Diagnostic and Prognostic Contribution of Cerebrospinal Fluid Analysis After Cardiac Arrest

Marine Paul (mpaul@ch-versailles.fr)
ICU Hopital Andre Mignot  https://orcid.org/0000-0002-0717-9555

sarah Benghanem
Hopital Cochin

sybille Merceron
Centre Hospitalier de Versailles

hugo bellut
Centre Hospitalier de Versailles

anne roche
Centre Hospitalier de Versailles

Mikhael Giabicani
Centre Hospitalier de Versailles

florence dumas
Hopital Cochin

amandine henry
Centre Hospitalier de Versailles

paul jaubert
Hopital Cochin

fabrice bruneel
Centre Hospitalier de Versailles

jean pierre bedos
Centre Hospitalier de Versailles

alain cariou
Hopital Cochin

stephane legriel
Centre Hospitalier de Versailles

Research

Keywords: cardiac arrest, lumbar puncture, cerebrospinal fluid, etiological diagnosis, prognosis

DOI: https://doi.org/10.21203/rs.3.rs-52762/v1
Abstract

Background: Lumbar puncture is among the investigations used to determine the aetiology and prognosis of cardiac arrest, despite a dearth of data on its performance. We aimed to assess the diagnostic and prognostic performance of lumbar puncture after cardiac arrest.

Methods: We retrospectively studied data from prospectively established databases of consecutive patients who were admitted to two French ICUs in 2007-2016 with sustained return of spontaneous circulation (ROSC) after cardiac arrest and who underwent lumbar puncture as an aetiological investigation.

Results: Of 1984 patients with sustained ROSC, 65 (3.3%) underwent lumbar puncture and were included. Lumbar puncture identified a neurological cause of cardiac arrest in 6/65 (9%) patients, including 5 with neurologic prodromal symptoms before cardiac arrest and 4 with the lumbar puncture done post-mortem. Lumbar puncture performed before death showed nonspecific cerebrospinal fluid abnormalities in 37/53 (69.8%) patients. By univariate analysis, factors significantly associated with cerebrospinal fluid abnormalities were shorter no-flow time (0 min [0-3] versus 4 min [2-10], \( p=0.004 \)) and post-resuscitation shock (26 [70%] versus 5 [31%], \( p<0.01 \)). Presence of cerebrospinal fluid abnormalities was non significantly associated with poorer outcomes (CPC 3-4-5) (\( p=0.06 \)).

Conclusions: Lumbar puncture, although rarely performed, can contribute to the aetiological diagnosis of cardiac arrest. As a second-line investigation, it identified the cause in 9% of our patients. Nonspecific cerebrospinal fluid abnormalities are common after cardiac arrest, perhaps due to blood-brain barrier disruption, and may carry prognostic significance.

Background

Cardiac arrest (CA) is among the most common causes of death in Europe and the United States despite advances in resuscitation and intensive care [1]. During the early phase after the return of spontaneous circulation (ROSC), identifying the cause is crucial to allow specific treatments that may improve patient outcomes and to lower the risk of recurrent CA. Recent guidelines recommend considering coronary angiography and cerebral and/or chest computed tomography (CT), depending on the CA circumstances and the electrocardiographic findings after ROSC, [2]. Unfortunately, even when these guidelines are applied, over 40% of patients receive no definitive aetiologic diagnosis and may therefore be at higher risk for delayed or inappropriate treatments and for poorer outcomes [3].

According to recent data, neurological causes explain 7% of CA cases [4]. CT of the brain should be the first-line investigation when a neurological cause is suspected. However, analysis of cerebrospinal fluid (CSF) obtained by lumbar puncture may be useful also. Surprisingly, whereas several studies have assessed the usefulness of various CSF biomarkers for neuroprognostication [5,6], the possible contribution of CSF analysis to the aetiological diagnosis has not been investigated. Apart from a neurological cause, another source of potential CSF abnormalities is blood-brain barrier (BBB) disruption.
due to CA [7]. Better knowledge of such abnormalities would help to interpret CSF findings after CA and might also assist in establishing the prognosis [5,8].

We therefore designed a retrospective study of prospectively established databases to evaluate the diagnostic and prognostic contribution of CSF findings in patients admitted to the ICU with ROSC after CA.

Methods

We used two prospectively collected databases established at the Cochin hospital and Versailles hospital (#NCT03594318), two reference CA centres serving the southern and southwest areas of the Paris metropolis (France), respectively. Data collection was approved by the ethics committee of the French Intensive Care Society (#CESRLF_12-384 and 20-41) and the data were collected in compliance with French data protection legislation (French Data Protection Authority #MR004_2209691).

Study setting and early patient management

In France, when the emergency services receive a call reporting a suspected case of OHCA, the fire department and mobile emergency unit system despatch a team to the scene. The staff in each mobile emergency unit includes at least one physician trained in emergency medicine in compliance with international guidelines [9], who performs resuscitation. Patients with in-hospital CA are initially managed by the nurses and/or bedside physician until the arrival of an emergency physician, intensivist, or anaesthesiologist, who performs resuscitation. Patients with a stable return of spontaneous circulation (ROSC) are then admitted to the intensive care unit (ICU).

Post-resuscitation diagnostic evaluation

As recommended in current guidelines [2], a standardized diagnostic workup is started immediately to allow the prompt identification and treatment of the cause of CA. In patients with clinical and/or electrocardiographic evidence of myocardial ischemia and in those with no obvious non-cardiac cause of CA, coronary angiography is performed at hospital arrival, before ICU admission. If prodromal symptoms or the clinical findings suggest a respiratory or neurological cause of CA, CT of the chest or brain, respectively, may be chosen as the best first-line investigation. When the first-line investigation fails to detect a cause, further tests are considered [10]. Additionally, after ICU admission, laboratory tests are performed routinely to look for metabolic abnormalities or toxic substances according to the clinical history. A lumbar puncture for CSF collection is performed in patients with meningeal syndrome and when deemed appropriate by the physician in charge. All these investigations were available in both participating centres 24 h a day and 7 days a week. No post-mortem examination was performed.

Study population

All eligible patients entered into the Cochin and Versailles CA databases between January 2007 and December 2016 were included if they were older than 18 years, had stable ROSC at hospital admission,
and underwent lumbar puncture as part of the aetiological CA work-up. We did not include patients who underwent lumbar puncture for other reasons or who had a traumatic lumbar puncture defined as a CSF white cell count/red cell count <1/1000.

**Study objectives**

The primary objective was to assess the potential contribution of CSF analysis to the aetiological evaluation of CA. The secondary objectives were to identify factors associated with CSF abnormalities (defined as protein >0.45 g/L and/or white cell count >5/mm³) and factors associated with survival and functional outcome at ICU discharge in those patients whose CSF analysis did not contribute to the aetiological diagnosis [11].

**Data collection**

Demographic data and data related to the CA were collected prospectively in the two electronic databases according to the Utstein style[12]. These data included age and sex, location at CA occurrence and initial rhythm, no-flow and low-flow times, presence of a witness, bystander CPR, number of defibrillations, and epinephrine use. We also recorded comorbidities, initial ECG ST-segment elevation, coronary angiography and/or CT findings, and definitive cause of CA. The following were collected in the ICU: use of targeted temperature management, presence of post-resuscitation shock, post-anoxic status epilepticus, and/or awakening defined as a response to commands with a motor Glasgow Coma Scale score of 6.

To further investigate the value of CSF analysis after CA, we used standardized forms to retrospectively collect the following from the pre-hospital and ICU records: symptoms preceding CA (e.g., headache, focal signs, confusion, coma, and seizures), CSF characteristics (biochemistry, cytology, and culture results), time to CSF collection, blood sample findings on the day of CSF collection, and CSF/serum protein quotient.

The functional outcome was assessed using the Cerebral Performance Category (CPC) at ICU discharge, and causes of death were recorded [13–15]. We defined a favourable outcome as a CPC score of 1 or 2 at ICU discharge.

**Statistical analysis**

Quantitative parameters were described as median (interquartile range [IQR]) and qualitative parameters as number (percentage). We compared categorical variables using Fisher's exact test and continuous variables using the Wilcoxon rank-sum test.

We first tested univariate associations between CA characteristics and whether CSF analysis contributed to the aetiological diagnosis of CA. We then looked for associations linking CA features to specific CSF abnormalities and to survival and functional outcome at ICU discharge.
All tests were two-sided and $p$ values <0.05 were considered significant. Analyses were performed using R statistical software version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org. accessed September 12, 2019).

**Results**

Figure 1 is the patient flow chart. Of the 1984 patients admitted with stable ROSC after CA, 65 (3.3%) had a lumbar puncture and were included in the study.

**Characteristics and diagnostic workup**

Table 1 and Table S1 report the patient characteristics and the diagnostic investigations performed to identify the cause of CA. Figure 2 shows the first-line, second-line, and third-line investigations. Overall, cerebral CT was done in 52 (80%) patients, cerebral MRI in 5 (8%) patients, coronary angiography in 31 (48%) patients, and chest CT in 33 (51%) patients. The cause of CA was identified in 52 (80%) of the 65 patients and was respiratory in 18 (27%) patients, neurologic in 16 (25%) patients, cardiac in 7 (11%) patients, metabolic in 7 (11%) patients, and septic in 4 (6%) patients.

**Contribution of cerebrospinal fluid analysis to the aetiologic diagnosis**

LP were assessed in cases of suspicion of a neurological cause for cardiac arrest in 69% of cases. CSF analysis identified a neurological cause of CA in 6/65 (9%) patients, including 3 with subarachnoid haemorrhage, 2 with non-specific encephalitis, and 1 with bacterial meningitis. In 4 of these 6 patients, the lumbar puncture was performed post-mortem.

Table 1 reports the results of the univariate analysis of factors associated with the CSF analysis contributing to the aetiological diagnosis of CA. In the patients with a contributory CSF analysis, lumbar puncture was mostly the second-line investigation, with a median time of 1.5 days (IQR, 1-2) after ICU admission. Neurologic prodromal symptoms before CA were more common in the patients whose CSF analysis was contributory compared to the other patients (83% vs. 68%), although the difference was not significant ($p=0.66$).

**Patients with nonspecific cerebrospinal fluid abnormalities**

We excluded the 6 patients whose CSF analysis was contributory (including 4 with post-mortem lumbar puncture) and the additional 6 patients with post-mortem lumbar puncture. Of the remaining 53 patients, 37 (70%) had abnormal CSF findings, which are reported in Table 2. Table 3 compares the patients with versus without nonspecific CSF abnormalities. Two factors were significantly associated with having nonspecific CSF abnormalities, namely, shorter no-flow time (0 min [0-3] versus 4 min [2-10], $p=0.004$) and having post-resuscitation shock (26 [70%] versus 5 [31%], $p<0.01$). All 5 patients with oedema by cerebral CT had CSF abnormalities.

**Patient outcomes**
Overall ICU mortality was 70% (46/65). Table 1 shows the causes of death. All 6 patients whose CSF analysis contributed to the aetiological diagnosis died. Nonspecific CSF abnormalities were more common in patients with poor outcomes defined as CPC 3, 4, or 5 (73% versus 27% of those with CPC 1 or 2), although the difference was not statistically significant ($p=0.06$). Table S2 reports the CSF features in patients with favourable versus unfavourable outcomes. The only factor significantly associated with outcome was the CSF/serum protein quotient ($p=0.017$), with higher values in patients with worse outcomes.

**Discussion**

To our knowledge, this study provides the first detailed information on the diagnostic and prognostic contribution of CSF analysis to the aetiological diagnosis of CA. Only 3.3% of all patients admitted to the ICU with stable ROSC after CA underwent CSF analysis, which contributed to the aetiological diagnosis in 6 (9.2%) patients, although in 4 this contribution was obtained only post-mortem. Of the patients alive at the time of lumbar puncture, many (69.8%) had nonspecific CSF abnormalities, among which the CSF/serum protein quotient was significantly associated with the outcome.

Our study design provides a pragmatic view of the contribution of CSF analysis to the aetiological diagnosis of CA in patients with sustained ROSC at hospital admission. Lumbar puncture was performed only very rarely in our study. Few previously published data are available with which to compare our results. Most studies of CSF analysis after CA focused on the neuroprognostication accuracy of CSF biomarkers reflecting neuronal damage [5,6,8]. We are not aware of previous studies investigating CSF analysis for the aetiological diagnosis or the presence of CSF abnormalities unrelated to the aetiology. In previous studies, CSF analysis was performed in 5.3% of patients with neurological causes of CA and stable ROSC at hospital admission, chiefly as part of the aetiological workup [4], and in 40% of patients with CA complicating convulsive status epilepticus [4,16].

Given, the low incidence of noncardiac causes of CA, recent guidelines focus on the indications of coronary angiography, cerebral CT, and chest CT. Important factors are the patient's medical history; the presence of cardiac, respiratory, or neurologic prodromal symptoms, the circumstances of CA onset, and the physical findings on the scene. In practice, lumbar puncture is not a first-line investigation, unless there is evidence of a neurological cause whose identification may be helped by CSF analysis. Obstacles to lumbar puncture include anticoagulant and/or antiplatelet treatments, and concern about inducing cerebral herniation. Thus, cerebral CT may be required before lumbar puncture is performed. As expected, lumbar puncture was mainly performed as a second- or third-line investigation in our study, predominantly in patients with neurological prodromal symptoms before CA. Interestingly, 10 (15%) lumbar punctures were post-mortem and contributed to the diagnosis in 4 patients. This finding suggests that the situations in which CSF analysis may be helpful may not be recognised sufficiently early. Work is clearly needed to determine the indications of lumbar puncture after CA. An optimal aetiological workup is crucial to determine when specific aetiological treatments are appropriate, thus improving patient outcomes. In previous studies, ICU survival was higher when the aetiology was identified [3,17]. In
addition, identifying the cause may allow measures to minimise the risk of recurrent CA. Finally, knowledge of the causes of CA is important from a public health perspective. Lumbar puncture identified the cause of CA in 9% of our patients, although this proportion dropped to 3% when only patients alive at the time of lumbar puncture were considered.

Over two-thirds of our patients without neurological causes of CA had nonspecific CSF abnormalities, of which the most common was an increase in protein (73%), followed by an increase in white cells (27%). Several hypotheses can be raised to explain these findings. First, we retrospectively identified neurological prodromal symptoms in 28 of the 59 patients whose CSF analysis did not contribute to the aetiological diagnosis, and many of these patients did not undergo a comprehensive neurological workup. For instance, cerebral MRI was performed in only 5 of these patients. Moreover, new tools for diagnosing auto-immune and/or infectious encephalitis were not available during the study recruitment period [18,19]. Thus, some of the patients whose CSF abnormalities were considered nonspecific may have had undiagnosed neurological conditions. Another hypothesis is that BBB disruption after CA may result in CSF abnormalities. In healthy individuals, most of the proteins found in the CSF are derived from the serum, although some are synthesized by the choroid plexus or within the brain. The passage of serum protein into the CSF varies with the condition of the BBB [20,21]. Normal BBB permeability is defined as a CSF/serum albumin quotient <0.007 [22,23]. BBB disruption may allow the passage of greater amounts of protein from the serum to the CSF. CSF findings may be difficult to interpret in patients with brain injury, as reported in a study of status epilepticus [24].

We identified post-resuscitation shock as factor associated with having nonspecific CSF abnormalities. The systemic inflammation seen in post-resuscitation shock may cause BBB alterations, as described in acute sepsis and cirrhosis, [25,26]. Moreover, patients presenting with confusion to coma before CA and who demonstrated oedema on cerebral CT Scan were more likely to have nonspecific CSF abnormalities. In the setting of primary brain injury, brain inflammation could cause BBB alteration as described in stroke and status epilepticus [24,27,28].

CSF changes may also occur in response to anoxic neuronal damage. Thus, elevated levels of pro-inflammatory cytokines in CSF have been reported after CA [29,30]. HMGB1 (high-mobility group box 1), released or secreted by necrotic brain cells, may act as an early inflammation trigger inducing the local recruitment of pro-inflammatory cytokines, independently of BBB alterations. [6] An increase in the levels of neuronal specific enolase, protein S100B, T-tau protein, neurofilament were also reported[6,31].Finally, CSF abnormalities can be induced by many factors including drugs, spinal cord compression, diabetes, and polyradiculoneuritis [32]. Influence of systemic and neuro inflammation after CA on CSF protein level could not be further explored because of the non-availability of albumin CSF/blood ratio or specific MRI exploration to assess the BBB function [33,34].

ICU mortality was 70% in the overall population of patients with lumbar puncture after CA. Of the 6 patients whose CSF analysis contributed to the diagnosis, 2 had the lumbar puncture done while alive but died subsequently and 4 had the lumbar puncture done post-mortem. Identifying a neurological cause of
CA has been reported to carry a very poor prognosis [4,35]. In our study, ICU mortality in the patients whose CSF analysis did not contribute to the diagnosis but showed nonspecific abnormalities was 73%. A higher CSF/serum protein quotient was the only variable significantly associated with a poor outcome. Similarly, a prospective study in 21 patients found that the CSF/serum albumin quotient was higher in the subgroup of 10 patients with poor outcomes than in the other patients [36]. These findings support the existence of BBB disruption after CA. Finally, in our cohort, 56% of deaths in case of nonspecific CSF abnormalities were ascribed to withdrawal of life-sustaining treatments due to severe post-anoxic encephalopathy.

Our study has several limitations. First, given the retrospective nature of this study design and our sample size, the extent to which our findings apply to the full spectrum of patients with CA is unclear. We included consecutive patients with lumbar puncture after ICU admission with stable ROSC after CA, but lumbar puncture was not performed according to predefined criteria, either in the ICU or post-mortem. Moreover, the two participating ICUs were in high-volume centres, and their recruitment may not reflect that of ICUs overall. However, one of the centres was a referring university hospital and the other a tertiary referral hospital. Second, we considered only CSF analysis performed at the early phase after CA, as part of the emergent aetiological workup. Delayed CSF analysis may provide important information. One study found that the CSF/serum albumin quotient increased between 24 h and 72 h after ROSC, and others reported an increase in protein levels after 2-3 weeks [7]. However, our focus was on the potential usefulness of CSF analysis for the aetiological diagnosis and the prognosis. Finally, CSF albumin values were not available, and we did not adjust the CSF protein values on age [37].

**Conclusion**

In conclusion, although rarely performed after CA, lumbar puncture may contribute to the diagnosis of a neurological cause. In our study, CSF analysis as a second-line investigation identified a neurological cause in 9% of patients. Nonspecific CSF abnormalities are common after CA, perhaps due to BBB disruption, and may have prognostic significance. Further studies are warranted to further assess these hypotheses.

**Abbreviations**

**BBB**: blood-brain barrier  
**CA**: cardiac arrest  
**CPC**: Cerebral Performance Category  
**CPR**: cardiopulmonary resuscitation  
**CSF**: cerebrospinal fluid
CT: computed tomography
EEG: electroencephalogram
ICU: intensive care unit
IQR: interquartile range
ROSC: return of spontaneous circulation

Declarations

Ethics approval and consent to participate
CESRLF 12-384 and 20-41

Consent for publication
Not applicable

Availability of data and material
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of interest statement
The authors declare that they have no conflict of interest.

Funding
There was no funding for the development and writing of this commentary.

Authors’ contributions
MP and SL wrote the first draft of the paper. All authors approved the final version of the manuscript.

Acknowledgements
The authors thank the Centre Hospitalier de Versailles for editorial assistance

References
1. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart Disease and Stroke Statistics—2017 Update: A Report From the American Heart Association. Circulation. 2017;135:e146.
2. Nolan JP, Soar J, Cariou A, Cronberg T, Moulaert VRM, Deakin CD, et al. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015: Section 5 of the European Resuscitation Council Resuscitation Guidelines 2015. Resuscitation [Internet]. [cited 2015 Oct 15]; Available from: http://www.sciencedirect.com/science/article/pii/S0300957215003305

3. Chelly J, Mongardon N, Dumas F, Varenne O, Spaulding C, Vignaux O, et al. Benefit of an early and systematic imaging procedure after cardiac arrest: insights from the PROCAT (Parisian Region Out of Hospital Cardiac Arrest) registry. Resuscitation. 2012;83:1444–50.

4. Legriel S, Bougouin W, Chocron R, Beganton F, Lamhaut L, Aissaoui N, et al. Early in-hospital management of cardiac arrest from neurological cause: Diagnostic pitfalls and treatment issues. Resuscitation. 2018;132:147–55.

5. Rosén C, Rosén H, Andreasson U, Bremell D, Bremler R, Hagberg L, et al. Cerebrospinal fluid biomarkers in cardiac arrest survivors. Resuscitation. 2014;85:227–32.

6. Oda Y, Tsuruta R, Fujita M, Kaneda K, Kawamura Y, Izumi T, et al. Prediction of the neurological outcome with intrathecal high mobility group box 1 and S100B in cardiac arrest victims: A pilot study. Resuscitation. 2012;83:1006–12.

7. Hayman EG, Patel AP, Kimberly WT, Sheth KN, Simard JM. Cerebral Edema After Cardiopulmonary Resuscitation: A Therapeutic Target Following Cardiac Arrest? Neurocrit Care. 2018;28:276–87.

8. Roine RO, Somer H, Kaste M, Viinikka L, Karonen S-L. Neurological Outcome After Out-of-Hospital Cardiac Arrest: Prediction by Cerebrospinal Fluid Enzyme Analysis. Arch Neurol. 1989;46:753–6.

9. Adnet F, Lapostolle F. International EMS systems: France. Resuscitation. 2004;63:7–9.

10. Ong MEH, Perkins GD, Cariou A. Out-of-hospital cardiac arrest: prehospital management. Lancet Lond Engl. 2018;391:980–8.

11. Deisenhammer F, Bartos A, Egg R, Gilhus NE, Giovannoni G, Rauer S, et al. Guidelines on routine cerebrospinal fluid analysis. Report from an EFNS task force. Eur J Neurol. 2006;13:913–22.

12. Perkins GD, Jacobs IG, Nadkami VM, Berg RA, Bhanji F, Biarent D, et al. Cardiac Arrest and Cardiopulmonary Resuscitation Outcome Reports: Update of the Utstein Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest: A Statement for Healthcare Professionals From a Task Force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Resuscitation. 2015;96:328–40.

13. Witten L, Gardner R, Holmberg MJ, Wiberg S, Moskowitz A, Mehta S, et al. Reasons for death in patients successfully resuscitated from out-of-hospital and in-hospital cardiac arrest. Resuscitation. 2019;136:93–9.
14. Taccone FS, Horn J, Storm C, Cariou A, Sandroni C, Friberg H, et al. Death after awakening from post-anoxic coma: the “Best CPC” project. Crit Care. 2019;23:107.

15. Paul M, Legriel S. Neurological prognostication after cardiac arrest: how the “Best CPC” project would overcome selection biases. Crit Care Lond Engl. 2019;23:246.

16. Legriel S, Bresson E, Deye N, Grimaldi D, Sauneuf B, Lesieur O, et al. Cardiac Arrest in Patients Managed for Convulsive Status Epilepticus: Characteristics, Predictors, and Outcome. Crit Care Med. 2018;46:e751–60.

17. Geri G, Passouant O, Dumas F, Bougouin W, Champigneulle B, Arnaout M, et al. Etiological diagnoses of out-of-hospital cardiac arrest survivors admitted to the intensive care unit: Insights from a French registry. Resuscitation. 2017;117:66–72.

18. Venkatesan A, Michael BD, Probasco JC, Geocadin RG, Solomon T. Acute encephalitis in immunocompetent adults. Lancet Lond Engl. 2019;393:702–16.

19. Wilson MR, Sample HA, Zorn KC, Arevalo S, Yu G, Neuhaus J, et al. Clinical Metagenomic Sequencing for Diagnosis of Meningitis and Encephalitis. N Engl J Med. 2019;380:2327–40.

20. Obermeier B, Daneman R, Ransohoff RM. Development, maintenance and disruption of the blood-brain barrier. Nat Med. 2013;19:1584.

21. Abbott NJ, Patabendige AAK, Dolman DEM, Yusof SR, Begley DJ. Structure and function of the blood-brain barrier. Neurobiol Dis. 2010;37:13–25.

22. Reiber H, Peter JB. Cerebrospinal fluid analysis: disease-related data patterns and evaluation programs. J Neurol Sci. 2001;184:101–22.

23. Stahel PF, Morganti-Kossmann MC, Perez D, Redaelli C, Gloor B, Trentz O, et al. Intrathecal Levels of Complement-Derived Soluble Membrane Attack Complex (sC5b-9) Correlate with Blood–Brain Barrier Dysfunction in Patients with Traumatic Brain Injury. J Neurotrauma. 2001;18:773–81.

24. Malter MP, Choi S, Fink GR. Cerebrospinal fluid findings in non-infectious status epilepticus. Epilepsy Res. 2018;140:61–5.

25. Weiss N, Rosselli M, Mouri S, Galanaud D, Puybasset L, Agarwal B, et al. Modification in CSF specific gravity in acutely decompensated cirrhosis and acute on chronic liver failure independent of encephalopathy, evidences for an early blood-CSF barrier dysfunction in cirrhosis. Metab Brain Dis. 2017;32:369–76.

26. Elwood E, Lim Z, Naveed H, Galea I. The effect of systemic inflammation on human brain barrier function. Brain Behav Immun. 2017;62:35–40.

27. Dénes Á, Ferenczi S, Kovács KJ. Systemic inflammatory challenges compromise survival after experimental stroke via augmenting brain inflammation, blood- brain barrier damage and brain oedema independently of infarct size. J Neuroinflammation. 2011;8:1–13.

28. Kimizu T, Takahashi Y, Oboshi T, Horino A, Omatsu H, Koike T, et al. Chronic dysfunction of blood-brain barrier in patients with post-encephalitic/encephalopathic epilepsy. Seizure - Eur J Epilepsy. 2018;63:85–90.
29. Youngquist ST, Niemann JT, Heyming TW, Rosborough JP. The central nervous system cytokine response to global ischemia following resuscitation from ventricular fibrillation in a porcine model. Resuscitation. 2009;80:249–52.

30. Oda Y, Tsuruta R, Kasaoka S, Inoue T, Maekawa T. The cutoff values of intrathecal interleukin 8 and 6 for predicting the neurological outcome in cardiac arrest victims. Resuscitation. 2009;80:189–93.

31. Rosén H, Karlsson J-E, Rosengren L. CSF levels of neurofilament is a valuable predictor of long-term outcome after cardiac arrest. J Neurol Sci. 2004;221:19–24.

32. Bihan K, Weiss N, Théophile H, Funck-Brentano C, Lebrun-Vignes B. Drug-induced aseptic meningitis: 329 cases from the French pharmacovigilance database analysis. Br J Clin Pharmacol. 2019;

33. Floris S, Blezer ELA, Schreibelt G, Döpp E, van der Pol SMA, Schadee-Eestermans IL, et al. Blood–brain barrier permeability and monocyte infiltration in experimental allergic encephalomyelitis: a quantitative MRI study. Brain. 2004;127:616–27.

34. Heye AK, Culling RD, Valdés Hernández MDC, Thrippleton MJ, Wardlaw JM. Assessment of blood-brain barrier disruption using dynamic contrast-enhanced MRI. A systematic review. Neuroimage Clin. 2014;6:262–74.

35. Arnaout M, Mongardon N, Deye N, Legriel S, Dumas F, Sauneuf B, et al. Out-of-hospital cardiac arrest from brain cause: epidemiology, clinical features, and outcome in a multicenter cohort*. Crit Care Med. 2015;43:453–60.

36. Park JS, You Y, Min JH, Yoo I, Jeong W, Cho Y, et al. Study on the timing of severe blood-brain barrier disruption using cerebrospinal fluid-serum albumin quotient in post cardiac arrest patients treated with targeted temperature management. Resuscitation. 2019;135:118–23.

37. Brooks JA, McCudden C, Breiner A, Bourque PR. Causes of albuminocytological dissociation and the impact of age-adjusted cerebrospinal fluid protein reference intervals: a retrospective chart review of 2627 samples collected at tertiary care centre. BMJ Open. 2019;9:e025348.

Tables
| N (%) or Median (Interquartile Range) | All patients n=65 (100%) | LP contributed to aetiologic diagnosis n = 6/65 (9.2%) | LP did not contribute to aetiologic diagnosis n = 59/65 (90.8%) | p value |
|-------------------------------------|--------------------------|--------------------------------------------------|--------------------------------------------------|---------|
| **Prodromal signs** | | | | |
| Neurological signs/symptoms before CA | 45 (69.2) | 5 (83.3) | 40 (67.8) | 0.66 |
| Confusion to coma | 20 (30.8) | 3 (50.0) | 17 (28.8) | 0.36 |
| Seizure | 20 (30.8) | 1 (16.7) | 19 (32.2) | 0.66 |
| Neurological focal signs | 6 (9.2) | 1 (16.7) | 5 (8.5) | 0.45 |
| Headache | 2 (3.1) | 1 (16.7) | 1 (1.7) | 0.18 |
| **Tests to identify cause of cardiac arrest** | | | | |
| Electrocardiographic ST-segment elevation | 6 (9.5) | 0 | 6 (10.5) | - |
| Coronary angiography | 31 (47.7) | 3 (50.0) | 28 (47.5) | 1.00 |
| Cerebral CT | 52 (80.0) | 4 (66.7) | 48 (81.4) | 0.59 |
| Cerebral MRI | 5 (7.7) | 1 (16.6) | 4 (6.8) | 0.39 |
| Chest CT | 33 (50.8) | 1 (16.7) | 32 (54.2) | 0.10 |
| **Lumbar puncture** | | | | |
| First-line test | 10 (15.4) | 0 | 10 (17.0) | 0.15 |
| Second-line test | 29 (44.6) | 5 (83.3) | 24 (40.7) | |
| Third-line test | 26 (40.0) | 1 (16.7) | 25 (42.4) | |
| Post mortem | 10 (15.4) | 4 (66.7) | 6 (10.2) | 0.004 |
| Time from cardiac arrest to LP, days | 1 (1-2) | 1.5 (1-2) | 1 (1-2) | 1 |
| **Cause of CA** | | | | |
| Respiratory | 18 (27.7) | 0 | 18 (30.5) | |
| Neurologic | 16 (24.6) | 5 (83.3) | 11 (18.6) | |

Table 1. Diagnostic workup, identified causes, and outcomes in 65 patients who underwent lumbar puncture after cardiac arrest.
|                      | ICU                     | 10000 Faster         | 10000 Faster 7         |
|----------------------|-------------------------|----------------------|------------------------|
| Cardiac              | 7 (10.8)                | 0                    | 7 (11.9)               |
| Metabolic            | 7 (10.8)                | 0                    | 7 (11.9)               |
| Septic shock         | 4 (6.2)                 | 1 (16.7)             | 3 (5.1)                |
| Undetermined         | 13 (20.0)               | 0                    | 13 (22.0)              |

**Outcomes**

| Outcome                          | ICU                  | 10000 Faster         | 10000 Faster 7         |
|----------------------------------|----------------------|----------------------|------------------------|
| ICU length of stay, days         | 6 (2-8)              | 2.5 (1.3-3)          | 6 (3-8.5)              |
| Awakening during ICU stay        | 20 (30.8)            | 0                    | 20 (33.9)              |
| CPC score at ICU discharge       |                      |                      | 0.48                   |
| 1-2                              | 19 (29.2)            | 0                    | 19 (32.2)              |
| 3-4                              | 0                    | 0                    | 0                      |
| 5                                | 46 (70.8)            | 6 (100)              | 40 (67.8)              |
| Reason for ICU death             |                      |                      | 0.006                  |
| Multiorgan failure               | 18 (39.1)            | 3 (50.0)             | 15 (37.5)              |
| Anoxic encephalopathy            | 20 (43.5)            | 0                    | 20 (50.0)              |
| Brain death                      | 7 (15.2)             | 3 (50.0)             | 3 (7.5)                |
| Other                            | 1 (2.2)              | 0                    | 1 (2.5)                |

CA: cardiac arrest; CPC: Cerebral Performance Category; CSF: cerebrospinal fluid; CT: computed tomography; ICU: intensive care unit; IQR: interquartile range; LP: lumbar puncture; MRI: magnetic resonance imaging.
Table 2.
Cerebrospinal fluid characteristics in patients whose lumbar puncture did not contribute to the aetiological diagnosis

|                                | All Patients | CSF analysis contributed to the aetiological diagnosis | CSF analysis did not contribute to the aetiological diagnosis | Postmortem CSF analysis did not contribute to the aetiological diagnosis | Abnormal CSF† in patients who were alive at the time of LP and whose CSF analysis did not contribute to the aetiological diagnosis |
|--------------------------------|--------------|--------------------------------------------------------|---------------------------------------------------------------|--------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|
| n (%) or Median (interquartile range) / mean [range] | n = 65 (100%) | n = 6/65 (9.2%)                                         | n = 59/65 (90.8%)                                             | n=6/59 (10.2%)                                                           | n =37/53 (69.8%)                                                                                                  |
| CSF white-cell count, per mm$^3$ | 1 (0-5) / 15.2 [0-297] | 1 (0-4) / 131 [6-297] | 111 (17-224) / 7 [0-30] | 2 (1-12) / 7 [0-144] | 2 (0-5) / 10 [0-144] |
| CSF neutrophil count, per mm$^3$* | 1 (1-9) | 18 (14-23) | 1 (1-3) | 2 (1-3) | 1 (1-5) |
| CSF lymphocyte count, per mm$^3$* | 0 (0-4) | 170 (87-229) | 0 (0-3) | 2 (1-3) | 0 (0-3) |
| CSF protein, g/L | 0.56 (0.40-0.70) / 0.79 [0.20-5.55] | 1.54 (1.30-2.60) / 2.30 [0.59-5.55] | 0.55 (0.42-0.65) / 0.68 [0.20-3.99] | 0.60 (0.40-0.80) / 0.66 [0.30-1.35] | 0.62 (0.54-0.76) / 0.83 [0.42-3.99] |
| CSF glucose, mmol/L | 4.8 (4.2-6.0) | 4.9 (4.8-5.3) | 4.8 (4.1-6.0) | 5.4 (3.7-6.1) | 4.8 (4.0-6.0) |
| CSF red-cell count, per mm$^3$ | 28 (1-322) | 9500 (4100-20000) | 15 (1-229) | 208 (14-1142) | 20 (1-221) |
| CSF lactate, mmol/L | 4.6 (4.1-8.0) | 5.4 (4.8-6.1) | 4.6 (4.1-8.7) | 7.9 (6.0-9.7) | 4.7 (4.3-7.7) |
| Blood protein, g/l | 62 (53-68) | 41 (41-57) | 63 (54-68) | 60 (60-60) | 60 (52-68) |
| Blood glucose, mmol/L | 7.3 (6.0-9.4) | 10.3 (8.2-16.6) | 7.1 (6.0-9.3) | 6.9 (5.7-8.1) | 7.3 (5.9-11.8) |
|                      |     |     |     |     |     |
|----------------------|-----|-----|-----|-----|-----|
| **Protein CSF/blood**| 0.009 (0.007-0.01) | 0.02 (0.01-0.02) | 0.009 (0.007-0.01) | 0.009 (0.009-0.009) | 0.01 (0.009-0.01) |
| **Glucose CSF/blood**| 0.6 (0.5-0.8) | 0.5 (0.5-0.95) | 0.65 (0.5-0.8) | 0.8 (0.6-0.8) | 0.7 (0.5-0.8) |
| **Positive CSF culture** | 1 (1.5) | 1 (16.7) | 0 | 0 | 0 |
| **Abnormal cells** | 0 | 0 | 0 | 0 | 0 |

CSF: cerebrospinal fluid; IQR: interquartile range; LP: lumbar puncture.

*in patients with CSF white cell count >4/mm$^3$

† Abnormal CSF was defined as CSF white-cell count >4/mm$^3$ and/or CSF protein >0.45 g/L.
Table 3:
Demographic and cardiac arrest characteristics in patients alive at lumbar puncture whose cerebrospinal fluid analysis did not contribute to the aetiological diagnosis of cardiac arrest (n=53)

| Demographic characteristics and comorbidities                           | N (%) or Median (interquartile range) | Normal LP n=16 (30.2%) | Abnormal LP† n=37 (69.8%) | p value |
|------------------------------------------------------------------------|----------------------------------------|------------------------|---------------------------|---------|
| Age, years                                                             |                                        | 49 (39-65)             | 56 (40-74)                | 0.24    |
| Male sex                                                               |                                        | 9 (56.3)               | 26 (70.3)                 | 0.36    |
| Diabetes mellitus                                                      |                                        | 17 (18.7)              | 6 (16.2)                  | 1.00    |
| Spinal cord compression                                                |                                        | 1 (6.3)                | 1 (2.7)                   | 0.52    |
| Haematological malignancy                                              |                                        | 0                      | 2 (5.4)                   | -       |
| Epilepsy                                                               |                                        | 4 (25.0)               | 5 (13.5)                  | 0.43    |
| Cardiac arrest characteristics                                         |                                        |                        |                           |         |
| Neurological signs/symptoms before CA                                  |                                        | 10 (62.5)              | 28 (75.7)                 | 0.34    |
| Confusion to coma                                                       |                                        | 2 (12.5)               | 13 (35.1)                 | 0.11    |
| Seizure                                                                |                                        | 8 (50.0)               | 10 (27.0)                 | 0.13    |
| Neurological focal signs                                               |                                        | 1 (6.3)                | 3 (8.1)                   | 1.00    |
| Headache                                                               |                                        | 0                      | 1 (2.7)                   | -       |
| Cardiac arrest in a public place                                       |                                        | 3 (18.7)               | 5 (13.5)                  | 0.69    |
| Arrest witnessed/monitored                                             |                                        | 13 (81.2)              | 32 (86.5)                 | 0.69    |
| Bystander CPR                                                          |                                        | 12 (75.0)              | 31 (83.8)                 | 0.47    |
| Shockable first recorded rhythm                                        |                                        | 5 (31.2)               | 6 (16.2)                  | 0.27    |
| Total number of defibrillations before ROSC                            |                                        | 0 (0-2)                | 0 (0-1)                   | 0.16    |
| Use of epinephrine                                                     |                                        | 11 (68.8)              | 30 (81.1)                 | 0.48    |
| Total epinephrine dose before ROSC, mg                                 |                                        | 1 (0-3)                | 2 (1-4)                   | 0.081   |
| Time from collapse to CPR (no-flow), min                               |                                        | 4 (2-10)               | 0 (0-3)                   | 0.004   |
| Time from collapse to ROSC (low-flow), min                             |                                        | 16 (9-21)              | 10 (6-20)                 | 0.41    |
| Lactate concentration on ICU admission, mmol/L                         |                                        | 3.9 (2.5-7.4)          | 6.5 (2.3-11.0)            | 0.40    |
| Event                                                                 | ICU 1 | ICU 2 | p-Value |
|----------------------------------------------------------------------|-------|-------|---------|
| Oedema on cerebral CT                                                | 0     | 5 (16.1) | -       |
| Targeted temperature management (32-36°C) on day 1                   | 14 (87.5) | 31 (83.8) | 1.00    |
| Sepsis before LP                                                    | 1 (6.3) | 9 (24.3) | 0.25    |
| Post-resuscitation shock                                            | 5 (31.2) | 26 (70.3) | 0.01    |
| Renal replacement therapy                                           | 4 (25.0) | 9 (24.3) | 1.00    |
| Status epilepticus as a cause of CA (before LP)                     | 2 (66.7) | 3 (42.9) | 1.00    |
| **Outcomes**                                                        |       |       |         |
| ICU length of stay, days                                            | 7 (5-9) | 6 (3-9) | 0.55    |
| Awakening during ICU stay                                           | 10 (62.5) | 10 (27.0) | 0.029  |
| CPC score at discharge                                              |       |       | 0.044   |
| 1-2                                                                | 9 (56.3) | 10 (27.0) |         |
| 3-4                                                                | 0     | 0     |         |
| 5                                                                  | 7 (43.7) | 27 (73) |         |
| Reason for ICU death                                                |       |       | 0.09    |
| Multiorgan failure                                                  | 1 (14.3) | 8 (29.6) |         |
| Anoxic encephalopathy                                              | 5 (71.4) | 15 (55.6) |         |
| Brain death                                                         | 1 (14.3) | 3 (11.1) |         |
| Other                                                              | 0     | 1 (3.7) |         |

CPC: Cerebral Performance Category; CPR: cardiopulmonary resuscitation; CT: computed tomography; ICU, intensive care unit; LP: lumbar puncture; ROSC: return of spontaneous circulation.

† Abnormal CSF was defined as CSF white-cell count >4/mm³ and/or CSF protein >0.45 g/L.

**Figures**
1984 patients with ROSC after CA over a 10-year study period

80 patients with lumbar puncture (LP)

15 patients not included
- 7 LP not performed for diagnostic workup
- 8 traumatic LP (white cells/red cells <1/1000)

65 patients with LP included in the study

6/65 (9%) patients whose LP contributed to the aetiological diagnosis of CA, including 2 during life and 4 post-mortem

59/65 (91%) patients whose LP did not contribute to the aetiological diagnosis of CA

53 patients alive at the time of LP

37/53 (70%) patients with nonspecific CSF abnormalities

16/53 patients with normal CSF

6 patients with post-mortem LP

Figure 1

Patient flow diagram ROSC denotes return of spontaneous circulation and CA cardiac arrest.
Figure 2

Diagnostic work-up in 65 patients with a lumbar puncture after cardiac arrest CT denotes computed tomography.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- ESM0308.docx