Munster, B.C. van, Korevaar, J.C., Korse, C.M., Bonfrer, J.M., Zwinderman, A.H., Rooij, S.E. de
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Serum S100B in elderly patients with and without delirium

BARBARA C. VAN MUNSTER[1,2], JOHANNA C. KOREVAAR[1,] CATHARINA M. KORSE[3], JOHANNES M. BONFRER[3], AEILKO H. ZWINDERMAN[1] AND SOPHIA E. DE ROOIJ[2]

1Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Centre, University of Amsterdam, the Netherlands 2Department of Internal Medicine, Academic Medical Centre, University of Amsterdam, the Netherlands 3Department of Clinical Chemistry, The Netherlands Cancer Institute, Amsterdam, the Netherlands

Objective: Elevation of S100B has been shown after various neurologic diseases with cognitive dysfunction.

The aim of this study was to compare the serum level of S100B of patients with and without delirium and investigate the possible associations with different subtypes of delirium.

Methods: Acutely admitted medical patients aged 65 years or more 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'. S100B levels were determined in serum by electrochemiluminescence immunoassay.

Results: Samples of 412 patients were included, 91 during delirium, 35 after delirium and 286 of patients without delirium. Patients with delirium (31%) were significantly older, 81.5 versus 76.6 years ($p<0.001$) and experienced significantly more often preexistent cognitive and functional impairment ($p<0.001$). S100B level differed significantly ($p = 0.004$) between the three groups: median 0.07mg/L (inter-quartile ranges: 0.05–0.14 mg/L) during delirium, 0.12mg/L (0.05–0.29mg/L) after delirium and 0.06mg/L (0.03–0.10mg/L) in patients without delirium. Combining the impact of cognitive impairment, infection and age on S100B, highest S100B was observed in the oldest patients after delirium with preexistent cognitive impaired and infection. Delirium subtype and S100B level were not significantly correlated.

Conclusion: Higher S100B levels were found in patients with delirium than in patients without delirium, with highest levels of S100B in samples taken after delirium. Future studies are needed to elucidate the mechanism responsible for the increase of S100B and the possible association with long term cognitive impairment. Copyright # 2009 John Wiley & Sons, Ltd.

INTRODUCTION

Delirium is an acute neuropsychiatric syndrome with a mean duration of 3 days characterized by fluctuating changes in cognition, consciousness, and attention (American Psychiatric Association, 2000). It occurs in acutely admitted elderly patients in up to 40%, many with pre-existing dementia (Siddiqi et al., 2006). Three clinical subtypes of delirium (a hyperactive, a hypoactive, and a mixed subtype) are known (Meagher and Trzepacz, 2000; de Rooij et al., 2005). The suggested pathophysiological mechanisms of delirium are mostly hypothetical, but lately there is growing interest in the neuroinflammatory system (Eikelenboom and Hoogendijk, 1999; Maclullich et al., 2008; van Munster et al., 2008). 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 impairment (Rockwood et al., 1999).

Possibly, the high frequency of dementia after delirium reflects irreversible brain damage caused by the detrimental effects of delirium or the underlying disease precipitating delirium, such as infection. The calcium binding protein S100B (S100B) has been used as marker of brain damage in delirium in patients after abdominal surgery (Rasmussen et al., 2000), after cardiac surgery (Herrmann et al., 2000), and in sepsisassociated delirium (Pfister et al., 2008). Importantly, S100B is a marker of damage of cerebral cells, but other factors raise the concentration in serum as well (Kleindienst et al., 2007). Firstly, the passage of cerebral S100B to serum is modulated by the blood brain barrier (BBB) and, therefore, serum S100B levels do not only reflect the corresponding cerebral S100B release but also permeability of the BBB. Secondly, except for astrocytes, known S100B-expressing cells are adipocytes, chondrocytes, lymphocytes, bone marrow cells, and melanoma cells (Goncalves et al., 2008). The release of S100B by damage of these extracerebral cells could, however, be indirectly related to the brain via stimulation by catecholamines during severe illness (Kleine et al., 2003). Thirdly, S100B release by astrocytes can be augmented upon stimulation by serotonin receptors (5-HT1A), lysophosphatidic acid, glutamate and the proinflammatory cytokines, tumor necrosis factor (TNF)-a and interleukin (IL)-1, and during metabolic stress (Donato et al., 2008).

Former studies of S100B in delirium included severely ill and surgical patients. In theory, it is possible that different etiologies may lead to delirium via different pathophysiological pathways. In the same respect, we do not know whether the hyperactive, hypoactive, and mixed subtypes of delirium are all part of the same syndrome (Meagher and Trzepacz, 2000).

Therefore, the aim of this study was twofold: (1) to compare the levels of S100B in patients with and without delirium in elderly medical patients and (2) to study the levels of S100B in different subtypes of delirium.

METHODS

Patients

From June 2005 to June 2008, consecutive patients 65 years of age or older who were acutely admitted to the Department of Medicine of the Academic Medical Center were invited to participate. Informed consent was obtained from all patients or substitute decisionmakers in cases of cognitive impairment within 48 h after admission. Patients were excluded from the study if they were unable to speak or understand Dutch or English and if they left the ward within 48 h. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki, and the study design was reviewed by the hospital's medical ethical committee.

Procedures

The presence or absence of delirium was scored within 48 h after admission by the geriatric team using the confusion assessment method (CAM) (Inouye et al., 1990). Delirium was

scored in a 24 h period from 0.00 to 0.00 h separately by a physician and a nurse trained in geriatrics and the diagnosis was based on psychiatric examination of the patient, medical, and nursing records including the Delirium Observation Screening Scale (DOS) (Schuurmans et al., 2003), and information given by the patient's closest relative. When there was disagreement about the diagnosis between the trained nurse and geriatrician, the patient was discussed in the geriatric consultation team to gain consensus. Delirious patients were assessed during weekdays till the end of the delirious episode. (For subtyping, the delirium symptom interview was used, resulting in three different subtypes: hyperactive, hypoactive, and mixed (Liptzin and Levkoff, 1992).

The Delirium Rating Scale-Revised-98 (DRS-R-98) was used to monitor the severity of delirium (Trzepacz et al., 1988; de Rooij et al., 2006).

Pre-existing cognitive functioning was scored at the time of hospital admission by two validated instruments, the Informant Questionnaire on Cognitive Decline-short form (IQCODE-sf) (Jorm, 1994) and the Mini-Mental State Examination (MMSE) (Folstein et al., 1975). For the IQCODE, the informant was asked to recollect the situation 2 weeks before the illness started for which the patient had been admitted and to compare it with the situation 10 years before. Preexisting cognition was scored to be impaired when participants had a medical history of dementia of any cause or had an IQCODE above the cut-off score of 3.9 (de Jonghe, 1997). In case of missing values, the MMSE was used but only in patients without delirium with a cut-off score of less than 24 (Heeren et al., 1990). To measure physical functionality, we asked patients or their closest relative in cases of cognitive impairment to complete the 15-item Katz Index of activities of daily living (ADL) based on the situation 2 weeks prior to admission (Weinberger et al., 1992).

S100B was measured in a blood sample drawn during weekdays in the morning within 1 week after inclusion, between 9 and 11.00 a.m. Serum was obtained by centrifugation for 15 min at 1780 g at 4°C, and aliquots were stored at -80°C. S-100B levels were measured on the Modular Analytics E170 (Elecsys module) analyzer (Roche Diagnostics, Mannheim) using the electrochemiluminescence immunoassays (ECLIA) technique. Levels below the detection limit of 0.020 (mg/L) were set at half the value, i.e., 0.01.

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 (IQR), whereas normally distributed were expressed as mean scores with standard deviation.

Differences in S100B levels in different subtypes were analyzed using the Kruskal–Wallis test. Correlations between S100B and DRS-R-98 score were determined using Spearman's rank correlation coefficient. The samples were divided in three groups depending on the timing of sample collection, samples taken during delirium, samples taken after delirium and samples taken of patients without delirium. We performed a multivariable linear regression analysis with the natural logarithm of S100B as dependent value to identify if S100B levels were associated with delirium after adjustment of the possible confounding factors preexistent cognitive impairment, infection, and age. A two-tailed criterion of $p<0.05$ was considered statistically significant.

[TABLE 1]

[TABLE 2]

RESULTS

Of a total of 634 available patients, serum samples for S100B determination were available of 416 patients. Of 4 patients with delirium the CAM score was unknown on the day of venipuncture, so these patients were excluded in the analyses. Non-selected and selected patients were similar with regard to the male/female ratio and age. Of the 412 included patients, 126 (31%) experienced delirium. Patients with delirium were significantly older, 81.6 versus 76.6 years ($p<0.001$), experienced significantly more often pre-existent cognitive and functional impairment ($p<0.001$) and consequently lived in either old-people's homes or nursing homes significantly more frequently than non-delirious controls ($p<0.001$) (Table 1). The main difference in reason for admission in patients with delirium compared to patients without delirium was the lower frequency of dehydration or electrolyte disturbances, and higher frequency of infectious diseases. Cerebral infections were absent in this population, but one patient without delirium experienced a cerebrovascular accident before the sample was taken (S100B level was 0.042 mg/L). The median time of admission was 11 days for patients with delirium and 7 days for patients without delirium ($p<0.001$).

S100B level was determined in 91 patients during delirium (median: 0.07mg/L, IQR: 0.05–0.14mg/L), in 35 patients after delirium (median: 0.12mg/L, IQR: 0.05–0.29mg/L) and in 286 patients without delirium (median: 0.06mg/L, IQR: 0.03–0.10mg/L). The levels of S100B differed significantly in the three groups (p¼0.004). Table 2 presents the association between S100B with the patients during delirium, after delirium and patients without delirium in groups separated for either absence or presence of cognitive impairment and separately for the presence or absence of an infectious disease. No differences in S100B levels for patients during, after or without delirium were found in the subgroup with cognitive impairment. In the cognitive intact subgroup, levels of S100B were significantly higher in the samples taken during and after delirium compared to the patients without delirium. No difference was found in the patients with an infection, whereas for the subgroup without infection a significant higher level of S100B was observed after delirium. Age in years and the level of S100B were positively correlated (r¼0.16, p¼0.001). Combining the impact of cognitive impairment, infection and age, the highest S100B levels was observed in patients after delirium with pre-existent cognitive impairment (Table 3). Delirium was independently associated with a higher level of S100B in patients without pre-existent cognitive impairment (p¼0.05), but not in patients with cognitive impairment (p¼0.29). Infection led to a significantly higher S100B level, adjusted for cognitive impairment, age, and delirium ($p<0.001$).

[TABLE 3]

Subtype was specified in 38 patients of the 91 patients with a sample available during delirium. One patient did not meet the criteria of any of the subtypes, 22 patients experienced the hyperactive, 7 patients the hypoactive, and 7 patients the mixed subtype of delirium. No difference was observed in S100B levels in patients with different subtypes (p¼0.57), nor was there a difference between delirious patients with known versus unknown subtype (p¼0.27). In the 39 patients the severity of delirium (DRS-R-98) was specified, Spearman's test revealed no significant correlation between severity of delirium and S100B (r¼_0.09, p¼0.58).

DISCUSSION

Higher S100B levels were found in patients with delirium than in patients without delirium, with highest levels of S100B in samples taken after delirium.

The expected risk factors for delirium in surgical patients, such as age, functional, and cognitive impairment were confirmed in our study, so the study population represents a typical sample of acutely admitted elderly patients (Elie et al., 1998).

A limitation of our study is that S100B values were measured in peripheral blood and may not necessarily correspond to values in the brain. Under normal conditions serum S100B content is lower than that in cerebrospinal fluid (CSF) (Goncalves et al., 2008), but we are not aware of studies that determined S100B in both CSF and blood among patients with cognitive deficits such as delirium. A second limitation of our study is that only 416 of the 634 (66%) patients consented to blood withdrawal. We speculate that most of the excluded patients for this study did not want an extra blood withdrawal because patients were overloaded with medical research in the first days of admission and when they refused we were not persistent but just offered to include them without blood withdrawal. Selection bias is unlikely as the excluded patients were comparable with respect to age and gender. A third limitation is that only one bloodsample is available during the 24 h period, and the half-life of S100B in the blood is less than 2 h. The conclusion would have been more strong if more samples were taken at the same period, but maybe even less patients would have given their permission.

Our results showing elevated S100B levels in delirious patients are in line with former studies in patients with delirium, although the exact mechanism responsible for the increase may depend on the population studied (Herrmann et al., 2000; Rasmussen et al., 2000; Pfister et al., 2008). All of the mechanisms causing an increase of S100B in blood, i.e., cerebral or extra-cerebral cellular damage, increased permeability of the BBB, and upregulation of S100B production by astrocytes takes place within 24 h (Townend et al., 2006; Donato et al., 2008). The fact that the level of S100B is highest after delirium, may indicate that not cerebral damage, but active stimulation of astrocytes or increased permeability of the BBB are the principal causal mechanisms for the increase. The reason these astrocytes would remain activated after delirium is unclear, as we know that levels of proinflammatory cytokines decrease after delirium (van Munster et al., 2008).

[FIGURE 1]

A beneficial effect of released S100B on neuronal maintenance, neurogenesis, and cognitive performance has been demonstrated promoting repair mechanisms particularly in the hippocampus (Donato et al., 2008; Goncalves et al., 2008).

Next to delirium, infection, cognitive impairment, and age were independently associated with S100B levels, which is supported by former studies (Mrak and Griffinbc, 2001; Unden et al., 2004). Patients with extracerebral infections showed raised S100B levels, which could indicate both an extracerebral source of S100B as well as increased release of S100B from astrocytes as response of the brain to proinflammatory cytokines. Positive correlations between serum S100B levels with lymphocyte and granulocyte counts, both induced by cytokines, have been described in noninfectious acute care patients as well (Kleine et al., 2003). The activated astrocytes were also shown to be an important feature in patients with cognitive impairment due to Alzheimer's disease (Mrak and Griffinbc, 2001). Activation of astrocytes with overexpression of S100B in amyloid-b plaques is promoted by high levels of IL-1, originating from activated microglia that are also components of the plaques in Alzheimer's disease. With normal aging there is a progressive increase in astrocytic expression of S100B within the cerebral cortex (Mrak and Griffinbc, 2001).

The concomitant age-associated increases in microglial activation and IL-1 expression, may explain in part the increased risk for Alzheimer's disease at rising age.

We did not find a difference in S100B levels between the different subtypes of delirium. This might possibly be due the small numbers of the different subgroups, therefore we could not adjust for confounders.

Whether there is a difference between subgroups need to be established in a larger cohort.

CONCLUSION

Future studies are needed to elucidate the mechanism responsible for the higher level of S100B in patients during and after delirium. It would also be interesting to find out if higher levels of S100B in the delirious patients are associated with a higher frequency of dementia after delirium. Recent magnetic resonance proton spectroscopy that can measure cerebral S100B more accurately, non-invasively, and repeatedly may assist in these studiesn (Donato et al., 2008).

ACKNOWLEDGEMENTS

The authors thank the other members of the research team, D Slats, JL Parlevliet, JL Popma, CMM van Rijn, ACL Scheffer, MJA van der Zwaan, and laboratory technician E Delic.

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TABLES AND FIGURE

Table 1

Table 1 Characteristics of patients with and without delirium

	Delirium ($N=126$)	No delirium ($N=286$)	p-value
Mean age-years (SD)	81.6 (7.9)	76.6 (7.6)	<0.001
Male (%)	54 (43)	139 (49)	0.45
Median education-years (IQR)	9 (7–11)	9 (7–12)	0.41
Living at home (%)	93 (74)	253 (89)	<0.001
Median number of ADL Disabilities (range)[a]	7 (4–12)	3 (1–7)	<0.001
Cognitive impairment[a] (%)	68 (57)	41 (14)	<0.001
Missing (%)	7 (2%)	0	
Median number of medication at home (IQR)	5 (2–7)	5 (3–8)	0.03
Main admission reason, N(%)			
Infectious diseases	68 (54)	105 (37)	<0.001
Malignancies	5 (4)	23 (8)	
Diseases of digestive system	17 (14)	28 (10)	
Water and electrolyte Disturbances	11 (9)	67 (23)	
Cardiovascular diseases	4 (3)	20 (7)	
Other	21 (17)	43 (15)	
Alcohol ≥3 units a day (%)	2 (2)	18 (6)	0.06
Median admission length-days (IQR)	11 (6–19)	7 (4–13)	<0.001
S100B (μg/L) (IQR)	0.08[b] (0.05–0.14)	0.06 (0.03–0.10)	0.001

ADL: activities of daily living; IQR: inter-quartile range.
[a]Impairment as determined 2 weeks prior to admission.
[b]Samples taken during delirium and after delirium taken together.

Table 2

Table 2 Median (IQR) values of S100B (μg/L) in patients with, after, and without delirium stratified for cognitive impairment and for infectious disease

	During delirium	After delirium	No delirium	p-value
Cognitive impairment	$N=50$ 0.07 (0.05–0.13)	$N=18$ 0.08 (0.07–0.16)	$N=41$ 0.10 (0.04–0.15)	0.35
Cognitively intact	$N=37$ 0.07 (0.05–0.19)	$N=15$ 0.10 (0.06–0.12)	$N=245$ 0.06 (0.03–0.10)	0.01[a]
Infectious disease	$N=45$ 0.08 (0.05–0.19)	$N=23$ 0.08 (0.06–0.12)	$N=105$ 0.08 (0.04–0.12)	0.41
No infectious disease	$N=46$ 0.07 (0.04–0.10)	$N=12$ 0.09 (0.07–0.14)	$N=181$ 0.05 (0.03–0.10)	0.02[b]

[a]*Post hoc* analysis showed that the significance in the cognitive intact group was caused by the difference between the patients with delirium during and after delirium compared to the patients without delirium.
[b]In the group without infection the significance was caused by the difference between the patients with delirium after the delirious episode and the patients without delirium.

Table 3

Table 3 Factors associated with the natural logarithm of S100B in a linear regression analysis. S100B levels of two example patients calculated with this model are shown

Variable	β	95% Confidence interval	p-value	Estimated S100B level in 80-year old patient *without* infection (μg/L)	Estimated S100B level in 80-year old patient *with* infection (μg/L)
No delirium, no cognitive impairment	−3.71	−4.58–−2.85	<0.001	0.05 (0.01–0.03)	0.07 (0.01–0.45)
During delirium, no cognitive impairment	0.31	0.00–0.62	0.05	0.07 (0.01–0.53)	0.10 (0.01–0.84)
After delirium, no cognitive impairment	0.26	−0.20–0.71	0.27	0.07 (0.01–0.58)	0.09 (0.01–0.92)
No delirium, cognitive impairment	0.21	−0.08–0.50	0.15	0.07 (0.01–0.47)	0.09 (0.01–0.75)
During delirium, cognitive impairment	0.15	−0.13–0.42	0.29	0.06 (0.01–0.44)	0.08 (0.01–0.69)
After delirium, cognitive impairment	0.40	−0.02–0.81	0.06	0.08 (0.01–0.64)	0.11 (0.01–1.02)
Age	0.01	−0.00–0.02	0.07		
Infection	0.28	0.12–0.46	0.001		

Figure 1

Key Points

- S100B levels are higher in patients with delirium
- No difference in S100B level between the different subtypes of delirium