The novel Seizure Quality Index for the antidepressant outcome prediction in electroconvulsive therapy: association with biomarkers in the cerebrospinal fluid.

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Abstract

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Keywords

Electroconvulsive therapy; depression; outcome; prediction, cerebrospinal fluid

Introduction

Electroconvulsive therapy (ECT) is an effective and safe treatment option for specific forms of depression, such as treatment-resistant depression, psychotic depression, bipolar depression or depression in the elderly. Despite a remarkable efficacy even in highly treatment-resistant depression, there is still a considerable group of non-responders and non-remitters to ECT. Therefore, a seizure quality index (SQI) that could predict the risk of non-response (and non-remission) - as early as after the second ECT session - based the extent of several ictal parameters of the seizure has been developed [16] and validated [26]. In contrast to other ictal indices [8, 28, 29, 32, 39], this index could be reliably calculated at the bedside in convenience for the clinician, who needs to know, whether there is an increased risk for an unfavorable outcome for the patient. Unlike demographic or clinical characteristics such as age or duration of the current depressive episode, it might be possible to modify certain features of the stimulation to enhance the chance of a favorable clinical outcome.

Seizure quality in general [5] and seizure quality measured by the SQI in special [20] is associated with brain-derived neurotrophic factor (BDNF) serum levels (refs), which fits nicely into the most prominent theory of the mode of action of ECT itself (ref). This theory proposes that ECT induces the expression of BDNF and other neurotropic factors that in turn induce neuroplastic changes [7, 13, 35]. Beside BDNF, there are no other biomarkers that have been correlated with any kind of seizure quality. This is especially true for markers measured in the CSF, which have the advantage compared to markers from blood that they are able to reflect cerebral processes much more directly and are more central nervous system (CNS)-specific.

Previously, we conducted a study in which CSF samples before and after a course of ECT in patients with severe, therapy-resistant depression were collected and several markers following different underlying hypotheses, such as hormones [12], lipids [22], neurotrophic factors [19], cytokines [24, 31], metabolites from the kynurenine pathway and markers of neurodegeneration [17, 18], were analyzed. Based on these analyses, we recently tested

several CSF biomarkers of those patients with depression on its ability to predict the antidepressant efficacy of ECT [23]. Here, we aim to test the same CSF biomarkers regarding their ability to predict the degree of seizure quality, measured by the novel SQI. Due to the variety of different markers included into the study, we decided to test the association in a hypothesis-free approach. In addition, we aimed to identify possible links between CSF markers that could predict the antidepressant outcome of ECT previous to ECT and knowledge on the SQI, and to identify possible factors, that could explain the variability of the seizure quality, in addition to the already known factors such as age, gender and medication [40, 41].

Subjects and methods

Patients

The study was approved by the institutional review board and was performed in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Written informed consent was obtained from all participants before enrolment. The study took place from 2012 to 2014 at the Department of Psychiatry at the Central Institute of Mental Health in Mannheim, Germany. Inclusion criteria were: i) a present treatment-resistant depressive episode (defined as failure to achieve response or remission to at least two proven antidepressant trial with adequate dosing and duration [36]) within the context of a diagnosis of either major depressive disorder or bipolar disorder according to DSM-IV, ii) age above 18 years, and iii) the clinical decision for an ECT treatment. Exclusion criteria were i) substance-related disorders including tobacco and alcohol, ii) the lifetime diagnosis of schizophrenia, iii) any signs of an on-going inflammatory process such as leucocytosis, elevated acute phase proteins or fever, iv) the intake of any medication with known immunomodulatory properties, such as non-steroidal anti-inflammatory drugs or glucocorticoids, and v) the reported use of Δ9-tetrahydrocannabinol (THC) twelve months before the study or detection of THC in urine drug screen. The patients continued their prior psychotropic medication during the ECT

treatment.

ECT treatment

Right unilateral brief pulse ECT was performed with a Thymatron IV device (Somatics, LLC. Lake Bluff, IL, USA), s-ketamine was used as the anaesthetic substance (~1.0 mg/kg) [11, 27] and succinylcholine for muscle relaxation (~1.0 mg/kg). Seizure threshold in all patients was titrated at the initial session and dosing at subsequent treatments was given at > 2.5 times above threshold. Mean charge administered was 60.1 mC ±39.8 mC. The energy was subsequently increased if patients did not respond clinically or if seizures were insufficient during the ECT course. Two or three ECT sessions per week were performed. All patients started with unilateral stimulation, in the case of non-response, it was possible to switch to bilateral stimulation at decision of the ECT supervisor.

Measures

The Hamilton Depression Rating Scale (HDRS; 21 items version) was used to assess the severity of depression before and after the ECT in each patient. Response was defined as a reduction of at least 50% in symptoms measured by the HDRS. Parameters documented for the second individual ECT session were: stimulation dose, (in mC), electrode placement (uni- or bilateral), type of narcotic agents (thiopental or S-ketamine), duration of the seizure measured by EMG (in seconds), concordance (EMG seizure duration/EEG seizure duration), midictal amplitude (in mV), peak heart rate (as beats per minute; bpm) and interhemispheric coherence (in %). The values for midictal amplitude, peak heart rate and interhemispheric coherence were produced by the built-in algorithm of the ECT device. To optimize accuracy, in all sessions baseline recordings prior to ECT were performed and relevant artifacts were eliminated.

Seizure quality index

The SQI for non-response and the SQI for non-remission are derived from the values from

those five ictal parameters [16]. For each ictal parameter (ictal duration measured by EMG, concordance, peak heart rate, midictal amplitude and interhemispheric coherence), a cut-off value for non-response and for non-remission was calculated. The ictal parameters from the second ECT session was used for the building of the SQI (Table 1). For each ictal parameter, whose value was above that cut-off point, one point could be added to the SQI sum score. Thus, the SQI spanned zero to five points. Non-response and/or non-remission are predicted in cases, where the sum score is below three points.

Sampling

Before the first ECT session, all CSF samples were drawn at around 9:00 am in non-fasting state after a light breakfast at 8:00 am. Lumbar punctures were performed in the sitting position according to standardized procedure. Samples were then aliquoted and transferred at -80°C within 30 min either in glass vials (Hycultec, Beutelsbach, Germany) for the analyses of the lipids, in polypropylene tubes for the analyses of the markers of neurodegeneration, or in protein LoBind tubes (Eppendorf, Germany) for all other substances. The samples were stored at -80°C and were never thawed or refrozen prior to the presented analyses.

CSF laboratory analyses

For each analysis, all samples were analyzed on one occasion on the same plates using the same batch of reagents.

Metabolites of the Kynurenine Pathway

CSF levels of tryptophan (TRP), kynurenine (KYN), kynurenic acid (KYNA), 3-hydroxykynurenine (3-HK) picolinic acid (PIC) and quinolinic acid (QUIN), were determined using an in-house established and validated LC-MS/MS method. From these values, the kynurenine-to-tryptophan ratio (KYN/TRP) was calculated.

Elements of the innate immune system

CSF concentrations were measured as instructed by the manufacturer, using either sandwich ELISA kits for interleukin-6 (IL-6), neopterin, soluble CD14 (sCD14), soluble CD163 (sCD163), macrophage migration inhibitory factor (MIF) and monocyte chemotactic protein 1 (MCP-1), or by using multiplex assay method for IL-1ß, IL-1RA, Il-2, IL-2R, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12 (p40/p70), IL-13, IL-15, IL-17, TNF-α, IFN-α, IFN-γ, GM-CSF, MIP-1α, MIP-1ß, IP-10, MIG, eotaxin and rantes, as described elsewhere [24, 31].

Tau proteins and β-amyloids

All samples were measured at the National TSE (Transmissible Spongiform Encephalopathies) Reference Centre (Göttingen, Germany). CSF levels of $A\beta_{1-40}$, $A\beta_{1-42}$, total tau (T-tau) and its phosphorylated isoform (P-tau) were determined with commercially available enzyme-linked immunosorbent assay (ELISA) kits, described elsewhere [17].

Neurogranin

All samples were measured at the Clinical Neurochemistry Laboratory at Sahlgrenska University Hospital. CSF Ng concentration was measured by enzyme-linked immunosorbent assay (ELISA), essentially as described [30], using the anti-Ng antibody pair Ng2 and Ng22. Intra-assay coefficients of variation were below 10%.

Vascular endothelial growth factor

All samples were measured at the Clinical Neurochemistry Laboratory at Sahlgrenska University Hospital. CSF levels of VEGF were analyzed using the V-PLEX Plus Human VEGF Kit (MesoScale, Rockville, Maryland), which is a validated immunoassay for generation of reproducible and reliable results to support the most demanding long-term studies.

Endocannabinoids

All samples were measured at the Lipidomics/Mass Spectrometry Facility at the Institute of Physiological Chemistry at the University Medical Center of the JGU Mainz. Endocannabinoids

were qualitatively and quantitatively analyzed using liquid chromatography/ multiple reaction monitoring (LC/MRM) according to the procedures described elsewhere [3, 21]. Levels of both AEA and 2-AG were measured, as well as levels of arachidonic acid (AA), which is both a metabolite of endocannabinoids and a substrate for their synthesis.

Phospholipids

Phosphatidylcholines, ceramides and sphingomyelin analyses were performed on a QTRAP5500 (ABSciex) coupled to a Triversa NanoMate device (Advion) as previously described [38].

Soluble Klotho

All samples were measured at the Department of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany. The concentration of soluble Klotho (sKlotho) in CSF was quantified using a human Klotho enzyme-linked immunosorbent assay (ELISA) kit measuring the entire soluble α-Klotho protein secreted in the systemic circulation after its release from the cell membrane via shedding (cleaved Klotho) or alternative splicing (secreted Klotho) (Immuno-Biological Laboratories Co., Ltd., Gunma, Japan).

Statistical analyses

Statistics were performed using STATA® (StataCorp, Texas 77845, USA, version 15) at a significance level <0.05. Normality was examined using the Shapiro-Wilk and data were log-transformed when necessary. No correction for multiple testing was performed to avoid type II errors in this study with its small sample size. Differences of the HDRS before and after ECT were examined with a paired t-test. Pearson's product-moment correlation or the point-biserial correlation were run to assess the relationship between the SQI and possible covariates. Pearson's partial correlation was run to assess the relationship between the SQI and each single CSF biomarker after adjusting for covariates. Multiple regression analyses were used to identify models, in which more than one marker - adjusted for identified covariates - could

add significantly to the prediction. In the case of values below the level of detection (LOD), it was decided to substitute them with LOD/2, although we are aware of the potential bias and imprecision [37].

Results

Twelve patients who completed a full course of ECT with prior lumbar puncture were enrolled into this study. In general, ECT was effective with a reduction of the mean initial HDRS from 29.9 ±6.6 to 9.0 ±5.2 after the final session ($p<0.001$). The mean SQI for response was 2.1 ±1.6 and the SQI for remission was 1.4 ±1.4. Further demographic and clinical features are shown in Table 2.

Possible covariates for the SQI

Age was negatively associated with the SQI for response ($r=-0.73$; $p=0.007$) and for remission ($r=-0.75$; $p=0.005$), whereas neither gender nor the type of depressive episode (unipolar or bipolar) was associated with the SQI for response ($p=0.62$ and $p=0.26$, respectively) or remission ($p=0.68$ and $p=0.082$). Additionally, no association of the BMI and the SQI for response ($p=0.98$) or remission ($p=0.64$) could be identified. All subjects were non-smokers; thus, tobacco use was not tested as a possible confounder. Thus, only the variable “age” was used as a covariate in the regression analysis between the SQI and the different markers.

Associations between the SQI for response and remission and CSF biomarkers

Negative, linear relationships with the SQI for response were observed for CSF levels of T-tau ($r=-0.69$, $p=0.019$), phosphatidylcholines ($r=-0.52$, $p=0.038$), and IL-8 ($r_l=-0.67$, $p=0.047$). Regarding the SQI for remission, a negative, linear relationship was noted with CSF levels of

the endocannabinoid AEA (r=-0.70, p=0.024) and CD163 (r_l=-0.68, p=0.029). By contrast, all other CSF markers included in this study were no significant correlates of SQI.

Prediction of the SQI for response and remission by CSF biomarkers

Multiple linear regression analysis revealed age and CSF levels of T-tau, phosphatidylcholines, and IL-8 as independent predictors of SQI for response (F=30.0, adj. R^2=0.94, p=0.003). Only the CSF levels of T-tau and IL-8 added statistically significantly to the prediction. Regression coefficients and standard errors are given in Table 3. By contrast, For the SQI for remission no regression model could be obtained.

Discussion

To the best of our knowledge, this is the first study investigating associations of the SQI - a novel predictor of antidepressant outcome of response and remission to ECT in patients with depression – and CSF biomarkers of various mechanisms of antidepressant action of ECT. In detail, we found that CSF markers of neurodegeneration, the innate immune system and lipids were those that associated with seizure quality measured by the SQI after adjusting for age. Consistently for all relationships, we found negative correlations. In other words, higher CSF levels of the markers were always associated with lower seizure quality.

Most prominently, the CSF concentrations of two proteins associated with the innate immune, IL-8 and sCD163 were found to be related with the seizure quality. Soluble CD163 is used as a marker for macrophage activition [33]. It has been linked to systemic chronic low-grade inflammation [1] and central nervous system inflammation [49]. In our previous studies, baseline CSF levels of sCD163 have been found to be positively correlated with an antidepressant response to ECT [23, 25]. IL-8 is produced by several cell types in the CNS, including microglia, astrocytes [47], and has mainly pro-inflammatory effects, such as chemotaxis [34]. Besides the suggested immune functions, IL-8 has been shown to be involved in neuronal electrical activity, neurotransmitter release, synaptic plasticity and neurotrophic function [10, 47, 50]. IL-8 has been related to affective disorders in that way that a gene set analysis of post-mortem brain tissue indicated an up-regulation of IL-8 expression in individuals with major depression [48], and that CSF IL-8 concentrations were higher in patients with bipolar disorder as compared to controls [14]. In one of our previous studies, CSF IL-8 was increased after ECT compared to baseline [31]. Thus, IL-8 and sCD163 are both markers of the monocyte/macrophage/microglia lineage and were increased, when the seizure quality was lower, it could be assumed, that enhanced pro-inflammatory activity, which is reflected by each of the marker leads to reduced seizure quality and an increased risk for a non-favorable outcome of ECT. One possible explanation for this relationship could be that in a more pro-

inflammatory environment in the CNS with a higher recruitment and density of immune cells leads simply to a small degree of impaired spreading of the induced seizure. However, it should be noted, that other cytokines with primarily pro-inflammatory properties, such as IL-6, IL-1 and IL-17, were not associated with the SQI in our analysis.

The CSF levels of the common marker of neurodegeneration T-tau were also higher in those patients, whose induced seizure were considered as possessing a lower quality. T-tau is normally expressed within neurons and is secreted into the brain interstitial fluid that communicates freely with the CSF [52]. Especially in Alzheimer's disease, but not exclusively, the neuroaxonal dysfunction results in increased release of tau from neurons, which is associated with future neurodegeneration and aggregation of tau in neurofibrillary tangles of the proximal axoplasm [52]. Thus, neuroaxonal degeneration and tangle formation are predicted by increased concentrations of T-tau in the CSF. Although depression has not been acknowledged as a neurodegenerative disorder with abnormal tau processing, it could be assumed that patients with a higher concentration of T-tau in their CSF may have neuroaxonal dysfunction that potentially could be related to Alzheimer-like brain changes. Parallel to the higher density of inflammatory cells, a certain degree of dystrophic or degenerated axons might be associated with lower quality seizures induced by ECT, as we have found in this study.

Last, we could identify two lipids, whose CSF levels were negatively correlated with the seizure quality. Namely the endocannabinoid AEA and phosphatidylcholine (PC), which is known to be a major component of cellular membranes. In neurons, an increased synthesis of PC is found in the axon [43]. An explanation for the negative correlation between CSF PC levels and seizure quality could be found indirectly, when taking into account, that PC is not only involves in the synthesis of cellular membranes, but also several other biological pathways, including the synthesis of inflammatory mediators [2, 42, 45, 46]. Above, we have already discussed a possible reduction of seizure quality due to a pro-inflammatory environment in the CNS. A certain amount of axonal dystrophy/dysfunction/degeneration could be an alternative explanation. In amyotrophic lateral sclerosis, the commonest adult-onset motor neuron

disease, characterized by the degeneration of upper and lower motor neurons, CSF PC levels were found to be markedly higher in patients compared with controls [4]. In line with this, it could be assumed, that certain patients from our study, who - due to unknown factors, but adjusted for age - possessed a slightly higher degree of axonal dystrophy, had higher CSF levels of PC. Consequently, this putative axonal dystrophy may be associated with - similar as proposed for T-tau - seizures with a lower quality within the ECT treatment.

The endocannabinoid AEA is known from preclinical [9] and clinical studies [6, 44] to be involved in suppressing pathologic neuronal excitability and in controlling the spread of activity in an epileptic network [15, 51]. Although seizures induced by ECT differ from epilepsy, our results of the negative correlation between AEA CSF levels and seizure quality fit nicely into this established knowledge. In accordance with this, in a previous study, we could detect an AEA increase in the CSF during ECT, which itself is known to raise seizure threshold [21].

Limitations

The major limitation of our study is probably the small sample size and therefore the increased risk for type II errors and at the same time an increased risk for type I errors due to the intentional relinquishment of correction for multiple testing. Nevertheless, the sample size was large enough to identify moderate to larger effects. Thus, these positive results from our small sample group seem promising and warrant future replication studies. Surely, we cannot exclude that with a larger sample size, smaller effects of certain markers could have been unveiled. Based on the clinical reality, the study was only possible to conduct with our patients continuing some of their psychotropic medication that consisted of antidepressants, antipsychotics and lithium, but no benzodiazepines during the ECT treatment. Due to the design of our study, it is not possible to unmask any causal relationship between ECT and the identified CSF markers that correlated with the seizure quality. We were able to offer plausible explanation for each marker that correlated with the seizure quality. However, it must be kept

in mind, that all interpretations, perhaps except the more established one of the endocannabinoid AEA result, must be considered as speculative.

In summary, our CSF study was primarily meant to identify CSF markers that are associated with the seizure quality, which itself can predict the antidepressant outcome of the ECT. Markers of the innate immune system, neurodegeneration and lipids metabolism were found to be associated with the SQI for response and remission after adjusting for age. Based on these markers, further research regarding the mechanism of seizure quality in ECT is suggested.

Conflict of interest

HZ has served at scientific advisory boards for Roche Diagnostics, Samumed, CogRx and Wave, has given lectures in symposia sponsored by Biogen and Alzecure, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg (all outside submitted work). All other authors declare that they have no conflict of interest.

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Tables

Parameters	Points to acquire	Outcome	
		Non-Response	**Non-Remission**
Seizure duration by EMG	1	≤ 30 seconds	≤ 55 seconds
Concordance	1	≤ 0.70	≤ 0.70
Midictal Amplitude	1	≤ 200 mV	≤ 215 mV
Peak heart rate	1	≤ 150 bpm	≤ 155 bpm
Interhemispheric coherence	1	≤ 98%	≤ 98%
Σ	**0-5**	**≤ 2: Prediction for non-response/non-remission** **> 2: Prediction for response/remission**	

Table 1. Summary of the Seizure Quality Index (SQI) for non-response and for non-remission. All parameters were derived from the second ECT session.

	Patients
Number of included subjects	12
Age (years)	59.0 ± 21.9
Female	7/12 (58)
Type of depression: unipolar/bipolar n/n (in %)	9/3 (75/25)
HDRS, sum score	
Baseline HDRS	29.9 ± 6.6
Final HDRS	9.0 ± 5.2
Mean change (%)	-20.9 (p<0.001)
Numbers of ECT sessions	10.6 ±5.0
Switch to bilateral stimulation	3 (25)
Responders/Non-responders* n/n (in %)	10/12 (83.4)
Baseline MMSE	26.1 ± 4.3
SQI for response	2.1 ±1.6
SQI for remission	1.4 ±1.4

Data are given as mean and SD or percentage as appropriate

Table 2: Patient characteristis.

	Coef.	SE	β	p	95% CI for Odds Ratio	
					Lower	Upper
T-tau	-0.005	0.001	-0.47	0.012	-0.009	-0.002
Phosphatidylcholines	-0.285	0.260	-0.18	0.34	-1.01	0.44
IL-8	-0.050	0.013	-0.54	0.018	-0.085	-0.014
Age	-0.100	0.016	-0.11	0.56	-0.53	0.33

Table 3: Summary of the multiple linear regression analysis for the prediction of the SQI for response

β= standardized coefficient