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Role of tissue plasminogen activator and plasminogen activator inhibitor as potential biomarkers in psychosis

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ABSTRACT

The identification of biological markers for psychosis has an impact on its diagnosis, prognosis, and likelihood of treatment response. Tissue plasminogen activator (tPA) is involved in important functions such as synaptic plasticity, long-term potentiation and neurogenesis. Plasminogen activator inhibitor (PAI-1) is the most important inhibitor of tPA. Preliminary studies have shown that schizophrenia patients have lower tPA and higher PAI-1 levels than the general population. The association of tPA and PAI-1 abnormalities with psychotic spectrum disorders, however, remains elusive. Our primary objective was to assess the plasma levels of tPA and PAI-1 in patients experiencing acute psychotic episodes as compared to those in healthy controls. In this prospective case-control study, we collected peripheral blood samples from psychiatric inpatients and healthy age, gender and race-matched subjects and determined plasma levels of tPA and PAI-1 by enzyme-linked immune-absorbent assays. Plasma levels of PAI-1 in patients with schizoaffective disorder were significantly lower as compared to those in control subjects (P = 0.03). tPA was lower in cases as compared to controls although it did not reach statistical significance. Asian patients and controls had lower PAI-1 levels. Further, Asian patients with schizoaffective disorder had significantly lower PAI-1 level compared to Asian patients with schizophrenia. Our results indicate that patients with schizoaffective disorder have lower PAI-1 levels than those with schizophrenia, affective psychosis, and healthy controls. Further studies are warranted to explore the potential of PAI-1 as a biomarker for diagnosing schizoaffective disorder.

1. Introduction

Psychosis is a set of symptoms in which a person's mental capacity, affective response and capacity to recognize reality, communicate and relate to others, is impaired. Schizophrenia is the most common and best known psychotic illness, however there are numerous other psychiatric conditions, cases of brain injury, learning disability, substance abuse and a range of metabolic disorders that present with psychotic symptoms. Psychosis is thus a descriptive term for a complex group of behaviors and experiences. Unfortunately, the current diagnosis and classification of schizophrenia is based solely on interpretation of clinical phenomenology (Schwarz and Bahn, 2008). The pathological mechanisms resulting in psychotic symptoms are not understood, nor is it understood whether the various psychotic illnesses are the result of similar biochemical disturbances. The identification of biological markers (so-called biomarkers) of psychosis is a fundamental step towards a better understanding of the pathogenesis of psychosis and holds the potential for more objective testing methods.

Investigations of blood-based biomarkers for schizophrenia and psychotic spectrum disorders have great potential in discovering diagnostic or prognostic indicators of clinical utility and may provide clues to the underlying pathophysiology as the circulatory system is a dynamic, sentinel tissue that is known to reflect immune and pathological status (Gladkevich et al., 2004). There are to-date no objective clinical laboratory blood tests for psychotic disorders. The current reliance on clinical assessment, including patient self-report, is a rate limiting step in timely and effective treatment and new drug development. Even if the etiologies for schizophrenia and other psychotic disorders remain unknown, a biomarker that accurately identifies the clinical syndrome would allow for improved diagnosis, prognosis, and disease monitoring as well as the development of novel therapeutic approaches (Huang et al., 2006).

The quintessential psychotic spectrum disorder, schizophrenia, is characterized by brain atrophy, especially in the superior temporal gyrus and the medial temporal lobe, which includes the hippocampus and the amygdala. A model that would explain brain atrophy would

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include triggers and predisposing conditions. A trigger could be illicit drugs or environmental stressors that promote release of substances harmful to the neurons, such as glucocorticoids or noradrenalin. Predisposed patients would have one or more conditions that impair neuronal plasticity and neurogenesis.

One of the factors that affect neuronal plasticity and neurogenesis include tissue plasminogen activator (tPA) and the end product of plasminogen activator-derived proteolysis, plasmin. For decades tPA, plasminogen and plasmin were known as proteins whose main role was to modulate coagulation, through intravascular fibrin degradation. However, this proteolytic system has numerous actions that go beyond the blood vessel. Neurons and glial cells also synthesize and release tPA, which is highly expressed in the cortex, amygdala, hippocampus and cerebellum. They are involved in synaptic plasticity, integrity of the blood-brain barrier, neurite outgrowth, cell migration, long-term potentiation and depression, neurogenesis, and excitotoxic cell death (Benarroch, 2007; Cesarman-Maus and Hajjar, 2005; Melchor and Strickland, 2005). It has been proposed that due to its proteolytic properties, tPA may be a key player in the biology of memory, learning, emotions, and the rewarding effect of licit or illicit substances (Madani et al., 2003; Nagai et al., 2006; Samson and Medcalf, 2006). Moreover, decreased levels of tPA or elevated levels of its main inhibitor, plasminogen activator inhibitor 1 (PAI-1), have been described in patients with major depression and with schizophrenia (Eskandari et al., 2005; Harris et al., 2012). tPA is involved in activation of brain derived neurotrophic factor (BDNF), mediates neuronal protection from excitotoxin induced cell death and restores neurogenesis.

Plasminogen activator inhibitor-1 (PAI-1) is a serine protease inhibitor that functions as the principal inhibitor of tPA and urokinase (uPA), the activators of plasminogen and hence fibrinolysis (Vaughan, 2005). Besides the main function of PAI-1 to inhibit the tPA/uPA induced fibrinolysis, it is also important in adhesion, migration, signal transduction and anti-apoptosis. Preliminary studies have shown significantly decreased tPA serum level in patients with schizophrenia compared with healthy controls whereas PAI-1 level between patients with schizophrenia and healthy controls was not significantly different, suggesting that tPA may be associated with the pathogenesis of schizophrenia (Hoirisch-Clapauch and Nardi, 2013; Carrizo et al., 2008).

Although the relationship between the levels of tPA and PAI-1 appears to be simply reciprocal, recent studies have shown that there is much that we do not know about the dynamic balance between tPA and PAI-1 activity, and its control (de Bono, 1994). There have been some studies which concluded that serum levels of PAI-1 were independent of schizophrenia but related to the metabolic syndrome (Lasić et al., 2014, 2015) which is not surprising given the role PAI-1 plays in various metabolic pathways. The vascular endothelium, contributes to the generation of altered coagulation process via increased expression of tissue factor, PA1-1, platelet activation and acute phase reactions that increase levels of coagulation factors such as fibrinogen. One well-known association of this cascade is with the risk of diabetes mellitus complications (Tousoulis et al., 2013). The PAI-1 promoter is activated by insulin, glucose, homocysteine, triglycerides, angiotensin and leptin, a hormone produced by adipocytes (Midorikawa et al., 2000). Metabolic syndrome is a well-known cause of morbidity and mortality in schizophrenia. It is estimated that 42% of patients with first-episode psychosis or medication-naïve patients with schizophrenia are obese or overweight, with a high prevalence of elevated fasting glucose and insulin levels, hypertriglyceridemia and high blood pressure (Hoirisch-Clapauch and Nardi, 2014). Current knowledge indicates tPA and PAI-1 being the important link connecting the schizophrenia and metabolic syndrome.

Although preliminary studies have shown that patients with schizophrenia have lower tPA and higher PAI-1 levels, their association with psychotic spectrum disorders, have not been elucidated. Our primary objective was to assess the plasma levels of tPA and PAI-1 in patients experiencing acute psychotic episodes as compared to those in healthy controls.

2. Methods

For this prospective case-control study, we recruited patients from the 70-bed psychiatric inpatient unit of a large, urban, community-based teaching hospital in New York, from January 2016 to January 2017. The study was approved by the Institutional Review Board. All non-organic psychotic patients, between the ages of 18–65 years were included in the study. Exclusion criteria were as follows: patients who were not able to consent, pregnant women, had history of stroke, seizure, anti-phospholipid antibody syndrome, systemic lupus erythematous, developmental disorder, substance abusers and those with known history of any deficiency of coagulation factor. For the control group, we enrolled healthy volunteers matched for age, gender and race with the study group patients. These healthy subjects were recruited by advertising throughout the hospital. Same exclusion criteria as that of study group were applied to the control group subjects. Both patients and healthy volunteers underwent the informed consent process and provided written consent prior to enrollment in the study.

Enrolled patients belonged to one of the following four clinical groups: Schizophrenia, Schizoaffective, Bipolar Disorder with psychotic features (this category included patients with Bipolar I disorder, single manic episode, severe with psychotic features and Bipolar I disorder most recent episode manic, severe with psychotic features) and Major Depressive Disorder with psychotic features. Psychiatric diagnoses were established according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fifth Edition, (DSM5), by a psychiatrist. The severity of psychotic symptoms was assessed by the Brief Psychiatric Rating Scale (BPRS) at the time of recruitment. The 24 BPRS items' total score rating from 1 (symptoms not present) to 7 (extremely severe symptoms) was calculated.

Fasting blood samples were collected between 7:30 and 8:30 am. Following data were collected from charts as well as by interviewing the patients: age, gender, height, body weight, BMI, ethnicity, diagnosis (during admission and at the time of discharge), lab test (including CBC, TSH, lipid panel, HbA1c and liver profile), psychiatric history, psychometric data, psychosocial history (including trauma), current medications, medical history, and substance abuse history.

Platelet-poor plasma was obtained in EDTA tubes by centrifugation of blood samples within 30 min after collection at 4 °C for 15 min at 2500 *g*. Plasma was aliquoted into microfuge tubes, labeled and stored at −70 °C until analyses. tPA and PAI-1 antigen (Ag) levels were measured by commercially available enzyme-linked immune-absorbent assays (R&D Systems, Inc. Minneapolis, MN). Basic lab measures were obtained either from patients' charts or samples were sent to hospital Pathology Lab for testing. For all control subjects these baseline lab tests were performed as well.

Statistical analysis

The data are shown as mean ± standard deviation (SD) or percentage as appropriate. Continuous variables were first checked for normal distribution by the Shapiro-Wilk test. The Mann-Whitney U or Student t-tests were used as appropriate. The $\chi 2$ test was used to compare the category frequencies. Data were analyzed using the SPSS 21.0 for Windows, and a p-value of < 0.05 was considered to be significant. Outlier measurement were ignored for analysis and PAI-1 value did not have normal distribution, as a result we used log PAI-1 in calculations of correlations. To study the correlation among different clinical indicators and the levels of PAI-1 and tPA, a log transformed value of PAI-1 level was used and only non-diabetic individuals were included to obtain a normal distribution. We also used ANCOVA and compared PAI-1 levels in different groups, trying to control for the effect of BMI as a co-variate. ANOVA or t-tests were used to compare the level of a continuous variable among different groups. When needed, a post-hoc analysis (Bonferroni) was applied.

Table 1
Demographics of Study Population.

	Patients (n = 42)	Controls (n = 20)
Age, mean (SD)	40.67 (2.09)	39.1 (2.51)
Female gender, n (%)	21 (50)	13 (65)
White, n (%)	21 (50)	9 (45)
Asian, n (%)	10 (24)	4 (20)
Hispanic, n (%)	6 (14)	5 (25)
African American, n (%)	5 (12)	2 (10)

Table 2
Final Diagnoses of Study Patients.

Final Diagnosis	N (%)
Schizophrenia	9 (24)
Major Depressive Disorder with psychotic features	6 (14)
Schizoaffective Disorder	21 (50)
Bipolar I Disorder current episode, manic with psychotic features	6 (14)

3. Results

Demographic data are summarized in Table 1 and final clinical diagnoses at discharge in Table 2. Based on final diagnoses, three patients' data were omitted as they had other diagnoses including dementia. Plasma levels of tPA were 2.99 ± 1.03 ng/mL in patients as compared to 3.37 ± 1.65 ng/mL in controls (p = 0.35). PAI-1 levels were lower in patients as compared to that in controls, 31.12 ± 26.0 ng/mL vs 45.92 ± 38.1 ng/mL (p = 0.07). There was no significant difference in the BMI between cases and controls (25.52 ± 6.87 vs 27.19 ± 5.43), nor in their HbA1c levels. Patients had significantly higher glucose level, neutrophil counts and lower LDL, HDL, as compared to controls.

Table 3 shows levels of tPA and PAI-1 stratified by diagnostic groups. Fig. 1 shows the intra-racial comparison of PAI-1 levels between patients with schizophrenia and those with schizoaffective disorder. There was a significant difference between PAI-1 levels in Asian and non-Asian patients (P = 0.009). (Table 4). Fig. 2 shows BMI among different races in the study population. After controlling for BMI using ANCOVA, significant difference was seen in mean PAI-1 levels in psychotic patients across different diagnoses (F: 6.34, P: 0.005). Schizoaffective subjects had significantly lower PAI-1 levels compared to the rest of the study subjects. The effect size was 0.284.

Overall, the tPA levels were lower in patients with psychosis as compared to healthy controls, although this was not statistically significant. Female patients and controls had higher levels of tPA than their male counterparts, but the differences did not reach statistical significance. PAI-1 levels were higher in female healthy controls but lower in patients as compared to their male counterparts.

Patients with schizophrenia and psychotic depression had higher BPRS scores as compared to other groups (67.2 and 72.5 respectively) although the difference was not statistically significant. (P > 0.05).

Table 3
Plasma levels of tPA and PAI-1 in the different groups.

	Mean tPA ng/mL (SD)	Mean PAI-1 ng/mL (SD)
Controls	3.37 (1.65)	45.9 (38.1)
Schizoaffective disorder	3.03 (0.98)	18.7 (14.4)*
- On mood stabilizers, Li and VPA (n = 12)	2.93 (0.98)	14.9 (10.1)
- Not on mood stabilizers (n = 9)	3.16 (1.05)	23.7 (18.0)
Schizophrenia	3.03 (0.99)	41.4 (25.6)
Bipolar disorder with psychosis	2.96 (1.54)	47.0 (38.1)
Major depression with psychosis	2.85 (0.98)	(30.2)

* Healthy controls had higher PAI-1 levels as compared to Schizoaffective patients (P = 0.03). However, there was significant variation of PAI-1 levels in our study population.

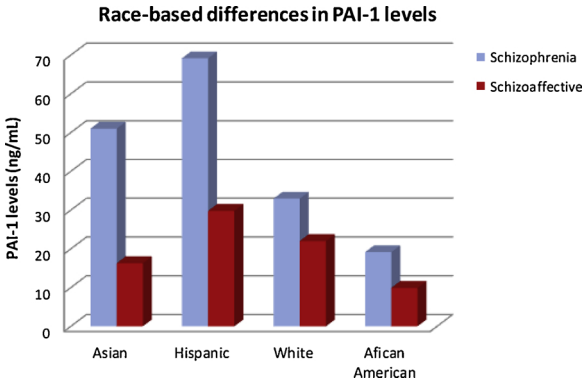

Fig. 1. Comparison of PAI-1 levels (ng/mL) in Schizophrenia and Schizoaffective patients based on their race.

Table 4
Plasma levels PAI-1 and tPA (ng/mL) in different Ethnic Groups.

	tPA Cases	tPA Controls	PAI-1 Cases	PAI-1 Controls
Asians	3.12 (0.84)	2.96 (1.19)*	30.9 (19.2)	16.0 (11.0)
Hispanics	3.28 (1.40)	4.92 (0.75)	50.1 (28.8)	62.4 (47.5)
White	3.09 (1.01)	3.35 (1.67)	32.0 (28.1)	55.2 (37.3)
African American	1.98 (0.58)	2.16 (1.12)	11.8 (8.8)	22.9 (17.2)

Data presented as mean (SD).

* There is significant difference (p = 0.02) between tPA levels in Asian and Hispanic healthy controls using ANOVA statistical test (95% confidence interval). Bonferroni corrected p = 0.044.

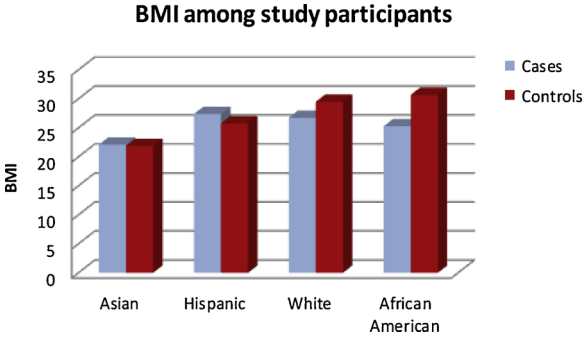

Fig. 2. Comparison of BMI among different races in the study population.

4. Discussion

Prior investigators have demonstrated that patients with schizophrenia exhibit high levels of PAI-1 independent of antipsychotics, and also report of elevated PAI-1 levels in their first-degree relatives (Carrizo et al., 2008). In this study, we found that cases had lower PAI-1 levels as compared to controls and this difference reached statistical significance when patients with schizoaffective disorder were compared to the control group. This finding is different from those in previous reports and requires further study to clarify the nature of the association between PAI-1 levels in patients with schizoaffective disorder.

4.1. Factors affecting PAI-1 levels

The PAI-1 promoter responds to tumor necrosis factor (TNF)-α, very-low density lipoproteins (VLDL), angiotensin, cortisol, aldosterone, and to insulin precursors (Vaughan, 2005). Out of these, TNF-α (Capuzzi et al., 2017), VLDL (Misiak et al., 2017), and insulin

precursors/angiotensin/aldosterone (Bernstein et al., 2016), have been shown to be abnormal in psychotic patients in previous studies. Leptin (Singh et al., 2010) and homocysteine (Midorikawa et al., 2000) also upregulate the expression of PAI-1 in human vascular endothelial cells. Studies have demonstrated possible role of leptin in various psychiatric disorders such as affective disorders, eating disorders, psychotic disorders and alcohol dependence (Zupancic and Mahajan, 2011). Similarly, hyperhomocysteinemia has been associated with various psychiatric illnesses (Tiemeier et al., 2002; de Haan et al., 2004). Cortisol, however, has been shown to be associated with mood symptoms more than psychotic symptoms in a recent meta-analysis (Zorn et al., 2017). Thus the existing data suggest the possibility of PAI-1 being a differentiating biomarker between schizophrenia and schizoaffective disorder, as it is influenced by factors affected in both mood and psychotic disorders.

4.1.1. Metabolic syndrome

Besides its prothrombotic effects, PAI-1 is associated with obesity development and maintenance through several mechanisms, such as influencing insulin signaling, adipocyte differentiation and by regulating recruitment of inflammatory cells within adipose tissue. It is known that PAI-1 is up-regulated in obesity. As a consequence, PAI-1 is considered by some authors as a true component of the metabolic syndrome (Alessi et al., 2007). In our sample, African American and Caucasian controls had higher BMI than cases, although the difference was not statistically significant. BMI was possibly a confounder in our study population.

4.1.2. Gender

Apart from studies showing PAI-1′s role in psychosis, it has been demonstrated that women with MDD have higher PAI-1 levels than normal controls (Eskandari et al., 2005). Similarly in a recent study of 231 men (123 without coronary heart disease and 108 with documented coronary heart disease), it was found that depressed subjects had higher levels of PAI-1 activity (Lahlou-Laforet et al., 2006). In our study population, PAI-1 levels were higher in female than in male controls but lower in female than in male patients.

4.1.3. Race

Our diverse study population provided a good opportunity to look at inter and intra racial differences. The data show statistically significant differences in PAI-1 levels in Asian patients with schizophrenia as compared to those with schizoaffective disorder. The data also point towards intra racial differences in PAI-1 levels, both when differentiating different psychotic disorders as well as with regards to metabolic syndrome. This aspect needs to be studied further, as it has the potential of opening new avenues of personalized medicine in patients with psychosis. We did not find studies that focused on PAI-1 and tPA which included participants from different racial/ethnic backgrounds. Hence a potential area for future study could be to examine polymorphisms and metabolic profiles of patients from various races/ethnicities and to correlate the data with psychosis.

4.2. Factors affecting tPA levels

We found that tPA level was lower in psychotic patients compared to controls, although it did not reach statistical significance. There have been studies reporting high prevalence of factors for low tPA activity in medication-naïve psychotic patients, such as antiphospholipid antibodies (Delluc et al., 2014), hyperinsulinemia (Kale et al., 2010), and hyperhomocysteinemia (Ryan et al., 2003). Additionally, tPA's catalytic activity is influenced by conditions such as hyperhomocysteinemia (Hajjar et al., 1998) or antiphospholipid antibodies (Krone et al., 2010). High tPA levels but low tPA activity may account for these findings. Focusing on these factors may shed some light on the role of tPA in patients with psychosis. In our study, females had higher levels of tPA than males, both among patients and controls, although the difference did not reach statistical significance.

4.3. Influence of medications on tPA and PAI-1

Analyzing the data based on the medications that the patients were taking, we found that mood stabilizers such as lithium and valproic acid (VPA) impact tPA and PAI-1 levels. In schizoaffective subgroup of psychotic individuals, majority of patients were on lithium or VPA. When PAI-1 and tPA levels in subjects with schizoaffective disorder that were not on mood stabilizers were compared to other groups of psychotic subjects, it showed lower levels of both markers (14.9 vs 23.7 ng/dL and 2.93 vs 2.16 respectively, $P = 0.21$ and 0.59). One possible explanation for this is that both lithium and VPA are linked to lower PAI-1 levels. VPA has been demonstrated to dose-dependently increase tPA and decrease PAI-1 activity in rat primary astrocytes (Cho et al., 2013). Lithium has been shown to inhibit Smad3/4-dependent transcriptional activation and decreasing Smad3/4-dependent gene promoter activity of PAI-1 and p21 in neuron-enriched cortical cultures (Liang et al., 2008). Further research in this area is necessary to clarify the role of mood stabilizers such as lithium and VPA in targeting specific biomarkers involved in the disease process.

In contrast, serotonin has been shown to increase PAI-1 levels in endothelial cells (Kawano et al., 2001). Furthermore, patients on serotonergic antidepressants appear to have fibrinogen and PAI-1 plasma levels that are similar to those of healthy controls, but lower than in depressed patients receiving non-serotonergic antidepressants (Geiser et al., 2011). Antipsychotics, especially clozapine and olanzapine, may promote weight accrual and increase the levels of insulin and triglycerides (Melkersson and Dahl, 2003; Wu et al., 2006). In their turn, both insulin and triglyceride carrier VLDL provide stimulus for PAI-1 synthesis (Vaughan, 2005). Although this study raises the possibility of a unique role of PAI-1 in differentiating patients with schizoaffective disorder from those with schizophrenia that their medications did not significantly alter, further studies in drug-naïve population are needed to establish this.

Of note, since the PAI-1 promoter responds to glucose and insulin (Vaughan, 2005), one would expect that interventions effective in decreasing glucose levels and insulin synthesis, such as regular aerobic exercises and carbohydrate-restricted diets, could help normalize tPA activity (Hoirisch-Clapauch and Nardi, 2015). Obese patients with schizophrenia or schizoaffective disorder who achieve weight reduction with a program incorporating nutrition counseling and aerobic exercise may experience significant improvement of the mental symptoms (Chen et al., 2009). Resolution of longstanding schizophrenia symptoms has been also reported after starting a low-carbohydrate, ketogenic diet (Kraft and Westman, 2009). It seems that lifestyle interventions, such as regular exercise and a low carbohydrate diet, are as important as pharmacological interventions in palliating mental symptoms.

Although the difference was not statistically significant, patients with schizophrenia and psychotic depression had higher BPRS scores as compared to other groups, perhaps due to the higher disease burden in these two groups. As sample collection and administration of scales took place when patients were closer to discharge, some may have been closer to remission.

4.4. Study limitations

One limitation of our study is that none of our patients were drug naive. Another limitation is that the relatively small sample size in each diagnostic group did not allow for comparisons between ethnic groups. One possibility is that patients with schizoaffective disorders could have low tPA activity due to conditions that do not necessarily affect PAI-1, such as hyperhomocysteinemia and antiphospholipid antibodies. Unfortunately, our subjects were not screened for hyperhomocysteinemia or the presence antiphospholipid antibodies. Also, no genetic

analyses were conducted to ascertain the role of gene polymorphisms in the disease process of these patients.

5. Conclusions

To the best of our knowledge, this is the first study to address the heterogeneity of psychotic spectrum disorders (in contrast to most previous investigations focused on schizophrenia) with regard to the search for biomarkers. It takes into account the context of psychosis (whether purely psychotic or driven by mood or a mix of both) which is more reflective of the real clinical world. Our patients were acutely psychotic and hospitalized while undergoing treatment. These factors are also limitations in our study and results should be interpreted cautiously and accordingly. Our preliminary findings are as follows: Plasma levels of PAI-1 in patients with schizoaffective disorder were significantly lower as compared to those in control subjects. tPA was lower in cases as compared to controls although it did not reach statistical significance. Asian patients and controls had lower PAI-1 levels. Further, Asian patients with schizoaffective disorder had significantly lower PAI-1 level compared to Asian patients with schizophrenia.

The preliminary data suggest the possibility of a relationship between PAI-1 and schizoaffective disorder, with the additional suggestion that these results may be more pronounced in Asian patients with schizoaffective disorder. It should be noted that this study found levels of PAI-1 to be lower in schizoaffective disorder compared to healthy controls, whereas prior studies have found elevated levels of PAI-1 in patients with schizophrenia, as well as first-degree relatives. These results warrant further clarification and exploration using larger samples, possibly from multiple centers. Additionally, clarification of the role of tPA and its inhibitors and activators may open up new ground in our understanding of psychotic spectrum disorders.

Compliance with ethical standards

This work was completed in compliance with federal, state and institutional regulations as well as confidentiality standards and was approved by the Maimonides Institutional Review Board /Research Committee (study # 2015−05-14-MMC).

Conflict of interest disclosure

The Authors have declared that there are no conflicts of interest in relation to the subject of this study.

Contributions

Authors SE and TJ designed the study and wrote the protocol. Authors KM and TJ obtained the grant. Author SE, GS and TJ managed the data collection. Author SE undertook the statistical analysis and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Role of funding source

The sponsors had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

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