Biogenic Amines Vol. 25, issue 4 (2011), pp. 253–261
BIA250411A02

White Matter Lesions (WMLs): a probable risk factor for Ischemic Stroke in a subset of Pakistani Population

Submitted: September 29, 2011 • *Accepted*: December 01, 2011.

Ghazala Naveed [1], Ambreen Butt [2],
Faraz A. Bokhari [3], Hasan S. Parvez [4]

1. Department of Physiology, Fatimah Jinnah Medical College (FJMC), Lahore
2. Department of Medicine Unit-4, Services Institute of Medical Sciences (SIMS), Lahore
3. Department of Physiology, Shaikh Zayed Federal Postgraduate Medical Institute (SZFPGMI), Lahore.
4. NEUROFON: Orsay Neuroscience, Orsay, France

Key words: white matter lesions; stroke; CT Scan

INTRODUCTION

Normal brain white matter contains nerve fibers, neuroglial cells, vascular structures, and interstitial space. The nerve structures in the white matter are mainly axons, surrounded by a myelin sheath. Ischemic lesions of the white matter, termed as white matter lesions (WMLs) can be caused by a chronic process produced by gradual occlusion of small vessels leading to hypoperfusion of white matter. There is loss of blood brain barrier which results in chronic plasma extravasation into the white matter. White matter looks pale due to loss of myelin, axons, and oligodendrocytes. These white matter lesions may appear as small punctuate to large confluent areas. Regions of white matter pathology show up on computed tomography (CT) as hypodense areas (Pantoni & Garcia 1997; Fazekas & Kleinert 1993; Roman & Erkinjuntti 2002; Wen *et al.* 2009).

Correspondence to: Faraz Ahmed Bokhari, Assistant Professor, Department of Physiology, Shaikh Zayed Federal Postgraduate Medical Institute (SZFPGMI), Shaikh Zayed Medical Complex, University Avenue, New Muslim Town, Lahore-54600.
phone: +0092-333-4769344, fax: 0092-35830639, e-mail: drfarazbokhari@yahoo.com

WMLs are found in many clinical settings. They are common in asymptomatic, young and elderly individuals as well as in patients of cardiovascular and cerebrovascular diseases (Enzinger *et al.* 2006; Hopkins *et al.* 2006; Launer 2004). A recent meta-analysis found WMLs to be associated with an increased incidence of stroke (Debette & Markus 2010).

Not many studies have looked at the relationship between WMLs and type of stroke. Kuller *et al.* found an association between WMLs and incidence of ischemic stroke, while Smith *et al.* did not find the same in haemorrhagic stroke (Kuller *et al.* 2004; Smith *et al.* 2004).

In this study, we look at the nature of relationship between WMLs in stroke subtypes, ischemic and haemorrhagic, in a consecutive sample of local stroke patients.

MATERIALS AND METHODS

Participant Selection

The experiments were undertaken with the understanding and written consent of each subject, and the study conforms with The Code of Ethics of the World Medical Association (Declaration of Helsinki), printed in the British Medical Journal (18 July 1964). Approval for our study was obtained from the Institution Review Board (IRB) Shaikh Zayed Medical Complex, Lahore and Services Institute of Medical Sciences, Lahore, including approval by human research ethics committees of the same. Participants in this study were recruited consecutively from the two mentioned hospital centers after informed consent was obtained. These hospital centers are government funded public general hospitals serving the district of Lahore and adjoining localities. There were 229 participants included from September 2010 to August 2011. All participants included were diagnosed as having stroke, ischemic or haemorrhagic (TIAs were excluded) based on NICE criteria (National Institute for Health and Clinical Excellence 2008). Since there is no local data available on stroke incidence, we used an approximated figure of about 200 samples based on examining similar studies (Debette & Markus 2010).

CT Scan And WML Diagnosis

CT scan was done using CT machine GE (64 slice, lightspeed VCT). Initial 10 CT brains were interpreted by two different radiologists and the findings were matched. Afterwards, all remaining CT brains were interpreted by the same

radiologist. Wahlund *et al.* scale was used to diagnose and classify WMLs. Briefly, this scale is applicable to both CT and MRI. The inter-rater reliability was found to be slightly better for MRI as it could detect small lesions; otherwise CT was as good as MRI in detecting moderate and large lesions. Many studies have shown that WMLs seen on CT correlate better with symptoms as compared to the changes detected with MRI (Wahlund *et al.* 2001).

Analysis of Data

All analyses were performed using SPSS for Windows, version 17. Descriptive statistics were given as means and standard deviations (SD) for quantitative variables and percent prevalence for categorical variables. A *t* test was used to compare differences in means and χ^2 test was used for differences in proportions. Binary logistic regression model was used to investigate the effect of various risk factors on stroke subtypes and WMLs. Differences were considered significant at $p<0.05$.

RESULTS

Results according to stroke subtype

Out of 229 participants, 165 ischemic and 64 hemorrhagic stroke were diagnosed, 117 males and 112 females. In the first phase we studied the data stratified for stroke subtype (see Table 1). Data showed significant association of presence of WMLs ($p=0.013$) and hypertension ($p=0.044$) with ischemic

Tab. 1. Clinical Characteristics of stroke sample stratified by diagnosis.

	IS n(%age)	HS n(%age)	Significance
Age Mean±SD	60.05±13.7	58.83±13.56	0.545
Gender	Females 79 (48%) Males 86 (52%)	Females 33 (52%) Males (31, 48%)	0.617
History of hypertension	109 (66)	51 (80)	0.044*
History of Heart disease	40 (24)	18 (28)	0.544
History of Diabetes Mellitus	54 (33)	24 (38)	0.494
Smoker	39 (24)	12 (19)	0.425
White matter lesions present	92 (56)	24 (38)	0.013*
BMI Mean±SD	25.03±8.51	29.66±11.18	0.001*

IS: Ischemic stroke, HS: hemorrhagic stroke,
*Significant difference between groups at $p=0.05$

stroke, and BMI in hemorrhagic stroke (Mean±SD: 29.66±11.18, p=0.001). After further stratifying data for gender, significant association was confirmed between WML presence and ischemic stroke (p=0.004) and BMI with hemorrhagic stroke (Mean±SD: 28.63±10.47, p=0.002), while no such effect was found in female stroke subjects.

Results according to WML presence/absence

In the second phase, we stratified the data by presence/absence of WMLs. Age, history of hypertension, and ischemic stroke were found to be significantly associated with presence of WMLs (p-values: 0.000, 0.045 and p=0.013 respectively). Furthermore, after gender stratification, male subjects showed significant association for age, history of hypertension, ischemic stroke and BMI (p-values: 0.000, 0.035, 0.004 and 0.046 respectively) with WML presence. There was no significant finding in female subjects.

Binary Logistic Regression

We conducted 2 regression models: with stroke subtype (ischemic or hemorrhagic), and WMLs (presence or absence) as dependent variables. Hosmer and Lemeshow test for model integrity was favorable in both cases (p=0.406 and p=0.839 respectively) and the data did not exhibit any significant multicollinearity (standard error values of all variables ranged between 0.013 to 0.954).

Tab. 2. Clinical Characteristics of stroke sample stratified by WML presence.

	WML=Yes n(%age)	WML=No n(%age)	Significance
Age Mean±SD	64.35±11.77	54.94±13.84	0.000*
Gender	Females 60 (52%) Males 56 (48%)	Females 52 (46%) Males 61 (54%)	0.388
History of hypertension	88 (55)	72 (45)	0.045*
History of Heart disease	32 (55)	26 (45)	0.426
History of Diabetes Mellitus	41 (53)	37 (47)	0.678
Smoker	26 (51)	25 (49)	0.958
Stroke Subtype Ischemic Hemorrhagic	 92 (79) 24 (21)	 73 (65) 40 (35)	 0.013*
BMI Mean±SD	25.25±8.8	27.43±10.17	0.085

*Significant difference between groups at p=0.05

Regression model for stroke subtype as independent variable

Regression results for stroke subtype as independent variable, and various covariates (see Table 3) revealed that presence of WMLs increased the risk for ischemic stroke two folds (p=0.026, OR:2.11, 95%CI: 1.092–4.076), while an increase in BMI of 1 kg/m^2 raised the odds of having hemorrhagic stroke four times (p=0.007, OR:1.042, 95%CI: 1.011–1.073), in unstratified data. In males, WML induced risk for ischemic stroke increased to two and a half times (p=0.009, OR:0.251, 95%CI: 0.089–0.706), while an increase in BMI of 1 kg/m^2 raised the odds of having hemorrhagic stroke six times (p=0.027, OR:1.061, 95%CI: 1.007–1.118). See Table 3 for details.

Tab. 3. Binary Logistic Regression Analysis of Stroke Subtypes.

	Ischemic Stroke
Age	p=0.925, OR=1.001,CI=0.977–1.026
Gender	p=0.741, OR=0.894,CI=0.461–1.735
Hypertension	p=0.066, OR=0.496, CI=0.235–1.048
Heart disease	p=0.836, OR=0.928,CI=0.459–1.876
Diabetes mellitus	p=0.590, OR=0.378,CI=0.440–1.596
Smoking	p=0.670, OR=1.196,CI=0.525–2.724
BMI*	p=0.007, OR=0.96, CI=0.932–0.989
White Matter Lesions (WMLs)*	p=0.026, OR=2.11, CI=1.092–4.076

*Significant difference between groups at p=0.05
OR: odds ratio, CI: 95% Confidence Interval

Tab. 4. Binary Logistic Regression Analysis of WMLs.

	WMLs
Age*	p=0.000, OR=1.061,CI=1.035–1.087
Gender	p=0.379, OR=0.757,CI=0.406–1.409
Hypertension	p=0.074, OR=1.823, CI=0.944–3.519
Heart disease	p=0.640, OR=1.174,CI=0.599–2.304
Diabetes mellitus	p=0.814, OR=0.929,CI=0.505–1.710
Smoking	p=0.622, OR=1.206,CI=0.573–2.539
BMI	p=0.083, OR=0.973, CI=0.943–1.004
Ischemic stroke*	p=0.026, OR=2.108, CI=1.091–4.073

*Significant difference between groups at p=0.05
OR: odds ratio, CI: 95% Confidence Interval

Regression model for WMLs as independent variable

Results showed an increase in age by 1 year raised the risk of WML occurrence 6 times (p=0.000, OR: 1.061, 95%CI: 1.035–1.087). The association between WMLs and ischemic stroke was confirmed (p=0.026, OR:2.108, 95%CI: 1.091–4.073). See Table 4 for details.

DISCUSSION

A summary of our key findings are:

1. White matter lesions (WMLs) are a probable risk factor for ischemic stroke in the local population. Males with WMLs are more prone to ischemic stroke than females.

2. BMI correlated significantly with hemorrhagic stroke, especially in males.

3. We found WMLs occurrence to increase with age.

Our findings on stroke and WMLs correlation are consistent with available literature (Vermeer *et al.* 2003). Only a few studies have looked at WML association with stroke subtype. Kuller *et al.* (2004) studied WMLs in ischemic and haemorrhagic stroke subtypes and found an association similar to our results (p=0.026, OR:2.11, 95%CI: 1.092–4.076 (current study) vs OR: 2.86, CI, 1.70 to 4 (Kuller *et al.* 2004)). Inflammation has been described as a basis of WML formation and progression (Rezaie & Dean 2002). And though, in our study white cell count in both stroke types was within normal limits, it was towards the higher side of the range (ischemic stroke mean WBC count: 10.26, hemorrhagic stroke mean WBC count: 10.21). Hence we cannot rule out at least an inflammatory component to this association. Another cause of WML has been described as vascular disease (Manolio *et al.* 1999). Therefore comorbid vascular influence also cannot be ruled out in the current study, as the case is in similar studies in the past. However, various studies show that the association of WMLs with stroke sustains even after adjustment for vascular risk factors (Debette & Markus 2010). Our regression analysis confirms the same pattern. We hypothesize that a generic ischemic phenomenon may be the basis of "flagging" the brain with WMLs, the number of which, along with age of the individual, indicates an incremental risk of incurring a major ischemic event – an ischemic stroke.

There is conflicting data on the association of BMI with stroke (Kurth *et al.* 2002; 2005; Asia-Pacific Cohort Studies Collaboration 2004; Hart *et al.*

1999; Cui *et al.* 2005). Most of the studies describe a positive association of BMI with ischemic stroke (Kurth *et al.* 2002). As far as hemorrhagic stroke is concerned, the literature is scarce and even more contradictory, with description of inverse association between the two parameters (Kurth *et al.* 2005; Cui *et al.* 2005). We report a significant association of BMI with hemorrhagic stroke at BMI >25 kg/m^2. A meta-analysis of 33 prospective studies from the Asia-Pacific region noted association with hemorrhagic stroke mainly at high BMI levels (Asia-Pacific Cohort Studies Collaboration 2004). There is a need of validation of these results in different areas of the country, keeping in view the diversity in ethnicity, culture, socioeconomic background especially living and eating habits.

In the general population the prevalence of white matter lesions ranges from 11–21% in adults aged around 64 to 94% at age 82 (Debette & Markus 2010). In that respect, our study population is relatively younger (Mean age for ischemic stroke: 60.05±13.7 years; Mean age for haemorrhagic stroke: 58.83±13.56 years). There is a need to replicate these findings in a wider age range.

One of the limitations of our study was the usage of CT scan instead of MRI. MRI now is the diagnostic gold standard for stroke especially for small lesions, though from a radiological standpoint, the usage of MRI and CT has been shown to be comparable (Inzitari 2003; Furie & Kelly 2006). Still we understand that with MRI, the WML results may have been more precise. Moreover a larger sample size would have been more representative of the issue at hand, especially with a broader group for age and BMI.

Lastly, it may also be useful to measure progression of WMLs as a prognostic marker in stroke (Kuller *et al.* 2004).

ACKNOWLEDGMENTS

The authors would like to thank Dr. Tania A. Shakoori for her contribution in data analysis, and Dr. Mubashar (consultant radiologist, Shaikh Zayed Hospital, Lahore) for help in validating CT scan findings.

COMPETING INTERESTS

The authors have no conflict of interest to report.

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