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Serum Albumin Levels Predict Cognitive Impairment in Elderly Hip Fracture Patients

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The aim of this study was to investigate the possible interrelation of serum albumin levels and cognitive function of elderly hip fracture patients. The study involved 331 elderly patients with hip fractures, admitted for rehabilitation. Cognition was assessed by Mini-Mental State Examination (MMSE). MMSE scores less than 24 points were considered suggestive of cognitive impairment. Age, serum albumin levels, and previous stroke emerged as the only statistically significant parameters differing between those with MMSE score less than 24 or higher. After adjusting for confounding variables, the middle and lowest tertiles of serum albumin levels were associated with an increased risk of cognitive impairment (odds ratio 1.97, 95% confidence interval 1.15-3.38, $P < .01$ vs 3.06 and 1.79-5.23, $P < .001$, respectively). This study shows that lower serum albumin levels are independently associated with lower MMSE scores in hip fractured elderly patients, supporting the possible role of chronic low-grade inflammation in age-related cognitive decline.

Keywords: albumin; cognitive impairment; hip fracture; elderly

Introduction

Several possible mechanisms related to inflammation may affect cognitive status and have recently been reviewed in this journal.[1] These include the direct effects of cytokines and other inflammatory agents on neurons and microglia, as well as a possible effect on vascular factors, thereby augmenting the risk for both cardiovascular and cerebral disorders. Inflammatory mechanisms are probably involved in the pathogenesis of Alzheimer disease.[2]

Immunopathologic brain studies have shown that amyloid plaques are associated with the deposition of acute-phase reactants such as C-reactive protein (CRP) and complement factors and that clusters of activated microglial cell express proinflammatory cytokines such as interleukin (IL)-1 and IL-6.[3-7] The peripheral immune system may be activated as well, and various inflammatory responses have been demonstrated that involve peripheral blood cells,[8,9] increased serum CRP[10] and IL-6[11] levels, and alpha-1-antichymotrypsin.[12] Recent longitudinal studies have indicated that inflammatory markers such as CRP and IL-6 are associated with cognitive decline in well-functioning white and Afro-American elders.[13] Levels of such markers were increased long before clinical onset of dementia, whether Alzheimer or vascular-type dementia.[14] Increased CRP levels have been shown to precede clinical onset of dementia by 25 years in the Honolulu–Asia Aging Study and to be involved in age-related cognitive impairment.[15] Results of an Italian study have also supported the hypothesis that chronic low-grade inflammation

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may be involved in age-related cognitive impairment,[16] whereas a more recent study[17] concluded that systemic markers of inflammation are moderately associated with cognitive function and decline. Taken together, the findings support the assumption that inflammatory processes may occur long before clinical symptoms of dementia appear. Acute-phase reactions stimulate the downregulation of albumin production. This may be initiated in response to inflammation, involves the release of cytokines (IL-1, IL-6, tumor necrosis factor) from macrophages, and results in downregulation of transcription of other proteins, including albumin.

Serum albumin is a well-known negative acute-phase protein, yet there is still a debate regarding the association of serum albumin levels and cognitive function. A study assessing cognition in heart failure patients concluded that low serum albumin levels were independently associated with cognitive impairment.[18] Only a single prospective study on markers of inflammation and dementia[12] has documented a cross-sectional association of albumin with cognitive performance. However, in that study the highest tertiles of albumin levels were not associated with cognitive decline longitudinally. On genetic grounds, there is also a considerable support for the assumption that the albumin gene is genetically related to the occurrence of late-onset Alzheimer disease.[19]

The aim of the present study was to investigate the possible interrelation between cognitive impairment and albumin level (being a serum-negative acute-phase reactant). We hypothesized that low serum albumin levels would be associated with cognitive impairment among nondemented hip fracture patients. Such data would assist in identifying patients in the early stages of dementia and perhaps in need of more careful medical evaluation and treatment.

Methods

Design and Setting

This is a retrospective chart survey comprising admissions between 1999 and 2004. The analyses included consecutive patients aged 65 years or older with a primary diagnosis of hip fracture and admitted to the orthogeriatric ward of a university-affiliated referral hospital. The nature and characteristics of this orthogeriatric facility has already been described in detail.[20] Briefly, this is geriatrics-based ward, admitting elderly hip fracture patients directly from the emergency department. The ward integrates a multidisciplinary staff and care is taken of patients' surgical, medical, and rehabilitation needs in a single setting, from admission to discharge. The standard rehabilitation course is based on an interdisciplinary rehabilitative team approach, and staff members meet twice a week to evaluate the status of each patient. A treatment plan is established and monitored with the purpose of coordinating and integrating the various aspects of the staff activities (medical, nursing, physical and occupational therapy, social work, and geriatric psychologist). These patients usually undergo a mean of 6 hours per week of physical and occupational therapy. The study was approved by the local institutional review board.

Study Population

The study sample consisted of 433 consecutive patients admitted with a diagnosis of recent hip fracture. We included all patients aged ≥ 65 years (range, 65-99; mean, 81.76 ± 7.04) with pertrochanteric (extracapsular) or subcapital (intracapsular) hip fracture. The presence of ischemic heart disease (manifested as stable or unstable coronary syndrome), previous stroke, diabetes mellitus, hypertension, hyperlipidemia, and atrial fibrillation had been established by medical history, obtained by interview and a complete physical examination.

Patients known to have prefracture dementia during hospital stay were excluded from this study. A patient was considered noneligible whenever a medical record contained a discharge diagnosis code indicative of dementia (ICD-9 code 290.0) or was considered as demented by the referring physician or by his or her close caregiver. The presence of a prefracture dementia was also determined after searching of previous hospital records indicating a diagnosis of dementia (reviewed by the study physicians [EHM and AA]). In addition, patients suffering from delirium according to the confusion assessment method[21] during hospital stay were excluded to avoid a biased Mini-Mental State Examination (MMSE) score. Overall, 102 patients were diagnosed a priori as having dementia prior to the present hospitalization and/or delirium and were excluded from this study. The final analysis included the data of the remaining 331 patients.

Cognitive Assessment

Patient's cognitive status was assessed by the MMSE[22] within 1 week after admission to the rehabilitation ward. MMSE scores lower than 24 points were considered suggestive of cognitive impairment.[23] However, subjects were not excluded on the basis of lower limits on the MMSE scores.

Assessment of Serum Albumin Levels

Serum albumin levels were determined after an overnight fasting from a blood sample collected within 3 days before discharge. Serum albumin levels were determined by using an automatic analyzer (Olympus, AU 2700, bromcresol purple, wavelength 603 nm).

Statistical Analysis

Comparisons between patients with MMSE score ≥ 24 and those with MMSE score <24 were performed on a list of clinical and functional measures using *t* tests for continuous variables and χ^2 tests for dichotomous variables. Linear regression analysis was performed to assess the independent associations of serum albumin levels and demographic and clinical characteristics to cognitive status scores. In addition, logistic regression adjusting for potential confounders was performed to study the risk of cognitive impairment associated with middle and lowest tertiles of albumin levels. A *P* value ≤ .05 was considered as statistically significant. All statistical analyses were performed using the SPSS system for Windows, version 10.0.1.

Results

The data of 331 consecutive hip fracture patients aged 65 and older and admitted during a 2-year period were available. The clinicodemographic characteristics of these patients are shown in Table 1. The mean age was 81.76 ± 7.04 years, mostly women (78.5%). The mean MMSE score and mean serum albumin levels were 22.03 ± 6.44 and 3.51 ± 0.47 g/dL, respectively (Table 1).

A total of 167 patients (50.5%) were found to be cognitively impaired (MMSE score <24). There were no statistically significant differences between these patients and the remaining patients (n = 164) with MMSE score ≥ 24 neither by gender nor by hypertension, ischemic heart diseases, and diabetes mellitus.

Table 1. Descriptive Characteristics of Patients' Sample (n = 331)

Age, years (mean ± SD)	81.76 ± 7.04
Female gender, n (%)	260 (78.5%)
MMSE scores (mean ± SD)	22.03 ± 6.44
Albumin level, g/dL (mean ± SD)	3.51 ± 0.47
Diabetes mellitus, n (%)	50 (15.1%)
Hypertension, n (%)	161 (48.6%)
Hyperlipidemia, n (%)	41 (12.4%)
Ischemic heart disease, n (%)	70 (21.1%)
Parkinson's disease, n (%)	19 (5.7%)
Previous stroke, n (%)	33 (10.0%)

Abbreviations: SD, standard deviation; MMSE, Mini-Mental State Examination.

Age (80.19 ± 6.52 vs 83.31 ± 7.24; $P < .001$), serum albumin levels (3.61 ± 0.41 vs 3.43 ± 0.51; $P < .001$), and previous stroke (11 [6.6.7%] vs 22 [13.2%]; $P = .04$) emerged as the only statistically significant parameters differing between those with and without cognitive decline, respectively (Table 2).

Because an MMSE score of ≥ 24 defined younger age group patients having higher serum albumin levels, we performed a linear regression analysis to test for predictors of MMSE scores. This showed (Table 3) that age was independently and inversely associated with MMSE scores ($\beta = -0.25$; $P < .001$). A higher serum albumin level ($\beta = 0.22$; $P < .001$) emerged as independently predicting higher MMSE scores. None of the other variables that we tested, including gender, hypertension, diabetes, ischemic heart disease, hyperlipidemia, Parkinson's disease, and previous stroke, were predictive of MMSE scores.

A significant correlation was found between serum albumin levels and MMSE scores (Spearman correlation coefficient = 0.28; $P < .001$), as shown in Figure 1. In addition, logistic regression analysis predicting cognitive impairment (MMSE score <24) and controlling for confounding variables showed that the middle and the lowest tertiles of albumin levels were associated with an increased risk of cognitive impairment (adjusted odds ratio, 1.97; 95% confidence interval, 1.15-3.38; $P = .01$; and odds ratio, 3.06; 95% confidence interval, 1.79-5.23; $P < .001$, respectively) (Table 4).

Discussion

The present study focused on the possible interrelation between serum albumin status and cognitive

Table 2. Clinical and Cognitive Characteristics of Patients by Mini-Mental Scores

	MMSE ≥ 24 (n = 164)	MMSE <24 (n = 167)	*P*
Albumin, g/dL (mean ± SD)	3.61 ± 0.41	3.43 ± 0.51	<.0001
Age, years (mean ± SD)	80.19 ± 6.52	83.31 ± 7.24	<.0001
Female gender, n (%)	124 (75.6%)	136 (81.4%)	.12
Diabetes mellitus, n (%)	25 (15.2%)	25 (15.0%)	.53
Hypertension, n (%)	83 (50.6%)	78 (46.7%)	.27
Hyperlipidemia, n (%)	23 (14.0%)	18 (10.8%)	.23
Ischemic heart disease, n (%)	33 (20.1%)	37 (22.2%)	.38
Parkinson's disease, n (%)	9 (5.5%)	10 (6.0%)	.52
Previous stroke, n (%)	11 (6.7%)	22 (13.2%)	.04

Abbreviation: MMSE, Mini-Mental State Examination.

Table 3. Influence of the Studied Variables on MMSE Scores[a]

Independent Predictors	β	*P*
Albumin level, g/dL	.22	<.001
Age	−.25	<.001
Gender	−.08	.12
Hypertension	.09	.06
Diabetes	.01	.81
Ischemic heart disease	−.01	.74
Hyperlipidemia	−.02	.71
Parkinson's disease	−.003	.95
Previous stroke	−.01	.72

Abbreviation: MMSE, Mini-Mental State Examination.
[a] Values calculated by linear regression analysis.

Table 4. Influence of Serum Albumin Levels on Cognitive Decline (MMSE <24)

Tertile of albumin (g/dL)	n	OR (CI 95%)[a]
High, 3.61-4.90	121	1.0 (reference)
Middle, 3.31-3.60	100	1.97 (1.15-3.38)[b]
Low, 1.90-3.30	110	3.06 (1.79-5.23)[c]

Abbreviations: MMSE, Mini-Mental State Examination; OR, odds ratio; CI, confidence interval.
[a] Adjusted for age, gender, diabetes, ischemic heart disease, hypertension, previous stroke, and hyperlipidemia.
[b] $P = .01$.
[c] $P < .001$.

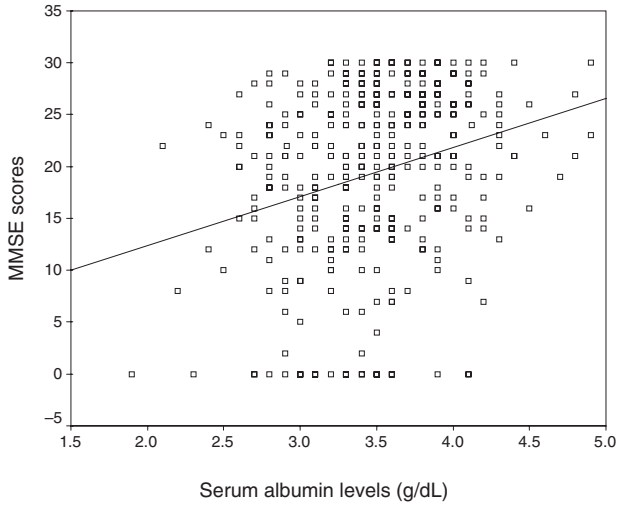

Figure 1. Interrelation of MMSE scores and serum albumin levels in elderly hip fracture patients.

impairment in a group of elderly hip fracture patients. Our data show that lower serum albumin levels were associated with lower MMSE scores, thus indicating cognitive impairment. In particular, patients in the middle and the lowest tertiles of serum albumin levels showed a statistically significant increased risk of having cognitive impairment. After multivariate adjustment (for age, gender, diabetes, ischemic heart disease, hypertension, previous stroke, and hyperlipidemia), the association between serum albumin and cognitive decline remained evident.

The significance of this finding may be questioned with regard to albumin being merely a marker or being an important mediator, contributing to cognitive decline in elderly hip fracture patients. It has been traditionally uncontested that low albumin is a marker for increased disease-related morbidity and mortality, independent of underlying disease type. However, a low albumin level itself has been suggested as precipitating various pathological conditions (heart failure, infections, renal failure, etc) in frail elderly, thereby adversely affecting these patients. It is therefore possible that low albumin levels may also be involved as a mediator of the various manifestations

of cognitive decline, so frequently seen shortly before, during, and after the period of hip fracture.[24]

A recently published study on markers of inflammation (other than albumin) in hip-fracture-operated elderly patients[25] has also raised questions about possible effects that inflammatory markers might have on cognition of such patients. We therefore suggest that hip fracture patients with hypoalbuminemia be routinely, and preferentially, screened for cognitive decline.

The association between serum albumin and cognitive impairment may reflect a completely different mechanism, unrelated to infection or nutritional state of patients. Such a lack of association between cognitive impairment and subnutritional status has already been shown previously in a study that excluded such patients from the study sample.[26]

Another study has concluded that nutritional factors other than albumin were significantly associated with measures of disability and presence of depression, whereas acute-phase factors, including albumin, were significantly associated with cognitive impairment in elderly residents.[27]

Some important caveats about the present study are worthy of mention, resulting from its retrospective nature and the fact that this is a single-site study: we used only a single cognitive screening tool, minimal cognitive impairment patients were not considered, and a comprehensive nutritional assessment was not carried out. Also, despite adjustment made for important confounders, still other could have been considered, in particular those relating to other inflammatory markers and illnesses. In addition, concerns must be exercised about extrapolation from findings of this study sample and drawing inferences about different populations. Despite these limitations, the present study is advantageous in the sense that it consisted of a relatively large sample of patients, focusing on the possible role of serum albumin level on cognitive level among hip fracture patients.

In conclusion, our findings suggest that hip fractured elderly patients with low serum albumin level during the rehabilitation course have lower MMSE scores. Whether correction of albumin would by itself affect cognition is doubtful, yet it suggests that patients admitted to rehabilitation wards may benefit from a more intensive protein supplementation aimed at improving their serum albumin level.

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