



## Electroconvulsive therapy and biomarkers of neuronal injury and plasticity: Serum levels of neuron-specific enolase and S-100b protein

Johanna Palmio<sup>a,b,\*</sup>, Martti Huuhka<sup>c</sup>, Seppo Laine<sup>d</sup>, Heini Huhtala<sup>e</sup>, Jukka Peltola<sup>b</sup>, Esa Leinonen<sup>c</sup>, Jaana Suhonen<sup>f</sup>, Tapani Keränen<sup>b</sup>

<sup>a</sup> Department of Neurology, University of Tampere, Tampere, Finland

<sup>b</sup> Department of Neurology, Tampere University Hospital, Tampere, Finland

<sup>c</sup> Department of Psychiatry, Tampere University Hospital, Tampere, Finland

<sup>d</sup> Department of Clinical Microbiology, Tampere University Hospital, Tampere, Finland

<sup>e</sup> Tampere School of Public Health, University of Tampere, Tampere, Finland

<sup>f</sup> Department of Neurology, Jokilaakso Hospital, Jämsä, Finland

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### ABSTRACT

Electroconvulsive therapy (ECT) is considered an effective and safe treatment in major depressive disorders. However, the possibility that it may induce cognitive adverse effects observed in selected patients has raised a concern that ECT may induce neuronal damage. The biomarkers of brain damage, neuron-specific enolase (NSE) and S-100b protein (S-100b), were measured in serum before and after ECT to determine whether this treatment induces neuronal injury or glial activation. ECT was administered to 10 patients with major depressive disorder. The serum samples were analyzed before (baseline) and after ECT at 1 h, 2 h, 6 h, 24 h and 48 h. The severity of depression was scored with the Montgomery-Åsberg Depression Rating Scale (MADRS) and Beck Depression Inventory (BDI) pre-to-post ECT. There were no statistically significant changes in the median concentrations of NSE or S-100b at various time points before or after ECT. However, there were substantial elevations in the levels of S-100b in four patients. High levels of S-100b at 2 and 6 h correlated with the response to the treatment. These results suggest that ECT does not produce neuronal injury. The transient increase in the levels of S-100b reflecting activation of glial cells may play a part in mediating the antidepressant effects of ECT.

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### 1. Introduction

Electroconvulsive therapy (ECT) is regarded as an effective treatment in major depressive disorders, especially in medication-resistant patients (American Psychiatric Association, 2001; Wahlund and von Rosen, 2003). Although ECT is considered safe, it may induce reversible memory deficits, i.e. acute postictal disorientation and anterograde or retrograde amnesia (Calev et al., 1991; Sackeim, 1992; Sackeim et al., 1993; Rose et al., 2003). Persistent cognitive adverse effects observed in selected patients have raised a concern that ECT may induce neuronal damage (Sackeim et al., 2007). However, no evidence of structural brain damage due to ECT has been found in brain imaging studies (Devanand et al., 1994; Puri et al., 1998; Angheliescu et al., 2001; Szabo et al., 2007).

Neuron-specific enolase (NSE) and S-100b protein (S-100b) are specific markers of brain damage. NSE, the  $\gamma$ -subunit of enolase, originates predominantly from the cytoplasm of neurons and neuroen-

docrine cells. S-100b is present in high concentrations in glial cells and Schwann cells and plays a regulatory role in the cytoskeleton and cell cycle (Donato, 2001). The serum levels of these proteins are elevated after different types of brain damage such as focal and global ischemia (Büttner et al., 1997; Missler et al., 1997; Rosén et al., 1998), head injury (Savola et al., 2004) and hemorrhagic brain damage (Persson et al., 1987). Increased levels of NSE have been reported in a subset of epileptic patients after seizures (Pitkänen and Sutula, 2002), but no postictal elevation of S-100b after single seizures has been observed (Büttner et al., 1999; Palmio et al., 2001; Leutmezer et al., 2002). Serum levels of NSE or S-100b after ECT at different time points have not been increased compared with the baseline in the majority of previous ECT studies (Greffé et al., 1996; Berrouschot et al., 1997; Zachrisson et al., 2000; Agelink et al., 2001). However, Arts et al. found a small rise in S-100b at 1 h after ECT (Arts et al., 2006). Only one study has used both NSE and S-100b as marker of brain damage after ECT, but the first samples after ECT were taken after 6 h (Agelink et al., 2001). Given the short half-life of S-100b, possible changes may not have been detected.

On the other hand, in the chronic electroconvulsive shock (ECS) model astrocytic responses have been interpreted as representing plastic reactions in rat brains. With the absence of evident neuronal

\* Corresponding author. Department of Neurology, FIN-33014, University of Tampere, Finland. Tel.: +358 3 31166783; fax: +358 3 35516164.

E-mail address: [johanna.palmio@uta.fi](mailto:johanna.palmio@uta.fi) (J. Palmio).

injury the observed elevations of S-100b levels suggest that ECS-induced astrocytic activation may also be neuroprotective (Busnello et al., 2006). Thus S-100b changes in ECT may not necessarily reflect neuronal damage but, rather, transient activation of glial cells associated with therapeutic responses of the treatment.

In the present study we measured NSE and S-100b levels in serum before and after ECT to determine whether this treatment is associated with either neuronal injury or glial activation.

## 2. Methods

### 2.1. Subjects

The study was performed at the Department of Psychiatry, Tampere University Hospital, Finland. Ten patients, seven women and three men, with a mean age of 56 years (range 28–70 years), were included in the study. All the patients were diagnosed with major depressive disorder (DSM-IV) (American Psychiatric Association, 1994); four of them showed psychotic features. The patients were otherwise healthy except for one patient (no. 7) who had ischemic heart disease and a history of a stroke 6 months before the treatment. The patients' psychotropic medications were continued unchanged during the treatment. The severity of depression was scored with the Montgomery-Åsberg Depression Rating Scale (MADRS) and Beck Depression Inventory (BDI) before and after the series of ECT. The median MADRS scores were 30/60 before and 8/60 after ECT and the median BDI scores 30/63 and 6/63, respectively. The median Mini-Mental State Examination (MMSE) scores were 28/30 before and 28/30 after ECT. Demographic data of the patients and their psychotropic medications are shown in Table 1.

All the patients gave their written informed consent. The study protocol was approved by the Ethics Committee of the Tampere University Hospital.

### 2.2. ECT procedure

All patients were treated with bitemporal ECT administered with a Thymatron DGx (Somatics, Inc, Lake Bluff, Ill) brief-pulse device. The initial stimulus dosage (millicoulombs) was adjusted with the age method (Swartz and Abrams, 1996). The duration of the electric stimulus is determined automatically by the device (mean 2.4 s). Anesthesia was induced with propofol (1.5 mg/kg) or methohexital (1 mg/kg) and muscle relaxation with succinylcholine (0.5 mg/kg). The arterial oxygen saturation, heart rate and three-lead ECG were continuously monitored. The seizure duration was measured with electroencephalogram (EEG; mean duration 45.7 s) and convulsive motor response with electromyogram (EMG, mean 31.2 s). All patients experienced an adequate electrical generalized seizure and the mean energy used was 272.2 mC. Three of the patients were studied at their first ECT session, and the remaining seven patients at the third to seventh ECT. Individual characteristics of the ECT parameters and the anesthetic used are presented in Table 1.

### 2.3. Blood sampling and biochemical analyses

The serum samples were collected before ECT and at 1 h, 2 h, 6 h, 24 h, and 48 h after the treatment. The samples were centrifuged at 3000 rpm for 10 min and stored at  $-70^{\circ}\text{C}$  prior to the analyses. The NSE assays were performed using a radioimmunoassay technique (Cobas Core NSE EIA, Hoffmann-La Roche, Switzerland). Hemolyzed samples were discarded from the NSE analysis. The S-100b concentrations

were measured by an immunoluminometric assay for the quantification of protein (LIA-mat<sup>®</sup> Sangtec<sup>®</sup>100, Sangtec Medical, Sweden). The assays were done according to the manufacturer's instructions. The sensitivity of the S-100b assay was  $<0.02\ \mu\text{g/l}$ .

### 2.4. Statistical methods

As the parameters were not normally distributed, non-parametric methods were used. Results are presented as medians at all the time points. Friedman and Wilcoxon signed ranks tests were used to determine individual and intragroup differences in NSE and S-100b. Spearman's correlation was calculated to evaluate the relationship between the changes in S-100b and MMSE, MADRS and BDI scores and the parameters of the treatment. Two-tailed *P*-values were used. No corrections for multiple comparisons were made. Findings were considered statistically significant at *P* values less than 0.05. Also power analysis was performed. All analyses were carried out with SPSS 14.0.

## 3. Results

ECT was effective for patients with medication-resistant depression. Only one patient (no. 9) had a higher MADRS score after the treatment. ECT was not associated with any alterations in the levels of NSE at various time points ( $P=0.34$ , Friedman test). There was a trend towards an increase in S-100b levels at 2 h ( $P=0.13$ , Wilcoxon). The changes were, however, not statistically significant ( $P=0.57$ , Friedman). The median serum concentration of NSE before ECT (baseline) was  $7.0\ \mu\text{g/l}$ . It was  $8.0\ \mu\text{g/l}$ ,  $8.0\ \mu\text{g/l}$ ,  $7.0\ \mu\text{g/l}$ ,  $7.5\ \mu\text{g/l}$  and  $8.5\ \mu\text{g/l}$  at 1 h, 2 h, 6 h, 24 h and 48 h after ECT, respectively. The S-100b levels at the respective time points were  $0.16\ \mu\text{g/l}$  (baseline),  $0.18\ \mu\text{g/l}$ ,  $0.25\ \mu\text{g/l}$ ,  $0.14\ \mu\text{g/l}$ ,  $0.15\ \mu\text{g/l}$  and  $0.11\ \mu\text{g/l}$  (Fig. 1). The baseline levels of markers and their peak values after ECT are presented in Table 1.

Power analysis performed on our data demonstrated that to show a negative association in the changes in S-100b concentrations at different time points, several hundred patients would be needed. To prove a positive association with the same degree of change that we now observed in S-100b concentrations from baseline to 2 h, we would need over 30 patients. From baseline to 6 h more than 160 patients would be needed.

However, in four patients the S-100b levels were increased at least 2-fold at 2 h compared to the baseline, the maximum elevation being 8-fold (patients no. 1, 3, 4, 6). The changes in the levels of S-100b did not correlate with the MMSE scores or with the parameters of the treatment, e.g. seizure duration, energy used or the number of ECT session. The pre-to-post ECT changes in MADRS and BDI scores correlated with the concentration of S-100b at 2 h (MADRS,  $r=0.68$ ,  $P=0.044$ ; BDI,  $r=0.65$ ,  $P=0.060$ ) and at 6 h (MADRS,  $r=0.73$ ,  $P=0.040$ ; BDI,  $r=0.77$ ,  $P=0.027$ ). Furthermore, the reduction of BDI

**Table 1**

Patient characteristics with baseline and peak levels of neuron-specific enolase (NSE) and S-100b protein (S-100).

Patient no.	Age/sex	No. ECTs	Medication group	Seizure duration (EEG) s	Energy mC	Stimulus duration s	Anesthesia	BDI Pre/post-ECT	MADRS Pre/post-ECT	MMSE Pre/post-ECT	Baseline/peak NSE levels $\mu\text{g/l}$	Baseline/peak S-100 levels $\mu\text{g/l}$
1	70/F	7	1,3	19	428.4	3.4	1	25/0	25/0	30/30	7/10	0.10/0.30
2	64/M	1	1,3	38	302.4	2.4	1	27/2	39/1	27/29	9/9	0.99/1.11
3	33/F	1	2,3	54	151.2	1.7	1	34/5	29/3	-/30	8/8	0.11/0.22
4	73/F	1	1,2,3	60	302.4	2.4	1	31/7	32/9	27/27	10/10	0.21/0.84
5	57/F	5	1,2	33	302.4	2.4	1	22/19	18/6	25/24	6/11	0.0/0.08
6	28/F	4	1,2	49	201.6	2.2	2	34/1	31/11	30/27	7/8	0.03/0.27
7	62/F	3	1,3	43	327.6	2.6	2	55/32	34/9	29/30	5/12	0.23/0.25
8	62/F	5	1,2	66	302.4	2.4	2	13/0	21/7	28/24	16/16	0.61/0.61
9	41/M	6	2	50	151.2	1.7	2	28/38	29/33	29/29	7/8	0.0/0.0
10	66/M	5	1,2,3	43	252.0	2.8	2	36/17	32/10	25/21	4/10	0.35/0.35
Mean	55.6			45.7	272.2	2.4						

F indicates female; M, male; EEG, electroencephalogram.

Medication group 1 = neuroleptics, 2 = antidepressants, 3 = benzodiazepines.

Anesthesia 1 = propofol, 2 = methohexital.

BDI = Beck Depression Inventory (maximum 63).

MADRS = Montgomery-Åsberg Depression Rating Scale (maximum 60).

MMSE = Mini-Mental State Examination (maximum 30).

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