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Brief report

S-100B is increased in melancholic but not in non-melancholic major depression

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Abstract

Background: Recent evidence suggests that neurodegeneration may be involved in the pathophysiology of major depression. The astroglial peptide S-100B was shown to be increased in many diseases causing neuronal cell damage or degeneration. *Method:* S-100B plasma levels were determined in 28 patients with major depression and 28 matched healthy controls using an immunofluorometric sandwich assay. *Results:* Patients suffering from melancholic depression showed significantly increased S-100B levels compared to healthy controls while non-melancholic patients demonstrated normal levels. *Limitations:* Medication of patients varied. The differentiation between melancholic and non-melancholic patients was performed clinically without using a standardized instrument. *Conclusions:* Neurodegeneration or axonal remodeling may be involved in the pathogenesis of melancholic depression.

Keywords: Major Depression; Melancholia; S-100B; Neurodegeneration

1. Introduction

S-100B is a calcium binding peptide produced by astroglial cells of the central nervous system with paracrine and autocrine effects on neurons and glia (Griffin et al., 1998). After release it acts as a trophic factor for serotonin neurons, and plays a role in axonal growth and synaptogenesis during development and synaptic remodeling (Whitaker-Azmitia et al., 1997). Increased CSF and plasma levels were detected after traumatic brain injury, toxic or ischemic brain damage, and in multiple sclerosis (Lamers et al., 1995; Missler et al., 1997; Wiesmann et al., 1997; Raabe et al., 1998). S-100B is elevated in several kinds of dementia, especially Alzheimer's disease (Griffin et al., 1998). Our group showed increased S-100B plasma levels in patients suffering from schizophrenia (Wiesmann et al., 1999).

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Recent studies reported volume loss in different brain regions in major depression (for review see Dougherty and Rauch, 1997; Parashos et al., 1998). Immunological processes (Maes, 1995) or viral infections (Dietrich et al., 1998) are discussed as possible pathogenetic mechanisms in the development of major depression implying damage to neurons as the pathological basis. To evaluate the possibility that structural neuronal damage may be involved in the development of major depression we investigated S-100B plasma levels in patients suffering from acute major depressive disorder.

2. Materials and methods

After written informed consent was acquired, plasma samples were taken by venipuncture from 28 inpatients (10 males, 18 females, aged 29–62, mean age 47.21±9.72 years) suffering from a major depressive episode (DSM-IV 296.2, 296.3) and 28 age- and sex-matched healthy controls (aged 29–62, mean age 47.21±9.72 years). Patients and controls were diagnosed independently by two psychiatrists according to DSM-IV criteria (M.R. and M.P.) and by application of the Composite International Diagnostic Interview (CIDI). 15 patients suffered from a recurrent, and 13 from a single, depressive episode. The severity of depressive symptoms was rated using the Hamilton Depression Rating Scale (HDRS). Sixteen patients were diagnosed as suffering from melancholic (MDM), and 12 from non-melancholic, depression (MDNM) according to DSM-IV criteria. The controls had no lifetime history of any psychiatric disorder. Systemic diseases (neoplasms, autoimmune diseases, infectious diseases, neurological, and cardiovascular diseases), brain injury, co-morbid psychiatric diagnosis (e.g. dementia) and substance abuse were excluded by taking a detailed history, reviewing charts, physical examination, and by measuring body temperature, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) in patients and healthy controls. The biochemical parameters (CRP, ESR) were used as indicators for possible infections. Increased CRP or ESR levels initiated a detailed search for an infection site. In case no clinically apparent infection was identified patients with increased CRP or ESR remained in the sample with the signs of inflammation being considered to be associated with the depression. Four patients did not receive any psychotropic medication (for at least 6 months prior to admission) while 18 took a tricyclic antidepressant and 6 a selective serotonin reuptake inhibitor (SSRI).

Heparinized plasma samples were centrifuged within 4 h, aliquoted, and frozen at $-70^{\circ}C$ until analysis.

S-100B concentrations were determined by an immunofluorometric sandwich assay using a monoclonal anti-S-100B chain antibody on the solid-phase and a polyclonal rabbit anti-S-100 antibody, as described previously (Missler et al., 1997). The assay's threshold for detecting S-100 is 0.015 μg/l. The assay is highly specific for S-100B which predominates in the brain (Donato, 1991). The intraassay (within-run) imprecision (CVs) is 3.2% at 0.51 μg/l, 2.1% at 5.97 μg/l, and 2.3% at 11.4 μg/l. The total imprecision (between-day, CVs) is 11.5% at 0.45 μg/l, 7.9% at 4.79 μg/l, and 7.8% at 15.45 μg/l.

Due to the non-Gaussian distribution of our data, non-parametric tests were employed for statistical evaluation. The Wilcoxon Matched-Pairs Signed-Ranks Test, the Mann–Whitney *U* test, the Spearman Correlation Coefficient and the multiple regression analysis (enter procedure) were used as provided by the SPSS 9.0 program.

3. Results

The mean score of the HDRS indicating the severity of depressive symptoms was 26.2 (S.D. 6.5). Melancholic patients showed a slightly higher HDRS (27.7±7.0) than non-melancholic patients (24.2±5.3) without reaching statistical significance ($Z = -1.79$, $P = 0.073$). The mean S-100B plasma levels in depressed patients (0.091±0.063 μg/l) were significantly higher than those of healthy controls (0.047±0.023 μg/l, $Z = -3.32$, $P = 0.001$). After subgroup categorization, patients with MDNM showed normal S-100B levels (0.056±0.031), and melancholic patients (MDM) significantly increased levels (0.117±0.069 μg/l, $Z = -3.46$, $P = 0.001$, Fig. 1). No significant corre-

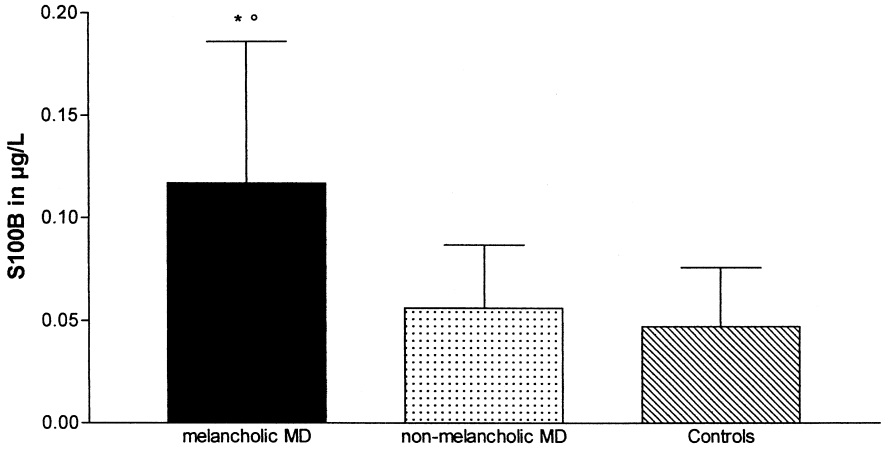

Fig. 1. S100B plasma levels in major depression. * Significantly different from matched healthy controls ($P = 0.001$). ° Significantly different from patients with non-melancholic major depression ($P = 0.001$).

Table 1
Multiple regression analyses including depression subtype and medication status (entered as two dummy variables)

Dependent variable	R^2	Adjusted R^2	F	df	P	Predictor with beta coefficient
S-100B	0.265	0.206	4.51	2, 25	0.021	Medication status (medicated vs unmedicated) (−0.150) Depression subtype (melancholic vs non-melancholic) (0.534)
S-100B	0.271	0.213	4.65	2, 25	0.019	Medication type (tricyclic vs. SSRI vs. unmedicated) (−0.175) Depression subtype (melancholic vs. non-melancholic) (0.555)

lations between S-100B level and age ($\rho = -0.52$, $P = 0.79$), sex ($\rho = -0.13$, $P = 0.53$), severity of symptoms ($\rho = 0.21$, $P = 0.28$) or recurrence of depression ($\rho = -0.20$, $P = 0.32$) were found.

To evaluate effects of the use of antidepressants on plasma S-100B multiple regression analyses were conducted. As can be seen in Table 1 the plasma level of S-100B was strongly predicted by the subtype of depression (melancholic vs. non-melancholic, $P = 0.005$). No significant influence of the medication status ($P = 0.41$) or the type of medication (tricyclic antidepressant vs. SSRI, $P = 0.35$) on the S-100B levels could be detected.

4. Discussion

Increased S-100B plasma levels were demonstrated in diseases regularly associated with structural brain damage or neurodegeneration; this parameter therefore represents a sensitive, although non-specific, indicator. Astrocyte damage causes leakage of S-100B into the extracellular compartment and cerebrospinal fluid, continuing to the bloodstream. Plasma levels have been proven to reflect S-100B CSF levels (Missler and Wiesmann, 1995). Several studies reported signs of decreased volumes of different brain regions in major depression

(Dougherty and Rauch, 1997; Parashos et al., 1998) that might reflect a degenerative brain process. The increased S-100B plasma levels found in melancholic depression suggest that structural brain damage is involved in the etiology or pathogenesis of this disease. On the other hand, S-100B is released by intact astrocytes and acts as a trophic factor for serotonin neurons and a neurite outgrowth and differentiation promoter (Whitaker-Azmitia et al., 1997). Therefore, increased S-100B levels could also indicate axon growth and synaptogenesis during synaptic remodeling.

Remarkably, only patients suffering from the melancholic subtype of MD exhibited increased S-100B plasma levels. Also, the S-100B levels were not correlated with symptom severity. Hence one can assume that the distinct quality of symptoms in melancholic depression assists identification of a specific subgroup of major depression that might differ etiologically or pathogenetically from other subtypes. From its clinical presentation and the results of research, melancholic depression has often been considered as the most ''biological'' form of depression. It is characterized by a loss of pleasure in almost all activities, a lack of response to usually pleasurable stimuli, a depressed mood distinct from the feeling of bereavement, excessive or inappropriate guilt, psychomotor retardation or agitation, and vegetative symptoms. The course of disease is episodic and the depression is often worse in the morning.

It is worthy of note that an earlier study by Jankovic et al. (1980) reported that 81.2% of patients diagnosed as suffering from depressive affective psychosis (ICD 9 criteria) showed a positive reaction in the local Arthus and delayed hypersensitivity reaction against S-100 protein; this frequency was 3.7% for normal controls and neurotic patients.

In experiments involving transgenic mice with a lifelong overproduction of S-100B, such mice showed significant learning deficits and signs of impaired short term memory leading to behavioural rigidity (Gerlai and Roder, 1996; Griffin et al., 1998). It would therefore be challenging to determine whether cognitive impairment and affective rigidity in melancholic depression are induced by minor brain damage or increased S-100B concentrations.

Further studies are needed to confirm our findings and reinvestigate patients after recovery to determine whether increased S-100B levels return to normal. Neuroimaging and neuropsychological testing should be included to investigate possible associations between increased S-100B levels and structural or cognitive deficits. The influence of psychotropic medication on plasma S-100B levels should be studied. It also remains to be seen why melancholic patients show increased S-100B levels and how increased S-100B is involved in the development of melancholia symptoms.

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