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Markers of cerebral damage during delirium in elderly patients with hip fracture

Submitted for publication.

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Abstract

Objective: S100B protein and Neuron Specific Enolase (NSE) can increase due to brain cell damage and/or increased permeability of the blood-brain-barrier. Elevation of these proteins has been shown after various neurologic diseases with cognitive dysfunction. The aim of this study was to compare the level of S100B and NSE of patients before, during and after delirium with patients without delirium and investigate the possible associations with different subtypes of delirium.

Methods: Consecutive patients aged 65 years or more acutely admitted after hip fracture were included from 2005 through 2008. Delirium was diagnosed by Confusion Assessment Method, delirium subtype by Delirium Symptom Interview and preexistent global cognitive function by the 'Informant Questionnaire on Cognitive Decline-short form'. In maximal four serum samples per patient S100B and NSE levels were determined by electrochemiluminescence immunoassay.

Results: Of 120 included patients with mean age 83.9 years, 62 experienced delirium. Delirious patients had more frequently pre-existing cognitive impairment (67% vs. 18%, $p < 0.001$). Comparing the first samples during delirium to samples of the non-delirious patients, a difference was observed in S100B (median 0.16 vs. 0.10 $\mu\text{g/L}$, $p < 0.001$), but not in NSE (median 11.7 vs. 11.7 ng/L , $p = 0.97$). S100B levels were higher during delirium from 1 day before up until 8 days after surgery. No significant difference in S100B ($p = 0.43$) or NSE levels ($p = 0.41$) was seen between the hyperactive, hypoactive and mixed subtype of delirium.

Conclusions: Delirium was associated with increased level of S100B which could indicate cerebral damage either due to delirium or leading to delirium.

Introduction

Postoperative delirium following orthopedic surgery for hip fracture occurs in up to 62% of the elderly patients, many with pre-existing dementia¹⁹. It is characterized by fluctuating changes in cognition, consciousness and attention and has a mean duration of three days^{7,19}. Three clinical subtypes of delirium (a hyperactive, a hypoactive, and a mixed subtype) are known^{33,124}. The suggested pathophysiological mechanisms of delirium are mostly hypothetical, but lately there is a lot of interest in the neuroinflammatory system^{42,118,199}. Although patients usually recover after resolution of the underlying cause, delirium appears to be an important risk factor for dementia, even in people without prior cognitive impairment¹¹⁷.

Possibly, the high frequency of dementia after delirium reflects irreversible brain damage caused by the detrimental effects of the pathophysiological mechanisms of delirium on the brain. Moreover, it can be hypothesized that postoperative delirium itself might be the consequence of transient cerebral neuronal damage caused by peri-operative hypoxia, micro embolisms¹¹ or hypotension⁴⁰. S100B-protein (S100B) and Neuron Specific Enolase (NSE) have been used as markers of brain damage in various diseases⁶². S100B belongs to the family of calcium binding proteins, is expressed mainly by astrocytes and is found both intra- and extracellularly in brain tissue¹³. It is usually elevated due to nervous system damage in CSF as well as in blood, due to functional disturbance of membrane integrity and/or increased permeability of the blood-brain barrier. NSE is the intracytoplasmic glycolytic enzyme enolase. It is found in neurons and neuro-endocrine tissue and it is elevated in the blood circulation after increased death rate of these cells.

Elevated levels of S100B have been shown to be associated with delirium in patients after abdominal surgery¹⁵¹, after cardiac surgery⁷² and in sepsis-associated delirium¹⁴². NSE has not been found in serum in delirium tremens⁷¹ but was found to correlate with the degree of cognitive dysfunction at discharge from hospital after cardiac surgery but not after non-cardiac surgery^{113,150}. In these previous studies the delirious state at the day the sample was taken including the subtype of delirium was not taken into account. The aim of this study in elderly hip fracture patients was twofold: (1) to compare changes before and after surgery of S100B and NSE in patients with and without postoperative delirium, and investigate the difference before, during and after delirium; (2) to study the levels of S100B and NSE in different subtypes of delirium.

Methods

Patients

From May 2005 through February 2008, consecutive patients 65 years of age or older who were acutely admitted with hip fracture and scheduled for operation at the Department of

Orthopedic Surgery or Traumatology of the Academic Medical Centre, Amsterdam were invited to participate. Informed consent was obtained from all patients or substitute decision-makers in cases of cognitive impairment. Patients were excluded if they were unable to speak or understand Dutch or English. The institutional Medical Ethics Committee approved the study.

Procedures

Members of the team completed a multidisciplinary evaluation for all study participants. Two geriatricians, a fellow in geriatric medicine, and four research nurses trained in geriatric medicine collected demographic and clinical data. The presence or absence of delirium was scored during weekdays separately by a physician and a nurse using the Confusion Assessment Method (CAM)⁸⁰. We based our information for the diagnosis on our psychiatric examination of the patient, medical and nursing records including the Delirium Observation Screening Scale¹⁷⁴, and information given by the patient's closest relative. When the diagnosis of delirium was doubtful, the patient was discussed in the geriatric consultation team to gain consensus. For subtyping, we used the Delirium Symptom Interview with the cut-off scores described by Liptzin et al., resulting in three different subtypes: the hyperactive, hypoactive and mixed subtype¹¹⁴. The Delirium Rating Scale-Revised-98 (DRS-R-98) was used to monitor the severity of delirium^{35,187}.

Possible confounding factors, including demography, fracture characteristics, type of anesthesia, type of surgery, peri- and postoperative complications, were registered for all patients. Number of medication at home was taken as global measure of co-morbidity. Pre-existent global cognitive functioning was based upon anamnesis, medical history, and 'Informant Questionnaire on COgnitive DEcline-Short Form (IQCODE-SF). The IQCODE-SF assesses the possible presence of global cognitive impairment based on the response of an informant who had known the patient for at least ten years⁸⁴. The informant was asked to recall the situation two weeks prior to the hip fracture and compare it with the situation ten years earlier. Patients with a mean score of 3.9 or higher were considered to have global cognitive impairment³². To measure pre-existent physical functionality, we asked patients, or their closest relative in cases of cognitive impairment, to complete the 15-item Katz ADL scale based on the situation two weeks prior to the hip fracture²⁰³.

A maximum of four blood samples was collected during the hospital stay under similar conditions around 11.00 am. Samples were taken during weekdays whenever patients were available for venipuncture. Blood was kept on ice after withdrawal. Serum was obtained by centrifugation for 15 minutes at 1780g at 4°C, and aliquots were stored at -80°C. S100B and NSE levels were measured on the Modular Analytics E170 (Elecsys module) analyzer (Roche Diagnostics, Mannheim) using the electrochemiluminescence immunoassays (ECLIA) technique. Normal values were established for S100B as below 0.10 µg/l and for NSE as below 12.5^{129,179}. NSE will not be determined in case of even light hemolysis, because hemolysis could substantially increase the NSE value in serum due to

the presence in erythrocytes¹³. The chemical analysts were blinded to the clinical diagnosis of the patients.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 15.0 was used for data analysis. We tested for differences in characteristics in patients with and without delirium using *t*-tests and Mann-Whitney tests. Variables that were not normally distributed were expressed as median scores and inter-quartile ranges. Differences in NSE levels in different subtypes were analyzed using ANOVA and in S100B levels using the Kruskal-Wallis test. A two-tailed criterion of $p < 0.05$ was considered statistically significant. Correlations between NSE and S100B and between S100B and DRS-R-98 score were determined using Spearman's rho test. The repeated measurements were analyzed through linear mixed models with e-based log transformed S100B value in the first model and NSE in the second model as the dependent variable; patient number as a random effect; and day of sampling counted from the day of surgery, delirious state, and the interaction between these two variables as fixed effects. 'Delirious state' was composed of four categories based on the CAM scores of the individual patient at the moment the sample was taken: samples from patients in the non-delirious group were all categorized (1)'non-delirious', samples from patients in the delirious group were categorized (2)'before delirium', (3)'during delirium' or (4)'after delirium'. In addition, pre- or postoperative status, type of fracture, type of surgery, type of anesthesia, global cognitive impairment, and age were considered as covariates in the mixed model. In a backward selection, all variables with p -value above 0.05 were removed. The goodness of fit of the mixed models was inspected by assessing the distribution of the residuals.

Results

During the inclusion period, 271 patients aged 65 years and older were admitted. A total of 55 patients were excluded due to lack of informed consent, 63 patients did not consent to extra blood withdrawal and 33 patients were excluded for logistic reasons. Non-selected and selected patients were similar with regard to the male/female ratio, but the excluded patients were younger (mean age of 81.3 years vs. 83.9 years, $p = 0.005$). In total 120 patients were included, 62 (52%) with delirium and 58 without. This resulted in 387 samples in total, 196 samples of the delirious patients (21 samples before the delirious episode, 120 samples during the delirious episode, 55 after the delirious episode) and 191 samples of the patients without delirium.

Patients with delirium experienced significantly more often pre-existent cognitive and functional impairment ($p < 0.001$) and lived in either old-people's homes or nursing homes significantly more frequently than non-delirious controls ($p < 0.001$) (Table 1). There was no significant difference in the type of anesthesia ($p = 0.35$), type of surgery ($p = 0.54$) or

total number of complications ($p=0.19$) between patients with and without delirium. The median time of admission was 14 days for patients with delirium and 11 days for patients without delirium ($p=0.04$).

Table 1: Characteristics of patients with and without delirium.

Variables	Delirium (N=62)	No delirium (N=58)	P-value
Age (yrs)	84.8 (6.9)	82.9 (7.0)	0.14
Male gender (%)	16 (26)	23 (40)	0.11
Living at home (%)	30 (48)	51 (88)	<0.001
Pre-admission functional impairment (number of ADL disabilities)	8 (6-11)	4 (2-6)	<0.001
Number of medication at home	5 (2-7)	4 (2-6)	0.18
Pre-admission cognitive impairment (%)	39 (67)	10 (18)	<0.001
Days between fracture and operation	1 (0-1)	1 (1-2)	0.49
Spinal anesthesia (%)	22 (36)	19 (33)	0.35
Fracture characteristics (%)			0.54
Femoral neck	25 (40)	28 (48)	
Intertrochanteric	33 (53)	25 (43)	
Other	4 (7)	5 (9)	
Type of surgery (%)			0.64
Internal fixation	40 (65)	35 (60)	
Hip replacement	22 (36)	23 (40)	
Complication (%) -total	29 (50)	22 (38)	0.19
Admission length	14 (8-23)	11 (8-14)	0.04
Death within 3 month (%)	11 (18)	5 (9)	0.14

ADL: Activities of daily living

Mean values (SD) are given for continuous variables with a normal distribution

Median values (inter-quartile ranges) are given for variables that are not normally distributed

Table 2 describes the levels of S100B and NSE in the first sample during the delirious episode in the delirious group compared to samples withdrawn at a comparable day before or after surgery of the non-delirious group (mean postoperative day 1.3, SD: 1.6). More delirious (81%) than non-delirious (50%) patients had levels above the normal values of S100B ($p=0.001$). Also, the levels of S100B were higher in delirious patients ($0.16 \mu\text{g/L}$) compared to the non-delirious patients ($0.10 \mu\text{g/L}$) ($p<0.001$). In our samples NSE was not determined in 153 (38%) of the samples, because of hemolysis due the preservation of the samples on ice after withdrawal. The NSE level was 11.7 (ng/L) both in cases and controls ($p=0.97$). There was no significant correlation with S100B and NSE levels length of admission, death within the first 3 month or preoperative cognitive impairment.

Table 2: S100B ($\mu\text{g/L}$) and NSE (ng/mL) values during delirium vs. no delirium.

	During delirium (N=57 ^a)	No delirium (N=58)	P-value
NSE - number	35	40	
N (%) > 12.5	9 (26)	15 (38)	0.28
Mean (SD)	11.7 (3.8)	11.7 (4.7)	0.97
S100B - number	57	58	
N (%) > 0.10	46 (81)	29 (50)	0.001
Median (IQR)	0.16 (0.10-0.25)	0.10 (0.08-0.15)	<0.001

^a In the group with delirium samples were the first samples during the delirious episode; in the group without delirium, samples of comparable postoperative day were taken. Of five patients in the delirious group no sample taken during delirium.

To study the course over time of S100B, we included samples from the day before surgery until post-operative day eight because during this period samples from both delirious and non-delirious patients were available. Following a backward approach, type of surgery, type of anesthesia, global cognitive impairment, and age were removed. The final statistical model included delirious state ($p < 0.001$), day of blood withdrawal ($p < 0.001$), pre- or postoperative status ($p = 0.001$) and type of fracture ($p = 0.036$). To illustrate the effect of delirium on S100B, three different example patients with an intertrochanteric hip fracture are presented in figure 1: 1) a patient who was delirious from one day before operation until eight days after operation (continuously delirious), 2) a patient who was never delirious during this period (continuously non-delirious), and 3) a patient who was delirious from the day after operation until postoperative day four (delirious day 1-4). S100B levels were highest 'during' delirium at all time-points. 'Before' and 'after' delirium S100B levels were still higher than those from 'non-delirious' patients. Delirious state was not significant associated in the mixed model analysis with NSE in 233 samples. Spearman's test showed no significant correlation between S100B and NSE levels in the first sample ($p = 0.99$).

In 34 delirious patients, delirium subtype was specified; one patient did not meet the criteria for any of the subtypes (Table 3). Specification of the subtype was missing for 23 delirious patients. Delirious patients with known subtype were similar to delirious patients with unknown subtype with respect to age, sex and cognitive impairment. No difference was observed in NSE and S100B levels in patients with different subtypes, nor was there a difference between patients with known vs. unknown subtype. Of 38 patients the severity of delirium (DRS-R-98) was specified. Spearman's test revealed no significant correlation between levels of DRS-R-98 and NSE ($r = 0.20$, $p = 0.32$) or S100B ($r = -0.08$, $p = 0.62$).

Figure 1: Three example patients with an intertrochanteric fracture to show the changes of S100B during admission based on mixed model analysis which included delirious state ($p < 0.001$), day of blood withdrawal ($p < 0.001$), pre- or postoperative status ($p = 0.001$) and type of fracture ($p = 0.036$). Postoperative day 0 is day of surgery.

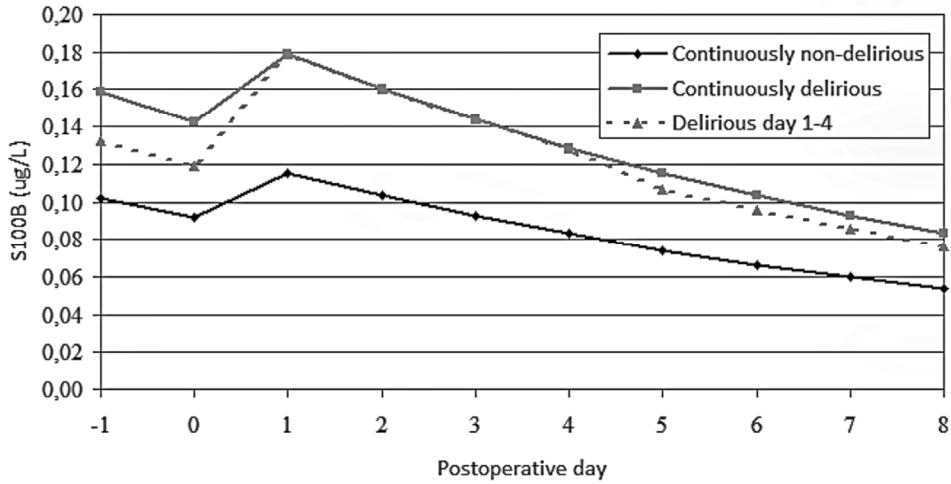


Table 3: Values of NSE (ng/mL) and S100B (µg/L) and DRS-R-98 scores during delirium in different subtypes^a.

	Hyperactive	Mixed	Hypoactive	<i>P</i> -value
NSE - number	11	8	4	
N (%) > 12.5	4 (36)	4 (50)	1 (25)	0.68
Mean (SD)	12.2 (3.8)	14.3 (5.5)	11.0 (2.8)	0.41
S100B - number	17	12	4	
N (%) > 0.10	13 (77)	11 (92)	3 (75)	0.54
Median (IQR)	0.17 (0.10-0.21)	0.23 (0.11-0.32)	0.12 (0.09-0.54)	0.43
DRS-R-98 ^b	19	20	18	0.25

IQR: inter-quartile-range; DRS-R-98: Delirium Rating Scale-R-98

^a Subtype is specified in 34 delirious patients; one patient did not meet the criteria of any of the subtypes

^b DRS-R-98 score is specified in 29 of the patients with known subtype

Discussion

We found higher S100B levels in patients with delirium than in patients without delirium with highest levels of S100B during delirium, in our study of elderly patients admitted for acute surgical repair of hip fracture. This study population represents a typical cross-section of elderly patients admitted for hip fractures. A similar frequency of delirium (52%) has been found in other large studies of hip fracture patients²². The expected risk factors for delirium in surgical patients, such as functional and cognitive impairment, were confirmed in our study³¹. Next to delirium, type of fracture, pre- or postoperative status and day of blood withdrawal were all associated with S100B levels. The effect of fracture and surgery and the time course were expected covariables based on the literature¹¹².

We found no difference in S100B and NSE levels in the different subtypes of delirium. Although the group of delirious patients with known subtype was small, the hyperactive type of delirium was the most common subtype of delirium in our study, similar to what has been described by others¹⁷⁰. Moreover, selection bias seems improbable since the delirious patients included in this analysis did not differ in risk factors for delirium and levels of NSE and S100B compared to the delirious patients without known subtype.

A limitation of our study is that the NSE and S100B values were measured from peripheral blood and may not necessarily correspond to values in the brain. Under normal conditions serum NSE and NSE in cerebrospinal fluid (CSF) show no significant correlation, whereas serum S100B content is lower than that in CSF^{26,62}. We are not aware of studies that determined NSE and S100B in both CSF and blood among patients with cognitive deficits such as delirium. A second limitation of our study is that only 120 of the 183 (66%) patients consented to multiple blood withdrawals. Although the excluded patients were 2.5 yrs. younger it is unlikely that this small difference would affect the protein levels.

Our results showing elevated S100B levels in delirious patients are in line with former studies^{72,142,151}. Studies looking at postoperative cognitive deficit (POCD) and S100B after surgery show however contradicting results, with no relation between S100B and cognitive performance after cardiac surgery at discharge¹⁵⁰, but higher levels of S100B in patients with POCD after non-cardiac surgery¹¹³. The definition of POCD remains controversial, but it seems likely that delirium and short-term POCD are on a continuum of postoperative cognitive brain disorders¹⁶¹. Seeing delirium as subset of POCD, our results of NSE correspond to former studies that found no association between NSE and POCD at discharge from hospital after non-cardiac surgery¹¹³. Maybe NSE is released only in cases of severe brain damage, such as stroke, after resuscitation or neurologically complicated surgery¹¹³.

Importantly, S100B is a marker of cerebral damage and/or reduced integrity of the blood brain barrier. According to Goncalves et al., this cerebral damage is leading to cognitive impairment after various neurologic diseases via neuroinflammatory mechanisms⁶². If we extrapolate these findings, we could hypothesize that the higher levels of S100B (and thus cerebral damage) in the delirious patients of this study could be

a possible explanation for the higher frequency of dementia after delirium found in other studies^{117,157}. On the one hand delirium and dementia (or cognitive impairment) could be caused by the same damaging factors of the surgical procedure⁴². It has been shown that preventing peri-operative cerebral damage by avoidance of systolic blood pressure declines and cerebral hypoxia can prevent patients from becoming delirious post-operatively, but it is not known whether these interventions have also any effect on the development of dementia¹¹⁷. On the other hand, the frequency of persisting cognitive impairment seems not higher after surgery compared to age matched controls without surgery, so it could be hypothesized that dementia is caused by the detrimental effects of delirium itself instead of the surgical procedure². Possibly, neuroinflammatory mechanisms play a role in this cerebral damage as well^{42,62,118,199}.

Future studies are needed to elucidate the place of S100B in the pathophysiological pathway leading to delirium (and possibly dementia) and investigate its role as biomarker for delirium.

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