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From Seizure to Epilepsy During Hypoxo-Ischemic Encephalopathy: EEG Role

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Abstract

Introduction: Although perinatal care has improved significantly, accurately predicting epilepsy in neonates with hypoxic-ischemic encephalopathy (HIE) remains challenging especially in Resource-limited settings. The primary objective of our study was to investigate the utility of standard conventional electroencephalography (C-EEG) for diagnosing and managing neonatal seizures associated with HIE and its ability to predict epilepsy.

Methods: This retrospective longitudinal study involved 56 full-term newborns who were admitted to the neonatology department for HIE between January 2014 and December 2019. Clinical data was collected, and the C-EEG results were re-analyzed blindly by an experienced electrophysiologist. The evaluation criterion for the study was the presence of epilepsy at 18 months of age.

Results: Out of the 39 video-EEG recordings, non-epileptic phenomena were observed in 10 newborns (17.86%). However, electroclinical seizures were observed in 7 newborns (12.5%) and were associated with electrographic seizures in 6 patients (10.71%). Seizure recurrence was observed in 47.8%(n=22) of newborns, and it was significantly correlated with background activity abnormalities on EEG tracings ($p<0.001$). We found a significant correlation between epilepsy and EEG immaturity ($p=0.031$), interhemispheric asynchrony asymmetry (p-0.001), and EEG scores (AUC>0.7). Epilepsy was also significantly correlated with electroclinical seizures ($p=0.019$) and electrographic seizures ($p=0.004$). Additionally, periodic lateralized epileptiform discharges (PLEDs) were significantly associated with epilepsy ($p=0.019$). However, other interictal abnormalities were comparable between the two groups.

Conclusion: The value of continuous EEG in the context of HIE is widely known in the literature. However, this study with markers that are specific to our daily clinical practice, reaffirms the value of standard EEG in resource-limited settings.

Keywords: Hypoxo-Ischemic Encephalopathy; EEG, Prognosis Factors; Epilepsy; Neonatal Seizure; Clonic Seizure; Epileptic Spasm; Myoclonic Seizure; And Tonic Seizures; Non-Motor Seizures; Hyperkplexia; Anti-Epileptic

Abbreviations: HIE: Hypoxo-Ischemic Encephalopathy; EEG: Electroencephalogram; C-EEG: Conventional EEG; PNA: Perinatal Asphyxia; CSE: Clinical Status Epilepticus; WA: Week of Age; BRDS: Brief Rythmic Discharges; PLEDS: Periodic Lateralized Epileptiform Discharges; ROC: Receiver Operating Characteristics ; AUC: Area Under the Cureve

Introduction

HIE occurs in 1 to 1.5 newborns per 1000 live births in developed countries and up to 10 times more in developing countries [1]. Neonatal epileptic seizures are the most frequent clinical manifestation of cerebral dysfunction [2] but determining their epileptic origin during HIE can be challenging due to their variable semiology and sometimes subtle or only electrographic presentation [3]. Therefore, performing an EEG within hours of suspected HIE is essential for both its management and the diagnosis of epileptic seizures [4].

Despite advances in perinatal care, 25% of HIE survivors are at risk of developing neurological disabilities such as cerebral palsy, intellectual disability, and epilepsy [5]. However, establishing an early and certain prognosis of HIE remains difficult in the neonatal period. This prognosis is aided by continuous EEG and new tools

of signal analysis [6-9] which may not be available in resource-limited settings [10]. Thus, they pose a significant clinical challenge for physicians in low- and middle-income countries (LMIC.

In this perspective, our main objective was to evaluate the usefulness of standard conventional EEG (C-EEG) in diagnosing and managing neonatal seizures during hypoxic events and its prognostic value for predicting the development of epilepsy.

Materials and Methods

Patients

This is a retrospective longitudinal study that included 56 newborns who were followed in the neonatology department of Hedi Chaker University Hospital and the functional explorations department of Habib Bourguiba University Hospital in Sfax between January 1, 2014, and December 31, 2019. The study included newborns with a gestational age of greater than 37 weeks who met the following criteria:

- Diagnosis of encephalopathy based on the presence of paroxysmal phenomena, neurological distress, and difficulties in maintaining spontaneous breathing [11]
- A likely hypoxic origin of the encephalopathy based on the presence of at least one perinatal asphyxia (PNA) criterion such as obstetric incident, fetal heart rhythm abnormalities, Apgar score at 5 min lower than 7, need for resuscitation at birth, a venous pH lower than 7.20 beyond 2 hours of life, meconial fluid, or signs of respiratory distress [1,5,12-14]
- Availability of clinical follow-up in the neonatal department
- Initial EEG during the first 15 days of life.

Newborns with infectious, genetic, metabolic, or hematological diseases were excluded from the study. None of the patients received hypothermia since it is not available in Tunisia

Methods

Data collection was performed in a double-blind manner by two examiners, with one examiner collecting clinical, biological, and radiological data from medical records, and a second examiner analyzing the EEGs carried out in the functional explorations department.

Clinical Data

We analyzed epidemiological and anthropometric data as well as neurological examinations. The severity of HIE was assessed using the Sarnat score [13,15] All paroxysmal phenomena were recorded, and jerkiness was classified as non-epileptic, while clinical seizures were diagnosed based on the definition of the ILAE [16]. The different types of seizures were classified according to the 2020 ILAE neonatal seizure classification into motor seizures (including automatism, clonic seizure, epileptic spasm, myoclonic seizure, and tonic seizures), non-motor seizures (autonomic seizure and behavioral arrest), sequential seizures, and unclassified seizures [17]. Clinical status epilepticus (CSE) was defined as repeated seizures lasting more than 15 minutes [3] .

We also noted cases of spontaneous resolution, defined as the cessation of paroxysmal manifestations without requiring antiepileptic treatment, as well as the recurrence of paroxysmal phenomena during hospitalization with or without treatment.

Electroencephalographic Data

C-EEG recordings were performed by a digital electroencephalograph of the "*Nihon Kohden EEG system*". A minimum duration of 60 minutes recording without artifacts, including a recording of wakefulness, calm sleep, and restless sleep, was required for EEG analysis. The analysis was performed on 20-second pages with longitudinal bipolar montage. The analyzed EEG features were background activity, interictal and ictal abnormalities, as well as the video recordings of paroxysmal phenomena.

Fellow Up

The evaluation criterion for this study was the presence of epilepsy, as defined by the International League Against Epilepsy (ILAE) [18], at 18 months of age.

Statistical Analysis

For statistical analysis, we used version 20 of the Statistical Package for the Social Sciences. We conducted a descriptive study and compared the groups of newborns with and without epilepsy using the appropriate statistical tests such as the chi-square, Fisher's exact test, t-test, and Mann-Whitney test depending on the type of variables. We set the confidence interval at 95% and considered a p-value of less than 0.05 to be significant. We also performed an analysis of Receiver Operating Characteristics (ROC) curves to compare the predictive value of the scores used. An area under the curve (AUC) greater than 0.7 was considered significant.

Results

We included 56 newborns in our study, with a sex ratio of 2.29. The mean gestational age was 39.54 ± 1.27 weeks.

Seizures Diagnosis

Clinically, seizures were suspected in 46 newborns (82.14%) with a mean onset age of 37.30 ± 40.06 hours. Tremor was reported in 22.64% (n=12) newborns, with 7 cases (58.33%) showing an association with epileptic seizures. EEGs were performed at a mean age sof 5.18 ± 4.19 days. Of the 39 EEG recordings that included a video, paroxysmal phenomena were captured in 7 newborns (43.59%). The non-epileptic nature of the paroxysmal phenomena was confirmed in 10 newborns (17.86%) and was significantly associated with spontaneous resolution (p=0.035).

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Electroclinical seizures were observed in 7 newborns (12.5 and were associated with electrographic seizures in 6 patients (10.71%). CSE was noted in 6 newborns, with two cases being electroclinical and four cases being electrographic.

Management of Epileptic Seizures

Out of the observed seizures, 30.4% (n=14) had spontaneous resolution, while 69.6% (n=32) required treatment with antiepileptic therapy, either a single dose or two doses of Phenobarbital. antiepileptic treatment was initiated only after EEG seizure detection in five patients, three of whom had electro-clinical seizures, and two had CSE. Seizure recurrence was noted in 47.8% (n=22) of cases and was significantly associated with background activity abnormalities on EEG tracings (Table 1).

Of the recurrent seizures, 66.7% (n=12) required treatment with Clonazepam used instead of Phenytoin, which was unavailable. Seven out of twelve newborns who experienced a second seizure recurrence required third-line antiepileptic therapy with Valproate. Drug-resistant seizures were significantly correlated with electrographic seizures (p=0.022), BRDs (p=0.014), and background activity abnormalities (p=0.043). Upon discharge, 14 newborns received anti-epileptic treatment for two months due to uncontrolled seizures.

Table 1: Relation between seizure recurrence and EEG background abnormalities.

	Seizure Recurrence		p
	No	Yes	
Background activity abnormalities	20.69	62.5	0.002
Absence of wake-sleep cycle	17.24	45.83	0.024
Asymmetry/ Asynchrony	6.90	45.33	0.001
Discontinuity	10.34	37.5	0.019
Immaturity	17.24	41.67	0.049

Epilepsy Prognosis Factors

Three patients died before reaching 18 months of age. Among the remaining 53 patients, only 38 newborns were followed up until the age of 18 months. Some patients were transferred to other departments, while others were unable to attend follow-up visits due to the *COVID-19* pandemic. We compared the group of newborns with epilepsy (n=11) to those without epilepsy (n=27) in order to determine prognostic factors.

Clinical Factors

No significant relationship was found between the two groups regarding epidemiological and obstetrical data. At admission all newborns who developed epilepsy had neurological abnormalities (p=0.038), while the frequency of neurological abnormalities at discharge was equal between the two groups

Furthermore, Out of the 27 newborns in the non-epileptic group, 24 of them, which accounts for 88.89%, were not prescribed any antiepileptic treatment at the time of discharge (p=0.003). In contrast, all newborns in the epilepsy group (n=11) received antiepileptic treatment since the first seizure, which was maintained until discharge (p<0.001) (Table 2).

Table 2: Comparison of clinical data between epileptic and non-epileptic groups.

		Non Epileptic (N=27)	Epileptic (N=11)	p
Clinical data	Sentinel event (%)	66.67	63.64	1
	Pathological Fetal heart rhythm (%)	33.33	45.45	0.712
	Mechonial amniotic liquid (%)	18.52	9.09	1
	Apgar 1st minute (min)	5.19 ∓ 2.59	5.82 ∓ 2.36	0.488
	Apgar 5th minute (min)	7.23 ∓ 2.18	7.70 ∓ 2.45	0.604
	Ressuscitation at birth (%)	62.96	63.64	1

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Clinical data	First neurological exam abnormalities (%)	66.67	100	0.038
	Age of first paroxysmal phenomena (years)	30.04 ± 39.94	31.00 ± 40.56	0.947
	Praxysmal phenomena (%)	96.3	81.82	0.196
	Non epileptic phenomena (%)	26.92	11.11	1
	Epileptic sizures (%)	70.37	72.73	1
	Subtle (%)	79.17	100	0.290
	Motor (%)	11.54	45.45	0.035
	Seizure recurrence (%)	19.23	100	< 0.001

Electroencephalographic Factor

In terms of background activity, a significant correlation was observed between epilepsy and EEG immaturity (p=0.031), as well as interhemispheric asynchrony asymmetry (p=0.001) (Table 3).

Table 3: Comparison of EEG data between epileptic and non-epileptic groups.

	Non Epileptic (N=27)	Epileptic (N=11)	p
Background abnormalities (%)	66.67	45.45	0.285
Dysmaturity	11.11	45.45	0.031
Discontinuity	11.11	36.36	0.161
Asymetry/Asynchrony	3.70	54.55	0.001
Absence of wake-sleep cycle	14.81	45.45	0.088
Interictal abnormalities (%)	25.93	54.55	0.135
PLEDs	3.70	36.36	0.019
BRD	7.41	27.27	0.134
Focal spikes	100	100	1
Multifocal spikes	18.52	18.18	1
Electroclinical seizure (%)	3.70	36.36	0.019
Electrographic seizure (%)	0	36.36	0.004
CSE (%)	3.70	36.36	0.019

Table Abbreviations: PLEDs: Periodic lateralized epileptiform discharges; BRD: Brief rhythmic discharges CSE: Clinical status epilepticus

Three studied scores were significantly correlated to epilepsy: Scavone classification (p=0.03), grade 3 of the French classification (p=0.032) and Murray score (p=0.022). These findings were further supported by ROC curve analysis, which yielded a highly significant area under the curve of over 0.7.

Regarding interictal abnormalities, a significant correlation was found between epilepsy and PLEDs (p=0.019). However, there was no significant difference in the incidence of other focal or multifocal interictal abnormalities between the two groups (Figure 1).

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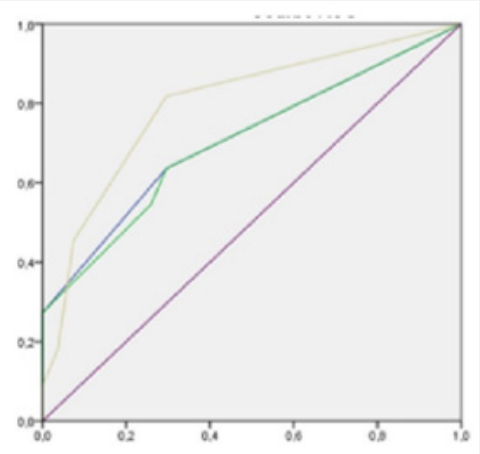

Figure 1: ROC curve analysis for EEG scores.
Scavone classification (blue): AUC = 0.710;
French classification (green): AUC = 0.704;
Murray score (brown): AUC = 0.798

Table 4 displays the association between ictal and interictal activities. The study found that both PLEDs and BRDs were significantly associated with ictal activity. Additionally, newborns with PLEDs associated with electrographic seizures had a significantly higher prevalence of epilepsy (p=0.004).

Table 4: Association between ictal and interictal activities.

	Background activity	Electroclinical Seizures	Electrographic Seizures	CSE
PLEDs	6 (p=0.047)	4 (p=0.005)	6 (p<0.001)	4 (p<0.001)
BRD	4 (p : NS)	3 (p=0.039)	3 (p=0.046)	3 (p=0.046)

Table Abbreviations: PLEDs: Periodic lateralized epileptiform discharges; BRD: Brief rhythmic discharges; CSE: Clinical status epilepticus.

Epilepsy was also significantly correlated to electro-clinical seizures (p=0.019), electrographic seizures (p=0.004) and CSE (p=0.019) (Table 3).

Discussion

Seizure Diagnosis

Non-Epileptic Phenomena

Various non-epileptic motor phenomena, such as tremors, jerkiness, and less frequently observed physiological sleep myoclonus and hyperkplexia [19], can mimic the clinical signs of an epileptic seizure. The high rate of clinically suspected epileptic seizures (82.14%) compared to the seizures confirmed by video EEG (12.5%) can be attributed in part to the over-diagnosis of epileptic seizures based on clinical signs, as well as the use of standard C-EEG recordings with limited duration, which decreases the likelihood of capturing electroclinical seizures. In fact, the probability of capturing epileptic seizures is higher with prolonged duration of C-EEG recordings [2].

It is crucial to take into consideration the high incidence of non-epileptic phenomena among newborns (17.86% in our study). In the literature, a discrepancy in the diagnosis of neonatal epileptic seizures was also observed depending on the diagnostic criteria used. Studies based on clinical diagnosis reported seizure rates ranging from 65% to 85% [20,21]. However, studies that based their diagnosis on EEG criteria found a lower seizure rate ranging from 30% to 40% [22-26]. Simultaneously recording a video alongside C-EEG enables the analysis of the paroxysmal phenomenon's semiotics and its potential association with concomitant critical electrical activity, resulting in a 45% increase in the diagnosis of epileptic seizures when adding a video recording to EEG [27].

Electrographic Seizures

During neonatal period, 50 to 80% of the recorded seizures were only electrographic [22,28,29]. In our study, 46.15% of EEG-recorded seizures were only electrographic without any obvious clinical manifestations.

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Several hypotheses have been proposed to explain the absence of clinical manifestations accompanying critical activity [3,17,21]:

- Clinical manifestations may be subtle and difficult to identify and analyze and may involve non-motor cerebral regions.
- The central nervous system depressant effect of anti-epileptic treatments, particularly phenobarbital, sedative drugs or therapeutic hypothermia, can lead to a clinical-electrical dissociation.
- Severe and extensive brain lesions may cause disconnection of the cortex from its efferent pathways.

Given the high frequency of electrographic seizures, the absence of obvious clinical expression and their unfavorable prognostic value [30], a C-EEG is strongly recommended in newborns [13,14,22,27,31].

CSE

The incidence of CSE in newborns has been poorly studied [32]. The ILAE definition of CSE [17] is partially applicable to newborns, and until 2021, no consensus could be reached regarding the definition of CSE in the neonatal period [29]. This is partly due to the frequent association of neonatal seizures with encephalopathy, making it challenging to assess the baseline neurological status between seizures. Thus, EEG criteria appear necessary for the diagnosis of CSE.

Management of Epileptic Seizures

Initiating and maintaining antiepileptic treatment for electrographic seizures in newborns is still a subject of debate [33,34]. Some studies suggest initiating treatment for electrographic seizures only if they are prolonged or associated with autonomic manifestations [33]. However, other studies strongly support the treatment of electrographic seizures [34,35]. In our study, nine newborns with epileptic seizures had antiepileptic drugs maintained ON long term due to seizures persistence. These seizures seemed to correspond to unprovoked seizures, likely due to structural and genetic abnormalities or severe brain damage following HIE according to Pisani [36].

On the other hand, 8 untreated newborns and 3 newborns treated for only one month did not develop subsequent epilepsy and likely correspond to acute symptomatic seizures self-limited in time, related to an acute cerebral insult such as metabolic or infectious pathology as part of HIE. They disappear in the following days with a low risk of recurrence. Prolonged antiepileptic treatment is not indicated in this case [36].

Prognosis Factors

Clinical Factors

The prognostic value of different types of seizures in HIE remains uncertain. While the presence of epileptic seizures has been linked to a higher risk of developing epilepsy regardless of their clinical semiology[12,37,38], certain types of seizures have been associated with either a favorable or unfavorable outcome. For instance, focal clonic seizures sparing the facial region have been linked to better outcomes [39,40], while myoclonic seizures have been linked to a worse prognosis [40].

In our study, we found a significant association between motor seizures and subsequent epilepsy development ($p=0.035$). However, no correlation was found between specific seizure types and their progression to epilepsy, likely due to the limited sample size and lack of detailed seizure semiology description. Seizures recurrence, quite common in literature (30 to 50% of cases) [34], was considered as a risk factor for unfavorable outcomes [38,41,42], a finding consistent with our study where all epileptic patients experienced recurrent seizures ($p<0.001$).

EEG Factors

Background Activity

Many previous studies have not provided detailed information on the specific EEG parameters analyzed and have instead focused on a global description of the background activity [43,44]. Pezzani reported a significant association between a normal initial EEG pattern and a favorable outcome [43], while abnormal background activity [39,45-49], such as the absence of the sleep-wake cycle, interhemispheric asymmetry [22], and dysmaturity [50] has been linked to an unfavorable evolution. The classification of the tracings based on background activity has shown strong prognostic value [51].

Both inactive [43,52] and paroxysmal trace [2,49,53] were associated with an unfavorable evolution.

In our study, we found a significant correlation between an initial inactive EEG and the later development of epilepsy ($p=0.048$). ROC curve analysis revealed highly significant AUC (>0.7) for the three electrographic scores used, confirming the prognostic value of EEG in predicting later epilepsy.

Interictal Activity

PLEDs have been reported to be associated with electroclinical or electrographic seizures in 40-90% of cases [54]. Furthermore, studies have shown a significant association between PLEDs and epilepsy, particularly if associated with subclinical seizures [54-56]. These findings were also confirmed in our study.

Due to the high epileptogenic potential of PLEDs, some authors suggest initiating antiepileptic treatment even in the absence of a definite epileptic seizure [57].

The epileptogenic nature of BRDs is still under debate. Although they were not found to be significantly associated with seizures in some studies [58], they may be an early warning signal of possible seizures. Therefore, prolonged C-EEG should be

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performed to detect electrographic seizures in their presence [17].

Ictal Activity

In our study, the percentage of electroclinical seizures was lower (12.5%) compared to other studies that used prolonged recordings [22,26], but we still found a significant association between epilepsy and both electroclinical and electrographic seizures. This is consistent with findings from other studies [22,43,59,60]. However, there are also studies that did not find a significant association between seizures and epilepsy [12,20,25,45,46,53].

It's important to note that the presence of a CSE is highly predictive of an unfavorable outcome, including the development of epilepsy [32,41]. In our study, we also found that all newborns with CSE had developed epilepsy, which further supports this association (p=0.019).

Limits

As a retrospective study, there were limitations in the availability of clinical and paraclinical data in the medical records. Additionally, some patients were lost to follow-up due to the impact of the *COVID-19* pandemic.

Conclusion

Undoubtedly, EEG has been extensively investigated for its diagnostic and prognostic value in HIE in the literature. However, this study is the first in our region to examine the contribution of C-EEG in HIE. Our findings provide more accurate markers for daily clinical practice, considering the diagnostic and therapeutic resources available in resource-limited settings. Our study confirms the usefulness of C-EEG with both visual analysis and score-based analysis and highlights the importance of incorporating video into C-EEG monitoring. Furthermore, C-EEG can guide the decision to perform prolonged video recordings in specific cases. Advancements in technology and resource availability can significantly impact the management and prognosis of HIE patients. Therefore, it is crucial to continue improving existing settings with simple interventions such as ensuring easier access to EEG and incorporating video into C-EEG monitoring. These measures can have a considerable impact on the management of HIE and subsequent prognosis for newborns in Tunisia.

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