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^{1}HMRS in the Hippocampus of the Female Patients with Conversion Disorder

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ABSTRACT

Introduction: Previously, we found a lower NAA (N-acetyl aspartate)/CRE (creatine) ratio in conversion disorder patients, when compared to healthy controls. In this context, the present study was designed to determine the changes in hippocampal NAA, CHO (choline), and CRE values in conversion disorder female patients, which has similar symptom basement and hypothesize that the patients with conversion disorder would have also changed neurochemicals in their hippocampal regions.

Method: Twenty female patients and healthy controls were included in the study. Proton magnetic resonance spectroscopy (^{1}HMRS) method was used to determine the NAA/CHO, NAA/CRE, and CHO/CRE ratios.

Results: The data were analyzed via age-controlled General Linear Model and it was found that the ratio of NAA/CHO was significantly lower in conversion disorder female patients when compared to healthy controls. However, NAA/CRE or CHO/CRE ratios were similar for conversion disorder patients and healthy controls.

Conclusion: It was concluded that conversion disorder female patients might have reduced NAA/CHO ratio which implicates reduced neuronal viability, possibly related to anxiety and indirectly to somatoform symptoms.

Keywords: ^{1}HMRS, NAA, conversion disorder

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INTRODUCTION

Conversion disorder, which was described as a functional neurological disorder in the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (1), was classified as a somatoform disorder in the Fourth Edition (DSM-IV) (2) of the same manual. Loss or distortion in neurological functions, not associated with an actual neurological disorder, characterizes conversion disorder. Conversion disorder is prevalent in Turkey and other eastern countries (3, 4). Such prevalence motivates us to explore the neurobiological nature of this disorder along with the psychodynamic and psychosocial explanations for its incident. We acknowledge that the psychodynamic roots of conversion disorder were thoroughly explained in psychodynamics literature. However, neurobiological explanations remain limited. Currently, there exist several studies published on conversion disorder. For instance, Vuilleumier et al. (5), used single-photon emission computerized tomography, $^{99\,m}$Tc-ECD, to examine the conversion disorder patients and reported a reduction in the regional cerebral blood flow in the thalamus and basal ganglia contralateral to the deficit, which indicated a functional disorder in the striatothalamocortical circuits that regulated sensorimotor and voluntary motor functions. Our research team published the first volumetric study in patients with conversion disorder (6). In our previous study, we established that conversion disorder patients had significantly reduced mean volumes of the right side of the caudate nucleus, lentiform nucleus, and thalamus and the left side of caudate nucleus and lentiform nucleus, when compared to control subjects and we concluded that such reduction was significant for construing the pathophysiology of conversion disorder, yet, the functional and psychopathologic outcomes were ambiguous. In another study (7), we examined the pituitary gland volumes in conversion disorder patients and determined that these patients had significantly smaller pituitary gland volumes when compared to healthy controls. The duration of the illness and pituitary gland volumes in conversion disorder patients were significantly negatively correlated when compared to those of the healthy controls. The literature review indicated that there existed no research that focused on the neurochemicals in conversion disorder patients. Similarly, research on neurochemical neuroimaging had a limited focus on conversion disorder patients. Proton magnetic resonance spectroscopy (^{1}HMRS) was acknowledged as a safe and non-invasive method for the in vivo examinations of brain chemistry and metabolism. This method essentially quantifies metabolite levels, such as *N*-acetyl-l-aspartate (NAA; neuronal viability marker), combined glutamate and glutamine, choline (CHO; cell membrane turnover marker), Myo-inositol, and creatine (CRE; cellular energy marker) in the brain tissue. In another study, we measured NAA, CHO, and CRE levels in the hippocampus of the somatization disorder patients, which is a somatoform disorder (8). Hence, we identified that mean NAA/CRE levels in the hippocampus were lower, in somatization disorder patients, when compared to the controls, yet were not affecting the hemisphere. Contrarily, the ratio of NAA/CHO did not exhibit significant differences between the patients with somatization disorder and the control group. Furthermore, it was established that the difference of CHO/CRE ratio between the groups was near-significant and such finding possibly indicated lower hippocampus NAA/CRE ratio, yet unchanged NAA/CHO or CHO/CRE ratios for the female somatization disorder patients, when compared

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to the healthy controls. Given the scope above, the present study was designed to determine the changes in hippocampal NAA, CHO, and CRE values in conversion disorder patients, with similar symptom basement and hypothesize that conversion disorder patients could as well exhibit changed neurochemicals in their hippocampal regions.

METHODS

The participants of the present study were selected among the patients of the out– and in-patient clinics of the Fırat University School of Medicine Department of Psychiatry. The participants were selected from both units, based on screening interviews and written informed consents. Twenty female patients with conversion disorder, based on the Text Revised Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders (9) were included in the study. All patients who volunteered to participate in the study were female and had psychogenic nonepileptic seizures as a leading symptom. Clinical interviews were carried out and written informed consent was collected by a senior psychiatrist (S.B.). The patients were those who participated in another study conducted by our research team (7). All patients were right-handed, as stated in the previous study. The exclusion criteria of the patients were: 1) significant current or existing diseases, 2) medical problems that are current and severe and might cause problems during MRI, 3) neurological diseases, 4) mental retardation, 5) factors that might cause problems during neuroimaging such as the presence of cardiac stents, or 6) alcohol/substance abuse in the prior 6 months. As stated in a previous study (7), comorbid psychiatric diagnoses were also an exclusion criterion for the present study. Healthy female controls, equal in numbers with the patient group, were included in the present study. The healthy controls were determined from a pool of brain neuroimaging of healthy subjects. Controls were meticulously selected from this pool, based on the criteria such as the absence of individual and family psychiatric disorders, major medical disorders, substance abuse, or any neurological disorders. On the other hand, depressive symptoms were tested via the Hamilton Depression Rating Scale (HDRS) both in the conversion disorder patient group and healthy control group. Participants of both groups were submitted the written consent form. Furthermore, ethics approval was obtained from the Fırat University Faculty of Medicine Ethics Committee before the initiation of the present study.

MRI Procedure

MRI scanner, with a 1.5-T General Electric (GE; Milwaukee, USA) was used to obtain all imagings. In the previous MRI studies conducted by our research team, MRI scans were obtained via the sagittally acquired 3D spiral fast spin-echo high-resolution images. The adjusted parameters were repetition time [TR]=2000 ms, echo time [TE]=15.6 ms, field of view [FOV]=240 mm, bandwidth=20.8, flip angle=20^0, echo spacing=15.6 ms, slice thickness=2.4 mm, 8 echoes, resolution=0.9375×0.9375×2.4 mm, matrix size=240. NAA, CHO, and CRE levels were determined during the [1]HMRS investigation. For all voxels, the peak levels of NAA, CHO, and CRE have been identified automatically. Three 18×18 arrays of metabolite signals were produced through the integration of the signal strength around NAA, CHO, and CRE signal positions. NAA/CHO, NAA/CRE, CHO/CRE values were estimated. Examples of the magnetic resonance spectrum were provided in Figure 1a-1b.

Statistical Analysis

Statistical evaluations were conducted via SPSS 13.0 (SPSS Inc., Chicago, IL) and the significance level was accepted as $P<0.05$. Metabolite ratio comparisons between patient and control groups were evaluated through an independent sample *t-test*. Chi-square analysis was used for categorical data, demographic dichotomous variables, and independent sample *t*-test was used for the demographic continuous variables. Pearson's correlation test was used to examine the relationships between metabolite ratios and several variables.

RESULTS

Primarily, there existed no statistically significant difference between the patient and control groups for demographic variables, such as gender, age, level of education, and handedness ($P>0.05$). HDRS scores were significantly different for the patient and control groups, where the conversion disorder patient group mean score was 13.67±5.83 and the mean score for the healthy controls was 6.44±2.72 ($P<0.001$).

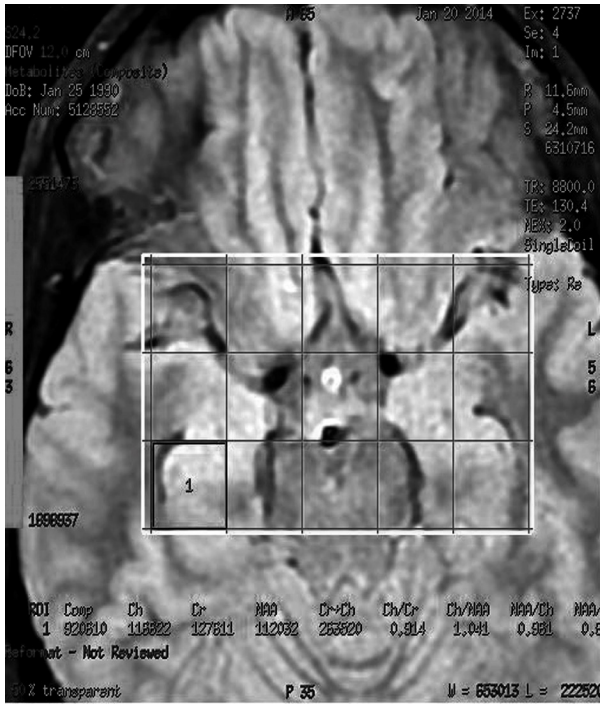

Figure 1a. Sample magnetic resonance spectrum.

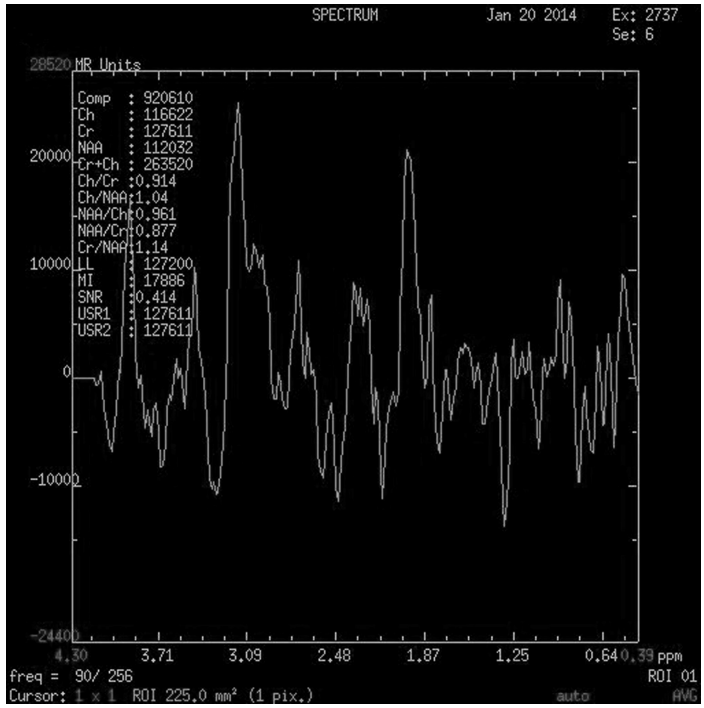

Figure 1b. Sample magnetic resonance spectrum.

Table 1. Some clinical, demographic and [1]HMRS characteristics of conversion disordered patients

	Patients	Controls
	(n=20)	(n=20)
Age	33.15±2.26	32.09±3.66
Gender (F/M)	20/0	20/0
Handedness (right)	20	20
Length of illness (years)	5.25±2.11	-
HDRS score	13.67±5.83	6.44±2.72*
NAA/CRE	1.15±0.50	1.25±0.61
NAA/CHO	2.63±0.55	3.30±1.02**
CHO/CRE	0.43±0.39	0.38±0.48

No significant differences exist between groups in age, handedness, education, and gender composition.
HDRS, Hamilton Depression Rating Scale; NAA, N-acetyl aspartate; CHO, choline; CRE, creatine.
*$p<0.001$
**$p<0.05$

Table 1 presents the findings on the hippocampus [1]HMRS for conversion disorder patients and healthy controls. Age-controlled General Linear Model analysis was performed, and it was determined that the conversion disorder patients exhibited a significantly lower ratio of NAA/CHO, when compared to healthy controls subjects, with a mean ratio of 2.63±0.55 for the patient group and 3.30±1.02 for the controls ($P<0.05$). However, conversion disorder patients exhibited similar ratios for CHO/CRE or NAA/CRE**,** where CHO/CRE mean ratios for conversion disorder patients and healthy controls were 0.43±0.39 and 0.38±0.48, respectively ($P>0.05$) and NAA/CRE mean ratios for patient and control groups were 1.15±0.50 and 1.25±0.61, respectively ($P>0.05$) when compared to the healthy subjects. There existed no significant correlation between NAA/CRE, NAA/CHO, or CHO/CRE ratios and age, duration of illness, or the HDRS scores for the patient and control groups ($P>0.05$).

DISCUSSION

The present study is the first study that examined the neurochemistry of the hippocampus in conversion disorder patients. Age-controlled General Linear Model analysis indicated that patient and control groups had similar mean ratios for CHO/CRE, 0.43±0.39 and 0.38±0.48, respectively ($P>0.05$) and for NAA/CRE, 1.15±0.50 and 1.25±0.61, respectively ($P>0.05$), whereas the conversion disorder patients had a significantly lower ratio of NAA/CHO, with a mean ratio of 2.63±0.55 for patient and 3.30±1.02 for the control group ($P<0.05$). First, it is essential to state that the present study was not intended for comparison with prior studies, which focused on patients with conversion disorder since no studies dealt with the neurochemistry of the hippocampal region of the conversion disorder patients. However, it is still possible to indirectly discuss the findings of the present study, in which we investigated the pituitary gland volumes in conversion disorder patients and established that pituitary gland volumes of patients were significantly smaller when compared to the healthy controls. It was also determined that there existed a statistically significant negative correlation between the illness duration and pituitary gland volumes of the conversion disorder patients; yet, such correlation was not evident for healthy controls. Considering that there was a close relationship between cortisol hypersecretion, the occurrence of somatoform symptoms, and anxiety, the findings of the present study on pituitary glands of conversion disorder and other somatoform disorder patients indicated a particular significance (10, 11). It is well-established that the hippocampus is closely related to the region that develops anxiety. Our research team measured NAA, CHO, and CRE levels in patients' hippocampus, for determining somatization disorder, which is a form of a somatoform syndrome (6). In our previous study, we determined that the mean NAA/CRE levels in the hippocampus were lower somatization disorder patients when compared to the controls and these levels did not affect the hemisphere. Contrastingly, NAA/CHO ratio in patients with somatization was not significantly different, when compared to the controls. Furthermore, a near-significant difference between groups in CHO/CRE ratio was established and this finding indicated lower hippocampus NAA/CRE ratios and unchanged NAA/CHO or CHO/CRE ratios in female somatization patients when compared to healthy controls. Given the scope above, the present finding of our study, which indicates that conversion disorder patients had significantly lower NAA/CHO ratio when compared to that of healthy controls, is significant, since lower NAA could be associated with anxiety and indirectly with somatoform symptoms including the conversion disorder. On the other hand, it is essential to keep in mind that NAA is a neuronal viability marker. Reduction in neuronal viability could be related to anxiety and indirectly to somatoform symptoms.

There are several limitations to the present study that need to be addressed. The first limitation is the limited number of samples that might prevent the generalization of the findings for all conversion disorder patients. However, it is essential to acknowledge the fact that it is a challenging task to find conversion disorder patients that fit strictly defined criteria. The second limitation is the lack of causal interpretation of the reduced NAA/CHO ratios in conversion disorder patients or the consequences of the disease or reflected on several life events, due to the nature of the cross-sectional study design. Third, the present study solely focused on female patients with conversion disorder, hence, the results could not be generalized to all conversion disorder patients. Therefore, it is essential to conduct further studies with a similar research design with male patients. On the other hand, the present study provided that there existed no other comorbidities apart from depression, and such finding is a strength of the study.

As a result, the present study suggested that conversion disorder female patients might exhibit reduced NAA/CHO ratio that implicates reduced neuronal viability and might be related to anxiety and indirectly to somatoform symptoms. We believe that the results of this research may contribute to a better understanding of the mechanisms underlying the psychopathology of conversion disorder and the development of more specific treatment methods. Further research is essential for the confirmation of the findings of the present study and for ascertaining whether the alterations observed in conversion disorder female patients could be improved due to treatment or over time.

Ethics Committee Approval: Ethics approval was obtained from the Fırat University Faculty of Medicine Ethics Committee before the initiation of the present study.

Informed Consent: Participants of both groups were submitted the written consent form.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- OM, MA; Design- OM; Supervision- MA; Resource- SB; Materials- HY; Data Collection and/or Processing- HY, MA; Analysis and/or Interpretation- SB, HY; Literature Search- OM; Writing- OM; Critical Reviews- SB, MA.

Conflict of Interest: There is no conflict of interest in this study.

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