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Strokes and traumatic spinal cord and brain injury

PROSPECTIVE STUDY OF THE PREDICTION OF GROWTH OF THE CEREBRAL HAEMORRHAGE USING CT PERFUSION

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1. Project summary

Intracerebral hemorrhage is a devastating disease with high morbimortality. It represents 15% of strokes and mortality rates range from 35 to 50%, most of them in the first two days from stroke onset. Only 20% of patients are independent at 6 months. Despite these alarming figures, the therapeutic options remain almost non-existent, partly due to the lack of knowledge of pathophysiological events that occurred after the vessel rupture.

The two main events after vessel rupture are hematoma growth (HG) and perihematomal edema. While the impact of perihematomal edema on prognosis is unclear, HG has been independently associated with a worse outcome. HG is present in approximately 38% of patients and is the main factor in neurological deterioration. However, its causes are still unknown.

Early hematoma growth has been related to the presence of multiple bleeding focus in the clot's periphery. This active bleeding might be produced by the rupture of vessels in the surrounding hematoma tissue, or as a secondary process due to the mechanical shearing produced by the hematoma and potentially aggravated by reduced perfusion in these perihematomal region.

The "spot sign" has been considered a marker of this continued bleeding and has been associated with hematoma expansion and poor functional outcome in patients with ICH. Nowadays the most widely available technique to study and identify spot sign is CT angiography (CTA), which identifies the spot sign in 25-35% of patients with ICH. However, approximately 20% of patients with negative spot sign in CTA later develop a hematoma enlargement.

The aim of our study is to evaluate whether perihematomal hypoperfusion assessed by computed tomography perfusion (CTP) is related to hematoma expansion in patients with ICH, and also to know if the addition of CTP to the current diagnosis protocol in ICH patients can improve the sensitivity and/or specificity of the spot sign detection as a predictive marker for hematoma enlargement.

We included 150 patients undergoing basal cranial CT, followed by perfusion CT and angio-CT. Perfusion maps were then post-processed, hematoma volume was calculated, and patients were clinically monitored.

This project suffered from two main problems: on the one hand the difficulties in calculating the perfusion maps and on the other hand the delay in the inclusion of patients and post-processing of images due to the Covid impact. To solve the first problem, we contacted a research group at the Polytechnic of Girona that used a system of "deep learning" for the calculation of perfusion maps. To solve the second problem, we requested an extension of the maximum time allowed, which was 3 months. Due to these two issues, we were not able to start the results analysis phase until February 2022, which also delayed the dissemination of the results. Below are partial results that focus on the study of the perihematomal area using perfusion maps and their impact on hematoma growth. We are currently working on the rest of our goals.

2. Results

Background

Hematoma growth (HG) is the main cause of neurological deterioration in patients with acute intracerebral hemorrhage (ICH), however its pathophysiology remains unclear. The presence of spot sign (SS) has been considered an independent predictor of HG. The aim of this study is to evaluate whether perihematomal hypoperfusion assessed by computed tomography perfusion (CTP) is related to hematoma expansion in patients with ICH, and also to know if the addition of CTP to the current diagnosis protocol in ICH patients can improve the sensitivity and/or specificity of the spot sign detection as a predictive marker for hematoma enlargement.

Methods

Patients with a primary and anticoagulation-associated ICH of 12 hours of evolution were included in the study. A non-contrast cranial CT (NCCT), CTP and CT angiography were performed at admission, and an NCCT was done at 24 and 72 hours. The presence of SS was assessed in the CTA and CTP studies. Hematoma and perihematomal edema volumes were quantified in all the NCCT by means of an automatic segmentation of deep learning previously validated by our group (Figure 1 and 2). The difference in

volume (> 33% and/or 6 ml) between the baseline CT and control CT determined the hematoma growth. CBV, MTT and CBF were calculated in the CTP. Neurological deficit was evaluated through the NIH stroke scale on admission, at 24 hours, 72 hours, 7 days and 90 days after onset. We assessed mortality during hospitalization and at 90 days. Functional impairment was assessed by modified Rankin scale at 90 days.

Results

A total of 150 patients were included (median age 73 years, 38% women). Median time from stroke onset to cranial CT was 3.25 hours [1.97; 7.69] and 14% of patients were taking anticoagulant treatment. Hematoma growth was detected in 22.67% of patients.

Female sex, and NIHSS were the only clinical variables associated with HG in the univariate analysis (Table 1). Blood pressure at different times had no impact on HG in our series. Hematoma expansion was associated with higher mortality during hospitalization and at 90 days.

Among radiological variables, baseline ICH volume, presence of spot sign, number of spots >1, size of spots, lobar location of ICH, TMAX and TTP values were associated with HG (Table 2). After adjustment for potential confounders, TMAX was the only CTP variable independently associated with HG and this association remains significant even including the presence of spot sign. In the ROC analysis TMAX ≥5,89 showed the best sensitive value for prediction of HG (sensitivity, 0.81; specificity, 0.41).

Conclusions: Delayed TMAX was associated with HG, suggesting a potential role of the perihematomal area in the mechanisms that lead to hematoma expansion.

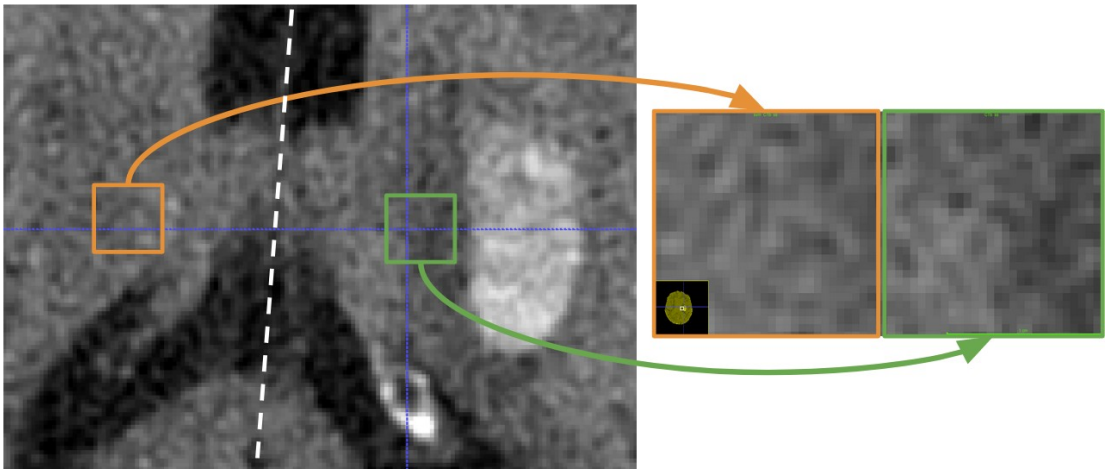

Figure 1. Example of two bilateral patches extracted from a patient with perihematomal hypodensity.

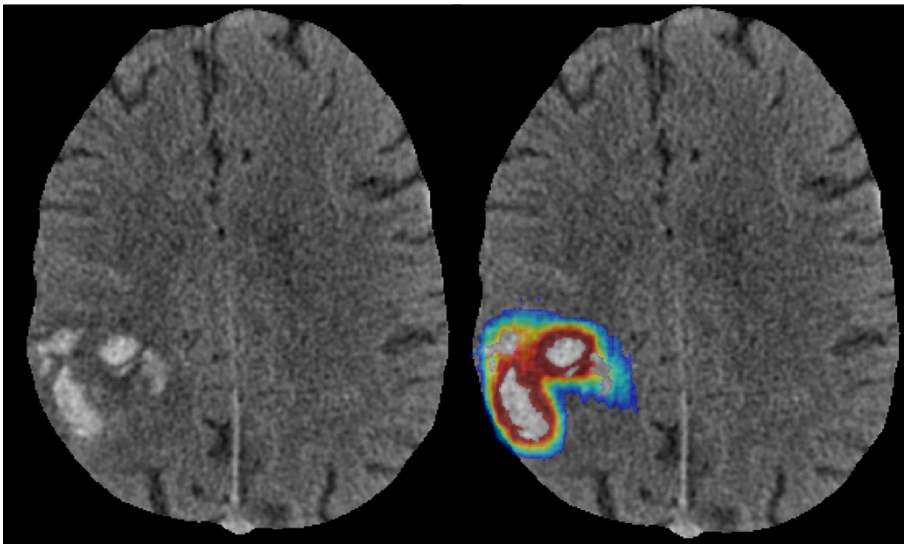

Figure 2. Non-contrast CT image slice and resulting perihematomal edema probability map

		Hematoma Growth		
	[ALL] N=150	**no N=109**	**yes N=41**	**p-value**
Age	73[62.25;83]	72 [61;82]	78[67;84]	0.115
Sex, Female	57 (38%)	34 (31.19%)	23 (56.10%)	**0.009**
Time onset-CT, hours	3.25 [1.97;7.69]	3.52 [2.20;8.22]	2.70 [1.73;7.07]	0.096
Hypertension	120 (80%)	90 (82.57%)	30 (73.17%)	0.29
Diabetes	41 (27.33%)	32 (29.36%)	9 (21.95%)	0.48
Cognitive impairment	17 (11.33%)	10 (9.17%)	7 (17.07%)	0.245
Smoking	28 (19.31%)	22 (20.75%)	6 (15.38%)	0.570
Alcohol intake	29 (20%)	19 (18.10%)	10 (25%)	0.444
Statins treatment	43 (28.67%)	34 (31.19%)	9 (21.95%)	0.361
Antidepressant treatment	28 (18.67%)	20 (18.35%)	8 (19.51%)	1.000
Anticoagulant treatment	21 (14.00%)	15 (13.76%)	6 (14.63%)	1.000
Antiplatelet treatment	38 (25.33%)	26 (23.85%)	12 (29.27%)	0.639
SBP, median admission, mmHg	170 [150.25;188.75]	169.5 [148;190]	170 [157;185]	0.812
DBP, median admission, mmHg	88 [77;105.25]	90 [75;106]	87 [80;100]	0.949
SBP, median 6 hours, mmHg	139 [125;151.75]	139 [125;150.75]	140.5 [124.5;152.5]	0.603
DBP, median 6 hours, mmHg	75 [65;85]	74 [63.25;85]	77 [68.50;83.5]	0.400
SBP, median 12 hours, mmHg	135 [123;148]	135 [125.25;143.75]	141 [121;155]	0.385
DBP, median 12 hours, mmHg	72. [60.5;81.5]	71 [60.75;81.75]	73 [62.5;80]	0.812
SBP, median 24 hours, mmHg	137 [123.75;150]	137 [123.25;149.75]	139.5 [124;150.75]	0.773
DBP, median 24 hours, mmHg	71.5 [62.00;82.25]	71 [61;83.5]	77. [65;81.75]	0.575
SBP, median 72 hours, mmHg	140 [127.5;150]	139 [128;148]	141.5 [123.75;152.75]	0.566
DBP, median 72 hours, mmHg	75 [64.5;84]	74. [65;82]	77.5 [63.5;85.75]	0.539
NIHSS admission	10 [5;18]	8 [5;15]	18 [10;21]	**<0.001**
Hematocrit	41[37.2;44]	41 [37.8;44]	41[37;44]	0.763
Platelets x1000	221 [182;250.75]	215[175;250]	231[200;251]	0.141
Leucocytes x1000	8.55 [7.06;10.11]	8.45 [7.13;10.03]	9.06 [6.68;10.41]	0.950
PTT	29.1 [26.72;32.27]	29.6 [27.3;32.6]	28.5 [26.4;31.1]	0.098
INR	1.06 [1.00;1.14]	1.07 [1.01;1.15]	1.03 [1.00;1.11]	0.079
LDL- Cholesterol	95 [74;117]	93[66.75;116.5]	98 [80;117]	0.486
END	31 (20.67%)	20 (18.35%)	11 (26.83%)	0.359
Intrahospital Mortality	18 (12.00%)	6 (5.50%)	12 (29.27%)	**<0.001**
Mortality 90 days	29 (19.73%)	12 (11.11%)	17 (43.59%)	**<0.001**

Table 1. Univariate analysis. Clinical variables associated with relevant hematoma growth. SBP, systolic blood pressure. DBP, diastolic blood pressure. END, early neurological deterioration.

		Hematoma growth		
	[ALL] N=150	**no N=109**	**yes N=41**	**p-value**
Presence of Spotsign	30 (20.13%)	10 (9.26%)	20 (48.78%)	**<0.001**
Number of SS	1.50 [1.00;2.00]	1.00 [1.00;1.00]	2.00 [1.00;2.00]	**0.018**
Size of SS	6.00 [4.00;8.00]	3.50 [2.25;4.75]	7.00 [5.75;9.00]	**0.001**
Lobar location	42 (28.00%)	24 (22.02%)	18 (43.90%)	**0.014**
Intraventricular blood	47 (31.33%)	36 (33.03%)	11 (26.83%)	0.59
ICH Volume, baseline, cc	9.23 [4.00;18.45]	6.98 [2.84;15.10]	19.14 [10.34;43.21]	**<0.001**
ICH Volume 24 hours, cc	12.20 [3.48;23.19]	6.58 [2.84;15.20]	31.51 [18.05;59.27]	**<0.001**
ICH Volume 72 hours, cc	9.43 [3.46;20.48]	7.00 [2.75;15.45]	35.09 [18.24;51.45]	**<0.001**
Edema Volume, baseline, cc	0.08 [0.03;0.12]	0.06 [0.03;0.11]	0.11 [0.07;0.16]	0.46
MTT	9.46 [8.24;11.54]	9.60 [8.79;11.57]	8.63 [7.46;11.45]	0.098
rBF	16.12 [10.58;26.12]	15.98 [10.56;26.24]	16.13 [10.77;25.53]	0.832
rBV	3.15 [1.98;4.74]	3.20 [2.00;4.72]	3.14 [1.80;4.74]	0.836
TMAX	7.57 [4.88;10.53]	6.99 [4.54;9.30]	9.72 [6.49;12.36]	**0.004**
tMIP	4886.55 [3802.69;6168.34]	5223.66 [3913.94;6271.70]	4414.34 [3729.32;5494.52]	0.26
TTP	24.28 [21.02;28.01]	23.37 [20.74;26.76]	26.28 [21.91;29.40]	**0.022**
rBF_5g:				0.809
<10	26 (20.47%)	19 (21.11%)	7 (18.92%)	
[10-20]	51 (40.16%)	36 (40.00%)	15 (40.54%)	
(20-40]	31 (24.41%)	23 (25.56%)	8 (21.62%)	
(40-55]	5 (3.94%)	4 (4.44%)	1 (2.70%)	
>55	14 (11.02%)	8 (8.89%)	6 (16.22%)	
rBV_2.5:				0.796
<2.5	52 (40.94%)	38 (42.22%)	14 (37.84%)	
>= 2.5	75 (59.06%)	52 (57.78%)	23 (62.16%)	
MTT_5:				0.155
<=5	5 (3.91%)	2 (2.22%)	3 (7.89%)	
>5	123 (96.09%)	88 (97.78%)	35 (92.11%)	
rBF_rBCV_MTT:				0.820
Ischemic	26 (20.47%)	19 (21.11%)	7 (18.92%)	
Penumbra_I	26 (20.47%)	19 (21.11%)	7 (18.92%)	
Penumbra_R	56 (44.09%)	40 (44.44%)	16 (43.24%)	
Normal	5 (3.94%)	4 (4.44%)	1 (2.70%)	
Hyperemia	14 (11.02%)	8 (8.89%)	6 (16.22%)	

Table 2. Univariate analysis. Radiological variables associated with relevant hematomagrowth. SS, spot sign.

3. Relevance with possible future implications

Our study shows that there is an area of penumbra in the perihematoma area and that this is associated with the significant growth of the hematoma, which is one of the main causes of neurological deterioration in patients with intracerebral hemorrhage and mortality. This fact is of particular interest because there is no effective treatment for these patients so far and this is partly due to the lack of knowledge of pathophysiological mechanisms related to the relevant growth of the hematoma. Future lines are to assess the impact of blood pressure and surgery on these patients, taking into account the thresholds obtained in our work, which identify as patients at risk those that detect levels of TMAX $\geq$ 5.86.

4. Generated scientific bibliography

[1] Abramova, V., Clèrigues, A., Quiles, A., Figueredo, D. G., Silva, Y., Pedraza, S., Oliver,A., & Lladó, X. (2021). **Hemorrhagic stroke lesion segmentation using a 3D U- Net with squeeze-and-excitation blocks.** *Computerized Medical Imaging and Graphics* 90, 101908 https://doi.org/https://doi.org/10.1016/j.compmedimag.2021.101908