White Matter Hyperintensity in Acute Ischemic Stroke: the “Silent Influencer”

Svetlana Lorenzano MD, PhD, MSc;¹ Natalia S. Rost MD, MPH;¹ Hua Li MD;² Aurauma Chutinet MD;¹ Fabricio Lima MD;¹ Rebecca E. Green, BA;¹ Tijj K. Thankachan BA;¹ Ona Wu PhD;³ Gordon J. Harris, MD;² Steven K. Feske, MD;⁴ Karen L. Furie, MD, MPH⁵

1. Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA; 2. Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA; 3. Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Charlestown, Massachusetts, USA; 4. Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; 5. Department of Neurology, Rhode Island Hospital, Alpert Medical School of Brown University, Providence, RI, USA

BACKGROUND AND OBJECTIVES

- White matter hyperintensity(WMH) represents a marker of chronic and apparently “silent” cerebrovascular injury that may be associated with higher susceptibility to acute ischemic injury.
- We sought to evaluate whether in patients with acute ischemic stroke (AIS) increased WMH burden may have an influence on ischemic penumbra volume, clinical and infarct progression, and unfavourable outcome.

METHODS

- Study subjects:** We analyzed data of AIS patients presenting within 9 hours of symptom onset and prospectively included in a multicenter acute ischemic stroke biomarker study over a period of 3 yrs.^{1,2}
- Outcome measures:** Early neurological deterioration [END] defined as (≥ 4 points at the NIHSS or death at 24 hrs), symptomatic intracerebral hemorrhage (defined as any bleeding plus any neurological deterioration [NIHSS score ≥ 1] or that leads to death within 7 days), modified Rankin Scale (mRS) score at 3 months of 3-6 indicating an unfavorable outcome, mortality).
- Neuroimaging analysis:**
 - WMH, PWI-DWI mismatch, and infarct volumes were measured using semi-automated volumetric method.
 - WMH volumes (WMHv) was measured on baseline FLAIR on the hemisphere contralateral to the index infarct.
 - Mismatch volumes were defined as the difference between baseline MTT and DWI volumes.
 - Infarct volumes were measured at baseline DWI and follow-up at DWI or CT scan performed at 48 hours (with a range from 24 to 96 hours) from symptom onset. Infarct growth volume was defined as the final infarct volume minus the baseline DWI volume.
- Statistical analysis:** Fisher exact test or χ^2 test and t-test or Mann Withney test, Spearman's coefficient and linear regression were used as appropriate. Multivariate linear and binary logistic regression analyses were used to adjust for the effects of potential confounders. A p value < 0.05 was considered statistically significant.

RESULTS

Overall, 489 patients (43.4% females; mean [SD] age 70.1[15.1]; median[IQR] NIHSS 6[3-13]; 40.7% treated with IV t-PA) had a median[IQR] WMHv of 3.40[1.40-9.51] cm³. As regards to main outcome measures in acute stroke, at univariate analyses higher WMHv was significantly associated with END, 3-month unfavorable functional outcome and death, while a lower WMH burden correlated with higher mismatch and mismatch salvage volumes ($P < 0.05$) (Table 1). In multivariate analyses, regardless the treatment with IV thrombolysis, WMHv resulted as independent predictor of mismatch volume (Beta -0.148, 95%CI -1.120,-0.053; $P = 0.031$), with a borderline statistical significance for mismatch salvage volume (Beta -0.319, 95%CI -1.173,0.023; $P = 0.059$) and of 3-month functional outcome (OR 1.43, 95%CI 1.001, 2.037; $P = 0.049$) Tables 2-4).

Table 1. Association between WMHv and baseline demographic, clinical/radiological characteristics, and outcome measures

	All (N=489)	WMHv		P
		Beta	95% CI	
Age, mean ($\pm$ S.D.)	70.1 (15.1)	0.533	0.030, 0.041	< 0.001
Gender (female) (%)	212/488 (43.4)	0.155	0.119, 9.516	0.002
Pre-stroke mRS (0-1) (%)	392/479 (81.8)	-0.372	-1.286, -0.778	< 0.001
Hypertension (%)	356/488 (73)	0.256	0.363, 0.791	< 0.001
Atrial fibrillation (%)	159/488 (32.6)	0.218	0.272, 0.697	< 0.001
Prior stroke (%)	96/488 (19.7)	0.177	0.209, 0.711	< 0.001
Congestive heart failure (%)	60/480 (12.5)	0.183	0.302, 0.981	< 0.001
BMI, mean ($\pm$ S.D.)	27.7 (6.2)	-0.119	-0.038, -0.002	0.026
Antiplatelet therapy prior to stroke (%)	221/452 (48.9)	0.131	0.012, 0.059	0.012
Warfarin prior to stroke (%)	60/452 (13.3)	0.123	0.065, 0.710	0.019
SBP, mean ($\pm$ S.D.)	155.3 (28.4)	0.246	0.005, 0.012	< 0.001
DBP, mean ($\pm$ S.D.)	82.2 (15.9)	0.135	0.002, 0.015	0.007
NIHSS at baseline, median (IQR)	6 (3-13)	0.148	0.008, 0.036	0.003
NIHSS at 48 h, median (IQR)	4 (1-10.8)	0.162	0.009, 0.041	0.002
NIHSS at discharge, median (IQR)	3 (1-8)	0.141	0.006, 0.044	0.011
IV t-PA (%)	198/487 (40.7)	-0.041	-0.289, 0.119	0.415
Cardioembolic stroke subtype (%)	249/489 (50.9)	0.132	0.072, 0.466	0.008
WMH V, median (IQR), cm ³	3.4 (1.4-9.5)	-	-	-
Baseline Infarct V, median (IQR), cm ³	6.7 (1.2-23.4)	0.029	-0.047, 0.085	0.572
Follow-up Infarct V, median (IQR), cm ³	19.5 (3.5-55.5)	-0.196	-0.304, 0.020	0.085
Infarct growth volume, median (IQR), cm ³	4.8 (0.2-27.3)	-0.118	-0.223, 0.080	0.352
MTT volume, median (IQR), cm ³	32.2 (7.5-91.9)	-0.166	-0.190, -0.022	0.014
Mismatch volume, median (IQR), cm ³	13.5 (0.1-58.5)	-0.143	-0.169, 0.001	0.054
Mismatch salvage volume, median (IQR), cm ³	-0.1 (-30.2, 35.5)	-0.414	-0.418, -0.042	0.018
SICH/NINDS (%)	12/73 (16.4)	0.188	-0.257, 1.1466	0.165
Early neurological deterioration (%)	54/455 (11.9)	0.108	0.024, 0.696	0.036
mRS 3-6 at 3 months (%)	187/428 (43.7)	0.272	0.359, 0.781	< 0.001
mRS 2-6 at 3 months (%)	240/428 (56.1)	0.251	0.307, 0.723	< 0.001
Death (%)	78/428 (18.2)	0.227	0.361, 0.952	< 0.001

Table 2. Multivariate linear regression analysis for mismatch volume

	Beta	95% CI	p
WMHv > 1.4 cm ³	-0.148	-1.120, -0.053	0.031
NIHSS at baseline	0.386	0.068, 0.140	< 0.001

Adjusted for WMHv, NIHSS at baseline, AF, IV t-PA (collinearity between age and WMHv)

Table 3. Multivariate linear regression analysis for mismatch salvage volume

	Beta	95% CI	p
lnWMHv	-0.319	-1.173, 0.023	0.059
ln baseline infarct V	0.387	0.109, 1.449	0.024

Adjusted for ln baseline infarct V, IV t-PA (collinearity between age and WMHv)

Table 4. Multivariate logistic regression analysis for unfavorable outcome (mRS 3-6)

	OR	95% CI	p
lnWMHv	1.43	1.001-2.037	0.049
Pre-stroke mRS 0-1	0.10	0.038-0.272	< 0.001
Diabetes mellitus	3.64	1.667, 7.953	0.001
NIHSS at baseline	1.32	1.226-1.414	< 0.001

Adjusted for lnWMHv, gender, pre-stroke mRS 0-1, AF, hypertension, diabetes mellitus, antiplatelet therapy prior to stroke, IV t-PA, glucose levels at baseline, NIHSS at baseline, ln baseline infarct V (collinearity between age and WMHv)

CONCLUSIONS

- Measuring WMH burden with automated software in the acute setting and its inclusion in risk scores might be helpful to better stratify AIS patients for improving prediction of brain tissue fate and clinical outcome.
- Individuation of specific quantitative WMH volume cutoffs may have implication for improving management of acute treatment strategies for ischemic stroke.

REFERENCES

- Natalia S Rost, MD, Kaitlin Fitzpatrick, BS, Alessandro Biffi, MD, Allison Kanakis, BS, William Devan, BS, Christopher D. Anderson, MD, Lynelle Cortellini, MS, Karen L Furie, MD MPH, and Jonathan Rosand, MD MSc. White Matter Hyperintensity Burden and Susceptibility to Cerebral Ischemia. Stroke 2010;41:2807-2811.
- 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.