TITLE PAGE

EARLY AUTOMATED CEREBRAL EDEMA ASSESSMENT FOLLOWING ENDOVASCULAR THERAPY: IMPACT ON STROKE OUTCOME

Authors' names, academic degrees and affiliations:

Marina Guasch-Jiménez[1]; Rajat Dhar[2]; Atul Kumar[2]; Julien Cifarelli[2]; Garbiñe Ezcurra-Díaz[1]; Álvaro Lambea-Gil[1]; Anna Ramos-Pachón[1]; Alejandro Martínez-Domeño[1]; Luis Prats-Sánchez[1]; Daniel Guisado-Alonso[1]; Israel Fernández-Cadenas[1]; Ana Aguilera-Simón[1]; Rebeca Marín[1]; José Pablo Martínez-González[3]; Joaquín Ortega-Quintanilla[4]; Isabel Fernández-Pérez[5]; Carla Avellaneda-Gómez[5]; Jorge Rodríguez-Pardo[6]; Elena de Celis[6]; Francisco Moniche[7]; María del Mar Freijo[8]; Elisa Cortijo-García[9]; Santiago Trillo[10]; Pol Camps-Renom[1*]; Joan Martí-Fàbregas[1*].

1. Stroke Unit, Neurology Department, Institut de Recerca Sant Pau, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona (Department of Medicine) Barcelona, Spain

2. Neurology Department, Washington University School of Medicine, Saint Louis, Missouri, USA

3. Neurointerventional radiology, Radiology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

4. Neurointerventional radiology, Radiology Department, University Hospital Virgen del Rocío, Sevilla, Spain

5. Stroke Unit, Neurology Department, Hospital del Mar, Barcelona, Spain

6. Neurology Department and Stroke Center, Hospital La Paz Institute for Health Research-IdiPAz (La Paz University Hospital, Universidad Autónoma de Madrid), Madrid, Spain

7. Stroke Unit, Neurology Department, University Hospital Virgen del Rocío, Sevilla, Spain

8. Stroke Unit, Neurology Department, University Hospital Cruces, Biobizkaia Health Research Institute, Barakaldo, Spain

9. Stroke Unit, Neurology Department, University Hospital of Valladolid, Valladolid, Spain

10. Stroke Unit, Neurology Department, University Hospital de La Princesa, Madrid, Spain

*Contributed equally.

Corresponding author:

Pol Camps-Renom

Stroke Unit, Neurology Department, Biomedical Research Institute Sant Pau (IIB-Sant Pau), Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona (Department of Medicine) Barcelona, Spain

Avda. Sant Antoni Maria Claret, 167

08025 Barcelona (Spain)

e-mail: pcamps@santpau.cat

Tel. +34935565986

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ABSTRACT

Background:

Cerebral edema (CED) is associated with poorer outcome in patients with acute ischemic stroke (AIS). The aim of the study was to investigate the factors contributing to greater early CED formation in patients with AIS who underwent endovascular therapy (EVT) and its association with functional outcome.

Methods:

We conducted a multicenter cohort study of patients with an anterior circulation AIS undergoing EVT. The volume of cerebrospinal fluid (CSF) was extracted from baseline and 24-hours follow-up CT using an automated algorithm. The severity of CED was quantified by the percentage reduction in CSF volume between CT scans (ΔCSF). The primary end-point was a shift towards an unfavorable outcome, assessed by mRS at three months. Multivariable ordinal logistic regression analyses were performed. The ΔCSF threshold that predicted unfavorable outcome was selected using ROC curve analysis.

Results:

We analyzed 201 patients (72.7 years, 47.8% women), of whom CED was assessable for 85.6%. Higher systolic blood pressure during EVT and failure to achieve mTICI 3 were found to be independent predictors of greater CED. ΔCSF was independently associated with the probability of 1-point worsening in the mRS score (cOR 1.05, 95%CI: 1.03-1.08) after adjusting for age, baseline mRS, NIHSS and number of passes. Displacement of more than 25% of CSF was associated with an unfavorable outcome (OR 6.09, 95%CI: 3.01-12.33) and mortality (OR 6.72, 95%CI: 2.94-15.32).

Conclusions:

Early CED formation in patients undergoing EVT was affected by higher blood pressure and incomplete reperfusion. The extent of early CED, measured by automated ΔCSF, was associated with worse outcomes.

KEY WORDS: ischemic stroke, cerebral edema, endovascular therapy, thrombectomy

KEY MESSAGES

What is already known on this topic

- Cerebral edema is a dynamic process that starts minutes after an acute ischemic stroke and is associated with poorer outcomes. Novel automated biomarkers have emerged for early-stage edema quantification in stroke, yet their impact on functional outcomes remains unclear.

What this study adds

- The extent of early cerebral edema, assessed with automated CSF volumetry by 24-hours, was associated with worse outcomes in stroke patients who underwent endovascular therapy.
- Early cerebral edema was found to be influenced by modifiable factors, such as higher blood pressure and incomplete recanalization.

How this study might affect research, practice or policy

- CSF volumetry emerges as a promising neuroimage marker to detect and quantify mild edema in an early stroke stage, were current and forthcoming therapeutic options may be more effective.

INTRODUCTION

Endovascular therapy (EVT) is a highly effective treatment for patients with an acute ischemic stroke (AIS) due to a large-vessel occlusion (LVO)[1]. However, half of these patients do not recover functional independence, even after successful recanalization[2,3]. This is termed clinically ineffective reperfusion (CIR)[4].

Several mechanisms underlying CIR have been postulated, including: reperfusion injury (caused by different degrees of blood-brain barrier dysfunction that may occur after blood flow restoration), the no-reflow phenomenon (defined as a persistent microvascular hypoperfusion despite angiographic recanalization), hemorrhagic transformation and procedural complications[5-8]. Cerebral edema (CED) linked to both, cerebral infarction and reperfusion injury, may also contribute to CIR and it has been consistently associated with mortality and unfavorable functional outcome after AIS[9,10].

However, studies of CED after AIS have largely employed midline shift (MLS) as a crude biomarker, which may not detect or quantify the early and full spectrum of edema severities, thereby obscuring the full impact of CED in all patients who do not have MLS but do have visible brain swelling. More recently, imaging-based quantitative measurements have been developed to detect and predict cerebral edema after AIS[11]. For example, the automated measurement of the displacement of cerebrospinal fluid (CSF) from serial brain images has demonstrated a strong association with classic markers, such as MLS and malignant cerebral edema (MCE)[12,13]. Considering that CED is a dynamic process that starts minutes after brain ischemia[10], automated CSF volumetry could provide a precise and dynamic biomarker capable of measuring even small degrees of CED in the first 24 hours after stroke.

The aim of the current study was to investigate clinical factors that influence the severity of CED formation over the first 24 hours after stroke, measured through automated CSF volumetry, and its impact on functional outcome in patients with anterior circulation AIS who underwent EVT. We hypothesized that patients who develop more severe early CED after EVT would have higher odds of worse functional outcome.

METHODS

Study design

We conducted an observational, prospective, multicenter cohort study of patients with AIS and anterior circulation LVO. Patients were recruited between January 2020 and June 2022. The study was approved by the Ethics Committee of each participating center. Patients or their legal representatives gave written consent to participate.

Study population

Inclusion criteria were: (1) age ≥18 years-old; (2) AIS secondary to LVO of the middle cerebral artery, segments M1 and M2, or terminal internal carotid artery, with or without extracranial occlusion or stenosis, as demonstrated by computed tomography (CT) angiography; (3) arrival within the first 24 hours after stroke onset (including wake-up strokes); (4) previous modified Rankin Scale (mRS) score of 0 to 2; (5) treatment with EVT; and (6) written consent to participate signed by the patient or a legal representative.

Exclusion criteria were: (1) unavailable baseline CT or 24±12 hours follow-up CT; (2) participation in a clinical trial; (3) insufficient quality CTs (due to motion artifact, too thick axial slices or any other technical constraints).

We collected the following variables: demographic, vascular risk factors, therapeutic data (including number of passes and final modified Thrombolysis In Cerebral Infarction -mTICI- score), workflow data and stroke etiology (as classified by the TOAST criteria[14]). Previous functional status and stroke severity were assessed at admission by certified neurologists using the mRS and the National Institute of Health Stroke Scale (NIHSS), respectively.

Baseline CT, CT-angiography and conventional angiography were evaluated by local neuroradiologists. Collateral circulation was automatically assessed using Brainomix Ltd. and classified in four categories (none, poor, good or excellent collateral circulation). Successful reperfusion was defined as mTICI score ≥2b.

Blood pressure (BP) was measured non-invasively at admission, every 10 minutes during EVT procedure and hourly for the following 24 hours. We recorded mean systolic BP (SBP), maximum SBP and SBP variability through coefficient of variation ($\frac{SBP\ standard\ deviation}{mean\ SBP} \times 100$) for each period of time.

During the follow-up we collected the type of hemorrhagic transformation on follow-up CT and symptomatic intracerebral hemorrhage (sICH), as defined by the Heidelberg bleeding classification[15]. mRS was assessed at three months of follow-up after a face-to-face interview by local investigators, who were blinded to CED measurement.

Cerebral edema analysis

CED was quantified by analyzing clinical head CT scans using an automated image analysis pipeline that incorporates CSF volumetry, as described previously[12]. In brief, CSF within the sulci and ventricles were segmented from head CT scans using a deep learning algorithm. Resulting CSF masks were manually reviewed to assess accuracy. See an example in Figure 1. CED was quantitatively assessed by calculating the percentage reduction in CSF volume between baseline and follow-up CT at 24±12 hours (ΔCSF). Those in whom CSF volume could not be measured due to poor scan quality, large amounts of contrast enhancement or hemorrhagic transformation located in the subarachnoid or intraventricular spaces were excluded from ΔCSF analysis.

When possible, to assess the reproducibility of the chosen edema biomarker, two other CED measurements were tested. CSF ratio between the affected and the unaffected cerebral hemispheres (excluding patients with old strokes or ventricular asymmetry) and Net Water Uptake -NWU- (excluding patients without visible infarction, with any hemorrhagic transformation or contrast enhancement in the infarcted tissue) were collected as other CED biomarkers measured automatedly, using the same approach as previously described[13], on follow-up CT.

Outcomes

The primary end-point was a shift towards higher mRS score at three months of follow-up. The secondary outcome was unfavorable outcome (mRS 3-6) at three months of follow-up.

Statistical analysis

Continuous descriptive variables were reported as means and standard deviations (SD) or medians and interquartile range (IQR) if they were not-normally distributed, as tested by the Shapiro-Wilk test. Categorical variables were expressed as counts and percentages. To test the correlation between the three CED measurements we calculated the Spearman's correlation coefficient (ρ).

First, variables associated with ΔCSF were studied using linear regression analyses after log transformation of the dependent variable (ΔCSF) to approach normality. Then, multivariable linear regression analysis was performed using a stepwise backward regression modeling from an initial model including all the variables showing a trend towards significance ($p<0.1$).

Second, for the primary outcome, ordinal regression analyses were performed to study variables associated with the mRS score at three months of follow-up. Then, multivariable ordinal regression analysis was performed also using a stepwise backward regression modeling as previously detailed. The common odds ratio (cOR) of worsening 1 point on the mRS score in the presence of a 1% increase of ΔCSF was calculated with its 95% confidence interval (CI). To study the secondary outcome, functional outcome was dichotomized into favorable (mRS 0-2) or unfavorable (mRS 3-6). Univariable analyses were performed to study variables associated with unfavorable outcome, using the Student's *t* test or the Wilcoxon Rank Sum test (when a non-parametric test was required) for continuous variables, and the χ^2 test for categorical variables. Then multivariable logistic regression analysis was performed to predict unfavorable functional outcome using the same approach as in the prior ordinal regression analysis.

A sensitivity analysis was performed excluding those patients with hemorrhagic transformation who could interfere in edema measurement through ΔCSF, such as hemorrhagic transformation causing significant mass effect (Heidelberg Bleeding classification PH2) or hemorrhagic transformation with any degree of subarachnoid or intraventricular hemorrhage.

Finally, sensitivity/specificity analyses using Receiver Operating Characteristic (ROC) curve analysis were performed to identify a ΔCSF threshold with a high a >85% specificity for unfavorable outcome. A multivariable logistic regression analysis was then repeated to calculate the OR of an unfavorable outcome with its 95% CI for the selected ΔCSF threshold.

Statistical significance for all the analyses was set at 0.05 (two-sided). All the analyses were performed using Stata v.17 (Texas, USA).

RESULTS

We initially recruited 279 participants with an anterior circulation LVO AIS, of whom 201 underwent EVT, had imaging available and were included in the current study (Suppplementary figure 1. Flow-Chart). The mean age was 72.7 years (SD 12.9) and 96

(47.8%) of them were women. Median baseline NIHSS score was 17 (10-21) and 100 (49.8%) had an LVO in the M1 segment. Supplementary table 1 shows the patients' baseline characteristics.

CED measurements were available for 167 (85.6%) patients using ΔCSF, for 155 (79.5%) using CSF ratio, and for 56 (28.7%) using NWU, as shown in the Flow-Chart. The median ΔCSF was 19.1% (10.8-31.1). CSF ratio and ΔCSF showed a very strong correlation with a Spearman's correlation coefficient (ρ: -0.70; $p<0.001$). NWU showed a non-significant correlation with both CSF volumetry measurements, probably due to the limited number of patients with this measurement available.

Predictors of cerebral edema after EVT

Variables associated with greater ΔCSF in univariable analyses are detailed in Supplementary table 2. In the multivariable analysis, higher number of passes, higher mean SBP during EVT, and not achieving mTICI 3 reperfusion were found to be independent predictors of early CED measured by ΔCSF (Table 1).

In the sensitivity analysis, we excluded 35 patients with hemorrhagic transformation who could interfere in edema measurement through ΔCSF. In the resulting model, not achieving mTICI 3 (ß standardized: -0.237) and higher mean SBP during EVT (ß standardized: 0.214) remained independently associated with CED.

Impact of edema on clinical outcome

mRS at three months of follow-up was available for 197 patients, the median mRS score was 3 (1-4).

Variables associated with mRS score in the univariable analysis are reported in supplementary table 3. In the multivariable ordinal analysis, early CED using ΔCSF was independently associated with the probability of worsening 1-point on the mRS at three months of follow-up when measured through ΔCSF [cOR 1.05 (95%CI 1.03-1.09; $p<0.001$)] (Table 2) and through CSF ratio [cOR 0.01 (95%CI 0.00-0.06; $p<0.001$)] (Supplementary table 4). This association of ΔCSF and outcome remained statistically significant in the sensitivity analysis model.

A favorable outcome, as defined in Methods, was observed in 87 (44.2%) participants, while the mortality rate was 19.8% (n=39).

After repeating a multivariable analysis using binary logistic regression, the same variables (except for number of passes and mean SBP after EVT) were selected for the final model, being ΔCSF associated to a higher likelihood of unfavorable functional outcome [OR 1.10 (95%CI 1.14-1.95; *p*<0.001)] (Supplementary table 5).

A ROC curve analysis was performed to find a ΔCSF cut off point for predicting unfavorable functional outcome. We found that a 25% change in the CSF volume between baseline CT scan and the 24h follow-up CT, provided a specificity of 88% and a sensitivity of 55% for predicting unfavorable outcome. A multivariable logistic regression analysis showed that the 25% threshold of ΔCSF was independently associated with an unfavorable outcome [OR 6.09 (95%CI 3.01-12.33; *p*<0.001)] and with mortality [OR 6.72 (95%CI 2.94-15.32; *p*<0.001)]. The distribution on the mRS score at three months of follow-up according to a ΔCSF > or ≤25% is illustrated in figure 2.

DISCUSSION

In this prospective multicenter study, we demonstrated that greater early CED severity was independently associated with worse functional outcome in patients with an anterior circulation AIS who underwent EVT. Patients with a >25% reduction in CSF volume on the 24-hour follow-up cranial CT showed a 6-time fold increased risk of presenting an unfavorable functional outcome. Our results are relevant in several ways.

First, we have confirmed the value of automated CSF volumetry measurement as an early prognostic marker in patients with AIS treated with EVT. CED is a dynamic process that starts minutes after ischemia onset and evolves over the following hours and days[10,17]. Several neuroimaging markers have been used to assess CED, being MLS a classical biomarker vastly used in research and clinical practice[11]. However, MLS develops later in the course of edema and is not suitable in cases of mild or moderate CED[18,19]. ΔCSF, instead, enables the detection of edema within the first 24 hours after AIS and can identify and quantify amounts of CED as small as a milliliter. As therapeutic options for MCE have demonstrated better results when applied in early stages[20], early CED detection through CSF volumetry could emerge as a viable tool for identifying potential candidates for hemicraniectomy or other forthcoming edema treatments[21].

Recently, other quantitative CED biomarkers have been described[11]. Densitometric parameters based on brain infarcted tissue density (such as NWU)[22,23] and volumetric edema measurements, which can be based on cerebral parenchyma (such as infarct volume) or in CSF volume displacement (such as ΔCSF, CSF ratio between

infarcted and non-infarcted hemisphere or CSF to intracranial volume ratio)[12,14,24], can also detect CED as early as in the 24-hour follow-up neuroimaging. While these neuroimaging biomarkers have been linked to MCE, our study reveals that ΔCSF is also associated with functional outcome. Furthermore, although densitometric and parenchymal based volumetric biomarkers are also early edema markers, they may be inaccurate or non-usable in the presence of hemorrhagic transformation or contrast enhancement, which are common findings after EVT[25]. In our study, NWU was available in less than a third of patients. Notwithstanding, as previously described[26], CSF based volumetric parameters were applicable in a high proportion of the participants (85.6% with ΔCSF and 79.5% with CSF ratio). CSF ratio between cerebral hemispheres has the advantage that it can be measured using only the follow-up CT but, as it is not usable in cases of malacic lesions of any etiology or ventricular asymmetry, a considerable proportion of patients won't be evaluable with this markers. In this regard, ΔCSF stands as the most useful biomarker due to its accuracy and reproducibility after EVT.

Second, we have described baseline and intraprocedural variables associated with early CED in patients treated with EVT. Among the modifiable predictors of CED analyzed, an association of attenuated edema with successful recanalization was detected. In addition, we showed that the number of passes was associated with more CED. These results agree with prior investigations, enhancing the role of reperfusion injury due to blood-brain barrier damage associated with a higher number of passes; and the reduction of edema related to penumbra salvage volume in greater recanalization degrees[6,24,27-29]. Noteworthy, higher mean SBP during EVT was also found to be associated with higher odds of CED. Management of BP during and after EVT is a topic of ongoing research. Thus, the relationship between BP and CED is still not well defined and randomized clinical trials are still warranted to address BP goals during and after EVT in order to reduce CED and improve functional outcomes. Our work suggests that using volumetric edema endpoints, such as ΔCSF, might be preferable to simply applying MLS as the endpoint of such investigations.

Finally, we have proposed a threshold of percentage of change in CSF volumetry that could be used in future studies and trials as an indirect marker of safety and efficacy after EVT and, perhaps, a suitable biomarker for early edema treatments consideration.

The main strength of the current study is its multicenter and prospective design, with a novel automated early CED measurement. However, it has several limitations. In the first place, although CSF volumetry has been shown to be an early and sensitive indicator of different edema degrees, CSF segmentation is not a pure CED measure in patients who present with some subtypes of hemorrhagic transformation (such as PH2 or subarachnoid hemorrhage) or in infarct growth situations. In these cases, ΔCSF could be more accurately interpreted as a measure of mass effect. Although we did not

record infarct volume to test its influence on ΔCSF, we did a sensitivity analysis excluding patients with any kind of hemorrhagic transformation that could interfere in the results and the association with outcome remained unchanged. Furthermore, to calculate ΔCSF at least two CT scans of an acceptable quality are needed (baseline and follow-up), which increases the rate of missingness. In contrast, other CED markers such as NWU or CSF ratio, are applied directly on follow-up CT without comparison to baseline. Notwithstanding, ΔCSF was the most applicable biomarker, due to the high frequency of malacic lesions or hemorrhagic transformation in EVT treated AIS population. In addition, ΔCSF is not suitable for posterior fossa strokes. Finally, some variables related to severe edema, such as the rate of MCE or hemicraniectomies performed, were not reported in our sample.

CONCLUSIONS

In conclusion, the current study suggests that early CED measurement based on ΔCSF is associated with functional outcome in patients with AIS who undergo EVT. ΔCSF emerges as a promising neuroimage marker to detect and quantify mild CED in an early stroke stage.

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COMPETING INTERESTS

None declared.

ETHICS APPROVAL

This study involves human participants and was approved by the Ethics Committee of Hospital de la Santa Creu i Sant Pau (CEIm Sant Pau). Patients or their legal representatives gave written consent to participate. All participating centers obtained ethical approval according to their local protocol for sharing retrospective and fully anonymized data.

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TABLES

Table 1. Multivariable linear regression analysis for predictors of cerebral edema.

	ß coefficient	95% CI	p	ß standardized
Number of passes	0.062	0.012 - 0.364	0.016	0.205
Mean SBP during EVT	0.006	0.002 - 0.011	0.008	0.215
mTICI 3	-0.272	-0.456 - (-0.088)	0.004	-0.245

CI, confidence interval.

*Adjusted for NIHSS, collateral circulation, EVT duration

Table 2. Multivariable ordinal regression analysis for predictors of an unfavorable outcome at three months of follow-up.

	cOR	CI	p
∆CSF	1.05	1.03 - 1.08	<0.001
Age	1.04	1.01 - 1.06	0.005
Baseline mRS score	1.90	1.37 - 2.63	<0.001
NIHSS	1.13	1.07 - 1.18	<0.001
Number of passes	1.22	1.02 - 1.46	0.027

cOR, common odds ratio; CI, confidence interval.

*Constructed from an initial model including also sex, glycemia, ASPECTS, collateral circulation, mTICI 3 and symptomatic intracranial hemorrhage, which were consecutively excluded in each iteration in a stepwise selection modeling approach.

FIGURE LEGENDS

Figure 1. Edema CSF segmentation and quantification in baseline CT (a) and follow-up CT (b).

CT, computed tomography; CSF, cerebrospinal fluid; NWU, Net Water Uptake.

Figure 2. Distribution on the mRS score at three months of follow-up according to cerebral edema measured by ΔCSF.

mRS, modified Rankin scale