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Epileptic Seizures in Neonates Treated with Hypothermia for Hypoxo-Ischemic Encephalopathy in Brazzaville, Congo: Types and Evolution

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Abstract

Background: Moderate to severe hypoxic-ischemic encephalopathy (HIE) in neonates is often treated with hypothermia. However, some neonates may experience epileptic seizures during therapeutic hypothermia (TH). Data on the electrophysiologic and evolutionary aspects of these seizures are scarce in African countries. **Objectives:** To determine the types of epileptic seizures caused by HIE in neonates in Brazzaville; to describe the evolution of background EEG activities during TH and rewarming; to report the evolution of epileptic seizures. **Methods:** This was a cross-sectional, descriptive study conducted from January 2020 to July 2022. It took place in Brazzaville in the Neonatology Department of the Blanche Gomez Mother and Child Hospital. It focused on term neonates suffering from moderate or severe HIE. They were treated with hypothermia combined with phenobarbital for 72 hours. **Results:** Among 36 neonates meeting inclusion criteria, there were 18 boys and 18 girls. Thirty-one (86.1%) neonates had grade 2 and 5 (13.9%) grade 3 HIE. In our neonates, HIE had induced isolated electrographic seizures (n = 11; 30.6%), electroclinical seizures (n = 25; 69.4%), and 6 types of background EEG activity. During TH and rewarming, there were 52.8% of patients with improved background EEG activity, 41.7% of patients with unchanged background EEG ac-

tivity, and 5.5% of patients with worsened background EEG activity. At the end of rewarming, only 9 (25%) patients still had seizures. **Conclusion:** Isolated electrographic and electroclinical seizures are the only pathological entities found in our studied population. In neonates with moderate HIE, the applied therapeutic strategy positively influences the evolution of both seizures and background EEG activity. On the other hand, in neonates with severe HIE, the same therapeutic strategy is ineffective.

Keywords

Epileptic Seizures, Neonate, Hypoxo-Ischemic Encephalopathy, Therapeutic Hypothermia, Antiepileptic Drugs, Brazzaville

1. Introduction

Neonatal hypoxic-ischemic encephalopathy (HIE) is a clinically defined syndrome resulting from the disruption of a neonate's neurological functions. The condition manifests in the form of sucking disorders, breathing and feeding difficulties, as well as altered consciousness, gross motor activity, posture, and tone [1]. HIE is the most common cause of epileptic seizures in neonates [2] [3].

Therapeutic hypothermia (TH) is the preferred strategy for neonates with moderate or severe hypoxic-ischemic encephalopathy (HIE). It has been shown to have a beneficial effect on long-term outcome, especially when initiated within 24 hours of birth. Moderate hypothermia, between 32˚C and 34˚C, preserves cerebral function by mitigating secondary cytotoxic edema, epileptiform activity, and damage to axons, myelin, and the blood-brain barrier [1].

Studies report high frequency of electroclinical and electrographic seizures in neonates treated with hypothermia for HIE (32% - 62%) [4] [5] [6] [7]. These seizures are often associated with a guarded prognosis due to their high epileptic load [2] [8] [9] [10]. It is crucial to note that this treatment approach is not a guarantee of a positive outcome. Therefore, the combination of TH and antiepileptic drugs during EEG monitoring is aimed at reducing the burden of seizures. However, the therapeutic strategy's benefits remain controversial [2] [11]. The International Neonatal Consortium and the ILAE Working Group on Neonatal Seizures have provided criteria for initiating anticonvulsant therapy [2] [10]. However, implementation of these guidelines is inadequate in many African countries due to lack of diagnostic resources such as MRI and video-EEG, and therapeutic deficiencies due to limited choice and availability of antiepileptic drugs [3] [12] [13].

There is no literature on epileptic seizures in Congolese neonates with HIE treated with hypothermia. The objectives of this study are to identify the types of epileptic seizures caused by HIE in neonates in Brazzaville, describe the changes in background EEG activity during TH and rewarming, and report the progress of epileptic seizures.

2. Methods

This study is cross-sectional and descriptive. It will be carried out in the neonatal unit of the Blanche Gomez Mother and Child Hospital in Brazzaville between January 2020 and July 2022. The investigation aims to evaluate the impact of combined hypothermia treatment and phenobarbital on fully termed neonates with moderate to severe HIE over 72 hours. The study fully complies with the Helsinki principles for medical research involving human subjects and was approved by the Ethics Committee on 22 November 2019 under certification 048/MRSIT/IRSSA/CERSSA.

Regarding the therapeutic approach, in accordance with institutional guidelines and those reported in the literature and intended for community hospitals, we used the method of passive whole-body cooling followed by rewarming for 6 hours. Strategies for analgesia, neuroprotection and prevention of discomfort associated with therapeutic hypothermia included magnesium sulphate infusion at a rate of 250 mg/kg/day for one hour over a period of five days. Paracetamol was administered in four slow intravenous doses for the duration of therapeutic hypothermia. Although morphine administration is critical for pain relief in ventilated neonates, this measure was not implemented in our neonates due to limited resources preventing adequate continuous monitoring [1] [14] [15].

Antiepileptic treatment was administered only when an epileptic seizure was confirmed by EEG monitoring and when the patient's epileptic load exceeded 30 seconds per hour [2] [10]. Diazepam 0.5 mg/kg was administered intra-rectally to treat epileptic seizures. This was followed by phenobarbital 20 mg/kg by slow intravenous injection over a 20-minute interval. If persistent epileptic seizures occur and second-line treatment is unavailable, phenobarbital can be renewed at a dose of 5 mg/kg for 10 minutes, without exceeding a maximum dose of 40 mg/kg in 24 hours [10] [15]-[20].

Patient inclusion criteria for this study were as follows: the presence of encephalopathy within 6 hours of birth, as demonstrated by seizures, hypotonia or flaccidity, lethargy or coma, primary reflex disorders (such as weak or absent Moro, oculomotor or pupillary abnormalities, absent or weak sucking), altered gross motor activity, and altered posture. Patients meeting the following criteria should be considered for hypothermia treatment: gestational age ≥ 36 weeks, Apgar score < 5 at 5 minutes, resuscitated for at least 5 minutes, and presenting clinical and/or biological signs of multivisceral failure such as hepatic cytolysis, renal failure, and respiratory distress [21] [22].

Patients were excluded from the study if they had congenital or genetic malformations, inborn errors of metabolism, coagulopathy, intracranial hemorrhage, head or spinal cord trauma, life expectancy greater than six hours, weight less than 1800 g, or shock [15] [21].

Patient recruitment was exhaustive. Information was collected using a data record. Study variables were: demographic (gestational age; gender; birth weight), electrophysiological (time of start of EEG monitoring; types of epileptic seizures;

period of onset of epileptic seizures according to TH phases; epileptic load; background EEG activity according to TH phases) and evolutive (existence or absence of epileptic seizures; types of epileptic seizures; types of background EEG activities; types of HIE).

EEG monitoring was initiated with a mean start time of 3 hours after admission to the neonatal intensive care unit (range: 1 to 8 hours), using the literature-recommended technique along with a standard portable video-equipped EEG unit, installed, parameterized, and calibrated by a specialized technician [23] [24] [25] [26]. In addition, EEG monitoring started with a mean start time of 11.2 hours after birth (range: 2 to 22 hours). Uninterrupted monitoring was conducted in all neonatal patients during TH and rewarming.

For the continuous video EEG recordings, background activity and critical discharges were analyzed in a standardized manner. Background EEG activities were classified into the following 9 patterns, as described by Lamblin *et al.* [27]: normal activity; subnormal activity; hyperactive rapid activity; pathologic slow activity; discontinuous type A activity; discontinuous type B activity; paroxysmal activity; low-voltage plus theta activity; inactive activity.

In addition, we used the classification system developed by Lamblin *et al.* [27] to assess the severity of hypoxic-ischemic encephalopathy based on background EEG activity. Grade 0: No HIE (normal activity); Grade 1: HIE with minimal abnormalities (subnormal activity); Grade 2: HIE with moderate abnormalities (hyperactive rapid activity, pathologic slow activity, discontinuous type A activity, discontinuous type B activity); Grade 3: HIE with severe abnormalities (paroxysmal activity, low-voltage plus theta activity, inactive activity).

To analyze the data related to the TH process, the intervals 0 to 24 hours, 25 to 48 hours, and 49 to 72 hours were considered as cold induction, cold maintenance, and end of cold phase, respectively.

An epileptic seizure was considered electrographic if repetitive, progressive, and stereotyped graphoelements were present for at least 10 seconds with minimum amplitude of 2 μV [16]. Status epilepticus was defined as continuous epileptic activity lasting at least 30 minutes [28].

SPSS version 21 software was used to analyze the collected data. Qualitative and quantitative variables were expressed as percentages and mean ± standard deviation, respectively.

3. Results

There were 18 male (50%) and 18 female (50%) neonates among the 36 neonates meeting the inclusion criteria. The average gestational age during continuous video-EEG was 39.1 ± 1.4 weeks of amenorrhea (range: 36 to 41 weeks of amenorrhea). The mean birth weight was 3105.8 ± 148.5 g (range: 2015 to 3940 g). The average Apgar score at 5 minutes was 3.7 ± 0.7 (range: 1 to 4).

3.1. Types of Epileptic Seizures

Table 1 shows the prevalence of epileptic seizures as a function of background

Table 1. Distribution of epileptic seizures according to background EEG activity.

Background EEG activity	Isolated electrographic seizures (n = 11)		Electroclinical seizures (n = 25)			
	Status epilepticus n (%)	Isolated focal seizures n (%)	Multifocal clonic seizures n (%)	Asymmetrical bilateral spasms n (%)	Unilateral spasms n (%)	Focal tonic seizures n (%)
Hyperactive rapid activity	-	-	3 (12)	-	-	4 (16)
Pathologic slow activity	-	-	-	3 (12)	4 (16)	1(4)
Discontinuous type A activity	-	3 (27.3)	7 (28)	3 (12)	-	-
Discontinuous type B activity	-	5 (45.4)	-	-	-	-
Paroxysmal activity	2 (18.2)	-	-	-	-	-
Low-voltage plus theta activity	-	1 (9.1)	-	-	-	-

EEG activity in neonates during hypothermia and rewarming. Of a total of 36 neonates, 11 (30.6%) showed isolated electrographic seizures, while 25 (69.4%) were identified as having electroclinical seizures. Of the 11 infants with isolated electrographic seizures, 2 (18.2%) had status epilepticus and the remaining 9 (81.8%) had recurrent focal seizures. Of the 25 neonates with electrographic seizures, 10 (40%) had multifocal clonic seizures, 6 (24%) asymmetric bilateral spasms, 4 (16%) unilateral spasms and 5 (20%) focal tonic seizures.

The six types of background EEG activity resulting from EHI are presented in Table 1. The most frequent background EEG activity was discontinuous type A activity, observed in neonates with electroclinical seizures (n = 10; 27.8%) and in neonates with isolated electrographic seizures (n = 3; 8.3%). A total of 13 patients (36.1%) had discontinuous type A activity. Discontinuous type B activity, paroxysmal activity and low-voltage theta activity were present exclusively in neonates with isolated electrographic seizures (n = 8; 22.2%). Only neonates with electroclinical seizures (n = 15; 41.7%) showed hyperactive fast activity and pathological slow activity.

The average time from seizure onset to the start of continuous video-EEG recording was 32.2 ± 2.1 hours (range: 3 and 78 hours).

Average epileptic load was 248.2 ± 10.6 seconds per hour (range: 30 - 2100 s/h). Electrographic status epilepticus was observed in two neonates with epileptic loads of 700 and 800 s/h, respectively.

Seizures occurred in neonates during the cold induction phase (n = 16; 44.4%), the cold maintenance phase (n = 14; 38.9%), and the warming phase (n = 6; 16.7%). Seven of the 16 neonates with cold induction seizures (43.7%) had episodes within the first 12 hours.

3.2. Evolutive Aspects

The progression of background EEG activity during therapeutic hypothermia and rewarming is shown in Table 2. In neonates with grade 2 HIE, background

Table 2. Changes in background EEG activity during therapeutic hypothermia and rewarming.

Background EEG activity	Therapeutic hypothermia								Rewarming		
	Cold induction phase		Cold maintenance phase			End of the cold phase					
	Grade 2 HIE n (%)	Grade 3 HIE n (%)	Grade 1 HIE n (%)	Grade 2 HIE n (%)	Grade 3 HIE n (%)	Grade 1 HIE n (%)	Grade 2 HIE n (%)	Grade 3 HIE n (%)	Grade 1 HIE n (%)	Grade 2 HIE n (%)	Grade 3 HIE n (%)
Subnormal activity	-	-	2 (5.6)	-	-	4 (11.1)	-	-	6 (16.6)	-	-
Hyperactive rapid activity	10 (27.8)	-	-	12 (33.3)	-	-	13 (36.1)	-	-	15 (41.7)	-
Pathologic slow activity	8 (22.2)	-		6 (16.7)			4 (11.1)			2 (5.6)	
Discontinuous type A activity	11 (30.5)	-	-	9 (25)	-	-	8 (22.2)	-	-	6 (16.6)	-
Discontinuous type B activity	2 (5.6)	-	-	-	-	-	-	-	-	-	-
Paroxysmal activity	-	2 (5.6)	-	-	4 (11.1)	-	-	2 (5.6)	-	-	2 (5.6)
Low-voltage plus theta activity	-	3 (8.3)	-	-	3 (8.3)	-	-	5 (13.9)	-	-	5 (13.9)

HIE = Hypoxo-ischemic encephalopathy.

EEG activity changes were hyperactive rapid activity (n = 10) transitioning to subnormal activity (n = 6), pathological slow activity (n = 8) transitioning to hyperactive rapid activity (n = 8), discontinuous type A activity (n = 11) transitioning to pathological slow activity (n = 5), and discontinuous type B activity (n = 2) transitioning to paroxysmal activity (n = 2), and then to low-voltage plus theta activity (n = 2). No changes in low-voltage plus theta activity (n = 3) and paroxysmal activity (n = 2) were observed in neonates with grade 3 HIE.

At the end of the warming period and after administration of phenobarbital at the loading dose, 9 neonates (25%) remained with isolated focal electrographic seizures. Of these 9 neonates, 2 experienced electrographic status epilepticus (as shown in **Figure 1**) and 7 initially presented with electroclinical seizures and subsequently developed isolated focal electrographic seizures with discontinuous type A activity (as shown in **Figure 2**).

4. Discussion

This study focuses on the types of epileptic seizures in neonates with HIE and the evolution of background EEG activity and seizures.

Neonates have electrographic seizures, electroclinical seizures, electrographic seizures mixed with electroclinical seizures, and seizures with unknown clinical

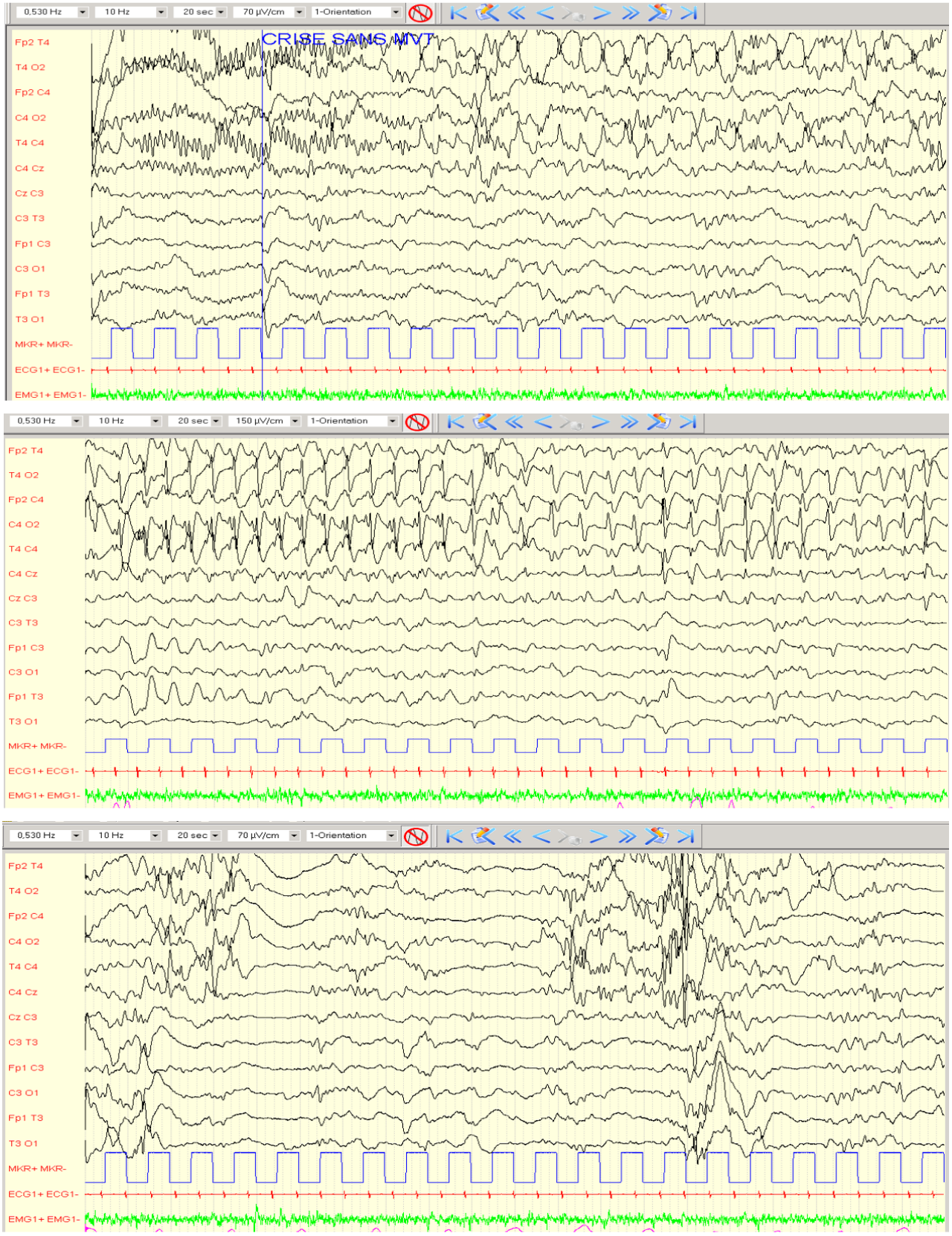

Figure 1. Electrographic status epilepticus with paroxysmal background EEG activity in a female neonate at 38 weeks of amenorrhea.

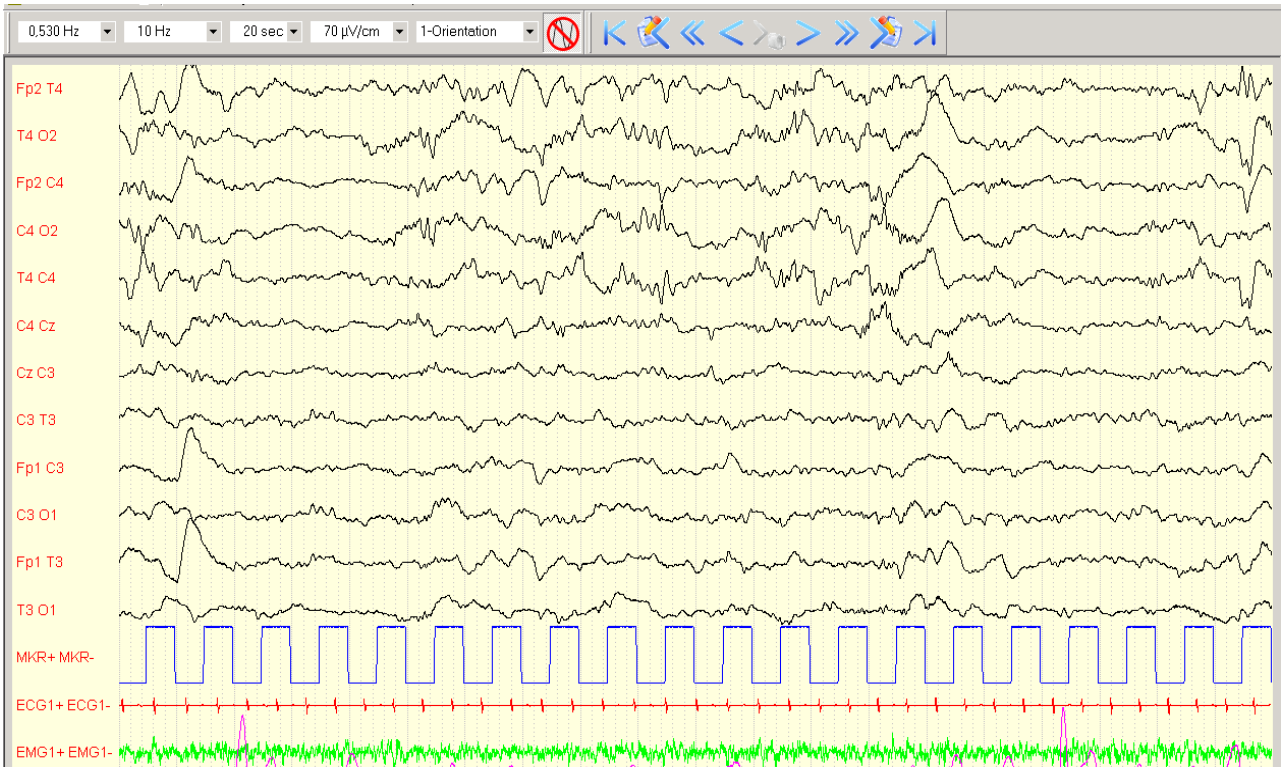

Figure 2. Right isolated focal electrographic epileptic seizure with discontinuous type A background EEG activity in a female neonate at 40 weeks of amenorrhea.

correlation [29] [30] [[31]. In our research, only electrographic and electroclinical seizures were found, with electroclinical seizures being predominant. The prevalence of electroclinical seizures has been reported by other researchers [6] [23] [25]. A predominance of electrographic seizures was found in a study by Wusthoff *et al.* [32]. The discrepancy between the incidence of electrographic seizures and electroclinical seizures may be attributed to factors such as sample size, criteria for selection of neonates, artifacts on electroencephalograms, expertise of investigators in interpreting EEG recordings in term neonates, and misinterpretation of clinical signs of epileptic seizures by medical staff in neonatal units [5] [6] [7] [23] [25] [33] [34] [35].

The incidence of electrographic status epilepticus in neonates treated by us (18.2%) is lower than that reported by Nash *et al.* (28.6%) [23] and Wusthoff *et al.* (23.5%) [32].

Epileptic seizures occur in neonates during different phases of TH and rewarming as reported in previous studies [23] [34] [36]. Our study also observed similar findings. In our neonates, the frequency of epileptic seizures during cold induction (44.4%) was lower than that reported by Wusthoff *et al.* (53%) [32].

During therapeutic hypothermia and rewarming, we identified three categories of background EEG activity: improved activity in 52.8% of neonates, unchanged activity in 41.7% of neonates, and worsened activity in 5.5% of neonates. Similarly, the study by Nash *et al.* [23] also distinguished three types of background EEG activity: improved activity in 49% of neonates, unchanged ac-

tivity in 38% of neonates, and worsened activity in 13% of neonates. Other investigators have reported changes in background EEG activity in neonates during TH [25] [37]. The duration and severity of cerebral anoxia, the location, extent, and number of cerebral lesions could explain the occurrence of the 3 types of background EEG activity [38]-[44].

Regression of seizures was observed in 75% of our neonates with moderate HIE, which was also reported by Srinivasakumar *et al.* [45]. These results indicate the efficacy of the treatment given to our neonates, namely TH combined with phenobarbital.

TH has been shown to decrease epileptic activity [1] [46] [47]. Nevertheless, ignoring the effect of phenobarbital on seizure regression in our neonates with moderate HIE would be challenging. Studies report phenobarbital efficacy in neonatal convulsions [7] [18] [48].

TH has been shown to reduce epileptic activity [1] [46] [47]. Nevertheless, ignoring phenobarbital's effect on seizure regression in our moderate HIE neonates is challenging. Studies reported phenobarbital efficacy in neonatal seizures [7] [18] [48]. Our results support these assertions.

This study has some limitations. First, it was conducted in a single referral hospital in Brazzaville. It has a limited number of patients. It is therefore important to continue it in other referral hospitals in Brazzaville to confirm our preliminary results. Second, the lack of MRI did not allow us to localize brain lesions, determine the type and number of brain lesions, and correlate background EEG activity with MRI brain lesion severity. Third, with regard to therapeutic management, the lack of comparison groups has not allowed us to conclusively demonstrate the efficacy of phenobarbital associated with HT.

5. Conclusion

In our study population, HIE caused 2 types of epileptic seizures: Isolated electrographic seizures consisting of 2 clinical entities and electroclinical seizures consisting of 4 clinical entities. In addition, it induced 6 types of background EEG activity. The applied therapeutic strategy positively influences the evolution of epileptic seizures and background EEG activities in neonates with moderate HIE. Neonates with severe HIE show no change of seizures or background EEG activities.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper. No financial support was obtained to carry out this work.

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