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EARLY LANCE-ADAMS SYNDROME AFTER CARDIAC ARREST: PREVALENCE, TIME TO RETURN TO AWARENESS , AND OUTCOME IN A LARGE COHORT

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Abstract

INTRODUCTION: Early myoclonus after Cardiac Arrest (CA) is traditionally viewed as a poor prognostic sign (status myoclonus). However, some patients may present early Lance-Adams syndrome (LAS): under appropriate treatment, they can reach a satisfactory functional outcome. Our aim was to describe their profile, focusing on pharmacologic management in the ICU, time to return of awareness, and long-term prognosis.

METHODS: Adults with early LAS (defined as generalized myoclonus within 96 hours, with epileptiform EEG within 48 hours after CA) were retrospectively identified in our CA registry between 2006 and 2016. Functional outcome was assessed through Cerebral Performance Categories (CPC) at three months, CPC 1-2 defined good outcome.

RESULTS: Among 458 consecutive patients, 7 (1.5%) developed early LAS (4 women, median age 59 years). Within 72 hours after CA, in normothemia and off sedation, all showed preserved brainstem reflexes and localized pain. All patients were initially treated with valproate, levetiracetam and clonazepam; additional agents, including propofol and midazolam, were prescribed in the majority. First signs of awareness occurred after 3-23 days (median 11.8); 3/7 reached a good outcome at three months.

CONCLUSION: Early after CA, myoclonus together with a reactive, epileptiform EEG, preserved evoked potentials and brainstem reflexes suggests LAS. This condition was managed with a combination of highly dosed, large spectrum antiepileptic agents including propofol and midazolam. Even if awakening was at times delayed, good outcome occurred in a substantial proportion of patients.

INTRODUCTION:

Nearly one fifth of patients resuscitated from cardiac arrest (CA) may develop myoclonus [1, 2]. However, clinical and electroencephalographic (EEG) differences exist between “status myoclonus”, a condition strongly related to poor prognosis [3], and myoclonus that is amenable to improvement, including awakening with awareness, which may represent early-appearing Lance-Adams syndrome (LAS)[2, 4, 5]. The latter has been defined as generalized action myoclonus appearing within a few days to weeks after CA and coma, mostly (but not exclusively) of hypoxic origin [6]. It is often accompanied by dysmetria, dysarthria and ataxia, with relative preservation of cognition [7]. This syndrome can become chronic, and patients usually need long-term antiepileptic treatment. Specific EEG features in patients with early myoclonus have been recently outlined [4]: suppression-burst background with high-amplitude, diffuse polyspikes correlate with dismal prognosis (“status myoclonus”), whereas continuous background with narrow, midline centered spike-waves correspond to LAS, and a relatively good outcome.

Clinically, it is of paramount importance to recognize early LAS patients in order to offer them a chance of regaining awareness. Our aim was to describe our experience, focusing on pharmacologic management in the ICU, time to awakening, and long-term prognosis.

METHODS:

Patients: From our prospective CA registry including consecutive adults admitted for CA from June 2006 to November 2016, we retrospectively identified subjects with early LAS defined as follows: survivors at discharge, having presented generalized myoclonus within 96 hours after CA (considering the masking effect of acute sedation) together with an epileptiform EEG on a continuous background within 48 hours [4].

Until July 2014, patients were managed at 33° during the first 24 hours, then increasingly at 36°C. Sedation/analgesia during targeted temperature management (TTM) in either approaches consisted of intravenous infusions of midazolam (0.1mg/Kg/h), or 2% propofol (2mg/kg/h), with fentanyl (1.5 µg/kg/h). Rocuronium

boluses were used for shivering prevention [2]. Sedation is routinely weaned within 36 hours after CA. The registry is approved by our Ethic's commission.

Data collection: Following variables were entered prospectively in the registry: demographics, CA type (ventricular fibrillation, versus asystole or pulseless electrical activity), aetiology (cardiac versus respiratory, or unknown), time to return of spontaneous circulation (ROSC), brainstem reflexes (pupillary, oculocephalic, corneal) within 72 hours following CA, serum neuron-specific (NSE), and time of EEG and somatosensory evoked potentials (SSEP) recording. Outcome was assessed at 3 months using a semi-structured phone interview using the Glasgow-Pittsburgh Cerebral Performance Categories (CPC)[8], CPC 1and 2 defining good outcome.

EEG and SSEP were prospectively interpreted by certified clinical neurophysiologists (JN, AOR). For this study, EEG findings were categorized as "reactive" (defined as a reproducible change in amplitude or frequency, excluding stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs) and muscle artifacts) [9] or not, and as "epileptiform" (any repetitive periodic or rhythmic spikes, or sharp waves, or spike-waves) or not [10]. NSE was repetitively analyzed with an automated immunofluorescent assay (Thermo Scientific Brahms NSE Kryptor Immunoassay, Henningsdorf, Germany). For the present analysis we considered peak values within 48 hours after CA.

We retrospectively retrieved antiepileptic drugs (AEDs) used within 10 days following CA, including daily dosages and their trough blood values, if tested; time to first myoclonus occurrence, and to first signs of awareness (interaction with the environment including targeted response on demand, and prolonged eye tracking).

RESULTS

Patient characteristics: Among the 458 CA patients, seven survivors (1.5%) developed early LAS as previously defined.

Median age was 57 years, most common CA etiology was cardiac, while first cardiac rhythms were evenly distributed. Median time to ROSC was 22 minutes. Their clinical characteristics are summarized in **Table 1**.

Neurological and neurophysiological assessments: Within 72 hours after CA, in normothermia and off sedation, all seven patients had preserved brainstem reflexes and localized pain; only two showed spontaneous eye opening (without interaction with the environment). Clinical myoclonus appeared after a median of two days (range 1-3 days). In all subjects, cortical SSEP responses were observed, and EEG recorded without sedation (figure1) showed epileptiform activity occurring together with background reactivity. In three subjects, EEGs were also recorded under TTM and sedation: none showed epileptiform discharges, as these appeared only after sedation weaning. The median serum NSE peak value was 17.1 ng/L.

Antiepileptic treatments and blood levels: Upon observation of an epileptiform EEG, every patient received intravenous valproate (30mg/kg, then 3x600mg/d), levetiracetam (20mg/kg, then 4x500mg/d), and clonazepam (up to 2mg/d) as a first line “cocktail”, according to our protocol. Additional AED were prescribed in most patients (see Table 1). All patients except one received a pharmacologic burst-suppression under continuous EEG for 24-48h with propofol (median dose 2.5mg/kg/h) and midazolam (median dose 0.18mg/kg/h). Total trough serum levels of valproate were below reference ranges in four of six tested subjects, despite high doses. However, albumine median level was 32g/L (reference: 35-52), and one patient received concomitantly meropenem. Regarding other AEDs, levels were within the reference range (levetiracetam and topiramate) or below (phenobarbital and another levetiracetam, see **Table 1** for details).

Outcome: The first signs of awareness appeared in median after 12 days, and in one patient were delayed up to 23 days. For comparison, median time to awakening in the last 30 consecutive patients of the registry was 2 days (1-12). At 3 months, a meaningful cognitive impairment (CPC 3) was found in four patients, while the other three achieved full recovery (CPC 1); all of them were still treated with AEDs. In two patients, reduction/interruption of AEDs several years after CA resulted in a myoclonic status

epilepticus. Of note, no other subject in the registry, regardless of survivorship, had myoclonus and epileptiform EEG after stopping sedation, occurring together with preserved EEG reactivity, brainstem reflexes and SSEP.

DISCUSSION

This series shows that early LAS, occurring in only 1.5% of our cohort, represents a rare diagnosis in patients after a CA. A combination of high dosed, relatively broad spectrum AED was used promptly, but the first signs of awareness were relatively delayed (up to three weeks); almost half of patients had a complete recovery.

In a previous assessment of our group, including 1 patient described here, 24.8% of the cohort developed a postanoxic status epilepticus, 2 of whom had LAS (3.1% of total) [5]; in another recent series, 1.9% developed LAS [4]. While our patients showed myoclonic jerks early following CA, after sedation weaning, awareness recovery occurred much later. LAS can appear a few days to few weeks after injury [6], but also while the patient is still in coma [7], as we observed. Status myoclonus usually starts also early, within the first 24-48 hours following CA [11], but "resists" to sedation during targeted temperature management[1]. As opposed to the present series, previous reports [12, 13] described LAS developing rather in patients with respiratory causes of CA; this suggests that LAS may not be preferentially linked to a specific pathophysiology.

In our cohort, antiepileptic treatment was started immediately after observing an epileptiform EEG, within 48 hours from CA. AEDs used as first line were broad-spectrum antimyoclonic agents given at relatively high doses. Additional treatments (including propofol and midazolam infusions) were necessary in all but one patient in order to control clinical myoclonus and EEG features. Total valproate serum levels were often low due to hypoalbuminemia or concomitant use of meropenem. Some case reports on LAS already mentioned treatment with clonazepam and valproate [7, 14, 15]; as postanoxic myoclonus associated with epileptiform discharges is heterogeneous in terms of clinical outcome [4], treatment escalation seems reasonable in patients with features compatible with favorable prognosis in a multimodal assessment, including EEG, SSEP and NSE[16].

Nevertheless, our series does not support the need of prolonged anesthetic treatment, as every patient showed improved EEGs after a first propofol/midazolam course and subsequently received non-sedative AEDs to allow awakening. Myoclonus recurrence after delayed AEDs withdrawal indicates that these patients should have a regular follow-up.

These observations may allow delineating an entity whose cornerstones are a combination of epileptiform EEG appearing only after sedation weaning, together with preserved background reactivity and cortical SSEP, and recovery of brainstem reflexes. This represents a composite hallmark of possible favorable prognosis. Indeed, even in the presence of myoclonus, this multimodal assessment allows a comprehensive clinical judgment: withdrawal of ICU support should never be based upon isolated signs [16-18]. This consideration seems especially pertinent in the light of delayed awakening to up to three weeks, as previously described [5, 7, 19], even longer than the longest delay reported in a recent large cohort study on CA patients[20].

Limitations of this study are the lack of detailed information on patients showing a similar clinical constellation but not surviving to hospital discharge, as we retrospectively identified the analyzed subjects from survivors; however, no other patients with similar clinical characteristics was identified in the registry. LAS definition for patients' identification was based on a recent study including EEG criteria [4], and is not universally accepted. Finally, we believe our approach of aggressive antiepileptic drug treatment has good face validity. However, our results simply demonstrate that with this strategy many patients can make a good recovery. Still, it remains unknown whether aggressive treatment is superior to expectant management.

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Legends:

Table 1**:** clinical features of 7 patients with early LAS

Abbreviations: M= male; F= female; VF= ventricular fibrillation; PEA= pulseless electrical activity; SR= sinus rhythm; EEG= electroencephalographic; SSEP= somatosensory evoked potentials; NSE= serum neuron specific; VS = vegetative state; VPA= valproate; LEV= levetiracetam; CLZ= clonazepam; TPM= topiramate; PER= perampanel; PB= Phenobarbital, PGB=pregabaline.

Therapeutic range of AEDs serum levels: VPA= 50-100mg/L; LEV= 12-46 mg/L; TPM= 5-20 mg/L; PB= 10-40 mg/L. Albumin levels 35-52 g/L

Figure 1: EEG recorded 2 days after CA under levetiracetam, clonazepam and valproate, showing abundant mid-voltage sharp waves with maximum on parietal and midline regions, superimposed on an irregular theta. Upon pain stimulus, a transitory diffuse acceleration of the background is seen.”

Age, Gender	Cause	First rhyhtm	Time to ROSC(min)	EEG (epileptiform activity) (h)	First EEG reactivity noted	Bilaterally cortical SSEP	Braisntem reflexes (pupils, oculocephalic, corneal)	Myoclonus (d)	NSE peak(ng/mL)	Antiepileptic medication during first 10d	Peak dosage during first 10d (mg/d)	Peak serum trough level (<10d) (mg/L)	Albumine levels (g/L)	Return of awareness (days after CA)	Best CPC 3 mo.
53, M	Cardiac	VF	20	48	Yes (96h)	120h	Present at 72h	2	Not done	A VPA B LEV	A .1500 B. 2000	A. Not measured B. 9.83	35	3 days	1
57, M	Cardiac	PEA	35	48	Yes (33h)	120h	Present	1	25.1 (day 1)	A.VPA B.LEV C.CLZ D.PRO E.PGB	A.1500 B.2500 C.5 D.300mg/h E:150m	A.42	32	19 days	3
62, F	Pulmonary	PEA	8	24	Yes (24h)	24h	Present	3	17.1 (day 1)	A.VPA B.LEV C.TPM D.CLZ E.Piracetam	A.3600 B. 4000 C.225 D.1 E.14.4	A.47	32	12 days	3
83, F	Cardiac	VF	25	40	Yes (64h)	72h	Present	3	24.5 (day 2)	A.VPA B.LEV C.CLZ	A.1500 B.1500 C.1	A.62	27	11 days	3
43, F	Cardiac	VF	26	32	Yes (32h)	48h	Pupils present, not corneal	2	15.2 (day 2)	A.LEV B VPA C.TPM D.PER	A.2000 B.1500 C.300 D.6	A.18.7 B.62 C.5.1	26	12 days	1
64, F	Not known	SR	Not known	30	Yes (30h)	32h	Present	2	14.5 (day1)	A.VPA B.LEV C.PB D.TPM	A.1500 B.2000 C.200 D.300	A.39 C.6.2	34	23 days	3
53, M	Cardiac	PEA	22	28	Yes (28h)	30h	Present	2	20.1 (day 2)	A.VPA B.LEV C.TPM	A.2500 B.3000 C.250	A.85	36	3 days	1

Table 1: clinical features of 7 patients with early LAS

Abbreviations: M= male; F= female; VF= ventricular fibrillation; PEA= pulseless electrical activity; SR= sinus rhythm; EEG= electroencephalographic; SSEP= somatosensory evoked potentials; NSE= serum neuron specific; VS = vegetative state; VPA= valproate; LEV= levetiracetam; CLZ= clonazepam; TPM= topiramate; PER= perampanel; PB= Phenobarbital, PGB=pregabaline.

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