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Clinically distinct electroencephalographic phenotypes of early myoclonus after cardiac arrest

Jonathan Elmer, MD, MS[*], **Jon C. Rittenberger, MD, MS**, **John Faro**, **Bradley J. Molyneaux, MD, PhD**, **Alexandra Popescu, MD**[3], **Clifton W. Callaway, MD, PhD**, and **Maria Baldwin, MD for the Pittsburgh Post-Cardiac Arrest Service**

[1]Department of Emergency Medicine, University of Pittsburgh, Pittsburgh PA

[2]Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh PA

[3]Department of Neurology, University of Pittsburgh, Pittsburgh PA

[4]Department of Neurology, Pittsburgh VA Medical Center, Pittsburgh PA

Abstract

Objective—We tested the hypothesis that there are readily classifiable electroencephalographic phenotypes of early post-anoxic multifocal myoclonus (PAMM) that develop after cardiac arrest.

Methods—We studied a cohort of consecutive comatose patients treated after cardiac arrest from January 2012 to February 2015. For patient with clinically evident myoclonus before awakening, two expert physicians reviewed and classified all EEG recordings. Major categories included: Pattern 1: Suppression-burst background with high-amplitude polyspikes in lock-step with myoclonic jerks; Pattern 2: Continuous background with narrow, vertex spike-wave discharges in lock-step with myoclonic jerks. Other patterns were subcortical myoclonus; and, unclassifiable. We compared population characteristics and outcomes across these electroencephalographic subtypes.

Results—Overall, 401 patients were included, of which 69 (16%) had early myoclonus. Among these patients, Pattern 1 was the most common, occurring in 48 patients (74%), whereas Pattern 2 occurred in 8 patients (12%). The remaining patients had subcortical myoclonus (n=2, 3%) or other patterns (n=7, 11%). No patients with Pattern 1, subcortical myoclonus or other patterns survived with favorable outcome (Table 2). By contrast, 4 of 8 patients (50%) with Pattern 2 on EEG survived, and 4 of 4 (100%) of survivors had favorable outcomes despite remaining comatose for 1–2 weeks post-arrest

Interpretation—Early PAMM is common after cardiac arrest. We describe two distinct patterns with distinct prognostic significances. For patients with Pattern 1 EEGs, it may be appropriate to abandon our current clinical standard of aggressive therapy with conventional antiepileptic therapy in favor of early limitation of care or novel neuroprotective strategies.

Corresponding Author: Jonathan Elmer, MD, MS, Iroquois Building, Suite 400A, 3600 Forbes Avenue, Pittsburgh, PA 15213, elmerjp@upmc.edu.

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Introduction

Early post-anoxic multifocal myoclonus (PAMM) after cardiac arrest is common. Previous literature describes distinct clinical syndromes of post-anoxic myoclonus including myoclonic status epilepticus (MSE), subcortical myoclonus and the Lance Adams syndrome. MSE has historically been defined as repeated myoclonic motor manifestations in a comatose patient beginning within 24 hours of anoxic injury and electroencephalographic (EEG) findings of generalized polyspikes, spikes or sharp waves that are time-locked with clinical myoclonus, although the term “status epilepticus” may be a misnomer as PAMM bears little resemblance to myoclonic epilepsy or status epilepticus.[1, 2] Subcortical myoclonus consists of myoclonic motor activity with no associated cortical EEG findings. The Lance Adams syndrome was first described in 1963 and is classically characterized by action myoclonus after awakening from anoxic injury, although modern critical care practices including routine use of sedative and antiepileptic drugs can mask signs of awakening and obscure this classic presentation.[34, 5]

The largest case series reported 40 subjects with PAMM before the modern era of post-arrest management, 83% of whom had a burst-suppressed background with generalized polyspikes and 13% of whom had epilepitiform discharges superimposed on a continuous background.[2] No patients survived, and the authors concluded that PAMM is an “agonal” phenomenon representing irreversibly, diffusely injured cortex and incompatible with meaningful recovery.[2] Subsequent case reports describe patients with PAMM who have survived or and had favorable neurological recoveries.[4, 6–8] It is unclear if post-arrest care has improved over time or if these survivors characterized in the literature as having “MSE” may actually have had early presentations of Lance Adams syndrome with awakening delayed by sedative drugs.

Based on clinical observation, we hypothesized that there are distinct electroencephalographic phenotypes of early post-anoxic myoclonus. We performed a large cohort study examining consecutive post-cardiac arrest patients with post-anoxic myoclonus to test this hypothesis.

Methods

Ethical Approval

All aspects of this study were approved by our Institutional Review Board and conducted with a waiver of informed consent because of minimal risk to subjects.

Patients and Setting

We examined a cohort of consecutive patients treated at a single academic medical center after cardiac arrest from January 2012 to February 2015. We excluded those who were awake in the first 6 hours of return of spontaneous circulation (ROSC); those who did not undergo EEG monitoring; those with arrest due to trauma, exsanguination or primary neurological catastrophe; and those transferred to our facility >48 hours after ROSC. Our Post-Cardiac Arrest Service (PCAS) cares for over 200 survivors of CA annually, representing over 90% of all post-arrest patients at our medical center, and we have

established hospital-wide care protocols including systematic use of targeted temperature management, continuous EEG, aggressive seizure control and best-practice critical care.[9] It is our local standard of care to monitor all comatose post-arrest patients with continuous EEG until awakening, death, or 48–72 hours of monitoring without actionable findings.

EEG acquisition and drug management

Our hospital has in-house EEG technologist coverage 24 hours a day. EEG recordings were started upon ICU arrival, an average of 6–8 hours after ROSC. We applied gold-plated cup electrodes to the scalp in the standard 10–20 International System of Electrode Placement and recorded data using XLTech Natus® Neuroworks digital video/EEG systems (Natus Medical Inc., Pleasanton, CA). Clinical care, including antiepileptic drug and sedation management, was carried out at the discretion of the treating clinician according to standardized treatment protocols. All continuous EEG data were recorded and archived as part of the electronic medical record.

EEG classification, covariates and outcomes

We maintain a prospective quality improvement database of consecutive post-arrest patients that includes clinical characteristics, including the development of any myoclonic movements. For patient with clinically evident PAMM, two expert physicians (an epileptologist and a neurointensivist, both specializing in anoxic brain injury) reviewed and classified all EEG recordings as one of four phenotypes:

- Pattern 1: Suppression-burst background with high-amplitude polyspikes in lock-step with myoclonic jerks (Figure 1);
- Pattern 2: Continuous background with narrow, vertex spike-wave discharges in lock-step with myoclonic jerks (Figures 2 and 3);
- Subcortical myoclonus (no epilepitiform discharges associated with myoclonic jerks); or,
- Other patterns of myoclonic status epilepticus not meeting the above classification system.

We examined all available EEG recordings for patients with myoclonus to describe the evolution of these patterns over time. We used Persyst v12 (Persyst Development Co., Prescott, AZ) to calculate baseline suppression ratio using standard processing engines. Briefly, the software breaks the EEG recording into 10-second epochs and calculates the total duration that epoch is “suppressed” (defined as a ≥0.5 seconds <3uV amplitude). Based on our previous work, we down-sampled these 10-second epoch, lead-by-lead data to calculate median whole brain suppression ratio during the first hour of EEG monitoring.[10]

For all patients, we abstracted standard clinical covariates from our existing database including age, gender, arrest location (in-hospital vs out-of-hospital), arrest rhythm (ventricular tachycardia or fibrillation (VT/VF) versus pulseless electrical activity (PEA) or asystole), use of targeted temperature management, and Pittsburgh Cardiac Arrest Category (PCAC). The PCAC is a validated clinical prediction tool that stratifies CA survivors by risk

of in-hospital death or neurological deterioration based on neurological examination and cardiopulmonary dysfunction in the first 6h after ROSC.[11]

Our primary outcome of interest was survival to hospital discharge, and our secondary outcome was functionally favorable survival, defined as discharge to home or acute rehabilitation.

Statistical methods

We summarized population characteristics using mean and standard deviation or number with corresponding percentages. We performed unadjusted logistic regression to test the association of candidate predictors with outcomes, then built an adjusted model including predictors with significant unadjusted with outcome at a level of $P \leq 0.1$.

Results

A total of 683 patients were treated after cardiac arrest during the study period, of which 135 were excluded for arrest due to trauma, exsanguination, or neurological catastrophe, 128 for awakening within 6 hours of arrest, and 19 for no available EEG data, leaving 401 patients with EEG data available for analysis. Overall, 131 of 401 patients (31%) survived and 70 (17%) were discharged with a functionally favorable outcome (Table 1). Early myoclonus developed in 69 patients (16%), of which 4 had missing EEG records. Among those with myoclonus, 7 patients (10%) survived and 4 (6%) were discharged with functionally favorable survival. Pattern 1 was the most common EEG pattern among those with myoclonus, occurring in 48 patients (74%), whereas Pattern 2 occurred in 8 patients (12%). The remaining EEGs were consistent with subcortical myoclonus (n=2, 3%) or other patterns (n =7, 11%). Of the overall cohort, 101 (25%) had burst suppression with identical bursts (Table 1). Of these, 48 patients had myoclonus and Pattern 1; one patient had myoclonus with polyspike bursts that initially appeared to be Pattern 1 but ultimately evolved into a continuous background with moderate generalized slowing, little variability and no reactivity; and the remaining patients did not have myoclonus. No patient with identical bursts, regardless of the presence or absence of myoclonus, had a favorable outcome.

No patients with Pattern 1, subcortical or other patterns of PAMM survived with functionally favorable outcomes (Table 2). By contrast, 4 of 8 patients (50%) with Pattern 2 on EEG survived, and 4 of 4 (100%) of survivors had functionally favorable outcomes despite remaining comatose for 1–2 weeks post-arrest (Supplemental Table).

Among patients with Pattern 1, we appreciated a particular stereotyped pattern and evolution illustrated in Figure 1. On the initial day of EEG recording (Figure 1a), Pattern 1 was notable for a suppression burst background with bursts consisting of high amplitude polyspike and lock-step with clinically observed myoclonus. On further inspection of the bursts, specific features were appreciated. Burst were invariant in their morphology (“identical bursts”), with an abrupt onset of high amplitude mostly regular fast-frequency polyspikes that typically lasted < 0.5 seconds. These high amplitude polyspikes were followed by a rapid decrescendo in amplitude and replaced with irregular sharp waves and

disorganized theta delta rhythms. Clinical myoclonus was seen only at the high amplitude initiation of the bursts.

Pattern 1 predictably evolved over the subsequent 2–3 days after ROSC and appeared to have 4 distinct stages. The first stage was the initial suppression burst pattern. Over the next 1 to 2 days, the polyspikes “softened” in character with a decrease in amplitude and variably lengthening duration (Figure 1b). Motor manifestations of myoclonus began to dissipate during this time. During this stage, the bursts continued to lengthen and became a uniform mixture of theta and delta rhythms with multifocal sharp waves (Figure 1c). Myoclonus was absent from this point onward. These changes, particularly the abatement of myoclonus, loss of polyspikes and lengthening of bursts, sometimes gave the recording the appearance of a developing background with a decrease in overall suppression. In other clinical contexts these findings might have been interpreted as hopeful sign. However, this background predictably and rapidly lost complexity and amplitude, progressing rapidly through a period of generalized periodic discharges (GPDs) (Figure 1d) to a suppressed recording or grossly attenuated background. This general progression was observed in 45 of 48 (94%) patients with Pattern 1 (Figure 4). In the remaining 3 patients, initial high-amplitude polyspikes evolved into intermittent, abrupt onset fast seizure activity superimposed on a suppressed background without associated myoclonus.

By contrast, Pattern 2 was also characterized by myoclonus in lock-step with epilepitiform discharges in the first hours after ROSC, but also had EEG features that were clearly distinct from Pattern 1. Pattern 2 was characterized by a continuous background with superimposed narrow spikes with a predominance over the parasagittal and midline regions (Figures 2a and 3a). With time, the EEG developed more complex background rhythms of varying frequencies and variability, with little or no periodicity to the discharges (Figures 2b and 3b). The discharges persisted over time, and though initially not easily controlled with antiepileptic drugs (Supplemental Table) in time did become treatment responsive. Among those surviving to hospital discharge, the four patients with Pattern 2 ultimately fulfill diagnostic criteria for Lance Adams syndrome after awakening.

Overall, 7 EEG recordings could not be classified into one of these two categories. Four of these began with innocuous-appearing bursts without high-amplitude polyspikes that evolved into a continuous, low amplitude background with rhythmic delta slowing. Three had broad generalized periodic discharges (GPDs) that were extremely periodic and monotonous, superimposed on an initially continuous background that became attenuated and ultimately isoelectric. None of these patients survived to hospital discharge.

Discussion

Post-anoxic multifocal myoclonus is common after cardiac arrest. Its clinical manifestations are easy to recognize, and for many years have been considered an ominous sign that is invariably associated with a poor prognosis.[1, 2] Diverse EEG patterns occur in patients with PAMM including burst suppression, GPDs, clusters of periodic complexes and irregular bursts. The EEG background has been described to range from suppression to a fully continuous background.[2] Despite multiple reports of favorable recovery after PAMM,[4, 6–8]

few studies offer a nuanced interpretation of specific electrographic subtypes and their prognostic significance. We describe two distinct EEG patterns in patients with PAMM that are consistent with what has previously been defined as MSE yet have very different prognostic significance. Myoclonus associated with what appears in this small cohort to evolve into the Lance Adams syndrome (Pattern 2) may develop early, many days before awakening from coma, yet portends a generally favorable prognosis. This phenotype appears to be rare in the post-anoxic coma cohort. By contrast, patients who develop early polyspike burst suppression with associated myoclonus (Pattern 1) do not survive with present therapy.

In Pattern 1, we observed a distinct burst discharge with a specific stereotyped morphology superimposed on a suppressed background. This pattern could be considered a subtype of the "identical burst pattern" described by Hofmeijer, *et al.*, which was also associated with high mortality.[12] Indeed, within our cohort there were no favorable outcomes in patients who had burst suppression with identical bursts, regardless of the presence or absence of a motor correlate. These identical bursts frequently evolve into GPDs as complexity and amplitude are lost over the first 2–3 days post-arrest (Figure 1C). Although GPDs are often seen in association with epileptic jerks in other patient populations, in this cohort periodic discharges seem to develop only after clinically apparent myoclonus has dissipated.

Many have hypothesized that PAMM is the result of diffuse cortical damage resulting in disinhibition of subcortical generators in the brainstem or thalamus.[13] After cardiac arrest, cerebral energy supply-demand imbalance,[12, 14] selective ischemic failure of excitatory synapses[15] and deafferation of cortical neurons[16] result not only in oscillation between bursts of cerebral activity and suppression but also loss of entropy with development of invariant burst morphology as we observe in Pattern 1.[12] Thus, the combined manifestation of disinhibition of deep brain generators with loss of cortical network functionality resulting in relatively invariant or identical bursts reflects catastrophic cortical damage.[12] The periodicity of bursts may be related to a "fusion" of neuronal processes causing increased excitatory interactions between neurons, or a subcortical or brainstem "pacemaker." Cobb and Celesia proposed the concept of a stimulus or "event" leading to generation of bursts and likened this to an evoked potential generated in the cortex but triggered from extracerebral sensory pathways.[17, 18] This concept of stimulus-induced bursting is intriguing given the observation in many post-arrest patients of stimulus-induced myoclonus.

By contrast, the Lance Adams syndrome is thought to develop after anoxic death of Purkinje cells in the fastigial nucleus of the cerebellum leading to loss of GABAergic tone, disinhibition of the reticular formation and synchronous firing of thalamic cells.[21, 22] Purkinje cells are exquisitely sensitive to anoxic injury, and may be lost despite cortical sparing. Thus, the Lance Adams syndrome may represent selective thalamic disinhibition in the absence of diffuse cortical damage, reflected in the relative normal EEG background these patients develop, with superimposed epilepitiform discharges and myoclonus that do not ultimately interfere with awakening or cognition. Pattern 2, which we propose may be the earliest manifestations of the Lance Adams syndrome, is characterized by a continuous background. This would suggest an intact cortical component of a complex cortical-subcortical network. The presence or development of a continuous background is of prognostic importance in this pattern along with characteristics of the epileptiform

discharges. Development of a continuous EEG background after cardiac arrest is associated with regaining consciousness and favorable neurological outcome.[23–25] The epileptiform discharges in these patients were not complex bursts, but rather single midline or parasagital spikes, implying a different generator than the bursts noted in Pattern 1. Finally, the Pattern 2 patients were clinically more likely to respond to addition of anticonvulsant medication, suggesting a degree of intact neuronal membranes and receptors.

Much work has been done recently to assist in standardizing critical care EEG terminology.[26] A more sophisticated understanding of subtypes of PAMM may help clinicians avoid inaccurate neurological prognostication or inappropriate withdrawal of life-sustaining therapies. It should be noted that no patients with Pattern 1 went on to experience favorable neurological outcomes, but these patients were cared for by clinicians who may have been influenced towards limitations in care based on these EEG findings. This creates the possibility of self-fulfilling prophecies, and we do not advocate withdrawal based solely on the development of PAMM with Pattern 1 morphology. A multi-modal approach is recommended.[27] In contrast, we conclude that development of myoclonus with Pattern 2 indicates that favorable neurological recovery is likely with a comprehensive post-arrest care bundle. If others replicate our finding that patients developing Pattern 1 do not survive with present therapy, particularly if replicated within a care system that does not withdraw life-sustaining therapy, it may be appropriate to abandon our current clinical standard of aggressive therapy with conventional antiepileptic therapy in favor of early limitations of care or novel neuroprotective strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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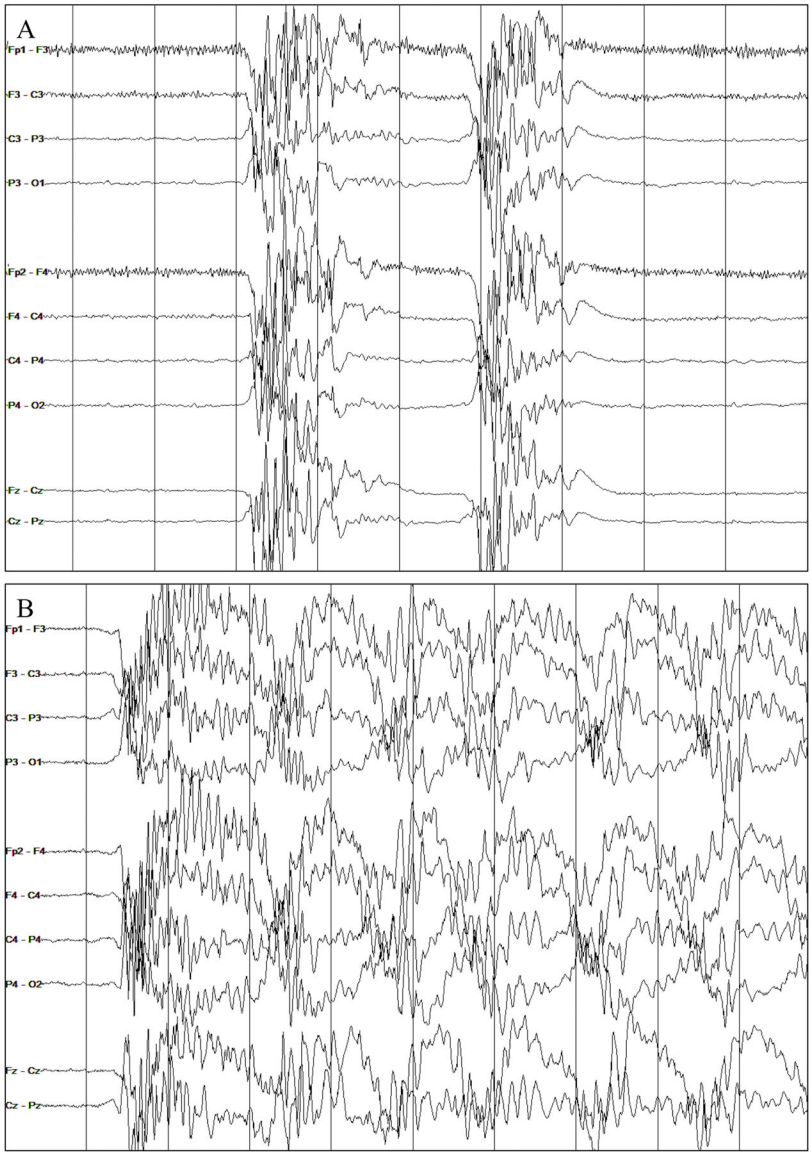

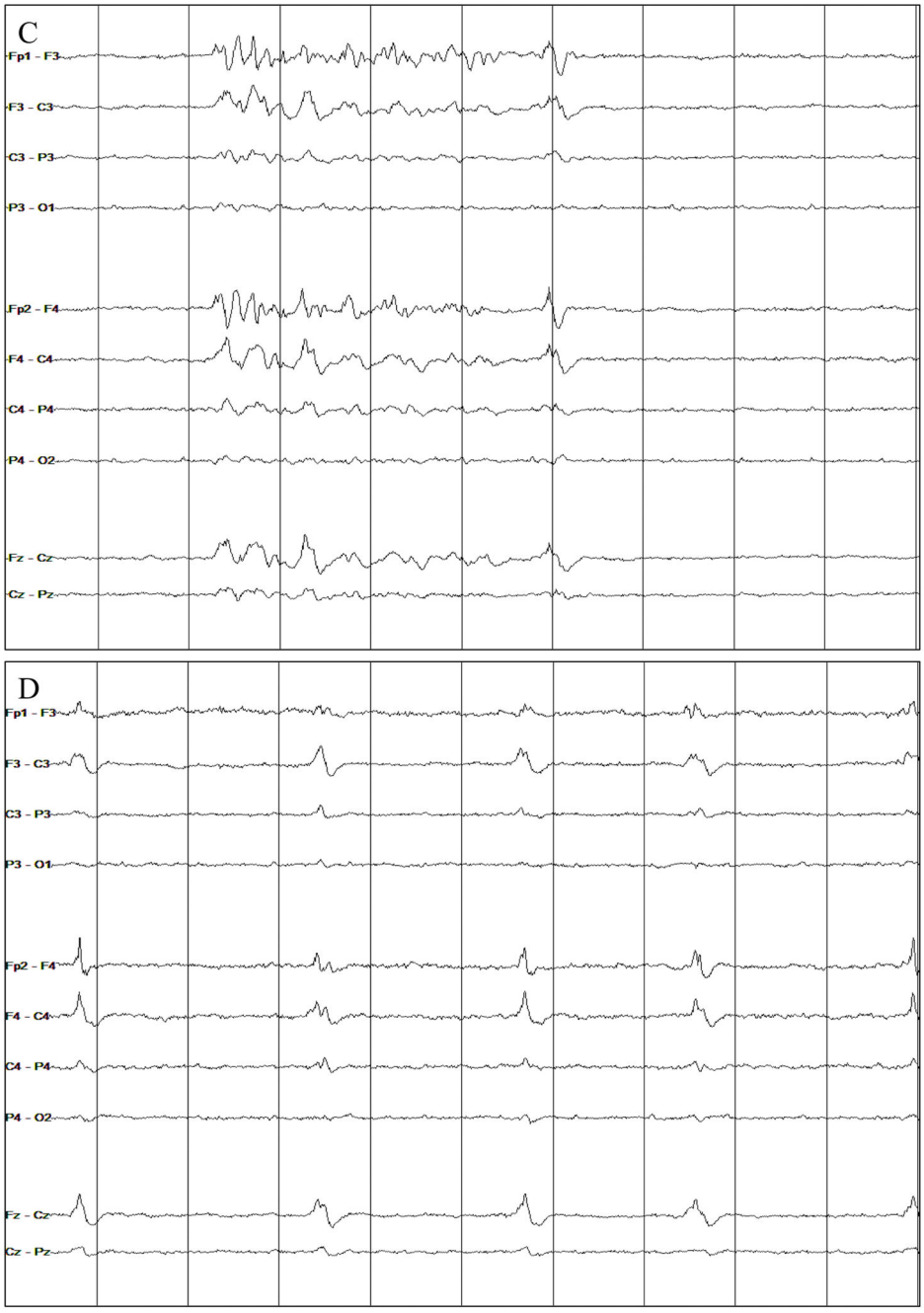

Figure 1.

A) This is the initial recording for Pattern 1 on post-arrest day 0. Note the bursts of high amplitude polyspikes with rapid decrescendo in amplitude. Bursts are superimposed onto a suppressed background. Clinical myoclonus is apparent in lock-step with the initial polyspikes. **B)** Post-arrest-day 1, stage 2 of Pattern 1. Bursts lengthen in duration and high amplitude polyspikes are decreasing in amplitude. Background remains suppressed. **C)** Hospital day 2, Stage 3 of Pattern 1. Bursts are “softening” and have lost the polyspikes and variation in amplitude and variable frequencies, instead becoming more uniform in

frequency and amplitude. Periods of suppression are still appreciated. **D)** Hospital day 3, Stage 4 of Pattern 1. Amplitude and variability rapidly decrease, ultimately progressing to a featureless, attenuated background. (30mm/second, 10uV/mm, bipolar longitudinal montage)

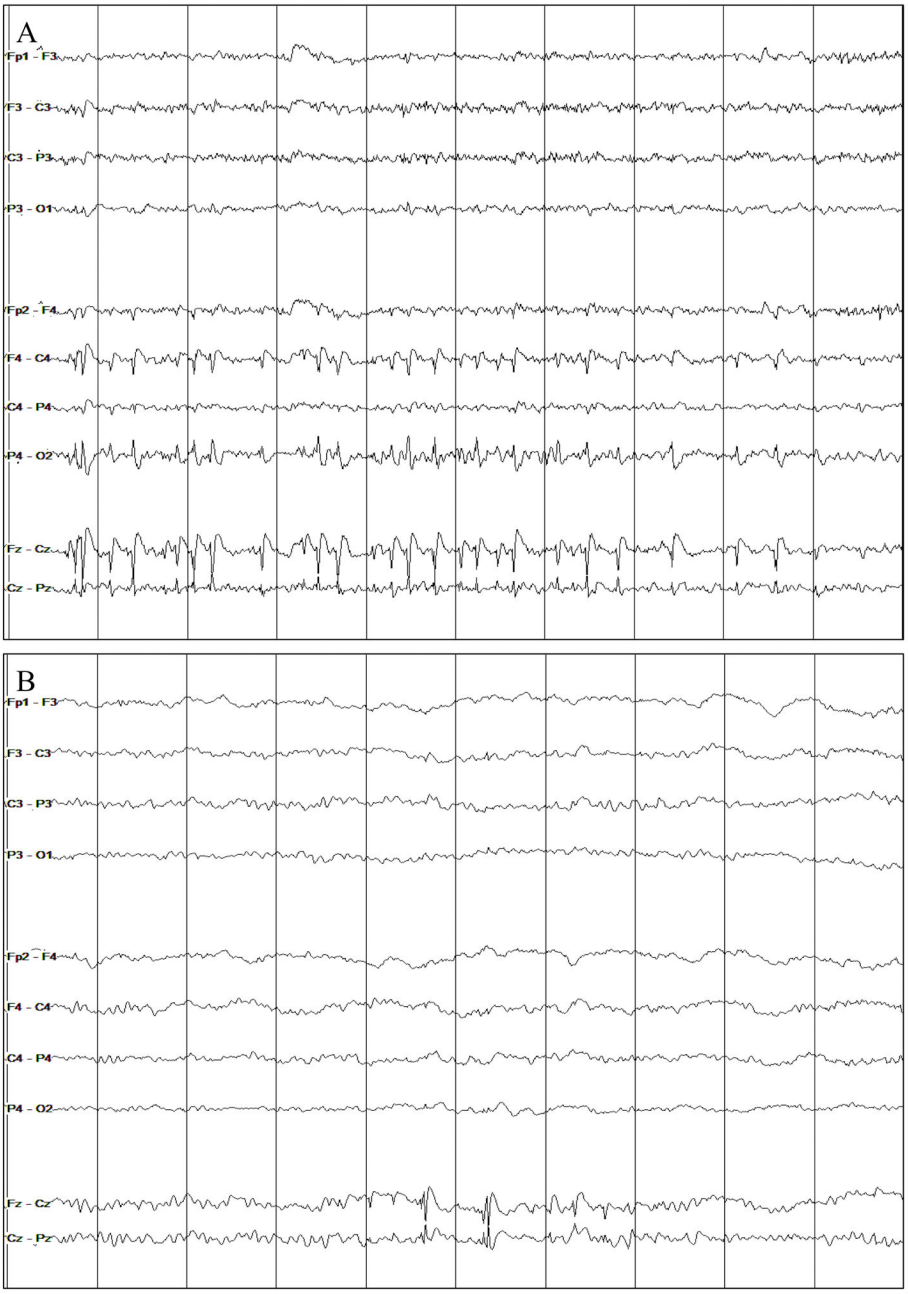

Figure 2.

A) Post-arrest day 0, recording suggestive of Pattern 2 with a continuous background of various frequencies and narrow spikes and polyspikes with midline with a parasagittal predominance. Myoclonus observed with spikes. **B)** Recording taken 1 month after arrest, with persistent parasagittal spike-wave discharges and action myoclonus typical of Lance Adams syndrome. Note improved background rhythms

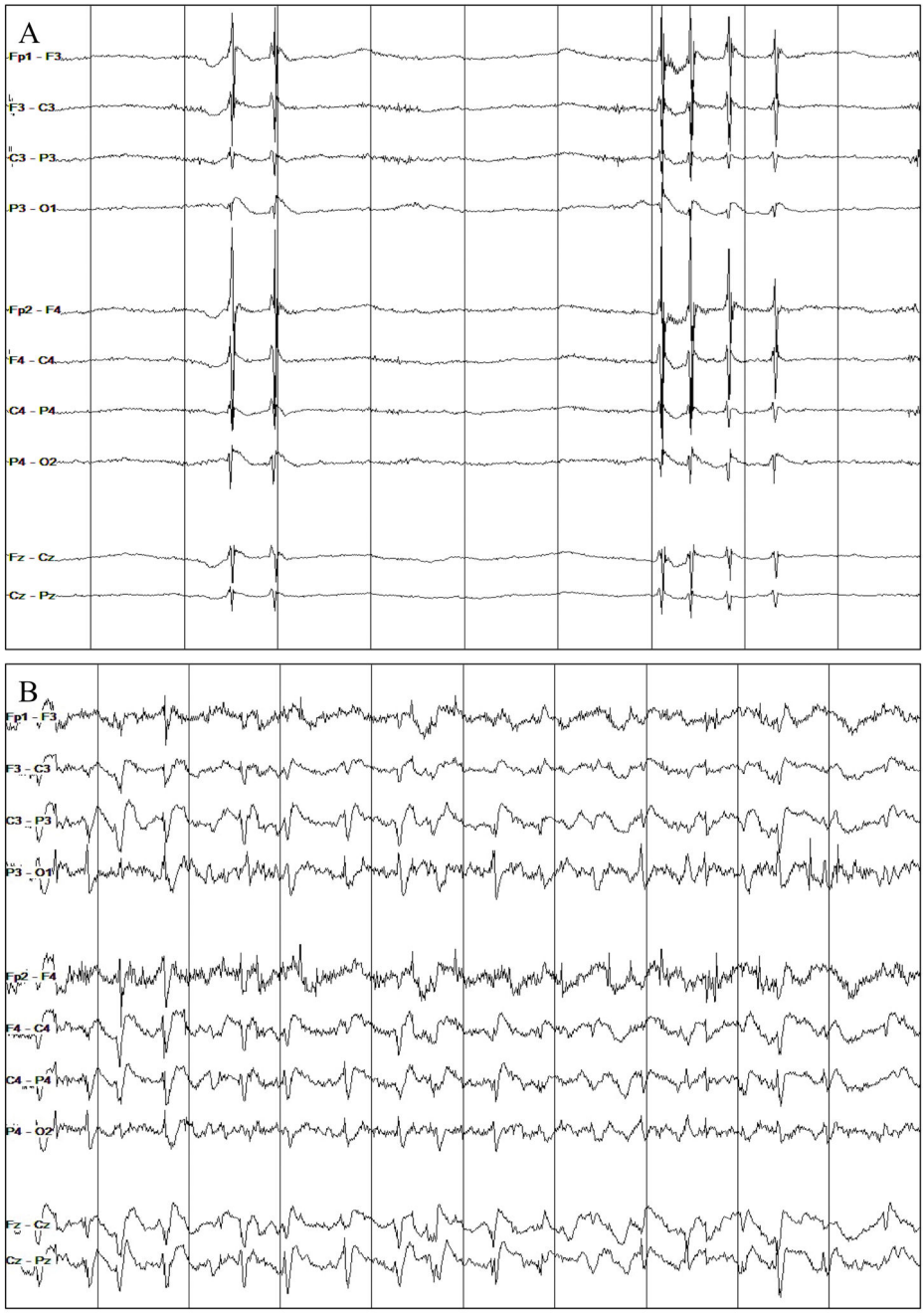

Figure 3.

A) Post-arrest day 0, another example of Pattern 2 with continuous background though of low amplitude with narrow small polyspikes. **B)** Post-arrst day 4, persistent spike-wave discharges with persistent myoclonus indicative of a patient likely to fulfill criteria for Lance Adams syndrome after awakening.

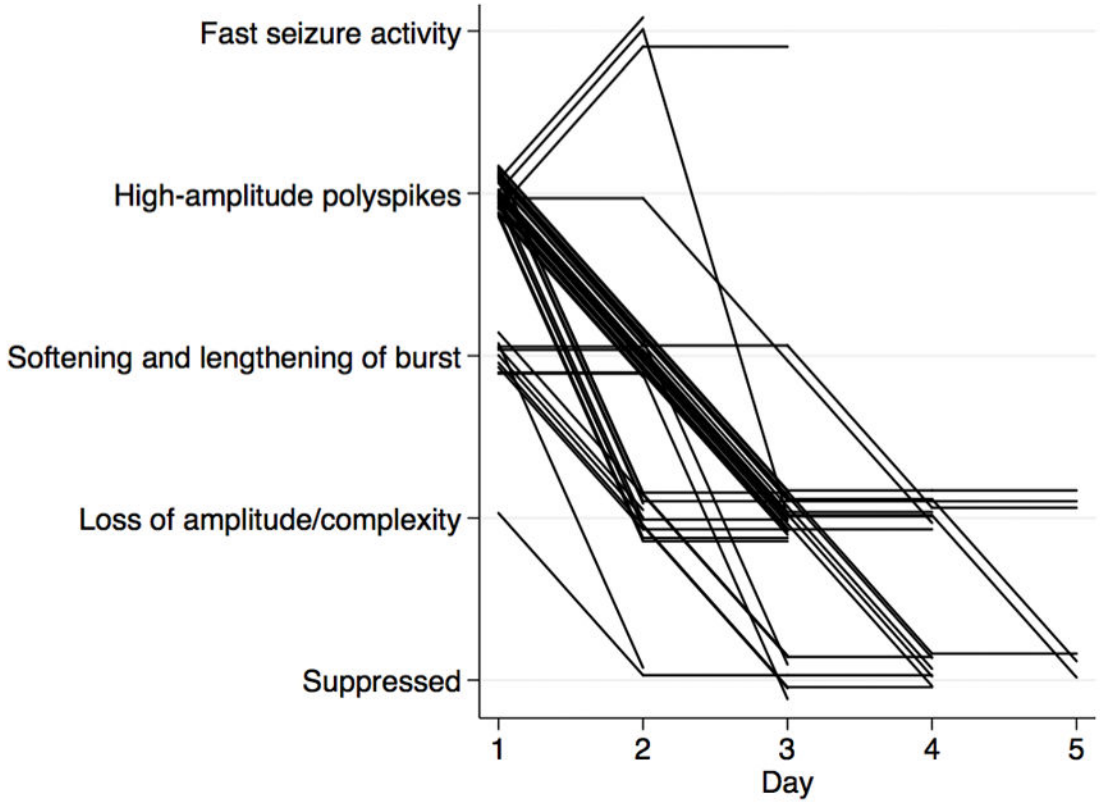

Figure 4.

The progression of patients with PAMM and Pattern 1 on their initial EEG is generally predictable, although a minority of patients do go on to develop fast seizure activity on the second and third day of monitoring.

Table 1

Population characteristics, treatments and outcomes

Characteristic	Overall comatose post-arrest cohort (n = 401)	Clinical myoclonus cohort (n = 69)
Age, years	58 ± 17	56 ± 16
Female	170 (41)	22 (32)
Out-of-hospital arrest	320 (77)	58 (84)
Shockable rhythm	118 (28)	17 (25)
Pittsburgh Cardiac Arrest Category		
2	83 (20)	10 (14)
3	49 (12)	3 (4)
4	224 (53)	47 (68)
Unknown	64 (15)	9 (13)
Survived	131 (31)	7 (10)
Favorable outcome *	70 (53)	4 (57)
Length of stay, days &		
Survivors	17 [12 – 26]	19 [10 – 29]
Non-survivors	4 [2 – 6]	4 [3 – 6]
Initial EEG findings		
Background		
Suppressed	89 (22)	5 (7)
Burst suppressed	140 (35)	52 (84)
Continuous	172 (43)	8 (12)
Superimposed patterns		
Ictal burst morphology		
Identical bursts	101 (25)	49 (71)
Non-identical ictal bursts	7 (2)	2 (3)
Seizures	13 (3)	2 (3)
Periodic discharges (GPDs, LPDs)	16 (4)	2 (3)
Non-periodic sharp waves	33 (8)	8 (12)
Nothing malignant	231 (58)	2 (3)
Antiepileptic drug use		
Propofol	239 (57)	55 (80)
Midazolam	190 (45)	60 (87)
Valproic acid	128 (30)	52 (75)
Levetiracetam	173 (41)	59 (86)
Phenytoin	77 (18)	29 (42)
Lacosamide	16 (4)	7 (10)
Phenobarbital	12 (3)	6 (7)
Total number of agents	2 ± 1	4 ± 1

Data are presented as means ± standard deviation or numbers with corresponding percentages, unless otherwise noted.

* Reported as percentage of survivors

[&] Data presented as median with interquartile ranges

Table 2

Incidence and outcomes of electroencephalographic myoclonus subtypes

	Pattern			
Characteristic	**1**	**2**	**3**	**4**
Description	Malignant PAMM	Possible precursor to Lance Adams	Subcortical	Other
Background	Burst suppressed	Continuous, although may be suppressed early	Variable	Variable
Suppression ratio, median [IQR]	83 [53 – 97]	52 [38 – 82]	91 [89 – 94]	28 [8 – 60]
Discharges	Identical high amplitude polyspike-wave bursts	Vertex spike-wave discharges	None	Variable, often periodic discharges or seizures
Treatment responsive?	No	Yes	N/A	No
Prevalence	48/69 70% (57 – 80%)	8/69 12% (5% – 22%)	2/69 2% (0 – 10%)	7/69 10% (4 – 20%)
Survival *	2/48 3% (0 – 14%)	4/8 50% (16 – 84%)	0/2 0% (0 – 84%)	1/71 4% (0 – 58%)
Favorable outcome *,&	0/2 0% (0 – 8%)	4/4 100% (40 – 100%)	0/0 N/A	0/1 0% (0 – 98%)

* Fisher's exact P <0.001 across levels

& Favorable outcome is expressed as percent of survivors