Homocysteine and Disability in Hospitalized Geriatric Patients

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Elevated total homocysteine (tHcy) concentrations have been found to be associated with cardiovascular disease and dementia in old age. The present study was performed to identify the prevalence of hyperhomocysteinemia (HHcy) and to analyze the association between tHcy concentration and sociodemographic characteristics, nutritional parameters, and cognitive and functional status in this sample of hospitalized geriatric patients. A total of 214 patients (77% females) 65+ years old admitted into an acute care geriatric ward of an internal medical department in the Northern Italy were studied. tHcy concentration was measured using a high-performance liquid chromatography with fluorescence detection (HPLC-F). Information about nutrition (body mass index [BMI], serum albumin, cholesterol, and transferrin) was collected on admission. Functional status was investigated with the Basic Activities of Daily Living scale (ADL) and the Instrumental Activities of Daily Living scale (IADL); cognitive and affective status were assessed by the Mini-Mental State Evaluation (MMSE) and the Geriatric Depression Scale (GDS). The mean tHcy concentration was 18.4 ± 13.1 μmol/L; 74.2% of males and 68.9% of females had HHcy (>12 μmol/L). Sixty-four percent of patients with normal serum vitamin B_{12} and folate concentrations had HHcy. Elevated tHcy concentrations were associated with older age, male gender, increasing serum creatinine, lower MMSE score, and disability. The mean tHcy concentration depended on the occurrence of different diseases. Patients affected by atherosclerotic diseases, such as ischemic heart diseases, cerebrovascular diseases, and dementia had higher mean tHcy concentration than those without diagnosed vascular diseases. In multivariate analysis, vitamin B_{12}, folate, serum albumin, creatinine, and disability emerged as factors associated with tHcy, adjusted for age, gender, education, MMSE score, and atherosclerotic diseases. Our results suggest that the prevalence of HHcy in hospitalized patients is very high, even in subjects with normal cobalamin and folate concentrations. High Hcy concentration can be associated with functional impairment.

HOMOCYSTEINE (Hcy) is a sulfhydryl amino acid formed during the conversion of methionine to cysteine. Hcy levels are normally kept low by 2 major mechanisms. First, Hcy is remethylated via methionine-synthase to form methionine by a reaction requiring folate and vitamin B_{12}. Second, Hcy can be converted to cystathionine by the activity of the enzyme cystathionine-β-synthase (CBS).[1,2] Therefore, alterations in the levels of expression or functional activity of enzymes or substrates can affect Hcy concentration. Aging-related disturbances in absorption, transport, and metabolism can cause cobalamin and folate deficiencies as well as hyperhomocysteinaemia (HHcy).[3] Dietary intake of folate has been found to correlate with homocysteinemia, and vitamin supplements have been reported to lower total Hcy (tHcy) concentrations in the elderly.[4,5] Studies of animal and in vitro models of atherosclerosis have provided evidence that even moderate elevations of Hcy concentration can promote damage to the vascular endothelium.[1] Hcy is a reactive molecule, which causes hydrogen peroxide formation, intimal injury, and fibrin deposition contributing to the development of endothelial lesions and the atherosclerotic process.[6-8] Numerous epidemiologic studies have established that elevated tHcy concentration is associated with an increased risk of coronary heart disease,[9] cerebrovascular disease,[10,11] carotid atherosclerosis,[12] and dementia.[13,14]

The present study was performed to identify the prevalence of HHcy in hospitalized patients 65+ years old and to analyze the association between tHcy and sociodemographic characteristics, nutritional parameters, and cognitive and functional status in this sample.

MATERIALS AND METHODS

From January 2001 to June 2002, 214 patients 65+ years old were admitted into an acute care geriatric ward, Division of Internal Medicine I, Spedali Civili of Brescia in Northern Italy. Information on sociodemographic characteristics, such as age, gender, years of education, and marital status was collected on admission. Each patient underwent a routine comprehensive medical, functional, neuropsychological, and nutritional assessment by the medical staff at both admission to and discharge from hospital.

Nutritional Assessment

Nutritional status was assessed using anthropometric and serologic indicators. Body mass index (BMI) was established by dividing body weight (to the nearest 0.5 kilograms) by squared height (in meters).

Serum albumin, total serum cholesterol, transferrin, and hemoglobin were assayed with routine methods. Serum vitamin B_{12} was measured with a carbonyl metallo immunoassay method (CMIA), and serum folate was measured with a microparticle enzyme immunoassay method (MEIA). Because elevated Hcy concentrations have been reported in association with plasma cobalamin < 258 pmol/L, this cobalamin value was taken to indicate inadequate status.[15,16] A serum folate concentration <13.6 nmol/L was taken as cut off value as it represents a negative folate balance.[17]

Hcy concentration was determined the day following admission after an overnight 8-hour fast. Venous blood samples were drawn in evacuated tubes with K-EDTA, placed immediately on ice, and centrifuged within 15 minutes. Total plasma Hcy was assayed by high-performance

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liquid chromatography with fluorescence detection (HPLC-F). HHcy was defined as fasting tHcy concentration >12 μmol/L.[18]

Functional Status Assessment

Functional status was investigated using the Basic Activities of Daily Living scale (ADL) to assess the individual's ability to manage activities, such as bathing, dressing, going to toilet, continence, feeding, and transference.[19] The ADL is a 6-point scale that ranges from 0 (independent in all activities) to 6 (totally dependent). The Instrumental Activity Daily Living scale (IADL) was used to assess more complex functions (cooking, washing clothes, going shopping, housekeeping, use of the telephone, budget management, outdoor mobility, and self-administration of medicines).[20] The IADL is an 8-point scale, from 0 (independent in all investigated functions) to 8 (dependent in all investigated functions). We used information on premorbid functional status reported by patients and their care takers or relatives. We asked about patients' ability to perform the activities 2 weeks before admission. Retrospective reports of patients' functional status before hospital admission were validated.[21]

Diseases

Diseases were diagnosed with the International Classification of Diseases, 10th revision (ICD-10). We grouped the most prevalent somatic disorders into 8 categories: coronary heart disease, cerebrovascular diseases, hypertension, diabetes, gastrointestinal diseases, lung diseases, malignancies, and osteoarticular diseases. Ischemic heart disease (CHD) consisted of electrocardiogram typical ischemic changes, stable or unstable angina, and previous myocardial infarction. Cerebrovascular diseases (CVD) involved both transient ischemic attack (TIA) and stroke, and carotid artery wall thickening. Gastrointestinal diseases consisted of gastritis, peptic ulcer, inflammatory bowel diseases, and intestinal obstruction. Lung diseases consisted of chronic obstructive pulmonary diseases and recurrent pneumonia. Malignancy involved both previous and current malignant tumors. Osteoarticular diseases were arthritis and arthrosis. For the purpose of the study, we created another variable called atherosclerotic diseases, which grouped together defined vascular disorders (coronary heart diseases and cerebrovascular diseases).

Comorbidity was measured by the Greenfield Index of Disease Severity (IDS) and the Geriatric Index of Comorbidity (GIC).[22,23] The IDS assesses the severity of disease: IDS = 1 refers to patients with asymptomatic, controlled disease; IDS = 2 refers to patients with symptomatic, controlled disease; IDS = 3 refers to patients with uncontrolled disease, and IDS = 4 refers to patients with uncontrolled, life-threatening disease. The GIC takes into account both the number and the severity of diseases. This is a 4-point scale that classifies individual diseases in 4 classes of comorbidity, which are defined as follows: class I, if only diseases with IDS = 1 are present; class II, if the patient is affected by at least one disease with IDS = 2; class III, if one disease with IDS >2 and one or more diseases with IDS = 2 are present; class IV, if 2 or more diseases with IDS >2 are present. The IDS and the GIC scores were assessed during hospitalization, and the acute diseases leading to admission were considered.

Mental Status

Cognitive status was assessed by the Mini-Mental State Examination (MMSE). The score of the MMSE was adjusted according to age and education by Magni et al,[24,25] who validated this test in a population of individuals 65+ years old institutionalized in Northern Italy.

Depressive symptoms were assessed with the Geriatric Depression Scale (GDS),[26] which is a 30-point depression-screening scale. Increasing score indicates increasing depressive symptoms. The GDS was administered only in patients scoring 17 points or more on the MMSE.

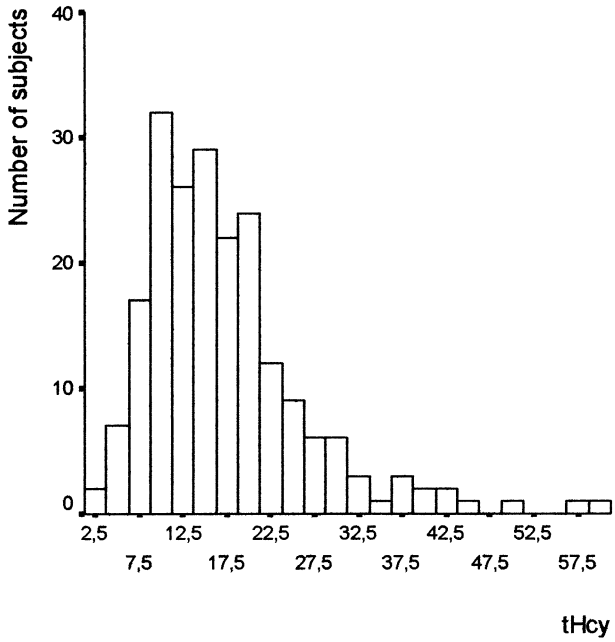

Fig 1. Frequency distribution for fasting plasma Hcy concentrations (μmol/L).

The Diagnostic and Statistical Manual (DSM)-IV criteria were used for dementia diagnosis.[27] Both possible and probable Alzheimer's disease (AD) cases, according to the National Institute for Neurological Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association, were included. Both possible and probable vascular dementia cases, according to the National Institute for Neurological Disorders and Stroke and Association Internationalle pour la Recherche et l'Enseignement en Neurosciences, were included.[28,29]

Statistical Analysis

Statistical analyses were performed by SPSS statistical software, version 11 (SPSS, Chicago, IL).[30] We used the following statistical tests. Correlations between continuous variables were studied using the Spearman correlation coefficient. The Student test was performed when the data were normal. For dichotomous and unordered categorical data, the Pearson chi-square test was used. Multivariate linear regression models were adopted to evaluate factors associated with tHcy concentrations. *P* values less than .05 were considered statistically significant.

RESULTS

Our study consisted of 214 (77% females) hospitalized 65+ years old patients (80.2 ± 7.4 years of age). The high mean score of the geriatric index of comorbidity (2.8 ± 0.9) was indicative of a frail and ill population in which multiple and severe diseases coexisted. The most prevalent diseases were hypertension (51%), osteoarticular diseases (47%), CHD (40%), CVD (37%), gastrointestinal diseases (35%), lung diseases (27%), malignancy (20%), diabetes (17%), and dementia (16%). Thirty-eight percent of demented patients were affected by AD, 50% by vascular dementia (VaD), and 12% by other types of dementia (Lewy body and Parkinson dementia).

The mean tHcy concentration was 18.4 ± 13.1 μmol/L; 74% of males and 69% of females had HHcy (>12 μmol/L). The frequency distribution for tHcy is reported in Fig 1. The mean

Table 1. Characteristics of the Population and Their Correlation Coefficients With tHcy

Characteristics	Mean ± SD	Correlation Coefficients
Age (yr)	80.2 ± 7.4	.193‡
Female (%)	76	−.016*
Education (yr)	5.5 ± 2.8	−.118
MMSE (score)	20.3 ± 9.2	−.173†
GDS (score)	10.5 ± 6.3	.096
ADL (score)	1.6 ± 1.8	.186†
IADL (score)	3.5 ± 3.0	.229†
BMI (kg/m^2)	24.2 ± 5.3	.179
Plasma albumin (g/dL)	3.4 ± 0.5	−.066
Total cholesterol (mg/dL)	193.1 ± 50.1	.036
Transferrin (mg/dL)	231.4 ± 66.7	−.088
Creatinine (mg/dL)	1.3 ± 0.7	.240‡
Hemoglobin (g/dL)	12.5 ± 2.6	.059
Vitamin B_{12} (pmol/L)	290.8 ± 149.1	−.149†
Folate (nmol/L)	12.1 ± 4.9	−.309‡
Smoke (% current smokers)	8.5	.121
Alcohol (% current drinkers > 0.5 L/d)	4.7	.032

Abbreviations: MMSE, Mini-Mental State Examination; ADL, Basic Activities of Daily Living; IADL, Instrumental Activities of Daily Living; GIC, Geriatric Index of Comorbidity; BMI, body mass index.

*$P < .05$; †$P < .01$; ‡$P < .001$.

tHcy concentration increased with age; ranging from 13.9 ± 6.9 μmol/L in the younger elderly (65 to 74 years) up to 20.4 ± 10.1 μmol/L in the oldest patients (90+ years). Twenty-four percent of patients had either vitamin B_{12} or folate deficiency; similar proportions of vitamin deficiency were found in men and women. Eigthy-six percent of patients with vitamin deficiency had HHcy, and 64% of patients with normal serum vitamin B_{12} and folate concentrations had HHcy.

Patients' characteristics and their simple correlation coefficients for tHcy are described in Table 1. In univariate analysis, tHcy was significantly associated with older age, male gender, higher serum creatinine, cognitive impairment, and number of lost functions (both ADL and IADL functions). No associations were found between tHcy and depressive symptoms (GDS), or nutritional indicators (BMI, serum albumin, total cholesterol, and transferrin), or with habits, such as alcohol consumption and smoking (cigarettes).

Mean tHcy concentration depended on the occurrence of different diseases. Patients affected by atherosclerotic diseases, such as CHD or CVD had higher mean tHcy than those without diagnosed vascular diseases (18.5 ± 12.2 μmol/L *v* 15.6 ± 9.5 μmol/L, $P < .01$). Patients affected at the same time by 2 or more atherosclerotic diseases and hypertension had the highest tHcy concentration (26.9 ± 23.4 μmol/L). Mean tHcy concentration was higher in demented compared with nondemented individuals (21.7 ± 14.6 μmol/L *v* 18.1 ± 10.5 μmol/L, $P < .01$, respectively). No differences were detected in the mean tHcy concentration in patients affected by AD or VaD or by other diseases (diabetes, malignancy, lung, gastrointestinal, and osteoarticular diseases).

We created a multivariate linear regression model to evaluate factors associated with tHcy, including age, gender, MMSE score, disability (ADL lost functions), serum albumin, creatinine, vitamin B_{12}, folate, and atherosclerotic diseases (presence *v* absence) as independent variables. Creatinine, albumin, vitamin B_{12}, folate, and disability emerged as factors associated with tHcy (Table 2). Finally, we created another multivariate linear regression model including the IADL as an independent variable instead of the ADL, and adjusting for the same independent variables. The number of lost IADL was correlated with tHcy (β coefficient = 0.229; 95% confidence interval [CI] = .19 to 1.8, $P < .01$).

DISCUSSION

Our study, performed in geriatric hospitalized patients, provides information about the occurrence of HHcy and related factors in patients 65+ years old. In community-based studies, the prevalence of HHcy in the elderly varies from 30% to 56%.[31,32] Few studies have been performed in hospitalized geriatric patients. We investigated elderly medical in-patients in whom the prevalence of HHcy was very high (74.2% in males and 68.9% in females). This percentage was similar to that reported by Ventura et al[33] in another hospitalized Italian population (67% in males and 56% in females). The large number of subjects affected by atherosclerotic diseases (CHD and CVD) and the very old age of some of our patients could explain the high prevalence of HHcy. Moreover, wide differences in mean tHcy concentrations emerged within age groups, suggesting that the elderly are not a homogeneous population and confirming previous results from population-based studies.[13] tHcy concentration was often associated with vitamin B_{12} and folate concentrations, but a large proportion of patients with HHcy did not have vitamin B_{12} and folate deficiency. Although there is no consensus about diagnosing vitamin B_{12} deficiency, some investigators have suggested that Hcy and methylmalonic acid concentrations (MMA) can be markers of cobalamin deficiency.[34] High tHcy can indicate an undiagnosed mild vitamin B_{12} or folate deficiency. Indeed, vitamin supplements significantly reduce tHcy and MMA in older adults with normal serum vitamin concentrations, supporting the hypothesis that vitamin deficiency is common in the elderly, even in the presence of normal serum vitamin concentrations.[35] On the other hand, Hvas et al[36] have shown that although vitamin B_{12} is efficient in decreasing MMA and tHcy, there is no improvement in neurologic manifestations related to cobalamin defi-

Table 2. Multiple Linear Regression Model: Regression Coefficients (β) for tHcy Concentrations on Indicated Covariates

Covariates	β	95%CI	*P*
Age (yr)	.059	−.15-.36	.413
Female	−.017	−5.4-4.1	.798
Education (yr)	−.062	−8.9-.31	.337
MMSE	−.072	−.32-.12	.361
ADL (lost functions)	.166	.05-2.2	<.05
Albumin	.155	.47-7.6	<.05
Creatinine	.254	2.5-7.6	<.001
Vitamin B_{12}	−.146	−.01-0.0	<.05
Folate	−.275	−1.6-−.56	<.001
Atherosclerotic diseases	−.037	−4.5-2.5	.571

Abbreviations: 95% CI, 95% confidence intervals; MMSE, Mini-Mental State Examination; ADL, Basic Activities of Daily Living.

ciency after treatment. Therefore, the clinical importance of diagnosing and treating mild vitamin B_{12} deficiency is still uncertain. It is unknown whether decreasing tHcy concentrations with vitamin supplements reduce the vascular risk of Hhcy.[36]

Besides cobalamin and folate concentrations, to analyze the association between protein-caloric malnutrition and HHcy, we included serum albumin in the multivariate analysis. Even though serum albumin emerged as a factor associated with tHcy concentration, we should consider this result carefully, as our study was performed in hospitalized patients in whom serum albumin concentrations varied with the acute disease.[37]

The most interesting finding of the study was the association between tHcy and disability, measured by the ADL and IADL scales. This association was not explained by age, cognitive impairment, atherosclerotic diseases, abnormal renal function, albumin, vitamin B_{12}, or folate concentrations. Many studies have shown that tHcy concentrations in the elderly are associated with an increased risk of stroke, ischemic heart diseases, and dementia,[11,13,38] which are all accepted causes of disability.[39,40] Recently, Kado et al[41] reported the results of a prospective cohort study in which older adults with elevated tHcy concentrations were at high risk of declining physical function, independently from stroke incidence. The investigators give numerous hypotheses about the putative mechanism of Hcy toxicity in relation to functional impairment.[41] Although these intriguing hypotheses need further evaluation and confirmation, it is becoming more and more evident that Hcy and its vitamin determinants can affect more than cardiovascular diseases.[42] Our results suggest that high Hcy concentration can be associated with functional impairment. Furthermore, in our population the correlation between tHcy and disability was independent of cognitive status. Disability and cognitive impairment often coexist and affect each other.[43] As elevated tHcy can be associated with cognitive decline,[44] the latter should be taken into account as a confounding factor.

Some limitations of the study should be cited. First, we performed a cross-sectional study, and our findings need to be confirmed in subsequent prospective cohort studies. Second, we investigated hospitalized geriatric patients who represent a selected part of the older population. Therefore, we cannot generalize our results to the broader elderly population. Third, despite adjustment for certain factors, it is possible that other unmeasured variables could explain our results.

The association between Hcy concentration and disability is a relevant topic that needs further longitudinal studies. Functional impairment affects 30% to 61% of hospitalized subjects, is a major cause of institutionalization, and increased mortality risk.[45,46] The possibility that prevention of elevated tHcy concentration reduces the chance of functional disability greatly increases the hope of maintaining self-sufficiency in old age.

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