

One week to 4 weeks :

1- Adrenoleukodystrophy, neonatal.
2- Cerebral dysgenesis.
3- Fructose dysmetabolism.
4- Gaucher disease type 1.
5- Gm 1 gangliosidosis type 1.
6- Herpes simplex encephalitis.
7- Ketotic hyperglycinemias.
8- Maple syrup urine disease, neonatal.
9- Tuberous sclerosis.
10- Urea-cycle disturbances.

Differential diagnosis of seizure movements from other movements:

1- Jitteriness:

Features characteristic of tremors include fast movements (4-6 per second), absence of a fast and slow component, provocation by stimulation of the infant or stretching a joint, termination by passive flexion of the limb, and absence of associated eye movements, autonomic changes or EEG correlates **(Sankar et al., 2008).**

Characteristics of Jitteriness and clonus that help to differentiate them from seizures are as follows **(Volpe, 2001):**

a) Absence of abnormal gaze or movements.

b) Provocation by stimulation of the infant or by stretching a joint, in contrast to the usual spontaneous occurrence of seizures.

c) Cessation of movement with passive flexion or gentle restraint.

d) Absence of fast and slow component characteristics of a clonic fit.

e) Tremors and clonus have no associated EEG abnormalities.

0 Repetitive jerks in seizures tend to be between 2 and 3 per second, whereas clonus tends to be faster (5 to 6 per second). **(Mizarhi, 1987).**

Normal movements seen more commonly in preterm infants:

• Benign neonatal sleep myoclonus occurs in preterm infants in the first week of life. Restraint and benzodiazepines may increase the frequency of jerks, while on arousal they are usually abolished. EEG will be normal in this condition.

•Fragmentary myoclonic jerks.

•Eye movements; roving or dysconjugate eye movements with occasional non-sustained nystagmoid jerks.

Recurrent apnea may be manifestation of a seizure, especially if associated with tonic posturing **(Sankar et al., 2008).**

2- Hyperekplexia:

Hyperekplexla is a rare differential diagnosis of neonatal fits. It is a rare autosomal dominant disorder characterized by hypertonia especially in infancy and an exaggerate startle response **(Tohier et al., 1991).**

The startles can look like myoclonic jerks, and the high tone hyper-reflexia and jitteriness can lead to an erroneous diagnosis of seizures **(Gordon, 1993).**

Hyperekplexia is probably the same condition previously known as hereditary Stiff baby syndrome which was described by **(Linghnm 1981).**

Treatment with clonazepam or diazepam results in marked improvement. The disorder is caused by mutations in the alpha subunit in the inhibitory glycine receptors **(Shiang et al., 1995)**

And very low cerebrospinal fluid GABA levels were found in one case **(Dubowitz et al., 1992).**

Seizures versus jitteriness and other non-epileptic movements:

Some movements e.g. jitteriness and other normal movement during sleep (myoclonic jerks or generalized myoclonic jerks as infant wakes from sleep) or when awake/drowsy (roving sometimes dysconjugate eye movements and sucking not accompanied by ocular fixation or deviation) in newborn may be mistaken for seizures.

Table (4): Jitteriness versus seizure

Clinical features	Jitteriness	Seizure
Abnormality of gaze or eye movement	0	+
Movements exquisitely stimulus sensitive	+	0
Predominant movement	Tremors*	Clonic. jerking"
Movements cease with passive flexion of affected limb	+	0
Autonomic changes (tachycardia, increased BP, apnea, salivation and cutaneous vasomotor phenomena)	0	+

*Tremors-alternating movements are rhythmical and of equal rate and amplitude

"Clonic jerking-movements with a fast and slow component. **(Volpe, 2001)**

III. TREATMENT OF NEONATAL SEIZURES

Table 5 Acute Management of Neonatal Seizures

After each step, evaluate the infant for ongoing seizures. If seizures persist, advance to next step :

Step 1. Stabilize vital functions

Step 2. Correct transient metabolic disturbances

a.Hypoglycemia (target blood sugar 70-120 mg/dL)

10% dextrose water IV bolus dose 2 mL/kg followed by a continuous infusion at 8 mg/kg/mln

b.Hypocalcemia 5% calcium gluconate IV at 4 mL/kg (need cardiac monitoring)

c.Hypomagnesemia 50% magnesium sulfate IM at 0.2 mL/kg

Step 3. Phenobarbital 20 mg/kg IV load

Cardiorespiratory monitoring

5 mg/kg IV (may repeat to total dose of 40 mg/kg)

Consider continuous EEG monitoring

Consider intubation/ventilation

Step 4. Lorazepam 0.05 mg/kg IV (may repeat to total dose of 0.1 mg/kg)

Step 5. Phenytoin 20 mg/kg slow IV load

(fosphenytoin)

5 mg/kg slow IV (may repeat to total dose of 30 mg/kg) Step 6.

Step 6.Pyridoxine 50-100 mg/kg IV (with EEG monitoring)

Step 7. Other agents

(Adre, 2008).

As a general rule, seizures in the newborn are less responsive to conventional anticonvulsants than are seizures in older patients. This is particularly true of seizures with electroclinical dissociation in which seizures may remain refractory to high doses and sometimes multiple anticonvulsants. The risk-benefit ratio of such high doses in the treatment of neonatal seizures has been questioned. Specifically, the potential for seizures to cause direct injury to the immature brain has to be weighed against the effect of high levels of anticonvulsants on the developing brain. These issues have triggered a vigorous but unresolved debate about the management of neonatal seizures **(Adre, 2008).**

A number of potentially deleterious effects on the systemic and cerebral systems support the treatment of neonatal seizures. **First,** seizures may cause significant hemodynamic and respiratory disturbances, which in the sick newborn, may complicate management and potentially extend brain injury. Seizures disrupt cerebral pressure autoregulation and cause wide fluctuations in blood pressure, a combination with potentially serious consequences for the immature brain. **Second**, massive amounts of cerebral energy are consumed during the repeated neuronal depolarization-repolarization associated with seizures. Neonatal seizures cause a rapid fall in cerebral glucose and rise in brain lactate, even with normal or elevated blood glucose levels. In the insulted brain, such energy depletion may seriously compromise recovery. **Third**, seizures release large amounts of glutamate, and, in conditions of cerebral energy failure, seizures inhibit the reuptake of glutamate. Together these mechanisms result in the accumulation of extracellular glutamate to toxic levels that are potentially lethal to postsynaptic neurons and immature oligodendrocytes **(Adre, 2008).**

In animal studies, the immature brain is remarkably resistant to even prolonged seizures induced by proconvulsant drugs. Conversely, in a model that mimics postasphyxial seizures in the human newborn, seizures preceded by an asphyxial insult cause extensive cellular loss in the immature brain. These studies suggest that seizures superimposed on insults that deplete or disrupt cerebral energetics are capable of causing or extending brain injury. Seizures may also disrupt protein and lipid metabolism of immature neurons, and activate genes that stimulate axonal growth and new synapse formation. These sublethal insults may result in aberrant neuronal pathways and a long-term reduction in seizure threshold. Together, these mechanisms likely contribute to the epilepsy, motor, and cognitive impairment seen in some survivors of neonatal seizures **(Adre, 2008).**

The lack of a single highly effective anticonvulsant regimen in the newborn has spawned many different approaches. However, the following protocol is used in many major centers, including our own (Table 4). The initial steps in management consist of stabilization of the vital functions, exclusion or treatment of rapidly correctable conditions, and establishing the diagnosis of seizures by the clinical or EEG criteria detailed in the preceding text. Specific therapies against other treatable conditions (e.g., meningitis, narcotic withdrawal) should commence but should not delay the initiation of anticonvulsant therapy **(Adre, 2008).**

A.Reversing rapidly correctable causes

1. Hypoglycemia: Even when other primary etiologies are identified for seizures, hypoglycemia should be excluded or corrected. In the newborn with seizures, the target goal for blood glucose should be 70 to 120 mg/dL. If the hypoglycemic infant is actively seizing, an IV loading dose of 10% dextrose at 2 mL/kg (0.2 g/kg) should be given, followed by a continuous infusion of up to 8 mg/kg/minute to achieve the target levels given in the preceding text. In rare cases where these measures do not achieve normoglycemia, glucagon or hydrocortisone may be necessary. Experimental studies show that (i) brain tissue levels of glucose may fall during seizures even when blood glucose is normal, and (ii) hyperglycemia may be neuroprotective. These data are interesting, but more data are required before supranormal blood glucose targets can be recommended **(Adre, 2008).**

2. Hypocalcemia and Hypomagnesemia: Even if hypocalcemic seizures respond to antiepileptic medications, the low calcium levels should be corrected. An IV dose of 5% calcium gluconate at 2 mL/kg (18 mg of elemental calcium/kg) should be given under careful cardiac monitoring. Hypomagnesemia is best treated with an IM dose of 50% magnesium sulfate at 0.2 mL/kg. Infants treated for hypocalcemia should also receive magnesium because calcium administration increases renal magnesium excretion, and magnesium administration increases serum calcium levels. Of note, magnesium administration may result in transient weakness and hypotonia, even with normal serum levels **(Adre, 2008).**

B.Specific anticonvulsant agents:

1. Acute management: Once the diagnosis of seizures is strongly suspected or confirmed, anticonvulsant agents should be started. The administration of these agents should occur with careful cardiorespiratory monitoring.

a. Phenobarbital should be started as an IV loading dose of 20 mg/kg given over 10 to 15 minutes. This usually achieves blood levels around 20 mg/dL, levels at which an anticonvulsant effect begins to be apparent in the newborn. If seizures persist, further bolus doses of 5 mg/kg should be given, up to a total dose of 40 mg/kg or control of seizures. At these levels, significant respiratory depression is usually not evident. However, in a recent randomized trial these levels achieved seizure control in less than half of infants. The use of higher levels has been advocated but remains controversial because additional therapeutic benefit may be outweighed by the risk of cardiorespiratory depression. In asphyxiated infants with hepatic dysfunction, the doses given in the preceding text may result in higher blood levels, with sedation that persists for days. For this reason, in the severely asphyxiated infant with hepatic dysfunction it may be advisable to add a second, less-sedating agent such as phenytoin if seizures persist after the first 20 mg/kg loading dose of Phenobarbital **(Adre, 2008).**

b. Phenytoin the usual second-line agent is given as an initial loading dose of 20 mg/kg, which usually produces therapeutic blood levels around 15 to 20 mg/dL. Phenytoin is given into normal saline (it precipitates in dextrose solutions) and not faster than 1 mg/kg/minute to avoid cardiac arrhythmias. If seizures persist, an additional dose of 5 mg/kg may be used. Fosphenytoin is a more recently developed prodrug form that is rapidly converted into phenytoin. This agent has several advantages over phenytoin including greater solubility in standard intravenous solutions (including dextrose-containing solutions), safe faster rates of infusion, safe IM dosing, and no tissue injury with IV infiltration. Initial studies have supported the use of this agent in the newborn **(Adre, 2008).**

c. Benzodiazepines. The combination of phenobarbital and phenytoin will control seizures in up to 85% of infants. For neonatal seizures that remain refractory to these measures, benzodiazepines may add further benefit. Lorazepam, diazepam, and midazolam have all demonstrated potent anticonvulsant effects in the newborn. Although all three agents gain rapid entry into the brain, important differences in their subsequent kinetics, efficacy, and adverse effect profile make lorazepam

the preferred agent for neonatal seizures. Lorazepam has several advantages over diazepam. Specifically: (i) diazepam is rapidly redistributed after an IV dose and cleared from the brain within minutes; (ii) diazepam has greater respiratory and circulatory depressant effects (particularly when used with a barbiturate); (iii) the anticonvulsant effect of diazepam lasts minutes, whereas its sedative effect exceeds 24 hours; and (iv) sodium benzoate, the vehicle for IV diazepam, uncouples bilirubin from albumin, increasing the risk for kernicterus in jaundiced infants. **Lorazepam** at 0.05 mg/kg IV has an anticonvulsant onset within 2 to 3 minutes, which lasts between 6 and 24 hours (and much longer in infants with postasphyxial liver dysfunction). The dose may be repeated after several minutes to a total dose of 0.10 mg/kg. **Diazepam** is an effective anticonvulsant in the newborn and is given as an IV dose of 0.1 mg/kg increasing slowly up to 0.3 mg/kg given until the seizure stops. Because of their short anticonvulsant half-lives, both diazepam and midazolam, the newest benzodiazepine to be used as an anticonvulsant in the newborn, are most effective when given as a continuous infusion. **Midazolam** is given at an initial IV dose of 0.02 to 0.1 mg/kg, followed by a continuous infusion of 0.01 to 0.06 mg/kg/hour.

If seizure are still, then three disorders need to be ruled out before more medications are given :**(Blume et al., 2009).**

i) Pyridoxin-dependent seizures

ii)Folinic acid responsive seizures(rare)

iii)De Vivo syndrome(glucose transporter deficiency)

d. Pyridoxin. When neonatal seizures prove refractory to the preceding regimen, pyridoxine dependency should be excluded. This condition is diagnosed by the rapid (within minutes) cessation of EEG seizures to an IV dose of 50 to 100 mg pyridoxine. Because pyridoxine administration increases the cerebral synthesis of the inhibitory transmitter GABA, apnea and hypotonia may occasionally develop, necessitating close respiratory monitoring. If the diagnosis is made, maintenance oral doses of pyridoxine should be given at 10 to 100 mg/day, depending on the response **(Adre, 2008).**

e.Folinic acid. Infants that fail to respond to adequate doses of anticonvulsant drugs and pyridoxine warrant a trial of folinic acid for 24 to 48 hours,the starting dose is 2.5mg of enteral folinic acid twice/day, but may have to increased up to 8 mg/kg/day

f. Other agents. Although not commonly used in the United States, lidocaine has been used in Europe as an effective adjunctive anticonvulsant for neonatal seizures, usually after failure of phenobarbital

and diazepam. The anticonvulsant effects are seen within 10 minutes after starting an IV infusion of 4 to 6 mg/kg/hour, with or without a preceding loading dose. Once seizures are controlled, the lidocaine infusion is tapered over several days. In spite of its potential cardiac toxicity, the only adverse effect described in these reports is recurrence of seizures during the weaning period **(Adre, 2008).**

2. Maintenance and withdrawal of anticonvulsant drugs. Decisions regarding duration of therapy depend on the underlying etiology. Certain conditions, such as primary hypocalcemia, cause acute ("symptomatic") seizures with relatively low risk of later recurrent seizures, if the primary condition is appropriately managed. In these conditions discontinuation of anticonvulsant medications may be considered before intensive care unit (ICU) discharge. In conditions such as cerebral dysgenesis, the high risk for subsequent epilepsy warrants ongoing anticonvulsant treatment. Infants with postasphyxial seizures, have a 20% to 30% incidence of epilepsy, although subsequent seizures may present months to years later. If at the time of discharge from the neonatal intensive care unit (NICU) the infant's neurologic exam and EEG show good recovery towards normal, an early withdrawal of phenobarbital may be considered. Otherwise, the need for continued phenobarbital treatment should be reevaluated at 6- to 12-week intervals, maintaining interim blood levels around 20 mg/dL. **(Adre, 2008).**

IV. PROGNOSIS AFTER NEONATAL SEIZURES.

The overall prognosis for survival in neonatal seizures is around 85%, a significant improvement from earlier decades. Unfortunately, the prognosis for long-term neurodevelopmental outcome remains largely unchanged. Specifically, an adverse outcome occurs in approximately 50% of cases, with sequelae such as mental retardation, motor dysfunction, and seizures. The range of outcomes after neonatal seizures varies widely, with the three major predictors of long-term outcome being (i) the underlying etiology, (ii) the electrographic features, and (iii) gestational age. Other useful predictors include the neonatal neurologic examination and neuroimaging findings **(Adre, 2008).**

A. Etiology as a prognostic factor (see Table 5):

Neonatal seizures reflect significant brain dysfunction. The nature and severity of the insult causing these seizures might be expected to influence long-term brain function. Therefore, it is not surprising that in most studies the underlying etiology of neonatal seizures is the most powerful predictor of long-term outcome. Infants with hypoxic-ischemic

encephalopathy, when accompanied by seizures, currently have an approximately50% chance for normal development **(Adre, 2008).**

Table 6: Prognosis of Neonatal Seizures by Etiology

Etiology	Normal outcome (%)
Hypoxia-ischemia	50
Meningitis	50
Hypoglycemia	50
Subarachnoid hemorrhage	90
Early hypocalcemia	50
Late hypocalcemia	100
Intraventricular hemorrhage	10
Dysgenesis	0
Unknown	75

Similarly, about half of infants with seizures due to bacterial meningitis have a favorable outcome. The overall outcome for infants with neonatal seizures after arterial or venous vaso-occlusive disease is relatively benign. However, there are certain features that predict a worse outcome. In arterial stroke, EEG and MRI studies may identify infants at risk for worse prognosis. Specifically, an abnormal interictal EEG background has a less favorable outcome. Likewise, an MRI study showing involvement of an entire vascular territory, for example, in the MCA with injury to the hemispheres, the basal ganglia, and the internal capsule, is associated with significant hemiparesis in the long term. Although uncommon, involvement of multiple arteries, especially if bilateral, predicts worse outcome. Approximately 75% of infants with cerebral vein thrombosis and seizures have a favorable outcome, and only 20% develop later epilepsy. Features that predict a worse outcome include the development of extensive hemorrhagic infarction, as well as venous occlusion that extends into the deep venous system **(Adre, 2008).**

The outcome of intracranial hemorrhage depends on the degree of parenchymal injury and the gestational age. Most infants who develop seizures after primary subarachnoid (parturitional) hemorrhage have a good long-term outcome. Conversely, premature infants who develop seizures after IVH are usually critically ill and often have parenchymal hemorrhagic infarction; consequently, the outcome is significantly worse in these infants.

In infants with transient or metabolic disorders that can be corrected, the outcome is usually favorable **(Blume et al., 2009).**

Hypoglycemia severe and persistent enough to cause seizures is associated with a normal outcome in around 50% of cases. This prognosis is substantially worse when hypoglycemia complicates postasphyxial encephalopathy. The prognosis for infants with cerebral dysgenesis who develop seizures in the newborn period is universally dismal. If a thorough diagnostic evaluation fails to identify an etiology for neonatal seizures, the outcome is likely to be favorable **(Adre, 2008).**

B.both the interictal and ictal EEG features have prognostic value: With severe interictal EEG background abnormalities, such as burst suppression, marked voltage suppression, and an isoelectric background, an adverse neurologic outcome occurs in 90% or more of cases. Conversely, a normal EEG background at presentation is associated with a favorable outcome. Although somewhat less reliable, the ictal EEG features may also be useful predictors of outcome. A better outcome may be expected when the clinical and EEG seizures are consistently correlated, whereas electrically silent clinical seizures or clinically silent EEG seizures are associated with a worse outcome. The EEG seizure morphology may also be helpful, with a-frequency seizures, seizures associated with electrodecremental changes, or myoclonic seizures coupled with spike bursts, having a worse prognosis. Others have associated an increased number and duration of EEG seizures (particularly seizures lasting >30 minutes) with a worse outcome **(Adre, 2008).**

C.Gestational age has prognostic significance:

With neonatal seizures in infants under 32 weeks' gestation having a high mortality up to 80% in some studies, and a significantly higher risk of adverse neurologic outcome in survivors, when compared to term infants. **(Adre,2008).**

Patients and methods

This study included cases complaining of neonatal convulsions in the period between July 2009 till June 2010 attending the neonatal intensive care unit at Benha children hospital,sixty three cases included in the study,nineteen cases were males (30.1%) and forty four cases were females (69.9%) with mean age five days.

A sheet for each of the studied cases including the following:

I- history taking:-

Personal:-

1-Name

2-Number (birth order)

3-Age in days at examination

4-Sex

5-Gestational age in weeks calculated by

- History taking
- Ultrasound examination
- New Ballard score **(New Ballard Score., 1991).**

NEUROMUSCULAR MATURITY

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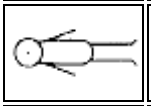
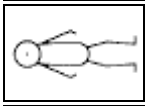
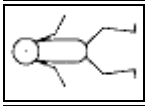
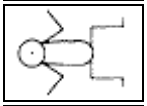
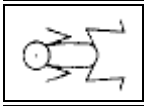
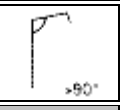
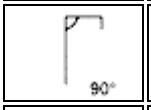
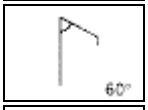
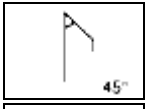
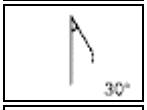
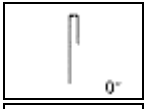
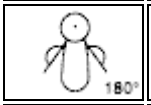
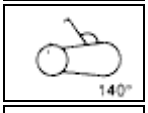
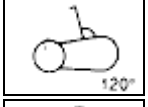
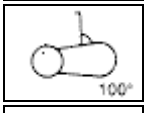
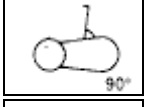
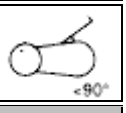
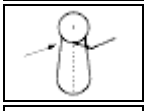
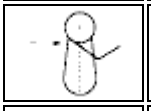
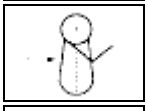
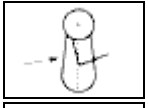
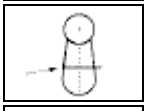
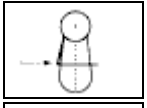
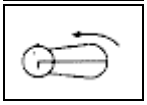
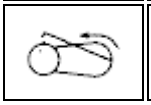
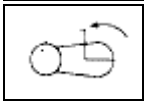
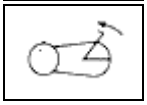
Posture								
Square Window								
Arm Recoil								
Popliteal Angle								
Scarf Sign								
Heel To Ear								
TOTAL NEUROMUSCULAR SCORE								

PHYSICAL MATURITY

SIGN	SCORE							SIGN SCORE
	-1	0	1	2	3	4	5	
Skin	Sticky, friable, transparent	gelatinous, red, translucent	smooth pink, visible veins	superficial peeling &/or rash, few veins	cracking, pale areas, rare veins	parchment, deep cracking, no vessels	leathery, cracked, wrinkled	
Lanugo	none	sparse	abundant	thinning	bald areas	mostly bald		
Plantar Surface	heel-toe 40-50mm: -1 <40mm: -2	>50 mm no crease	faint red marks	anterior transverse crease only	creases ant. 2/3	creases over entire sole		
Breast	imperceptable	barely perceptable	flat areola no bud	stippled areola 1-2 mm bud	raised areola 3-4 mm bud	full areola 5-10 mm bud		
Eye / Ear	lids fused loosely: -1 tightly: -2	lids open pinna flat stays folded	sl. curved pinna; soft; slow recoil	well-curved pinna; soft but ready recoil	formed & firm instant recoil	thick cartilage ear stiff		
Genitals (Male)	scrotum flat, smooth	scrotum empty, faint rugae	testes in upper canal, rare rugae	testes descending, few rugae	testes down, good rugae	testes pendulous, deep rugae		
Genitals (Female)	clitoris prominent & labia flat	prominent clitoris & small labia minora	prominent clitoris & enlarging minora	majora & minora equally prominent	majora large, minora small	majora cover clitoris & minora		
TOTAL PHYSICAL MATURITY SCORE								

MATURITY RATING

TOTAL SCORE (NEUROMUSCULAR + PHYSICAL)	WEEKS
-10	20
-5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

Prenatal: -

- Maternal steroid intake
- Maternal diabetes
- Pre-eclampsia
- Premature rupture of membrene
- Ant partum hemorrhage

Natal:-

-Mode of delivery: - vaginal, caesarean section (cause section), forceps or ventouse

-Apgar score: - at birth, 5min, 10min, and 15min.

-Resuscitation measures: - bag and mask or ET tube

-Chest compression inotropes& buffer

-Birth weight

Postnatal:-

-Respiratory symptoms. (apnea or not)

-Neurologic symptoms. (convulsion in details as regard onset ,type)

-GIT symptoms (hematemesis, NEC, others).

-Others (oliguria or not, hypotension requiring inotropes)

II-Examination:-

Weight:-

Vital data:- pulse, respiratory rate, blood pressure &temperature.

Measures: - occipito-frontal circumference, length & weight.

Face: - Mouth, eyes, ear, nose.

Skin: cyanosis (peripheral or central), pallor, jaundice, angiomas, petechiae, eechymmosis, purpra and scleroderma.

Traumatic lesions: Cephalhematoma, caput succedanum and abnormal shape of skull.

Limbs: Hands and feet creases, fingers and toes.

Chest examination: Cyanosis, retraction, grunting, stridor.

Heart examination: Heart sound, murmur, femoral pulse and peripheral circulation.

Abdominal examination: Distension, organomegaly, umbilical area, examination of anus and genitalia.

Neurological:- -Level of consciousness
-Muscle tone
-Posture
-Reflexes
-Seizures
-Sarnat and Sarnat stages of HIE in details **(Aurora and Snyder. 2004).**

(Table 7): Sarnat and Sarnat stages of HIE:

Mild HIE Sarnat Stage I	Moderate HIE Sarnat Stage II	Severe HIE Sarnat Stage III
Hyper-alert	Lethargy (difficult to rouse)	Coma (cannot be roused)
Eyes wide open	Reduced tone of the extremities and/or trunk	Weak or absent respiratory drive
Does not sleep	Diminished brainstem reflexes (pupil/gag/suck)	No response to stimuli (may have spinal reflex to painful stimuli)
Irritable	Possible clinical seizures	Flaccid tone of the extremities and trunk (floppy)
No seizures		Diminished or absent brainstem reflexes (pupil/gag/suck)
Usually lasts < 24 hours		Diminished tendon reflexes
		EEG severely abnormal (suppressed or flat EEG with or without seizures)

Sarnat and Sarnat stages of HIE **(Aurora and Snyder. 2004).**

III-Imaging:-

- Trans-cranial ultrasound was used via anterior fontanel using Toshiba ECCOCEE, SSA-340A 2B730-501, JAPAN using 7.5 MHz probe.
- C.T for some cases.

IV- Lab investigations:-

All studied neonates were subjected to the following:

A-Complete blood count

Using Automated Hematology analyzer Model: SYSMEX KX-21 serial umber: A6787

Including:-

TLC Absolute neutrophils

Hemoglobin

Platelets

B-Serum Electrolytes (Na, K, Ca, Mg and glucose)

By using Rapid lab, ABG 348 BAYER

C- C- reactive protein:-

By using Latex agglutination test Bio Med Diagnostics

D- Blood culture.

By using Bactic 9050 N B 5491.

We depend on the following criteria for diagnosis of hypoxic-ischemic encephalopathy(Santina,2009):

History:-

Maternal diseases e.g antipartum hemorrhage and pre-eclampsia.

Delayed first cry and persistence of an Apgar score of 0-3 for longer than 5 minutes.

Examination:-

Weak neonatal reflexes, hypertonia, convulsion and multiple organ involvement.

Investigation:-

Profound metabolic or mixed acidemia (pH <7) in an umbilicalartery blood sample, if obtained

Cranial ultrasound e.g HIE changes and brain edema.

CT for some cases.

We depend on the following criteria for diagnosis of neonatal sepsis (Karen, 2008):

History:-

Maternal disease e.g infection as cytomegalo virus infection and premature rupture of membrane.

Poor feeding , vomiting or baby not doing well.

Examination:-

Lethargy, temperature instability, poor prefusion and hypotension

Disseminated intravascular coagulopathy with purpura .

Weak neonatal reflexes.

Organomegally.

Investigation:-

CBC abnormalities e.g leucocytosis, anaemia and thrombocytopenia.

Positive CRP.

Positive blood and CSF culture.

Results

Table (I) Incidence of neonatal seizures in total cases in NICU

	No	%
Study group	63	7%
Cases without seizures	839	93%
Total population in NICU	902	100%

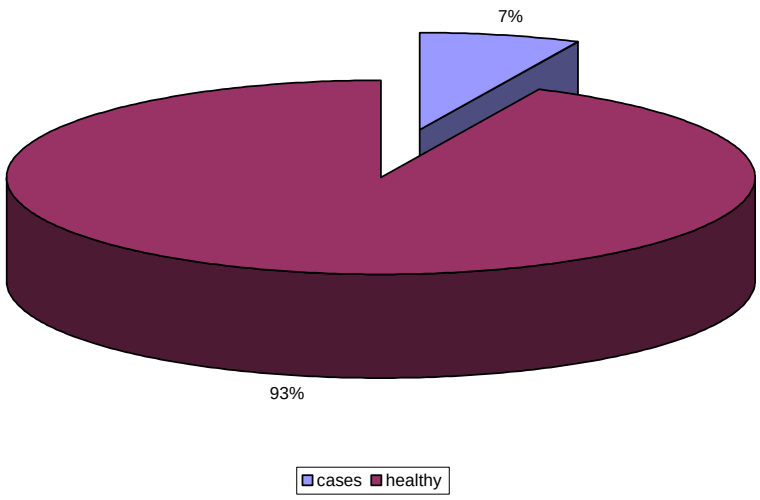


Fig (I) Incidence of neonatal seizures in total cases in NICU

Table (I) and figure (I) showed that 63 cases (7%) with neonatal convulsion from the total cases admitted to neonatal ICU (NICU) 902(93%).

Table (IIA) Demographic and clinical data of the studied cases

Demographic data	NO	%	Z	P
Sex				
Males	19	30.1	3.15	< 0.01
Females	44	69.9		
Mode of delivery				
C.S	24	38.1	1.89	< 0.05
N.V.D	39	61.9		
Gestational age				
Preterm	18	28.6	3.4	< 0.001
Full term	45	71.4		
Birth weight				
AGA	29	46.1	Z1=2.11	<0.05
SGA	15	23.8	Z2=1.44	>0.05
LGA	19	30.1	Z3=.96	>0.05

$X \pm SD = 2.7 \pm 0.8$

Z1= AGA versus SGA Z2= AGA versus LGA Z3= SGA versus LGA

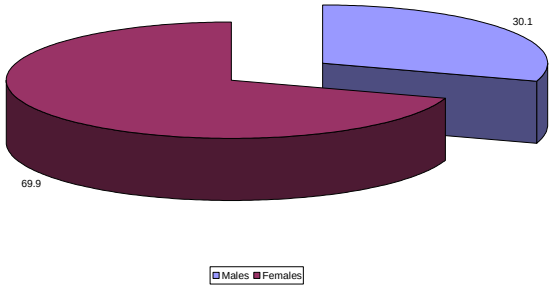


Fig (II a) Distribution of Sex in the studied cases

Table (IIA) and Figure (II a) showed that 19 cases were males (30.1%) and 44 cases ware Females (69.9%)

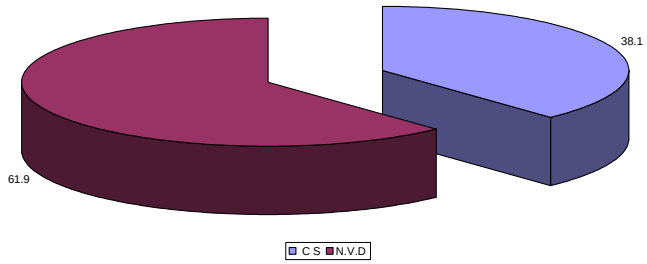


Fig (II b) Distribution of cases according to mode of delivery

Table(IIA) and figure(II b)showed that 24 cases were delivered by cesarean section(CS) (38.1%)and 39 cases by normal vaginal delivery(61.9%)

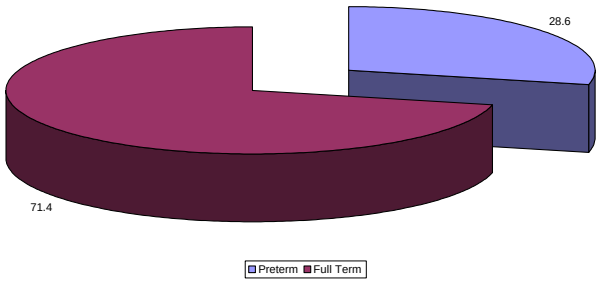
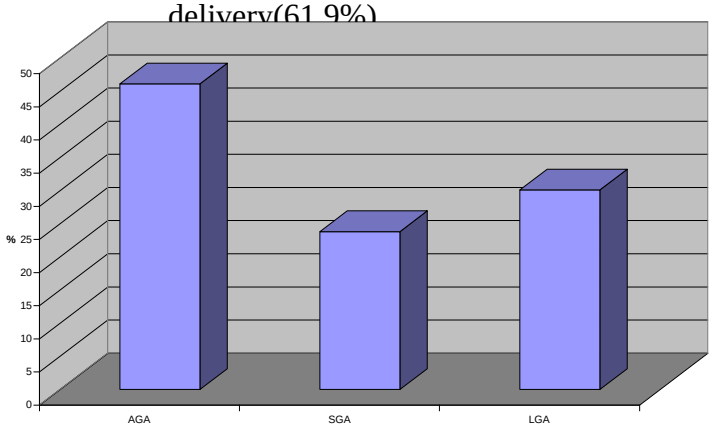


Fig (II c) Distribution of cases according to gestational age

Table (IIA) and figure (II c) showed that 18 cases were preterm (28.6%) and 45 cases were full term (71.7%).



Fi g(II d) Distribution of cases according to Birth weight

Table(IIA) and figure(II d)showed that 29 cases were appropriate for gestational age (46.1%), and 15 cases were small for gestational age (23.8%) and 19 cases were large for gestational age (30.1%).

Table (IIB) Demographic and clinical data of the studied cases

Demographic data	NO	%
Maternal diseases		
CMV infection	1	1.6
Cervical erosion	1	1.6
Rupture uterus	1	1.6
Antipartum hemorrhage	1	1.6
Pre-eclampsia	4	6.3
Premature rupture of membran	8	12.7
Delayed first cry	32	50.8
Respiratory distress	31	49.2
Weak neonatal reflexses	17	27
Hypertonia	4	6.3

Table (IIB) showed that by history eight cases gave history of maternal diseases and premature rupture of membrane and 32 cases(50.8%) had delayed first cry.And during clinical examination 31cases(49.2%) had respiratory distress, ,17 cases(27%) had weak neonatal reflexses and 4 cases(6.3%) had hypertonia.

Table (III) Data of cases with hypoxic-ischamic encephalopathy

History	No	%	Clinical examination	No	%	Investigation	No	%
Maternal diseases			Weak neonatal reflexes	17	27	Cranial ultrasound		
Rupture uterus	1	1.6	Hypertonia	4	6.3	HIE	16	25.4
Antipartum hemorrhage	1	1.6				Brain edema	5	7.9
Pre-eclampsia	4	6.3				HIE and IVH	2	3.2
Delayed first cry	32	50.8						

Table (III) showed that data of cases with hypoxic-ischamic encephalopathy by history maternal diseases of the studied cases were 1 case(1.6%) had rupture uterus,1 case(1.6%) had antipartum hemorrhage,4cases(6.3%) had pre-eclampsia, 32 cases(50.8%) had delayed first cry and by clinical examination17 cases(27%) had weak neonatal reflexses and 4 cases(6.3%) had hypertonia and by investigation cranial ultrasound showed that 16 cases(25.4%) had HIE,5 cases(7.9%) had brain edema and 2 cases(3.2%) had HIE and IVH.

Table (IV) Data of cases with neonatal sepsis

History	No	%	Clinical examination	No	%	Investigation	No	%
Maternal diseases			Weak neonatal reflexses	17	27	Leucocytosis	36	57
Cytomegalo virus infection	1	1.6				Anaemia	8	12.6
Cervical erosion	1	1.6				Thrombocytopenia	20	31.7
Premature rupture of membrane	8	12.7				CRP +ve	29	46
						Blood culture +ve	6	9.5
						CSF culture +ve	10	15.9

Table (IV) showed that data of cases with neonatal sepsis by history maternal diseases of the studied cases were 1 case (1.6%) had CMV infection, 1 case (1.6%) had cervical erosion and 8 cases(12.7%) had premature rupture of membran and by clinical examination17 cases(27%) had weak neonatal reflexses and by investigation 36 cases(57%) had leucocytosis,8 cases (12.6%) had anaemia ,20 cases(31.7%) had thrombocytopenia,29 cases(46%) had positive CRP ,6 cases(9.5%) had positive blood culture and 10(15.9%) cases had positive CSF culture.

Table (V) Distribution of cases according to onset of seizure

Onset	No	%
With in 1st day	13	20.6
› 1 day	50	79.4
Total	63	100.0

Z = 4.66 P < 0.001

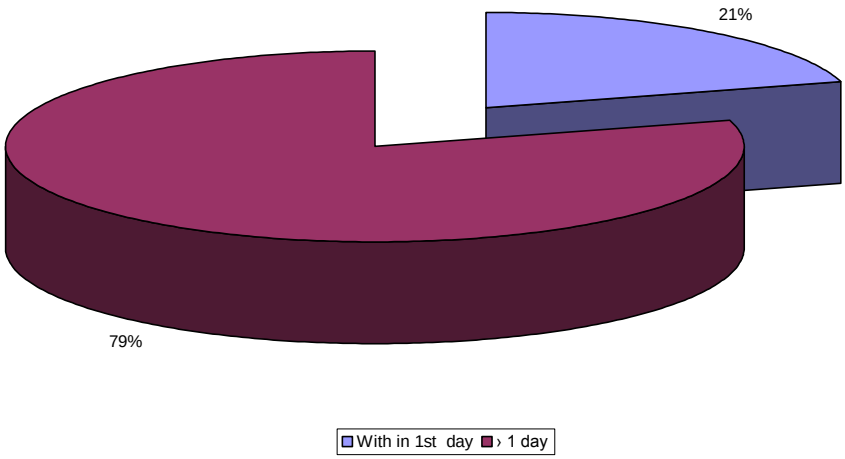


Fig (III) Distribution of cases according to onset of seizures

Table (V) and figure (III) showed that 13 cases (20.6%) presented with seizures in the first day of life and 50 cases (79.4%) after the first day.

Table (VI) Distribution of cases according to types of seizures

Total	No	%
Generalized	39	61.9
Focal	7	11.1
subtle	17	27.0
Total	63	100.0

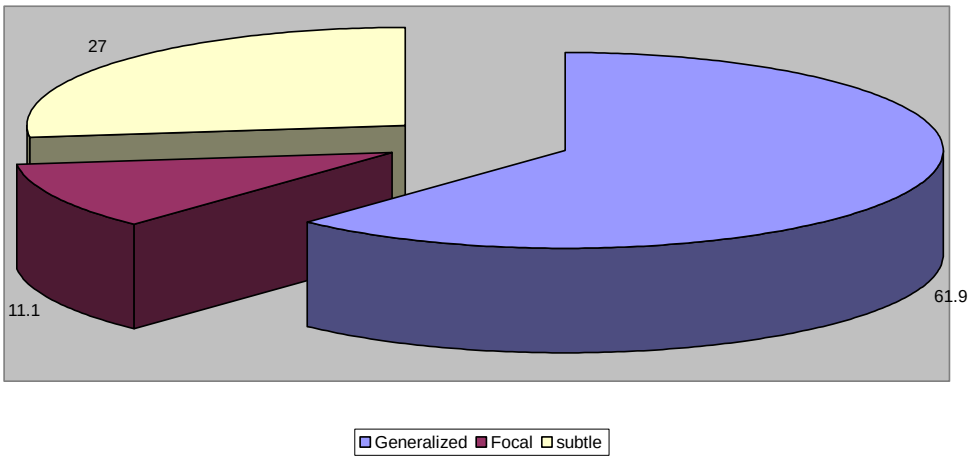


Fig (IV) Distribution of cases according to type of seizures

Table (VI) and figure (IV) showed that seizures varied in types: 39 cases (61.9%) presented with generalized seizures, 7cases (11.1%) presented with focal seizures and 17 cases (27%) presented with subtle seizures.

Table (VII) Hematological findings in the studied cases

St. group / Hematological findings	Normal		Abnormal		T	P
	No	X ± SD	No	X ± SD		
TLC(1000\mm)	27 (43%)	10.4 ± 3.1	36 (57%)	24.3 ±15.6	5.25	<0.0001
Hb(gm\dl)	55 (87.4%)	16.2 ± 2.4	8 (12.6%)	9.7 ±2.1	8.03	<0.0001
Platelets(1000\mm)	43 (68.3%)	247.7 ± 62.2	20 (31.7%)	159.6 ±174.7	2.19	<0.005
CRP (mg\dl)	34 (54%)	35.8 ± 0.7	29(46%)	34.9 ± 14.7	10.7	<0.001

Means (x) ± standand deviation (SD)

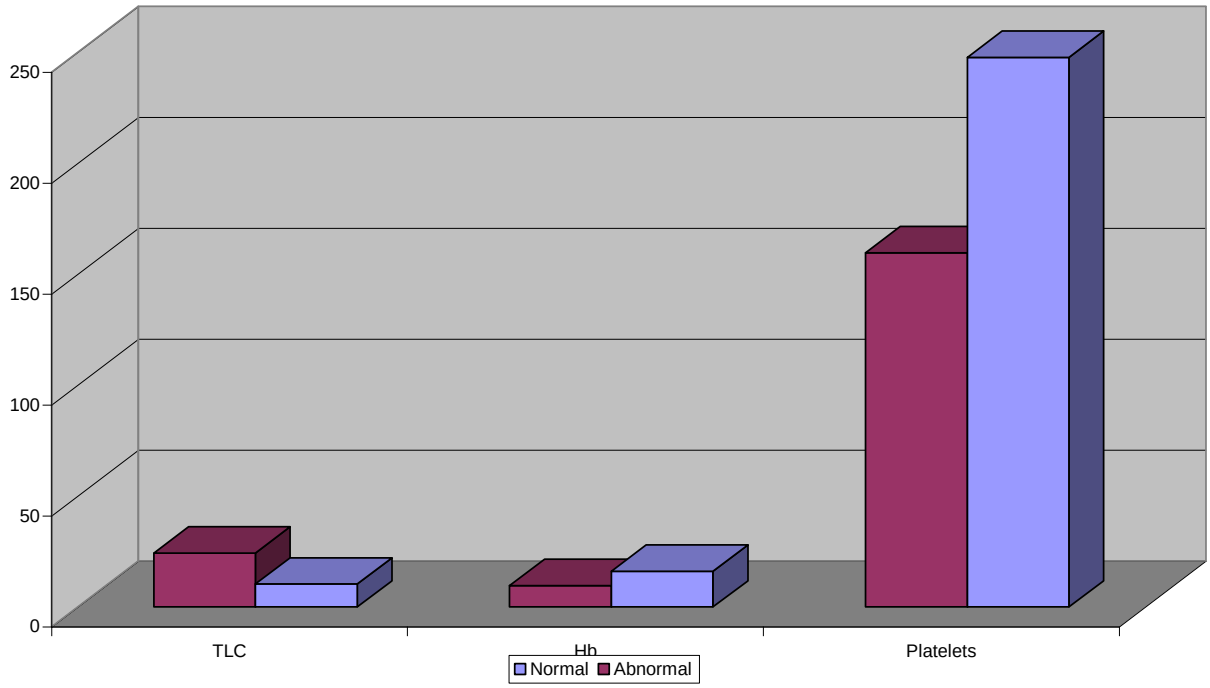


Fig (V) Hematological findings in the studied cases

Table(VII) and figure(V) showed that there were a significant increase in total leukocyte count(TLC) in 36 cases (57%),but there were a significant decrease in hemoglobin(Hb) level in 8 cases (12.6%) , decrease in platelets count in 20 cases (31.7%) and positive CRP in 29 cases(46%) which are criteria of neonatal sepsis which contribute in etiology of neonatal seizures.

Table (VIII) Biochemistry findings among the studied cases

Biochemistry findings	Normal			Abnormal			T	P
	No	%	X± SD	No	%	X± SD		
Ca(mg\dl)	27	42.8%	9.7 ±0.8	36	57.2%	7.8±0.9	8.89	<0.001
Na(mEq\l)	46	73%	141.4±27.1	17	27%	129±13.5	2.4	<0.05
K(mEq\l)	45	71.4%	3.7 ±0.4	18	28.6%	6.6±1.1	10.6	<0.001
Mg(mg\dl)	63	100%	1.8 ±0.5	0	0	0.0	——	——
Glucose	20	31.7%	132.5±11.5	٤٣	68.3%	91.4±23	11.3	<0.001

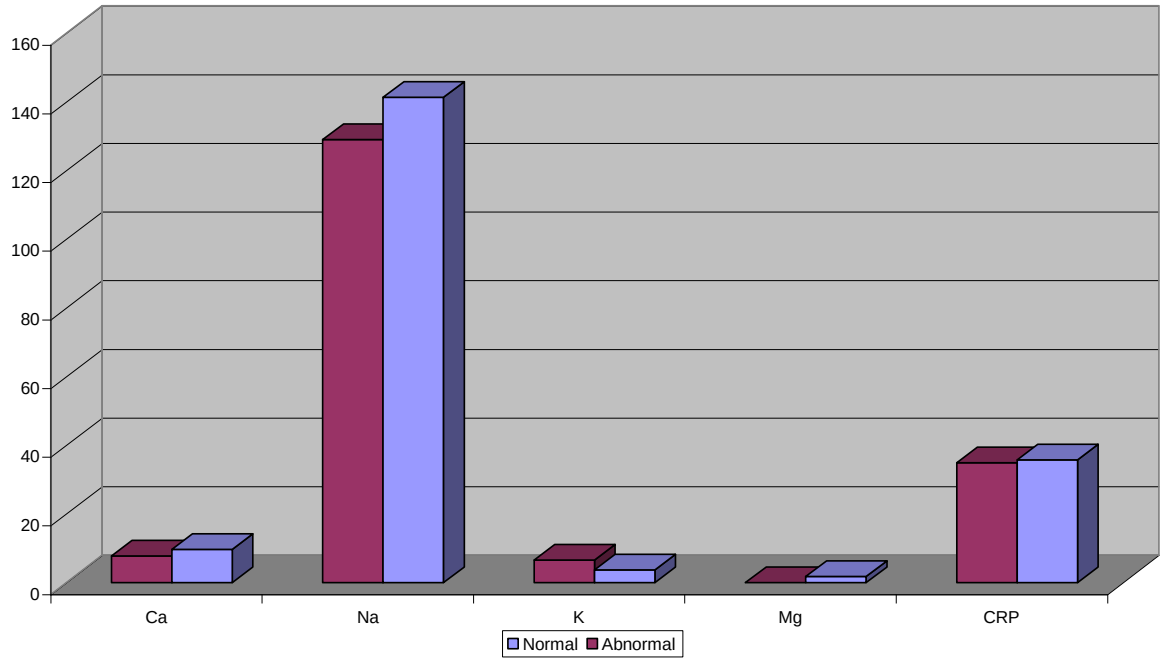


Fig (VI)Biochemistry findings among the studied cases

Table (VIII) and figure (VI) showed that there were significant serum electrolytes changes where 36 cases (57.2%) had low calcium serum level, 17 cases (27%) had low sodium serum level but 18 cases (28.6%) had significant increase in potassium serum level, 43 cases (68.3%) had abnormal serum glucose and all cases had normal magnesium serum level.

Table (IX) CSF and blood culture among the studied cases

St.group / Variable	Negative No	Negative %	Positive No	Positive %	Z	P
CSF culture	57	90.5	6	9.5	6.43	< 0.001
Bl.culture	53	84.1	10	15.9	5.42	<0.0001

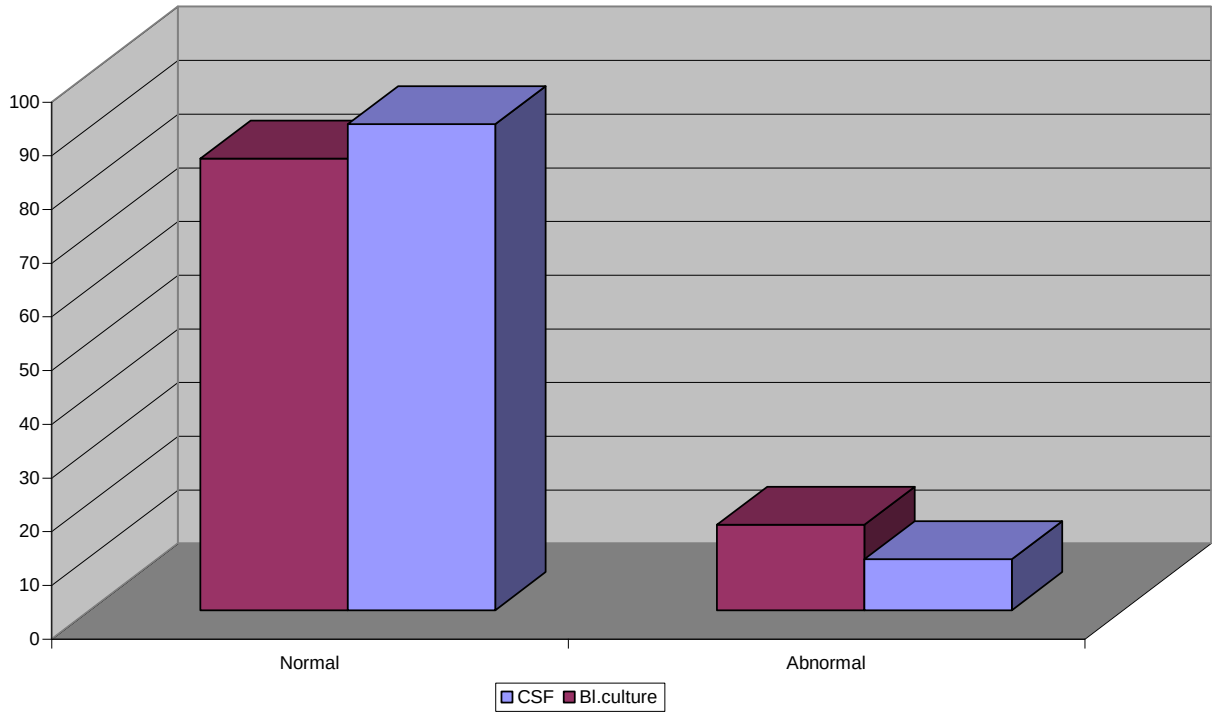


Fig (VII) CSF and blood culture among the studied cases

Table (IX) and figure (VII) showed that there were 6 cases (9.5%) from total cases gave positive CSF culture and 10 cases (15.9%) gave positive results for blood culture from total cases.

Table(X) Results of cranial US findings

Cranial US findings	No	%
Normal	31	49.2
H I E	16	25.4
Brain Edema	5	7.9
I V H	3	4.7
Subdural Hge	2	3.2
Brain atrophy	2	3.2
H I E & I V H	2	3.2
Arnold chiarii syndrome	1	1.6
Dandy .walker syndrome	1	1.6
Total	63	100.0

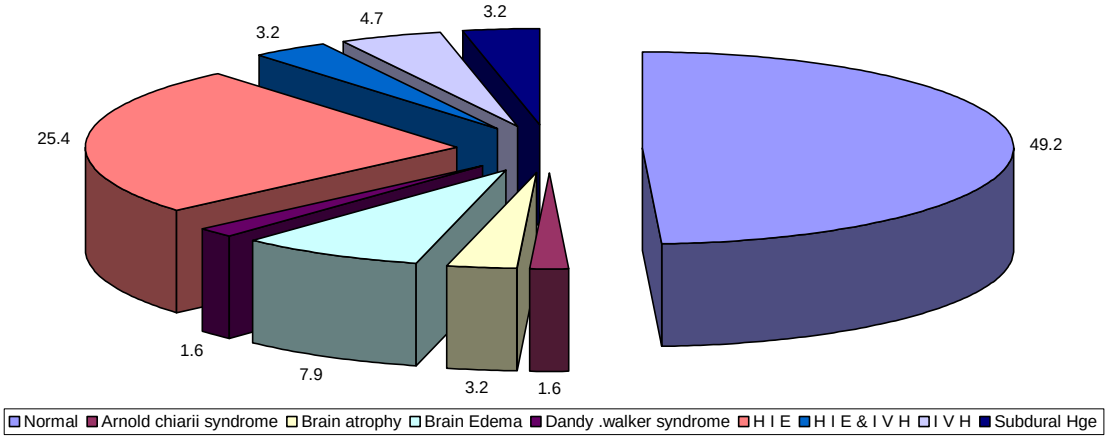


Fig (VIII) Cranial US findings

Table(X) and figure(VIII) show that cranial ultrasonography was carried out to all cases .Where 31 cases (49.2%) were found to have a normal cranial ultrasound while 32 cases (50.8%) had abnormal findings in the form of:

1- Hypoxic changes in 18 cases(28.6%)

2- Arnold Chiari and Dandy Walker syndromes in 2 cases (3.2%)

3- Intraventricular and subdural hemorrhage in 7 cases (11.1%).

4- Brain edema in 5 cases (7.9%)

5- Brain atrophy in 2 cases (3.2%)

Table (XI) Distribution of cases according to etiology of seizures

Cases / Etiology		
	NO	%
Hypoxic-ischamic encephalopathy	32	50.8%
Neonatal.Sepsis	20	31.7%
Metabolic and electrolyte disturbance	6	9.6 %
ICH	3	4.7%
Syndromes	2	3.2 %
Total	63	100%

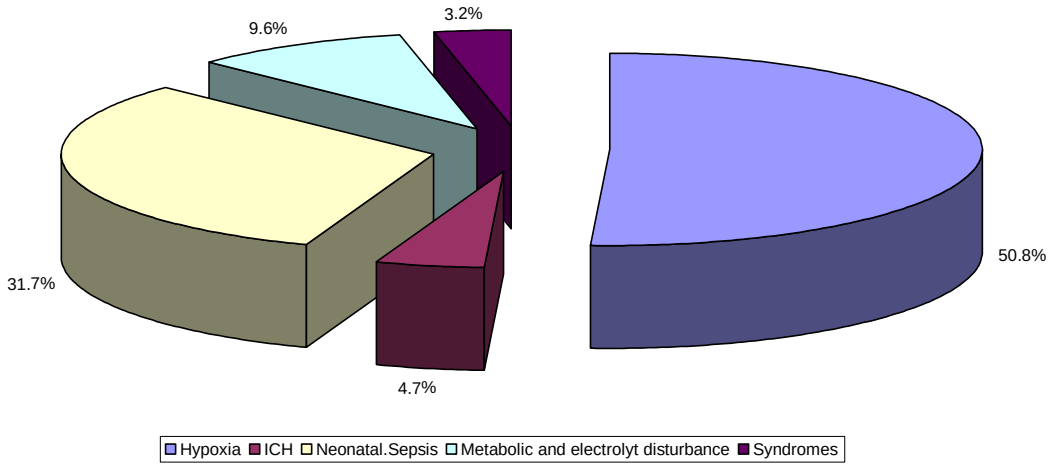


Fig (IX) Distribution of cases according to etiology of seizures

Table(XI) and figure(IX) showed the distribution of cases according to etiology of seizures where we found that the most common causes of neonatal seizures were hypoxia (50.8%), followed by neonatal sepsis (31.7%), while the least common causes of neonatel seizures were ICH (4.7%), followed by syndromes (3.2%).

Table (XII) Distribution of cases according to commonest etiology of neonatal seizures

Studied group	Commonest etiology	Number	Total	%
Full term	HIE	29	45	64.4 %
Preterm	IVH	6	18	33.3 %
Seizure in 1St day	HIE	11	13	84.6 %
Seizure > 1St day	HIE	21	50	42 %
N.V.D	HIE	18	39	46.2 %
C.S	HIE	14	42	33.3 %

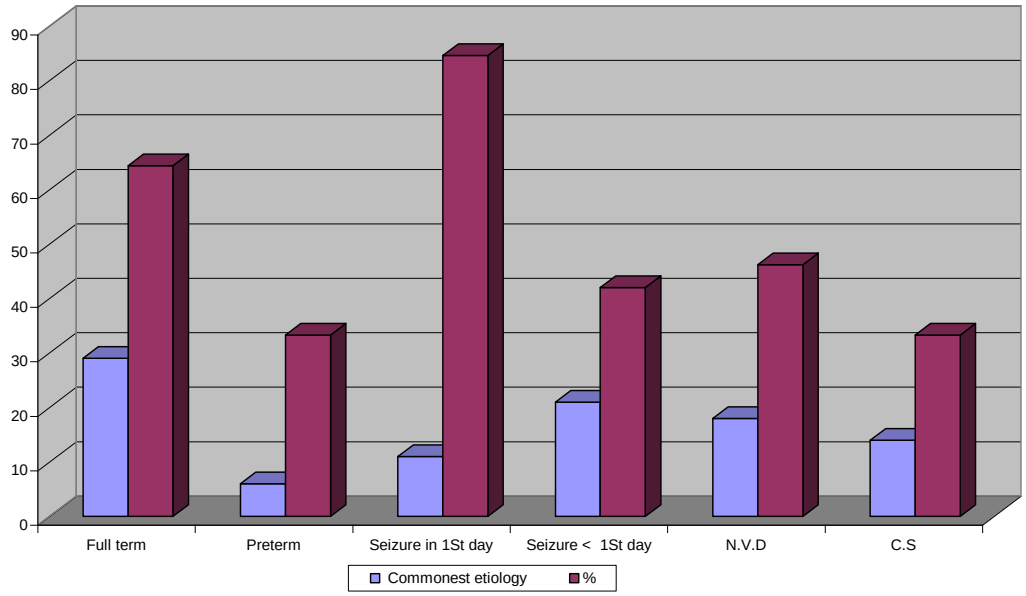


Fig (X) Distribution of cases according to commonest etiology

Table (XII) and Fiugre (X) showed that the distribution of cases according to commonest etiology, the hypoxia was the commonest etiology in full term, seizure in 1St day, seizure >1St day, N.V.D and C.S while IVH was the commonest etiology in preterm.

Discussion

The neonatal period is the most vulnerable period of life for developing seizures. Neonatal epileptic seizures often constitute a neurological emergency demanding urgent diagnosis and management. Neonatal seizures are paroxysmal, repetitive, and stereotyped events ***(Panayiotopoulos, 2010)***

Neonatal seizures are risk factors for long term neonatal morbidity and mortality.The presence of neonatal seizures is the best predictor of long term physical and cognitive deficits.Seizures are usually related to significant illness.There is increased evidence that neonatal seizures have an adverse effect on neurodevelopmental outcome and predispose to cognitive, behavioural or epileptic complication in later life ***(Olusegun, 2010)***

Among term infants hypoxic ischemic encephalopathy due to acute perinatal insult remains an important cause of neurodevelopmental deficits in childhood ***(Seetha and Abbot, 2007)***

Hypoxia-ischemia, the most common cause of neonatal seizures, may occur before, during, or after delivery. Such seizures may be severe and difficult to treat, but they tend to abate after about 3 to 4 days. ***(Margaret, 2009).***

The most likely overriding factors that affect long-term outcome are the etiology, degree of seizures and distribution of brain injury caused by the underlying disturbance. **(Eli M et al., 2010).**

The underlying causes of seizures in preterm infants are not as well understood as those for term infants. The preterm group is etiologically heterogeneous, and no consensus exists for an epileptic basis of paroxysmal clinical "seizures" (variable occurrence of electrographically detected seizures**)** ***(Robert ,2006).***

Mortality associated with neonatal seizures has declined although long-term neurodevelopmental morbidity remains unchanged. Seizure etiology remains powerful prognostic factors. Diagnostic advances have changed the etiologic distribution for neonatal seizures and improved accuracy of outcome prediction. Global cerebral hypoxia-ischemia, the most common etiology, is responsible for the large majority of infants with poor long-term outcome. ***(Hasan et al., 2006).***

In our study:

We observed the incidence of neonatal seizures was 7% from the total newborn admitted in NICU. **Adre, 2008** reported that the incidence of neonatal seizures varied widely across studies, a variability that is primarily the result of inconsistent diagnostic criteria, as well as the often subtle clinical manifestations of neonatal seizures, and their potential confusion with nonepileptic neonatal behavior.

As regard the onset of seizure we found that13 cases (20.6%) of our cases experienced seizure on the first day of life and the majority of them due to hypoxic-ischemic encephalopathy, which is consistence with ***(Fenichel et al., 2004)*** who found that the time of onset of neonatal seizures may be useful as certain aetiologies more likely to occur early (first 24 hours) while others typically occur later in neonatal period.

We also observed that generalized clonic seizure was the most commonas a type of clinical presentation among the studied cases as we found that 39 cases (61.9%) presented with generalized seizures, 7cases (11.1%) presented with focal seizures and 17 cases (27%) presented with subtle seizures,which is consistent with ***(Jehan, 2002)*** who made a study on 30 newborn presented with neonatal seizures where 10 cases (33%) presented with generalized tonic seizures, 16 cases (53%) presented with generalized clonic seizures, 2 cases (7%) presented with tonic clonic seizures, 2 cases (7%) presented with subtle seizures.

In contrast to our result (**mark et al., 1993)** who found subtle seizures occurred prominently in their studied group.They make a study over a 4-year period, 92 neonates from a neonatal intensive care unit population of 4020 admissions at a large obstetric hospital. Sixty-two neonates were preterm and 30 were full-term for gestational age. Subtle seizures were the most predominant clinical type 71%. This is probably due to involving of the preterm neonates in most of these studies; however in our study full term was involved more than preterm neonates.

In our study we found that serum electrolytes changes attribute to neonatal seizures where 36 cases (57.2%) had low calcium serum level, 17 cases (27%) had low sodium serum level but 18 cases (28.6%) had significant increase in potassium serum level and 43 cases(68.3%) had abnormal serum glucose and all cases had normal magnesium serum level. This in aggrement with**(Griffiths , 1968)** who made a study on 100 neonates and serum electrolytes changes were present in 45 cases where hypoglycemia was in 6 cases , hypocalcemia was in 34 cases , hypernatremia was in one case and 4 cases had hypoglycemia and

hypocalcemia so electrolytes changes are important causes of neonatal seizures in old and recent studies.

We also observe in our study that: The abnormal CNS electrical discharge may be caused by a

- Primary intracranial process (e.g, meningitis, , encephalitis, intracranial hemorrhage, malformation)
- Systemic problem (e.g, hypoxia-ischemia, hypoglycemia, hypocalcemia, hyponatremia, or other disorders of metabolism).

As we found in our study that were 6 cases (9.5%) from total cases gave positive CSF culture and 10 cases (15.9%) gave positive results for blood culture from total cases.

Cranial ultrasound is the most common neuro-imaging modality in the preterm infant used to assess the presence of cerebral injury. Cranial ultrasound is useful in the detection of intraventricular hemorrhage and cystic periventricular leucomalacia, but has poor sensitivity in the detection of diffuse white matter (WM) abnormalities that are detected by MR imaging ***(Inder et al., 2003).***

Ultrasonography is method of choice for routine screening of the premature brain. It is of particular value in the identification of PIVH and necrosis of basal ganglia and thalamus ***(Stoll. 2004*).**

The use of sonography to examine these infants has rapidly increased in the last few years for the relative simplicity for early detection of complications and follows up of these patients ***(Nzeh et al, 2004).***

Repeated cranial ultrasound studies performed several days later may show diffuse echo densities reflecting neuronal necrosis ***(Attia et al., 1997)***.

For early prediction of neurological outcome cranial ultrasound examination was found to be more reliable. **(Amess et al., 2009)**.As we found in our study that 31 cases (49.2%) were found to have a normal cranial ultrasound while 32 cases (50.8%) had abnormal findings in the form of:

Hypoxic changes in 18 cases (28.6%) Arnold Chiari and Dandy Walker syndromes in 2 cases (3.2%) Intraventricular and subdural

hemorrhage in 7 cases (11.1%). Brain edema in 5 cases (7.9%) Brain atrophy in 2 cases (3.2%).

Perinatal asphyxia was the main cause of seizure occurrence among the studied group where we found that the most common causes of neonatal seizures was hypoxia (50.8%), followed by neonatal sepsis (31.7%), followed by metabolic and electrolyte disturbance (9.6%) (2 of them are metabolic) followed by ICH (4.7%), while the least common causes of neonatal seizures was syndromes (3.2%). This is in agreement with ***(Panayiotopoulos, 2010)*** who postulate that eighty percent of neonatal seizures occur in the first 1 to 2 days to the first week of life. The etiology of neonatal seizures is extensive and diverse.Hypoxic-ischemic encephalopathy is the most common cause (80% of all seizures).Our result also in aggrement with **(*Olusegun, 2010)*** who make study of 866 neonates admitted, 59 (6.8%) had seizures , *37* of them (%٦٢.٧)were considered to have had birth asphyxia. Meningitis, hypoglycaemia, and hypocalcaemia occurred in 7 (11.9%), 6 (%١٠.٢) and 2 (3.4%) of cases, respectively, and 7 (11.9%) had undiagnosed causes.

Our results go in hand with**(Hasan *et al., 2006)*** who make a study on Eighty-nine newborn infants with clinical neonatal seizures underwent neurologic examination, electroencephalography (EEG), neuroimaging, and extensive diagnostic tests in the newborn period ,etiology was found in 77 infants. Global cerebral hypoxia-ischemia, focal cerebral hypoxia-ischemia, and intracranial hemorrhage were most common.

In fact, the number of infants without identified etiologies was significantly lower than in previous studies. **Lombroso, 1970** made a prospective study of 144 infants who developed seizures during the first 3 weeks of life where no etiological clues were found in one fourth of the neonates, factors of probable etiological importance were established in three-fourths.

We also observe in our study that intracranial haemorrhage is more common in preterm infants.This is in agreement with **(*Janet, 2008)*** who postulated that germinal matrix hemorrhage and intraventricular hemorrhage were found principally in preterm infant, where the incidence is currently 15% to 20% in infant born <32 weeks gestational age but is uncommon in term newborn.

Summary and conclusion

Neonatal seizures are a risk factor that markedly increases rate of long term morbidity and neonatal mortality and the presence of neonatal seizures is the predictor of long term physical and cognitive deficits.

The overall prognosis for survival in neonatal seizures is around 85% a significant improvement from earlier decades; unfortunately, the prognosis for long-term neurodevelopmental outcome remains largely unchanged. Specifically, an adverse outcome occurs in approximately 50% of cases, with sequelae such as mental retardation, motor dysfunction and seizures.

The range of long-term outcome being (i) the underlying etiology, (ii) electrographic features, and (iii) gestational age. Other useful predictors include the neonatal neurologic examination and neuroimaging finding.

This work was done to evaluate the clinical aspects of seizures in the neonatal intensive care units as regard the incidence, the clinical types, etiology and time of onset of seizure.

This study included cases complaining of neonatal convulsions in the period between July 2009 till June 2010 attending the neonatal intensive care unit at Benha children hospital ,sixty three cases included in the study, nineteen cases were males (30.1%) and forty four cases were females (69.9%) with mean age five days.

A sheet for each of the studied cases including the following:

I-Complete history taking:-personal, prenatal, natal and postnatal

II- Complete physical examination:-General and local

III-Imaging:-

Trans-cranial ultrasound and CT.

IV- Lab investigations:-

All studied neonates were subjected to the following:

A-Complete blood count.

B-Serum Electrolytes (Na, K, Ca, Mg and glucose).

C-C- reactive protein.

D- Blood culture.

E-CSF culture.

The data obtained from the 63 cases are:

63 cases (7%) with neonatal convulsion from the total cases admitted to neonatal ICU (NICU) 902(93%).

19 cases were males (30.1%) and 44 cases ware Females (69.9%).

24 cases were delivered by cesarean section (CS) (38.1%) and 39 cases by normal vaginal delivery (61.9%).

18 cases were preterm (28.6%) and 45 cases were full term (71.7%).

29 cases were appropriate for gestational age (46.1%), and 15 cases were small for gestational age (23.8%) and 19 cases were large for gestational age (30.1%).

Maternal diseases of the studied cases 1 case(1.6%) had CMV infection , 1 case(1.6%) had cervical erosion, 1 case(1.6%) had rupture uterus,1 case(1.6%) had antipartum hemorrhage,4cases(6.3%) had pre-eclampsia,8 cases(12.7%) had premature rupture of membran,31cases(49.2%) had respiratory distress,32 cases(50.8%) had delayed first cry,17 cases(27%) had weak neonatal reflexses and 4 cases(6.3%) had hypertonia.

13 cases (20.6%) presented with seizures in the first day of life and 50 cases (79.4%) after the first day.

Seizures varied in type: 39 cases(61.9%) presented with generalized seizures,7cases (11.1%)presented with focal seizures and 17 cases (27%) presented with subtle seizures.

There were a significant increase in total leukocyte count(TLC) in 36 cases (57%),but there were a significant decrease in hemoglobin(Hb) level in 8 cases (12.6%) , decrease in platelets count in 20 cases (31.7%) and positive CRP in 29 cases(46%) which are criteria of neonatal sepsis which contribute in etiology of neonatal seizures

There were significant serum electrolytes changes where 36 cases (57.2%) had low calcium serum level, 17 cases (27%) had low sodium serum level but 18 cases (28.6%) had significant increase in potassium serum level,43 cases(68.3%) had abnormal serum glucose and all cases had normal magnesium serum level.

There were 6 cases (9.5%) from total cases gave positive CSF culture and 10 cases (15.9%) gave positive results for blood culture from total cases.

Cranial ultrasonography was carried out to all cases .Where 31 cases (49.2%) were found to have a normal cranial ultrasound while 32 cases (50.8%) had abnormal findings in the form of:

1- Hypoxic changes in 18 cases(28.6%)
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3- Intraventricular and subdural hemorrhage in 7 cases (11.1%).
4- Brain edema in 5 cases (7.9%)
5- Brain atrophy in 2 cases (3.2%)

The distribution of cases according to etiology of seizures where we found that the most common causes of neonatal seizures was hypoxia (50.8%), followed by neonatal sepsis (31.7%), followed by metabolic and electrolyte disturbance (9.6%) (2 of them are metabolic) followed by ICH (4.7%), while the least common causes of neonatal seizures was syndromes (3.2%).

The distribution of cases according to commonest etiology, the hypoxia was the commonest etiology in full term, seizure in 1St day, seizure >1St day, N.V.D and C.S while IVH was the commonest etiology in preterm.

Conclusion:

Early detection and management of neonatal seizures with delineation of their causes are one of the most importance ways to prevent morbidity and mortality in NICU.

Etiologies of neonatal seizures remain powerful prognostic factors. Diagnostic advances have changed the etiologic distribution for neonatal seizures and improved accuracy of outcome prediction. Global cerebral hypoxia-ischemia is the most common etiology

With the advent of cranial ultrasound technology, physicians acquired a rapid, noninvasive, bedside opportunity to investigate the anatomy of the newborn brain. Previous attempts to view the newborn brain required either exposure to radiation with a computed tomographic scan or could not be done until autopsy.

Recommendation

Neonatal seizures are a serious disease and its sequels may cause permanent handicapping so the best way to prevent seizures is to prevent its causes.

As the most common cause of neonatal seizures is hypoxic-ischemic encephalopathy so prevention of hypoxic-ischemic encephalopathy by good antenatal care and appropriate delivery is a cornerstone in prevention of neonatal seizures and its sequels.

Prematurity and its sequels is a major component in etiology of neonatal seizures so we shouldn't forget that the best way to prevent neonatal seizures is to prevent prematurity itself.

Cranial ultrasound is safe and accurate practical method for detection of preterm neonates at risk for brain injury, and some brain abnormalities which causes neonatal seizures so ultrasound is recommended in all preterm neonates as a screening protocol, in all cases admitted to NICU.

More prospective studies should be done aiming at correlating the ultrasound results with neurodevelopmental outcome at older ages and laying stress on cognitive functions.

More attention should be aimed to neonatal sepsis and its complication as an important cause of neonatal seizurs so prevension of sepsis by proper treatment of maternal diseases during pregnancy like infection and premature rupture of membrane and proper treatment of sepsis if occure prevent neonatal seizures and its sequels.

EEG is recommended to be performed for all infants with neonatal seizures both as a diagnostic and prognostic tool as it was found to correlate with the early onset, frequency and outcome of seizures in many studies.

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N	SEX	AGE	ONSET OF SEIZURE	TYPE OF SEIZURE	MODE OF DELIVERY	NATALH.		POST NATAL H.
						MATERNAL DISEASE	PROM	
1	F	2	2	Focal	C.S	CMV	7day	Post arrest
2	F	3	3	Generalized	N.V.D	- ve	5day	R.D
3	M	5	5	Subtle	N.V.D	Cervical erosion	- ve	R.D
4	M	2	2	Subtle	C.S	- ve	24hour	R.D
5	M	6	6	Generalized	N.V.D	- ve	- ve	R.D
6	M	2	2	Generalized	C.S	- ve	- ve	Delayed first cry
7	M	3	3	Generalized	C.S	- ve	- ve	IUGR
8	M	3	3	Subtle	C.S	- ve	- ve	Delayed first cry
9	M	2	2	Focal	N.V.D	- ve	- ve	Delayed first cry - MAS
10	M	27	27	Subtle	N.V.D	- ve	- ve	Delayed first cry
11	M	1	1	Focal	C.S	Rupture uterus	- ve	Delayed first cry
12	M	2	2	Generalized	N.V.D	- ve	- ve	Delayed first cry
13	F	2	2	Generalized	C.S	- ve	- ve	Delayed first cry
14	M	5	5	Focal	N.V.D	- ve	- ve	Delayed first cry
15	M	3	3	Generalized	N.V.D	- ve	- ve	Delayed first cry
16	M	6	6	Generalized	N.V.D	- ve	- ve	Delayed first cry
17	F	2	2	Generalized	N.V.D	- ve	- ve	Delayed first cry
18	F	4	4	Generalized	N.V.D	- ve	- ve	R.D
19	F	1	1	Generalized	N.V.D	Pre-eclampsia	- ve	R.D
20	M	2	2	Subtle	C.S	Threatened abortion	- ve	R.D & Delayed first cry
21	M	6	6	Generalized	C.S	- ve	- ve	R.D
22	M	27	27	Generalized	N.V.D	- ve	- ve	R.D & Delayed first cry
23	F	2	2	Subtle	C.S	Pre-eclampsia	- ve	R.D & Delayed first cry
24	M	2	2	Generalized	C.S	- ve	- ve	R.D
25	M	2	2	Subtle	N.V.D	- ve	- ve	Delayed first cry
26	F	2	2	Generalized	C.S	- ve	- ve	Delayed first cry
27	F	3	3	Generalized	N.V.D	- ve	- ve	R.D
28	F	1	1	Subtle	C.S	- ve	- ve	Delayed first cry
29	M	1	1	Generalized	C.S	Antipartum Hge	- ve	R.D
30	F	4	4	Generalized	C.S	- ve	- ve	Delayed first cry
31	M	14	14	Generalized	N.V.D	- ve	- ve	R.D
32	M	4	4	Subtle	C.S	- ve	- ve	R.D
33	F	1	1	Generalized	N.V.D	- ve	- ve	Delayed first cry
34	M	3	3	Subtle	C.S	Pre-eclampsia	- ve	R.D
35	F	3	3	Generalized	N.V.D	- ve	30hour	R.D
36	M	1	1	Generalized	C.S	Pre-eclampsia	- ve	R.D
37	M	11	11	Subtle	N.V.D	- ve	1 week	Delayed first cry
38	M	4	4	Focal	C.S	- ve	- ve	R.D
39	M	1	1	Generalized	N.V.D	- ve	- ve	Delayed first cry
40	M	16	16	Generalized	N.V.D	- ve	- ve	R.D
41	M	2	2	Generalized	N.V.D	- ve	- ve	Delayed first cry
42	M	5	5	Subtle	C.S	- ve	- ve	R.D

N	SEX	AGE	ONSET OF SEIZURE	TYPE OF SEIZURE	MODE OF DELIVERY	N ATALH.		POST NATAL H.
						MATERNAL DISEASE	PROM	
43	F	4	4	Subtle	N.V.D	- ve	- ve	R.D
44	M	3	3	Generalized	N.V.D	- ve	- ve	R.D
45	F	4	4	Subtle	N.V.D	- ve	- ve	Delayed first cry
46	M	3	3	Generalized	C.S	- ve	- ve	R.D
47	M	1	1	Generalized	N.V.D	- ve	- ve	Delayed first cry
48	M	13	13	Subtle	N.V.D	- ve	2 week	R.D
49	F	12	12	Focal	N.V.D	- ve	20hour	R.D
50	M	1	1	Generalized	C.S	- ve	- ve	Delayed first cry
51	M	1	1	Subtle	N.V.D	- ve	- ve	R.D
52	M	5	5	Focal	N.V.D	- ve	- ve	R.D
53	F	16	16	Generalized	N.V.D	- ve	- ve	R.D
54	M	1	1	Generalized	C.S	- ve	- ve	Delayed first cry
55	M	4	4	Generalized	N.V.D	- ve	- ve	Delayed first cry
56	M	1	1	Subtle	N.V.D	- ve	7day	Delayed first cry
57	M	2	2	Generalized	N.V.D	- ve	ve	Delayed first cry
58	F	1	1	Generalized	N.V.D	- ve	ve	Delayed first cry
59	M	10	10	Generalized	N.V.D	- ve	ve	R.D
60	F	24	24	Generalized	N.V.D	- ve	ve	R.D
61	M	12	12	Generalized	C.S	- ve	ve	Convulsion
62	M	1	1	Generalized	N.V.D	- ve	ve	Delayed first cry
63	M	1	1	Generalized	N.V.D	- ve	ve	Delayed first cry

Abbreviations: M = male F=female

EXAMINATION

N	WT	GENERAL	LOCAL
1	4Kg	Bad	Edema
2	1.5 Kg	Bad	Decrease air entry
3	2.9 Kg	Fair	Decrease muscle tone & reflexes
4	2.6 Kg	Fair	Fair
5	3.1 Kg	Fair	Fair
6	3.1 Kg	Fair	Fair
7	2 Kg	Bad	Decrease air entry & crepitation
8	2.8 Kg	Bad	Hypotonia
9	3.7 Kg	Bad	Crepitation
10	3 Kg	Bad	Weak reflexes
11	4 Kg	Bad	Absent muscle tone & reflexes
12	4.4 Kg	Bad	Decrease air entry
13	2.6 Kg	Fair	Fair
14	3.3 Kg	Fair	Fair
15	3.5 Kg	Fair	Fair
16	3.4 Kg	Bad	Decrease air entry & crepitation
17	3.3 Kg	Fair	Fair
18	1.4 Kg	Fair	Fair
19	2.2 Kg	Bad	Decrease air entry & crepitation
20	1.5 Kg	Fair	Fair
21	3 Kg	Fair	Fair
22	3.1 Kg	Fair	Fair
23	1.1 Kg	Bad	Weak neonatal reflexes
24	3.1 Kg	Fair	Fair
25	3 Kg	Bad	Neck rigidity
26	3.1 Kg	Bad	Decrease air entry & crepitation
27	3.5 Kg	Bad	Decrease air entry & hypertonia
28	2.5 Kg	Fair	Fair
29	2.3 Kg	Fair	Fair
30	3.1 Kg	Bad	Weak neonatal reflexes
31	3.3 Kg	Bad	hypertonia
32	2.7 Kg	Fair	Fair
33	2.5 Kg	Bad	Weak neonatal reflexes
34	2.3 Kg	Bad	Decrease air entry & poor perfusion
35	1.7 Kg	Bad	Weak neonatal reflexes
36	2.6 Kg	Fair	Fair
37	3 Kg	Bad	Decrease air entry & crepitation
38	0.9 Kg	Bad	Bleeding from puncture sites
39	2 Kg	Fair	Fair
40	3.4 Kg	Bad	Weak neonatal reflexes
41	3.8 Kg	Bad	Weak neonatal reflexes
42	1.7 Kg	Fair	Fair

EXAMINATION

N	WT	GENERAL	LOCAL
43	1.3 Kg	Fair	Fair
44	1.6 Kg	Fair	Fair
45	2.2 Kg	Bad	Weak neonatal reflexes
46	2.5 Kg	Bad	Absent muscle tone & reflexes
47	3 Kg	Bad	Systolic murmur
48	1.2 Kg	Bad	Hepatosplenomegally
49	1.5 Kg	Fair	Fair
50	2.3 Kg	Bad	Weak neonatal reflexes & neck rigidity
51	2.2 Kg	Bad	Weak neonatal reflexes
52	0.9 Kg	Bad	Decrease air entry & crepitation
53	3.1 Kg	Bad	Hypertonia
54	2.9 Kg	Bad	Decrease air entry & crepitation
55	3.4 Kg	Fair	Fair
56	3.9 Kg	Fair	Fair
57	2.7 Kg	Bad	Weak neonatal reflexes
58	2.9 Kg	Bad	Absent muscle tone & reflexes
59	2.6 Kg	Bad	Decrease air entry & crepitation
60	3.5 Kg	Bad	Weak neonatal reflexes
61	3.4 Kg	Bad	Decrease air entry & crepitation
62	2.8 Kg	Bad	Decrease air entry & crepitation
63	3.6 Kg	Fair	Fair

INVESTIGATION												
N	HAEMATOLOGICAL			CHEMISTRY								Other
	CBC			GLUCOSE	Ca	Na	K	Mg	CRP	CSF	BLOOD CULTURE	
	TLC	HB	PLATELET									
1	٣٨.9	14.4	102	102	8.4	135	٤.٥	٢	-		No Growth	
2	15	15.1	273	١٢٤	٩.٥	١٣٤	٥.٧	1.9	+		No Growth	
3	1.8	10.6	28	٩٧	٧.١	١٣٥	٤.٥	2	+		+	
4	9.3	17	223	٨٨	٩.٥	٣١٩	٤.٨	2	-		No Growth	
5	4.8	14	354	٢٥٣	٦.٥	١٣٤	٣.٦	2	-		No Growth	
6	6.2	18.1	١٤٨	٤٠	٩.٥	١٤٥	٣.٥	1.8	+	meningitis	No Growth	
7	28.8	18.8	١٠٦	١١٦	٨.٨	١٤٠	٦	1.8	+	meningitis	No Growth	
8	8.4	16.5	٢٩٠	١٢٠	٨.٥	١٣٨	٦.٥	1.5	-		No Growth	
9	31	14.1	٢٣٢	١٠٨	٨.٦	٩٩	٨.٦	2.7	-		No Growth	
10	16.2	8.2	٣٧	٣٠٠	١١	١٣٩	٨.١	2	+		No Growth	
11	20	18.6	١٨٠	٧٨	٨.٧	١٣٥	٤.٥	٢	-		No Growth	
12	11.1	9.5	٢٢٨	٤٢	٥.٢	١٣٤	٥.٨	٢	+		No Growth	
13	14.2	18.6	٢٣٠	٦٨	١٠.٨	١٣٢	٧.٧	2.4	+	Normal	No Growth	
14	9.1	10.8	٢٦٥	٦٤	٧.٦	١٣٥	٤.٥	1.7	+		No Growth	
15	14.6	17.5	٣٤٩	١٤٥	٧.٥	١٣٥	٤.٥	2	+		No Growth	
16	89.5	17.5	٣١	١٢٠	٩.٣	١٣٥	٤.٥	٢	+		+	
17	16.6	14.4	١٨٢	٩٥	٨.٨	١٣٥	٥	٢	+		No Growth	
18	7.4	13.9	١٤	١٠٠	٩.٨	١٣٥	٥	٢	+		No Growth	
19	13.4	19.1	٢٨٣	١٢٧	٨	١٣٠	٣.٩	1.4	+		No Growth	
20	8.4	13.2	٢١٦	٥٤	٧.٧	١٣٥	٥	٢	-		No Growth	
21	8.6	15.5	٢٤١	١٦٥	٨.١	١٣٥	٥	2.5	-		No Growth	
22	5.4	15.3	٤١٤	١٠٨	٨.٣	١١٦	٥.١	1.2	-		No Growth	
23	20.7	14.6	٢٥٧	١٠٢	٥.٧	١٣٦	٦.٢	1.8	-		No Growth	
24	6.2	18.1	١٤٨	40	٩.٥	١٤٥	٣.٥	1.8	+		+	
25	19.4	15.6	٢٦٨	٦٠	٩.٢	١٣٥	٤.٥	2	-		No Growth	
26	14.4	12.6	٢٢٦	١١٢	٨.٨	١٣٦	٤	2.7	-		No Growth	
27	21.6	19.1	٢١٧	٢٠٩	٨.٢	١٣٥	٥	2	+		No Growth	
28	8.2	14.9	٤١٨	٩٦	٩.٤	١٤٤	٤.١	1.8	-		No Growth	
29	12.6	١٦.9	٢٠٧	٩٣	٨.١	١٣٥	٥	2.9	-		No Growth	Ammonia
30	14.4	12.6	٢٢٦	١١٢	٨.٨	١٣٦	٤	2.7	-		No Growth	
31	28.6	17	٨٣	٦١	٧.٦	١٣٥	٥	2.5	-	meningitis	No Growth	
32	6.9	19.6	٢٣٧	80	٨.٣	١٢٩	٣.٦	2.8	+		+	
33	8.4	11	٢٨٩	٧٦	١٠.٦	١٤٣	٤.١	2.8	+		No Growth	Ammonia
34	12.8	18.7	٢٤٩	١١٢	٩.٣	١٣٥	٥	2	-		No Growth	
35	19.6	17.5	١٤٨	٨٠	٧	١٤٩	٤.٢	2	-		No Growth	
36	25.9	١٦.4	٣٤٢	٧٦	٨.٦	١٣٤	٤.٤	3	+		No Growth	
37	12.6	13.2	٢٤١	٥٣	٧.٥	١٥١	٣.٤	2	-		No Growth	
38	5.8	10.2	١٣٣	١٠٥	٨	١٦٣	٥.٤	2.5	+		No Growth	
39	17	18.3	٢٥٦	١١٣	٨.١	١٣٨	٣.٧	٢	-	Normal	No Growth	
40	10.2	12.7	٢٦١	٥٨	6.6	١٣٥	٥	2.2	+	meningitis	No Growth	
41	24.8	15.5	٢٠٠	١٠٠	٧.١	١٣٥	٥	٢	+		No Growth	
42	٨.3	18.4	٢٦٨	٩٢	٨.٩	١٤٠	٥.٩	2.4	-		No Growth	

INVESTIGATION												
N	HAEMATOLOGICAL			CHEMISTRY								Other
	CBC			GLUCOSE	Ca	Na	K	Mg	CRP	CSF	BLOOD CULTURE	
	TLC	HB	PLATELET									
43	7.3	12.5	266	126	٩	١٣٦	٧.٢	2.3	-		No Growth	
44	8.2	18.3	٢١٤	١٠٤	٦.٤	١٣٥	٥	1.6	-		No Growth	
45	13	20.8	١٧٨	١٢٧	٩	١٣٥	٥	2	-	meningitis	+	
46	7.6	16.3	٢٠١	٥٣	١١.٨	١٣٥	٥	2.7	+		No Growth	
47	11.2	16.5	٢٢٤	١٦٤	٨.٢	١٢٨	٧.٩	1.7	-		+	
48	30.9	12.7	١٥	١٠٤	٨.٦	١٤١	٣.٣	2	+		+	
49	23.8	18	١٣٥	٩٥	٩.٨	١٣٥	٤.٥	٢	+		No Growth	
50	11.3	11.8	٦٩٥	٧٨	١١	١٤١	٥.٣	1.5	-	Normal	No Growth	
51	28.6	13.2	٢٥٠	٩٢	٦.٥	١٣٩	٨.١	1.8	+		No Growth	
52	7.2	11.9	٥٩	٣٣	٩	١٠٧	٥.٧	2	+		+	
53	19.5	13.9	٤٦١	١٣٩	١٠	١٣٥	٥	1.3	+	Normal	No Growth	
54	14	18.2	١٣٦	٨٠	٩.٥	١٣٥	٥.٥	٢	-		No Growth	
55	6.2	15.1	٢٥٠	١٥٦	٨.٦	١٢٩	٤.٨	2	-		No Growth	
56	21.2	21.8	٢٠٢	١٠٢	٨.٥	١٣٢	٤.٥	2.5	-		No Growth	
57	25.4	18.3	٤١	١٠٩	٨.٨	١٣٩	٥.٩	2	-		No Growth	
58	23.7	19.4	١٣٩	١٠٢	١٠.٢	١٣٥	٥	2.1	-		No Growth	
59	13.3	15.4	٩٩	١٣٦	٩	١٣٥	٥	2	+	meningitis	No Growth	
60	23.8	5.2	٤٤٠	٩٩	٩	١٣٣	٤.٧	٢	+		No Growth	
61	12.2	14.1	٣٦٠	١٥٦	٩.٨	١٣٥	٣.٩	1.7	-	Normal	+	
62	27.4	17.1	١٨٩	٥٢	١٠.٢	١٢٤	٤	1.8	-		+	
63	9.9	١٣.٩	١٤٥	١٢١	٨.٣	١٣٥	٣.٣	1.6	-		No Growth	

Imaging

N	Cranial u/s	C.T	Chest x-ray
1	Normal		Normal
2	Subdural Hge		RDS
3	Normal		Normal
4	Normal		Congenital Pneumonia
5	Normal		Normal
6	HIE		Normal
7	Normal		Normal
8	HIE		Normal
9	HIE		Normal
10	Normal		Normal
11	Normal		Normal
12	HIE		Pneumonia
13	Normal		Normal
14	HIE		Normal
15	Normal		Normal
16	HIE	Brain Edema	Normal
17	Normal		Normal
18	Normal		Normal
19	Normal		Normal
20	Normal		RDS
21	Dandy Walker Syndrome	MRI=Dandy Walker Syndrome	Normal
22	Normal		Pneumonia
23	IVH		Normal
24	Normal		Normal
25	Brain Atrophy		Normal
26	HIE		Normal
27	Normal		Normal
28	Brain Atrophy		Normal
29	Normal		Normal
30	HIE		Normal
31	Brain Edema		Normal
32	Arnold Chiarri & IVH		Normal
33	HIE		Cardiomegally
34	Normal		Normal
35	Normal		Normal
36	HIE		Normal
37	HIE		Pneumonia
38	HIE & IVH		RDS
39	HIE		Normal
40	Normal		Normal
41	Brain Edema		Lung Collapse
42	Normal		Normal

Imaging

N	Cranial u/s	C.T	Chest x-ray
43	IVH		RDS
44	Normal		RDS
45	Normal		Normal
46	Brain Edema		Normal
47	Brain Edema		Normal
48	Subdural Hge		Normal
49	Normal		RDS
50	Normal		Normal
51	Normal		Normal
52	HIE & IVH		Normal
53	Brain Edema		Normal
54	Normal		RDS
55	Normal		Normal
56	HIE		Pneumonia
57	HIE		Lung Collapse
58	HIE		Normal
59	Normal		Normal
60	IVH		Normal
61	Normal		Normal
62	HIE		Normal
63	Normal		Normal