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Homocysteine level in stroke patients in the rehabilitation setting: a prospective observational study

Abstract

Introduction: Homocysteine (HC), at normal levels, is an important micronutrient in the human body. Elevated HC may be a risk factor for stroke in the elderly population. Serum levels for HC were used as an index of HC status in thirty patients with stroke. The incidence of hyper-homocysteinaemia was compared with their prognosis and outcome, particularly in terms of the improvement in their function.

Objectives: To determine the incidence of hyper-homocysteinaemia in an inpatient population with stroke, in order to identify the linkage of the HC level and the stroke outcome.

Methods: The research was conducted as a prospective data collection and analysis over a period of six months, using a snapshot view of patients with stroke admitted to a tertiary rehabilitation unit. Quantitative measures and analysis were utilized for data analysis. HC level, other inflammatory markers, demographic details and outcome measures were employed to detect the linkage between the hyper-homocysteinaemia and the outcome of stroke.

Results: A total 27% of the stroke patients in the Rehabilitation Unit demonstrated hyper-homocysteinaemia. Patients with hyper-homocysteinaemia were found having markedly lower cognition as compared to the ones with normal HC levels.

Conclusion: Incidence of the hyper-homocysteinaemia was 27% in the patients with stroke in the acute rehabilitation setting. The length of inpatient stay was relatively longer in the patients with hyper-homocysteinaemia as compared to the patients with normal homocysteine levels. These patients also had lower cognition as compared to the patients with normal homocysteine levels.

Keywords: homocysteinaemia, rehabilitation, stroke, serum levels

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Abbreviations: HC, homocysteine; CRP, C-reactive protein; FIM, functional independence measure; MMSE, mini mental status examination; LOS, length of stay

Introduction

Hyper-homocysteinaemia is an emerging risk factor for ischaemic stroke,[1-3] but its role in the outcome of the stroke population is controversial.[4-8] In one study hyper-homocysteinaemia was found in 60.6% of the patients with ischaemic stroke, which was related to low vitamin B_{12}.[4] Hyper-homocysteinaemia has been linked to inadequate intake of vitamins and therefore can be amenable to dietary interventions. Poor oral intake of folic acid, vitamin B_6 and vitamin B_{12} are linked to an increased risk for ischaemic stroke and cardiovascular disease[1]. Increased intake of fruits and vegetables has a protective role against stroke.[9-11] Antioxidant nutrients have important roles in the cellular function and have been implicated in the process associated with ageing including vascular, inflammatory and neurological damage.[12-17] But, there is insufficient evidence to support the routine use of the vitamins for stroke prevention.[1] Currently, there is little information available on the inflammatory markers such as HC in the stroke population regarding the outcome. This prospective observational study looks at this issue in order to help us understand the risk factors for stroke and the correlation between the HC and its linkage with the outcome and prognosis in stroke patients.

Methods

All identified patients with a diagnosis of stroke, who were admitted to the Rehabilitation Unit over a period of six months in 2010, were included in this study. The inclusion criteria for this study required the patients to be of age forty years and above with a stroke (ischaemic or haemorrhagic). Those with haemorrhagic stroke due to underlying causes other than hypertension were excluded. Data collected included demographic information, risk factors for stroke, usual accommodation, pre-morbid use of walking aids, HC levels at pre and post treatment, C-reactive protein (CRP) level, Functional Independence Measure (FIM), Mini Mental Status Examination (MMSE), length of stay (LOS), and the discharge destination. The level of HC was recorded in micromoles/litre (L). The normal value was considered to be <15 micromoles/L. The CRP was considered as normal if ≤5mg/L. The fasting blood HC level was taken in the morning and was analysed by the same laboratory within the hospital campus using the standard protocols and conditions. All identified patients had nutritional assessment by the clinical examination, dietetic assessment and biomarkers such as albumin, vitamin B_{12} and folate levels. This study was approved by the hospital ethics committee. Data analysis was assessed using a two-sample *t*-test. P values of less than 0.05 were considered to indicate statistical significance. To address the confounding factor of small sample of group with hyper-

homocysteinaemia, a matched control analysis was conducted by age (within 4 year) plus MMSE (within 2 points).

Results

Study population

The baseline demography of both groups (normal vs. high HC levels) of patients is depicted in the Table 1. The age of the study population ranged between 42 and 89 years with the mean age of 71.7 years. Out of the total number of 30 patients, 29(97%) were of the European origin. The remaining 1(3%) patient was of the Chinese origin. Four (13%) out of the thirty patients were from a non-English speaking background. These patients with non-English speaking background had normal HC levels. Nine (30%) patients were females and 21(70%) were males. There was only one patient below 55 years of age, aged 42 years. This patient shared the similar risk factors as the other subjects in this study.

Table 1 The baseline characteristics.

Characteristics	High HC n=8(26.66%)	Normal HC n=22(73.33%)
Age (years)	76(±9.18)	70.14(±11.54)
Sex		
Male	5(62.5%)	16(72.73%)
Female	3(37.5%)	6(27.27%)
BMI	27.62(±3.81)	27.63(±4.22)
Language	English	English: 18(81.82%) Others: 4(18.2%)
Ethnicity		
White	8(100%)	21(95.45%)
Others	0(0%)	1(4.54%)
History of EtOH use	7(87.5%)	20(90.90%)
History of Smoking	4(50%)	17(77.27%)
Family History of stroke	0(0%)	5(22.73%)
Prior IHD	3(37.5%)	8(36.36%)
Prior vascular diseases	3(37.5%)	8(36.36%)
Type 2 Diabetes Mellitus	3(37.5%)	7(31.82%)
Anxiety/depression	0(0%)	7(31.82%)
Dwelling – Home	8(100%)	21(95.45%)
Marriage	5(62.5%)	12(54.55%)
Walking Aids	1(12.5%)	4(18.18%)

Data was expressed as mean±SD. There were no significant differences between the two observational groups at baseline.

EtOH, alcohol; Walking aids, usage of walking aids prior to the stroke; IHD, ischemic heart disease

The HC levels ranged between 7 and 26 micromoles/L. Twenty eight (93%) patients had ischaemic stroke and the remaining two (7%) had an intracranial haemorrhage as a result of hypertension (no underlying vascular aneurysm, arterio-venous malformation, tumour or metastatic brain lesions were identified). All the patients with the haemorrhagic stroke had normal HC levels. These two patients shared the similar risk factors as the patients with the ischaemic stroke. A total of 8(27%) patients had hyper-homocysteinaemia and the remainder of the 22(73%) had normal HC levels. Among the eight patients with hyper-homocysteinaemia, six patients received treatment with folic acid. The mean age (76) was higher in the group with high HC levels as compared to the group with the normal HC levels, mean age of 70.14. However, there was no statistical significance ($p = 0.21$). Over all, there were a significantly higher number of males as compared to the females in both of these groups. It is of worth noting that in both of high and normal HC groups there was a significant history of smoking. A total of 77% of the patients in the normal HC group were heavy smokers as compared to 50% in the group with the high HC level. There were no significant differences in terms of the BMI, past history of ischaemic heart disease, vascular disease or Diabetes mellitus in both of these groups. However the percentage of the patients with these complications was slightly higher in the hyper-homocysteinaemia group.

Similarly, there were no significant differences in terms of the marital status, premorbid use of walking aids and the community dwelling between both groups. It is interesting to note that a total of seven patients with the diagnosis of anxiety and depression were identified having normal HC levels. In terms of the functional profile (Table 2A), the mean LOS in the group with high HC was 63.63days as compared to 51 days in the group with normal HC (Figure 1). The admission scores of the MMSE for the patients with hyper-homocysteinaemia were significantly lower as compared to the group with the normal HC levels (Figure 2). Similarly, the admission FIM scores were lower in the group with hyper-homocysteinaemia than the other group but showed slightly higher FIM gains as compared to the other group (34.75 vs. 27.09) (Figure 3) (Table 2A). The gender distribution was equal in the group with the normal HC as compared to a slightly higher number of female patients (37.5% vs. 27.27%) in the group with the high HC.

Table 2A Functional profile.

Measures	High HC(n=8)	Normal HC(n=22)
MMSE at admission*	21.50(± 4.7)	26.95(± 3.2)
MMSE at discharge*	21.50(± 4.7)	27.04(± 3.3)
GDS(total 15)	0.50(± 0.9)	1.3(± 2.7)
FIM at admission (total 126)	70.62(± 21.0)	81.59(± 32.0)
FIM gain	34.75(± 13.9)	27.09(± 18.2)
FIM efficiency	0.74(± 0.4)	0.66(± 0.4)
LOS (days)	63.63(± 42.9)	51(± 36.0)
Discharge to home rate(%)	7(87.5%)	20(98.1%)
Discharge support rate	7(87.5%)	17(77.2%)

The data was expressed as mean±SD. There was significant difference in MMSE between the two observational groups (*$p<0.05$). No significant differences were observed in other functional profiles.

In terms of the discharge to the community dwelling, 7(87.5%) patients, with hyper-homocysteinaemia, were discharged to home and one of the inpatients was transferred to other unit and subsequently passed away due to severe pneumonia and renal failure. All of these patients required community supports. On the other hand, from the group with the normal HC levels, 20(98.1%) patients were discharged home, 17(77.27%) required the community support. Due to limited

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participants in the hyper-homocysteinaemia group, it is reasonable to use an age-matched control analysis to limit the multiple confounding factors. Matched control analysis involved matching individual in the hyper-homocysteinaemia group with one from the other group by age within 4 years and MMSE within 2 points was attempted. Unfortunately, only 5 patients were identified within these criteria.

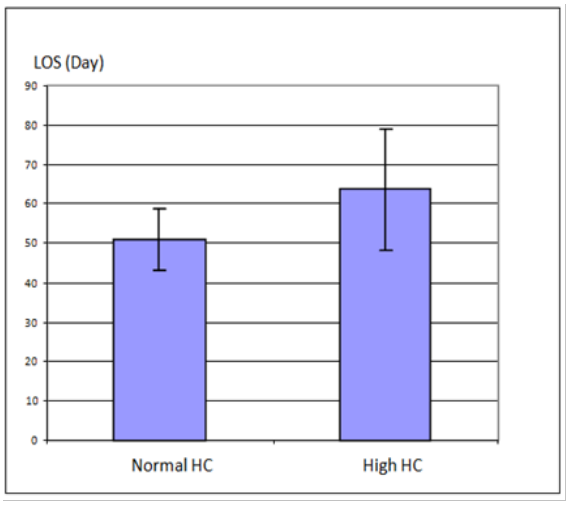

Figure 1 Length of stay between patients with normal and high HC (the data was expressed as mean±SE)

Table 2B Functional profile after age and MMSE matched-control analysis.

Measures	High HCS(n=5)	Normal HCS(n=5)
Age(years)	74.6(±10.4)	74.2(± 10.5)
MMSE at admission	24.4(±2.6)	24.8(± 3.4)
MMSE at discharge	24.4(±2.6)	24.8(± 3.4)
FIM at admission(total 126)	68.2(±27.0)	71.6(± 36.0)
FIM gain	29.4(±15.4)	36.2(± 24.1)
FIM efficiency	0.52(±0.4)	0.55(± 0.3)
LOS(days)	78.2(±50)	62.8(± 27.7)
Discharge to home rate(%)	4(80%)	5(100%)
Discharge support rate	4 out of 4(100%)	4 out of 5(80%)

The data was expressed as mean±SD. There were no significant differences between the two groups in the functional profiles.

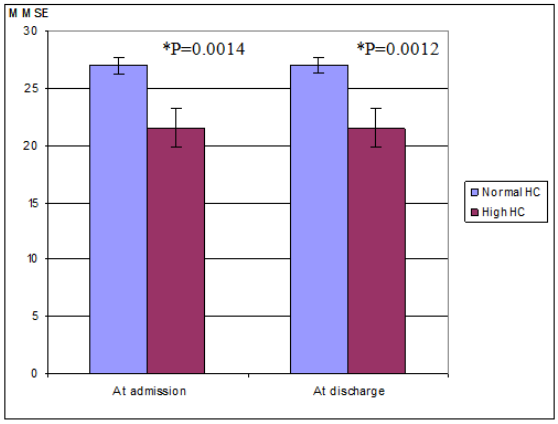

Figure 2 Cognition (MMSE) and level of HC (the data was expressed as mean±SE).

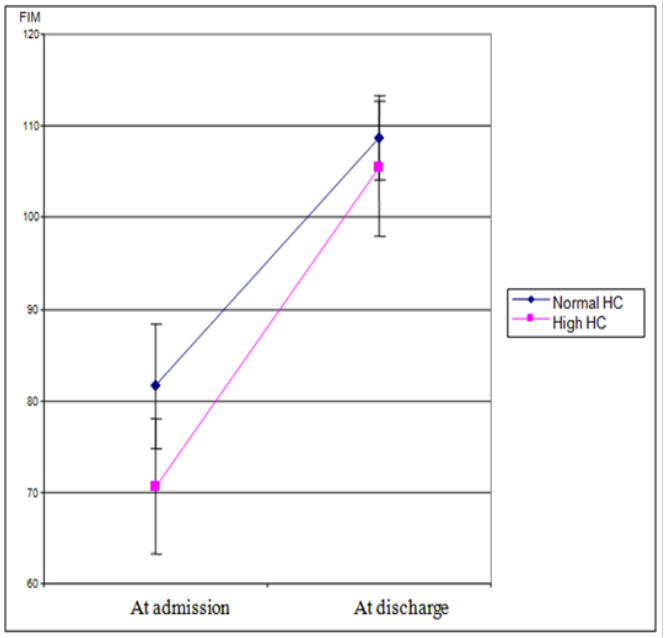

Figure 3 Functional outcome (FIM) at admission and discharge (the data was expressed as mean±SE).

As per the figures shown in Table 2B, a moderate difference in functional profile was noticed in terms of the FIM gain, LOS and discharge to home rates, but these differences did not reach statistical significance.

Serum biochemical markers

The analysis of the nutritional profile suggested that all the parameters assessing nutritional status were within the normal range in both groups, as shown by the serum analysis for vitamin B_{12}, folate and albumin levels (Table 3). There was no significant difference in the levels of CRP in these two groups, which ruled out any other concomitant inflammatory process which could affect the serum levels of these biochemical markers. The levels of HC improved after treatment with folic acid in the group with hyper-homocysteinaemia. This group also demonstrated improvement of functional status following rehabilitation intervention as shown by FIM score in Table 4.

Table 3 Serum biochemical markers.

Biochemical markers	High HCS(n=8)	Normal HCS(n=22)
CRP–mg/L	9.1(±5.6)	8.5(±7.7)
Vitamin B_{12}– pmol/L	316.6(±161.1)	358.6(±277.5)
Folic acid–nmol/L	1678.8(±476.2)	1251.3(±505.6)
Albumin–g/L	36.3(±2.6)	37.6(±2.3)

The data was expressed as mean±SD. Normal range of biochemical markers was defined as CRP ≤5mg/L, Vitamin B_{12} 133-180pmol/L, Folate >356nmol/L, Albumin 35-50g/L.

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Table 4 Functional status pre and post treatment in the high HCS group.

	Pre treatment	Post treatment
HCS	19.1(±3.2)	15.7(±2.8)
FIM	70.6(±21.0)	105.4(±20.7)

The data was expressed as mean±SD. There were no significant differences in functional status pre and post treatment.

Discussion

Overall, the incidence of hyper-homocysteinaemia was about 27% in stroke patients in the acute rehabilitation setting, which was slightly lower as compared to the previous studies[4]. The length of stay for the patients with hyper-homocysteinaemia was longer as compared to the patients with a normal level. Similarly, the admission FIM was lower for the group with the high HC level than the group with the normal HC. Although, the normal HC group demonstrated higher FIM, shorter length of stay, and higher independence and rate of returning home, there were no statistically significant differences in functional profile. The limited sample size may attribute to the non-significant statistical finding.

This study aims to address the question of the association of hyper-homocysteinaemia with rehabilitation outcomes. However, the results are confounded by the greater cognitive impairment and greater age of the hyper-homocysteinaemia group. Due to the limited sample size in hyper-homocysteinaemia group, we were unable to apply a linear regression analysis. Therefore, an age-matched control analysis was applied between hyper-homocysteinaemia participants and control group with normal HC level. When the match-analysis by both age and MMSE was performed, there were no significant statistical differences in most of the functional profile. There was non-statistical significance of moderate improvement in LOS in normal HC group compared to the high-HC group. However, due to limited sample size, the results remain inconclusive.

This study provides us the evidence of lower cognition in the patients with a higher homocysteine level as compared to the patients with a normal HC value. This evidence can be linked to cognitive decline as a result of hyper-homocysteinaemia, as per previous studies.[8,18,19] The mean age difference in the patients between the two groups was of about 6 years (older age in the patients with hyper-homocysteinaemia); however, there is no statistically significant difference. A matched control analysis showed less difference in cognition in these two groups, which may due to limited number of patients. Therefore, the lower cognition in the patients with the higher HC levels cannot be fully excluded from the association of the age related decline in our limited study. Further studies are needed to elaborate this association.

The average age was 71.7 years. Only one patient aged 42 years shared the similar risk factors as the other older subjects. Therefore, it is considered very unlikely that this would skew of our data. The normal results for the biochemical profile to assess for malnutrition ruled out malnutrition and poor general health as a confounding factor in this study. There are a few limitations in this study. The sample size of the present study is small. The effects of treatment on the long term outcomes for the patients who received treatment for hyper-homocysteinaemia are not available. There is no long term follow up organised for the subjects in this study. Given very limited number of patients with hemorrhagic stroke, we did not separate our data between patients with ischaemic stroke from hemorrhagic stroke. This may produce some potential flaw of our data. Broader scale studies are needed to exclude and evaluate the pre-morbid environmental and personal factors that likely contribution to hyper-homocysteinaemia e.g. poor nutritional status, chronic disease, and alcohol abuse. Furthermore, a larger analysis of randomized controlled study is worthwhile to be considered to better define the potential adverse association of the hyper-homocysteinaemia and function.

Conclusion

Hyper-homocysteinaemia is associated with ischaemic cerebrovascular and cardiovascular disease. Over all, the incidence of hyper-homocysteinaemia in the patients with stroke was about 27% in this acute rehabilitation setting which was slightly lower than the previous studies. The length of stay for the patients with hyper-homocysteinaemia was relatively longer as compared to the patients with a normal level of HC. Although, the group with the normal HC levels demonstrated higher FIM, shorter length of stay, higher independence and rate of returning home, there were no statistically significant differences between the two groups. In this study, we found some level of evidence of lower cognition in the patients with a higher HC level as compared to the patients with a normal HC value. In other words, our data demonstrate that higher homocysteine levels are associated with impaired cognition, as previously reported by others.[8,19,20] Further large-scaled studies are needed to elaborate the association between the lower cognition and functional outcomes of hyper-homocysteinaemia with and without treatment.

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Conflict of interests

The author declares no conflict of interest.

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