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Comparison of Right Thalamus and Temporal Cortex Metabolite Levels of Drug-Naive First-Episode Psychotic and Chronic Schizophrenia in Patients

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SUMMARY

Objective: The aim of this study was to use Magnetic Resonance Spectroscopy (MRS) to investigate whether patients with chronic schizophrenia have different brain metabolite levels in the temporal cortex and thalamus than drug-naïve first-episode patients.

Method: We compared right-handed male first-episode patients (n=13) and chronic schizophrenic cases (n=15) with gender- and handedness-matched controls (n=10). Right temporal and right thalamic N-Acetylaspartate (NAA)/ Creatine (Cre), NAA/Choline (Cho), and Cho/Cre ratios were obtained with MRS.

Results: Right temporal NAA/Cre, NAA/Cho, and right thalamus NAA/Cre ratios were significantly lower both in the chronic and first-episode patient groups when compared to normal controls (p<. 001), suggesting decreased neuronal integrity in both patient groups. There were no significant correlations between symptom severity and functional status with MRS variables (p=.027). These results suggested that both patient groups had neural integrity problems. Duration of illness (days) in the first-episode patients was significantly correlated with right temporal NAA/Cre and NAA/Cho.

Conclusions: These results suggested that first-episode and chronic patients had significantly impaired neural integrity, particularly in the temporal cortex. It seems that in the acute phase of the first-episode, neural integrity impairment increased along with days elapsed without treatment.

Key Words: Schizophrenia, Magnetic Resonance Spectroscopy, Temporal Lobe, Thalamus, First-Episode

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INTRODUCTION

Magnetic Resonance Spectroscopy (MRS) has been used extensively in psychiatric studies due to the fact that it does not contain ionized radiation, its use is not known to have any side-effects (Guze, 1991), it provides both in vivo quantitative biochemical data and high spatial resolution, and it also helps to provide a better understanding of the relationship between brain metabolism and structure (Vance et al., 2000). There are two methods by which MRS can be employed: one, which uses ^{31}P and the other, which uses ^{1}H. Both of these methods are used to study neuropsychiatric disorders, such as scizophrenia, dementia, and epilepsy.

^{1}H MRS studies performed on schizophrenic patients have revealed that there are metabolic differences between various parts of the brain, such as the nucleus caudatus (Bustillo et al., 2002), frontal cortex (Hagino et al.; Kegeles et al., 2000), thalamus (Ende et al., 2001; Auer et al., 2001; Omori et al., 2000), anterior singulat cortex (Theberge et al., 2003; Yamasue et al., 2002), the medial temporal lobe structures (Maier et al., 2000; Kegeles et al., 2000), and the cerebellum (Deicken et al., 2001). These studies showed that N-acetylaspartate (NAA) and cholin levels are low in these areas of the brain because of compromised neuronal integrity and failure to convert the lipid membrane (Sigmundsson et al. 2003, Delamillieure et al. 2002, Wood et al. 2003). In some other studies, however, no difference was found between schizo-

prenic patients and control groups (Sigmundsson et al., 2003; Delamillieure et al., 2002; Wood et al., 2003). The relationship between brain metabolites and certain cognitive functions, such as working memory, verbal memory, and procedural learning tasks, has been extensively investigated and these results have led to the belief that there is an association between observed MRS changes and cognitive function.

Using MRS, groups of individuals with different types of schizophrenia, such as chronic schizophrenics (Theberge et al., 2003), those with no previous exposure to medication (drug-naive) (Bustillo et al., 2002; Gimenez et al., 2003), and childhood-onset schizophrenics (O'Neill et al., 2004), as well as individuals with an ultra high-risk for developing the disease, have all been analyzed. Studies have been performed to determine the association between age and duration of the disease and corresponding NAA levels, and it was found that as both age and duration of the disease increased, NAA levels were found to decrease (Ende et al., 2000,; Bustillo et al., 2002). However, in some studies, no relationship was found between these variables (Delamillieure et al., 2002), and so the presence of such an association remains uncertain. It is of great importance to better understand this relationship, because it could help to provide valuable information about whether or not NAA levels decrease as the period since the onset of the disease increases.

The aim of the present study was to compare the metabolite levels in both the right temporal cortex and thalamus of two groups of schizophrenics using MRS: the first group being drug-naïve first-episode psychotic cases and the other group being chronic schizophrenics that demonstrated an acute recurrence of the disease. In such studies, chronic cases are stable, but acute cases exhibit obvious symptoms, and so these results may not be related to the duration of the disease, but rather to the presence of symptoms in acute cases. Therefore, to control for the presence of obvious psychotic symptoms during this study, only subjects who had recently experienced their first psychotic episode and subjects who were chronic schizophrenics with acute recurrence of the disease were included.

MATERIALS and METHODS

Sampling

The sample population was composed of 13 first-episode psychotic patients (average age ± standard deviation: 21.9 ± 2.5 years) and 15 individuals with chronic schizophrenia (average age ± standard deviation: 40.1 ± 11.2 years). All of the patients were right-handed males. Furthermore, all study subjects were chosen from among psychiatric inpatients according to specific criteria. All first-episode psychotic patients were recently diagnosed as having had their first attack and none of them had received any previous medications to treat their disease. These first-episode psychotic patients were not diagnosed with schizophrenia, according to DSM-IV criteria, and none of them had any symptoms of a mood disorder, but all were diagnosed as having schizophreniform disorder. The control group was composed of right-handed males who didn't have schizophrenia and who volunteered to take part in the study (n=10; average age ± standard deviation; 30.9 ± 7.2 years). The age was found to be significantly different between the three groups; the chronic schizophrenia group was significantly older than the other two groups ($F=17.4$; df: 2.8; $p<0.001$). Also, none of the subjects used in this study had a history of psychotic disorders in their families.

The criteria used to select subjects for this study were: 1. Diagnosed as having either schizophrenia or schizophreniform disorder (first-episode psychotic patients) according to SCID-I and DSM-IV criteria (First et al.,1997); 2. First-episode psychotic patients could not have been previously exposed to medication; 3. Chronic schizophrenic patients had to have had the disease for more than 2 years. Exclusion criteria were: 1.Having another diagnosed axis-1 disease according to SCID-1 criteria; 2. A history of head trauma, which might have resulted in unconsciousness or a neurological disorder; 3. A history of drug abuse, except nicotine use. These same criteria were used when selecting the control group.

The average disorder duration (from the time of being admitted for care until the MRS procedure) for first-episode cases was 15.7 days (range: 10-25 days; sd: 4.9 days). For chronic cases, the average disorder duration was the time from when they were first diagnosed with schizophrenia to the time they were analyzed by MRS for this study. The average disorder duration for chronic schizophrenics was 196.8 months (range: 36-362 months; sd: 122.7 months). It was thought that the average disorder duration found for first-episode psychotic

Table 1. Right temporal and thalamic N-Acetylaspartate (NAA)/Creatinine (Cre), NAA/Choline (Cho) and Cho/Cre levels, and F and p values, and MANOVA (age used as a covariant).

Metabolite	First Episode (n=13)	Chronic (n=15)	Control (n=10)	F
Right temporal				
NAA/Cre	1.32±.28	1.48±.27	2.13±.88	7.94[a]
NAA/Cho	1.12±.19	1.46±.22	1.70±.38	10.91[a]
Cho/Cre	.90±.11	.89±.19	.98±.26	.831
Right thalamus				
NAA/Cre	1.69±.18	1.85±.24	1.93±.27	6.56[a]
NAA/Cho	1.55±.29	1.65±.26	1.75±.23	1.52
Cho/Cre	1.12±.24	1.13±.20	1.1±.11	.613

[a]$p<.01$

cases was very reliable due to the fact that all of these subjects experienced their first episode during military service, and were then promptly referred to our hospital with their medical evaluations from the military.

Scales of the Clinical Evaluation

Negative and positive symptoms were evaluated with the Scale for Assessment of Negative Symptoms (SANS) and the Scale for Assessment of Positive Symptoms (SAPS), and the severity of general symptoms was measured using the Brief Psychiatric Rating Scale (BPRS). The severity of the disease was evaluated using Clinical Global Impressions (CGI).

The Scale for Assessment of Negative Symptoms (SANS): This scale was developed by Andreasen (1983) and validated for the Turkish population by Erkoç et al. (1991a), who also performed the validity and reliability study for use of this scale with the Turkish population. This test is comprised of five subscales: affective blunting; alogia; avolition/apathy; anhedonia-asociality; disturbance of attention.

The Scale for the Assessment of Positive Symptoms (SAPS): Developed by Andreason (1984), this scale was validated for the Turkish population by Erkoç et al. (1991b), the latter again also performing the validity and reliability studies for use of this scale in Turkey. This test is composed of five subscales: delusions; hallucinations; bizarre behavior; conceptual disorganization; inappropriate affect.

The Brief Psychiatric Rating Scale (BPRS): This scale was developed by Overall and Gorham in 1963 for evaluating the severity of the psychotic characteristics of schizophrenia and other psychotic disorders, and it is also used to detect changes during antipsychotic treatment. The total score provides information about the severity of the psychotic disorder. It is composed of five subscales: unusual thought content; emotional withdrawal; anxiety-depression; aggression; agitation. Soykan (1989) performed both the validity and reliability studies of this scale for use with the Turkish population.

The Clinical Global Impressions (CGI): The CGI is a scale that can evaluate either the severity of a given disease or to evaluate attenuation of the symptoms for a given disease. The clinician, using both his experience with and knowledge of the disease, scores the severity of, or reduction in the symptoms of the disease according to the following scale: 1-normal, not ill; 2-very mild; 3- mild; 4- moderate; 5- moderately severe; 6- severe; 7-extremely severe illness (Guy, 1976).

Procedure

Every subject admitted to the Haydarpaşa GATA Hospital fit the criteria for inclusion in this study, and all were clinically evaluated (HK, CB). DSM-IV diagnosis was performed by four clinicians (MÇ, ŰBS, SE, ŐO), and in every case there was complete diagnostic agreement. To allow participation in the study, consent was granted by first-degree relatives of the subjects in the

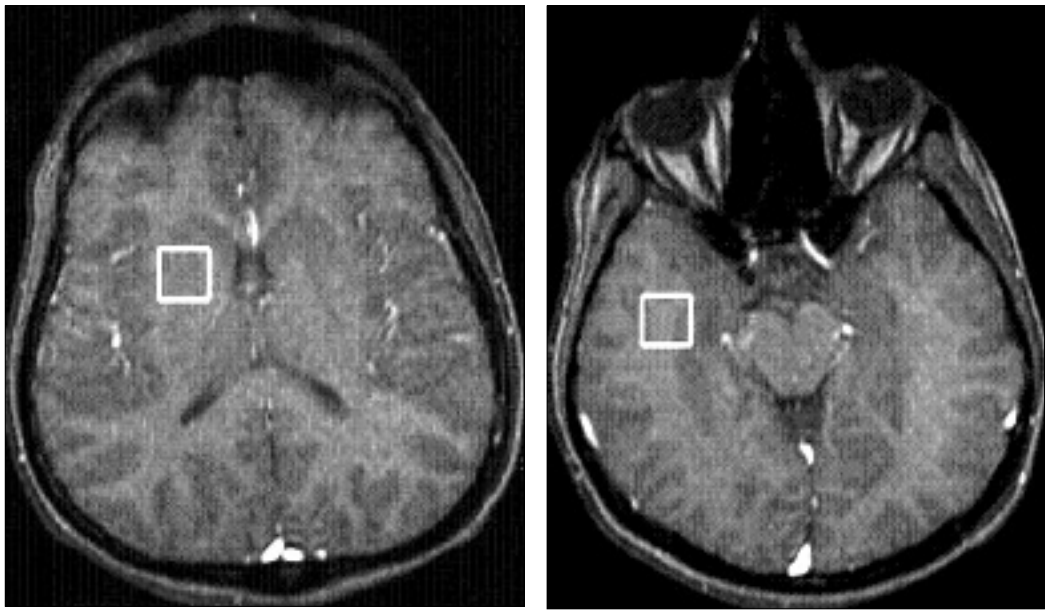

Figure 1. The thalamic (above) and temporal (below) areas of interest in the MRS procedure.

case group and by the volunteering subjects themselves for those in the control group. After the semi-structured interview forms and scales were completed, evaluations using MRS were carried out.

Image Acquisition

Single volume proton MRS images were obtained with a 1.5-T Magnetron Vision system (Siemens, Erlangen, Germany). The ^{1}H-MRS protocol used one standard head-coil with PRESS sequence (TR/TE=1600/135 ms, 256 acquisition). Suppression of the water signal was performed automatically with single proton MRS software. One voxel sagittal, which was 2x2x2 centimeter^{3}, was chosen from the coronal and transverse sections. Voxel of interests (VOI) were directed toward the right thalamus and the right temporal cortex, and were situated at least 15mm away from the subject's skull in order to minimize contamination due to fat (oil). VOI were placed between the ascendant ramus and the lateral sulcus in the temporal cortex and into the center of the thalamus. Baseline and face corrections, and the Fourier transformation procedure were all manually performed, and metabolite peaks were calculated from the spectrum. The evaluation of the MRS images was performed by evaluators who were blind to the subject groups. The imaging procedure lasted, on average,120 minutes per subject. One subject, from the first-episode psychotic patient group, was unable to complete the procedure and was therefore excluded from the study.

Data Analysis

For determining the NAA/Cr, NAA/Cho, and Cho/Cr differences between the groups, a multivariate analysis of variance (MANOVA), with age as the covariant, was used. Significant differences between the three groups were further evaluated using Analysis of Variance (ANOVA) and post-hoc Turkish HSD test. The association between age, duration of the disease, and clinical variables was analyzed using the Pearson correlation coefficient. The scores for both case groups on the SANS, SAPS, BPRS, and CGI scales were compared with the results of a t-test on both groups. The two tail $p<0.05$ values were found to be significant. SPSS 10.0 (SPSS Inc.) statistical software was used for the analysis.

RESULTS

Comparison of the Scales used in the Clinical Evaluation

The scale scores for the chronic group and first-episode psychotic group, respectively, were as follows: BPRS (27.5±7.2; 27.7±4.7), SANS (27.8±21.3; 29.5±17.5), SAPS (47.2±23.9; 49.8±27.5), and CGI (4.6±1.88; 4.8±1.54). No significant difference was found between the two groups on any of the scales ($t=0.1$-1.1; $p>0.05$).

Comparison of MRS Variables

In Table 1, the metabolite ratio for both the right temporal cortex and the right thalamus are noted (NAA/Cre, NAA/Cho, Cho/Cre). The ratio of both NAA/Cre and NAA/ Cho in the right temporal cortex and the ratio of NAA/Cre in the right thalamus all showed a significant difference between the groups ($F=7.95$; $df=2.38$; $p=0.001$; $F=10.91$; $df=2.38$; $p<0.001$; $F=6.57$; $df=2.38$; $p=0.004$). Post-hoc comparisons showed that NAA/Cre and NAA/Cho values ($p<0.001$ for both case groups) of both the chronic ($p=0.003$) and first-episode psychotic patients ($p=0.001$) were lower than the control group values. According to post-hoc analyses, NAA/Cre levels in the thalamus for the first-episode psychotic group were significantly lower ($p=0.01$) than the levels of NAA/Cre in the control group. No significant difference was found between the chronic case group and the control group in terms of NAA/Cre levels. The difference was also not found to be significant between the chronic case group and the first-episode psychotic case group.

The severity of the symptoms and their relationship to cognitive status

An association was not found between the temporal and thalamic metabolite ratios and the scores of SANS, SAPS, BPRS, and CGI ($p>0.05$).

The association between age and duration of the disease and metabolite levels

When calculated separately, a significant negative correlation was found between the duration of the disease (in days) and the ratios of NAA/Cre and NAA/Cho in the right temporal cortex among first-episode cases ($r = 0.71$; $p=0.006$ and $r = 0.64$; $p=0.020$, respectively). A negative correlation was also found between the duration of the disease (in months) and the NAA/Cre in the right thalamus among the chronic case group ($r = 0.57$; $p=0.027$). No significant association was found between age and the MRS variables ($p>0.44$).

DISCUSSION

This study compared the metabolite levels in the right temporal cortex and thalamus of drug-naïve first-episode psychotic patients, chronic schizophrenic patients who have had acute episodes, and normal controls. The major findings were that the right temporal NAA/Cre and NAA/Cho levels, in both first-episode and chronic cases, and the right thalamic NAA/Cre level in first-episode cases were lower than the levels in the control group. Also, the temporal NAA/Cre and NAA/Cho levels didn't show any negative correlation with the duration of the disease (in days) in first-episode psychotic cases. No difference in MRS variables was found between the first-episode cases and the chronic cases.

NAA is an amino acid that exhibits effects upon glutamergic N-Methyl-D-Aspartic Acid (NMDA) receptors (Moffett and Namboodiri, 1995; Rubin et al., 1995). It has been shown that decreased NAA levels are associated with decreased neuronal integrity (Maier et al., 1995; Yurgelun-Todd et al., 1996; Bertolino et al., 1996; Bertolino et al., 1998; Deicken et al., 1998; Bustillo et al., 2002; Nasrallah et al., 1994). We found the ratio of right temporal NAA/Cre to be significantly lower in both the first-episode and chronic psychotic cases. These findings are not concordant with other studies that have reported that NAA levels did not change in first-episode cases (Bartha et al., 1999; Bustillo et al., 2002; Wood et al., 2003). On the other hand, there are some studies that have reported that first-episode cases do have lower NAA/Cre levels than those found in either controls or chronic cases (Fannon et al., 2003; Cecil et al., 1999). These latter two studies, especially Fannon et al. (2003), led us to think that antipsychotic therapy might have a protective effect on neuronal integrity in chronic cases.

Our results lead us to think that neuronal integrity isn't altered greatly after the first psychotic episode. This result did not depend on the presence of acute psychotic symptoms, since chronic cases were also admitted with acute episodes. No difference was found in the severity of positive, negative, and general symptoms between chronic and first-episode cases. This fact helped us to control the effect of the acute psychotic symptoms.

According to the neurodevelopmental model first suggested by Jackson, the evolution of the brain has resulted in a tendency for cognitive disorders to be more present in phylogenetically younger and more complex areas of the brain, such as the frontal cortex (Heinz et al., 2003). Cognitive loss in complex areas of the brain results in the negative symptoms of schizophrenia, while cognitive loss in less complex areas of the brain leads to the positive symptoms of schizophrenia, with these

symptoms appearing due to dysinhibition in these areas of the brain. Currently, the neurodevelopmental hypothesis asserts that cognitive disorder of the temporo-limbic frontal network, which appears early in life, results in the negative symptoms of schizophrenia. And, related with it, dysinhibition in the subcortical network causes the release of dopamine in the striatum, and this release results in the positive symptoms of schizophrenia (Heinz et al., 2003). Our results, which are in concordance with this hypothesis, showed that there was no difference in neuronal integrity between first-episode cases and chronic cases. This is in conflict with the widely held belief that schizophrenia is a degenerative and progressive disease.

We found that the thalamic NAA/Cre levels were significantly lower in the first-episode cases than in the controls. This is not consistent with all studies in the literature; while some studies have reported lower NAA or NAA/Cre in the thalamus (Ende et al., 2001; Auer et al., 2001; Omori et al., 2000), others have reported different findings (Bertolino et al., 1996, 1998). Many studies, using different methods of analysis, have shown that the thalamus plays a key role in the pathophysiology of schizophrenia. The differences between these studies may due to the characteristics of the subjects and the imaging methods used in a particular study.

An association was not found between the severity of the disease and the temporal and thalamic MRS variables. This result is in concordance with other studies (Fukuzako et al., 1999a; Fukuzako et al., 1999b; Bartha et al. 1999; Fukuzako et al., 1995). On the other hand, it has been reported that there is a positive correlation between phophodiester levels and the severity of positive symptoms found on the BPRS (Fukuzako et al., 1996). For this reason, there is a greater need for further study of the relationship between NAA, Cho, and Cre levels, and the severity of symptoms.

In this study, as in some others, absolute numbers for NAA, Cre, and Cho were not used; instead we analyzed the ratios of these metabolites. This is why it was not possible for us to directly analyze the levels of these metabolites. While the ratio of Cho/Cre wasn't different between the groups, the ratios of NAA/Cre and NAA/Cho were significantly different, which led us to think that the reported changes must be dependent upon varying NAA levels.

Briefly, the most important finding of this study was that the ratio of temporal NAA was lower in both the first-episode and chronic psychotic cases than in the control group, leading us to consider that neuronal integrity is only disrupted in the early period of the disease and there is no progression of this damage during the chronic period of the disease. The other important finding was that the period without medication in first-episode cases was associated with decreased NAA levels. The fundamental limitation of this study was that we were not able to use volumetric or segmentation methods. These measurements might have allowed us to find changes in the levels of NAA, Cho, and Cre (Vance et al. 2000). Additionally, another important limitation was that the described area in the temporal cortex was too large. The third limitation was the size of the sample population. The possibility of both type 1 and type 2 errors should be considered. Another important point is related to the diagnosis of first-episode psychotic cases. While the chronic cases had already been diagnosed as schizophrenic, no mood disorder symptoms were present in the first-episode disorder cases; therefore, these patients can't be definitively diagnosed as schizophrenic, due to the time-limitation of the DSM-IV diagnosis scale. This might affect the reliability of the comparisons.

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