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ORIGINAL PAPER

S100B and homocysteine in the acute alcohol withdrawal syndrome

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Abstract Elevations of serum homocysteine levels are a consistent finding in alcohol addiction. Serum S100B levels are altered in different neuropsychiatric disorders but not well investigated in alcohol withdrawal syndromes. Because of the close connection of S100B to ACTH and glutamate secretion that both are involved in neurodegeneration and symptoms of alcoholism the relationship of S100B and homocysteine to acute withdrawal variables has been examined. A total of 22 male and 9 female inpatients (mean age 46.9 ± 9.7 years) with an ICD-10 diagnosis of alcohol addiction without relevant affective comorbidity were examined on admission and after 24, 48, and 120 h during withdrawal. S100B and homocysteine levels in serum were collected, and severity of withdrawal symptoms (AWS-scale), applied withdrawal medication, initial serum ethanol levels and duration of addiction were recorded. Serum S100B and homocysteine levels declined significantly ($P < .05$) over time. Both levels declined with withdrawal syndrome severity. Females showed a trend to a more intense decline in serum S100B levels compared to males at day 5 ($P = .06$). Homocysteine levels displayed a negative relationship to applied amount of clomethiazole ($P < .05$) and correlated with age of onset of addiction. No withdrawal seizures were recorded during the trial. As it is known for homocysteine, S100B revealed to decline rapidly over withdrawal treatment in alcoholism. This effect is more pronounced in female patients. S100B could be of relevance in the neurobiology of alcohol withdrawal syndromes. It may be indirectly related to the level of stress level or glutamatergic activity during alcohol withdrawal.

Keywords Alcohol addiction · Homocysteine · S100B · Withdrawal

Abbreviations

ACTH	Adrenocorticotropin
AWS-scale	Acute withdrawal-scale
ELISA	Enzyme-linked-immuno-sorbent-assay
GABA	Gamma-amino-butyric acid
HPA	Hypothalamo-pituitary-adrenomedullary (axis)
HRP	Horseradish-peroxydase
ICD-10	International classification of diseases, 10th revision
kDA	kilo-Dalton
MALT	Munich alcoholism test
MRI	Magnetic resonance imaging
NMDA	*N*-methyl-D-aspartate
RAGE	Receptor for advanced glycation end products
SAH	*S*-adenosyl-L-homocysteine
WHO	World Health Organization

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Introduction

Alcohol addiction and alcohol withdrawal syndromes have been related to numerous biologic markers indicating syndrome severity or detrimental effects. The GABAergic system undergoes distinct adaptive processes over alcohol addiction going in line with receptor down-regulation and altered sensitivity [1]. During withdrawal, reduced GABA agonistic effects coincide with an increase in glutamatergic neurotransmission [2]. A compensatory up-regulation of glutamatergic NMDA receptors over chronic alcohol intake has been described [3].

Elevations of homocysteine and its main metabolite homocysteic acid in serum are a consistent finding in alcohol addiction [4–6] and withdrawal [7–9]. Due to excitatory NMDA and glutamatergic effects and reduction of inhibitory GABAergic drive by lack of ethanol, homocysteine has been related to excitatory somatic and psychic withdrawal symptoms, risk of withdrawal-related seizures, and excitotoxic neurodegenerative phenomena [10–12].

S100 proteins are small, acidic proteins of 10–12 kDa. S100B is a calcium-binding astroglial peptide which has trophic or deleterious effects on neural cells in a dose-dependent manner [13]. Mild S100B levels have been associated with stimulatory effects on neuronal growth, sprouting, and plasticity (e.g. concerning the central nervous serotonergic system and a diminution of glutamate-driven cytotoxicity) [14, 15]. High levels of S100B, on the other hand activate early immediate genes (c-fos) [13] and long-term high levels of S100B by increasing intracellular calcium levels have been related to neurotoxicity and degeneration at different sites [16]. Besides astrocytes and other brain tissues [17], S100B is secreted by the folliculostellate cells in the anterior pituitary after stimulation of the stress axis and ACTH secretion [18]. Simultaneously, glutamate synthetase is secreted from folliculostellate cells. S100B has the highest density of intracellular binding sites (receptor for advanced glycation end products: RAGE) in neurons and glial cells of the hippocampus. Certain regions of this structure have been reported to be highly vulnerable to neurotoxic effects by S100B or glucocorticoids [13]. Such effects are thought to be glutamate driven.

Elevated levels of serum or cerebrospinal fluid S100B have been reported for psychiatric disorders such as schizophrenia [19–21] or affective disorders [22–26] which often co-occur with alcohol addiction [27, 28]. The role of S100B in psychiatric disorders is still not very clear. Taken together, it can be assumed that psychopathological alterations in different syndromes represent a fairly unspecific condition deriving from a general stress-level or increased glutamatergic drive leading to conditions of restricted declarative memory or emotional processing abilities. There seems to be a crucial role of the central nervous serotonergic system in this respect. On the one hand, Serotonin 1a receptor stimulation increases S100B levels, on the other hand S100B has been considered to improve serotonergic neuron regeneration [29] most probably in mild concentrations.

Data on S100B in addictive disorders, in particular in alcohol dependence is still scarce. Animal data demonstrated that S100B reduces ethanol-induced apoptosis [30]. One clinical study measure S100B in patients undergoing inpatient withdrawal treatment assessed a significant elevation of S100B at admission compared to discharge after approximately 4–5 weeks. However, this effect was only found in patients with severe addiction and previously high average alcohol consumption [31].

An association between homocysteine and S100B levels over the alcohol withdrawal syndrome can be hypothesized. Homocysteine levels correspond with NMDA and glutamate activity in the withdrawal period. Neurotoxic effects in certain brain areas correspond with dramatically raised S100B levels. These are facilitated by glutamate activity. However, mild S100B increases may diminish glutamate-driven neurotoxicity. This study was performed in order to further elucidate the role of S100B in alcohol withdrawal syndromes and to correlate respective levels with withdrawal syndrome severity and the well-known alterations in serum homocysteine over the withdrawal period. Furthermore, it was of interest if values showed a connection to addiction severity, duration of addictive drinking or gender.

Methods

The study was approved by the local ethics committee

Thirty-one inpatients undergoing a qualified alcohol withdrawal treatment at the department of psychiatry and psychotherapy of the University of Goettingen were included into this study during October 2007 and August 2008. Patients were males or females 18–70 years of age hospitalized for voluntary qualified detoxification treatment and suffering from alcohol addiction according to ICD-10 criteria [32]. Patients with any psychotic symptoms, clinically relevant major depression, polyvalent substance use (except for nicotine), incapacitating organic brain disorder, risk factors for hyperhomocysteinaemia, or regular psychotropic drug treatment in the 4 weeks before admission were excluded from participation. Subjects with relevant language problems or patients unable to give free informed consent were not included.

Patients were recruited within the first 24 h after admission to the clinic. After checking for in and exclusion criteria and having given informed consent a serum sample for the assessment of S100B, homocysteine, and alcohol

concentration was drawn. Further serum samples were drawn after 24, 48, and 120 h. On the latter 3 occasions, the AWS scale [33] in order to assess withdrawal syndrome severity was applied. Blood pressure and heart rate was recorded on each of the 4 occasions, and the amount of applied withdrawal-related medication during the past 24 h was recorded. Blood ethanol concentration was controlled 24 h after the first sampling. In the end of the study (120 h after the first blood sample), participants completed a severity scale for alcohol addiction (MALT [34]). Sociodemographic data and information about duration of alcohol addiction/age of onset of alcohol addiction was collected.

S100B was measured by ELISA according to Leite [35]. Fifty-microliter serum samples were analyzed using Clone SH-B1 (Sigma Chemical Co.) as a capture antibody and a polyclonal detecting antibody (Dako). Homocysteine was measured by ELISA according the method described by Frantzen [36]. Twenty-five-microliter serum samples were analyzed using anti-SHA-antibody (Abbot Labs.) and HRP-conjugated antibody (Dako).

Treatment during study

All participants received a qualified detoxification treatment with uniform supplementation of vitamins (B1, B6, B12) and potassium (taken orally). Qualified detoxification treatment comprised psychosocial treatment (including motivational training), physiotherapy and prescription of withdrawal related medication following cardiovascular monitoring.

Statistical analysis

Statistical analyses were performed by using SPSS (version 17.0). Pearson correlations were computed for age and gender related to S100B and homocysteine at the respective time-points. Pearson correlations for S100B/homocysteine and syndrome severity according to the AWS score was calculated as well as for age of addiction onset and duration of alcohol addiction and for applied clomethiazole medication.

Repeated measures analysis (ANOVA, SPSS method Bonferroni) was performed for S100B, homocysteine, and AWS scores over the study period. P values below .05 were considered significant.

Results

Study population

Of the included 31 subjects (22 men, 9 women), 30 subjects completed the trial. Subjects were between 28 and 68 years old (mean 46.9 ± 9.7). No significant age differences between men (45.8 ± 7.3) and women (49.4 ± 12.0) were detected. Mean duration of alcohol addiction was 13.4 ± 8.7 years (range 1.5–33) mean age of onset of addiction was at the age of 33.5 ± 10.5 years (range 19–60 years). Mean daily consumption of alcohol prior to admission was 262 ± 124 g/day (range 95–631 g/day). Mean blood alcohol concentration at the first sampling time-point was 1.41 ± 1.09 per mille (range 0–3.5 per mille). MALT-scores had a mean of 15.5 ± 4.7.

Serum S100B and homocysteine

A comparable course was detected for S100B levels in serum with a linear and significant decline over the investigational period. Mean baseline values, however, were still in the normal range (74 ± 8 ng/l) and declined to 51 ± 6 ng/l over the following 120 h ($F = 5.88$; $P < .05$; see Table 1). There was no significant correlation between age and homocysteine levels, neither was there any significant correlation between age and S100B levels.

On average, subjects displayed mildly elevated homocysteine serum-levels at baseline (19.3 ± 2.2 μmol/l) that declined significantly over the following 120 h ($F = 10.71$; $P < .05$; see Table 1). There was no significant correlation between age and homocysteine levels.

As an effect of gender, females displayed more rapidly declining S100B values; however, this was just a statistical trend ($r = 0.35$; $P = .064$; at 120 h; women vs. men).

A correlation between age of onset of alcohol addiction and homocysteine levels could be detected. This correlation was most evident from values after 48 h ($r = 0.43$; $P < .05$) and was slightly less after 24 ($P = .076$) and 120 h ($P = .052$).

Another remarkable finding were the lower homocysteine levels after 24 h in patients the more clomethiazole they received ($r = -0.64$; $P < .05$). This effect could not be demonstrated for the subjects receiving diazepam.

Table 1 Mean S100B and homocysteine serum levels over the investigational period incl. 95% confidence interval

	0 h	24 h	48 h	120 h
Homocysteine μmol/l				
Mean ± SD	19.3 ± 2.2	17 ± 1.4	14.8 ± 1.1	13.6 ± 1
95% CI	14.9–23.8	14.3–19.8	12.6–17.1	11.5–15.6
LOS vs. 0 h				$P < .05$
S100B ng/l				
Mean ± SD	74 ± 8	61 ± 9	54 ± 6	51 ± 6
95%CI	58–90	43–78	41–67	38–63
LOS vs. 0 h				$P < .05$

SD standard deviation, *CI* confidence interval, *LOS* level of significance

Correlations between S100B, homocysteine, and AWS-scores

Despite the linear decline of values for all three categories, no significant direct correlations could be detected between these variables.

Withdrawal syndrome severity

No withdrawal related seizures nor any withdrawal delirium was recorded in the sample over the study period.

AWS-scale

Scores on the AWS scale declined significantly ($F = 4.81$; $P < .05$) over time with highest scores after 24 h (5.97 ± 2.97). Scores after 48 h were 4.63 ± 1.62 and 3.43 ± 0.96 after 120 h. There were no significant differences in AWS-scores between men and women at any assessment point.

Blood pressure and heart rate

Blood pressure showed a slight but non-significant decline between 24 and 120 h (145.5 ± 5.2 mmHg for systolic and 88.4 ± 8.5 for diastolic values at 24 h vs. 132 ± 16.2 for systolic and 84.3 ± 9.4 at 120 h).

Heart rate declined non-significantly over time (94 ± 12.8 at 24 h vs. 85 ± 13 at 120 h).

Applied withdrawal medication

Clomethiazole ($n = 13$), diazepam ($n = 12$), phenobarbital ($n = 3$), and carbamazepine $n = 11$) were used in the population. Phenobarbital was used for patients with mild withdrawal syndromes who had adverse medication effects from diazepam or clomethiazole during previous withdrawal treatments.

Number of individuals treated with clomethiazole decreased from 13 at time 0 h to 2 at 120 h. Applied amount of clomethiazole decreased from a mean of 7.4 ± 4.2 capsules (192 mg each) at baseline to 1.5 ± 0.5 capsules at 120 h. Mean intake of clomethiazole capsules did not differ between men (3.9 ± 3.0 capsules/day) and women (3.5 ± 2.4 capsules/day). Three subjects did not need any withdrawal-related medication.

Discussion

In support of our hypothesis, a significant decline of serum S100B levels over time could be detected, although average levels were in the normal range (compared to values from the literature). However, 95% confidence interval values support the likelihood of higher S100B levels at the beginning of withdrawal treatment. Although no direct correlation with withdrawal severity according to the AWS could be demonstrated, all 3 variables decline in a linear fashion. S100B appears to be of certain relevance in the biology of alcohol withdrawal syndromes, maybe giving indirect reference to stress level or glutamatergic activity. Probably these alterations are not particularly specific for alcohol withdrawal syndromes. In major depression correlations of S100B and symptom, severity could be demonstrated and also in schizophrenia. Yet, these entities represent syndromes connected to cognitive or emotional impairment with distinct hippocampal impairment (e.g. [37]). It could be speculated that S100B as well as homocysteine are related to effects on e.g. hippocampal areas that cause unspecific symptoms that occur in different psychiatric disorders. Yet, actions of S100B are concentration dependent. Those higher levels at baseline compared to endpoint in this population are likely to be in the neuroprotective and trophic range of S100B, and probably represent a protective, counter-regulatory mechanism against the harmful effects of hyperhomo-cysteinemia and associated glutamate-mediated neurotoxicity.

Just slightly missing the level of significance ($P = .064$; $r = 0.35$) women tended to have lower level of serum S100B at endpoint. This is a finding that in a way contradicts the results by Yang [26] who found higher cerebrospinal fluid S100B in depressed women compared to men. However, women had no significantly different withdrawal severity scores according to the AWS scale. Neither were women significantly different with regard to age or in the amount of applied withdrawal medication such as clomethiazole. Therefore, despite the small n, this may reflect a gender effect. It could be hypothesized that neuroprotective effects of S100B are expressed to a lower degree in female alcohol addicted subjects. Age as well as blood ethanol levels at admission were comparable in men and women. One contributing factor, a lower average consumption of alcohol prior to withdrawal in women compared to men, cannot be excluded and would be in line with the findings of Liappas et al. [31].

As expected, homocysteine serum values declined significantly from a moderately elevated level over the 120-h investigational period in this population undergoing qualified alcohol detoxification treatment.

One interesting issue deriving from our data is the significant inverse relationship between serum homocysteine levels and clomethiazole intake. This effect was not immediately observable but after 1 day of intake which could represent an adaptive GABA mediated effect. In contrast to this, S100B levels were not moderated by clomethiazole. Possibly, clomethiazole treatment may need to

be considered as relevant in the interpretation of homocysteine levels in alcohol addiction.

Correlations between homocysteine and age have been consistently reported, and as a trend can be adapted from our data. Also amount of alcohol intake prior to admission has been found to be associated with higher serum homocysteine. This may correspond with higher stress levels and a higher risk for cardiovascular diseases. However, as suggested by some authors (e.g. [38]), we could not find gender specific effects. Animal studies have indicated circadian variations of serum homocysteine and age-related effects [39]. However, we could not detect any relationship to age of subjects. Circadian shifts in homocysteine levels were controlled by comparable time frames for all subjects. The fact that our data revealed a positive correlation between homocysteine serum levels and age of onset of alcohol addiction appears surprising. It implies an association between a shorter duration of the disorder with higher serum levels of excitatory homocysteine. Alimentary reasons for this effect due to reduced intake of methyl-group-donators [40] can be hypothesized.

Nevertheless, the results presented here should not be over-interpreted due to several limitations of the study. The rather small study population was probably too heterogeneous. Less than a third ($n = 9$) of the subjects were women, and the recruited subjects did not necessarily have to have positive blood alcohol concentrations at inclusion. Five patients in this population in fact were admitted to the clinic without blood alcohol, whereas several previous studies (e.g. [7, 8, 41] did not include patients with negative blood alcohol due to a certain determination of homocysteine levels by the degree of blood ethanol levels [7].

According to our hypothesis of a diagnosis unspecific phenomenon of elevated S100B in parallel with elevated stress markers, we must admit that no statement at all on HPA function can be made from our study. Compared to another open-label study on S100B in alcohol withdrawal by Liappas [31] who measured S100B levels in alcohol-addicted subjects undergoing withdrawal treatment at admission and at discharge (after 4–5 weeks), this appears to be a clear limitation of that study. The investigational period in this trial was very much shorter. It was comparable with other investigations on homocysteine in alcohol withdrawal (e.g. [7, 8] stressing the relevance of the acute detoxification period over the first days of treatment.

Finally, although serum S100B measurements are a valid measure, we cannot entirely exclude alterations of blood–brain–barrier functioning in alcohol-addicted subjects [42] as the cause of these slightly higher initial S100B serum levels. One recent publication [43] identified the body-mass-index (BMI) as a contributing factor to serum S100B levels, which we did not take into account.

Conclusions

Serum S100B levels show a decline over a 5-day period similar to homocysteine in alcohol-addicted subjects undergoing acute inpatient alcohol withdrawal. Due to the well-known concentration-dependent trophic or neurotoxic effects of S100B, the demonstrated data may represent an adaptive, counter-regulatory function of S100B protecting sensitive neuronal brain structures against deleterious effects mediated by homocysteine or glutamate. Further investigations on larger populations taking HPA-function into account appear useful. S100B serum levels and their relationship to homocysteine in non-abstinent alcoholics could be of interest due to the often postulated NMDA balance of excitatory homocysteine and inhibitory, GABAergic ethanol effects.

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