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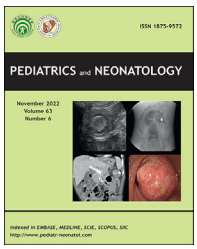

Original Article

Clinical profile of a cohort of neonates with seizures: Association between semiology, etiology, and electroencephalographic findings☆

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Key Words
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Background: Seizures are the most common sign of neurologic dysfunction, reflecting a wide variety of central nervous system disorders.
Methods: A retrospective cross-sectional study of neonates with a clinical diagnosis of seizures was conducted in order to verify relationships between clinical aspects and EEG findings. Patients were divided into 3 groups according to the EEG recording available as: 1) with confirmatory ictal EEG; 2) with altered but non-ictal EEG; and 3) without any EEG recording. Variables related to pregnancy and birth history, neonatal complications, and seizure semiology (by video or clinical description) were compared to EEG findings.
Results: 97 neonates were included (39.1% preterm, 54.6% male), 71 with available EEG data (56.3% with ictal EEG). The group without EEG presented clinical characteristics significantly different from the others such as extreme prematurity, low birth weight, and higher neonatal mortality (P = 0.002, 0.001, and 0.003, respectively). The most common etiology was hypoxic-ischemic encephalopathy (HIE) (46.4%) followed by vascular disorders, which predominated in extremely preterm neonates (P = 0.006). Sequential seizure was the most common type (44.6%) and was more frequently identified in term neonates (46%). In 51.2% of the ictal recordings the main finding was electrographic seizure without clinical manifestation. Discharge

Abbreviations: EEG, electroencephalography; NICUs, neonatal intensive care units; ILAE, International League against Epilepsy; HIE, hypoxic-ischemic encephalopathy.

☆ This work was performed at the University Hospital São Lucas (Laboratory of Clinical Neurophysiology) and Brain Institute (BraIns) affiliated with Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, RS, Brazil.

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using antiseizure medication was higher among those with ictal or altered non-ictal EEG ($P < 0.001$).
Conclusions: HIE is still a frequently etiology for neonatal seizures. Even if the patients in the sample were not under continuous EEG, the substantial proportion of electrographic seizures without clinical manifestations detected suggests the importance of continuous EEG monitoring in neonates at increased risk of seizures.

1. Introduction

During the neonatal period, seizures are the most common sign of neurologic dysfunction, reflecting a wide variety of central nervous system disorders.[1—3] The incidence of neonatal seizures reported in population-based studies ranges from 1 to 5 per 1000 live births, but it tends to be higher in studies conducted in tertiary care centers or neonatal intensive care units (NICUs).[4—6] Seizures in the first weeks of life are associated with unfavorable short- and long-term outcomes; more than 50% of survivors have a number of deficits in various developmental domains.[3,6—11]

Over the past decades, with the advances in genetic testing, it has been possible to broaden the spectrum of etiologic factors and the differential diagnosis of neonatal seizures, but their management remains complex, particularly in severely ill neonates.[12—14]

Recently, the International League against Epilepsy (ILAE) has presented a revised operational classification of seizure types. This new classification improves the understanding of seizure types as well as of seizure triggers, prognosis, and comorbidity risks, while also serving as a guide to select the best antiepileptic therapy.[15,16] The ILAE Task Force on Neonatal Seizures has proposed a modification of this classification: the same categories and terminology are used but adjusted to the neonatal period.[17]

The multiple epileptic and non-epileptic clinical manifestations that occur during the neonatal period make the clinical diagnosis of seizures difficult in this age group, since any abnormal movements may raise a diagnostic suspicion; conversely, neonates may have electrographic seizures with no clinical correlates.[2,18,19] Thus, electroencephalography (EEG) is essential for the detection and classification of neonatal seizures. However, EEG monitoring is not always available in some settings or occasions, and the decision to initiate treatment needs to be based on clinical judgment. Therefore, identifying associations between seizures, semiology, and EEG features may help to distinguish between acute symptomatic seizures and epilepsy-related seizures, which might improve the treatment approach.[20—22]

The objectives of the present study were to describe the profile of a sample of neonates who had seizures in the neonatal period and to evaluate the relationships between gestational age, semiology, etiology, EEG findings, and initial treatment at NICU.

2. Methods

This was a retrospective cross-sectional study of neonates with a clinical diagnosis of seizures during NICU stay at Hospital São Lucas, affiliated with Pontifical Catholic University of Rio Grande do Sul (PUCRS), from January 2010 to December 2017. Cases were identified from NICU database records and neonatal EEG database records of the Clinical Neurophysiology Laboratory of the institution.

All patients with a diagnosis of seizures recorded in the list of problems were included. Patients were excluded if they had the first seizure after the neonatal period (defined as the first 28 days of life for term neonates and up to 44 weeks of corrected gestational age for preterm neonates) or had questionable medical record data, such as the term 'seizure' recorded in the list of problems but without compatible data throughout the medical record.

The following variables were evaluated: maternal and gestational characteristics including type of delivery, birthweight and gestational age (GA). GA was determined by early fetal ultrasound or, in its absence, by the Capurro method for term neonates and the New Ballard method for preterm neonates (term, 37 weeks or more; moderate and late preterm, 32 weeks—36 weeks and 6 days; very preterm, 28 weeks—31 weeks and 6 days; and extremely preterm, up to 27 weeks and 6 days). The clinical features of seizures were analyzed according to the current ILAE classification adapted to neonatal seizures, when ictal EEG was available, and divided on electro-clinical (clonic, tonic, myoclonic, automatisms, spasms, autonomic or sequential-several seizure manifestations occurring in sequence, not necessarily simultaneously, in a given seizure) or electrographic only.[17] In the cases where ictal EEG during seizure was not available, Volpe classification[23] was used (clonic, tonic, myoclonic, automatisms, spasms, autonomic) according to the description in the medical record data. Seizure etiology, as diagnosed by the neonatal team during hospitalization, was classified as hypoxic-ischemic encephalopathy (HIE), structural cause, infectious cause (early or late neonatal sepsis, bacterial or viral meningitis, and meningoencephalitis or encephalitis of any etiology co-occurring with seizures), metabolic or vitamin-related cause, genetic cause, vascular cause (ischemic or hemorrhage), or undetermined cause. The definition of HIE was based on Sarnat & Sarnat's classification.[24] Data on seizure treatment and prescribed medications for use after discharge were also included in the analysis.

For the EEG variable, the results related to the description of background rhythm and the presence of epileptogenic activity were considered.[13,20] Cases in which EEG was obtained during seizures were allocated to the ictal EEG group. Ictal activity was defined as the co-occurrence of clinical manifestation and EEG changes or the occurrence of electrographic seizures with no clinical features. Ictal activity was classified as focal, multifocal, or burst-suppression. Cases in which one or more EEGs were obtained outside the seizure episode were allocated to the non-ictal EEG group. In non-ictal records, background rhythm (classified as normal, low voltage, or burst-suppression) and presence of interictal paroxysmal activity (classified as focal or multifocal) were considered. The neonates who did not undergo EEG during hospitalization were allocated to a third group.

All EEG records were obtained in a digital polygraph (EMSA®), they had a duration that varied from 1 to 2 h and were reviewed by a physician specializing in neonatal neurophysiology. Recordings consisted of 10 channels of EEG, electro-oculogram, submental electromyogram and electrocardiogram. Bipolar montage was used, with electrodes placed based on the 10—20 system as modified for newborns. The recording speed was 15 mm/s. The state of the newborn and all the movements during the exam were recorded by the technician and reviewed through the simultaneous video.

This study was approved by the Scientific Committee of the Brain Institute of Rio Grande do Sul (BraIns) and by PUCRS Research Ethics Committee. Informed consent was waived due to the retrospective nature of database and medical record data collection. All investigators signed a data use agreement to ensure the ethical and secure use of the data. All procedures involving human participants were in accordance with the ethical standards of Resolution 466/2012 of the Brazilian National Health Council/Ministry of Health and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Quantitative variables were expressed as mean and standard deviation or median and interquartile range. Qualitative variables were expressed as absolute and relative frequencies. Categorical variables were compared by Pearson's chi-square test with adjusted residual analysis or Fisher's exact test as appropriate. The Kruskal—Wallis test was used for between-group comparisons of numerical variables with skewed distribution, followed by Dunn's or Tukey's post hoc test. The level of significance was set at 5% ($P < 0.05$), and all analyses were performed using SPSS, version 21.0.

3. Results

During the study period, 104 medical records were identified with the term 'seizure' recorded in the list of problems at some time during the neonate's NICU stay. Seven patients were excluded because the first seizure occurred after the neonatal period or the suspected seizures were not confirmed (seizures recorded in the medical records but without compatible semiology). Thus, the study sample consisted of 97 neonates, of whom 26 did not undergo EEG (Fig. 1).

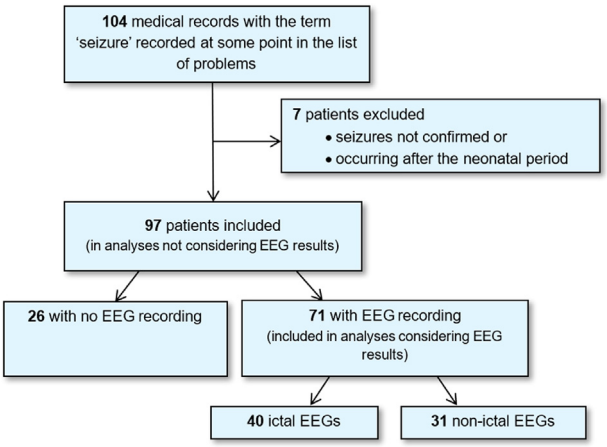

Figure 1 Flow diagram of study population, consisting of neonates admitted to the neonatal intensive care unit of Hospital São Lucas of PUCRS with seizures based on data obtained from the medical records. EEG = electroencephalogram.

Table 1 shows the clinical profile of the neonates included in the study; 75.2% were born in our institution, while others were transferred from nearby hospitals without NICU. Based on the timing of EEG (ictal × non ictal), the groups had similar clinical features. The group of neonates without EEG was significantly different from the ictal and non ictal groups as it included all the extremely preterm neonates ($P = 0.002$). Further, in this group, who did not undergo EEG, birth weight was lower and mortality was higher ($P = 0.001$ and $P = 0.003$ respectively).

Table 2 analyzes the seizure profile (semiology, etiology, treatment) of study participants as stratified by gestational age and timing of EEG. Term neonates had multiple seizures ($P = 0.041$) earlier ($P = 0.015$) and were discharged using antiepileptic drugs ($P < 0.001$). The groups did not differ significantly in the semiology or etiology of seizures, but extremely preterm neonates more frequently had a vascular etiology ($P = 0.006$). Neonates who did not undergo EEG predominantly had a single seizure and structural etiology ($P < 0.001$ and $P = 0.021$, respectively). Discharge using antiseizure medication was higher among those with ictal or altered non-ictal EEG ($P < 0.001$).

When the association between EEG findings and seizure etiology was analyzed, despite the lack of significant differences, patients with HIE tended to have more electrographic seizures (n = 36, 36.8%).

Table 3 evaluates the associations of the semiological classification of seizures with gestational age, seizure etiology, and EEG findings. There were no statistically significant associations between these variables. Electrographic seizure only (without clinical manifestation) accounted for 51.2% of the ictal recordings.

4. Discussion

This study characterized the types of neonatal seizures in a sample of neonates receiving intensive care using, when possible, the new ILAE classification adjusted to the neonatal period,[17] it gathered data on perinatal factors,

Table 1 General characteristics of the study population, 97 neonates with seizures during NICU stay, classified according to the timing of EEG (ictal or non-ictal).

Clinical Characteristics	Confirmatory ictal EEG n=40	Altered non-ictal EEG n=31	No EEG n=26	*P*
Sex— n (%)				
Female	16 (40.0)	14 (45.2)	14 (53.8)	0.543
Male	24 (60.0)	17 (54.8)	12 (46.2)	
Maternal age (years) (n=94)*				
Minimum — maximum	15-37	15-43	16-36	0.513
Mean ± standard deviation	27.5±6.3	26.4±7.2	25.6±5.9	
Maternal gestational morbidities (n=81)** — n (%)				
No	18 (51.4)	13 (48.1)	11 (57.9)	0.807
Yes	17 (48.6)	14 (51.9)	8 (42.1)	
Hypertensive disorders	8 (22.9)	7 (25.9)	5 (26.3)	0.945
Gestational diabetes mellitus	6 (17.1)	4 (14.8)	2 (10.5)	0.808
Drugs/alcohol/smoking	4 (11.4)	5 (18.5)	0 (0.0)	0.144
TORCH infections	4 (11.4)	3 (11.1)	1 (5.3)	0.743
Other	6 (17.1)	4 (14.8)	3 (15.8)	0.969
Categorized gestational age — n (%)				
Term (37 weeks or more)	27 (67.5)	20 (64.5)	12 (46.2)	0.002
Moderate and late preterm (32 to 36 weeks and 6 days)	9 (22.5)	9 (29.0)	5 (19.2)	
Very preterm (28 to 31 weeks and 6 days)	4 (10.0)	2 (6.5)	2 (7.7)	
Extremely preterm (up to 27 weeks and 6 days)	0 (0.0)	0 (0.0)	7 (26.9)***	
Mode of delivery — n (%)				
Vaginal delivery	25 (62.5)	14 (45.2)	15 (57.7)	0.335
Cesarean section	15 (37.5)	17 (54.8)	11 (42.3)	
Apgar score - median (P25 — P75)				
1st minute	4 (2 — 8)	4 (1 — 7)	6 (2 — 9)	0.288
5th minute	7 (4 — 9)	7 (3 — 8)	4 (3 — 7)	0.161
10th minute	6 (2 — 9)	8 (6 — 9)	7 (3 — 7)	0.425
Birth weight (g)				
Minimum — maximum	1430-4280	1100-4105	590-4090	0.001
Mean ± standard deviation	2.871±732*	2.941±766[b]	2.126±1070[a]	
Neonatal death — n (%)	5 (12.5)	3 (9.7)	11 (42.3)***	0.003

OBS: * In 3 cases, there was no record of maternal age; **In 16 cases, information was not recorded in the medical record. In 18 cases, there was more than 1 maternal comorbidity. *** Statistically significant association by adjusted residual analysis at 5% significance level; [a,b] Means with the same superscript letter do not differ by Tukey's test at 5% significance level.
Statistics: chi-square test with adjusted residual analysis or Kruskal-Wallis test with Tukey's test.
NICU, neonatal intensive care unit; EEG, electroencephalogram; TORCH, toxoplasmosis, other (syphilis), rubella, cytomegalovirus, and herpes.

mortality, seizure etiology, and EEG findings and established some interrelationships between these variables.

The clinical features of neonates with EEG recording, either ictal or non-ictal, were similar in all the variables evaluated. As suggested in the algorithm developed by the Brighton collaboration[25] to determine degrees of diagnostic certainties for neonatal seizures, observation of events by experienced personnel has a level 2B (probable diagnosis) of certainty for clonic and tonic seizures, which were the majority described in our non — ictal group, either alone or as part of a sequential event.

However, the group without any EEG recording had all the extremely preterm neonates of the sample, the lowest birthweight and the highest neonatal mortality. Heterogeneity and clinical instability might be reasons why the EEGs were not performed even with the clinical suspicion of seizures. The fact that around half had just one single episode of seizure reported but that most received antiseizure medication (phenobarbital) reinforces the need to have those high risk infants continuously monitored to avoid overtreatment or mistreatment.

There was a predominance of seizures in term neonates. However, the rate of seizure identification in preterm neonates increased when compared to two recent studies conducted in the United States[11,12] and a previous study conducted in the same NICU as the present study.[9] This improvement in identification may be related to increased EEG monitoring in high-risk neonates, since the clinical expression of seizures may be subtler in preterm than in term neonates.

The overall neonatal mortality rate (19.6%) was comparable to that reported in the literature.[11,12,26] However, preterm mortality (26.3%) was slightly lower than that reported by Glass et al.[26] in a collaborative study conducted in the United States. A possible explanation for the higher mortality in those who did not undergo EEG is that this

Table 2 Seizure clinical features, etiology, treatment, and mortality in all patients and as stratified into 4 gestational age categories and by the Electroencephalogram (EEG).

Variables	All (n=97)	Gestational Age					Electroencephalogram			
		Term (n=59)	Moderate and late preterm (n=23)	Very preterm (n=8)	Extremely preterm (n=7)	p	Ictal Confirmatory (n=40)	Non ictal but abnormal (n=31)	No EEG (n=26)	p
Number of seizures (n=92)*										
Single	25 (27.2)	11 (19.6)	9 (42.9)	1 (12.5)	4 (57.1)†	0.041	4 (10.8)	6 (20.0)	15 (60.0) †	<0.001
Multiple	67 (72.8)	45 (80.4)†	12 (57.1)	7 (87.5)	3 (42.9)		33 (89.2) †	24 (80.0)	10 (40.0)	
Age in days of the 1st seizure Median (P25-P75)	2 (0.5-11)	1 (0.4-3.5)[a]	5 (0.8-20)[b]	10 (2.5-72)[b]	2 (0.8-20)[ab]	0.015	2 (1 − 13)	1 (0.4 − 3)	2 (1 − 16)	0.132
Seizure type (n=92)* (ILAE classification)										
Clonic	14 (15.2)	7 (12.5)	4 (18.2)	2 (25.0)	1 (16.7)	0.660	5 (12.8)	5 (17.2)	4 (16.7)	0.519
Tonic	20 (21.8)	12 (21.4)	5 (22.7)	2 (25.0)	1 (16.7)		8 (20.5)	3 (10.3)	9 (37.5)	
Myoclonic	2 (2.2)	1 (1.8)	0 (0.0)	0 (0.0)	1 (16.7)		1 (2.6)	0 (0.0)	1 (4.2)	
Automatism	6 (6.5)	4 (7.1)	1 (4.5)	1 (12.5)	0 (0.0)		2 (5.1)	4 (13.8)	0 (0.0)	
Spasms	4 (4.3)	3 (5.4)	0 (0.0)	0 (0.0)	1 (16.7)		2 (5.1)	1 (3.4)	1 (4.2)	
Autonomic	5 (5.4)	2 (3.6)	2 (9.1)	1 (12.5)	0 (0.0)		2 (5.1)	2 (6.9)	1 (4.2)	
Sequential	41 (44.6)	27 (48.2)	10 (45.5)	2 (25.0)	2 (33.3)		19 (48.7)	14 (48.3)	8 (33.3)	
Etiology (n=97)										
HIE	45 (46.4)	26 (44.1)	11 (47.8)	5 (62.5)	3 (42.9)	0.396	21 (52.5)	15 (48.4)	9 (34.6)	0.021
Structural	5 (5.1)	3 (5.1)	2 (8.7)	0 (0.0)	0 (0.0)		1 (2.5)	0 (0.0)	4 (15.4) †	
Infection	10 (10.3)	6 (10.2)	3 (13.0)	1 (12.5)	0 (0.0)		4 (10.0)	4 (12.9)	2 (7.7)	
Metabolic	12 (12.4)	9 (15.3)	2 (8.7)	1 (12.5)	0 (0.0)		7 (17.5)	4 (12.9)	1 (3.8)	
Genetics	2 (2.1)	1 (1.7)	1 (4.3)	0 (0.0)	0 (0.0)		1 (2.5)	0 (0.0)	1 (3.8)	
Vascular	13 (13.4)	6 (10.2)	3 (13.0)	0 (0.0)	4 (57.1)***		0 (0.0)	7 (22.6)	6 (23.1)	
Undetermined	10 (10.3)	8 (13.6)	1 (4.3)	1 (12.5)	0 (0.0)		6 (15.0)	1 (3.2)	3 (11.5)	
Seizure treatment (n=96)										
No AED	3 (3.1)	2 (3.4)	0 (0.0)	1 (12.5)	0 (0.0)	0.684	3 (7.7)	0 (0.0)	0 (0.0)	0.100
Phenobarbital	62 (64.6)	38 (64.4)	13 (59.1)	5 (62.5)	6 (85.7)		24 (61.5)	17 (54.8)	21 (80.8)	
Phenobarbital plus other	29 (30.2)	17 (28.8)	9 (40.9)	2 (25.0)	1 (14.3)		12 (30.8)	13 (41.9)	4 (15.4)	
Other	2 (2.1)	2 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	1 (3.2)	1 (3.8)	
AED use at discharge (n=73)**										
Yes n=53	53 (72.6)	39 (81.3)	13 (72.2)	1 (50.0)	0 (0.0)	<0.001	29 (87.9) †	20 (76.9) †	4 (28.6)	<0.001
No n=20	20 (27.4)	9 (18.8)†	5 (27.8)	1 (50.0)	5 (100)†		4 (12.1)	6 (23.1)	10 (71.4) †	

OBS: EEG= electroencephalogram; ILAE= International League Against Epilepsy; HIE= hypoxic-ischemic encephalopathy; AED= antiepileptic drug.

* There was no information on number of seizures and seizure type for 5 patients, and on treatment for 1 patient.

** 19 patients died, and in 5 medical records there was no record of maintenance of anticonvulsants after discharge.

*** Extremely preterm: higher proportion of vascular etiology in relation to the other gestational age groups together (Fisher's exact test; p=0.006)

† Statistically significant association by adjusted residual analysis at 5% significance level.

a,b Means with the same superscript letter do not differ by Dunn's test at 5% significance level.

Statistics: chi-square test with adjusted residual analysis or Kruskal-Wallis test with Dunn's test.

Table 3 Associations of seizure type with gestational age, seizure etiology, and EEG findings.

Characteristic	Seizure type								*P*
	Clonic	Tonic	Myoclonic	Automatisms	Spasms	Autonomic	Sequential	No clinical manifestation during EEG	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Gestational age (n = 92)[a]									
Term	7 (50.0)	12 (60.0)	1 (50.0)	4 (66.7)	3 (75.0)	2 (40.0)	27 (65.9)	–	0.861
Preterm	7 (50.0)	8 (40.0)	1 (50.0)	2 (33.3)	1 (25.0)	3 (60.0)	14 (34.1)	–	
Total	14 (100)	20 (100)	2 (100)	6 (100)	4 (100)	5 (100)	41 (100)	–	
Seizure etiology (n = 92)[a]									
HIE	7 (50)	9 (45)	1 (50)	3 (50)	3 (75)	2 (40)	19 (46.3)	–	0.884
Structural	0 (0)	2 (10)	0 (0)	0 (0)	0 (0)	1 (20)	2 (4.9)	–	
Infectious	2 (14.3)	4 (20)	1 (50)	0 (0)	0 (0)	0 (0)	2 (4.9)	–	
Metabolic/vitamin-related	1 (7.1)	2 (10)	0 (0)	2 (33.3)	0 (0)	1 (20)	5 (12.2)	–	
Genetic	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.4)	–	
Vascular	1 (7.1)	2 (10)	0 (0)	1 (16.7)	1 (25)	1 (20)	6 (14.6)	–	
Undetermined	3 (21.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (14.6)	–	
Total	14 (100)	20 (100)	2 (100)	6 (100)	4 (100)	5 (100)	41 (100)	–	
Ictal EEG (n = 39)[a]									
Burst-suppression	0 (0)	2 (25)	1 (100)	0 (0)	0 (0)	0 (0)	4 (21.1)	–	0.659
Focal	1 (20)	1 (12.5)	0 (0)	0 (0)	0 (0)	1 (50)	3 (15.8)	–	
Multifocal	2 (40)	0 (0)	0 (0)	1 (50)	1 (50)	0 (0)	3 (15.8)	–	
Sz description before or after EEG[b]	2 (40)[b]	5 (62.5)[b]	0 (0)[b]	1 (50)[b]	1 (50)[b]	1 (50)[b]	9 (47.4)[b]	–	
Electrographic seizure	–	–	–	–	–	–	–	20 (100)[c]	
Total	5 (100)	8 (100)	1 (100)	2 (100)	2 (100)	2 (100)	19 (100)	20 (100)	
Non-ictal EEG (n = 29)[a]									
Normal	0 (0)	0 (0)	–	1 (25)	0 (0)	0 (0)	4 (28.6)	–	0.599
Low voltage	1 (20)	0 (0)	–	1 (25)	1 (100)	0 (0)	1 (7.1)	–	
Burst-suppression	0 (0)	0 (0)	–	1 (25)	0 (0)	0 (0)	2 (14.3)	–	
Focal	3 (60)	3 (100)	–	1 (25)	0 (0)	2 (100)	6 (42.9)	–	
Multifocal	1 (20)	0 (0)	–	0 (0)	0 (0)	0 (0)	1 (7.1)	–	

EEG, electroencephalogram; HIE, hypoxic-ischemic encephalopathy.
Statistics: chi-square test with adjusted residual analysis.
[a] In 5 of 97 patients, there was no description of seizure type (1 of 40 patients with ictal EEG recording, 2 of 31 patients with non-ictal EEG recording, and 2 of 26 patients with no EEG recording).
[b] This line includes seizures reported before or after EEG in 19 patients, because 1 of the 20 patients with electrographic seizure had no description of clinical seizure at any point in time.
[c] These 20 patients correspond to the same ones from the previous line plus the only 1 who had a record of electrographic seizure with no record of clinical seizure before or after EEG.

group consisted mostly of extremely preterm neonates who had unfavorable clinical conditions for such examination.

HIE was the most frequent etiology to be identified, which is consistent with previous reports.[6,9,11,26,27] In the extremely preterm, however, vascular disorders predominated. In 10 neonates, it was not possible to identify the etiology of seizures, among whom 6 had sequential seizures. This semiology is highly associated with genetic etiology,[13,14,17] which might have been underdiagnosed in this sample because the tests were not easily available at the time patients were hospitalized.

An association was found between the time of first seizure and gestational age: term neonates had the first seizure earlier (median of 1 day) than preterm neonates in general, and this was especially the case with very preterm neonates (median of 10 days). This is in agreement with the literature[6,26,28] and it is generally attributed to the fact that seizures resulting from HIE, the most common etiology in term neonates, usually begin in the first hours of life, while seizures resulting from common preterm etiologies, such as intraventricular hemorrhage and infection, usually occur later. However, the present study found no association between gestational age and seizure etiology, i.e., HIE occurred in similar proportions in both term and preterm neonates. Therefore, it is valid to assume that other factors influenced the temporal association between seizures and gestational age. According to Glass et al.,[26] the reason for later onset of seizures in preterm neonates remains unclear.

Some reasons other than etiology can be considered, such as the fact that respiratory problems are the main focus of attention in the first days of life of preterm neonates, and seizures may go unnoticed unless the patient is under continuous EEG monitoring. Clinical manifestations of seizures are inherently subtle in preterm neonates, as compared with normal movements. The use of sedation at doses below those used to treat seizures may also mask the clinical features of seizures. In addition, detecting seizures in a patient who is inside an incubator and often covered due to attention to developmental aspects may be a difficult task. Other factors may also be related to the pathophysiology of seizures in preterm neonates, in whom seizures tend to be of shorter duration and to remain localized.[26,28,29] The explanation proposed by Carrasco & Stafstrom[30] is that multiple, complex, dynamic, interacting factors come into play to determine the time course, clinical manifestations, and electrographic expression of seizure activity during early brain development. They suggest that seizure features at various gestational ages are a direct consequence of physiologic factors that change during fetal life, conferring different manifestations during development. Several key steps in brain development must be completed before a symptomatic seizure can occur.[30]

Although there was no statistically significant difference in the proportion of term neonates versus preterm neonates who had electrographic seizures with no clinical features, a previous report found a much higher rate of these seizures in preterm neonates. It is important to note that in their sample, unlike ours, many neonates were monitored by continuous video EEG.[26]

An interesting finding of the present study is that half of the cases with ictal EEG recording had only electrographic seizures. Shellhaas et al.[12] reported that neonates with acute symptomatic seizures more commonly had subclinical seizures than those with neonatal-onset epilepsy syndromes, highlighting the importance of EEG monitoring in patients at risk for seizures even before clinical manifestation. Electroclinical dissociation is common in neonatal seizures, and a limitation of the present study was the impossibility of performing continuous EEG monitoring.

Phenobarbital was the most commonly used antiepileptic drug in the NICU and at discharge, which is consistent with the specialized literature.[31,32] In the study by Shellhaas and collaborators,[12] prescription of continued anticonvulsant medication at the time of discharge was associated with the use of EEG to confirm the diagnosis of seizures, a result also found in the present study, in which most patients who were prescribed this therapy had an abnormal EEG.

Unlike in a recent systematic review of the individual data of 151 neonates with seizures where several associations were identified between semiology, etiology, and EEG findings,[13] in the present study no statistically significant associations were detected between these variables. One of the main differences between the above-mentioned study and ours is that their sample, obtained from literature data that included some case reports and series, had an important selection bias, since most of the reported cases referred to genetic etiologies that garnered more attention and publications over recent years. Thus, that study included only 6 cases of HIE, which was the main etiology found in the present study as well as in previous cross-sectional studies investigating the prevalence of etiologies in neonatal seizures.[6,7,9,11,17,26,27,31]

Limitations of the present study include its retrospective data collection and relatively small sample size. The lack of ictal EEG recording in all patients to prove or disprove the epileptic nature of the event can also be seen as a limitation of this study. Electrographic seizures in neonates can be underdiagnosed by more than 65% when only clinical detection is used. In addition, no EEG monitoring may lead to overdiagnosis of seizures.[18,19] For effective screening and accurate diagnosis, continuous video EEG monitoring should be performed in all suspected cases. However, video EEG monitoring requires expensive equipment, skilled technicians, and clinical neurophysiologists trained in neonatal EEG interpretation; and such equipment or personnel are not always available in some settings or occasions, so the decision to initiate treatment needs to be based on clinical features.[31]

The fact that the study was conducted in a single neonatal care center could be considered a limitation, but this actually contributed to ensure that the diagnosis and management of cases followed a uniform approach, and that EEGs were interpreted by the same professional.

In conclusion, in this study, developed in a tertiary center of a developing country, we have found HIE to be the most common etiology and sequential seizure to be the most frequent type. Even if the patients in the sample were not under continuous EEG, the substantial proportion of electrographic seizures without clinical manifestations detected suggests the importance of continuous EEG monitoring in neonates at increased risk of seizures.

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Declaration of competing interest

None.

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