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RESEARCH ARTICLE

Management of neonatal seizures developed after the first 24 hours of life: a clinical audit from a tertiary children's hospital, Sri Lanka

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Abstract

Neonatal seizures represent the most frequent emergency encountered during the neonatal period. Improved diagnosis of both clinical and subclinical seizures, evaluation of specific aetiologies and optimized treatment help reduce mortality and morbidity associated with neonatal seizures.

Methods: A longitudinal, descriptive study was performed at the Lady Ridgeway Hospital for Children over a 12-month period. Neonates admitted or transferred due to neonatal seizures that occurred after the first 24 hours of life were included. Details pertaining to clinical presentation, evaluation of aetiology and the management of seizures were extracted from a parental interview and review of medical records.

Results: There were 31 neonates admitted with seizures during the study period. The majority were born at term. The number of seizures experienced was few (<5) in 48%. A definite aetiology was identified only in one third (n=9). The majority were considered as being related to a central nervous system infection, though none were microbiologically confirmed.

Electroencephalographic confirmation of seizures was not performed. Advanced neuroimaging was not offered to the majority. Detailed evaluation for metabolic diseases or for genetic epilepsies was not feasible.

The recommended first-line medication was prescribed to 93% of neonates. However, irregularities pertaining to the appropriate dose and route were noted in 22%. Therapeutic drug monitoring was unavailable in this hospital.

Conclusion: This study depicts the current practice regarding diagnosis, evaluation of aetiology and treatment of neonatal seizures in a low resource setting. The knowledge on the deficiencies is envisaged to divert focus onto areas needing improvement of care.

KEYWORDS
Low-income country, electrographic seizures, therapeutic drug monitoring

INTRODUCTION

Neonatal seizures are one of the most frequent emergencies in the newborn period. The physiological status of hyperexcitability of the immature neurons as well as their susceptibility to excitation by even subtle alterations in the external milieu, are causative.[1] They differ from seizures that occur in older age on their phenotypic expression, cortical network activation process, regulation of the excitatory and inhibitory receptors and response to conventional therapy.[2] The spectrum of aetiologies responsible for the seizures, differ according to the age of the neonate and its gestational maturation.[3]

Significant advancement in the understanding of the phenotypical manifestation, underlying aetiologies as well as

the electrophysiological changes of neonatal seizures is evidenced in the recently published classification of neonatal seizures from the International League Against Epilepsy.[4] Importance of early and comprehensive diagnosis which includes diagnosis of both clinical and electrographic seizures is emphasized. Optimal management of neonatal seizures is of extreme importance to improve on the overall long-term neurodisability and mortality.[5]

Sri Lanka is a low-middle income country and the field of neonatology is slowly expanding with the establishment of subspecialty services since 2008. Considering the requirement of technology and investigation capacity for optimal management of neonatal seizures, understanding the ground situation provides a base for planning improvisations. Hence, this study was performed to describe the current management of neonatal seizures at the premier children's hospital in the country. Findings will aid develop strategies for the improvement of services.

METHOD

This is a prospective study, performed over a 12-month period, at the Lady Ridgeway Hospital, Sri Lanka, to audit the current management of neonatal seizures. This is the premier children's hospital in the country, with a bed strength of over 900. The first half of the study was performed during the last six months of 2019. During the COVID-19 outbreak the study was temporarily withheld due to limited admissions and hospital infection control guidelines. The second six months of the study was performed during the last six months of 2022. A neonate was defined as a newborn who is within the first 28 days of life if born term and up to its 44th week of gestation if born preterm. Preterm were those born before the completion of the 37th week of gestation. Two categories of neonates were included in this study. They were those who were admitted directly to the hospital after discharge from their birthing centers due to development of seizures or those neonates who were transferred from a peripheral hospital for evaluation of seizures. Only those with seizures that occurred after the first 24 hours of life were included in this study. These neonates were identified from the admission register of the hospital as well as by visiting the respective wards daily. This included six general medical wards and the Premature Baby Unit of the hospital.

Information was gathered from the hospital clinical health records, transfer forms and by talking to the mother. Details of the neonatal seizures, underlying aetiology, investigations performed, antiseizure medications given and their duration of therapy were obtained from these hospital records. These babies were followed up from admission till the time of discharge regarding seizure recurrence, completion of evaluation of aetiology and therapy. This study was granted ethical approval from the institutional Ethics Committee.

RESULTS

There were thirty-one neonates reviewed during the one-year period (thirteen in 2019 and 19 during 2022). Twenty-four were born at term and the balance seven were born pre-term. Median age at presentation was five days [SD 7.95]. It ranged from 1-29 days. The mean number of days to onset of seizures was different in the two groups; it was 5.5 days (SD 7.76) for those born at term and 2.0 days (SD 2.14) for those born preterm. The largest group experienced their seizures after the first seven days of life (39%). The clinical details of these babies are given in Table 1.

TABLE 1 Demographic features of neonates admitted due to seizures after 24 hours of life

Feature	Number	Percentage (%)
Birth weight		
< 2.8 kg	16	51.6
> 2.8 kg	15	48.3
Gestational age		
< 37 weeks	8	25.8
> 37 weeks	23	74.2
Parity		
1	15	48.38
2	7	22.58
>2	9	29.03
Total number of seizures		
<5 seizures	15	48.38
5-10 seizures	6	19.35
>10 seizures	10	32.25

Neonatal seizures

The majority of neonates (n=15) developed a limited number (<5) of seizures (48%); but 30% experienced numerous seizures (>10). The mean age of onset was four days (1-28 days). This was within the first week in 19 (most within 72 hours) and beyond in 12. All thirty-one babies were diagnosed based on "clinical only" seizures as reported by parent or care providers. None of the babies had evidence of seizures recorded on to a smart phone as a video or had any EEG monitoring such as continuous electroencephalographic (cEEG) or amplitude integrated electroencephalographic (aEEG) monitoring, which is not available in the hospital. All diagnosis of seizures were not made by a neonatologist or an experienced paediatrician, for example, some of the seizures were based on verbal reporting by health care staff of baby units and parents. Even the basic electroencephalographic evaluation with a 30-minute recording with video surveillance was performed only in 19 patients (61%). Description of the seizure type was available only in 20 (65%). This included 15 with tonic seizures, four with clonic seizures and one with myoclonic seizures.

Aetiology

Regarding the aetiology, a definitive cause for the neonatal seizures was identified only in nine babies (29%). These causes included acute metabolic derangement in four, maternal abstinence syndrome in two, intracranial haemorrhage in one, structural brain anomaly in one and inborn error of metabolism in one. Most frequent, postulated probable aetiology was central nervous system infection. This was noted in thirteen (42%) babies. However, none of these babies had a confirmatory isolation from cerebrospinal fluid culture or polymerase chain reaction. In five, cerebral hypoxia secondary to respiratory or post-natal complications was implicated. There were four (13%) babies with completely unknown aetiology. Establishment of aetiology was not vigorous. Advanced microbiological testing was not available and radiological investigations were limited to ultrasonic examination in the majority. Only five babies were evaluated using computerized tomography. Magnetic resonance imaging was offered only to three babies. Limited access to advanced neuro-imaging modalities, absence of sophisticated microbiological testing and screening for inborn errors of metabolisms contributed towards the low proportion with a definitive aetiology.

Treatment

Eighty-four percent (n=26) were given initial medication for the treatment of seizures via the intravenous route. The drug used was the recommended first line medication: phenobarbitone, in 93%. However, despite the correct choice, four babies (16.6%) were not commenced with a loading dose. In the balance two patients, the first medication offered intravenously was levetiracetam and midazolam. Three babies were treated with oral medications (phenobarbitone, clonazepam and levetiracetam). Two babies were not offered any antiseizure therapy. Therapeutic drug monitoring for phenobarbitone was not performed in all patients. This test is unavailable in the hospital.

TABLE 2 Aetiology of neonatal seizures occurring after the first 24 hours of life

Aetiology	N (%)
Possibly causative	18 (58)
Probable CNS infection	13 (42)
Cerebral hypoxia	5 (16)
Definite	9 (29)
Acute metabolic derangement	4 (13)
Intracanial haemorrhage	1 (03)
Maternal abstinance syndrome	2 (06)
Structural abnormality	1 (03)
Inborn error of metabolism	1 (03)
Unknown	4 (13)

DISCUSSION

Neonatal seizures are associated with significant mortality and subsequent long-term neurological morbidity. The underlying aetiology in most instances is acute symptomatic. Hence optimal management of both the underlying aetiology as well as control of seizures is vital. Deficiencies in neonatal seizure identification and evaluation, limitations in establishment of the aetiology of these seizures and suboptimal standards in use of antiseizure therapy were three important highlights identified in this study that require attention to improve the standards of care.

Identification of neonatal seizures is challenging. The subtleness in clinical manifestation, the brevity in duration and high frequency of subclinical seizure activity, are chief contributors to the difficulty. Even among the most experienced, the possibility of missed diagnosis of a true seizure based on clinical observation only, is as high as 66%.[6] The vice versa is also reported where neonatal behaviours had been erroneously diagnosed and managed as neonatal seizures in 73%.[6] Considerable improvements in seizure detection rates are facilitated by the use of advanced technology. Use of continuous electroencephalography monitoring using a full set of electrodes with concomitant video recording is the gold standard for neonatal seizure detection. Since this is technically laborious and costly,

amplitude integrated EEG (aEEG) is utilized as a cheap and less labour intensive alternative. This second technology is a lot simpler and requires the use of a limited number of electrodes. Interpretation is possible even by a trained non-expert. In our study, even the use of routine EEG recording over 30 minutes was performed in only two thirds of patients. No patient was requested to be continuously monitored. This shows inadequate utilization of electrophysiological diagnostics and that improvements are required to reach recommended standards in diagnostics in this hospital.

The aetiology of neonatal seizures is a strong predictor of long-term prognosis.[1] The seizure type and the timing of seizure occurrence may indicate specific aetiologies. For example, focal clonic seizures in the neonate are strongly associated with central nervous system infection or stroke. On the other hand, seizures due to hypoxic ischaemic encephalopathy occur mostly within the first 6 hours of birth.[7] In our study we attempted to look at the spectrum of aetiologies that present beyond the immediate post-delivery period, to understand more on the non-encephalopathic group of neonatal seizures. The distribution of identified aetiologies in our study lacked rigour, with only postulated causations in the majority. Though central nervous system infection was the most attributable aetiology, there were none with confirmatory isolates of any specific bacterial organism. Viral isolations were not attempted due to nonavailability of viral studies in the state healthcare system. Investigations for rarer but potential aetiologies such as genetic, inborn errors of metabolism were not investigated adequately. Structural aetiologies were also sub optimally investigated. Hence, in comparison to the 94% of cases of neonatal seizures in high income settings being attributable to an identified aetiology,[8] we were able to reach a precise diagnosis only in one third of the babies. The distribution of aetiologies reported in most studies from low-income settings, follows a similar pattern (Table 3).[9, 10] For example, neonatal stroke which has an incidence of 1/2300-1/4000[11] and frequently presenting with seizures was not reported in either studies from the region. Similarly, the identification of inborn errors of metabolism and genetic aetiologies of neonatal seizures was very low in studies across these resource limited settings.[12-14] The spectrum of variable aetiologies in less resourced settings is likely amplified due to inadequate recognition due to investigatory limitations.

The rapid control of neonatal seizures using the most appropriate antiseizure medication is important considering the effects on the developing brain. Phenobarbitone is the only recommended first line medication for neonatal seizures.[15] however, using appropriate doses and duration has specific implications for the neonate. A loading dose of 20mg/kg titrated to a maximum of 40mg/kg is recommended to achieve control of seizures within 15 minutes.[15] However, this was not the observation in over one quarter (27%) babies of our cohort. The duration of therapy with phenobarbitone should be the minimum required considering the effects of phenobarbitone on acceleration of neuronal cell death.[16] It is recommended that neonates be taken off regular therapy when ready to be sent home regardless of the abnormalities in neuroimaging or electroencephalography except in those with neonatal epilepsy. The proposed draft on treatment of neonatal seizures from the International League Against Epilepsy addresses both choice of first- and second-line medications and the recommended route and duration.[17]

TABLE 3 Comparison of the reported aetiologies of neonatal seizures in studies from low-income settings

Setting	N	HIE	Stroke	ICH	Metabolic/ electrolyte	Infections	CNS malfor-mations	IEM	Genetic/ epilepsy syndromes	Unknown/ other
India[9]	N = 75	52%	-	6%	16%	20%	-	-	-	-
India[10]	N = 84	33%	-	5%	25%	25%	5%	-	-	-
India[12]	N = 172	78%	-	2%	9%	-	-	-	-	-
Iran[13]	N = 25	32%*	-	4%	4%	42%	6%	4%	-	4%
Brazil[14]	N = 104	54%	-	13%	32%	1%	5%	1%	-	-
Sri Lanka	N=31	16%*	-	3%	13%	42%	3%	3%	-	13%

HIE – Hypoxic ischaemic encephalopathy, ICH – Intracranial Haemorrhage, CNS – Central Nervous System, IEM – Inborn Errors of Metabolism

Although rectifying some of the above deficiencies may require investment and advanced technology, other aspects, particularly some related to therapy are achievable with improved understanding. Emphasis on the use of electroencephalography in all patients and subsequent expansion to perform EEG monitoring will help improve seizure detection. Early lumbar puncture and appropriate interpretation of the CSF findings are imperative for establishment of infective aetiologies. Expansion of diagnostics for inborn errors of metabolism, epilepsy genes and access to MRI imaging in this group of babies are goals to campaign for; the study setting being the premier children's hospital in the country. Our study findings add to the limited understanding on the treatment gap in low-income settings related to the diagnosis and management of neonatal seizures.[18]

CONCLUSION

Management of neonatal seizures optimally helps save the brain due to the extreme vulnerability of the immature brain to damage. This clinical audit attempted to gauge the current practice at the premier children's hospital in the country to identify gaps in its care. The identified deficits will help focus on improvements in the standards of care.

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