Atherosclerosis 240 (2015) 149–153

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Metabolic determinants of white matter hyperintensity burden in patients with ischemic stroke

Lisa Cloonan [a], Kaitlin M. Fitzpatrick [a], Allison S. Kanakis [a], Karen L. Furie [a, 1], Jonathan Rosand [a, b, c], Natalia S. Rost [a, b, *]

[a] J. Philip Kistler Stroke Research Center, Department of Neurology, Massachusetts General Hospital, Boston, MA 02114, USA
[b] Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA 02114, USA
[c] Division of Neurocritical Care and Emergency Neurology, Department of Neurology, Massachusetts General Hospital, Boston, MA 02114, USA

ARTICLE INFO

Article history:
Received 20 September 2014
Received in revised form
12 February 2015
Accepted 24 February 2015
Available online 2 March 2015

Keywords:
White matter hyperintensity
Hyperglycemia
Hyperhomocysteinemia
Endothelial dysfunction
Acute ischemic stroke
Blood biomarkers
Small vessel disease

ABSTRACT

Objective: Increasing white matter hyperintensity (WMH) burden is linked to risk of stroke and poor post-stroke outcomes. While the biology of WMH remains ill-defined, several lines of evidence implicate endothelial dysfunction. In this study, we sought to assess the association between metabolic markers of endothelial dysfunction and WMH severity in patients with acute ischemic stroke (AIS).

Methods: In this retrospective study, consecutive subjects, ≥18 years of age, admitted to our ED with AIS, brain MRI, and blood homocysteine (Hcy) and hemoglobin A1c (HgbA1c) measurements were eligible for this analysis. WMH volume (WMHV) was quantified using a validated semi-automated algorithm and log-transformed for linear regression analyses.

Results: There were 809 AIS subjects included (mean age 65.57 ± 14.7, median WMHV 6.25 cm^3 (IQR 2.8 −13.1)). In univariate analysis, age, female gender, race, ethnicity, systolic blood pressure, history of hypertension, atrial fibrillation, coronary artery disease, prior stroke, and current alcohol and tobacco use (all $p < 0.05$), as well as Hcy ($p < 0.0001$) and HgbA1c levels ($p = 0.0005$) were associated with WMHV. However, only Hcy ($\beta = 0.11$, $p = 0.003$) and HgbA1c levels ($\beta = 0.1$, $p = 0.008$) independently predicted WMHV in the multivariate model, along with age ($\beta = 0.03$, $p < 0.0001$), race ($\beta = 0.39$, $p = 0.01$), ethnicity ($\beta = -0.11$, $p = 0.03$), and current alcohol use ($\beta = 0.26$, $p = 0.002$).

Conclusions: Elevated levels of Hcy and HgbA1c have been previously linked to endothelial dysfunction related to oxidative stress. The association between Hcy and HgbA1c and WMH burden in AIS suggests that the degree of endothelial dysfunction may be greater in patients with increased WMHV, and may in part explain the relationship between WMHV and poor post-stroke outcomes.

1. Introduction

White matter hyperintensity (WMH), also known as leukaraiosis, is an abnormality in cerebral tissue architecture, detected on neuroimaging and is most commonly present in the elderly and patients with stroke [1–3]. WMH is considered to be a part of small vessel disease pathology; and therefore, WMH burden is greater in individuals with common cerebrovascular risk factors, such as hypertension, diabetes mellitus (DM), and smoking [1,4]. The exact pathophysiology of WMH remains poorly understood, but some studies suggested that inflammatory markers, such as the intercellular adhesion molecule-1 (sICAM-1) [5], and plasma markers linked to endothelial health such as homocysteine (Hcy) may contribute to WMH burden in addition to traditional vascular risk factors [6].

The endothelium plays a key role in maintaining vascular tone, vessel-wall permeability, and thromboresistance [7]. Atherogenic states including DM and hyperhomocysteinemia are thought to promote endothelial dysfunction via the metabolites associated with these conditions, such as plasma Hcy and chronic hyperglycemia (as measured by plasma levels of hemoglobin A1c (HgbA1c)),

* Corresponding author. J. Philip Kistler Stroke Research Center, Massachusetts General Hospital, 175 Cambridge Street, Suite 300, Boston, MA 02114, USA.
E-mail addresses: lcloonan@partners.org (L. Cloonan), kaitlin.fitzpatrick@gmail.com (K.M. Fitzpatrick), allison.kanakis@gmail.com (A.S. Kanakis), kfurie@lifespan.org (K.L. Furie), jrosand@partners.org (J. Rosand), nrost@partners.org (N.S. Rost).
[1] Present address: Department of Neurology, Rhode Island Hospital, Alpert Medical School of Brown University, 110 Lockwood St., Suite 324, Providence, RI 02903, USA.

http://dx.doi.org/10.1016/j.atherosclerosis.2015.02.052
0021-9150/

which increase oxidative stress, thrombogenicity, over-activation of redox-sensitive inflammatory pathways, and atherogenesis [8–10]. In comparison to the previously validated experimental biomarkers of endothelial dysfunction [11], such as sICAM-1, vascular cell adhesion molecule-1 (VCAM-1), E-selectin, P-selectin and others, plasma Hcy and HgbA1c maintain relatively stable levels during acute events, are linked to the direct markers of endothelial function through common metabolic disease pathways, and importantly, are readily available for use in clinical practice [12–14]. These characteristics render Hcy and HgbA1c as relevant and readily generalizable, albeit surrogate, biomarkers of endothelial function for use in applied clinical research.

In this study, we hypothesized that the severity of WMH is linked, in part, to the degree of endothelial dysfunction, and this relationship can be assessed through the use of commonly available clinical biomarkers of endothelial function, such as Hcy and HgbA1c. In this analysis, we examined the association between the plasma levels of Hcy and HgbA1c and the severity of WMH measured on the brain MRI of patients with ischemic stroke.

2. Methods

2.1. Subjects and data collection

All consecutive patients ≥18 years old, arriving to Massachusetts General Hospital Emergency Department (MGH ED) between July 2000 and October 2010, with signs and symptoms of acute ischemic stroke (AIS) were considered for this study. In this retrospective analysis of prospectively collected data, we included all consenting patients with: (1) evidence of acute cerebral infarct confirmed by diffusion-weighted imaging (DWI), (2) admission T2 fluid attenuated inversion recovery (FLAIR) MRI sequences available for volumetric WMH analysis, and (3) plasma Hcy and HgbA1c values drawn upon hospital admission. The Partners Institutional Review Board (IRB) approved of human subjects participation in this study. IRB-approved subject or proxy informed consent was obtained prior to subjects' enrollment into the study.

Data were obtained through medical record review and/or in-person interviews. Baseline clinical characteristics and laboratory values, including plasma Hcy and HgbA1c levels were obtained on ED admission. Based on MGH Pathology service classification, normal ranges of Hcy and HgbA1c values are defined as 0–12 μmol/L and 3.8–6.4%, respectively.

2.2. Neuroimaging protocol and analysis

We have previously published a volumetric analysis method used to assess WMH severity in this cohort [15]. The semi-automated protocol used MRI scans obtained from a 1.5T scanner. Scans acquired closest to stroke onset were analyzed. Prior to analysis, MRI scans were converted from DICOM into Analyze format through the use of MRICro (University of Nottingham School of Psychology, Nottingham, UK; www.mricro.com). DWI and T2 FLAIR sequences were collated and cross-referenced to identify and exclude edema, hemorrhages, and infarcts from the WMH volume (WMHV) measurement. WMHs present in the supratentorial region were manually outlined and saved as a region of interest (ROI). A ROI matching the signal threshold of the WMH was created and intersected with the manually outlined WMH ROI. The intersection of these two ROIs was then manually touched up by a trained reader. The total WMHV was calculated by doubling the WMHV on the hemisphere unaffected by the stroke. Patients who presented with bilateral supratentorial lesions or brainstem infarcts were included in this analysis by combining both hemispheres' WMHVs to determine the total WMHV. To control for variation in head size, the intracranial area (ICA) was measured from two midline sagittal T1 slices, and then the total WMHV was multiplied by the mean-to-the-individual ICA ratio.

2.3. Statistical analysis

WMHV values adjusted for head size were log-transformed for all analyses in this study. All variables were reported as either a mean value (±standard deviation (SD)), a median value with an interquartile range (IQR), or a proportion/percentage of the total. Univariate linear regression analysis was used to assess the association between WMHV and the clinical variables, including quartiles of Hcy and HgbA1c. Those variables that reached a p-value <0.10 in univariate analysis were used in the multivariate linear regression analysis of WMHV. Statistical significance was set at p-value <0.05 in all analyses. Quantitative variables were treated as continuous variables. Quartiles of plasma Hcy and HgbA1c levels were derived and used in univariate and multivariate linear regression analyses. The statistical analysis was conducted using the SAS 9.1 statistical packages (*SAS Institute Inc, Cary NC*).

2.4. Experimental results

Demographic and clinical data are reported in Table 1. There were 809 subjects included in this analysis (mean age 65.57 ± 14.69 years, 37% female), of whom 750 (92.8%) were White and 718 (88.9%) were non-Hispanic. The median WMHV in this cohort was 6.25 cm^3 (IQR 2.8–13.1).

In univariate analysis, Hcy ($\beta = 0.23$, $p < 0.0001$), HgbA1c ($\beta = 0.12$, $p = 0.0005$) (Fig. 1), as well as age ($\beta = 0.04$, $p < 0.0001$), White race ($\beta = 0.63$, $p < 0.0001$), non-Hispanic ethnicity ($\beta = -0.19$, $p = 0.0002$), female gender ($\beta = 0.24$, $p = 0.004$), admission systolic blood pressure ($\beta = 0.008$, $p < 0.0001$), prior history of hypertension ($\beta = 0.55$, $p < 0.0001$), atrial fibrillation ($\beta = 0.49$, $p < 0.0001$), coronary artery disease ($\beta = 0.29$, $p = 0.005$), current alcohol ($\beta = 0.31$, $p = 0.0001$) and tobacco use ($\beta = -0.32$,

Table 1
Demographic and clinical characteristics of 809 subjects with ischemic stroke.

Variables	
	Mean (SD)
Age (years)	65.57 (14.7)
Systolic blood pressure (mmHg)	151.76 (29.5)
Diastolic blood pressure (mmHg)	79.62 (15.4)
lnWMHV	1.83 (1.14)
	Median (IQR)
nWMHV (cm^3)	6.25 (2.8–13.1)
Homocysteine (μmol/L)	8.90 (7.2–11.4)
Hemoglobin A1c (%)	5.90 (5.5–6.5)
Creatinine (mg/dl)	1.00 (0.8–1.2)
NIHSS score	3.00 (1–7)
	N (%)
Gender (female)	299 (37)
Race (white)	750 (92.8)
Ethnicity (non-Hispanic)	718 (88.9)
Hypertension	507 (63.4)
Diabetes mellitus	165 (20.4)
Atrial fibrillation	118 (14.6)
Coronary artery disease	155 (19.2)
Hyperlipidemia	326 (40.3)
Prior TIA	64 (7.9)
Prior stroke	126 (15.6)
Tobacco use	159 (20.1%)
Alcohol use	420 (53.2%)

Abbreviations: β, beta; SD, standard deviation; lnWMHV, natural log transformed white matter hyperintensity volume; IRQ, interquartile range; nWMHV, normalized white matter hyperintensity volume; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.