Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/15j8zb76

FREQUENCY OF HYPERHOMOCYSTEINEMIA IN YOUNG PATIENTS WITH ACUTE ISCHEMIC STROKE

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Abstract

Introduction: Hyperhomocysteinemia, characterized by elevated homocysteine levels, is an emerging risk factor for acute ischemic stroke in young adults (≤45 years). Its role in stroke pathogenesis, particularly in South Asia, remains understudied despite its potential for early intervention.

Objective: To determine the frequency of hyperhomocysteinemia in young patients with acute ischemic stroke and evaluate its role as a risk factor.

Materials and Method: This cross-sectional study, conducted at Hayatabad Medical Complex Peshawar, Pakistan, from January 2024 to June 2024, enrolled 150 patients aged 18–45 years with confirmed ischemic stroke. Serum homocysteine levels were measured, with >15 µmol/L defined as hyperhomocysteinemia. Data were analyzed using SPSS version 25.

Results: Hyperhomocysteinemia was observed in 44.7% (n=67) of patients, predominantly males (71.6%). It was significantly associated with moderate-to-severe stroke ($p<0.05$), with smoking (46.3%) and hypertension (35.8%) as common coexisting risk factors.

Conclusion: Hyperhomocysteinemia is prevalent in young stroke patients in Pakistan and is linked to increased stroke severity. Routine screening and targeted interventions, such as vitamin supplementation, could reduce stroke burden.

Keywords: Hyperhomocysteinemia, ischemic stroke, young adults, risk factors, homocysteine.

INTRODUCTION

Hyperhomocysteinemia, or an increase in plasma homocysteine levels, has gradually become a well-accepted cause and a reasonable drug target for the pathogenesis of acute ischemic stroke, especially

in younger individuals. Although more classical drivers of stroke risk, like high blood pressure (hypertension), diabetes, and tobacco, are still most common, there is even a new rise of homocysteine as an independent risk factor of cerebrovascular accidents, particularly in patients younger than 45 years of age (1). This relationship is especially worrying as there is a rising incidence of cases of ischemic stroke in the young, causing a lifetime of disability and a high impact on socio-economics. The occurrence of hyperhomocysteinemia among the population of this age group has not been explored in Pakistan, although in international research, it has been highlighted (2).

The pathophysiology of the connection between homocysteine and stroke is complex. Homocysteine is a sulfur amino acid that is generated in the process of methionine metabolism and may cause toxicity against the vascular endothelium, stimulating oxidative stress, inflammation, and thrombogenesis. These vascular insults eventually culminate in the emergence of atherosclerosis and arterial closure, causing the manifestation of ischemic events (2). Various case reports and clinical studies have confirmed that there have been incidences of higher levels of homocysteine to be the only detectable risk factor amongst the young patients who presented with acute ischemic stroke, supporting the importance of a higher level of clinical alertness (3). The study undertaken in Bangladesh on the population of young adult stroke cases found that the association between the increased serum homocysteine level and acute ischemic stroke was statistically significant, which once again signifies the regional focus of the said biomarker (4).

The evidence provided by the global literature is very strong as far as the association of hyperhomocysteinemia and ischemic stroke is concerned. The greater homocysteine concentrations have continually been demonstrated to confer the association of a greater risk of ischemic stroke in a dose-dependent fashion, indicating that even the mildly inflated values of homocysteine may be debilitating (5, 6). The risk of strokes, despite the traditional vascular risk factors adjustment, is still very pronounced, which means that homocysteine plays an independent role in stroke pathology. Further, a high concentration of homocysteine has been associated with different subtypes of stroke, namely, small vessel disease, large artery atherosclerosis, and cardioembolic stroke, which shows its wide effects on the health of cerebrovascular vessels (5).

There is a huge difference between the prevalence and risk profile of ischemic stroke in young adults and older individuals. The role of non-traditional risk factors, which include genetic predisposition, autoimmune diseases, and metabolic disorders, including hyperhomocysteinemia, is more important in young adults (7). Rare cases of stroke presentation in extremely young people have even been reported, as in the case of a four-year-old child whose hyperhomocysteinemia was found to be the leading cause (8). Such findings open up important questions as to whether early screening and prevention approaches toward metabolic risk factors should be applied to younger generations. The value of hyperhomocysteinemia as a risk factor for stroke also shows significance in South Asia. The results of a retrospective study in Tyrkiye revealed that in young adults, ischemic stroke often appealed to the non-traditional cause, implying the presence of biochemical imbalances such as hyperhomocysteinemia (9).

Moreover, homocysteine levels have also been suggested to serve as a prognostic sign to the level it is one of the predictors of the occurrence of recurrent stroke and poor clinical outcomes (10, 11). This especially applies to young patients who risk having recurrent and long-term disability, and this should prompt early treatment and diagnosis. The association between high levels of homocysteine and the recurrence of strokes is potentially imminent in patients who have comorbid illnesses like hypertension. A Chinese study demonstrated that patients with hyperhomocysteinemia and hypertension had increased recurrence following a stroke during a period of one year, indicating the synergetic effect of different risk factors (12). Genetic factors also play a role in homocysteine metabolism and include methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism in affecting the risk of stroke.

Data have revealed that carriers of this genetic variant are more liable to develop a high homocysteine level and that supplementing them with vitamins is less likely to reduce levels in such patients (13). That even small increases can be clinically important in predisposed patients is indicated by additional evidence in Asian communities, such as spontaneous cervical artery dissection that is possibly related

to slightly elevated homocysteine levels (14). Moreover, a case-control study carried out in China pointed to the relationship between the MS1 variant of the MTHFR gene and stroke severity, even further emphasizing the necessity of genetic screening in young patients with high levels of homocysteine (15). Homocysteine levels have also been linked with cognitive impairment in the post-stroke population, showing that its effects cannot be confined to acute occurrence and potentially cause long-term neurological sequelae (16).

The multicenter study conducted in Japan has proved that the causes of bleeding stroke differ considerably among the older and younger populations through huge observational studies. There is a change in the etiological range, where rare or modifiable risk factors such as hyperhomocysteinemia have increased in young patients (17). Further, it has also been recorded in local studies in Pakistan where increased homocysteine has been reported in patients with essential hypertension who presented with ischemic stroke in tandem with its feasibility as a pathophysiology factor in stroke among the local population (18). Besides diagnostic importance, measurement of homocysteine can provide nutritional information. Lack of vitamins B6, B12, and folate have been identified to increase the levels of homocysteine. Another recent study emphasized the role of combined serum vitamin B12, folate, and homocysteine concentrations in predicting the risk of ischemic stroke, insisting on a more comprehensive nutritional and biochemical screening in subjects at risk (19).

Lastly, hyperhomocysteinemia has more clinical implications than stroke. This condition has been associated with other thrombotic diseases, including myocardial infarction and cerebral venous thrombosis, through case reports, which highlight its systemic effects on vasculature and the need to intervene at an early stage (20). All these results imply that hyperhomocysteinemia cannot be regarded as a biochemical form of abnormality but as a risk factor that may be altered with important prognostic and treatment consequences.

Objective:

The aim of the study was to find out how common hyperhomocysteinemia was in young patients who experienced acute ischemic stroke (<=45 years of age) and its possible role as a co-morbid risk factor.

MATERIALS AND METHODS

Design: Cross-Sectional Study.

Study setting: The study was done in the Department of Neurology, Hayatabad Medical Complex Peshawar, Pakistan.

Duration: The study was carried out over a period of six months, from January 2024 to June 2024.

Inclusion Criteria: Patients included those who had clinically and radiologically proven acute ischemic stroke at the age range of 18 to 45 years. Those presenting within 72 hours and who voluntarily consented to the participation were only admitted. The male, as well as female patients were considered eligible.

Exclusion Criteria: The excluded patients were the patients with hemorrhagic stroke, transient ischemic attacks (TIA), chronic underlying known metabolic disorders, renal or hepatic failure, malignancies, or patients on vitamin supplementation that can affect homocysteine levels.

Methods

The orifice and Department of Neurology, Hayatabad Medical Complex Peshawar, Pakistan, recruited patients consecutively by including all patients who fulfilled the inclusion criteria. Informed consent was obtained, and then a detailed clinical history was taken, which included age, gender, time symptom started, what was/is a family history of the stroke, whether you smoke or not, and whether the patient has been found to have other conditions like hypertension or diabetes mellitus. The neurological tests were performed, and the neuroimaging confirmation of ischemic stroke was done by either CT or MRI. Drawing of blood was done within a period of 24 hours of admission, and serum levels of homocysteine were analyzed by enzymatic immunoassay technique. Hyperhomocysteinemia

was considered a homocysteine level that exceeded 15 µmol/L. Patients were also stratified according to the levels of homocysteine to obtain levels on the frequency and the possible association with the severity of stroke. Besides CBC, fasting lipid profile and vitamin B12 and folate were done as additional laboratory tests. The SPSS version 25 was used to analyze the data, and descriptive statistics and chi-square tests were used in the assessment of significance.

RESULTS

A total of 150 young patients (≤ 45 years) with acute ischemic stroke were enrolled in the study. Among them, 96 (64%) were male and 54 (36%) were female, with a mean age of 38.2 ± 4.9 years. The frequency of hyperhomocysteinemia in the entire study population was found to be 44.7% (n = 67), indicating a significant burden of elevated homocysteine levels among young stroke patients.
The majority of patients with hyperhomocysteinemia were male (n = 48, 71.6%) compared to females (n = 19, 28.4%). A strong male predominance was observed in both the overall stroke population and within the hyperhomocysteinemic subgroup.

Table 1: Frequency of Hyperhomocysteinemia among Stroke Patients

Homocysteine Status	Frequency (n)	Percentage (%)
Elevated (>15 µmol/L)	67	44.7
Normal (≤15 µmol/L)	83	55.3
Total	**150**	**100**

Most patients with elevated homocysteine levels had additional risk factors such as smoking and hypertension. Smoking was present in 46.3% of hyperhomocysteinemic patients, while 35.8% had hypertension. Diabetes mellitus was less frequently observed (14.9%).

Table 2: Risk Factors Among Patients with Hyperhomocysteinemia

Risk Factor	Number of Patients (n = 67)	Percentage (%)
Smoking	31	46.3
Hypertension	24	35.8
Diabetes Mellitus	10	14.9
Dyslipidemia	18	26.9
Family History	12	17.9

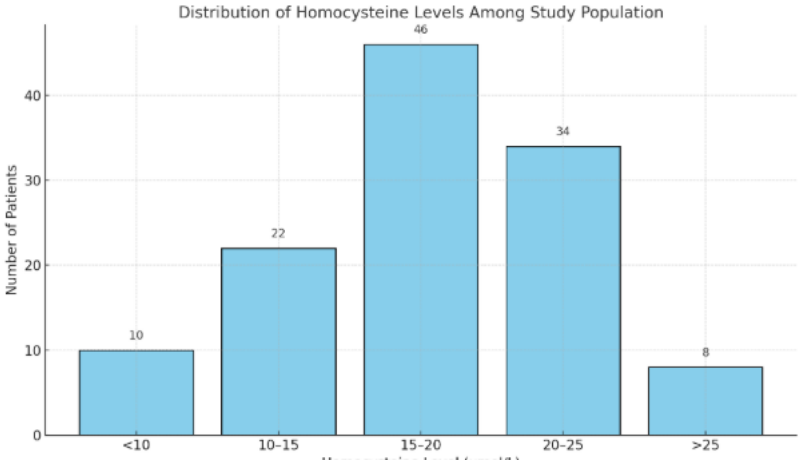
Patients with hyperhomocysteinemia also showed a greater severity of stroke symptoms at presentation, with 52.2% falling into the moderate-to-severe category based on the NIH Stroke Scale (NIHSS).

Table 3: Stroke Severity Based on Homocysteine Levels

NIHSS Severity	Hyperhomocysteinemia (n = 67)	Normal Homocysteine (n = 83)
Mild (NIHSS ≤ 5)	18 (26.9%)	43 (51.8%)
Moderate (NIHSS 6–14)	34 (50.7%)	31 (37.3%)
Severe (NIHSS ≥ 15)	15 (22.4%)	9 (10.8%)

The distribution of homocysteine levels among all patients ranged from 6.4 µmol/L to 37.1 µmol/L, with a mean of 18.6 ± 5.3 µmol/L in the hyperhomocysteinemia group.

Graph 1: Distribution of Homocysteine Levels Among Study Population



A peak of frequency was observed on the histogram of 15 20 Micro-moles per liter, which was within the stated cut-off of the hyperhomocysteinemia (more than 15 µmol/L). There were only eight patients (5.3%) with very high levels of above 25 2muxcve molo L, but statistical evaluation confirmed the findings using the chi-square tests to determine a significant relationship between hyperhomocysteinemia and high stroke incidence ($p < 0.05$), which indicates that an elevated level of homocysteine may be a surrogate indication of the high severity level of the disease presentation.

DISCUSSION

The results of this paper establish major symptoms of hyperhomocysteinemia in young patients (<=45 years) who are admitted with acute ischemic stroke, which is consistent with past research of regional and international origin. The proportion of patients in the cohort with elevated homocysteine levels was 44.7 percent, indicating a high burden of this modifiable risk factor among younger patients living with cerebrovascular disease. The prevalence is similar to that discussed by Bullo et al., which found prevalence in the Pakistani population (1). It supports the necessity to explore homocysteine in the blood as a routine component of both the diagnostic and preventive measures for stroke in young patients. The connection between hyperhomocysteinemia and ischemic stroke has been increasingly mentioned over the past few years. Holmen et al. found a definite dose-response connection between homocysteine level and the threat of a stroke in connection with the probability of ischemic episodes increasing with even moderate elevations of the homocysteine level (2).

The study substantiates this claim since a high percentage of patients receiving high homocysteine had more severe strokes as per the National Institute of Health stroke scale per unit. This gradient of severity is replicated in other reports of cases and observational studies like the one reported by Rafay et al., where a young person without any other conventional risk factors was shown to develop an early stroke due to hyperhomocysteinemia (3). The study population had a mean age of 38.2 years, and this implies that hyperhomocysteinemia-related strokes occur in younger people, usually at the peak of their productive years. Similar age distribution was described by the study by Uddin et al. in Bangladesh, which also concluded a similar pattern of increased homocysteine among stroke patients below the age of 45 (4). The results indicate that hyperhomocysteinemia must be viewed as a key screening and intervention burden at both early and low-middle income levels, similar to the countries of Pakistan and Bangladesh since the burden of stroke is increasing in such countries.

There is still more evidence in favor of the possible biological correlation between homocysteine and stroke due to systematic reviews and meta-analyses. According to both Pinzon et al. and Rabelo et al., hyperhomocysteinemia not only causes an augmented risk of stroke occurrence but is also a contributory factor in atherothrombotic processes, including endothelial malfunction and oxidative anomalies (5, 6). Nutritional deficiencies in South Asian populations, especially vitamin B12 and folate, are important in homocysteine metabolism, and perhaps high prevalence is partly attributable

to nutritional deficiencies in South Asian populations. Gender variations noted in this study, where males made up more than 70 percent of the hyperhomocysteinemia cases, are supported by other regional research. Such male predominance with stroke cases was also observed in young Chinese adults by Tang et al. (7). This gender pattern may be explained by items in lifestyle wherein there are more men smoking whose lifestyle is associated with higher homocysteine levels (8).

Smoking, hypertension, and the presence of dyslipidemia were also noted in the subgroup of hyperhomocysteinemia and indicate a clustering of potentially modifiable risk factors, which may act synergistically to modify the risk of stroke. Regarding the etiology, young and old patients with stroke are mostly different. Beta b et al. pointed out that older risk factors become less significant in the young stroke populations, and genetic and metabolic risk factors, such as hyperhomocysteinemia, rise significantly (9). Pezeshgi et al. also supported this by stating that homocysteine should be assessed routinely in younger stroke patients to provide a cost-effective measure of secondary prevention (10). Moreover, Gomes stressed the fact that recurrent stroke among young people with untreated hyperhomocysteinemia happens, so early diagnosis and regular follow-up are required (11).

The research also corresponds with those in bigger registry studies. Specifically, Zhang et al. found that raised levels of homocysteine were an independent predictor of stroke recurrence within one year, especially among patients with H-type hypertension (12). This could have significant implications for stroke management, particularly in South Asian nations where H-type hypertension is on the rise. Therapeutically, the present literature has expounded on homocysteine-lowering using vitamin supplementation. Li et al. and Lin et al. concluded that folate and vitamin B12 treatment reduced homocysteine concentration substantially and might have a positive effect on stroke outcome, specifically in people with MTHFR gene amino acids substitutions (13, 14). The intervention could be essential in Pakistani contexts where most people are diet deficient, and it is high time to have a cost-effective intervention.

Interestingly, Huang et al. have also found that there are minor rises in the concentration of homocysteine, even within the so-called normal range, which can lead to vascular weakness and the development of spontaneous artery dissection among young Asian people (15). This refined perception signifies that even the lowering points can be considered a sufficient concern in the cases of high-risk populations. The study did not examine cognitive outcomes after stroke, but other studies, including those by Zhou et al., indicate that high homocysteine could lead to long-term adverse cognitive outcomes of stroke, especially among older stroke patients (16). Although in the research, attention was paid to younger subjects, these findings should be concerned with the possible long-term effects of high homocysteine levels in survivors. The age-specific study of the causes of an ischemic stroke done by Ohya et al. showed that metabolic abnormalities are more often prevalent among younger adults (17).

This is also confirmed by the results, which underline the need to include homocysteine testing in stroke management trends in younger people. In addition, Aslam et al. affirmed an increased incidence of hyperhomocysteinemia among hypertensive stroke patients in Pakistan, which highlights the connection between these two diseases in the community (18). Zhou et al. also indicated the role of vitamin levels in the regulation of stroke risk, stating that both B12 and folate deficiencies were independent predictors of stroke risk due to their increase in homocysteine levels (19). Lastly, other instances of well-documented cases, like the case of Avinash et al., show how hyperhomocysteinemia has systemic thrombotic potential, such as in incidences like cerebral venous thrombosis and myocardial infarction in young people, which is evidence of how it goes past stroke (20).

CONCLUSION

Hyperhomocysteinemia was found in nearly one-half of young adults with acute ischemic stroke in the tertiary-care center, indicating that it will play a significant role in early cerebrovascular disease in Pakistan. The hyperhomocysteinemia subgroup included male sex, smoking, hypertension, and dyslipidemia and was significantly related to moderate-to-severe neurological deficits at admission. These data reconfirm the idea that homocysteine may serve as both an independent and a multiplier of other vascular injuries. Since the improvement of homocysteine levels can be achieved by relatively

cheap dietary adjustment and with the same supplementing vitamin B and complex, homocysteine levels measurement in young stroke patients can widely be viewed as a valuable prospect in purposeful secondary prevention and health management. The homocysteine screening, completed along the cancer pathways and administration of co-morbid risk factors, can bring about a decrease in disability, recurrence, and economic cost. Multicentre prospective trials should consider comparing the effectiveness of intervention strategies as well as setting population-specific reference rates to enable population-specific risk stratification. Decisions on policy allocation will be based on evidence.

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