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N-acetyl-l-aspartate values of hippocampus are reduced in patients with hypochondriasis

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ABSTRACT

Background: Given that on the one side considerable similarities between hypochondriasis and obsessive-compulsive disorder (OCD) by means of sharing a number of features, including intrusive thoughts and repeated checking (Barsky, 1992), on the other side similar structural neuroimaging data that found hypochondriac patients to have significantly smaller mean left and right OFC, and greater left thalamus volumes compared to those of healthy controls. Aims: We considered to investigate the hippocampal neurochemicals, found changed in OCD patients, in hypochondriac patients. Methods: Fifteen patients with hypochondriasis, recruited from our out- or in-patient clinics, were compared with 15 healthy control comparisons in regard to proton magnetic resonance spectroscopy (^{1}H-MRS) imaging of hippocampus. Results: The patients with hypochondriasis had lower right and left NAA/CHO, and NAA/CRE, and near-significant lower right CHO/CRE hippocampal ratios than healthy matched comparison subjects. Conclusion: The data of the present investigation in patients with hypochondriasis provide preliminary evidence of lower right and left NAA/CHO, and NAA/CRE, near-significant lower right CHO/CRE hippocampal ratios, revealing neurochemical alterations in hippocampus and a further support the notion that hypochondriasis shares a variety of neurobiological similarities with OCD.

Keywords: Hypochondriasis; NAA/CHO; NAA/CRE; CHO/CRE; MRS

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1. INTRODUCTION

Hypochondriasis, a somatoform disorder according to Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV), preoccupation with fears of having, or the idea that one has, a serious disease based on the person's misinterpretation of bodily symptoms despite repetitive medical evaluation and reassurance. In the etiology of hypochondriasis, psychosocial factors particularly psychodynamic explanations have been always leaded until last years. However, even though they are limited, investigations have been started to account for neurobiological basis of hypochondriasis. In this context, our research team also carried out some neuroradiological studies in hypochondriasis. One of them, we volumetrically evaluated the orbito-frontal cortex (OFC), anterior cingulate, caudate nucleus, and thalamus volumes in hypochondriac patients and determined that hypochondriac patients had significantly smaller mean left and right OFC, and greater left but not right thalamus volumes compared with healthy controls, without any differences on caudate and anterior cingulate volumes. So, in that investigation, we suggested that abnormalities in the OFC and thalamus might play an important role in the pathophysiology of hypochondriasis. In another structural study, we examined possible alterations in the pituitary anatomy in patients with hypochondriasis by means of quantitative MRI which was the first MRI investigation of pituitary of the patients with hypochondriasis [1]. We detected significantly smaller pituitary volumes of the group of hypochondriac patients compared with the those of healthy controls concluded that this could be the keystone to a better understanding of the neurobiological basis of hypochondriasis. Magnetic resonance spectroscopy (MRS), increasing trend in psychoneuroradiology, is a safe and non-invasive technique for the *in vivo* study

of brain chemistry and metabolism, which investigate basic brain metabolites such as *N*-acetyl-l-aspartate (NAA; a marker of neuronal viability), combined glutamate and glutamine, choline (CHO; a marker of cell membrane turnover), myo-inositol, and creatine (CRE; a marker of cellular energy). We previosly reported structurally hippocampal and amygdalar abnormalities OCD [2]. On the other hand, in a MRS investigation of hippocampus of OCD patients, we showed that OCD patients had a significant diagnostic effect for NAA/CHO, with a near-significant diagnostic effect for NAA/CRE and concluded that these data might suggest a neuronal degeneration. Given that on the one side considerable similarities between hypochondriasis and OCD by means of sharing a number of features, including intrusive thoughts and repeated checking [3], on the other side similar structural neuroimaging data that found hypochondriac patients to have significantly smaller mean left and right OFC, and greater left thalamus volumes compared to those of healthy controls, we considered to investigate the hippocampal neurochemicals in hypochondriac patients.

2. METHODS

2.1. Subjects and Clinical Evaluation

Fifteen patients recruited from the psychiatric in or outpatient's clinic, at the Firat University School of Medicine Department of Psychiatry in Elazig, and eighteen healthy controls who were all right handed, and had a mean age of 28.1 ± 3.4 and 30.6 ± 4.2 years, respectively, were the subjects of this study. Normal volunteers were recruited from the hospital staff. Diagnoses were made by using the Structured Clinical Interview for DSM-IV (SCID) [4]. Ratings of obsessive and compulsive symptoms, and depressive signs were ascertained using the Yale-Brown Obsession Compulsion Scale (Y-BOCS) and Hamilton Depression Rating Scale (HDRS), respectively. This study was carried out under guidelines of Helsinki Declaration. Written informed consent was obtained from all subjects. The exclusion criteria consisting of the presence of any current comorbid psychiatric disorder, current severe medical problems, problems that prevent suffering from MRI investigation, presence of any neurological disease, any worry about willingness to participate in the study procedures, expressed by providing written informed consent after complete description of the study, or alcohol/substance abuse within the 6 months preceding the study. Of the patients, one had lifetime history of major depressive disorder, and one had simple phobia. On the other hand, some criteria were administered to the healthy control subjects. For inclusion in the study, healthy subjects had to meet the following inclusion criteria: Not having DSM-IV Axis I disorders in self or in a first-degree relative, as determined by the SCID non-patient version, no current or previous history of medical problems, neurologic or psychiatric disorders, no previous history of severe mental retardation, alcoholism and drug dependence or abuse in the last 6 months, and willingness to participate in the study procedures, expressed by providing written informed consent after complete description of the study. If the patients and healthy control subjects fulfilled the inclusion criteria, they were asked to participate in the study.

2.2. Procedure

Briefly, MRI and ^{1}H-MRSI scans were acquired using a GE Signa Excite 1.5 T whole body scanner (GE Medical Systems, Milwaukee, Wisconsin), with the following values (repetition time [TR] = 2000 ms, echo time [TE] = 15.6 ms, field of view [FOV] = 240 mm, flip angle = 20^{0}, bandwidth = 20.8, slice thickness = 2.4 mm, echo spacing = 15.6 ms, 8 echoes, resolution = 0.9375 × 0.9375 × 2.4 mm).

We investigated following neurochemical markers; NAA, CRE, and CHO. For all voxels, NAA, CHO, and CRE peaks were determined automatically. Position of hippocampal voxels and sample magnetic resonance spectrum are presented in **Figure 1**.

In addition to ^{1}H-MRSI scans, hippocampus of the patients and healthy controls were structurally measured. In the tracings of the hippocampus, it was benefited from standard anatomic atlases [5-7] and from Caetano *et al.* [8] and Brambilla *et al*. [9]. As described earlier [2], for the tracing of hippocampus, the process was started on the coronal slice at the point that the superior colliculus

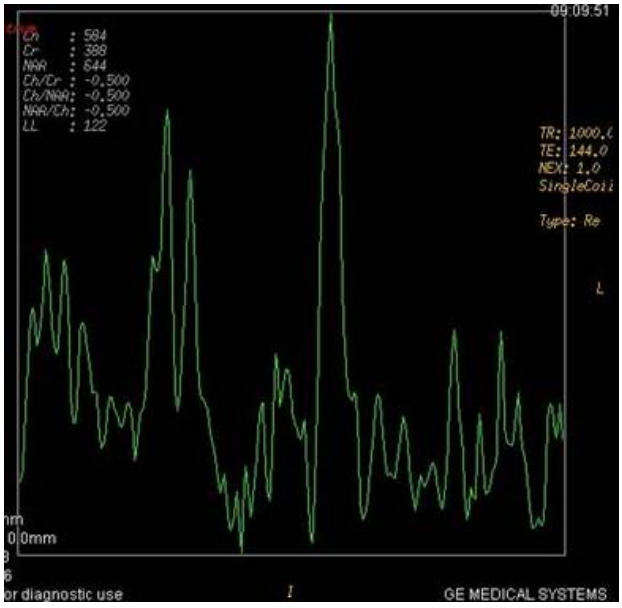

Figure 1. A sample spectrum, representing of the hippocampal region.

completely connected with the thalamus and finished one slice before the mammilary bodies appeared. The lateral border was accepted as the inferior horn of the lateral ventricle. As the superior border of the hippocampus, the corona radiata and ambient cistern were accepted. The inferior border was selected as the white matter.

2.3. Statistical Analysis

The statistical analyses were performed using SPSS version 13.0 (SPSS, Chicago, IL). Independent *t* test was used to assess differences in the volumes of hippocampus, whole brain, metabolite values, and some demographical data. Correlation analyses between volume measurements and clinical and demographic variables were carried out by means of Pearson's correlation coefficients. For the camparisons of each metabolite ratio, NAA/CRE, NAA/CHO, and CHO/CRE, independent t test was used. The criterion of significance level was set at $p < 0.05$.

3. RESULTS

Figure 2 displays the hippocampal neurochemical ratios of ^{1}H MRS for the hypochondriac patients and healthy controls. On the other hand, no difference was found in regard to age (31.00 ± 5.13 for patients and 29.20 ± 5.99 for controls; $t = 0.88$, $p > 0.05$), gender (nine females and six males for patients and eight females and seven males for controls; $p > 0.05$), HDRS scores (9.47 ± 3.76 for patients and 7.20 ± 2.27 for controls; $t = 1.99$, $p > 0.05$) or whole brain volumes (1348.11 ± 51.23 for patients and 1358.59 ± 36.53 for controls; $t = –0.65$, $p > 0.05$).

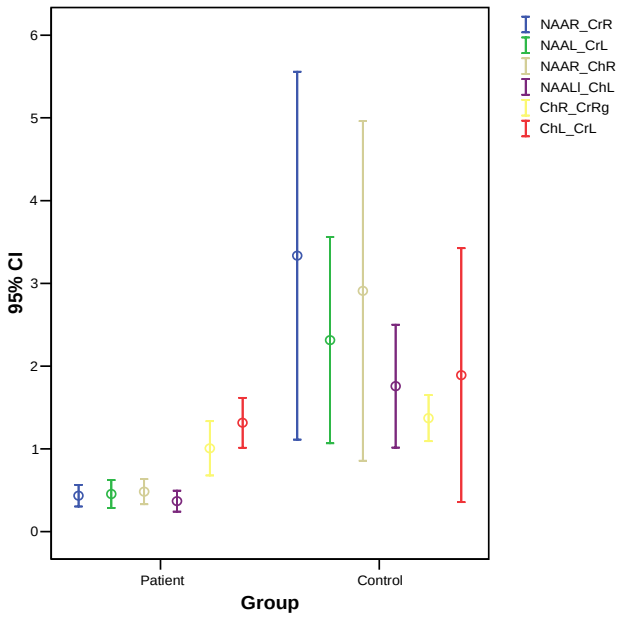

Figure 2. The error bars belonging to the patient and control groups.

For the right side, the mean NAA/CRE ratio was statistically significantly lower in the hypochondriac patients compared to that of healthy control subjects (mean ratio; 0.43 ± 0.24 for patients and 3.34 ± 4.01 for controls; $t = –2.79$, $p = 0.009$), while the mean NAA/CHO ratio was also statistically significantly lower in the hypochondriac patients compared to that of healthy control subjects (mean ratio; 0.48 ± 0.27 for patients and 2.91 ± 3.71 for controls; $t = –2.53$, $p = 0.017$). The mean CHO/CRE ratio did not differ between patient and healthy control groups (mean ratio; 1.00 ± 0.59 for patients and 1.37 ± 0.50 for controls; $t = –1.81$, $p = 0.08$).

For the left side, the mean NAA/CRE ratio was statistically significantly lower in the hypochondriac patients compared to that of healthy control subjects (mean ratio; 0.45 ± 0.30 for patients and 2.31 ± 2.25 for controls; $t = –3.17$, $p = 0.004$), while the mean NAA/CHO ratio was also statistically significantly lower in the hypochondriac patients compared to that of healthy control subjects (mean ratio; 0.37 ± 0.23 for patients and 1.31 ± 0.28 for controls; $t = –3.96$, $p < 0.001$). The mean CHO/CRE ratio did not differ between patient and healthy control groups (mean ratio; 1.32 ± 0.55 for patients and 1.89 ± 2.77 for controls; $t = –0.79$, $p = 0.44$).

When Pearson's correlation test was performed, there were no significant correlations between right or left NAA/CRE, NAA/CHO or CHO/CRE ratios and age or HDRS scores.

4. DISCUSSION

In the present investigation, patients with hypochondriasis had lower right and left NAA/CHO, and NAA/CRE, and near-significant lower right CHO/CRE hippocampal ratios than healthy matched comparison subjects. To our the best of knowledge, this is the first study to evaluate the hippocampal neurochemicals in hypochondriac patients, and our results are the first MRS evidence of reduced NAA in this disorder. One important strength of our present study comes from its purity because, of the patients, only one had lifetime history of major depressive disorder, and one had simple phobia. Another important strength of the present investigation was that the patient and healthy control groups were matched well in regard to age, gender, or whole brain volumes that might be able to contribute as confounding factors. First of all, our finding of lower NAA values in the patients with hypochondriasis, as supported by lower right and left NAA/CHO, and NAA/CRE ratios, compared to those in healthy comparison subjects supports the possibility that the hippocampal neuronal density or at least neuronal function in patients with hypochondriasis might have been affected. We have previously evaluated neurochemicals of hippocampus in a variety of psychiatric

disorders. In one of them, we examined the hippocampal neurochemicals of eighteen patients meeting Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria for OCD who consecutively applied to our department and 18 healthy controls by using ^{1}H-MRS and found that the ratios of NAA/CRE and NAA/CHO in patients with OCD relative to healthy control subjects were reduced [10]. We concluded that those data might point a neuronal degeneration in OCD. In another investigation, we scanned 20 patients meeting Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria for panic disorder and 20 matched healthy controls with a 1.5 Tesla GE Signa Imaging System and measured of NAA, CHO, and CRE in hippocampal regions and found that compared to healthy controls, NAA, CHO and CRE values were statistically significantly lower in the patients with panic disorder [11]. Also, we performed a ^{1}H-MRS investigation in somatization disorder, a somatoform disorder like hypochondriasis and detected that the mean hippocampal NAA/CRE levels were lower in female patients with somatization disorder compared to those in control subjects while no differences were determined for NAA/CHO or CHO/ CRE ratios. At this point, it is useful to mention about the role of hippocampus on human behaviors and emotions. Hippocampus is an anatomic region that is accepted as a glucocorticoid feedback area. It has a sensivitivity to endogenous glucocorticoid levels, involving in stress modulation organized by the hypothalamo-pituitary-adrenal axis (HPA) [12-14]. When we consider that somatoform disorders are related to problems of overcoming stress and emotional regulation, the importance of our findings obviously appears. If we add this knowledge on to NAA's role on neuronal viability, our findings of lower NAA values may be accounting for important things in hypochondriac patients. On the other hand, NAA is determined just in neurons and axons, lower levels may reflect loss of neurons, interneuronal connection problems, or metabolic dysfunctions in anywhere of the hippocampus, without any proof of myelin breakdown because of normal choline values of the left hippocampus, but right hippocampus, because we found lower right CHO/CRE hippocampal ratios in the patients with hypochondriasis compared to those of healthy matched comparison subjects.

When commenting our present findings, some limitation factors should be taken into consideration. Firstly, our sample size of 15 patients with hypochondriasis is quite small. Secondly, in the present study, because of the fact that it was not evaluated other brain regions excluding hippocampus, it is not known the status neurochemical ratios for other brain regions.

Despite of some limitation factors, the data of the present investigation in the patients with hypochondriasis provide preliminary evidence of lower right and left NAA/CHO, and NAA/CRE, and lower right CHO/CRE hippocampal ratios, revealing neurochemical alterations in hippocampus and a further support the notion that hypochondriasis shares a variety of neurobiological similarities with OCD. Future 1HMRS studies will probably need to determine whether there are changes for other brain regions and whether psychopharmacological and psychotherapeutic approaches affect the neurochemical alterations.

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