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Medial Prefrontal Cortex Neurochemical Metabolites in Schizophrenia and Schizoaffective Disorder: A Proton Magnetic Resonance Spectroscopy Study

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ÖZET:

Şizofreni ve şizoaffektif bozuklukta medial prefrontal korteks nörokimyasal metabolitler: Bir proton MRS çalışması

Amaç: Bu çalışmada, şizofreni ve şizoaffektif bozuklukta medial prefrontal korteks nörokimyasal metabolit düzeylerinin araştırılması amaçlanmıştır.
Yöntem: Çalışmaya 15 şizofreni (SCH), 15 şizoaffektif bozukluğu (SAD) olan hasta ve 15 sağlıklı kontrol katıldı. Medial prefrontal korteks (mPFC) N-asetil aspartat (NAA), kreatin içeren bileşikler (Cr), kolin içeren bileşikler (Cho) ve myo-inozitol (myo-I) düzeyleri proton manyetik rezonans spektroskopi (1H-MRS) ile araştırıldı.
Bulgular: Gruplar arasında NAA, Cr, Cho ve myo-I düzeylerinde farklılık olduğu tespit edildi. Şizofreni hastalarında sağ ve sol mPFC NAA düzeyleri, sol mPFC Cho düzeyi kontrol grubuna göre düşük bulundu. Şizoaffektif bozukluğu olan hastalarda sağ ve sol mPFC NAA, Cho, Cr ve myo-I düzeyleri kontrol grubuna göre düşük bulundu. Şizofreni ve şizoaffektif bozukluk arasında mPFC nörokimyasal metabolit düzeylerinde farklılık saptanmadı.
Sonuç: Bu çalışmada şizofreni ve şizoaffektif bozuklukta NAA ve Cho düzeylerinin azaldığını, dolayısıyla bu iki hastalıkta medial prefrontal bölgede nöronal canlılık ve bütünlüğün bozulduğunu, membran fosfolipid metabolizmasında düzensizlikler olduğu bulundu. Şizoaffektif bozuklukta Cr ve myo-I düzeylerinde de azalma olması bu bozuklukta medial prefrontal bölgede enerji metabolizmasında ve glial hücrelerde anormallikler olduğuna işaret etmektedir.

Anahtar sözcükler: şizofreni, şizoaffektif bozukluk, magnetik resonans spektroskopi, medial prefrontal korteks

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ABSTRACT:

Medial prefrontal cortex neurochemical metabolites in schizophrenia and schizoaffective disorder: a proton magnetic resonance spectroscopy study

Objectives: The aim of this study was to investigate medial prefrontal cortex neurochemical metabolite levels in patients with schizophrenia and schizoaffective disorder.
Method: The subjects comprised 15 patients with schizophrenia (SCH), 15 patients with schizoaffective disorder (SAD), and 15 healthy controls. Levels of N-acetyl aspartate (NAA), choline-containing compounds (Cho), creatine-containing compounds (Cr), and myo-inositol (myo-I) were measured in the medial prefrontal cortex (mPFC) using 1H-MRS.
Results: Differences were detected in NAA, Cho, Cr, and myo-I levels among the groups. In schizophrenic patients, the left and right mPFC NAA levels and left mPFC Cho level were found to be lower, compared to the control group. In patients with schizoaffective disorder, left and right mPFC NAA, Cho, Cr, and myo-I levels were found to be lower compared to the control group. No difference was detected in mPFC neurochemical metabolite levels between schizophrenia and schizoaffective disorder patients.
Conclusion: In this stud were found that in schizophrenia and schizoaffective disorder, NAA and Cho levels are reduced. Consequently, in these two diseases, neuronal activity and neuronal integrity are impaired in the medial prefrontal region, and there are defects in membrane phospholipid metabolism. In addition, the decreases in Cr and myo-I levels in schizoaffective disorder patients point to abnormalities in energy metabolism and glial cells in the medial prefrontal region.

Key words: Schizophrenia, schizoaffective disorder, magnetic resonance spectroscopy, medial prefrontal cortex

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INTRODUCTION

Schizophrenia and schizoaffective disorder are two separate diseases within the group of psychotic disorders as defined in the Diagnostic and Statistical Manual of Mental Disorders-IV. Schizoaffective disorder is diagnosed when symptoms of both schizophrenia (delusions, hallucinations, bizarre behavior, and negative symptoms) and mood disorders (depressive or manic attacks) are combined. Mood symptoms should be present during a significant portion of the total duration of the illness, and psychotic symptoms must be present during periods without mood symptoms. Schizoaffective disorder differs from schizophrenia in terms of the presence of distinct mood episodes (1). It has been concluded that schizoaffective disorder runs a different course than schizophrenia and mood disorders in terms of both the presence of psychotic symptoms and the results of the illness, and schizoaffective disorder has therefore been defined as a separate illness (2). The prognosis of patients with schizoaffective disorder is accepted to be characterized by better social and professional functionality compared to those with schizophrenia (3).

Proton magnetic resonance spectroscopy (1H-MRS) is an imaging technique that can noninvasively measure the biochemical structures and the metabolites of tissues and present the two in one spectrum. In the evaluated region, the levels of neurochemical compounds containing N-acetyl aspartate (NAA), creatine (Cre), or choline (Cho) and compounds such as myo-inositol (Myo-I) can be determined in vivo. NAA is a compound found in adult neurons and is recognized as a marker for neuronal integrity, viability, and/or function. For the synthesis of one mole of NAA, 40 moles of glucose or its equivalent must be oxidized in the brain. Therefore, a reduction of NAA in the frontal region indicates insufficient glucose consumption, namely hypofrontality. A Cho peak originates from a compound consisting of both phosphorylcholine and glycerophosphorylcholine. A Cho peak provides information about myelination, cell density, proliferation, and functions within the membrane. Total creatine, which comprises creatine and phosphocreatine, is a marker for energy metabolism. The creatine peak is used as a reference value because it remains consistent throughout 1H-MRS, which is based on the assumption that Cr resonance is constant and is not affected by various pathologies. The function of myo-inositol (myo-I) is not completely known; however, it is found only in glial cells. The level of myo-I increases in conditions such as Alzheimer's disease, diabetes mellitus, as well as head and neck tumors and decreases in conditions such as infarction, hypoxia and during lithium treatment (4,5).

In schizophrenia, changes in neurochemical metabolite levels in different brain regions have been identified. The following results have been reported regarding schizophrenia: NAA/Cr and Cho/Cr levels were decreased in the thalamus, and the levels of neurochemical metabolites were similar to those of controls in the frontal lobe (6); NAA/Cho levels in the frontal lobe were lower compared to those of controls and unaffected family members (7); NAA/Cr levels were decreased in the anterior cingulate cortex, whereas Cho/Cr levels were increased (8); glutamine and glutamate levels were decreased in the anterior cingulate cortex (9); and NAA levels were decreased in the anterior cingulate cortex, whereas glutamate+glutamine levels were not changed (10). It has been found that NAA, Cho, and Cr levels were decreased in the thalamus of individuals with high genetic loading for schizophrenia. It has also been claimed that neuronal dysfunction, especially in the thalamus, leads to a predisposition for the development of schizophrenia (11). In a study by our group, dorsolateral prefrontal cortex neurochemical metabolite levels in schizoaffective disorder were compared to those in schizophrenia and bipolar disorder. In that study, it was established that although NAA levels decrease in all three diseases, Cho and Cr levels decrease in schizoaffective disorder and bipolar disorder (12).

The frontal cortex is composed of structurally and functionally different sections. The medial prefrontal cortex (mPFC) receives mostly dopaminergic and serotonergic extensions, mainly

from the thalamus, hypothalamus, amygdala, hippocampus, and limbic and medial temporal cortex. The medial prefrontal cortex is responsible for emotionally and instinctively organized aspects of behavior (13,14). When this region is damaged, impairments emerge in social behaviors that involve planning, judgment, and decision making. Inadequacy in impulse control, euphoria, increased energy, aggression, and a propensity for violence have also been observed (15-17). In schizophrenic patients who are hospitalized during the acute psychotic relapse phase, functional abnormalities in the medial PFC have been reported, and these abnormalities are corrected by antipsychotic treatment (18). Ventromedial prefrontal cortex NAA/Cr levels were lower in patients with a deficit syndrome than in control groups and patients with schizophrenia who did not have apparent deficits. No difference was detected in Myo-I/Cr and Cho/Cr ratios (19). Medial prefrontal cortex glutamine levels have been reported to be higher than those of controls (20).

Data obtained from previous studies suggest that there might be abnormalities in medial prefrontal cortex neurochemical metabolite levels in patients with schizophrenia. Schizoaffective disorder is a disease which has both psychotic and affective features. The pathology of schizoaffective disorder would contribute to understanding the effects of psychotic and affective processes on neuronal functions. This study has evaluated the medial prefrontal cortex neurochemical metabolite levels in patients with schizophrenia and schizoaffective disorder.

MATERIAL AND METHODS

Study Design

Fifteen healthy controls, 15 patients diagnosed with schizophrenia (SCH), and 15 patients with schizoaffective disorder (SAD), according to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) diagnostic criteria, were included in the study. The patients had been followed by the Psychosis clinic in the Department of Psychiatry at the Pamukkale University School of Medicine. For inclusion in the study, the individuals were required to be between the ages of 18 and 60 with no psychotic episodes in the last 3 months. Exclusion criteria were mental retardation, congenital malformation of the brain, alcohol or substance abuse before the study that could affect the symptom distribution, electroconvulsive therapy in the previous six months, and neurological and organic mental disorders. The control group was composed of healthy individuals whose age and gender were similar to those of the patient groups and who had no physical or mental disorders. Approval was obtained from the local ethics committee of Pamukkale University in accordance with the Declaration of Helsinki. The patients were informed about the study, and only those who gave written consent were included.

Psychiatric diagnoses were made using Structured Clinical Interviews (SCID- I) for the DSM-IV (21,22). To determine the presence of psychotic symptoms, the Positive and Negative Syndrome Scale (PANSS) (23-25) and the Brief Psychiatric Rating Scale (BPRS) (26) were used to assess the SCH and SAD patients. A bilateral proton magnetic resonance spectroscopy (1H-MRS) of the medial prefrontal region was conducted for the patient and control groups.

A Proton Magnetic Resonance Spectroscopy (^{1}H-MRS)

A proton magnetic resonance spectroscopy (^{1}H-MRS) scan was conducted using a standard head coil and a 1.5 Tesla magnetic resonance scanner (GE Medical Systems, Milwaukee, WI, USA). The magnetic resonance spectroscopy protocol was conducted over the coronal plane with a T2-weighted fast spin-echo (FSE) sequence, with a 10-mm thickness, and using the following parameters: time of repetition (TR)/time of echo (TE), 3000/85; field of view (FOV), 14; matrix, 352x352; and Next, 1. MR spectroscopy was measured using a single-voxel (^{1}H-voxel) 1H-MRS technique and was directed at each medial frontal cortex region. The volume being analyzed (volume of interest, VOI) was manually

and visually determined in the relevant regions, which were primarily located in the frontal lobe, to ensure that the relevant brain tissue was covered. The volume of interest (VOI) in which neurochemical metabolites were measured was 2x2x2 cm^3. To suppress the signal originating from water, a chemical shift selective pulse (CHESS) was used. A point-resolved spectroscopy (PRESS) technique was then used, which localized the volume of the spectroscopy (TR/TE: 3000/144 and 3000/35 ms). As a result, short and medium duration TE spectra were obtained across the VOI in each of the two medial frontal cortex regions, and these data were evaluated using General Electric's spectral analysis program. The metabolite ratios were evaluated (Figure 1).

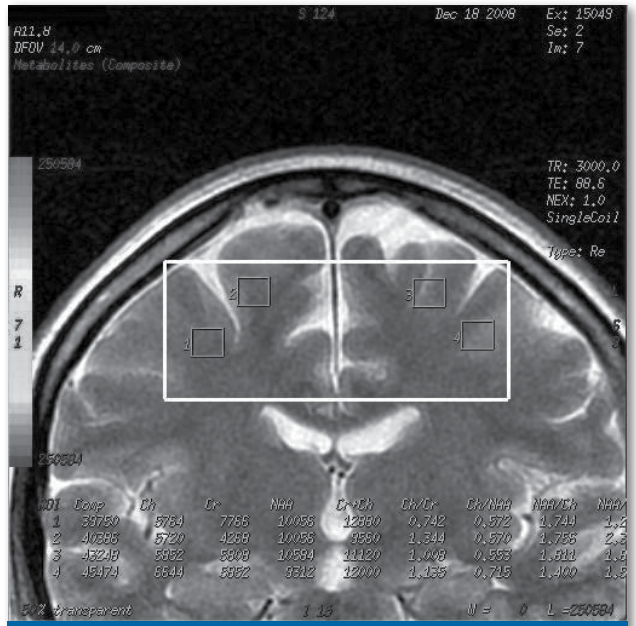

Figure 1: Application of single voxel magnetic resonance spectroscopy in the medial prefrontal region (mPFC) in a patient with schizo affective disorder. The outlined frame 2 indicates the right mPFC and corresponding neurochemical metabolite values.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) 10.0 software was used for the statistical data analysis. The variables were evaluated for normal distributions using the Kolmogorov-Smirnov goodness-of-fit test. Nonparametric statistical methods were used for variables that were not normally distributed. Kruskal-Wallis analyses of variance were used to determine whether groups displayed differences in terms of the measured variables ($p<0.05$ significant). For variables with statistically significant differences, a Mann-Whitney U-test with a Bonferroni correction was applied to determine from which group the difference resulted ($p<0.016$ significant). Finally, a Spearman correlation analysis was used to determine whether the duration of illness, age of illness onset, and the Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS) scores were correlated with the 1H-MRS values ($p<0.05$ significant).

RESULTS

Demographic and Clinical Characteristics

The sample was composed of a control group and patients with schizophrenia (SCH) and schizoaffective disorder (SAD); each group comprised 15 people between the ages of 18 and 60. There were six women and nine men in each group. The average age was 37.60±7.17 years for SCH, 40.13±9.26 years for SAD, and 38.73±8.61 for the control group, and the average ages of the groups were similar ($\chi^2=0.623$, $p=0.430$). There was no difference between groups in levels of education ($\chi^2=1.794$, $p=0.408$).

The clinical features of the diagnostic groups and psychiatric rating scale scores are presented in Table 1. There was no significant difference between the groups in terms of age of illness onset, illness duration, or positive symptoms scores on the Positive and Negative Syndrome Scale (PANSS). The negative symptoms scores on the PANSS and the Brief Psychiatric Rating Scale (BPRS) scores for the SCH group were significantly higher than those for the SAD group.

^{1}HMR Spectroscopy Findings

Differences among groups were detected for NAA, Cho, Cr, and myo-I levels. A comparison of the

Table 1: Comparison of clinical characteristics and scale scores in patients with schizophrenia versus schizoaffective disorder

Variable	SCH mean±SD (min-max)	SAD mean±SD (min-max)	z*	p
Age of illness onset	24.67±7.92 (11-42)	23.07±6.20 (15-40)	0.855	0.393
Illness duration	12.73±7.48 (3-26)	16.60±8.61 (4-34)	1.289	0.197
PANSS-negative	10.07±6.33 (0-23)	2.73±3.67 (0-10)	3.317	0.001
PANSS-positive	1.33 ±2.79 (0-8)	1.93±1.98 (0-5)	1.226	0.220
BPRS	7.00±3.44 (0-12)	2.87± 2.97 (0-8)	2.973	0.003

SCH: Schizophrenia, SAD: Schizoaffective Disorder, PANSS-negative: Positive and Negative Syndrome Scale-negative symptoms score PANSS-pozitive: Positive and Negative Syndrome Scale-positive symptoms score. BPRS: Brief Psychiatric Rating Scale, *MannWhitney U test, p≤0.05 significant

Table 2: Comparison of neurochemical metabolites in the medial prefrontal cortex in patients with schizophrenia versus schizoaffective disorder

Neurochemical values	SCH	SAD	Control	Analyses*		Analyses**
				χ^2	p	
NAA						
right	9256	6792	12048	19.389	<0.001	SAD, SCH<C
left	9412	7553	12432	17.541	<0.001	SAD, SCH<C
Cho						
right	5764	4686	6798	15.102	0.001	SAD<C
left	3588	3588	7348	17.612	<0.001	SAD, SCH<C
Cr						
right	5632	4658	6292	8.654	0.013	SAD<C
left	4664	4323	5544	11.528	0.003	SAD<C
Myo-Inositol						
right	2439	1525	2551	8.947	0.011	SAD<C
left	2182	1546	1546	9.297	0.010	SAD<C
NAA/Cho						
right	18.30	25.23	25.47	1.607	0.448	NS
left	24.29	24.27	19.07	3.333	0.189	NS

SCH: Schizophrenia, SAD: Schizoaffective Disorder, NAA: N-Asetil aspartat. Cho: Choline. Cr: Creatine,
* Kruskal Wallis test, ** Bonferroni correction Mann Whitney U test, p≤0.016 significant

medial prefrontal cortex (mPFC) neurochemical metabolite levels among the groups is shown in Table 2. In schizophrenic patients, right and left mPFC NAA levels (z=2.759 p=0.006, z=3.090 p=0.002, respectively) and left mPFC Cho levels (z=2.883 p=0.004) were found to be lower than those of the control group.

Right and left mPFC NAA levels (z= 4.252 p<0.001, z=3.795 p<0.001), right and left mPFC Cho levels (z=4.045 p<0.001, z=4.003 p<0.001), right and left mPFC Cr levels (z=2.953 p=0.003, z=3.367 p=0.001), and right and left mPFC myo-I levels (z=2.800 p=0.004, z=2.945 p=0.002) of patients with schizoaffective disorder were found to be lower than those of the control group.

No statistically significant difference was detected between the schizophrenia and schizoaffective disorder patients in mPFC neurochemical metabolite levels (for all, p>0.016). No correlations between mPFC neurochemical metabolite levels and the duration of illness, age of illness onset, PANSS scores, or BPRS scores were detected (for all, p>0.05).

DISCUSSION

Our research sample was composed of middle-aged patients who were in a remission period of

schizophrenia or schizoaffective disorder. The ages and the level of education of the groups were similar. No differences were detected between the two groups in terms of age of illness onset, duration of illness, and positive symptom severity. Negative symptom severity was found to be higher in schizophrenic patients than in patients with schizoaffective disorder. According to our results, schizophrenia and schizoaffective disorder show differences in terms of negative symptom severity.

Conflicting results have been obtained in studies that were performed on different brain regions in schizophrenia patients. For schizophrenic patients, it has been reported that frontal NAA levels were decreased and that Cho levels were higher compared to those of controls (27); NAA/Cr and NAA/Cho levels were decreased in the hippocampus and dorsolateral prefrontal cortex (28); NAA/Cr and NAA/Cho levels were decreased in the temporal cortex and thalamus (29); NAA and Cr levels were similar to those of controls but that Cho levels were higher in the caudate nucleus (30); Cr levels in the anterior cingulate cortex and parieto-occipital cortex were decreased in schizophrenic patients who were in the acute psychotic period (31); and there were no abnormalities in dorsolateral prefrontal cortex NAA levels in the early phase and chronic schizophrenic patients (32). Previous studies have shown that in schizophrenic patients, NAA levels either were decreased or did not change and that Cho and Cr levels either increased or decreased. In our study, it was determined that the mPFC NAA and Cho levels of schizophrenic patients and mPFC NAA, Cho, Cr, and myo-I levels of schizoaffective disorder patients all decreased. Our results suggest that in schizophrenia and schizoaffective disorder, neuronal integrity and activity decrease in the medial prefrontal cortex and that there are defects in membrane phospholipid metabolism. In addition, these results point to abnormalities in energy metabolism and glial functions in schizoaffective disorder. Decrease of Cr and myo-I levels may be related to the existence of an affective pattern in schizoaffective patients.

The number of studies that have investigated mPFC metabolite levels in schizophrenia and schizoaffective disorder is limited. Bartha et al. (20) reported that in schizophrenic patients there was an increase in only glutamine levels in mPFC, and there was no change in the levels of other neurochemical metabolites. Medial prefrontal cortex NAA/Cr levels in schizophrenic patients with deficit syndrome were detected to be lower than those of a healthy control group and of schizophrenia patients without deficit syndrome (19). In residual type and paranoid type schizophrenic patients, it was reported that mPFC NAA, Cho, and Cr levels did not change and that the glutamine/glutamate ratio and taurine levels were higher. In addition, glial functions have been reported to be decreased in schizophrenia (33). Previous studies have pointed to possible differences in mPFC neurochemical metabolite levels among subtypes of schizophrenia. Patients with schizophrenia who were not in a psychotic attack were included in our study; however, no evaluation was performed in terms of schizophrenia subtypes. Our results may have been affected by the fact that our study groups were formed without taking schizophrenia subtypes into consideration.

It has been reported that in patients with schizophrenia, the duration of illness and psychotic symptom severity affects neurochemical metabolite levels (34,35,29). Correlations have been found between the duration of psychotic episodes that passed without treatment and the NAA/Cho ratio and between the duration of illness and the glutamine/glutamate ratio (33). In first episode schizophrenia patients who do not use medication, neurochemical metabolite levels such as NAA, Cho, Cr, and myo-I in the frontal lobe, temporal lobe, and hippocampus were not found to be different from those of the controls (36,37). No changes in neurochemical metabolite levels have been found between first episode schizophrenic patients, which is a group that carries a high risk for schizophrenia, and healthy controls (38). However, it has been reported that especially for early onset first episode schizophrenic patients, prefrontal NAA levels are low, and this condition points to a decrease in dendrite proliferation and synaptic connections (39). We did not find a relationship between

neurochemical metabolite levels and the duration of illness, age of illness onset, or psychotic symptom severity.

Normal neurochemical levels are an indication that neuron functions are healthy. It has been reported that in the medial frontal region, there is positive correlation between blood oxygen levels and NAA/Cr levels; as oxygenation decreases, NAA levels also decrease, and NAA levels reflect neuronal dysfunction (40). In our study, our patients were not in psychotic, manic, or depressive episodes. Nevertheless, abnormalities in neurochemical metabolite levels were detected; problems were observed in neuronal functions in the medial prefrontal regions. There is a need for studies that are directed towards investigating the relationship between these neurochemical variables and social behavior and social knowledge by taking the medial prefrontal cortex functions into consideration.

It is known that in the etiopathogenesis of schizophrenia, neurodevelopmental factors or neurodegenerative processes are highly important (41). In a review paper, it was concluded that in patients with schizophrenia, NAA levels decrease especially in the medial temporal and prefrontal regions and that this condition is associated with the presence of neurodegenerative processes (42). Buckley et al. (27) reported that there was no relationship between neurochemical metabolites and neurodevelopmental indicators such as obstetric complications, a family history of schizophrenia, and minor physical abnormalities. However, the questions regarding whether changes in neurochemical metabolite levels are related to neurodegenerative processes and/or neurodevelopmental factors have to be clarified.

Steen et al. (43) reviewed 1H-MRS studies and evaluated the results of 1209 control and 1256 chronic schizophrenia patients. In that study, it was concluded that there was no consistent evidence pointing to low NAA in schizophrenia patients, including in the frontal cortex. It was claimed that most of these studies were inadequate in terms of patient numbers and that studies in this area should be performed with at least 39 patients and 39 controls to be able to reach a true conclusion. Our low sample number is a limitation of our study and may have affected our results. The fact that all patients participating in the study used psychotropic drugs, particularly atypical antipsychotic and mood-regulating drugs, is another limitation. The drugs may have caused neurochemical changes in the brain. These factors must be considered upon evaluation of our results.

In conclusion, we detected that in schizophrenia, right and left mPFC NAA and left mPFC Cho levels decrease and that in schizoaffective disorder, right and left mPFC NAA, Cr, Cho, and myo-I levels decreased. Our results show that in schizophrenia and schizoaffective disorder, there is a disruption in the medial prefrontal cortex neuronal functions. These results illustrate the need for more comprehensive studies with larger samples.

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