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INVITED ARTICLE

Seizures in small brains

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Abstract

Neonatal seizures are the most common neurological emergency in newborns; often signalling significant neurological dysfunction. Their pathophysiology is complex and relates to the imbalance between excitatory and inhibitory neurotransmitters in the immature brain. During the neonatal period, excitatory circuits mediated via neurotransmitters like glutamate predominate while inhibitory circuits mediated via gamma-aminobutyric acid (GABA) signalling are underdeveloped. Additionally, immature ion channels, such as sodium, chloride, potassium, and calcium, increase neuronal excitability. The most common aetiology of seizures is attributed to neonatal hypoxic cerebral injury. However, metabolic vulnerabilities, such as hypoglycaemia and electrolyte imbalances, can also precipitate seizures. Identifying the underlying cause, which in a large majority is acute symptomatic, is critical for prompt treatment. Early intervention is essential to prevent long-term neurodevelopmental consequences.

Diagnosing neonatal seizures is challenging due to their subtle presentations. Distinguishing them from non-seizure events is crucial. Accurate diagnosis is essential for appropriate treatment and management. Continuous electroencephalography (cEEG) is the gold standard for diagnosis, but an amplitude-integrated EEG (aEEG) is a useful alternative tool in neonatal intensive care units (NICUs), for high-risk infants. This facilitates diagnosis of electroclinical as well as electrical seizures; commonly encountered in the very sick newborns and those born prematurely. Neuroimaging, like magnetic resonance imaging (MRI) and computed tomography (CT) is required to identify structural causes, while laboratory and genetic tests check for infectious, metabolic and genetic aetiologies. The new classification proposed by the International League Against Epilepsy (ILAE), underscores the importance of recognition of electrical seizures and highlights the value of recognising the seizure semiology for the diagnosis of the underlying aetiology.

KEYWORDS
Neonatal seizures, low-income settings, prevalence

INTRODUCTION

The neonatal period spans up to 4 weeks post-delivery in a term baby and up to 44 weeks of gestation in a preterm baby. The neonatal brain is in an electrically hyperstimulated status, to meet the demands of rapid brain activation. This in return poses the risk of a lower threshold for the development of neonatal seizures.

Neonatal seizures are a critical and frequently encountered neurological emergency. They are most frequently experienced in the neonatal intensive care unit. The proportions affected vary according to the gestational age[1] and birth weight;[2] affecting approximately 1.5 to 3.5 per 1000 live births in term babies and 10-130 per 1000 live births in the preterm deliveries in the United States.[3] The incidence is also heavily influenced by the healthcare status of the country, being higher and much more variable in low-income settings.[4, 5] A previous study in Sri Lanka estimated a prevalence of 4.0 per 1000 live births.[6] These seizures can be the first indication of a significant underlying pathology, the aetiology of which is divided into six broad categories in the recent position paper from the ILAE;[7] i.e. hypoxic-ischaemic encephalopathy (HIE), structural, infective, metabolic disturbances, genetic disorders and unknown aetiology.

This article emphasizes the clinical importance of neonatal seizures, the complexities of their identification, and the implications for long-term outcomes. It sets the stage for a detailed discussion on the state-of-the-art in diagnosis of neonatal seizures, and the areas needing advancement and further research in low-income settings.

Pathogenesis

The neonatal brain is particularly susceptible to seizures due to its unique developmental stage, characterized by high neuronal excitability and immaturity of its inhibitory mechanisms.[8] This susceptibility, combined with the evolving process of developing synaptic connections and neurotransmitter systems, differentiates neonatal seizures from those occurring in older children and adults.[9] Understanding the pathophysiology of neonatal seizures is crucial for accurate diagnosis and effective management.

The main determinants of this heightened excitability rest on the enhanced excitability, immature synaptic networks, and increased susceptibility to channel expression.

The high degree of excitability is due to the predominance of excitatory neurotransmitters like glutamate, and the relative imbalance due to the delay in expression of inhibitory neurotransmitters such as γ-aminobutyric acid (GABA).[10] During early development, GABA has a paradoxical depolarizing rather than its usual hyperpolarizing effect.[11] This is due to the higher intracellular chloride (Cl^-) concentration relative to the extracellular Cl^- in the neonate resulting in an efflux of Cl^- facilitating the depolarisation. This is facilitated by the upregulation of the expression of the NKCC1 chloride co-transporter in utero and in early post-natal life.[12] This NKCC1 transporter imports Cl^- into the cells. This is in contrast to the relatively low concentration of intracellular Cl^- levels in the adults triggering the influx of Cl^- thus maintaining the neuron in a hyperpolarised status.[8] This effect is mediated by the KCC2 chloride co-transporter, which exports Cl^- ions to the extracellular space by becoming activated beyond the neonatal period and infancy. This depolarising effect of GABA may also remove the voltage-dependent magnesium block from NMDAR channels for magnesium, allowing the entry of calcium into the immature neurons. This also adds to the enhanced activation of the neuronal network in the newborn.[13]

The enhanced excitability is supported by the enhanced expression of the excitatory glutamate receptors, found in abundance in the neonate.[2] There are three types of ionotropic glutamate receptors active in the neonate i.e. ∞- amino-3 hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, and N-methyl-D-aspartate (NMDA)[14]. These are expressed in higher densities in different regions in the immature brain. These synergistic effects of the depolarising GABAergic currents and the glutamatergic NMDA-R depolarising currents result in physiological network-driven events called Giant Depolarising Potentials (GDPs),[13] essential for early brain development. However, their facilitated synchronous firing may contribute towards a pathological excess of activity as well.

The immaturity of the synaptic network also renders a hyperexcitable status. This increased density of synapses and the active process of synaptogenesis are requirements of the still-developing brain for its numerous activity-dependent developmental processes during which the inhibitory connections are maintained at a lower concentration.[14] Alterations in channel expression also contribute towards increased neonatal seizure generation. Increased expression of NKCC1 in neonates with perinatal injury and reduced expression of KCC2 in those with HIE are examples.[12]

Disease burden

Seizures are the most common neurological emergency in the neonatal period. The reported incidence varies based on the income status of the study setting, mean gestation at birth and inclusion of electrographic seizures in the estimate. The significantly higher incidence in low income settings relates to the increased burden of pregnancy complications, birth related trauma, hypoxic ischaemic injury and congenital as well as post-natal aquired infections.[5] The reported incidence ranges between 36-90 per 1000 live births in contrast to 1-4 per 1000 in resourceful settings.[15] However, reports on the incidence of neonatal seizures in low-income countries are sparse. Further, due to technical and economical constraints of EEG based diagnosis, these studies include only those diagnosed clinically, resulting in an underestimation.

In the Sri Lankan setting, we ventured to perform a population-based evaluation of the incidence of neonatal seizures within the Colombo District.[6] All births at the two premier maternity hospitals in the district over a three-month period, were followed up during the neonatal period. For those born at term, it included the first 28 days; for those born preterm, it continued up to completion of 44 weeks of gestation. All admissions to NICU, Premature Baby Unit (PBU) with HIE, neonatal sepsis, and or neonatal seizures itself during the neonatal period were evaluated. All mothers who were discharged following uncomplicated delivery were contacted by telephone on day 14 and day 28 to assess for the development of seizures. If any baby was admitted to a hospital during the neonatal period, relevant information was gathered by visiting the relevant wards. The diagnosis of neonatal seizures was based on clinical evaluation only. Hence, this included only Level 2 (Probable seizure) and Level 3 (Possible seizure) patients.[7] There was no EEG monitoring performed for this purpose.

The total number of live births during this period was 2906. There were 1447 (49.8%) males and 1459 (50.2%) females with an almost equal male-to-female ratio. There were 2639 term births and 267 preterm births. The total number of Intensive/ Special Care Baby Unit admissions was 73.

The total number of babies with neonatal seizures was nine. The incidence of neonatal seizures was 4 per 1000; 3.6 per 1000 in term babies and 7.8 per 1000 in preterm babies. This population-based estimate though based only on clinical judgement, indicates a true estimate of the disease burden in comparison to a NICU based estimate of neonatal seizures. However, this estimate runs the risk of both over and underestimation due to false positivity as well as false negativity considering the subtlety of neonatal seizures,[16] particularly those in babies with HIE and those born prematurely, since the gold standard for diagnosis of neonatal seizures requires the use of video-EEG monitoring.

Aetiology

Neonatal seizures are predominantly related to an acute illness or a brain insult (provoked) and falls into the broad category of acute symptomatic seizures.[17] This proportion accounts for more than 75-85%.[18] Unprovoked seizures or epilepsy syndromes are a rarity, accounting only for about 15% of neonatal seizures.[19] The aetiology of neonatal seizures is identifiable in up to 93% following detailed evaluation in advanced settings.[10] They can be considered under the 6 broad categories listed in the ILAE classification.[7] These are HIE, structural (which includes brain malformations and vascular injuries), genetic, infection, metabolic and unknown. The most common group of aetiology across the globe remains to be HIE.[18, 21] Other causes which contribute to acute provoked aetiologies include drug withdrawal and birth-related head trauma.

The proportion of each of these aetiologies is influenced by the income status and the standard of antenatal health care provision in each country.[15] Even in resource rich countries, HIE remains the most predominant aetiology (40-46%), particularly in term babies. This is followed by intracranial haemorrhage (12-17%) which is the most frequent in the preterm, stroke (venous or arterial) in 13.5-18%, transient metabolic disorders (including hypoglycaemia) in 9%, central nervous system (CNS) infections in 7%, congenital structural causes in 2.9% and other causes such as genetics, and non-CNS infections in 2.6%. Seven to nine percent had no identifiable aetiology.[20, 22] The proportions of these aetiologies differ according to gestational age.[5]

The proportions of the above aetiologies of neonatal seizures differ according to resource availability as well.[15, 23, 24] A comparison of aetiologies across resource-limited settings such as India, Iran, and Brazil show a significantly higher proportion of neonatal seizures related to HIE.[25] This is shown in Table 1.[26] Further, proportions identified with an underlying inborn error of metabolism, as well as with genetic epilepsies are underestimated due to the challenges in performing advanced investigations.[4, 25] In a study performed in Sri Lanka in those presenting with neonatal seizures after the first day of life, there were none with genetic epilepsies and only 3% were related to metabolic disorders.[26] This may be compounded by the relative lack of facilities for performing MRI, the recommendation for the detection of neonatal stroke.[27] Another important difference in studies in low and low-middle income settings, compounded by the limited investigative capacity, is the relatively higher proportion of those with an unknown aetiology.[25] This proportion was as high as 16% in the Sri Lankan study.[26] This contrasted with nearly 95% of neonatal seizures being related to a known aetiology in resourceful settings.

Diagnosis of neonatal seizures

Clinically, neonatal seizures present a significant diagnostic challenge. They often exhibit subtle and atypical manifestations that can be easily overlooked in the absence of continuous electroencephalographic (EEG) monitoring.[28] Unlike seizures in older children, neonatal seizures may not always correlate with visible motor activity and clinical-only seizures have been shown in a large proportion not to be frank seizures.[29] This necessitates the use of advanced neuro-diagnostic tools for their accurate detection and characterization.

Neonatal seizures are different in the focus of origin and their ability to propagate. They are entirely focal, brief, and clinically subtle.[30] The incomplete myelination and the developing stages of synaptogenesis preclude the inability to generate generalised seizures as well as tonic-clonic seizures from the onset. These also curtail the spread of ictal activity resulting in electro-clinical dissociation increasing the burden of undetected subclinical seizures.[31] Electrographic seizures are

TABLE 1 Comparison of reported aetiologies of neonatal seizures in studies from low-middle income countries[26]

Setting	N	HIE	Stroke	ICH	Metabolic/ electrolyte derangement	Infections	CNS malformations	IEM	Genetic/ epilepsy syndrome	Unknown
India	75	52%	-	6%	16%	20%	-	-	-	-
India	84	33%	-	5%	5%	25%	5%	-	-	-
India	172	78%	-	2%	9%					
Iran	25	32%	-	4%	4%	42%	6%	4%	-	4%
Brazil	104	54%	-	13%	32%	1%	5%	1%	-	-
Sri Lanka	31	16%	-	3%	13%	42%	3%	3%	-	13%

HIE – Hypoxic ischaemic encephalopathy, ICH – Intracranial haemorrhage, CNS – central nervous system IEM – inborn errors of metabolism

defined as sudden, evolving rhythmic electrical activity, with a beginning and an end lasting a minimum duration of 10 seconds.[7] However, in some seizure types, it may even be of a shorter duration than 10 seconds, often known as brief rhythmic discharges (BRDs) or brief interictal / ictal rhythmic discharges (BIRDs), and are considered to be part of a continuum of interictal ictal subclinical seizure activity.[32] BRDs with evolution patterns are considered to be ictal.[33]

The occurence of subclinical seizures is greatest in the most sick babies and premature newborns.[34] Their detection requires EEG monitoring using the standard EEG monitoring with video, which is the currently accepted gold standard.[35] This is known as continuous EEG (cEEG) monitoring. However, considering the practical difficulties and the expertise required, the at-risk babies can be screened for seizures using amplitude-integrated EEG (aEEG) monitoring.[36] The accuracy of aEEG for identification of seizures is less, with a mean sensitivity of 39% because it employs fewer electrodes covering only a smaller surface area.[37] Further in a EEG the display is filtered and time-compressed making it harder to identify brief seizures. Despite these limitations, it is a useful and cost-effective modality to determine the presence or absence of seizures, even by a non-expert.[38]

The concept paper from the Neonatal Seizures Task Force of the ILAE in the year 2021 described a new classification of neonatal seizures.[7] It considered the seizure types relevant to this age group, determined by the predominant clinical feature. This predominance is often determined by the first appreciated clinical change. The seizures are focal only and are of two types; motor and non-motor seizures. In the motor seizures, a new type named sequential seizures is included. In the non-motor group, sensory seizures are not included recognizing the inability to diagnose these seizures in the neonate. A predominance of autonomic seizures in this age group is highlighted in the non-motor category. This classification considered the significance of electrographic confirmation of seizures; therefore, all seizures were divided into either electroclinical or electrographic only. This inclusion mandated the use of EEG monitoring for diagnosis. Despite the limitations in performing these evaluations, the new classification underscored the importance of the use of EEG monitoring for the diagnosis of neonatal seizures.[7] (Figure1).

The importance of recognising the type of seizure is associated with early recognition of the potential underlying aetiology. [21, 39]

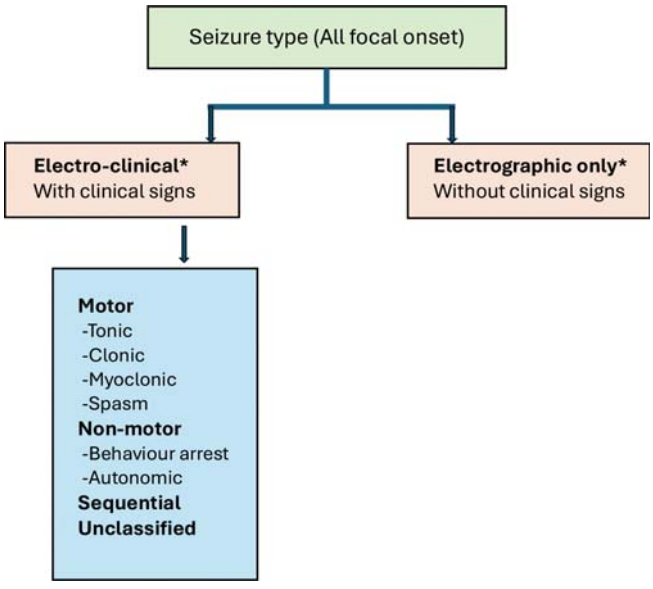

FIGURE 1 Classification of neonatal seizures according to electroencephalography and semiology.[7]

Similarly the timing of neonatal seizures also hints at the potential of certain aetiologies. For example, first seizures due to HIE occur within the first 24 hours of birth. Similarly, seizures due to acquired infection and or infarction occur after the first 24-48 hours, but during the first week of life.[39] Seizures due to cortical malformations, self-limited neonatal epilepsies as well as epileptic encephalopathies tend to occur after the first few days of life.[19]

Longterm outcome

Despite the relative increased incidence of seizures in the neonate, the neonatal brain is less susceptible to seizure-induced brain damage.[9] Part of this is related to these brains being less vulnerable to the toxic effects of glutamate. On the other hand, the impact of frequent and or prolonged seizures in the newborn chiefly results in alteration of the development of the neuronal circuitries and developmental processes rather than cell loss and mossy fiber sprouting which is seen in the adult. The neonatal brain also harbours several protective functions such as having a lesser inflammatory response towards seizures, reduced oxidative stress in neonatal seizures, and having a high concentration of brain-protective factors such as brain-derived neurotrophic factor.[8] However, the seizures would likely aggravate the acute injury on the immature brains caused by the causative aetiology of the seizures. Examples to support this observation include the worse cognitive and motor long-term disability in neonates with hypoxia who had seizures over those not experiencing seizures. Similarly, a greater degree of brain injury is reported in those with seizures than in those without. Early detection of those likely to manifest long-term disability should be attempted to minimize developmental adversities.[40]

CONCLUSION

Seizures in newborns exhibit a different pathophysiology and pose a significant risk of substantial long-term neuronal injury. The importance of correct diagnosis using electrophysiological screening tools is emphasized due to the poor sensitivity of clinical diagnosis. The incidence of neonatal seizures is difficult to establish accurately in low-income settings, for reasons explained. Still, reports of even clinical-only seizures are much higher than those reported in advanced settings.

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