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

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29 Abstract

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

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

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

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

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56 **INTRODUCTION:**

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

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

75

76 **METHODS:**

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

82 Until July 2014, patients were managed at 33° during the first 24 hours, then
83 increasingly at 36°C. Sedation/analgesia during targeted temperature management
84 (TTM) in either approaches consisted of intravenous infusions of midazolam
85 (0.1mg/Kg/h), or 2% propofol (2mg/kg/h), with fentanyl (1.5 µg/kg/h). Rocuronium

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

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

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

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

108

109 **RESULTS**

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

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

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

124 **Antiepileptic treatments and blood levels:** Upon observation of an epileptiform EEG,
125 every patient received intravenous valproate (30mg/kg, then 3x600mg/d), levetiracetam
126 (20mg/kg, then 4x500mg/d), and clonazepam (up to 2mg/d) as a first line “cocktail”,
127 according to our protocol. Additional AED were prescribed in most patients (see Table
128 1). All patients except one received a pharmacologic burst-suppression under
129 continuous EEG for 24-48h with propofol (median dose 2.5mg/kg/h) and midazolam
130 (median dose 0.18mg/kg/h). Total trough serum levels of valproate were below
131 reference ranges in four of six tested subjects, despite high doses. However, albumine
132 median level was 32g/L (reference: 35-52), and one patient received concomitantly
133 meropenem. Regarding other AEDs, levels were within the reference range
134 (levetiracetam and topiramate) or below (phenobarbital and another levetiracetam, see
135 **Table 1** for details).

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

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

145

146 **DISCUSSION**

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

151 In a previous assessment of our group, including 1 patient described here, 24.8% of the
152 cohort developed a postanoxic status epilepticus, 2 of whom had LAS (3.1% of total) ⁵;
153 in another recent series, 1.9% developed LAS ⁴. While our patients showed myoclonic
154 jerks early following CA, after sedation weaning, awareness recovery occurred much
155 later. LAS can appear a few days to few weeks after injury ⁶, but also while the patient is
156 still in coma ⁷, as we observed. Status myoclonus usually starts also early, within the
157 first 24-48 hours following CA ¹¹, but “resists” to sedation during targeted temperature
158 management¹. As opposed to the present series, previous reports ^{12, 13} described LAS
159 developing rather in patients with respiratory causes of CA; this suggests that LAS may
160 not be preferentially linked to a specific pathophysiology.

161 In our cohort, antiepileptic treatment was started immediately after observing an
162 epileptiform EEG, within 48 hours from CA. AEDs used as first line were broad-spectrum
163 antimyoclonic agents given at relatively high doses. Additional treatments (including
164 propofol and midazolam infusions) were necessary in all but one patient in order to
165 control clinical myoclonus and EEG features. Total valproate serum levels were often
166 low due to hypoalbuminemia or concomitant use of meropenem. Some case reports on
167 LAS already mentioned treatment with clonazepam and valproate ^{7, 14, 15}; as postanoxic
168 myoclonus associated with epileptiform discharges is heterogeneous in terms of clinical
169 outcome ⁴, treatment escalation seems reasonable in patients with features compatible
170 with favorable prognosis in a multimodal assessment, including EEG, SSEP and NSE¹⁶.

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

176 These observations may allow delineating an entity whose cornerstones are a
177 combination of epileptiform EEG appearing only after sedation weaning, together with
178 preserved background reactivity and cortical SSEP, and recovery of brainstem reflexes.
179 This represents a composite hallmark of possible favorable prognosis. Indeed, even in
180 the presence of myoclonus, this multimodal assessment allows a comprehensive clinical
181 judgment: withdrawal of ICU support should never be based upon isolated signs ¹⁶⁻¹⁸.
182 This consideration seems especially pertinent in the light of delayed awakening to up to
183 three weeks, as previously described ^{5, 7, 19}, even longer than the longest delay reported
184 in a recent large cohort study on CA patients²⁰.

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

194 **References**

- 195 [1] Oddo M, Rossetti AO. Early multimodal outcome prediction after cardiac arrest in patients treated
196 with hypothermia. *Critical care medicine*. 2014;42:1340-7.
- 197 [2] Seder DB, Sunde K, Rubertsson S, et al. Neurologic outcomes and postresuscitation care of patients
198 with myoclonus following cardiac arrest. *Crit Care Med*. 2015;43:965-72.
- 199 [3] Krumholz A, Stern BJ, Weiss HD. Outcome from coma after cardiopulmonary resuscitation: relation to
200 seizures and myoclonus. *Neurology*. 1988;38:401-5.
- 201 [4] Elmer J, Rittenberger JC, Faro J, et al. Clinically distinct electroencephalographic phenotypes of early
202 myoclonus after cardiac arrest. *Ann Neurol*. 2016;80:175-84.
- 203 [5] Rossetti AO, Oddo M, Liaudet L, Kaplan PW. Predictors of awakening from postanoxic status
204 epilepticus after therapeutic hypothermia. *Neurology*. 2009;72:744-9.
- 205 [6] Lance JW, Adams RD. The syndrome of intention or action myoclonus as a sequel to hypoxic
206 encephalopathy. *Brain : a journal of neurology*. 1963;86:111-36.
- 207 [7] Accardo J, De Lisi D, Lazzerini P, Primavera A. Good functional outcome after prolonged postanoxic
208 comatose myoclonic status epilepticus in a patient who had undergone bone marrow transplantation.
209 *Case reports in neurological medicine*. 2013;2013:872127.
- 210 [8] Booth CM, Boone RH, Tomlinson G, Detsky AS. Is this patient dead, vegetative, or severely
211 neurologically impaired? Assessing outcome for comatose survivors of cardiac arrest. *Jama*.
212 2004;291:870-9.
- 213 [9] Tsetsou S, Novy J, Oddo M, Rossetti AO. EEG reactivity to pain in comatose patients: Importance of
214 the stimulus type. *Resuscitation*. 2015;97:34-7.
- 215 [10] Rossetti AO, Carrera E, Oddo M. Early EEG correlates of neuronal injury after brain anoxia.
216 *Neurology*. 2012;78:796-802.
- 217 [11] Lucas JM, Cocchi MN, Saliccioli J, et al. Neurologic recovery after therapeutic hypothermia in
218 patients with post-cardiac arrest myoclonus. *Resuscitation*. 2012;83:265-9.
- 219 [12] English WA, Giffin NJ, Nolan JP. Myoclonus after cardiac arrest: pitfalls in diagnosis and prognosis.
220 *Anaesthesia*. 2009;64:908-11.
- 221 [13] Frucht S, Fahn S. The clinical spectrum of posthypoxic myoclonus. *Movement disorders : official
222 journal of the Movement Disorder Society*. 2000;15 Suppl 1:2-7.
- 223 [14] Malhotra S, Mohinder K. Lance-Adams syndrome: Difficulties surrounding diagnosis,
224 prognostication, and treatment after cardiac arrest. *Anesthesia, essays and researches*. 2012;6:218-22.
- 225 [15] Rajamani A, Seppelt I, Bourne J. Difficulties with neurological prognostication in a young woman
226 with delayed-onset generalised status myoclonus after cardiac arrest due to acute severe asthma. *Indian
227 J Crit Care Med*. 2011;15:137-9.
- 228 [16] Rossetti AO, Rabinstein AA, Oddo M. Neurological prognostication of outcome in patients in coma
229 after cardiac arrest. *Lancet Neurol*. 2016;15:597-609.
- 230 [17] Nolan JP, Soar J, Cariou A, et al. European Resuscitation Council and European Society of Intensive
231 Care Medicine 2015 guidelines for post-resuscitation care. *Intensive Care Med*. 2015;41:2039-56.
- 232 [18] Horn J, Cronberg T, Taccone FS. Prognostication after cardiac arrest. *Current opinion in critical care*.
233 2014;20:280-6.
- 234 [19] Paul M, Bougouin W, Geri G, et al. Delayed awakening after cardiac arrest: prevalence and risk
235 factors in the Parisian registry. *Intensive Care Med*. 2016;42:1128-36.
- 236 [20] Westhall E, Rundgren M, Lilja G, Friberg H, Cronberg T. Postanoxic status epilepticus can be
237 identified and treatment guided successfully by continuous electroencephalography. *Ther Hypothermia
238 Temp Manag*. 2013;3:84-7.

241 **Legends:**

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

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

248 Therapeutic range of AEDs serum levels: VPA= 50-100mg/L; LEV= 12-46 mg/L; TPM=
249 5-20 mg/L; PB= 10-40 mg/L. Albumin levels 35-52 g/L

250

251

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

256

257

Age, Gender	Cause	First rhythm	Time to ROSC(min)	EEG (epileptiform activity) (h)	First EEG reactivity noted	Bilaterally cortical SSEP	Braintem 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=pregabalin.

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.