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Low frequency nonevolving generalized periodic epileptiform discharges and the borderland of hypoxic nonconvulsive status epilepticus in comatose patients after cardiac arrest

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ABSTRACT

To explore the EEG boundary of nonconvulsive status epilepticus (NCSE) and the concept of "possible NCSE", we studied 14 consecutive patients with ≤2-Hz nonevolving periodic generalized epileptiform discharges (GPDs) in their first EEG after out of hospital cardiac arrest (OHCA). The pattern was associated with myoclonus in 11 patients. EG reactivity to antiseizure drugs (benzodiazepines and propofol), but without clinical improvement, was noted in 8 patients, satisfying the diagnostic criteria of "possible NCSE". Resolution of GPDs and emergence of physiological rhythms in follow-up EEGs and/or subsequent clinical improvement were noted in 6 of them, strongly suggesting that the initial slow nonevolving GPD pattern reflected NCSE significantly contributing to their coma. Background rhythms from 10 to 90% of the periods between GPDs were noted in 9 patients and appeared to correlate with reactivity of the GPD pattern to antiseizure drugs when 20% or more. Ten patients died, and four were discharged to longer care rehabilitation centers. Although based on few observations, preliminary evidence appears to indicate that in this context, nonevolving GPD frequencies as low as 0.8 Hz *can* reflect clinically significant NCSE and, therefore, warrant appropriate testing for possible reactivity. There is also some preliminary indication that background rhythms may be another important diagnostic and, perhaps, prognostic indicator, but this needs to be tested in large prospective studies.

This article is part of a Special Issue entitled "Status Epilepticus".

1. Introduction

The frequency of nonevolving repetitive or periodic generalized epileptiform discharges (PEDs) in the critically ill has been the cornerstone of the diagnosis of nonconvulsive status epilepticus (NCSE) [1,2], with the low cutoff frequency limit currently set at 2.5 Hz. For lower frequencies, EEG *and* clinical improvement after IV administration of a rapidly acting antiepileptic drug (AED) is also diagnostic for NCSE, while EEG improvement alone only suggests the *possibility* of NCSE [3].

Conceivably, the EEG expression is dynamic, and important variables that serve as NCSE diagnostic tools, such as GPD frequency and variability, any response to external stimuli or to antiseizure agents, and perhaps, possible background activities and their frequencies and amounts may be variably affected by the interplay between known modulators, such as time from insult, type and dose of sedation and AED, therapeutic hypothermia (TH) or active normothermia (AN) [4], and other factors that we may be unaware of at the time of EEG reporting, such as the degree of the anoxic insult and possible confounders. The latter include coexisting sepsis or metabolic derangements, the degree of secondary (possibly reversible) cerebral edema, and comorbidities, like dementia. Such factors account for the fact that a clear clinical improvement after IV AED is rare in comatose patients [5].

We reviewed the EEG and clinical findings of patients with hypoxic encephalopathy after out of hospital cardiac arrest (OHCA) and nonevolving GPD at ≤2 Hz in their first video-EEG to explore the electrographic boundaries of NCSE and gain some further insight into the current concept of "*possible NCSE*", including the lowest frequency limits of reactive GPDs. We also investigated the possible relationships between background rhythms, reactivity, and outcome and explored the potential of the former as a useful NCSE diagnostic tool.

2. Patients and methods

We studied the video-EEG and clinical data of a cohort of consecutive patients with OHCA, treated over the last 4 years at St. Thomas'

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Table 1
Clinical and EEG features of the first two post-insult video-EEG recordings and outcome.

	EEG1					EEG2					Outcome	Comorbidities
Sex/age	Day/propofol/AED	GPD frequency/ reactivity/MJ	Biological rhythms	IV AED	Propofol window	Day/propofol/AED	GPD frequency	Biological rhythms	IV AED	Propofol window		
1/F/75	D3/no/no	0.8–1.5 Hz/ → 2 Hz on stimulation/random multifocal	θ ~50%	No	N/A	D6/no/LEV 1000 mg bd	None	Fast θ; cycling	N/A	N/A	Deceased D16	COPD–AF–cardiac failure myeloma
2/M/60	D2/yes/PHT 300 mg od	1 Hz/none/axial time locked as propofol ↓	Fast δ ~20%	No	GPDs ceased; δ/θ/faster	D4/no/PHT 300 mg od–VPA 500 mg bd	2 Hz	Similar to EEG1	N/A	No	ICU discharge–deceased D69	MI–COPD–renal
3/M/60	D2/yes/LEV 500 mg bd	1.2–2 Hz/none/facial twitching → axial time locked as propofol ↓	θ and faster ~90%	No	No	D4/yes[c]/LEV 1500 mg bd–VPA 300 mg bd	<2 Hz	Similar to EEG1	No	GPDs ceased δ/θ/faster	LCRC; lost to FU (France)	None; cyclist, marathon runner
4/M/76	D2/no[a]/PHT 300 mg od	1.2–2 Hz/none/axial time locked	None	LRZ: no effect	GPDs attenuated; δ	No further EEG					Deceased D6	Dementia–COPD–DM–blind
5/M/71	D4/no/PHT 300 mg od	1.2–1.8 Hz/none/no	Sharp δ ~30%	No	N/A	D6 (present N20)/no/PHT 300 mg od	1.0–1.8 Hz	Similar to EEG1	DZP: GPDs ceased; θ and faster	N/A	LCRC; deceased 2.5 years later	Aortic valve disease; AF
6/M/62	D4/yes[b]/LEV 1000 mg bd	0.8–1.2 Hz/ → 2 Hz on stimulation/random multifocal	δ and θ ~60%	CNZ: GPDs ceased; θ/δ	N/A	No further EEG; LEV continued at 1000 mg bd					LCRC; 3 years later he walks with a stick, continent	Multiple organ failure
7/M/76	D4/no/LEV 750 mg bd	0.8–1.5 Hz/none/no	δ ~30%	LRZ: GPDs ceased; θ/δ/faster	N/A	D9/no/LEV 1500 mg bd–PHT 300 mg od	1.5 Hz	None	LRZ: GPDs ceased; slow θ/δ; flat epochs	N/A	Deceased D10	Prostate Ca COPD
8/M/58	D3/yes[b]/PHT 300 mg od–VPA 300 mg bd	1.5–2 Hz/none/axial time locked as propofol ↓	Mainly θ ~60%	No	No	D7/no/LEV 1000 mg bd–PHT 400 mg	2 Hz	Fewer θ than in EEG1	LRZ: GPDs ceased; slow θ/δ flat epochs	N/A	LCRC; deceased 16 months later	None, CA while jogging; septic crises in ICU
9/M/78	D2/no[a]/LEV 1000 mg bd	0.7–1.5 Hz/none/axial time locked	Sharp δ <20%	LRZ: no effect	No	D6/no/LEV 1000 mg bd	2 Hz	None	LRZ/PHT: no change	Yes–no change	Deceased D11	MI–AF–DM
10/M/36	D3/no/LEV 750 mg bd	1–1.5 Hz/none/axial time locked	Sharp δ <10%	No	N/A	D5/no/LEV 1500 mg bd–VPA 1000 mg bd	0.5–1 Hz	None	MDZ: no change	Yes (to scan)–no change	Deceased D13	Meningococcal septicaemia; COPD
11/M/33	D2/yes/LEV 1000 mg bd–PHT 300 mg od	1–1.5 Hz/none/axial time locked	None	No	No	D4/no/LEV 1000 mg bd	1 Hz	None	No	Yes–no change	Deceased D5	Asthma
12/M/71	D2/yes/PHT 300 mg od DZP	1–1.2 Hz/none/axial time locked	None	No	No	D9/no/LEV 1500 mg bd–VPA 300 mg bd	1 Hz	None	MDZ: no change		Deceased D9	Unknown
13/M/64	D3/yes/PHT 300 mg od–LEV 500 mg bd	2 Hz/none/axial time locked	None	DZP ×2: no effect	No	D4 (absent N20); no further EEG					Deceased D5	Unknown
14/F/58	D3/yes/PHT 300 mg od–LEV 500 mg bd–VPA 1200 mg	1.5 Hz/none/axial time locked	None	LRZ: no effect	No	No further EEG					Deceased D4	DM, renal failure, amputated legs

AED: antiepileptic drugs, MJ: myoclonic jerks (axial/head–neck–shoulders/limbs/eyes–facial), D: day postinsult, LEV: levetiracetam, PHT: phenytoin, VPA: valproic acid, LRZ: lorazepam, DZP: diazepam, MDZ: midazolam, LCRC: longer care rehabilitation centers, COPD: chronic obstructive pulmonary disease, MI: myocardial infarct, AF: atrial fibrillation, DM: diabetes mellitus. , AED: antiepileptic drugs; COPD: chronic obstructive pulmonary disease; AF: atrial fibrillation; PHT: phenytoin; LEV: levetiracetam; VPA: valproate acid; ICU: intensive care unit; MI: myocardial infarct; LCRC: longer care rehabilitation center; FU: follow-up; LRZ: lorazepam; DM: diabetes mellitus; DZP: diazepam; CNZ: clonazepam; CA: cardiac arrest; NCSE: non convulsive status epilepticus GPD: generalized periodic discharges; SSEP: somatosensory evoked potentials; MDZ: midazolam.

[a] Stopped 15–30 min before EEG recording.

[b] Reduced during EEG recording.

[c] To control hypertension.