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Short communication

Changes in Brain Metabolites Measured with Magnetic Resonance Spectroscopy in Antidepressant Responders with Comorbid Major Depression and Posttraumatic Stress Disorder

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A B S T R A C T

In a present pilot study, performed on 11 subjects, we studied proton magnetic resonance spectroscopy (1H-MRS) changes in early to intermediate (3-6 weeks) responders to antidepressant treatment with selective serotonin reuptake inhibitors (SSRIs). All subjects had diagnosis of major recurrent depression comorbid to posttraumatic stress disorder (PTSD). Magnetic spectroscopy was done in the region of dorsolateral prefrontal cortex on a 3T MRI-unit. Participants were selected out of the larger sample due to an early response to antidepressant treatment within 3–6 weeks, measured with Beck Depression Inventory (BDI). We measured levels of neuronal marker N-acetyl-aspartate (NAA), choline (CHO) and creatine (Cr). There was no difference in NAA/Cr ratios between the first and the second spectroscopic scans (p= 0.751). However, CHO/Cr ratios showed increasing trend with mean value at the first scan of 1.09 (SD=0.22) while mean value at second scan was 1.25 (SD=0.24), displaying statically significant difference (p=0.015). In conclusion, significant increase in choline to creatine ratio from the first to the second spectroscopic scan during the antidepressant treatment, compared to almost identical values of NAA to creatine ratio, suggests increased turnover of cell membranes as a mechanism of the early response to the antidepressant drug therapy.

Key words: *PTSD, major depression, spectroscopy, SSRI*

Introduction

PTSD is still an underresearched area in modern psychiatry. One of the reasons behind this is a complex overlapping of symptoms usually seen in such patients. Both anxiety and depression as comorbid symptoms frequently dissolve focus of clinician's attention and mask the underlying (and possibly leading) diagnosis of PTSD. This is one of the reasons why in the present study we focused on a specific type of comorbidity – that of PTSD and major depression (MDD). At first, this connection seems plausible albeit far-fetched. However, number of studies confirming this relation is quite significant.

For example, approximately one-third of men and one-quarter of women who developed PTSD after being involved in a mass-shooting also developed a major depression[1]. In another study, similar proportion (approximately one-third of persons studied) of young urban adults with PTSD of various origins was described as having the same combination of symptoms[2]. In studies with Vietnam veterans, proportions of subjects with PTSD/ MDD comorbidity were even higher, ranging from 29% to 68%[3]. In one of the best epidemiological studies covering the topic of PTSD in modern US society, Kessler

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et al. describe a mean »lifetime« prevalence of PTSD to be around 8%, with mean incidence of major depression in these individuals as high as 48%[4].

Such observations, although being interesting from both diagnostic and therapeutic standpoints, are not without certain shortcomings. Perhaps the most interesting one is described in papers by Blanchard[5] and Yehuda. Namely, according to DSM-IV, 3 (of total number of 17) symptoms of PTSD – insomnia, impaired concentration and loss of interest for things that person has previously enjoyed, are also shared with major depression. It is therefore possible that subjects with PTSD, exhibiting these symptoms (among others), are »hastily« diagnosed with comorbid depression, providing they also have two additional symptoms needed for MDD diagnosis (MDD is diagnosed in subjects having at least 5 of 9 MDD symptoms).

In the light of the above mentioned, we suspect that PTSD/MDD comorbidity, although perhaps being overdiagnosed to some measure, cannot be an exception. Proportion of PTSD among survivors of serious trauma is reported to be between 14% and 25%[6], while the proportion of individuals developing MDD after such an event is estimated at 26%[7]. The correct answer to problem of actual PTSD/MDD prevalence in subjects with PTSD could consequently be the combination of the mentioned proportions, lying between 5 and 15%.

While the proportion of individuals with PTSD as a result of various traumatic events was already mentioned to be in the vicinity of 8% in American population, Croatian population, due to its recent exposure to war trauma is significantly more affected by this problem. In the most recent paper dealing with this issue, Priebe et al.[8] describe prevalence rates of different mental disorders in 5 countries affected by recent wars in ex-Yugoslavia. The prevalence rates in war-affected communities, although varying, are generally very high, especially compared to populations in Western countries[9,10]. Prevalence of MDD in war-affected communities in Croatia was 21.1%, while the prevalence of PTSD in the same population was 18%.

However, neither antidepressant nor psychotherapeutic solution to PTSD/MDD comorbidity is as straightforward as in cases where subjects suffer from either of these conditions[11]. Seeing this as a therapeutic challenge, our goal was to objectivize positive therapeutic outcome in such patients by using magnetic spectroscopy.

Subjects and Methods

Following the methodology described by Dow et al.[12] subjects included in the outpatient PTSD program were screened for PTSD by means of taking their clinical history and doing a mental status exam. With clinical history and status exam done, several diagnostic instruments, including the Clinician-Administered PTSD Scale (CAPS), 17-item Hamilton depression rating scale (HAM-D) and Beck Depression Inventory were used to confirm subjects' diagnosis. After all procedures were done, each case was presented at a staff meeting to discuss treatment options available.

All subjects included in the study received a standard SSRI therapy routinely used in treatment of PTSD. During the study period, some of the subjects attended either individual or group psychotherapy, while some chose to attend both. Since the scope of the interest in the present study was comorbidity of PTSD and MDD, a clinical diagnosis of major depression was further prerequisite for inclusion. Exclusion criteria were[12]: (a) current drug or alcohol abuse/dependence, (b) primary psychotic illness such as schizophrenia or bipolar disorder, and (c) poor compliance or frequent missed appointments. All 28 patients meeting all inclusion and exclusion criteria were male. Mean age of the participants was 41 years.

Over the study period, responders to antidepressant treatment were defined as individuals whose CAPS, HAM-D and BDI scores decrease confirmed subjective symptom improvement seen by the psychiatrist. Symptom improvement described in the present study was observed over the initial treatment period of 3 to 6 weeks.

1-H MR spectroscopy was performed on a Siemens 3 T machine, using a radiofrequency transmit/receive head coil suited for cerebral MRI and magnetic resonance spectroscopy. The spectroscopic volume of interest (VOI) of 25 x 25 x 25 mm was positioned in the right dorsolateral prefrontal cortical region (Figure 1). The angulation of the VOI was achieved either directly by appropriate switching of the magnetic field gradients or by reclining the subject's head in an adequate position. Metabolite signal ratios of NAA and Cr were determined from the spectra with TE=272 msec. Appropriate filtering was applied to improve the signal to-noise ratio and to convert the lines into a Gaussian shape.

Statistical analysis was done in Statistica software package (Statsoft, Tulsa, OK, USA), version 8. Due to small sample size, nonparametric methods had to be used to compare NAA/Cr ratios before and after the treatment. To test the null hypothesis that there is no difference between the distributions of NAA/Cr ratios before and after antidepressant treatment was administered, i.e. to compare paired samples of ratios, Sign test was used.

Results

From a total number of 28 subjects discussed here, 11 could be considered as early to intermediate responders

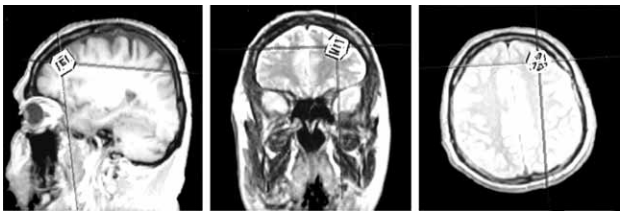

Fig. 1. Spectroscopic Volume of Interest (VOI) in the dorsolateral prefrontal cortex.

to antidepressant therapy according to previously mentioned criteria. In all 11 subjects NAA, Cr and CHO levels were measured in the DLPFC area using the above mentioned technique before and after the 3–6 weeks (mean value of 34,7 days; standard deviation of 6,62 days) of antidepressant treatment. Measurement results were combined to calculate a NAA/Cr ratio and are displayed in Figure 2.

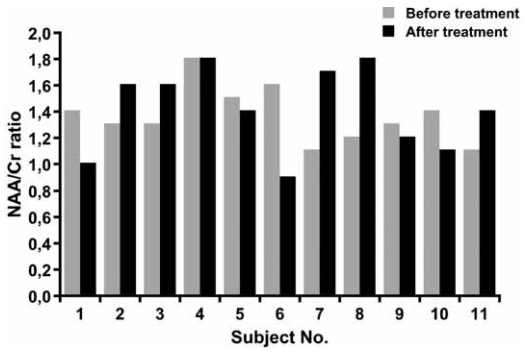

Fig. 2. NAA/Cr ratios for each of 11 responders, before (grey) and after (black) the 3–6 weeks antidepressant treatment.

We found NAA/Cr ratios to be almost the same at the baseline visit compared to the visit after the treatment. In subjects Nos. 1, 5, 6, 9 and 10 first visit values were higher than the second visit values, while subjects 2, 3, 7, 8 and 11 showed the opposite tendency. Subject No. 4 had exactly the same NAA/Cr rate values at both visits. Mean values between two visits did not differ significantly either, with mean value at the first visit of 1.36 (SD=0.21; –/+95% CIs of 1.22 and 1.51, respectively) and at the second visit of 1.41 (SD=0.32; –/+ 95% CIs of 1.19 and 1.62, respectively). Differences between measurements were compared by the appropriate non-parametric test, as described before and were found to be statistically not significant (p=0.751, Z=–0.316).

On the other hand, the CHO/Cr ratios showed a different trend with mean values significantly higher at the second visit, compared to the first one. Only one out of 11 subjects studied (subject No. 1) had higher CHO/Cr ratio at the first visit, while the remaining 10 subjects all showed higher ratios after the treatment (Figure 3). Mean value of CHO/Cr ratio at the first visit was 1.09 (SD=0.22; –/+ 95% CIs were 0.95 and 1.24, respectively), while at the second visit it was 1.25 (SD=0.24; –/+95% CIs of 1.09 and 1.41, respectively). Unlike the NAA/Cr ratios discussed before, CHO/Cr ratios differed significantly before and after 3–6 weeks of treatment with p-value of 0.015 (Z=2.41).

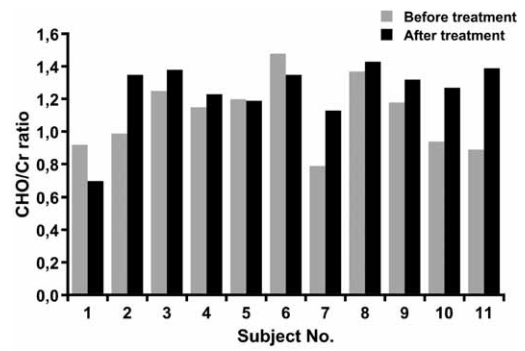

Fig. 3. CHO/Cr ratios for each of 11 responders, before (grey) and after (black) the 3–6 weeks antidepressant treatment.

The conclusion can be made that there was no statistically significant increase in NAA/Cr ratios after 3–6 weeks of antidepressant treatment in subjects with PTSD/MDD comorbidity, while the CHO/Cr ratios increased significantly over the same period.

Discussion

In the present study, we demonstrated that CHO/Cr ratios increase in early (after the initial treatment period of 3–6 weeks) responders to antidepressant treatment among patients suffering from MDD comorbid to PTSD, while the NAA/Cr ratios showed no statistically significant differences between the initial and the post-treatment visit. The latter finding supports the opinion that NAA/Cr ratios have inverse relation to illness duration[13], so in our sample with short inter-observation interval, these ratios could not change significantly. On the other hand, CHO/Cr relation to MDD is described before as being both higher[19] and lower[14] in MDD patients, while it is known to be a predictor of Alzheimer's disease (AD) in elderly[15]. However, in perhaps the most ambitious review article about this issue, authors found CHO/Cr ratios over the study period to increase in some studies, decrease in others, while in most cases the changes remained non significant[16].

Of the more recent studies, only a few were performed to evaluate pre- and post-treatment NAA/Cr and CHO/Cr changes in DLPFC brain metabolites measurable by 1H-MRS in depression. Kaymak et al., analyzing change in DLPFC metabolite ratios in female MDD patients did not find any post-treatment changes in CHO/Cr ratios, compared to healthy controls. However, authors do describe changes in inositol (Ino) to Cr ratios after the treatment[17]. Being primarily a glial-cell marker, Ino levels are associated with various aspects of depressive disorder[18], from lower post-mortem values[19], to decreased levels in suicide victims[20]. Any future study should clearly consider this marker as well as the ones described before (i.e. CHO and NAA).

Another study, performed in pediatric population has shown a significant increase in Cho in left but not right DLPFC in MDD patients *versus* control subjects. Similarly to our findings, no significant differences in NAA or Cr were observed between case-control pairs[21]. One study in amygdala[22] and another in basal ganglia[23] reported increased NAA levels after antidepressant treatment in MDD patients, the effect we did not find in our pilot-study. The reason may be related to NAA changes in specific brain region, or to MDD that was comorbid to PTSD.

Previous studies analyzing changes in CHO/Cr have shown consistent decrease in CHO/Cr levels in MDD patients after antidepressant treatment, although different regions than DLPFC were analyzed. A meta-analysis has displayed that MDD patients had higher CHO/Cr values than healthy controls in the basal ganglia, but not in the frontal lobe[16].

Our pilot-study could not provide definite answer about the nature of increase in CHO/Cr ratio in patients with PTSD comorbid with MDD. Namely, it could be either specific to certain brain regions such as DLPFC, or this change could be caused by (also possibly) different etiology of depression in patients with MDD comorbid to PTSD. Additional studies are needed to clarify possible region-specific differences in brain metabolite changes after antidepressant treatments both in MDD patient population and in population of patients suffering from MDD comorbid to other psychiatric disorders. Clearly, besides a small number of studies available, the problem is also in great inconsistence in those previously published. Differences in comorbidity, age and, perhaps the most important, drugs subjects currently use or have used before, make any meta analysis of the result virtually impossible. Thus, besides increasing only number of studies, a consensus on their methodology is very much needed.

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PROMJENE RAZINA MOŽDANIH METABOLITA MJERENIH MAGNETSKOM REZONANTNOM SPEKTROSKOPIJOM U ISPITANIKA S KOMORBIDITETOM DEPRESIJE I POSTTRAUMATSKOG STRESNOG POREMEĆAJA KOJI SU ODGOVORILI NA ANTIDEPRESIVNO LIJEČENJE

SAŽETAK

U ovom pilot-ispitivanju, provedenom na 11 ispitanika, koristili smo metodu protonske magnentno rezonantne spektroskopije (1H-MRS) kako bismo prikazali promjene u osoba koje su imale pozitivan rani odgovor (3–6 tjedana) na antidepresivno liječenje selektivnim inhibitorima ponovne pohrane serotonina (SSRI). Svi ispitanici imali su dijagnozu teške rekurentne depresije u komorbiditetu s posttraumatskim stresnim poremećajem (PTSP). Magnetskom spektroskopijom na uređaju od 3T promatrano je područje dorzolateralnog prefrontalnog korteksa. Iz većeg uzorka izabrani su oni ispitanici koji su pokazali rani odgovor na antidepresivno liječenje tijekom 3–6 tjedana, mjereno ljestvicom Beck Depression Inventory (BDI). Metodom 1H-MRS mjerene su razine neuronskog markera N-acetil-aspartata (NAA), kolina (CHO) i kretina (Cr). Između prvog i drugog spektroskopskog mjerenja nije bilo značajnih razlika u omjeru NAA/Cr (p=0,751). S druge strane, omjeri CHO/Cr pokazali su tendenciju povećanja sa srednjom vrijednosti na prvom mjerenju od 1,09 (SD=0,22), dok je srednja vrijednost na drugom mjerenju iznosila 1,25 (SD=0,24), što je rezultiralo statistički značajnom razlikom (p=0,015). Značajno povećanje omjera kolina prema kreatinu od prvog do drugog spektroskopskog mjerenja, tijekom antidepresivnog liječenja, u usporedbi s gotovo identičnim vrijednostima omjera NAA prema kreatinu, sugerira da bi za mehanizam ranog odgovora na liječenje antidepresivnim lijekovima mogao biti odgovorno pojačano prepravljanje staničnih membrana.