

ORIGINAL ARTICLE

ASSOCIATION OF PLASMA HOMOCYSTEINE AND WHITE MATTER HYPODENSITIES IN A SAMPLE OF STROKE PATIENTS

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Background: Studies of homocysteine in vascular disorders have yielded conflicting data. There are also differences based on various ethnicities and cultures. In this study, we have examined the homocysteine patterns in local stroke patients, so as to ascertain the homocysteine status in a sample of local population. Homocysteine-white matter hypodensities relationship in stroke is emerging, as an important aspect in stroke pathophysiology and is thought to have prognostic and therapeutic values. **Methods:** We included 150 stroke patients who were diagnosed as having clinical stroke on the basis of history; physical examination and CT (Computerized Tomography) scan of brain. These patients were recruited from neurology and emergency wards of two public sector hospitals of Lahore. The presence or absence of white matter hypodensities were diagnosed after consultation with a radiologist. Blood samples were collected from the same stroke patients.

Results: We found a strong association between white matter hypodensities and total homocysteine in plasma of stroke patients $p < 0.001$. **Conclusion:** Homocysteine is a risk factor for white matter hypodensities in stroke patients in our study.

Keywords: Homocysteine; Stroke; White Matter Hypodensities; CT scan

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INTRODUCTION

Cerebral stroke is the leading cause of physical disability.¹ There are two types of strokes: ischemic and hemorrhagic stroke. Ischemic stroke has the higher incidence, i.e., 88%; 22% of these cases are due to small vessel disease, called lacunar strokes. While 12% percent are hemorrhagic strokes; out of these 9% are cases of intracerebral hemorrhagic strokes while 3% are subarachnoid in origin.²

Ischemia of the white matter can manifest as demyelination, destruction of axons, change in glial cell numbers and vascular changes. There is tissue necrosis with scarring and finally cavities and infarction.³ Regions of white matter pathology show up on computed tomography (CT) as hypodense lesions. These lesions are known as White Matter Hypodensities (WMHs).⁴ These are caused by a chronic process produced by gradual occlusion of small penetrating vessels leading to hypoperfusion of white matter. White matter looks pale due to loss of myelin, axons, and oligodendrocytes.⁵

WMHs are not benign; they are associated with several impairments such as cognitive deficits, depression, dementia, urinary dysfunction, gait and balance problems.⁶ WMHs predict the risk of stroke, dementia, and mortality. These lesions are also responsible for psychiatric disorders like major depression, bipolar disorder and schizophrenia.⁷

The hypodensities are distributed throughout the white matter in patients of stroke and healthy older people. The periventricular region is affected more by this change in both groups.⁴ An ischemic attack is not

the basis for WMHs because WMHs are not caused by sudden infarction but by small vessel disease produced by gradual occlusion of small penetrating vessels leading to hypoperfusion of white matter. This small vessel disease also somewhat contributes to infarction. The presence of these lesions indicates that strokes occur in brains that are affected by much ischemic pathology. Sensory and motor deficit seen after stroke should not be attributed to the recent infarction but may be a result of accumulation of pathology, much of which has been unrecognized previously in the form of WMHs.⁸ Finally there is an increased risk of stroke in patients with a progression of WMHs.⁷

Homocysteine (Hcy) has been recognized as a risk factor for atherosclerosis. The incidence of cardio and cerebrovascular disease is mounting, particularly in Asians. It has been claimed that traditional risk factors alone cannot be held responsible for the higher prevalence of the disease.

McCully, in 1969, was the first to suggest that Hcy may be involved in pathophysiology of atherosclerosis.⁸ Since then, numerous studies have associated hyperhomocysteinemia (HHcy) with cardiovascular risk and have recognized Hcy as a strong, graded, independent risk factor for vascular disease including cerebral stroke.

WMHs occur due to cerebral small vessel disease (SVD), which can be secondary to HHcy.⁹ However, the data on this connection is inadequate, and therefore this study was designed. This study was designed to measure plasma Hcy levels in a sample of stroke patients and to evaluate an association of Hcy level with WMHs in a sample of stroke patients.

MATERIAL AND METHODS

Approval of our study was obtained from the research ethic committee, Institution Review Board (IRB), Sheikh Zayed Medical and Dental Complex.

This cross sectional study was carried out on 150 stroke patients. The stroke patients admitted in Neurology and Emergency wards of Sheikh Zayed Medical and Dental Complex and Jinnah Hospital Lahore, were included in this study. Demographic data was collected on a *pro forma* along with history of patients. They were diagnosed on the basis of history, physical examination and CT scan of brain. The Glasgow coma scale (GCS) was employed to assess the conscious state of the stroke patient at the time of admission and subsequently at the time of discharge. The presence or absence of WMHs was duly mentioned in the *pro forma* after consultation with a radiologist. Blood samples were also collected from these stroke patients; blood samples were then centrifuged, plasma was separated and aliquots of plasma were kept frozen at -80°C. The tHcy level was, later, estimated in plasma using commercially available ELISA kit (Axis-Shield Homocysteine ELISA kit UK).

The data was analysed using SPSS-15.0. Chi-square test was used in the categorical outcome

like presence of WMH and Mann Whitney U test was used in the case of quantitative outcome like homocysteine levels with $p \leq 0.05$ as statistically significant. Our study showed that as the tHcy went higher than 10µmol/ L the frequency of WMHs amplified. This is the value above which HHcy exists as defined by American Heart Association/American stroke Association Council.¹⁰

RESULTS

Out of 150 stroke patients 93 were males and 57 females. The participants' in the age range from 60-69 were 46 (30.6%) and above 60 were 95(63.3%). The average age was 60.2±14.5 years. Stroke patients were categorized into three groups according to Hcy level.

The association of Hcy with WMHs was found to be highly significant with p -value <0.001. A positive trend of occurrence of WMHs was found with an increase in tHcy level as shown in table-1.

The Hcy levels were found 23.0±10.7 and 17.3±9.2 for stroke patients with and without WMHs respectively. The median Hcy levels were 22.1 and 13.8 for the two groups respectively. The difference was found statistically significant with the p -value <0.001 (Table-2).

Table-1: Distribution of cases by white matter hypodensities as per homocysteine level

WMHs	<15		15-30		30-100		Total	
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
Present	29.0	39.2	29.0	67.4	26.0	78.8	84.0	54.0
Absent	45.0	60.8	14.0	32.6	7.0	21.2	66.0	44.0
Total	74.0	100.0	43.0	100.0	33.0	100.0	150.0	100.0

Chi-square likelihood ratio=16.77, p -value <0.001*, p -value <0.05 is significant

Table-2: Comparison of Homocysteine levels between the groups with white matter hypodensities present and absent.

WMHs	n	Mean Rank	Mean±SD (Range)	Median
Present	84	86.9	23.0±10.7 (7.9-47.9)	22.1
Absent	66	61.1	17.3±9.2 (1.6-37.8)	13.8

Mann Whitney U=1819, Z=-3.61, p -value <0.001*

DISCUSSION

To our knowledge this study is the first of its kind in the Pakistani context. The study showed significant association between plasma Hcy level and cerebral WMHs in stroke patients <0.001.

This association between tHcy and WMHs is consistent with results from previous studies which depicted HHcy as a risk factor for the development of WMHs.¹⁰⁻¹⁴ WMHs in turn are associated with symptomatic neurological impairments. WMHs have been found to be significantly associated with an increased risk of stroke both in general population and in high risk population with a history of stroke or vascular disease. The association with stroke is confounded presence of vascular risk factors such as smoking, diabetes, hypertension and a history of

vascular disease, though the association between WMHs and stroke remained significant after adjustment for these risk factors. This suggests the presence of still unknown vascular risk factors that play a role in this association.⁷ The tHcy has been implicated as an independent risk factor for the presence of silent brain infarcts and WMHs.¹¹⁻¹⁴

A prospective study by Dufouil *et al.* examined the relationship between tHcy and cognition decline in 1241 subjects aged 61-73 years; they reported that WMHs were not associated with Hcy in healthy elderly people.¹⁵ Some prior studies have also described a lack of relation between plasma tHcy levels and WMHs.^{16,17} However, large prospective studies like Rotterdam and Framingham support the causal relation between tHcy and risk of stroke.^{12,18}

A study conducted in Abbottabad also concluded that Plasma tHcy level has a powerful predictor value of CHD and the authors recommended routine screening for elevated Hcy especially for persons who manifest atherothrombotic disease without their traditional risk factors.¹⁹ There are some limitations of this study. It was a cross sectional study and the causal role of Hcy for ischemic change in white matter would be better clarified by a prospective longitudinal analytical study like a cohort study. Further, the progression of WMHs due to elevated tHcy could be followed by regular imaging. Although, it has been recognized that deficiency of folates and vitamin B12 can lead to elevation of Hcy,¹⁰ budgetary limitations restricted us in estimating these vitamins.

CONCLUSION

The study showed that Hcy is a risk factor for cerebral WMHs in stroke patients. We found a strong relation between plasma tHcy and WMHs with a *p*-value <0.001. Mild HHcy can significantly increase the severity of cerebral SVD.

Neurologists should emphasize on the clinical importance of WMHs even when found as an incidental finding on brain imaging as they indicate a risk of cerebrovascular disease. If the presence of WMHs is confirmed, the treating physician should consider screening for risk factors for stroke and dementia. The treatment for risk factors would reduce the progress of WMHs.

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AUTHOR'S CONTRIBUTION

GN and FAB conceived the basic idea of the paper and designed the study. Additionally GN took samples, FAB applied statistics. Both GN and FAB interpreted the results.

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