Decreased serum levels of glial markers and their relation with clinical parameters in patients with schizophrenia

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SUMMARY

Objective: The neurodevelopmental hypothesis of schizophrenia suggests that alterations of glial fibrillary acidic protein (GFAP) and glial cell line-derived neurotrophic factor (GDNF) functions may play a role in the pathogenesis of schizophrenia. However, there is limited information about the relationship of these molecules with the clinical features of schizophrenia. In this study, it was aimed to compare patients with schizophrenia and healthy controls in terms of serum GFAP and GDNF levels and to investigate the effects of clinical parameters on serum levels of molecules in patients with schizophrenia.

Method: 37 patients with schizophrenia followed in the psychosis unit and 37 age- and sex-matched healthy controls without a history of psychiatric disease were recruited in study. The patients evaluated through the Turkish version of positive and negative syndrome scale. On the other hand, sociodemographic question form was applied to both the patients and the healthy controls.

Results: Serum GDNF and GFAP levels of patients with schizophrenia were significantly lower than those of healthy controls. Furthermore, serum GDNF levels were negatively correlated with general and negative syndrome scales (PANSS) in these patients.

Conclusion: It has been observed that there is a relationship between PANSS and changes in the GDNF levels of schizophrenia patients. However, larger clinical studies in which these markers are also measured in cerebrospinal fluid are needed to understand the biological mechanisms underlying these associations and to understand whether glial markers could be useful as biomarkers for the diagnosis of schizophrenia.

Keywords: Schizophrenia, Neurodegeneration, GFAP, GDNF, Glial Markers, PANSS Scores

INTRODUCTION

Synaptic, metabolic and inflammatory dysregulations were documented in schizophrenia and bipolar disorder, leading to speculation that astrocyte dysfunction occurs in these disorders (1). Accordingly, in great number of investigations carried out on astrocytes in schizophrenia and bipolar disorder, glial fibrillary acidic protein (GFAP) was used as a marker (2). Astrocytes are the most prevalent cell types in human brain; and they serve for a range of functions including regulation of neuronal metabolism, modulation of central nervous system inflammation, conducting direct and indirect roles in synaptic transmission (2, 3). It was reported that regional and antigen-specific downregulation of GFAP protein in orbitofrontal cortex in schizophrenia and bipolar disorder may be related to disease mechanisms of psychosis (4). It was determined that there is increasing GFAP protein expression in prefrontal cortex of patients with psychotic illness indicating a role for this protein in the pathophysiology of psychosis (2). GFAP and glutamine synthetase in subregions of prefrontal cortex in schizophrenia and mood disorders were studied by some researchers, and an increase in GFAP immunoreactivity in area 9 in schizophrenia was detected, and the case was stated to be a conse-

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quence of chronic antipsychotic medication (4). However, decreased GFAP immunoreactivity in area 11/47 in schizophrenia and bipolar disorder was observed and it was suggested that this could not be attributed to drug treatment (4). Besides pathological findings of GFAP pathology, serum study results also differed. When compared to healthy controls, lower serum GFAP levels were determined in patients with schizophrenia, (5) while Steiner at al. could not found this (6).

It was suggested that neurotrophic factors such as nerve-growth factor and brain-derived neurotrophic factor have significant parts in pathophysiology of schizophrenia (7). On the other hand, glial cell line-derived from neurotrophic factor (GDNF) is one of the strongest trophic factors for dopaminergic neurones within the central nervous system of the mammalian (8). Functionally, GDNF is thus potentially related to the dopaminergic and neurodevelopmental hypothesis of schizophrenia. GDNF and its related genes are integrated with the pathophysiology of neurodegenerative and neuropsychiatric disorders, for example; addiction of drug, (9) Parkinson's disease, (10) Alzheimer's disease, (11) mood disorders, (9,12,13) stress vulnerability and schizophrenia (14, 15). Focusing on schizophrenia, although there are studies with no significant association with GDNF genes, it was reported by a study that there is nominally positive interaction between GDNF family receptor genes and schizophrenia (10,16,17). Serum GDNF investigations on patients with schizophrenia were performed by Niitsu et al. (17) and Tunca et al. (14). Niitsu et al. (17) found no difference between serum GDNF levels of schizophrenia patients and healthy controls, although it may be associated with working memory in healthy controls and the pathophysiology of attention deficits in schizophrenia. Tunca et al. (14) on the other hand, found that patients with schizophrenia have had significantly lower GDNF levels. Furthermore, the therapy of rat C6 glioma cells in an artificial environment with not just typical (haloperidol) but also atypical (quetiapine and clozapine) antipsychotic drugs proved to change GDNF (18) which happened with phencyclidine, a drug producing symptoms similar to schizophrenia in healthy humans (19,20).

Considering these aspects, it is understood that the structural and/or functional modifications in the brain associated with astrocyte and synaptic functions may be involved in pathogenesis of schizophrenia (4, 6, 14, 16). On the other hand, few studies studying astrocytic and trophic factors including GDNF and GFAP serum levels in patients with schizophrenia are available. Moreover, there is a considerable uncertainty about the clinical characteristics such as the number of hospitalizations, type of antipsychotic and positive and negative syndrome scale (PANSS) on the serum levels of these molecules in patients with schizophrenia. Therefore, we aimed to compare control and patient groups in terms of serum levels of GFAP and GDNF, and also to investigate their clinical characteristic effects on serum levels with the help of these parameters in patients with schizophrenia.

METHOD

Participants and procedures

This study was performed in psychotic disorders unit of department of psychiatry of Cerrahpaşa Medicine Faculty of Istanbul University between January 2015 and August 2015. There were 37 patients with schizophrenia, who were followed by psychotic disorders unit and were consecutively included in the study. The patients met the DSM-5 criteria for schizophrenia, and they were all under drug treatment (21). Exclusion criteria for all participants included mental retardation, history of neurological disease, clinically significant head injury and active substance abuse or dependence. In addition, patients with co-morbid psychiatric illness were excluded. The healthy controls consisted of 37 (age and gender matched) volunteers from hospital staff or their relatives with no psychiatric history, neurological disorder and alcohol and substance dependence.

The research protocols were approved by the Ethics Committee of Cerrahpaşa Faculty of Medicine at Istanbul University and were therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The study was carried out according to the principles of the Helsinki

Convention on Human Rights and good clinical practice. Participants were informed that the study was confidential, anonymous and voluntary. Consent forms were confirmed by both patients and healthy controls after they were explained the complete description of the study. In addition, before the consent forms were taken from the patients, both the patients and their first-degree relatives, accompanying them in the hospital during the examination, were informed about the purpose and scope of the study in detail. Turkish version of PANSS was applied to patients, while sociodemographic form was applied to both the patients and control groups (22).

Determination of serum GDNF and GFAP levels

Laboratory measurements were accomplished in microbiology laboratory of Istanbul University Medicine Faculty. Blood samples were drawn by the venepuncture technique and transferred into three different tubes without anticoagulant. This sample collection task was conducted for both patient and control groups after an overnight (≥12 h) fast. Afterwards, blood specimens were allowed to clot for 30 minutes. And then, they were centrifuged at 4000 rpm for 10 min as usual. Thus, blood cells and all large particles in blood samples were precipitated. Yellow and clear serum samples were selected for the study. Both haemolysed and lipemic blood samples were removed. The aliquots of serum samples were kept at −70 °C for measurement of GDNF and GFAP concentrations. Measurements of glial markers serum levels were made after all samples were frozen and completed.

Serum concentration of GDNF and GFAP were determined by Enzyme-Linked Immuno Sorbent Assay (ELISA) test. These kits (SUNRED Biotechnology, Shanghai / Catalog Number is 201-12-0123 for GDNF and is 201-12-2095 for GFAP) use a double-antibody sandwich ELISA to assay the level of human GDNF and GFAP in samples. Procedures were performed as follows; 50µl standards were added into standard solution wells, 40µl serum samples and 10µl GDNF and GFAP antibodies were added into sample wells. Then 50µl streptavidin-HRP was added to each well except blank well and the plate was covered with seal plate membrane. Plate was shaken gently so that it would mix and then it was let to be incubated at 37 0C for 60 minutes away from light. The plate was washed carefully four times and then it was blotted. 50µl chromogen reagent A was added to each well, then 50µl chromogen reagent B was added to each well and plate was incubated for 10 minutes at 37 0C away from light for colour development.

Finally, 50µl stop solution was added to each well. The optical density (OD) of each well was measured under 450 nm wavelength within 10 minutes after having added stop solution. According to standard concentrations and corresponding OD values, the linear regression equation of the standard curve was calculated and GDNF and GFAP concentration of samples were determined as Intra-Assay CV<10% and Inter-Assay: CV<12% for both parameters. Assay ranges were 0.1 ng/ml→20 ng/ml for GDNF and 0.1 ng/ml→15 ng/ml for GFAP. A measurement result for each molecule belonging to different patients exceeded the limit values during the measurement; and the result of this patient was not included in the statistical analysis.

Data analysis

All statistical analyses were performed using the IBM SPSS Statistics 22.0 package program (IBM Corp., Armonk, New York, USA). Chi-square and Fisher Exact Tests were applied to compare the categorical variables. Kolmogorov–Smirnov test (K–S test) was used; and histogram and q-q plots were examined to assess the data normality. A two-sided Mann-Whitney test was applied to compare the differences between groups for continuous variables. Effect Size analysis was performed with GPower software 3.1 (Düsseldorf University, Germany). Binary correlations and multiple regression analysis were performed between the parameters. Data were expressed as frequencies, median (min-max), and mean ± standard deviation. The value of $p<0.05$ denoted statistical significance.

RESULTS

The number of participants with schizophrenia was 37 and there were also 37 healthy individuals in the

Table 1. Clinical characteristics and pharmacological treatment of patients with schizophrenia

Patients (n=37)		
Parameters		Results
Disease Onset Age		24.4–5.7
Duration of Illness		15.1–9.3
Number of Hospitalizations		3.29–2.3
Psychiatric History in Family		14(37.8%)
Medication Use	Typical antipsychotics	17(45.9%)
	Atypical antipsychotics	35(94.5)
PANSS	Total	70.8–27.1
	Positive	15.3–8.4
	Negative	22.6–9.9
	General	39.5–16.9

Data are expressed as number for categorical variables and mean–SD for continuous variables.

Table 3. Correlation between glial markers and clinical characteristics levels in patients with schizophrenia

	GDNF		GFAP	
Parameters	rho	p	rho	p
Number of Hospitalizations	0.308	0.063	0.362	0.030
Duration of Illness	0.405	0.016	0.300	0.080
PANSS Total	-0.177	0.301	-0.015	0.932
PANSS Positive	-0.062	0.713	-0.070	0.685
PANSS Negative	-0.485	0.002	-0.220	0.197
PANSS General	-0.378	0.021	-0.088	0.609

*rho = Spearman correlation coefficient

study. When groups were compared in terms of sociodemographic and clinical characteristics: There were not any significant differences across the groups in terms of gender (p=0.816), age (years, p=0.375), marital status (p=0.278), smoker (p=0.482), number of siblings (p=0.177), duration of marriage (p=0.617), number of children (p=0.335), number of cigarettes (p=0.961). Yet, the duration of education was higher in control group (16 years for controls and 12 years for patients with schizophrenia; p=0.001) and there was a difference between the groups in terms of employment status (Employed / Unemployed, 20/17 for controls and 31/6 for patients with schizophrenia).

Clinical characteristics and pharmacological treatments of patient group are given in Table 1. Mean age for first psychotic episode was 24.4±5.7. Duration of illness was 15.1±9.3, and patient's mean number of hospitalization was 3.29±2.3 (Table 1).

Serum GDNF and GFAP levels for both of the groups, smokers and non-smokers are given in Table 2. Serum GDNF and GFAP levels of patients with schizophrenia were significantly lower than those of healthy controls (p<0.001). There was not any gender difference within the patients and between groups. There was no significant difference between smokers and non-smokers in groups in terms of glial marker levels (p<0.05).

There was no significant relationship between sociodemographic parameters and serum levels in the control group. On the other hand, in patients with schizophrenia, the number of hospitalizations was positively correlated with GFAP levels (rho=0.362, p=0.030). Duration of illness was positively correlated with GDNF and GFAP (rho=0.405, p=0.016 and rho=0.300, p=0.080; respectively, Table 3). Serum GDNF levels were negatively correlated with PANSS Negative (Figure 1) and PANSS General (rho=-0.485, p=0.002 and rho=-0.378, p=0.021; respectively) in the patients. We did not observe any relationships between other clinical parameters such as medication use, psychiatric history in family and disease onset age with serum levels of GDNF and GFAP in patients with schizophrenia.

DISCUSSION

Results of our study revealed that serum GFAP and GDNF levels in patients with schizophrenia were significantly lower than those of healthy controls. In patients with schizophrenia, GFAP levels were positively correlated with the number of hospitalizations. Moreover, serum GDNF levels were negatively correlated with PANSS Negative and PANSS General in patients with schizophrenia.

While Niitsu et al. (17) found no differences between serum GDNF levels of patients with schizophrenia and healthy controls, Tunca et al. (14) found that patients with schizophrenia had significantly lower GDNF levels. To our best knowledge, our study is the first study searching serum

Table 2. The comparison of the study groups in terms of the glial markers

			95% CI			
Parameters	Controls (n=37)	Patients (n=37)	L	U	P Values	Effect Size
GDNF (ng/ml)	11.49(2.56-18.7)	3.95(0.80-9.63)	5.2736	8.9821	<0.001	3.2681
GFAP (ng/ml)	7.12(1.70-10.2)	3.67(0.89-9.64)	1.9624	9.0046	<0.001	1.3526

Data are expressed as median (min-max) for continuous variables.

levels of both GFAP and GDNF, which are two important markers for astroglial function and neurotrophy in patients with schizophrenia.

A significant increase was found in GFAP levels in the post-mortem dorsolateral prefrontal cortex of patients with schizophrenia and bipolar disorder, which indicates the role of this protein in the pathophysiology of psychosis (2). Several possibilities were suggested as to why GFAP expression may increase in the absence of changes in other astrocyte-associated proteins. It is plausible that GFAP proteins are malfunctioning by leading to protein accumulation (2, 23). Lower serum GFAP levels in our study, when compared to healthy controls, can be explained with the proposal of protein accumulation resulting from lower serum levels of the molecules. However, factors influencing GFAP production and/or breakdown could also be altered in psychosis. For example, the RNA-binding protein quaking, which is downregulated in schizophrenia, has recently been found to be regulating GFAP mRNA expression (24, 25). Furthermore, GFAP is a cytoskeletal protein; and a growing body of evidence supports the role of cytoskeletal pathology in patients with schizophrenia and bipolar disorder (26,27). Increases in GFAP were most pronounced when cases were divided into psychotic and non-psychotic cohorts suggesting that increased GFAP may be associated with psychotic symptoms (2). Positive correlation between the number of hospitalizations and serum GFAP levels in our study also might be related with the cytoskeletal pathology of the illness.

Perhaps one of the most important findings of our study is that the demonstration of GFAP levels was positively correlated with the number of hospitalizations, while serum GDNF levels were negatively correlated with PANSS Negative and PANSS General in patients with schizophrenia.

The Positive and Negative Syndrome Scale is one of the most widely used methods for standardized measurement of core symptoms of schizophrenia (28). It is a well-known phenomenon that negative symptoms tend to increase with the duration of illness (6). In our study, correlation between serum GDNF levels with PANSS Negative in patients with schizophrenia is consistent with correlation between serum GDNF levels with PANSS General in in patients with schizophrenia. Moreover, in our study, it has been found that astrocyte and synaptic function deficiency can change the severity of schizophrenia.

While GFAP and GDNF are typically regarded as intracellular protein, they have, however, been discovered to be normally present in extracellular biological fluids, including human cerebrospinal fluid (CSF) and blood plasma (6,11,13,29). The CSF is in touch with the brain interstitial fluid directly; therefore, great likely it supplies a more accurate assessment than surrounding blood of GFAP and GDNF metabolism. However, the constant yielding of CSF entails that it should depart the subarachnoid space circumambient of the brain; and possibly, as CSF flows down the subarachnoid granulations into the venous circulation, products set free from the brain into the CSF could be carried into blood when CSF goes into the venous circulation (30). As a result, serum levels of GFAP and GDNF may cast back the intracellular level of these molecules.

The association between serum levels of GDNF and attention deficits in schizophrenia was studied, and it was demonstrated that GDNF serum levels showed no differences between patients with schizophrenia under treatment and healthy controls (17). According to these results, researchers suggest that GDNF serum levels may be utilized unsuitably as biomarkers for schizophrenia (23). Contrary to this research, our study revealed that lower serum GDNF levels in patients with schizophrenia are compatible with the results of Tunca et al. (14) who found that patients with schizophrenia had significantly lower GDNF levels. Another important finding is that higher serum levels of GDNF were associated with better performances on the digit span in healthy controls, yet greater severity of attention deficits in patients with schizophrenia (17).

In a previous study, GDNF was found to be increased after the phencyclidine subchronic administration and it was proposed that subchronic phencyclidine may modulate the function of the GDNF system (31). Another study showed that

serum levels of GDNF gradually increased during antipsychotic therapy and it was suggested that stimulation of GDNF release from glial cells by antipsychotic drugs might underlie some of their neuroprotective properties in situ. Furthermore, a negative association between GDNF levels following pharmacotherapy and disease duration in subjects with schizophrenia could be observed (32).

In the correlation analysis, we did not observe any relationships between typical antipsychotics and medication use with serum levels of glial markers in patients with schizophrenia.

Since GDNF signaling regulates neural activity, reduced expression of GDNF levels implicated neuronal damage, it was stated that antipsychotic medications stimulated C6 glioma cells to secrete GDNF in experimental and clinical reports (33). On the other hand, Xiao et al. proposed that the length of illness was positively correlated to glial cells and the number of neurons impairments, which led to perturbed GDNF synthesis (32). Although lifetime chlorpromazine dose and duration of illness correlated positively with GFAP levels, these correlations were no longer significant when age at death was controlled for (34). Rats exposed to antipsychotics did not display significant differences in any astrocytic protein, proposing that elevated GFAP levels in schizophrenia is not ascribable to antipsychotic treatment. Elevated levels of GFAP may imply that astrocyte numbers are unaffected but astrocytes are partially activated, or may demonstrate a dysregulation of GFAP (2).

In a longitudinal survey, it was expressed that during both manic and depressive episodes of bipolar disorder, patients showed lower serum levels of GDNF compared with healthy controls. In the same study, it was found that after the pharmacotherapy lasted for eight weeks, these levels rose with those of healthy controls (35).

Limitations

On the other hand, this study has some limitations including a small sample size and absence of CSF GFAP and GDNF levels, and absence of neuroimaging. However, if we could compare patients as first episode psychosis and chronic, undertreated psychotic patients, results might be more precise. Lastly, drug doses and chlorpromazine equivalant could increase the power of this study. For these reasons, results of this study need to be replicated by future studies.

The decrease of serum GFAP and GDNF may provide evidence for relationship between schizophrenia and changes of glial cells. We suggest that the negative correlation between GDNF with PANSS Negative and PANSS General and between GFAP levels with the number of hospitalizations may reveal that patients with schizophrenia may be affected by astrocyte and synaptic functions. It will be of great contribution to determine other potential causes of decrease in the serum GFAP and GDNF, and to clarify their usefulness in the clinical practice of serum GDNF as a biomarker in diagnosis for schizophrenia. Moreover, comparison of the patients as first episode psychosis and chronic, undertreated psychotic patients might be more precious and deserves further investigation.

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Ethical statement The research protocols were approved by the Ethics Committee of Cerrahpaşa Faculty of Medicine at Istanbul University and consent forms were confirmed by both patients and healthy controls after they were explained the complete description of the study.

Conflicts of interest There are no conflicts of interest

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