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Bilateral independent periodic discharges are associated with electrographic seizures and poor outcome: A case-control study

Gamaleldin Osman[a,b,c,1], **Rahul Rahangdale**[b,d,1], **Jeffrey W. Britton**[e], **Emily J. Gilmore**[b], **Hiba Arif Haider**[f], **Stephen Hantus**[g], **Aline Herlopian**[b,h], **Sara E. Hocker**[e], **Jong Woo Lee**[i], **Benjamin Legros**[j], **Michael Mendoza**[f], **Vineet Punia**[g], **Nishi Rampal**[b], **Jerzy P. Szaflarski**[k], **Adam D. Wallace**[e], **M. Brandon Westover**[h], **Lawrence J. Hirsch**[b], **Nicolas Gaspard**[b,j,*]

[a]Department of Neurology, Henry Ford Hospital, Detroit, MI, USA

[b]Department of Neurology, Yale University School of Medicine, New Haven, CT, USA

[c]Ain Shams University, Cairo, Egypt

[d]Department of Neurology, Allegheny General Hospital, Pittsburgh, PA, USA

[e]Department of Neurology, Mayo Clinic, Rochester, MN, USA

[f]Division of Epilepsy, Department of Neurology, Emory University, Atlanta, GA, USA

[g]Cleveland Clinic Epilepsy Center, Cleveland, OH, USA

[h]Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

[i]Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

[j]Service de Neurologie et Centre de Référence pour le Traitement de l'Epilepsie Réfractaire, Université Libre de Bruxelles - Hôpital Erasme, Bruxelles, Belgium

[k]University of Alabama at Birmingham, Birmingham, AL, USA

Abstract

Objective: To determine the clinical correlates bilateral independent periodic discharges (BIPDs) and their association with electrographic seizures and outcome.

Methods: Retrospective case-control study of patients with BIPDs compared to patients without periodic discharges ("No PDs") and patients with lateralized periodic discharges ("LPDs"), matched for age, etiology and level of alertness.

Results: We included 85 cases and 85 controls in each group. The most frequent etiologies of BIPDs were stroke, CNS infections, and anoxic brain injury. Acute bilateral cerebral injury was

[*]Corresponding author at: Service de Neurologie, Université Libre de Bruxelles - Hôpital Erasme, Route de Lennik, 808 1070 Bruxelles, Belgium. nicolas.gaspard@ulb.ac.be (N. Gaspard).

[1]These authors contributed equally to this work.

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more common in the BIPDs group than in the No PDs and LPDs groups (70% vs. 37% vs. 35%). Electrographic seizures were more common with BIPDs than in the absence of PDs (45% vs. 8%), but not than with LPDs (52%). Mortality was higher in the BIPDs group (36%) than in the No PDs group (18%), with fewer patients with BIPDs achieving good outcome (moderate disability or better; 18% vs. 36%), but not than in the LPDs group (24% mortality, 26% good outcome). In multivariate analyses, BIPDs remained associated with mortality (OR: 3.0 [1.4– 6.4]) and poor outcome (OR: 2.9 [1.4–6.2]).

Conclusion: BIPDs are caused by bilateral acute brain injury and are associated with a high risk of electrographic seizures and of poor outcome.

Significance: BIPDs are uncommon but their identification in critically ill patients has potential important implications, both in terms of clinical management and prognostication.

Keywords

Bilateral independent periodic discharges; Periodic discharges; Seizures; Continuous EEG monitoring

1. Introduction

Bilateral independent periodic discharges (BIPDs; previously known as bilateral independent periodic lateralized epileptiform discharges or BIPLEDs) are EEG abnormalities consisting of discharges that occur repeatedly with a quantifiable and nearly regular inter-discharge interval, and independently (asynchronously) over each hemisphere (Hirsch et al., 2013). The prevalence and clinical and prognostic significance of BIPDs in patients undergoing continuous EEG monitoring (CEEG) remains unclear. One study previously showed prevalence of 0.1% in unselected sets of inpatient and outpatient EEGs (Chatrian et al., 1964; Gross et al., 1999; Fitzpatrick and Lowry, 2007; Orta et al., 2009) while studies focusing on critical care EEG reported a prevalence of approximately 0.5–1 %. (Struck et al., 2017). The clinical and prognostic significance of BIPDs has not been thoroughly studied. They typically occur with acute bilateral or diffuse cerebral injury involving the cortical grey matter (Raroque and Purdy, 1995; Orta et al., 2009) and most commonly due to anoxia, infection or stroke (Chatrian et al., 1964; Fitzpatrick and Lowry, 2007). Prior series predating the widespread use of CEEG have reported varying but high associated rates of clinical seizures, coma, and mortality (Chatrian et al., 1964; De la Paz and Brenner, 1981; Snodgrass et al., 1989; Fitzpatrick and Lowry, 2007; Orta et al., 2009). The rate of electrographic seizures associated with BIPDs has been explored in a single study, which did not find a statistical association (Rodriguez Ruiz et al., 2016). The small sample size and the uncontrolled design of the aforementioned studies preclude the generalization of these findings.

We aimed to determine the etiologies and clinical correlates of BIPDs in patients undergoing CEEG, and compare their associated risk of electrographic seizures and prognostic significance to matched controls without periodic discharges and with lateralized periodic discharges (LPDs).

2. Methods

2.1. Study sample

This retrospective study was performed through eight member centers of the Critical Care EEG Monitoring Research Consortium (CCEMRC; see https://www.acns.org/research/critical-care-eeg-monitoring-research-consortium-ccemrc/list-of-members-and-site-principal-investigators and the Supplementary Appendix). Institutional review boards of each center approved the study. Investigators at participating centers identified cases with BIPDs using local EEG databases and reports. The study period varied between centers. Two control groups were selected. In one group, we selected patients matched to cases for age (+/– 10 years), presence or absence of coma, and etiology (see below for etiological categories), whose CEEG did not demonstrate any periodic or rhythmic discharges (referred to as the "No PDs" control group). In the second group, we selected patients matched to cases for age and etiology, whose CEEG demonstrated lateralized periodic discharges (LPDs; referred to as "LPDs group"). Each center had to contribute at least 5 cases and 5 matched controls for each control group (total of 15 patients) to be included in the study. We also attempted to match for presence of coma but were only partly successful, as finding comatose cases with LPDs was not possible for each combination of age and etiology (see Results section).

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.clinph.2018.07.025.

2.2. Variables

We collected the following variables from medical charts, EEG and imaging reports: age, gender, etiology (categorized as acute brain injury [ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, subdural hemorrhage, traumatic brain injury, CNS infection, CNS inflammatory disorder, CNS neoplasm, posterior reversible encephalopathy syndrome]; toxic/metabolic encephalopathy; anoxic brain injury; or seizure disorder), level of consciousness at time of CEEG (categorized as coma [defined, as lack of purposeful response to noxious stimulation and other meaningful interaction], lethargy/stupor, and fully awake), presence of a focal neurological deficit, report of clinical seizure or status epilepticus (SE) prior to CEEG, reason for CEEG (detection of electrographic seizures, prognostication or characterization of motor spells), duration of CEEG (in hours), seizures or SE during monitoring (as per the EEG report), presence and location of acute brain injury on imaging (categorized as bilateral or diffuse/unilateral/none and as cortical involvement/no cortical involvement). Outcome was determined with the Glasgow Outcome Score (5: mild disability; 4: moderate disability; 3: severe disability; 2: vegetative state; and 1: death) at discharge from hospital, and by the disposition at discharge from hospital (death; transfer to skilled nursing facility, rehabilitation or long-term assisted living; discharged home).

2.3. Statistics

Variables were described as count (percentage) or median [interquartile range] and compared using Mann-Whitney's or Fisher's exact test. Comparisons were performed between the BIPDs and the No PDs groups, and between the BIPDs and LPDs groups. For univariate comparisons, a corrected p-value <0.0013 according to Bonferroni's method was considered significant, with values between 0.0013 and 0.05 being considered trends. We assessed the independent association of BIPDs with outcome (both in-hospital mortality and poor outcome at hospital discharge [defined as GOS 1 to 3: severe disability, vegetative state or death]) in multivariate logistic regression models adjusting for variables associated with outcome in univariate analysis with a $p < 0.05$. Age was dichotomized as ≥ or < 65 years and a p-value < 0.05 was considered significant for the purpose of the multivariate analysis.

3. Results

We included 85 BIPDs cases, 85 No PD controls and 85 LPD controls. Examples of BIPDs are presented in Figs. 1 and 2.

The demographic and clinical data are summarized in Table 1. The most common etiologies of BIPDs were stroke (12 [14%] ICH, 10 [11%] ischemic strokes), CNS infection (9 [10%]), and anoxic brain injury (9 [10%]). The most frequent reason for CEEG was detection of NCSz and reasons did not differ between groups. Seventy-seven of 85 (91%) patients with BIPDs had stupor or coma, including 26 (31%) in coma. Forty-eight (56%) had a focal neurological deficit and 32 (38%) had clinical seizures prior to CEEG. These characteristics were not statistically different in the control and LPDs groups. Electrographic seizures and SE during CEEG were more common in the BIPDs group compared to the No PDs group (38/85 [45%] vs. 7/85 [8%]; $p < 0.0001$ and 19/85 [22%] vs. 3/85 [4%]; $p = 0.0002$, respectively) but not compared to the LPDs group (44/85 [52%] seizures and 23/85 [27%] SE). Seizures at any time (clinical seizures before or any seizures during CEEG) occurred in 53 [62%] of BIPDs, 28 [33%] of No PDs and 54 [64%] of LPDs cases, respectively. ($p < 0.0001$ comparing BIPDs to No PDs, and $p = 0.88$ comparing BIPDs to LPDs). Seventy patients with BIPDs received anti-seizure medications during their stay, compared to 42 (49%) in the No PDs groups and 77 (91%) in the LPDs group ($p < 0.001$ and $p = 0.12$, respectively).

Acute bilateral or diffuse cerebral injury was more common in the BIPDs group than in the No PDs and LPDs groups (57 (70%) vs. 26 (37%) vs. 28 (35%); $p < 0.0001$ for both comparisons).

Outcome was worse in the BIPDs group, compared to the No PDs group, with a higher mortality rate (31/85 [36%] vs. 15/85 [18%]), a lower proportion of patients achieving mild to moderate disability (15/85 [18%] vs. 31/85 [36%]; $p< 0.001$ for comparison of all outcome categories between groups; Table 1) and a lower proportion of patients discharged home (7/85 [8%] vs. 27/85 [32%]; $p < 0.0001$ for comparison of all discharge dispositions). Among patients with BIPDs and anoxic brain injury, 8/9 (88%) died. Outcome in the LPDs group was similar to the BIPDs group (Table 1). In multivariate analysis, including age and presence of electrographic seizures on CEEG, of patients with BIPDs and no PDs, BIPDs (OR: 3.0 [1.4–6.4]) and coma (OR: 6.8 [3.1–14.7]) were independently associated with mortality (Table 2). Similarly, compared to the No PDs group, BIPDs (OR: 2.9 [1.4–6.2]), coma (OR: 3.6 [1.5–9.2]) and age ≥ 65 years (OR: 2.7 [1.3–5.7]) were independently associated with poor outcome (severe disability, vegetative state or death; Table 2), even when adjusting for age and presence of electrographic seizures on CEEG.

4. Discussion

In this retrospective multicenter study, we aimed to determine the etiologies, clinical correlates, and prognostic significance of BIPDs in critically ill patients undergoing continuous EEG monitoring. We found that (1) BIPDs were most often due to bilateral or diffuse acute brain injury, especially stroke, CNS infections, and anoxic brain injury; (2) most patients with BIPDs were lethargic, stuporous or comatose; (3) BIPDs were associated with electrographic seizures, with a risk similar to LPDs; and 4) BIPDs were associated with poor outcome (severe disability, vegetative state or death), even after matching or adjusting for potential con-founders (coma, age and electrographic seizures).

Our findings are in line with previous studies (Table 3) (De la Paz and Brenner, 1981; Snodgrass et al., 1989; Fitzpatrick and Lowry, 2007; Orta et al., 2009), albeit with some differences. With the exception of one study that focused on post-cardiac arrest patients (San-Juan and Costello, 2009), others have repeatedly found stroke, CNS infections, anoxic brain injury and metabolic encephalopathy to be the most common etiologies of BIPDs. As in prior series, and not unexpectedly, we found that bilateral or diffuse brain injury underlies the occurrence of BIPDs in three-quarter of cases (Fitzpatrick and Lowry, 2007). Not all patients received magnetic resonance imaging so this might be underestimated. Also, a substantial proportion of our cases suffered from septic, metabolic or post-anoxic encephalopathy that might have caused diffuse cerebral dysfunction and BIPDs without evidence of structural damage on brain imaging. The rate of clinical seizures prior to CEEG was somewhat lower in our series (38%) than in earlier studies, which reported seizure rates >70% (De la Paz and Brenner, 1981; Fitzpatrick and Lowry, 2007). This may reflect changes in clinical practice, especially the expanding routine use of CEEG in critically ill patients, and not only in those with clinical seizure activity. Ours is the first study to formally show a statistical association between B]PDs and the occurrence of electrographic seizures during CEEG (45%) in a large series. This association was not significant in previous studies (Ruiz et al., 2016; Struck et al., 2017), probably due to the unmatched design of the first one and the small size (N = 6) of the subgroup of patients with BIPDs in the latter, thus further highlighting the importance of multicenter collaborative case-control studies for uncommon EEG patterns. We confirm that the mortality associated with B]PDs is high and that poor outcome is common (De la Paz and Brenner, 1981; Fitzpatrick and Lowry, 2007; Orta et al., 2009). Although this association likely depends on the underlying etiology, it remained significant after matching for etiology, age and coma and controlling for the presence of electrographic seizures. Whether BIPDs directly cause metabolic distress and neuronal damage or simply provide independent information on the extent of brain injury beyond the neurological examination remains an open question.

The main strength of our study is its case-control design, which allows separating the independent effect of B]PDs from the underlying illness, at least to some degree. While we matched cases and controls for etiology, we did not directly match them for the severity of the specific underlying illness, which could have affected the association between BIPDs and outcome. However, we find it unlikely as this association remained statistically significant after stratifying for the presence of coma, which largely reflects disease severity in acute brain injury, which is the major cause of BIPDs. By doing this, however, we likely selected the sickest patients with LPDs and possibly underestimated the differences between the two groups. Limitations include the retrospective non-systematic and variable identification of cases. This is mitigated by the facts that all investigators have extensive experience in critical care EEG and are certified with the ACNS terminology (Hirsch et al., 2013), and that all participating centers routinely use local EEG databases. Another limitation was the difficulty to find matched cases with LPDs for both etiology and level of consciousness, further indicating that BIPDs are associated with more diffuse or severe brain injury and more coma than LPDs. Our outcome was only measured at hospital discharge, and we cannot comment on patients' long term outcome. Lastly, we did not study the electrographic characteristics of BIPDs, such as frequency and prevalence, which are known to increase the risk of electrographic seizures associated with PDs (Ruiz et al., 2016) and might also possibly determine their ability to cause secondary brain injury (Witsch et al., 2017).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Bilateral independent periodic discharges (BIPDs) are caused by bilateral acute brain injury.
- BIPDs are associated with electrographic seizures, which occur in close to half of patients.
- BIPDs are associated with worse functional outcome.

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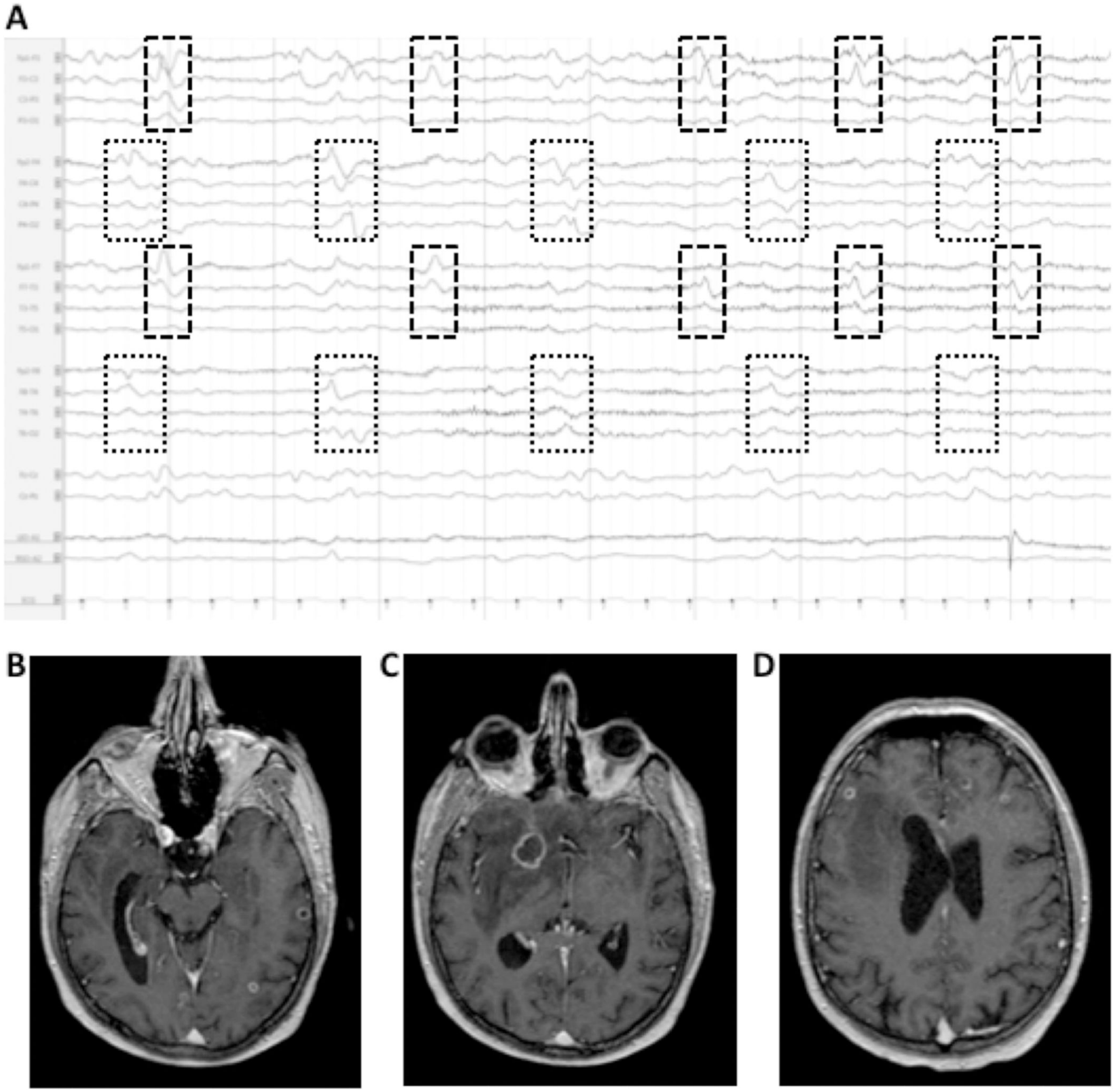

Fig. 1.

69-year old stuporous male with multiple pyogenic cerebral abscesses from bacterial endocarditis. The EEG (**A**) showed bilateral independent periodic discharges that occur at approximately 0.5 per second over each hemisphere, predominantly in the frontotemporal regions (dashed boxes). Low-frequency and high-frequency filters were set at 0.5 and 70 Hz, respectively; notch filter was off. Brain MRI (**B-D**) demonstrated disseminated ring-enhancing lesions with surrounding edema located at the grey-white matter junction. Several electrographic seizures were recorded, which ceased upon treatment with anti-seizure medications. The patient partially recovered and was discharged to a skilled nursing facility.

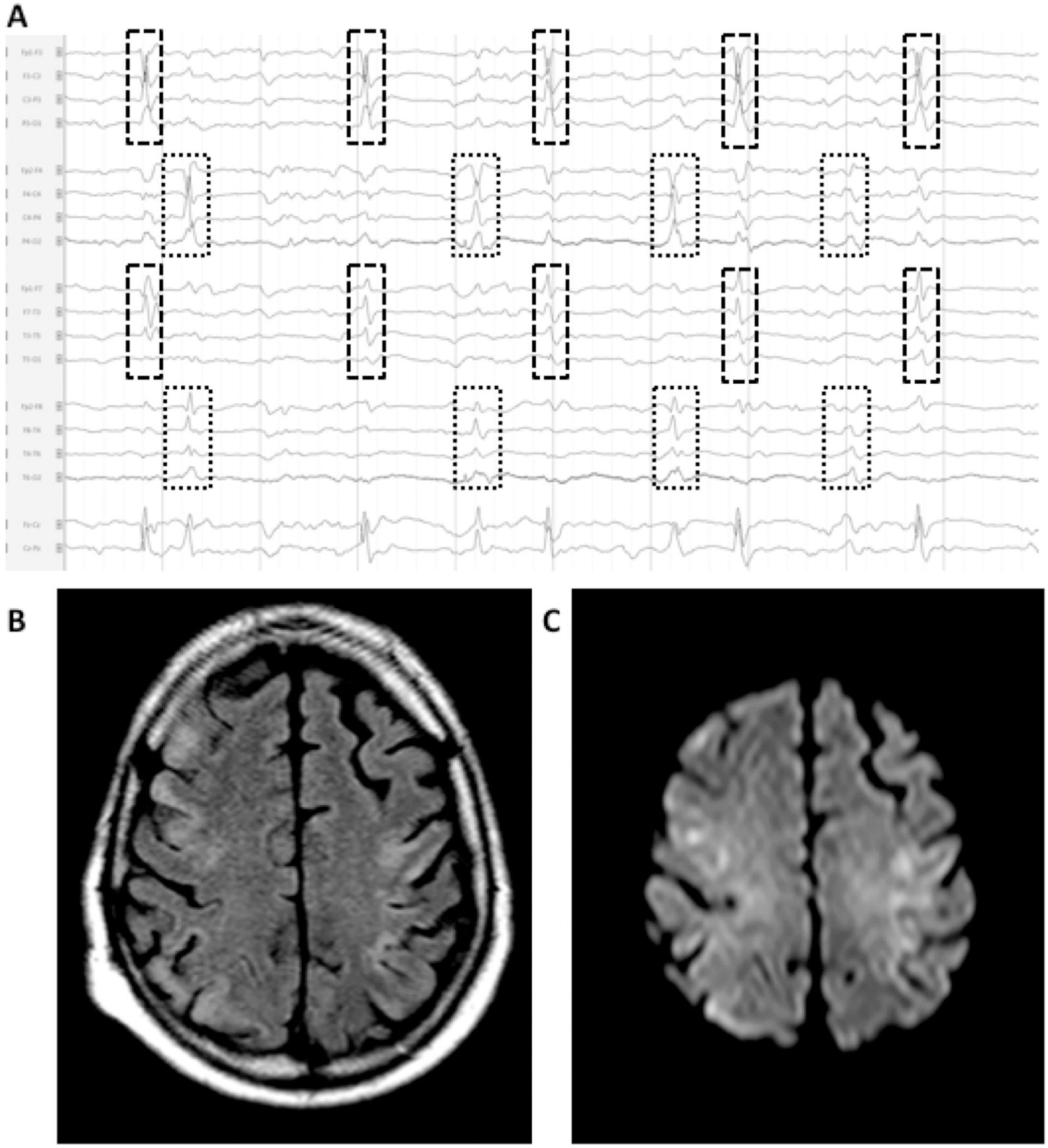

Fig. 2.

74-year old comatose female with post-anoxic brain injury after cardiac arrest. The EEG (**A**) showed bilateral independent periodic discharges that occurred at approximately 0.5 per second over each hemisphere (dashed boxes). Low-frequency and high-frequency filters were set at 0.5 and 70 Hz, respectively; notch filter was off. Brain MR] demonstrated diffuse cortical hyperintense signal changes on fluid-attenuated inversion recovery (**B**) and diffusion-weighted imaging (**C**). No clinical or electrographic seizures occurred. The patient did not regain consciousness and died in the hospital.

Table 1

Demographics and clinical features. Patients were matched for age, etiology and presence of coma (see methods). Data are presented as count (percentage) and median [interquartile range].

	BIPDs (N = 85)	No PDs (N = 85)	p-value*	LPDs (N = 85)	p-value*
Gender, female	58 (68%)	40 (47%)	*0.006*	50 (59%)	0.21
Age (years)	64 [56–72]	66 [57–75]	0.17	65 [58–73]	0.27
Etiology			NA		NA
Acute brain injury	60 (71%)	60 (71%)		60 (71%)	
Traumatic brain injury	8 (9%)	8 (9%)		8 (9%)	
Intracerebral hemorrhage	12 (14%)	12 (14%)		12 (14%)	
Ischemic stroke	10 (12%)	10 (12%)		10 (12%)	
Subarachnoid hemorrhage	4 (5%)	4 (5%)		4 (5%)	
Subdural hemorrhage	2 (2%)	2 (2%)		2 (2%)	
CNS infection	9 (11%)	9 (11%)		9 (11%)	
CNS inflammatory disorder	2 (2%)	2 (2%)		2 (2%)	
CNS neoplasm	6 (7%)	6 (7%)		6 (7%)	
Post-neurosurgery	4 (5%)	4 (5%)		4 (5%)	
PRES	3 (3%)	3 (3%)		3 (3%)	
Toxic/metabolic/septic encephalopathy	10 (12%)	10 (12%)		10 (12%)	
Anoxic brain injury	9 (11%)	9 (11%)		9 (11%)	
Seizure disorder	6 (7%)	6 (7%)		6 (7%)	
Reasons for CEEG					
Detection of electrographic seizures	80 (94%)	80 (94%)	0.99	81 (95%)	0.99
Prognostication	7 (8%)	7 (8%)	0.99	6 (7%)	0.99
Characterization of motor spells	2 (2%)	2 (2%)	0.99	2 (2%)	0.99
Duration of monitoring (hours)	65 [37–140]	27 [19–44]	<0.001	54 [33–105]	0.31
Consciousness			0.20		0.67
Coma	26 (31%)	26 (31%)		24 (28%)	
Stupor	51 (60%)	43 (51%)		49 (58%)	
Awake but abnormal	8 (9%)	16 (19%)		12 (14%)	
Focal neurological deficit	48 (56%)	36 (42%)	0.07	48 (56%)	0.99

	BIPDs (N = 85)	No PDs (N = 85)	p-value*	LPDs (N = 85)	p-value*
Clinical seizures before CEEG	32 (38%)	25 (29%)	0.27	31 (36%)	0.88
Clinical SE	8 (9%)	3 (4%)	0.13	16 (19%)	0.08
Anti-seizure medications	70 (82%)	42 (49%)	<0.0001	77 (91%)	0.12
Seizures during CEEG	38 (45%)	7 (8%)	<0.0001	44 (52%)	0.36
SE during CEEG	19 (22%)	3 (4%)	0.0002	23 (27%)	0.48
Seizures at any time (including clinical seizures before and seizures during CEEG)	53 (62%)	28 (33%)	<0.0001	54 (64%)	0.88
Location of acute brain injury on imaging	*(N = 81)*	*(N =71)*	<0.0001	*(N = 81)*	<0.0001
-Bilateral or diffuse	57 (70%)	26 (37%)		28 (35%)	
-Unilateral	21 (26%)	40 (56%)		50 (62%)	
-None	2 (2%)	5 (7%)		3 (4%)	
Acute cortical injury on imaging	58 (72%)	37 (52%)	*0.02*	61 (75%)	0.60
Glasgow outcome scale at discharge			<0.001		0.27
Dead	31 (36%)	15 (19%)		20 (24%)	
Vegetative	12 (14%)	4 (5%)		13 (15%)	
Severe disability	27 (32%)	35 (40%)		30 (35%)	
Moderate disability	14 (16%)	24 (28%)		22 (26%)	
Mild disability	1 (1%)	7 (8%)		0 (0%)	
Disposition at discharge			<0.0001		0.10
Death	31 (36%)	15 (18%)		20 (24%)	
Skilled nursing facility/rehabilitation/long-term assisted living	47 (55%)	42 (49%)		53 (62%)	
Home	7 (8%)	27 (33%)		12 (14%)	

*Abbreviations: BIPDs = bilateral independent periodic discharges; CEEG = continuous EEG monitoring; LPDs = lateralized periodic discharges; NA = not applicable; SE = status epilepticus.

*Comparison performed with the BIPDs group. A p-value < 0.0013 was considered significant.

Table 2

Clinical features associated with mortality and poor outcome (BIPDs and control groups; N = 170).

	Dead (N = 46)	Alive (N = 124)	p-value (univariate)	OR (multivariate)
Coma	28 (61%)	24 (19%)	**<0.0001**	6.8 [3.1–14.7]
Age ≥ 65 years	25 (54%)	60 (48%)	0.5	NA
BIPDs	31 (67%)	54 (44%)	*0.03*	3.0 [1.4–6.4]
Seizures during CEEG	17 (37%)	28 (23%)	0.08	NA
	Poor outcome[a] (N = 124)	**Good outcome (N = 46)**	**p-value (univariate)**	**OR (multivariate)**
Coma	45 (36%)	7 (15%)	*0.009*	3.6 [1.5–9.2]
Age ≥ 65 years	69 (56%)	16 (35%)	*0.01*	2.7 [1.3–5.7]
BIPDs	70 (56%)	15 (33%)	*0.006*	2.9 [1.4–6.2]
Seizures during CEEG	37 (30%)	8 (17%)	0.12	NA

Data are presented as count (percentage) and OR [95% confidence interval].

Abbreviations: BIPDs = bilateral independent periodic discharges; CEEG = continuous EEG monitoring; NA = not applicable; OR = odds ratio. Hosmer-Lemeshow statistic: 3.77; p = 0.88; df=8, for the model of mortality, and Hosmer-Lemeshow statistic: 10.81; p = 0.21; df = 8, for the model of poor outcome. Variables associated with the outcome measure with a p-value < 0.05 were included in the multivariate models.

[a]Poor outcome defined as severe disability, vegetative state or death at hospital discharge.

Table 3

Etiology, risk of clinical seizures, coma and mortality in patients with BIPDs in the current and prior studies.

Studies	N	Most Common Etiologies				Clinical seizures	Seizures during CEEG	Coma[b]	Mortality
		Stroke[a]	Anoxic injury	CNS infection	Metabolic				
De la Paz and Brenner (1981)	18	1 (6%)	5 (28%)	5 (28%)	1 (6%)	14 (78%)	NA	13 (72%)	11 (61%)
Snodgrass et al. (1989)	4	NA	NA	NA	NA	4 (100%)	NA	NA	3 (75%)
Fitzpatrick and Lowry (2007)	21	8 (38%)	2 (10%)	3 (14%)	0 (0%)	16 (76%)	NA	NA	11 (52%)
San-Juan et al. (2009)[c]	8	0 (0%)	8 (100%)	0 (0%)	0 (0%)	2 (25%)	NA	8 (100%)	8(100%)
Orta et al. (2009)	23	7 (30%)	NA	3 (13%)	5 (22%)	10 (43%)	NA	11 (48%)	9 (39%)
Present study	85	22 (26%)	9 (11%)	9 (11%)	10 (12%)	32 (38%)	38 (45%)	26 (31%)	31 (36%)

Data are presented as count (percentage).

[a] Including ischemic and hemorrhagic strokes.

[b] The definition of coma was not always specified and, when specified, varied across studies.

[c] Included only patients with anoxic brain injury.