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Research paper

Diagnostic performance of increased prolidase activity in schizophrenia

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HIGHLIGHTS

- Prolidase activity may be a diagnostic marker for schizophrenia.
- Prolidase level 392.65 U/L could be a valid diagnostic measure.
- Increased prolidase activity is related to the pathogenesis of the disease regardless of antipsychotic medications.

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ABSTRACT

We investigated whether prolidase activity has a diagnostic test value in schizophrenia and assessed the relation between prolidase activity and sociodemographic-clinical characteristics of patients with schizophrenia. Fifty patients with schizophrenia (diagnosed as schizophrenia according to DSM-V criteria) and 50 healthy volunteers were included in this study. Case and control groups had a similar distribution in age, sex, body mass index (BMI), and smoking status. Serum prolidase activity was measured in both groups and was determined to be significantly higher in the patient group (509.706 ± 41.918) compared to the control group (335.4 ± 13.6; $t = 6.231$; $p = 0.0001$). A cut-off point of 392.65 U/L prolidase was determined for diagnostic measures from the plotted ROC curve. The area under the ROC curve was 1.000, which was significant ($p < 0.0001$). Higher values were assigned as the disease state. Both positive predictive value (PPV) and negative predictive value (NPV) were 100% at the cut-off point of 392.650 U/L. The prolidase levels of the control group were all below the cut-off point. There were no statistically significant differences between the two groups with regard to age, gender, or BMI ($p > 0.05$), and no correlation was found between mean prolidase activity and age of onset of the disease, family history, disease duration, number of hospitalizations, subtypes of schizophrenia, PANSS scores or subscores, CGI-S scores, S-A scale scores, and the antipsychotic treatment ($p > 0.05$). The results of this study indicate that serum prolidase activity may be a useful diagnostic test for schizophrenia; however, further studies are needed to verify this.

1. Introduction

Schizophrenia is a chronic and severe psychiatric disease that affects about 1% of the population and causes disability [1,2]. There are genetic and biochemical studies focused on the etiopathogenesis of schizophrenia [3]. Current diagnostic approaches for schizophrenia are based on patient interviews, which entail a subjective assessment of clinical symptoms. In many areas of

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the world, cost and availability of clinicians trained in diagnostic interviewing limit patient access to quality mental health care. Inter-rater reliability and cultural bias are some factors that further confound schizophrenia diagnosis [4,5]. Prolidase (AK 3.4.13.9) is a hemodynamic and manganese-dependent member of the matrix metalloproteinase family; it catalyzes the hydrolysis of imidodipeptides with a proline or hydroxyproline in the C-terminal and exists in the plasma [6,7]. Prolidase enzyme activity is determined in the plasma and also in various tissues, including brain, erythrocytes, leukocytes, dermal fibroblasts, kidney, heart, thymus, and uterus [8,9]. In different studies, proline and its dipeptides have been shown to play a role in biological processes with various vital functions [10,11]. Proline accounts for 5% of the amino acid residues of brain proteins and is considered to be a neurotransmitter [12]. Additionally, it is involved in various physiological processes, such as the remodeling of extracellular matrix (ECM), embryonic development, tissue resorption, wound healing, cell migration, and cell differentiation [13,14].

Several studies have investigated the pathophysiological role of prolidase in different diseases, including diabetes mellitus, hypertension, liver diseases, and coronary artery disease [15–18]. Prolidase is important for the functional metabolism of proline in the brain [19]. Increased prolidase activity results in increased proline and proline peptides, and increased proline levels, through prolidase activity, lead to glutamate excitotoxicity [20]. It has been shown that disordered proline metabolism is related to various disorders, including schizophrenia and behavioral disorders [21–23]. Furthermore, increased prolidase activity has been reported in schizophrenia and bipolar disorder, and it has been claimed that prolidase is a reliable diagnostic test for bipolar disorder [23,24].

The diagnostic value of prolidase activity in schizophrenia has not been investigated. Because schizophrenia and bipolar disorder reportedly share common etiopathologic mechanisms, in the present study we investigated whether prolidase activity has a diagnostic test value in schizophrenia.

2. Materials and methods

The patient group consisted of 50 patients chosen from 132 patients admitted to the psychiatry outpatient clinic of Dicle University who met the inclusion criteria of the study and who had been diagnosed as having schizophrenia according to DSM-V criteria. We excluded inpatients and treatment-resistant patients. Patients with a history of drug abuse, chronic systemic diseases (such as diabetes mellitus, hypertension), severe head injury, seizure disorders, vitamin B12 deficiency, or a schizoaffective disorder and those using agents that may affect prolidase levels, such as beta-blockers (carvedilol, nebivolol), statins, vasoactive medications, diuretics, and antioxidant drugs, were also excluded from the study. The control group consisted of 50 healthy individuals, suitable for study criteria, among 157 individuals who applied to donate to the blood bank.

Patients and controls were matched by age, gender, body mass index (BMI), and smoking habits. Sociodemographic data and clinical features were recorded. After 12 h of fasting, blood samples were taken from both groups, and serum prolidase activity was measured. The severity of schizophrenia symptoms in the patients was evaluated using the Positive and Negative Syndrome Scale (PANSS) [25] and the Clinical Global Impression Severity of Illness Scale (CGI-S) [26]. All patients were using pharmacotherapy. To evaluate pharmacotherapy-induced extrapyramidal symptoms (EPS), the Simpson–Angus (S–A) Scale was applied. Approval was obtained by the ethics committee of Dicle University. The DSM-V diagnosis of schizophrenia was established by a psychiatrist.

Table 1
The clinical and demographic data of study population.

	Patient	Control	p;x²
Gender (male/female)	10/40	9/41	$p = 0.799$;0.065
Smokers	32/50 (64%)	37/50 (74%)	$p = 0.280$;1.169
Family history	21/50 (42%)		
Treatment			
Typical antipsychotic	12/50 (%24)		
Atypical antipsychotic	23/50 (%46)		
Combined antipsychotic	15/50 (%30)		
	Patient	Control	p;t
Mean age (years)	32.26 ± 10.18	33.58 ± 9.46	$p = 0.504$;0.671
BMI (kg/m²)	27.4 ± 5.49	26.61 ± 3.29	$p = 0.374$;0.894
Mean number of cigarettes	32.18	29.95	$p = 0.499$;0.680
Mean scale scores			
CGI-S	3.72 ± 1.27		
PANSS-T	93.00 ± 33.39		
PANSS-P	22.60 ± 9.06		
PANSS-N	22.98 ± 10.86		
PANSS-G	47.32 ± 16.65		
S-A	3.66 ± 4.22		

BMI: Body mass index.
PANSS-T: positive and negative syndrome scale-total scores.
PANSS-P: positive and negative syndrome scale-positive scale.
PANSS-N: positive and negative syndrome scale-negative scale.
PANSS-G: positive and negative syndrome scale-general psychopathology scale.
CGI-S: clinical global impression-severity scale.

2.1. Statistical analysis

SPSS® for Windows 15.0 was used for the statistical analysis of data. The significance of differences between groups was estimated by the *t*-test. The chi-square test was used when comparing proportions. Differences were accepted as significant when the p value was <0.05. Bivariate comparisons were examined via Spearman correlation coefficients, and values were corrected for ties. The receiving operator characteristics (ROC) curve was plotted to find the cut-off point. Positive predictive and negative predictive values were determined for the diagnostic performance of serum prolidase activity.

3. Results

There were no statistically significant differences between the two groups with regard to age, gender, or BMI ($p > 0.05$) (Table I). Prolidase activity was significantly higher in the patient group (509.7 ± 41.9) compared to the control group (335.4 ± 13.6; $t = 6.231$; $p = 0.0001$) (Fig. 1).

We found no significant correlation ($p > 0.05$) between serum prolidase activity and clinical characteristics (age of onset, family history, duration of illness, number of hospitalizations, schizophrenia subtype), scales (PANSS, PANSS subscales, CGI-S, or SA), or antipsychotic type (Table 1). The ROC curve of prolidase was plotted, and the cut-off point for diagnostic measures was determined as 392.65 U/L from the curve (Fig. 2). The area under the ROC curve of prolidase was 1.000, which was significant ($p < 0.0001$). Higher values were assigned as the disease state. Both PPV and NPV were 100% with a cut-off point of 392.650 U/L. All prolidase levels of the control group were below the cut-off point.

4. Discussion

To the best of our knowledge, this is the first study to examine the diagnostic potential of serum prolidase in schizophrenia patients. Our main finding was that significantly higher serum prolidase activity levels occur in schizophrenia patients compared to