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Elements Levels and Glucose-6-Phosphate Dehydrogenase Activity in Blood of Patients with Schizophrenia

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ABSTRACT

Elements levels and glucose-6-phosphate dehydrogenase activity in blood of patients with schizophrenia

Objectives: Glucose-6-phosphate dehydrogenase (G6PD) is the rate limiting enzyme of the hexose monophosphate cascade which plays role in the synthesis of nucleotide, reduced glutathion, fatty acid and cholesterol precursors. At the same time, it is an important enzyme for neuronal development during and after fetal life and for neurotransmitters. Serum elements are necessary for neuronal development and synthesis and activity of enzymes and hormones. The aim of this study was to compare serum levels of some elements and G6PD enzyme activity in schizophrenic patients with those in healthy individuals.

Methods: This study involved blood serum analysis of 32 schizophrenia patients and 32 age- and sex-matched healthy controls. Copper, zinc, iron, magnesium levels were determined with a double lighted, deuterium sourced, background proof reading fire atomic spectrophotometer and in order to determine aluminum and manganese levels, a graphite tube atomizer spectroscope was used. G6PD enzyme activity was analyzed by the Glock and Mclean Method.

Results: This analysis revealed higher levels of G6PD activity, copper, iron, magnesium and aluminum in schizophrenia patients compared to controls, whereas zinc and manganese levels showed a decreasing trend on the contrary.

Discussion: The higher levels of G6PD activity in schizophrenic patients is not consistent with the literature in general. It is considered that results on G6PD and element levels may be explained as the effects of specific hormones, antipsychotic medications, or by schizophrenia itself.

Conclusion: The elements we investigated and G6PD are important for the antioxidant system. Thus changing levels of elements in patients with schizophrenia may lead to disturbed functions of antioxidant enzymes and G6PD. Further researches on this subject conducted with larger and drug naïve patient groups are needed.

Key words: Schizophrenia, glucose-6-phosphate dehydrogenase, serum element level

ÖZET

Şizofreni hastalarında kanda glukoz-6-fosfat dehidrogenaz aktivitesi ve element düzeyleri

Amaç: Glukoz-6-fosfat dehidrogenaz (G6PD); nukleotid, indirgenmiş glutatyon, yağ asidi ve kolesterol öncüllerinin sentezlerinde rol alan heksoz monofosfat kaskadının hız kısıtlayıcı enzimidir. Aynı zamanda, fetal dönem sırasında ve sonrasında nöral gelişim ve nörotransmitterler için önemli bir enzimdir. Serumda bulunan elementler nöral gelişim, enzim ve hormonların sentez ve aktiviteleri için gereklidirler. Bu çalışmanın amacı, şizofreni hastaları ve sağlıklı kontrollerin bazı serum element düzeylerini ve G6PD enzim aktivitelerini karşılaştırmaktır.

Yöntem: Çalışmaya, 32 şizofreni hastası ile yaş ve cinsiyet açısından eşleştirilmiş 32 sağlıklı kontrol dahil edilmiştir. Bakır, çinko, demir ve magnezyum düzeyleri çifte ışıklandırılmış, döteryum kaynaklı, zemin düzeltmesi yapabilen alevli atomik spektrofotometre ile belirlenmiş; alüminyum ve manganez düzeylerini belirlemek içinse grafit atomizer tüp spektroskop kullanılmıştır. G6PD enzim aktivitesi Glock ve Mclean yöntemiyle değerlendirilmiştir.

Bulgular: Analiz sonuçları; G6PD aktivitesi, bakır, demir, magnezyum ve alüminyum düzeylerinin hastalarda kontrol grubuna göre daha yüksek olduğunu, çinko ve manganez düzeylerinin ise tersine düşüş gösterdiğini ortaya koymuştur.

Tartışma: Şizofreni hastalarındaki G6PD aktivite yüksekliği, literatürle uyumlu bir bulgu değildir. G6PD aktivitesi ve element düzeyleri ile ilgili bu sonuçların, belirli hormonların, antipsikotik tedavilerin ya da şizofreninin doğrudan etkileri ile ilgili olabileceği düşünülmektedir.

Sonuç: Araştırdığımız elementler ve G6PD, antioksidan sistemler için önem taşımaktadır. Bu nedenle, şizofreni hastalarındaki element düzey değişiklikleri antioksidan enzimlerin ve G6PD'nin işlevlerinde bozulmaya neden olabilir. Bu alanda daha geniş hasta grupları ile ve ilaç kullanmayan hastalarla yapılacak çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Şizofreni, glukoz 6 fosfat dehidrogenaz, serum element düzeyi

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INTRODUCTION

Schizophrenia is a brain disease with an unclear etiology, despite ongoing intensive researches. With the aid of biological and neuroimaging techniques, brain has been found to be the organ that uses the largest amount of glucose. Because of this, the relationship between glucose and neurochemical systems may provide a new perspective on the etiology of schizophrenia (1). Glucose-6-phosphate dehydrogenase (G6PD) undertakes the synthesis of nicotinamide-adenine dinucleotide phosphate (NADPH), which is the precursor of molecules like nucleotid, reduced glutathione, cholesterol and phospholipid. It also stimulates protective systems against free radicals in cells without mitochondria, like erythrocytes (2,3).

Elements are known to be vital for cellular multiplication and differentiation processes, neuronal development, and synthesis and activity of enzymes and hormones (4,5). Among many mechanisms, manganese, copper, and zinc participate in enzymatic mechanisms that protect against free radicals also. In recent researches, abnormal serum concentrations of elements have been shown in cases of schizophrenia and epilepsy (4-6).

The reports regarding the status of oxidative stress markers in schizophrenia are very inconsistent. In various researches, both increased and decreased activities of the main antioxidant enzymes as well as different element levels are reported. Despite the large number of studies in the literature that explore the pathogenesis of schizophrenia, we could not find any studies analyzing the protective function against free radicals' harmful effects on G6PD enzymes, or on enzyme activator elements or serum elements.

Neurons and peripheral tissues like leukocytes, trombocytes, cutaneous fibroblasts, and erythrocytes have similar receptor and enzyme systems (7). For this reason, the changes observed in diseased neural cells may also be observed in erythrocytes. In this study, we investigated the level of G6PD enzyme and serum iron (Fe), copper (Cu), zinc (Zn), manganese (Mn), magnesium (Mg) and aluminum (Al) levels in schizophrenia patients. Our aim was to determine the differences of these substances' levels in schizophrenic patients and healthy individuals and consider the importance of them in the pathogenesis of schizophrenia. Regarding to the previous researches and the role of oxidative stress in schizophrenia, we suggested to determine decreased levels of G6PD and changed levels of elements in the patient group compared to the healthy controls.

MATERIALS and METHODS

Patients and Control Groups

A total of 32 hospitalized patients (7 female, 25 male) from Elazığ Psychiatric Disease Hospital with a diagnosis of schizophrenia according to DSM-IV (8) criteria were included in this study. Patients diagnosed with organic brain syndrome, alcohol and substance abuse disorders, dementia or any kind of chronic physical diseases were excluded. We informed patients and their families about the study and obtained informed consent from them. This study was approved by the local ethical committee. Patient records were checked by a psychiatrist and each patient underwent a detailed psychiatric examination by the same clinician. The control group was composed of physically and mentally healthy individuals, including 9 females and 23 males. They were selected from among the physicians, nurses and staff who work at the hospital. When selecting the controls, we adjusted age, sex and social status variables so that they matched the patient group.

All patients were taking at least one antipsychotic medication. 81.3% percent were taking a typical antipsychotic (75% percent were on haloperidol treatment) and the remaining 18.7% percent were taking atypical antipsychotic drugs. Nineteen patients were also receiving additional antipsychotic drugs, namely 100 mg/day of chlorpromazine or its equivalent (e.g., thioridazine) to improve sleep. In the patient group, the average dose of antipsychotic medication, whether typical or atypical, was a dose equivalent to chlorpromazine 810.5±401.4 mg daily (9).

It was not possible to determine diagnostic subtypes among the schizophrenia patients due to the fact that hospital records were inadequate and difficulties were encountered in evaluating patient histories.

Blood Samples and Preparation

Heparinized 10 ml venous blood samples were obtained from schizophrenic patients and control groups. After the plasma was separated, the buffy coat was discarded. The erythrocytes were then washed three times with the same volume of 5% isotonic dextrose solution and centrifuged for 10 minutes at 3500 rpm. 200 µl erythtocytes were hemolysed with bidistiled water and the total volume of 5 ml was made up with water and centrifuged to seperate the membranes. The washed erythrocytes were preserved in a deep-freeze at - 80°C until the process day.

Analysis of Enzymes and Elements

Chemical materials used to determine essential and non-essential elements (Al, Cu, Zn, Fe, Mn, Mg) were supplied from Sigma. Sample Cu, Zn, Fe, Mg levels were determined with a double lighted, deuterium sourced, background proof reading fire atomic spectrophotometer supported by a computer that controlled the samples automatically (Varian 30/40 model PSC-56, Australia). Following the manufacturers' advice, for each examined element, different hollow-cathode lamps were used. Under stabilized pressure, an air-acetyl fire flame system was used. However, in order to determine Al and Mn levels, a Graphite Tube Atomizer spectroscope was used at a very high temperature (Varian GTA-96, Australia) with the help of an automatic sampler and a computer system attached to a printer. For each element, sample measurements were performed twice.

In order to measure G6PD enzyme activity, we used the Glock and Mclean Method (10). The detection method for G6PD enzyme activity level was based on the triphosphopyridine reduction rate at room temperature, and this was determined spectrophotometrically. An incresase in the density above 340 µm in the first 5 minutes was considered G6PD activity (Shimadzu UV-1601, Japan).

Statistical Analysis

Data was analyzed using a commercially available statistics software package (SPSS for Windows v. 9.0, Chicago III. USA). Normal distribution was checked using Kolmogorov–Smirnov test. Normal distribution differences between groups were assessed by unpaired t test. Mann-Whitney U test was used to check abnormal distribution. Spearman and Pearson correlation tests were performed to compare sub-groups. The significance rate was set at $p<0.05$.

RESULTS

The average age was 35.3±5.8 in the patient group and 34.5±5.2 in the control group. The age of the patients and the control group ranged between 25 and 46. The education level of the controls was significantly higher than the patients'. Demographic variables for patients and controls are shown in Table 1.

Enzyme activity and element levels for the patients and control group are shown in Table 2. Table 3 shows enzyme activity and element levels for male patients and male controls. Table 4 shows the same data for females.

G6PD enzyme levels were significantly higher in the patient group compared to the control group ($p<0.05$). Serum Cu, Fe, Mg, and Al levels in the patient group were higher in comparison to the control group ($p<0.05$). On the other hand, Mn and Zn levels were lower in the patient group when compared to the control group ($p<0.05$).

G6PD activity levels for the male schizophrenic patients were higher than that of the male control group ($p<0.05$) (Table 3). The evaluation of element levels in males revealed a statistically significant difference (Table 3). Even though there were no differences in G6PD activity levels for female patients and female controls, there was a significant difference in the element levels ($p<0.05$) (Table 4).

Smoking was more common within the patient

Table 1: Demographic Variables for Patient and Control Groups

Demographic Variables	Patients n=32		Controls n=32		χ^2/t	p
	Mean	SD	Mean	SD		
Age	35.3	5.8	34.5	5.2	0.581	>0.05
	n	%	n	%		
Sex					0.333	>0.05
Male	25	78.1	23	71.9		
Female	7	21.9	9	28.1		
Education					27.807	<0.05
≤5 years	25	78.1	4	12.5		
5-11 years	6	18.8	16	50.0		
11≤	1	3.1	12	37.5		
Marital Status					12.600	<0.05
Single	13	40.6	5	15.6		
Married	11	34.4	25	78.1		
Divorced	8	25.0	2	6.3		
Smoking Habits					6.478	<0.05
Smokers	24	75.0	14	43.8		
Nonsmokers	8	25.0	18	56.2		

χ^2: chi-square, t: Student t test, SD: Standard deviation

Table 2: Activity Level of G6PD and Element Levels in Patient and Control Groups

	Patients n=32 Mean±SD	Controls n=32 Mean±SD	t	p
G6PD (mg/ml)	4.02±3.0	2.13±1.4	3.229	=0.002
Copper (µg/dl)	130.8±35.9	78.2±12.7	7.813	<0.001
Zinc (µg/dl)	53.4±11.5	85.1±13.8	9.699	<0.001
Iron (µg/dl)	85.5±10.3	45.3±6.5	18.671	<0.001
Magnesium (mmol/L)	1.62±0.3	1.00±0.2	9.727	<0.001
Aluminum (µg/dl)	80.2±16.7	25.2±6.5	17.391	<0.001
Manganese (ng/dl)	1.31±0.3	2.05±0.3	9.866	<0.001

*G6PD: Glucose-6-phosphate dehydrogenase; t: Student t test, SD: Standard deviation

Table 3: Activity Level of G6PD and Element Levels in Male Patients and Control Group

	Patients n=25 Mean±SD	Controls n=23 Mean±SD	Z	p
G6PD (mg/ml)	4.11±3.0	2.20±1.4	2.862	0.015
Copper (µg/dl)	132.2±36.2	77.0±14.6	7.028	<0.001
Zinc (µg/dl)	54.7±11.7	84.0±12.7	8.291	<0.001
Iron (µg/dl)	84.3±10.9	43.0±6.1	16.363	<0.001
Magnesium (mmol/L)	1.58±0.3	0.95±0.2	8.621	<0.001
Aluminum (µg/dl)	80.7±17.8	25.5±6.2	13.251	<0.001
Manganese (ng/dl)	1.28±0.2	1.98±0.2	12.113	<0.001

*G6PD: Glucose-6-phosphate dehydrogenase; Z: Mann Whitney U test, SD: Standard deviation

group than within the control group (p<0.05). Fe levels for patients were significantly higher when compared to the control group (p<0.05). We also analyzed the relationship between Fe levels and smoking. Fe levels indicated no difference between smokers and non-smoking patients but showed a significant difference for the control group. Smokers' Fe levels were higher than non-smokers' in the control group (p<0.05). Also a positive correlation was found between the enzyme activity and the serum Fe level.

Table 4: Activity Level of G6PD and Element Levels in Female Patients and Control Group

	Patients n=7 Mean±SD	Controls n=9 Mean±SD	Z	p
G6PD (mg/ml)	3.68±3.1	1.96±1.3	1.376	0.112
Copper (µg/dl)	125.9±37.4	81.2±47.9	2.096	<0.05
Zinc (µg/dl)	49.0±10.3	87.9±16.7	5.726	<0.001
Iron (µg/dl)	89.9±6.7	50.9±3.6	13.917	<0.001
Magnesium (mmol/L)	1.75±0.4	1.14±0.1	3.940	<0.001
Aluminum (µg/dl)	78.29±12.9	24.4±7.4	9.862	<0.001
Manganese (ng/dl)	1.44±0.2	2.25±0.3	6.461	<0.001

*G6PD: Glucose-6-phosphate dehydrogenase; Z: Mann Whitney U test, SD: Standard deviation

In the patient group, there was a positive correlation between Mn and Mg (r= 0.555, p<0.05). This correlation was also observed for Zn and Al (r=0.433, p<0.05) as well as for Fe and Mn (r=0.356, p<0.05). In the control group, there was a correlation between G6PD and Al (r=0.418, p<0.05). There was a positive correlation between Fe and Mg as well (r=0.402, p<0.05). On the other hand, there was a negative correlation between Zn and Al (r= -0.377, p<0.05).

DISCUSSION

G6PD is the key enzyme of the hexose monophosphate shunt pathway through which NADPH is synthesized (11). Reduced glutathione is a subunit of the complex system that inhibits the biological effects of free radicals. Glutathione peroxidase converts hydrogen peroxide to water making it harmless (12). The number of free radicals in the neural system varies in line with alterations in G6PD activity.

We found that G6PD activity was higher in the patients than in the controls and this result was not concordant with the literature. In the literature there are several studies that report decreased levels of glutathione and G6PD in schizophrenic patients (13,14). The source of this difference may stem from: 1. The effects of hormones on G6PD enzyme such as thyroxine, cortisone and insulin (15), 2. Antipsychotic medication side effects such as hypoglycemia (16), 3. The rise in isoprenoid and its metabolite digoxin, through the inhibition of the erythrocyte membrane Na^+-K^+ ATPase mechanism. This may be caused by a decrease in the intracellular concentration of the enzyme activator Mg (17), 4. Antipsychotic medication's effects on this enzyme are unknown. There is no research about antipsychotic treatment effects on the G6PD levels in schizophrenic patients. But a number of studies have examined neuroleptic's effects on antioxidant enzymes in schizophrenia (18,19). Padurariu et al. reported that long-term treatment with both typical and atypical antipsychotics may produce similar effects on the activity of antioxidant enzymes and on levels of lipid peroxidation (20).

Zn deficiency causes abnormal brain development in the prenatal and early postnatal period. It can also affect the brain via hormones, proteins and aminoacids that affect neuronal functions (21). In our study, serum Zn concentration levels were found to be lower than in the control group. This coincides with the findings in the literature (22). There are also studies that report no difference between the serum zinc levels of the patients and the controls, or elevated Zn levels in patients (5,23). The serum Zn concentration may change depending on the acuity or chronicity of the illness (5). In our study, all of the patients were chronic and the majority of them were undergoing multi-drug treatment. Moreover, there was a correlation between serum Zn and Cu levels. It is known that higher serum Cu concentration disturbs Zn absorption (24). Another factor may be the high prevalence of low serum levels of Zn in the Turkish population (25).

Cu serves in the dopamine and norepinephrine synthesis and joins many metalloenzymes like dopamine hydroxylase and thyrosine. These enzymes have important roles in the pathogenesis of schizophrenia. Excess Cu causes free radical production and also leads to xhanthine oxidase enzyme inhibition (24). In our study, serum Cu levels were higher in

schizophrenics compared to the control group. There are various studies reporting high Cu levels in schizophrenics (5,26). This result may be explained by the inhibition of Zn re-uptake by neuroleptics and an antagonistic relationship between Zn and Cu concentrations. Neuroleptics also affect serum Cu levels (5). High serum Cu levels in our patients may be a consequence of antipsychotic treatment.

Mg levels were higher in the schizophrenic group compared to the control group in this study. The increase of G6PD activity in our patients may be linked with increased serum Mg levels since Mg is the cofactor of this enzyme (10). Mg stabilizes DNA, RNA, and ribosomes, and activates approximately 300 enzymes including those used in energy metabolism. Its role in neuronal functions is not completely understood. Calcium (Ca) has a basic function in neurotransmitter secretion and Mg blocks the entrance of Ca into the cell (27). For this reason, patients' serum Mg levels have a critical importance. Antipsychotic medications may alter serum levels of this important element. Nechifor (28) reports that in patients with acute paranoid schizophrenia, erythrocyte Mg concentration is decreased and after antipsychotic treatment, Mg concentration is significantly increased. Our result could be explained by antipsychotic usage or by the direct effects of schizophrenia.

Serum Fe levels of the schizophrenia group were higher compared to the control group in our study. Fe combines with myoglobin, cytochrome, peroxidase and catalase enzymes and is also a functional component of hemoglobin (29). Under normal conditions, antioxidant systems and transition metals like Fe and Cu remove superoxide anions from the environment and prevent them from damaging the organism (30). Smoking may increase serum Fe concentrations since it increases oxidative damage first through Cu, and then through Fe accumulation (24). Smoking rates are higher among the patients compared to the control group. However, among the patients, there was no significant difference in Fe levels between smokers and non-smokers. Because of this, we speculate that Fe level differences between the patients and controls are not a result of smoking and instead are related to the direct effects of illness or effects of the antipsychotic treatments.

The mean serum Al level of the patients was higher than the control group in our study. In mammalian tissues, Al is present in minute amounts. Various studies highlight the neurotoxic effects of Al and although the neurotoxic mechanism of Al has not been determined, there is proof that Al is incorporated in glutaminergic neurotransmission (31-33). Brain glutamate levels can change in cases of protein deficiency. Limited consumption of protein food may modify Al inducted neurological responses in different parts of the brain (34).

Mn is a necessary element for activation of many enzymes such as hydrolase, kinase, decarboxylase, and transferase that participate in metabolic processes like protein and lipid metabolism, energy production and bone formation. It stimulates adenylate cyclase in the brain and other tissues and free radicals that cause lipid peroxidation and protein oxidation. Lipid peroxidation and protein oxidation damage DNA and RNA, and increase Mn deprivation. In our study, the serum Mn levels of the patients were lower compared to the control group and this finding was concordant with the literature (23,35). Mn is also a component of superoxide dismutase (SOD). Reduced levels of Mn may be a result of the low antioxidant capacity of MnSOD, resulting in increased oxidative stress (23).

Serum Mn level of individuals is also closely related to the levels of different elements such as Zn and Cu, as there is a negative relationship between Mn absorption and Zn and Cu levels. Mn has a role in thyroxine synthesis and thyroxine effects G6PD enzyme synthesis in a similar way. There is also a relationship between Mn and dopamine and it has been reported that antipsychotic drugs chelate body Mn (16,36).

There were positive correlations between Mn and Mg, between Zn and Al, and between Fe and Mn in the patient group. In the control group, positive correlations between G6PD and Al, beside Fe and Mg were determined also. Because it is already difficult to discuss changes in the element levels in the light of the literature, to make a meaningful interpretation on these correlations seems difficult, either.

CONCLUSION

Mn, Cu, and Zn are important components of SOD and Fe in catalase. Mg is the cofactor of G6PD. G6PD is an important enzyme for some molecules like nucleotid and reduced glutathione. It also stimulates protective systems against free radicals in cells without mitochondria like erythrocytes. Thus, changing levels of elements in patients with schizophrenia may lead to disturbed functions of antioxidant enzymes and G6PD. One of this study's limitations was the small size of the patient group. The other limitation was that our patients were taking antipsychotic drugs and these drugs may effect enzyme and element levels. It's difficult to observe a direct relationship between G6PD levels and antioxidant activity without working the important antioxidant enzymes. In order to eliminate these limitations, it would be good to compare drug naive patients and patients with a similar duration of illness who are under treatment and focus also on the other antioxidant enzymes.

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