White Matter Hyperintensity Severity Predicts Development of Cerebral Edema in Patients with Ischemic Stroke Treated with IV Thrombolysis: Implications for Infarct Growth and Functional Outcome

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BACKGROUND AND OBJECTIVES

- Increased white matter hyperintensity (WMH) burden may be associated with chronic endothelial injury, impaired cerebrovascular reactivity, blood-brain barrier (BBB) disruption, and chronic hypoperfusion.^{1,2}
- The aim of this study was to evaluate whether in patients with acute ischemic stroke (AIS) treated with IV thrombolysis, moderate to severe WMH predicts development of cerebral edema (CE) with consequent implications for infarct growth (IG) and functional outcome.

METHODS

- Study subjects:** AIS patients treated with IV rt-PA at the stroke unit of the Policlinico Umberto I Hospital, Sapienza University of Rome, from January 2012 to December 2015 and entered into SITS-ISTR (Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Register).
- Data collection:** Demographic and clinical data (including common vascular risk factors, pre- and post-stroke therapy, NIHSS at baseline, 2h, 24h, and 7days/discharge, baseline and follow-up BP values, blood glucose levels, stroke subtype) neuroimaging data, and outcome measures.
- Outcome measures:** (early neurological deterioration [END], symptomatic intracerebral hemorrhage [SICH] by NINDS, ECASS and SITS-MOST definitions, 3-month mRS [3-6 as poor outcome], mortality).
- Neuroimaging analysis:**
 - WMH was measured by modified Fazekas scale on baseline FLAIR mainly on the contralateral hemisphere;
 - CE was measured by a visual score (used for SITS-MOST) on baseline FLAIR performed within 24 h of symptom onset;
 - Infarct volume was measured by using the formula ABC/2 at baseline DWI performed within 24h of symptom onset and at follow-up on DWI/FLAIR or CT performed >24h from symptom onset in order to measure also IG.
- Statistical analysis:** Fisher exact test, χ^2 test and t-test or Mann Withney test were used as appropriate. Multivariable binary logistic regression was used to adjust for the effects of potential confounders. A p value <0.05 was considered statistically significant.

RESULTS

Overall, 440 patients were included (mean age [SD] 69.3 [13.6]; 41.4% women; median [IQR] NIHSS 8 [4-15]); 84 (22.6%) patients had moderate/severe WMH. CE was observed in 121 (36.8%) patients.

In univariate analyses, moderate/severe WMH was significantly associated with the development of CE ($p=0.005$). Patients with CE at baseline were more likely to have END, SICH, and IG ($p<0.05$ each) (Table 1).

Both WMH and CE resulted significantly associated with 90-day poor functional outcome ($p<0.01$) (Table 1 and Figure).

In multivariate analysis, after adjusting for confounding variables, moderate/severe WMH independently predicts development of CE (OR 5.52, 95% CI 2.08-14.62, $p=0.001$) (Table 2).

Table 1. Baseline demographic and clinical/radiological characteristics by cerebral edema

	All (N=329)	No cerebral edema (N=208)	Cerebral edema (N=121)	p
Age, mean ($\pm$ S.D.)	69.3 (13.6)	68.5 (14.3)	73.1 (10.6)	0.024
Gender (female) (%)	134 (40.5)	85 (40.9)	49 (40.5)	0.948
Atrial fibrillation (%)	58/327 (17.7)	29/206 (14.1)	29/121 (24.0)	0.024
NIHSS at baseline, median (IQR)	8 (4-15)	6 (4-10)	16 (10-19.75)	<0.001
NIHSS at 2h, median (IQR)	6 (3-12.75)	4 (2-8)	16 (7-20)	<0.001
NIHSS at 24h, median (IQR)	4 (1-11.25)	2 (1-7)	13.5 (5-20)	<0.001
NIHSS at 7d/discharge, median (IQR)	2 (0-9)	1 (0-3)	12.5 (2-20)	<0.001
Stroke subtype (%)				<0.001
- Atherothrombotic	24/305 (7.9)	10/187 (5.3)	14/118 (11.9)	0.040
- Cardioembolic	111/305 (36.4)	58/187 (31.0)	53/118 (44.9)	0.014
- Lacunar	31/305 (10.2)	30/187 (16.0)	1/118 (0.8)	<0.001
- Large vessels, Other	24/305 (7.9)	14/187 (7.5)	10/118 (8.5)	0.755
- Multiple causes/Unknown	101/305 (33.1)	66/187 (35.3)	35/118 (29.7)	0.309
- Unusual	14/305 (4.6)	9/187 (4.8)	5/118 (4.2)	0.815
Neuroimaging				
WMH, moderate/severe (%)	71/2171 (26.2)	35/171 (20.5)	36/100 (36.0)	0.005
Early ischemic sign (%)	49/311 (15.8)	24/198 (12.1)	25/113 (22.1)	0.020
Dense artery sign (%)	52/310 (16.8)	15/196 (7.7)	37/114 (32.5)	<0.001
Baseline Infarct V, median (IQR), cm ³	2.0 (0.2-12.7)	0.7 (0-2.4)	17.9 (6.8-64.8)	<0.001
Follow-up Infarct V, median (IQR)	4.8 (0.3-24.8)	1.4 (0-10.4)	19.9 (9.3-82.4)	0.001
Infarct growth (%)	58/101 (57.4)	30/64 (46.9)	28/37 (75.7)	0.005
Vessel occlusion (%)	76/273 (27.8)	29/172 (16.9)	47/101 (46.5)	<0.001
Outcome measures				
SICH/NINDS (%)	29/314 (9.2)	5/198 (2.5)	24/116 (20.7)	<0.001
SICH/ECASS (%)	10/313 (3.2)	2/197 (1.0)	8/116 (6.9)	0.006
Early neurological deterioration (%)	20/315 (6.3)	7/201 (3.5)	13/114 (11.4)	0.006
mRS 3-6 at 3 months (%)	109/286 (38.1)	41/173 (23.7%)	68/113 (60.2)	<0.001
mRS 2-6 at 3 months (%)	151/289 (52.2)	63/175 (36.0)	88/114 (77.2)	<0.001
Mortality (%)	39/290 (13.4)	14/176 (8.0)	25/114 (21.9)	<0.001

Figure. Significant associations between WMH severity and cerebral edema and poor outcome (mRS 3-6)

Table 2. Multivariate logistic regression models for cerebral edema

	OR	95% CI	p
WMH moderate/severe	5.52	2.08-14.62	0.001
NIHSS at baseline	1.15	1.07-1.24	<0.001
Infarct V at baseline	1.12	1.07-1.17	<0.001
Atherothrombotic stroke subtype	5.72	1.49-21.90	0.011
Cardioembolic stroke subtype	3.76	1.53-9.22	0.004

CONCLUSIONS

- In AIS patients treated with IV thrombolysis, WMH severity, as potential sign of chronic microvascular dysfunction and increase of BBB permeability, predicts the development of CE.
- Individuation of specific quantitative WMH volume cutoffs may have implication for improving infarct growth and functional outcome prediction.

REFERENCES

- Rost NS, Cougo P, Lorenzano S, Li H, Cloonan L, Bouts MJRJ, Lauer A, Etherton MR, Karadeli HH, Musolino PL, Copen WA, Arai K, Lo EH, Feske SK, Furie, KL, Wu O. Diffuse microvascular dysfunction and loss of white matter integrity predict poor outcomes in patients with acute ischemic stroke. J Cereb Blood Flow Metab 2018;; 38:75-86.
- Thorén M, Azevedo E, Dawson J, Egido JA, Falcou A, Ford GA, Holmin S, Mikulik R, Ollikainen J, Wahlgren N, Ahmed N. Predictors for cerebral edema in acute ischemic stroke treated with intravenous thrombolysis. Stroke 2017; 48:00-00. DOI:10.1161/STROKEAHA.117.018223.