European Geriatric Medicine 6 (2015) 314–318

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Research paper

Vitamin deficiency as a risk factor for delirium

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ARTICLE INFO

Article history:
Received 21 May 2014
Accepted 4 September 2014
Available online 27 May 2015

Keywords:
Delirium
Vitamin D
Hip fracture
Malnutrition
Hypovitaminosis

ABSTRACT

Purpose: Hip fracture patients constitute a frail group and are often at risk of malnutrition. These patients are also at great risk of delirium. We aimed, in a case control study, to assess the relationship between specific hypovitaminoses and the risk of delirium in hip fracture patients.
Subjects: Blood was drawn for measurements of vitamins A, B1, B6, B12, C, 25(OH)D, E, and K1, as well as folic acid, in 115 patients upon admission for hip fracture. Delirium was assessed daily preoperatively and 5 days postoperatively (all patients) or until discharge (delirious patients) using the Confusion Assessment Method. Patients with delirium were classified as cases and patients without delirium as controls.
Results: A total of 59 (51%) patients had delirium during their hospital stay. Concentrations of 25(OH)D and vitamin C were significantly lower in cases compared with controls (median nmol/L 25(OH)D: 41 (32–52) vs. 52 (34–77), $P = 0.05$; mean μmol/L vitamin C: 25 ± 16 vs. 35 ± 20, $P = 0.01$). A concentration below 50 nmol/L for 25(OH)D was an independent and significant risk factor for delirium (odds ratio = 2.7; 95% confidence interval: 1.04–7.2, $P = 0.04$) in a multivariate regression analysis adjusted for all registered confounders.
Discussion and conclusion: Vitamin D deficiency may increase the risk of delirium after hip fracture.

1. Introduction

Hip fractures constitute a major health problem in older people, and are an important cause of loss of function and increased need of care. A total of 20–50% of hip fracture patients experience delirium [1], which is defined as an acute and fluctuating change of attention and cognition. Delirium is associated with a poor outcome with respect to long-term cognitive status and mortality [2].

Old age, cognitive impairment, low body mass index (BMI), and multi-morbidity are risk factors for delirium [1]. In patients with several predisposing factors, few or relatively benign precipitating factors (e.g., urinary tract infection) can trigger the onset of delirium. In contrast, patients without predisposing factors may develop delirium after a severe insult [3].

Hip fracture patients are frequently reported to be at risk for malnutrition, and malnutrition is associated with delirium [4,5]. In a previous study, we found that a low BMI was associated with an increased risk of delirium in hip fracture patients [1]. However, whether a low body mass *per se* is associated with delirium or whether this association is due to specific micronutrient deficiencies is unknown. Lack of thiamine, which is important for neurotransmitter synthesis, has long been associated with wet beriberi. Wet beriberi affects the central nervous system, with symptoms of hallucinations and delusional thinking as in delirium, among others [6]. Vitamins C, D, and E are considered to have antioxidant properties, and have been shown to decrease neuronal damage, possibly through scavenging free radicals. These vitamins may also be involved in the metabolism of cytokines reported to be of pathophysiological significance in delirium [6–10]. However, the association between these vitamins and delirium has been poorly examined. Low vitamin K1 is common in hip fracture patients [11] and vitamin K is associated with cognitive decline [12].

We hypothesize that specific micronutrient deficiency is involved in the pathophysiology of delirium. This study aimed to determine whether the micronutrients vitamin A, vitamin B1, vitamin B6, vitamin B12, folic acid, vitamin C, 25(OH)D, vitamin E, and vitamin K1 are related to delirium in hip fracture patients.

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http://dx.doi.org/10.1016/j.eurger.2014.09.002
1878-7649/

2. Methods

2.1. Hip fracture patients

This case control study was a substudy of the Oslo Orthogeriatric Trial (OOT) [13]. The patients were consecutively included upon admission for hip fracture as a result of a low energy trauma, which was defined as a fall from their own height or from a level not higher than 1 m. Patients were excluded if the hip fracture was part of a multi-trauma. We also excluded patients who were regarded as moribund at admittance (as determined by the admitting orthopaedic surgeon based upon their clinical experience).

Inclusion of patients started in September 2009, and patients who were included until April 2011 were eligible for the vitamin status substudy. A total of 216 patients were enrolled in the OOT during the substudy period. One hundred and fifteen patients had preoperative blood samples drawn, were assessed for delirium, and were included in the analysis of vitamin status and risk for delirium. Missing patients were due to a low capacity to draw blood for project purposes at weekends, holidays, and at night, and delirium status was unknown in one patient. For technical reasons, we were not able to obtain vitamin analyses for all micronutrients from all of the patients, described in the tables. The OOT was negative with respect to prevention of delirium. Therefore, the intervention and control groups were merged for the purpose of the present study.

2.2. Data collection

Delirium was assessed daily throughout the hospital stay using the Confusion Assessment Method criteria [14]. In patients without delirium, assessment was stopped after 5 days.

Data were collected by designated project staff. Weight was measured using a class 3 chair scale as soon as possible after the operation, and patients wore light clothing. Height was calculated from measured knee height at bed rest [15], with flexion of the knee of the non-operated leg so that the angle between the foot and the leg was approximately 90 degrees. Knee height was measured from the anterior surface of the thigh near the patella to under the heel. The participants were categorized as follows: home dwelling versus institutionalized; smoking habits in current smokers and non-current smokers; and alcohol consumption in total abstainers and non-abstainers. Comorbidity was classified according to the Charlson comorbidity index [16]. Four classes of psychoactive drugs were considered: ATC N06A antidepressants, ATC N05A antipsychotics, ATC N05B anxiolytics and ATC N05C hypnotic and sedatives. The patients were dichotomized in users versus non users of any psychoactive drug based on the regular prescriptions on the admission for hip fracture. Activities of daily living were measured using the Barthel Activities of Daily Living Index [17] and hand grip strength was examined by hand dynamometry (Jamar, Germany, three repetitions per examination) daily throughout the hospital stay. The best handgrip test was used for analysis. Pre-fracture cognitive decline was assessed by the 16-item version of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), a validated method for proxy-based assessment of cognitive decline [18]. The IQCODE was completed based on an interview with a close relative, staff in nursing home or home nursing. A cut-off of 3.44 was used as an indicator of pre-fracture cognitive impairment.

2.3. Preparation of blood samples and laboratory analyses

Blood was collected by venipuncture shortly after admission and prior to the operation. Analyses were carried out in serum unless otherwise stated. Vitamin A (retinol) was measured by the Bio-Rad Laboratories kit (Munich, Germany). Vitamin B1 (thiamine) and vitamin B6 (pyridoxal-5′-phosphate) in whole blood were measured by high pressure liquid chromatography (Chromsystems, Munich, Germany). Folic acid and vitamin B12 (cobalamin) were measured by a Hitachi 717 Modular multianalyser (Boehringer Mannheim, Mannheim, Germany). Vitamin C was measured by the method described by Zannoni et al. [19]. The vitamin D precursor 25(OH)D was measured by radio-immunoassay (DiaSorin, Stillwater, MN USA) and vitamin E was measured by radio-immunoassay (Bio-Rad Laboratories). Vitamin K1 was measured by high-pressure liquid chromatography with on-line electrochemical reduction and fluorescent detection (Takara Bio Inc., Japan).

The coefficient of variations for the analysis of these vitamins ranged from 2.5–4.5%. The coefficients of variation remained stable over time. None of the methods were changed and we used the same laboratories during the entire project period.

Standard preoperative blood analyses for C-reactive protein (CRP) and albumin were carried out in all patients ($n = 216$) according to the routine of the hospital laboratory.

2.4. Statistical analyses

Data are shown as mean ± SD, median (interquartile range), or numbers (percentages). The Student's t test or Mann-Whitney U test was used to compare continuous data between groups and the chi-square test was used to compare categorical data.

For the regression analyses, continuous explanatory variables were initially categorized in quintiles as recommended by Hosmer [20], and the linearity of the relationship between the outcome and the dependent variable was examined. When clear threshold effects were displayed, with a decrease in the odds for delirium when the explanatory variable exceeded a certain level, the relevant explanatory variable was categorized accordingly. Other explanatory variables were treated as continuous. In a multivariate logistic regression model, proposed risk factors with a P-value < 0.1 from the bivariate analyses were added in a stepwise forward manner and kept in the model when significant in order to identify independent risk factors. Statistical analyses were performed in SPSS 21 for Windows (SPSS Inc, Chicago, IL).

2.5. Ethics

The Regional Committee for Medical Research Ethics, the Data Inspectorate, and the Directorate for Health and Social Affairs approved the study protocol. Most patients, or next of kin, gave informed written consent before enrolment. Some of the patients were included based on presumed consent, confirmed by next of kin shortly after enrolment. This procedure was approved by the Regional Ethics Committee. The study was performed according to the Helsinki declaration.

3. Results

Of the 115 patients included in the sub-analysis of nutrition, 59 (51%) had delirium during their hospital stay (either preoperatively, postoperatively, or both), and were defined as cases, whereas the remaining 56 were free from delirium throughout the stay and served as controls. Cases were older ($P = 0.01$), were more often prescribed psychoactive drugs upon admission for hip fracture ($P = 0.05$), scored lower on the Barthel Activities of Daily Living Index ($P < 0.001$), had lower hand grip strength ($P = 0.03$), scored higher on the IQCODE ($P < 0.001$), were institutionalized more often ($P < 0.001$), and had lower albumin concentrations in serum ($P = 0.05$) than controls. There were no statistically significant