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Research Article

Attitude and Approach of Neonatologist and Pediatric Neurologist towards Neonatal Seizures: A Multicenter Study from the United Arab Emirates

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Abstract

Background: Neonatal seizures are difficult to diagnose due to their varied clinical presentation and they can be misdiagnosed or misinterpreted by an unexperienced clinician. Most of the studies in this area are retrospective and the clinical seizures have been included in such studies. The real seizure burden is known to be much higher as the electrographic seizures can often be missed and hence not treated. This study aims to assess the attitudes of neonatologists and pediatric neurologists in the United Arab Emirates (UAE) in diagnosing and managing neonatal seizures.

Materials and Methods: A self-administered questionnaire was sent to all the licensed neonatologists and pediatric neurologists in the UAE. The survey data was segregated into the demography of responders, diagnosis, and treatment approaches.

Results: A total of 31 responses were received, among which 25 (80%) were neonatologists and six (19%) were pediatric neurologists. About 80% of the responders felt that seizures cause no brain damage. Although 80% have access to Electroencephalogram (EEG) facility, only 54% of the respondents believe that it should be used in all the cases of suspected neonatal seizures. Phenobarbital remained the choice as the first-line drug by more than 80% of the responders to treat seizures in preterm and term neonates. Phenytoin was the second-line choice by 40% of responders.

Conclusion: There were variabilities noted in the clinical practice while managing the neonatal seizure management among the neonatologists and pediatric neurologists in the UAE. There seem to be a need for a national level standard guidelines for clinical management of neonatal seizures.

Keywords: neonatal seizures, EEG, phenobarbital, neonates; UAE; neonatologist; paediatric; neurologist; WHO

Introduction

The incidence of epilepsy is highest in the youngest and oldest population [2]. The prevalence of seizures in the neonatal period was reported as 1-4 per 1000[3]. More cases are reported in developing nations than their counterparts [3, 4]. The prevalence of seizures among preterm neonates is almost 40 times more than the full-term newborns [5, 6]. Immature brain of premature infants does not produce the clinical events which are often noted in full-term neonates. This is due to the incomplete myelination of descending corticospinal tracts. The unique coincidental timing of risk factors such as infection, genetic disorders, metabolic derangement, and development of GABA and glutamate receptors are considered as the critical reasons for seizures. There is difference seen between the clinical correlates, incidence, etiology and outcomes in the term and preterm neonates [7]. Electrographic-only seizures or sub-

clinical seizures only have EEG changes, without the apparent clinical correlate. Whereas clinical only seizures are sudden paroxysm of abnormal clinical changes without EEG association. Electro-clinical seizures have definite clinical signs along with electrographic seizure [8].

Accurate recognition of seizures among newborn infants is essential to prevent unnecessary exposure of them to anti-epileptic drugs. It is challenging to diagnose neonatal seizures, as most are electrographic only. Clinical seizures can be subtle and hard to distinguish from the usual repetitive movements of neonates [9]. The neonatal seizures are hence often misdiagnosed, leading to either under or overestimating clinically diagnosed seizure occurrence [10].

The neonatologists and the pediatric neurologist need to decide if the seizures need to be treated. There is no consensus on the threshold to treat the neonatal seizures. A rare or brief seizures may not require treatment, but EEG monitoring may be required to evaluate seizure burden. Seizure burden of >30–60 s per hour is often considered as an indication to start treatment [10]. There is also variation in practice when it comes to initiation of treatment including the decision on the drug dose to be administered, whether a single dose or regular maintenance dose [1]. Many antiepileptic drugs are available, but none of them have proved to be effective and safe in the long term. Therapeutic hypothermia is advocated in babies with perinatal asphyxia. Still, there is a need for a specific, effective, and safe pharmacological treatment for neonatal seizures. Phenobarbital has been recommended as the first-line drug for treating seizures in new-born infants by World Health Organization (WHO) [12]. There is low-quality evidence supporting its efficacy, potential side effects leading to long-term neurological damage, and adverse neurocognitive outcomes [13]. There is also lesser consensus among neonatologists and pediatric neurologists about when to stop the treatment post-initiation. However, early termination of pharmacological treatment and more cautious use of phenobarbital is recommended across the globe to decrease the side effects [14].

So far, no studies have been conducted in the UAE to understand the attitudes of the healthcare professionals regarding the diagnosis and the treatment of neonatal seizures. Here we have attempted to assess the similarities and variations in approach towards the management of neonatal seizures by neonatologists and pediatric neurologists through a pilot survey.

Material and Methods

Through a questionnaire survey, we attempted to examine the approach in diagnosing and treating neonatal seizures in real-world settings by healthcare professionals. A self-administered Google questionnaire was e-mailed to all the licensed neonatologists and pediatric neurologists in the UAE (Annexure 1). The questionnaire was categorized to focus on the demography of respondents, diagnosis, and treatment of the neonatal seizures. The data was analyzed.

Results

A total of thirty-one responses were collected between September 2021 and November 2021 which included 25 (80%) neonatologists and six (20%) pediatric neurologists. 27 (87%) were affiliated to a level 3 neonatal intensive care unit. Most of them were from Dubai (64%) whereas 22% were from Abu Dhabi and 10% were from Sharjah emirates. Most healthcare professionals (64%) dealt with less than one case of neonatal seizure per month. Also, most of the units (87%) had their own guidelines on the clinical management of neonatal seizures.

Most of the responders (84%) agreed that a clinical description of an event was not sufficient to diagnose neonatal seizures and they would prefer to gather more information like a video of the event. The same number of responders believed that any epileptic seizure could cause harm to the brain and hence should be treated in a timely manner.

Use of EEG is gold standard in the diagnosis of neonatal seizures and in absence of such facility, cerebral function monitoring with the help of amplitude EEG can be useful. There was a variation in such practice which was noted in our cohort. 87% mentioned that they have access to EEG facility. However, 61% usually use this facility in all the suspected cases of neonatal seizures for confirmation although 55% believed that it must be used for confirmation in any suspected or clinically reported neonatal seizure. When EEG facility is not available, only 38% use amplitude EEG in all the neonates with the risk of seizures. (Table 1).

Questions		**Responders**			
		Neonatologists NICU-Level 2	Neonatologists NICU-Level 3	Pediatric Neurologists Level 3	All Responders
Do you think that seizures can cause harm to the developing brain?	No	1	4	-	5
	Yes	2	15	6	23
Do you routinely use cerebral function monitoring (aEEG) for monitoring neonates having recurrent seizures?	Do not have facility	2	6	1	9
	Do not use it at all	1	-	-	1
	Use it in all neonates at risk of having seizures	-	9	2	11
	Use it in selected cases only (e.g. refractory seizures)	-	2	-	2
	Use it only in those with HIE (hypoxic ischaemic encephalopathy)	-	2	3	5

When do you call for an EEG?	All the cases with suspected neonatal seizures	1	10	5	16
	Any baby with suspected seizures started on antiepileptic therapy	1	1	-	2
	Based on recommendations of neurologist	1	6	1	8
	If confirmation is required for suspected seizures on EEG	-	2	-	2
Is EEG confirmation of neonatal seizures?	Not sure	1	-	-	1
	Must and should be done in any suspected neonatal seizures	1	11	3	15
	Not always required as clinical suspicion and clinical pattern is enough to treat	1	8	3	12
When do you consider MRI?	All cases of HIE stage 2 and above	1	3		4
	All neonates with neonatal seizures irrespective of the etiology	-	7	4	11
	All neonates with seizure with neurologic abnormality	2	8	2	12
	Selected neonates	-	1		1
In case of unavailability of aEEG /EEG data to confirm abnormal movements are seizures, would you still treat them as clinical seizures?	I do not know	-		1	1
	No	-	2	1	3
	Yes	-	17	4	24
Would you treat if EEG is abnormal and shows electrographic seizures only (without any clinical seizure)?	No	-	6	-	6
	Yes	3	13	6	22

Table 1: *Attitude towards Diagnosis of Neonatal Seizures*

Blood glucose and serum electrolytes were the most performed first line investigations for neonatal seizures whereas metabolic investigations including ammonia and lactate, neuroimaging in the form of cranial ultrasound topped the second line investigations. MRI brain and genetic testing were the most sought third line investigations. However, 96% of the neonatologist agreed that they would consider an opinion by a pediatric neurologist or metabolic disease specialist before performing any third line investigation. There was also variation in the practice noted while choosing when to do brain MRI. 38% order this investigation in all the cases of neonatal seizures irrespective of the etiology whereas 13% only considered it in the cases of hypoxic ischemic encephalopathy.

With regards to the management, most of the respondents considered phenobarbital as the first-line drug for both term and preterm neonates. We saw a difference between specialties as neonatologists were more prone to using phenytoin as a second-line drug. At the same time, pediatric neurologists advocated for levetiracetam for both term and preterm neonates with seizures (Table 2). The diversity was observed among the responders for continuing prophylactic antiepileptic medications after the acute treatment and management as half of the neonatologists and 80% of the pediatric neurologists advocated the continuation of medicines. There was, however, variation in the duration of such treatment between one week to even two years.

Question		Responders			
		Neonatologists NICU-Level 2	Neonatologists NICU-Level 3	Pediatric Neurologists Level 3	All Responders
Antiepileptic drug for term neonates as first choice	Levetiracetam	1	-	1	2
	Phenobarbital	2	18	5	25
	Midazolam	-	-	-	1
Antiepileptic drug for term neonates as second choice	Levetiracetam	-	7	5	12
	Phenytoin	2	11	-	13
	Phenobarbital	1	1	1	3
Antiepileptic drug for preterm neonates as the first choice	Levetiracetam	-	1	2	3
	Phenytoin	-	1	-	1
	Phenobarbital	3	16	4	23
	Midazolam	-	1		1
Antiepileptic drug for preterm neonates as the second choice	Levetiracetam	-	7	4	11
	Phenytoin	3	9	-	12
	Phenobarbital	-	-	2	2
	Toperamide	-	1	-	1
	No Answer	-	2	-	2
After acute treatment and management, do you continue any prophylactic antiepileptic medications?	No	-	3	-	3
	Occasionally	1	8	2	11
	Yes	2	8	4	14

Table 2: *Attitude towards Treatment of Neonatal Seizures*

Discussion

The neonatal period is the period of life which is most prone to the epileptic seizures due to higher excitability of the nerve cells. Both the diagnosis and the treatment of neonatal seizures have their challenges due to poor clinical correlate and unavailability of high standard evidence for their management. Although timely recognition and treatment of the seizure is needed, poor inter-observer agreement is known for identification of clinical seizures.

With this study, we have tried to understand the variation in the clinical practice of managing neonatal seizures. Our results are not different than the similar studies performed in the other countries [15, 16].

Most of the respondents in our study (80%) think that epileptic seizures cause damage to the brain. Studies have shown that there is enhanced susceptibility to further seizures and increased risk of brain injury with seizure in later life. In a retrospective analysis, seizures were not independently associated with cognitive outcome [17]. There is also an association between the frequency and duration of the neonatal seizures and the outcome in the later life years [18]. This subject will remain a matter of controversy until backed up by robust clinical trials.

In a UK-based population survey on neonatologists and pediatric neurologists, 66.7% of responders showed agreement for the treatment of clinical seizures (when no aEEG /EEG data was available for confirmation). In contrast, the diversity was found in the opinion of responders on the treatment of electrical seizures [15]. Although use of EEG or amplitude EEG, when EEG is not available, is required for the accurate diagnosis of neonatal seizures, most of the neonatal units may not have access to such facilities [8]. Interpretation of neonatal EEG also requires a trained clinical neurophysiologist or pediatric neurologist. This can be rarely seen in most of the secondary level hospitals.

Phenobarbital remains the first choice as the anti-epileptic drug for treating neonatal seizures in both the preterm and term neonates. This seems to be the first choice by most of the clinicians treating neonatal seizures [19, 20]. Phenytoin and Levetiracetam were most opted second line anti-epileptic medications. Levetiracetam seems to be gaining popularity among the neonatologists which is also seen in our cohort.

There is a wide variation in clinical practice and opinions on the duration of the treatment. This could be due to the lack of randomized clinical trials addressing this concern. A study from North America evidenced a more cautious use and short duration of continued phenobarbital treatment [14]. However, there is a need to shift the focus or consider prescribing safer treatment options.

Various parameters like birth weight, Apgar scores at first and fifth minutes, abnormal neurological examination, etiology of the neonatal seizures, treatment response to the seizures, EEG and cranial ultrasound findings are known to be the risk factors for developing future epilepsy in the neonates [21] . Although neonatal seizures are more common in the

preterm neonates, gestational age does not seem to be an independent predictor for the epilepsy in the post neonatal period [22].

Limitation

The sample size for the survey was small. Our study was conducted in only Dubai and Abu Dhabi emirates. These two out of total seven emirates of the UAE have most of the hospitals and almost 68% of the population lives in these two emirates [23]. There is no possibility of determining whether the views and practices of individuals who responded are the same as those who did not. Our survey did not address the etiology of the neonatal seizures.

Conclusion

Our study shows the variation in the management of the neonatal seizures among the neonatologists and pediatric neurologists. Such variation seen in the study may reflect differences in the training, as most of the clinicians working in the UAE come from different countries. They are usually trained and worked in different countries before arriving in the UAE. The other reason for such variation could be lack of uniform or national guidelines. This study, hence, highlights the importance of designing and carrying out clinical trials determining the optimal treatment of neonatal seizures. Also, a uniform national clinical guideline for managing neonatal seizures is also needed to reduce such variation in the clinical practice.

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Annexure 1

Section 1: About the respondent

What is the level of Neonatal Intensive Care Unit you are affiliated with?

Which Emirate do you work in?

What is your subspecialty?

What is the capacity of your NICU? (please specify in numbers)

Roughly, how many annual admissions take place in your NICU?

Roughly, how many neonates with seizures do you deal with?

Does your neonatal unit have any local guidelines for the management of neonatal seizures?

Section 2: Diagnosis and Approach towards Neonatal Seizures

Do you think that seizures (and not the underlying aetiology) can cause harm to the developing brain of the neonate?

For diagnosing neonatal seizures, do you rely on the nurse/registrar assessment or information?

Do you routinely use cerebral function monitoring (aEEG) for monitoring neonates having recurrent seizures?

Do you have access to EEG if needed?

If yes, when do you call for an EEG?

When is the EEG confirmation of neonatal seizures required?

Section 3: Investigations

What investigation do you advise in a neonate with seizures as the first line? (please specify)

What investigation do you advise in a neonate with seizures as the second line? (please specify)

What investigation do you advise in a neonate with seizures as the third line? (Please specify)

Do you seek paediatric neurologist/metabolic medicine specialist/geneticist opinion before proceeding with any third line investigation?
When do you consider MRI brain?

Section 4: Management

If there is no available aEEG / EEG data to confirm the abnormal movements are seizures, would you still treat them as clinical seizures?

Would you treat if the EEG is abnormal and shows electrographic seizures only (without any clinical seizure)?

Which antiepileptic drug do you use for treating neonatal seizures in a term neonate as the first choice?

Which antiepileptic drug do you use for treating neonatal seizures in a term neonate as the second choice?

Which antiepileptic drug do you use for treating neonatal seizures in a term neonate as the third choice?

Which antiepileptic drug do you use for treating neonatal seizures in a term neonate as the fourth choice?

Which antiepileptic drug do you use for treating neonatal seizures in a preterm neonate as the first choice?

Which antiepileptic drug do you use for treating neonatal seizures in a preterm neonate as the second choice?

Which antiepileptic drug do you use for treating neonatal seizures in a preterm neonate as the third choice?

Which antiepileptic drug do you use for treating neonatal seizures in a preterm neonate as the fourth choice?

Section 5: Follow up

After the acute treatment and management, do you continue any prophylactic antiepileptic medications?

If yes, for how long would you consider the prophylactic treatment for? (please specify)

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