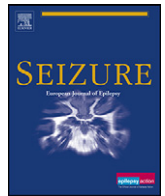




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## Periodic epileptiform discharges in hypoxic encephalopathy: BiPLEDs and GPEDs as a poor prognosis for survival

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### ABSTRACT

**Introduction:** Electrophysiologic tests in hypoxic encephalopathy consist of EEG and evoked/event-related potential studies. In most studies the generalized periodic epileptiform complexes have been reported combined with other EEG patterns and were indicators of a poor outcome in different etiologies of hypoxic encephalopathy (HE), but these have rarely been examined independently.

**Methodology:** We analyzed from 2000 to 2007 the outcome of patients with HE and generalized periodic epileptiform complexes. We abstracted and tabulated clinical information, imaging findings, and outcome from the medical records.

**Results:** We found 52 patients in our database. Fourteen patients (eight BiPLEDs and six GPEDs) were associated with HE. Patients with BiPLEDs were  $68 \pm 19.4$  years old, 5 female (62%) and 3 (38%) men. GPEDs patients were  $52.5 \pm 19.1$  years old, 2 women (20%) and 4 (80%) men. Myocardial infarction and ventricular tachycardia were responsible of 57% of the HE cases. Neuroimaging studies in both groups showed cortical structural lesions in 84%. All patients were comatose and died. Two GPEDs patients developed status epilepticus.

**Conclusion:** GPEDs and BiPLEDs after an anoxic insult carried a poor prognosis for survival. Aggressive treatment of patients may not be warranted when these EEG patterns are seen after anoxic brain injury.

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### 1. Introduction

Hypoxic–ischemic injury to the brain is a major cause of morbidity and mortality in infants and adults. Hypoxic encephalopathy (HE), after cardiac arrest and traumatic brain injury represent the most common etiologies.<sup>1</sup> In current practice, prognostic decisions rest principally on clinical observations, neuroimaging studies, neurochemical tests and neurophysiologic evaluation. Clinical assessment of the unresponsive patient is limited to examination of brainstem reflexes and simple motor responses to stimulation. Neurochemical tests have not been validated and have significant limitations. However, electrophysiologic investigations provide a window into cerebral function and are clinically safe, available, and inexpensive.<sup>2</sup> Electrophysiologic tests in HE consist of EEG and evoked/event-related potential studies. In most studies, EEG results are divided into two categories: (1) malignant and (2) benign or uncertain. Most malignant categories are indicators of a poor outcome. These

include suppression, burst-suppression, alpha and theta pattern coma, and generalized combined periodic complexes.<sup>3,4</sup> Generalized suppression to  $\leq 20 \mu\text{V}$ , burst-suppression patterns with generalized epileptiform activity, or generalized periodic complexes on a flat background are strongly but not invariably associated with poor outcome in HE, but these have rarely been examined separately.<sup>5,6</sup> We analyzed retrospectively our experience in patients with HE and generalized periodic epileptiform complexes.

### 2. Materials and methods

In our EEG lab during a period of 2000–2007 we performed 25,486 inpatients and outpatients EEGs. The EEG database was searched for all EEGs performed during this period of time, using the key words; repetitive discharge, periodic discharge, PLEDs, BiPLEDs, GPEDs, periodic epileptiform, bilateral periodic epileptiform discharge and generalized periodic epileptiform discharge. Initially we found 340 patients with this method. Of these, we identified 52 BiPLEDs and GPEDs patients with different etiologies. The prevalence of the BiPLEDs and GPEDs patients was 0.2%. Then, we identified 14 patients (7 men), 23–85 years old ( $61.7 \pm 20.3$  years old) who developed BiPLEDs or GPEDs within 24 h after

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cardiopulmonary resuscitation. We abstracted and tabulated clinical information (etiology, age, gender, physical findings, clinical seizures at onset, AED therapy), imaging findings (cortical and subcortical injuries or both), and outcome from the medical records. Acute seizures occurred at onset or within 24 h after hypoxic event. All patients had digital EEG recordings with 24 scalp electrodes positioned according to the standard 10–20 system of electrode placement, reformatted to both bipolar and off-head referential montages. The filter setting was 0.3 s (0.53 Hz) and 70 Hz. GPEDs were defined as the occurrence of periodic complexes occupying at least 50% of a standard 20 min EEG, over both hemispheres in a symmetric, diffuse and synchronized manner.<sup>7,8</sup> BiPLEDs were defined as bilateral independent periodic lateralized epileptiform discharges.<sup>9</sup> All EEGs were recording without sedative drugs and within 24–48 h after cardiopulmonary resuscitation. All patients, but one underwent imaging studies including CT and MRI scans; when both studies were available we considered only the MRI findings. Relevant cortical imaging abnormalities (on CT and MRI) included increased signal intensity within the cortical ribbon, border-zone infarctions, and laminar necrosis. Notable subcortical imaging findings included increased signal intensity in the deep gray matter nuclei and white matter abnormalities.

### 3. Results

We found 52 patients in our EEG database including 33 with BiPLEDs and 19 with GPEDs with different etiologies. Fourteen patients (eight BiPLEDs and six GPEDs) were associated with HE. Organized electrographic seizure activity was not seen in any of these EEG recordings. Nine (64%) patients had at least one EEG in their follow up after their diagnostic EEG. The age and gender distribution of the patients with BiPLEDs associated with HE were from 23 to 85 ( $68 \pm 19.4$ ) years old, 5 female (62%) and 3 (38%) men, respectively. The age and gender distribution of the patients with GPEDs associated with HE were from 26 to 76 ( $52.5 \pm 19.1$ ) years old, 2 women (20%) and 4 (80%) men, respectively (Fig. 1) (Table 1).

Myocardial infarction and ventricular tachycardia were responsible of 57% of the HE patients. Neuroimaging studies were abnormal in 11/13 (85%), normal 2/13 (15%) and 1 was not performed in the patients. Both normal studies were CT head scans. All studies showed cortical injury and only 3/13 (23%) cases showed a mixed subcortical injury as well (Fig. 2). In reference to the clinical findings all the patients were in a coma and only two (14%) patients also showed motor focal neurological findings. Acute seizures were seen in four (28%) cases with the same frequency distribution between BiPLEDs and GPEDs patients. The tonic clonic generalized seizure type was the only kind reported in both groups. Only one patient had a history of epilepsy.

After electrophysiological diagnosis, two GPEDs patients developed status epilepticus. All patients received multidisciplinary management including ventilatory support with propofol or phenobarbital and treatment with multiples antiepileptic drugs (Table 1). All patients died within 4 week of the original incident.

### 4. Discussion

Electroencephalography provides data that influences clinical decision-making in the setting of epilepsy related situations, hypoxic encephalopathy and brain death examination.<sup>10</sup> Previous studies have showed that different EEG patterns which are related to HE include suppression, burst-suppression, alpha and theta pattern coma, and generalized periodic complexes in combination with burst-suppression. These EEG patterns had a poor correlation with the outcome, but they have rarely been examined separately, specifically GPEDs.<sup>4</sup> Our study is the first report that specifically makes a correlation between generalized periodic complexes and the outcome including a higher number of patients with HE.

BiPLEDs are usually caused by anoxic encephalopathy or central nervous system infections (thus the high incidence of coma), and are typically associated with a poorer prognosis than PLEDs.<sup>9</sup> A recent study that included 21 patients with BiPLEDs with a variety

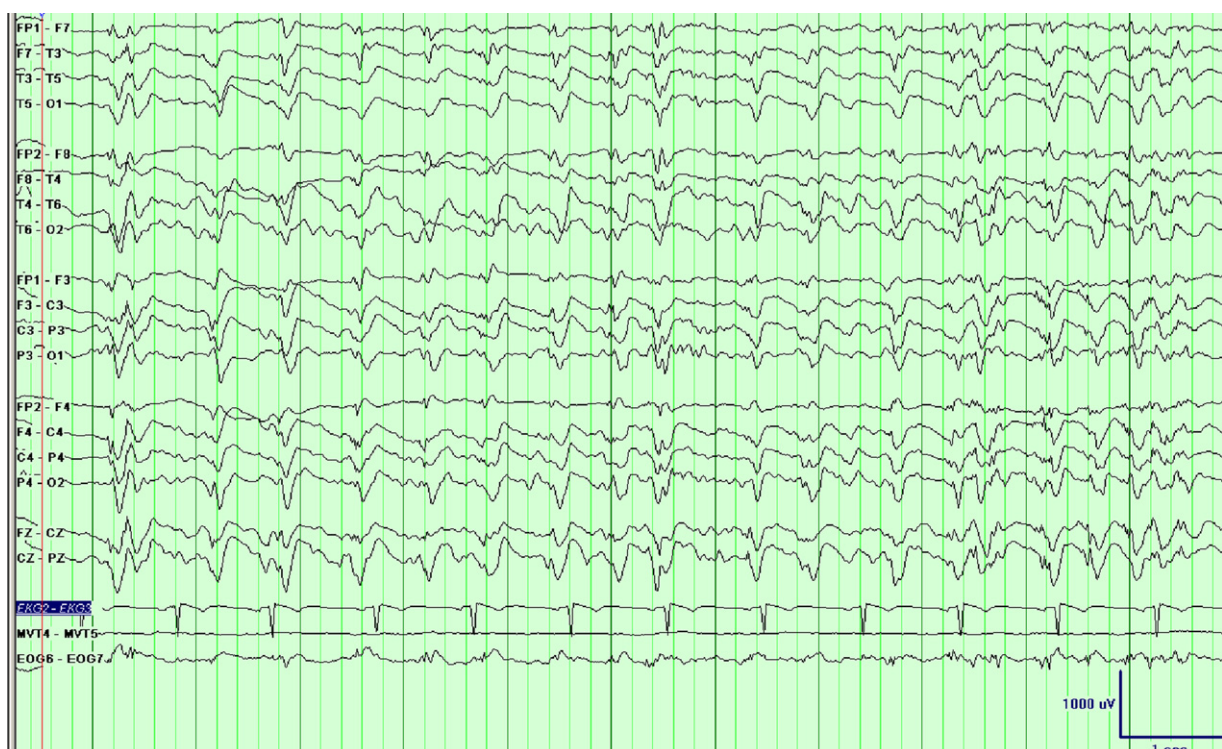


Fig. 1. 72 years old M with generalized periodic discharges. LFF 0.3 HFF 70. Sensitivity 50 µV/mm.

**Table 1**

Clinical findings, neuroimaging studies and outcome of the 14 patients with BiPLEDs and GPEDs and HE.

Pt	Age (year)	Sex	Type of PED	Diagnosis	MR/CT (abnormal)	Localization: Cortical +	Mental status: Coma +	Clinical seizures at onset	SE	AED therapy	Death
1	23	M	BiPLED	Laceration myocardial	+					PRO, PHT	+
2	67	F	BiPLED	Heroin overdose	+		Focal	+		PRO	+
3	72	F	BiPLED	Myocardial infarction	+					PRO, PHT	+
4	74	F	BiPLED	Myocardial infarction	+	Subcortical				PRO, PHT, DZP	+
5	83	F	BiPLED	Cardiogenic shock	+					PRO, CNZ, PHT, LEV, VPA	+
6	85	M	BiPLED	Ventricular tachycardia	NI <sup>a</sup>					PRO, PHT, VPA, CNZ	+
7	71	M	BiPLED	Myocardial infarction	+			+		PRO, GBP	+
8	75	F	BiPLED	Laceration myocardial	?	?				PB, PHT	+
9	26	M	GPED	Carbon monoxide poisoning	+	Subcortical		+	+	PRO, CNZ	+
10	51	M	GPED	Myocardial infarction	+			Focal	+	PRO	+
11	76	F	GPED	Bithalamic stroke	+					PRO	+
12	71	M	GPED	Respiratory failure	+	Subcortical			+	PRO	+
13	37	M	GPED	Ventricular tachycardia	NI <sup>a</sup>					PRO	+
14	54	F	GPED	Ventricular tachycardia	+					PRO	+

(?) Not performed; SE, status epilepticus; PRO, propofol; PHT, phenytoin; DZP, diazepam; CNZ, clonazepam; LEV, levetiracetam; VPA, valproate; PB, phenobarbital; GBP, gabapentine.

<sup>a</sup> CT head normal.

of etiologies showed a mortality of 52%, twice of that of PLEDs patients.<sup>11</sup> However, they only included two BiPLEDs patients with HE. De la Paz and Brenner,<sup>9</sup> included 5 patients with BiPLEDs and HE in their clinical report of 18 patients with BiPLEDs, and all patients died. A similar mortality rate was seen in our patients, independently of the etiology or management.<sup>9</sup>

GPEDs are very rare patterns and may be classified as periodic short-interval diffuse discharges (PSIDDs), periodic long-interval diffuse discharges (PLIDDs) and suppression burst patterns according to the interval between the discharges.<sup>8</sup> They occur in hypoxic or hepatic encephalopathy, drug toxicity and degenerative disorders such as Creutzfeldt–Jakob disease.<sup>8</sup> PSIDDs due to anoxia were reported to be associated with a fatal outcome or severe neurological sequelae especially if associated with repetitive myoclonic jerks<sup>12–14</sup> Yemisci et al.<sup>15</sup> reported 37 GPEDs patients with different etiologies, of these, 7 (18%) GPEDs patients were associated with HE. However, the authors did not describe the clinical findings of this specific population and neuroimaging studies were performed only in three patients with cortical and subcortical lesions. The EEGs features were classified as three

PSIDDs, one PLIDD and three burst-suppression patterns. The overall mortality within the first month, after GPEDs were seen on EEG was 48%, without information regarding the differential mortality rate between the patients with HE and GPEDs.<sup>15</sup> Husain et al.,<sup>16</sup> reported 25 patients with GPEDs, 10 (40%) had anoxia and toxic-metabolic encephalopathy with a 90% mortality rate, 3 (30%) patients developed status epilepticus and only 1 of 10 (10%) had a history of seizures.<sup>16</sup> Our GPEDs patients showed the same percentage of status epilepticus previously reported. GPEDs are considered by some authors to represent an EEG pattern of status epilepticus.<sup>17</sup>

In our series, neuroimaging studies in both BiPLEDs and GPEDs showed structural lesions in 78% of the patients; however, two patients had CT imaging. All lesions were cortical and only three patients had subcortical lesions, two of these were GPEDs patients. Yemisci et al.<sup>15</sup> found structural lesions in 78% of the GPEDs patients and the most common were subcortical lesions, detected in 75% of the patients either alone (25%) or together with cortical lesions (50%). Solely, cortical lesions were seen in 1 patient (3.6%) suggesting the role of subcortical involvement in the pathogenesis of GPEDs. However, the three patients with GPEDs and HE showed mixed cortical and subcortical lesions.<sup>15</sup> In relation to BiPLEDs the previous reports found injury to the hippocampus bilaterally,<sup>18</sup> bilateral infarction in the ACA territory<sup>19</sup> or gray and white matter involvement on MRI.<sup>18</sup> CT scans usually are normal in patients with BiPLEDs or GPEDs.<sup>9,15</sup> However, with the development of neuroimaging techniques it is now possible to demonstrate structural lesions in most patients with BiPLEDs.<sup>18,20</sup> To our knowledge, there is no study investigating the role of cortical and subcortical structural lesions in patients with BiPLEDs and HE. Post-mortem studies are naturally superior to neuroimaging studies because they provide microscopic delineation of the extent of the lesions. Despite the difference in the material analyzed our findings correlate with those of the post-mortem study of Gloor et al.<sup>20</sup> Of their nine patients with generalized periodic EEG patterns, five had cortical and subcortical gray matter (GM) and white matter (WM) lesions, three had cortical and subcortical GM lesions and one had a cortical GM lesion; none had WM lesions.<sup>20</sup> Ours results support the theory that cortical involvement is necessary in the pathogenesis in both BiPLEDs and GPEDs in patients with HE.<sup>16</sup> Brenner and Schaul,<sup>8</sup> suggested that the pathophysiology of PLEDs range from abnormal interactions between the “deranged cortex” and deeper “triggering” structures to increased local cortical irritability, possibly with involvement of normal and abnormal intracortical circuits.<sup>8</sup>



**Fig. 2.** Patient 9; 71 years old M. MRI FLAIR sequence shows multifocal areas of hyperintensity involving cerebral cortex.



However, the pathophysiological mechanism responsible for periodicity in the EEG is unknown.<sup>15</sup>

As in prior studies, GPEDs and BiPLEDs after an anoxic insult carried a poor prognosis for survival. Thus aggressive treatment of patients may not be warranted when these EEG patterns are seen after anoxic brain injury.<sup>17</sup>

## 5. Conclusion

GPEDs and BiPLEDs after an anoxic insult carried a poor prognosis for survival.

## Conflict of interest

The authors report no disclosures or any conflict of interests.

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