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Increased prolidase activity and high blood monocyte counts in pediatric bipolar disorder

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ABSTRACT

Various psychological, genetic, and biochemical factors are thought to be involved in the aetiology of pediatric bipolar disorder (PBD). However, few studies have evaluated the biochemical basis of PBD. The level of peripheral blood mononuclear cells and serum prolidase activity were determined in PBD and matched healthy comparison subjects.

Blood from 38 (age range: 14–17) PBD-type I and 37 age- and gender-matched healthy comparison subjects was analyzed for numbers of neutrophils, lymphocytes, monocytes, lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR) and serum prolidase activity. The prolidase activity and monocyte count were significantly higher in PBD than the control group. There were no significant differences in numbers of neutrophils, lymphocytes, LMR and NLR between the patient and control groups. These results suggest that the immune system and prolidase activity may be activated in PBD. There is a clinical benefit from the early detection of PBD using serum prolidase activity levels and monocyte counts. Especially, prolidase activity may be a trait marker for diagnosing PBD. However, further studies are needed to verify these findings.

1. Introduction

Bipolar disorder (BD) is a serious neuropsychiatric disorder characterized by episodes of depression and mania/hypomania/mixed states with interepisodic phases of remission (APA, 2013). Even if the disorder diagnose after adolescence, it is known that 59% of the cases experience their first episode in childhood or adolescence (Lish et al., 1994). In the past decade, there has been an increase in the number of children and adolescents diagnosed with pediatric bipolar disorder (PBD). Recent studies on PBD estimate that the disorder afflicts 1–2% of children and adolescents (Hafeman et al., 2016). PBD more often presents with higher rates of mixed episodes, rapid cycling, prominent irritability, psychotic symptoms and co-occurring Attention-Deficit/Hyperactivity Disorder (ADHD) than adult patients with BD (adult-BD) (DelBello et al., 2006; Ceylan et al., 2012). Additionally, these deficits correlate with impairments in social functioning, and reduced quality of life (Fulford et al., 2014).

The cause and pathophysiology of BD is incompletely understood. Various, genetic, enviromental, psychological stress and biochemical factors are thought to be involved in the aetiology of BD (McGuffin et al., 2003; Marangoni et al., 2016). However, few studies have evaluated the biochemical basis of PBD. Prolidase is a hemodynamic and manganese-dependent member of the matrix metalloproteinase family. Matrix metalloproteinases are enzymes which are involved in the degradation of extracellular matrix into proline and hydroxyproline (Tsuruda et al., 2004). Prolidase enzyme activity is determined in the plasma and also in various tissues including, erythrocytes, leukocytes, dermal fibroblasts, kidney, heart, thymus, and brain (Zanaboni et al., 1994; Vural et al., 2010). Its main physiological activity is related to collagen synthesis, protein synthesis and cell growth (Palka, 1996; Wu et al., 2011). Prolidase is important for the functional metabolism of proline in the brain and prolin exist in central nervous system (CNS) commonly (Hui and Lajtha, 1978; Hauptmann et al., 1983). Prolin is accepted as a neurotransmitter and increases in prolidase levels are associated with increaeses in prolin levels. Prolidase enzyme is esential for prolin metabolism in brain (Lajtha and Toth, 1974; Selek et al., 2011). Increased prolidase activity results in increased proline and proline peptides, and increased proline levels, through prolidase activity, lead to glutamate excitotoxicity (Cohen and Nadler, 1997). It has been shown that disordered proline metabolism is related to various disorders, including, behavioral disorder, adult-BD, and schizophrenia (Wyse and Netto, 2011; Selek et al., 2011; Gunes et al., 2016). Hyperprolinemia is also regarded as a risk factor for schizoaffective disorder (Jacquet et al., 2005). In addition to that, increased prolidase

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activity has been reported that prolidase is a reliable diagnostic test for adult-BD (Selek et al., 2011).

Recent studies indicate that immune activation may contribute to the etiopathogenesis of BD. Anderson and Maes (2015) have demonstrated that low-grade chronic inflammation and T-cell activation features in the etiology of the disorder. Benros et al. (2013) suggested that bacterial infections are a source of immune activation and have been shown to be a risk factor for the subsequent development of mood disorders. The studies on the effect of immunity on BD are conducted mainly on adult-BD samples. This is the first study that examines both the effect of immune system and prolidase activity in PBD. In this study, the level of peripheral blood mononuclear cells and serum prolidase activity were determined in PBD and matched healthy comparison subjects and its effect on the etiopathogenesis of the disorder will be discussed.

2. Method

2.1. Subjects

The patient group consisted of 38 child and adolescent patients (14–17 age range) chosen from 50 patients admitted to the child and adolescent psychiatry clinic of Ankara Yildirim Beyazit University Yenimahalle Education and Research Hospital who met the inclusion criteria of the study and who had been diagnosed as having BD-type I according to DSM-5 criteria (APA 2013). The severity of BD symptoms in the patients was evaluated using the Young Mania Rating Scale (YMRS) (Young et al., 1978), Children's Depression Inventory (CDI) (Kovacs, 1981) and Clinical Global Impression-severity (CGI-S) (Guy, 1976). The patients in the remission period of the PBD are included in the study. We excluded mania, hypomania and mixed states BD patients. The cases with PBD that has YMRS scores < 12 (McIntyre et al., 2006), CDI scores < 12 (Tashakori et al., 2007), and CGI-S = 1 had included in the study. Patients with a comorbid drug abuse, acute systemic diseases, neurologic, or genetic disorder were excluded, as were patients with a history of chronic systemic diseases, such as endocrinologic and allergic diseases. The control group consisted of 37 age- and gender-matched healthy comparison subjects. Sociodemographic data and clinical features were recorded. This study was approved by the ethics committee of the Ankara Yildirim Beyazit University Yenimahalle Education and Research Hospital.

2.2. Blood samples

Venous blood samples were collected at 9.00 a.m. from an antecubital vein after a 12-h overnight fasting period; 10 mL of venous blood from each patient were sampled in biochemistry tubes. The biochemistry tubes were centrifuged at 2000 × g for 15 min after an incubation period of 30 min. The remaining serum specimens were kept at − 20 °C until serum prolidase activity analyses were performed. Additionally, monocyte count, neutrophils, lymphocytes, lymphocyte-to-monocyte ratio (LMR) and neutrophil-to-lymphocyte ratio (NLR) were determined in Ankara Yildirim Beyazit University Yenimahalle Education and Research Hospital.

Serum prolidase activity were measured by human prolidase (peptidase D) ELISA (enzyme linked immunosorbent assay method) Kit (E-EL-H5575). This ELISA kit uses the Sandwich-ELISA principle. The micro ELISA plate provided in this kit has been pre-coated with an antibody specific to Human PEPD. Standards or samples are added to the micro ELISA plate wells and combined with the specific antibody. Then a biotinylated detection antibody specific for Human PEPD and Avidin-Horseradish Peroxidase (HRP) conjugate are added successively to each micro plate well and incubated. Free components are washed away. The substrate solution is added to each well. Only those wells that contain Human PEPD, biotinylated detection antibody and Avidin-HRP conjugate will appear blue in color. The enzyme-substrate reaction is terminated by the addition of stop solution and the color turns yellow. The optical density (OD) is measured spectrophotometrically at a wavelength of 450 nm ± 2 nm. The OD value is proportional to the concentration of Human PEPD. You can calculate the concentration of Human PEPD in the samples by comparing the OD of the samples to the standard curve.

2.3. Statistical analysis

SPSS® for Windows 20.0 was used to analyse the data statistically. In the case of normally distributed and homogenous variables, the significant differences between groups were estimated using two tailed *T*-tests. The Mann–Whitney *U test* was used to investigate the non parametric hypotheses when comparing two independent samples. Bivariate comparisons were examined via Spearman correlation coefficients; values were corrected for ties. In addition, Chi square tests were used to evaluate categorical data. Differences were considered significant when p was less than 0.05.

3. Results

Thirty-eight PBD patients and 37 healthy controls were included in this study. In the PBD group, the mean age was 16.3 years (0.9 SD; range, 14–17 years of age). The control group's mean age was 16.8 years (0.6 SD; 14–17 years of age). In the PBD group, 10 of the patients were male and 28 were female; in the control group, 10 of the participants were male and 27 were female. There were no differences in mean age or gender distribution between the groups ($p > 0.05$). Off the 38 patients with PBD, 13 of them had a familial history of BD. The sociodemographic and clinical characteristics of the subjects are summarized in Table 1 and Table 2.

The prolidase activity and monocyte count were significantly higher in PBD in the comparison subjects (Table 3, Figs. 1 and2). There were no significant differences in numbers of neutrophils, lymphocytes, LMR and NLR between the patient and control groups (Table 3).

There was no statistically significant correlation between prolidase level and age ($r = 0.04$; $p = 0.80$), age of onset ($r = -0.03$; $p = 0.85$) and duration of the disease ($r = 0.01$; $p = 0.90$).

Also there was no statistically significant correlation between monocyte count and age ($r = -0.03$; $p = 0.84$), age of onset ($r = -0.11$; $p = 0.50$) and duration of the disease ($r = -0.28$; $p = 0.07$).

There were no statistical correlation between prolidase activity and neutrophil ($r = 0.133$; $p = 0.256$), lymphocyte ($r = 0.063$; $p = 0.588$), monocyte counts ($r = 0.210$; $p = 0.070$), LMR ($r = -0.150$; $p = 0.199$), and NLR ($r = 0.031$; $p = 0.793$).

A Receiver Operating Characteristics (ROC) analyse for prolidase activity between groups is conducted. The area under the curve = 0.354. The likelihood ratio is calculated as 2.3; the cut off point was calculated as 182.81 for prolidase activity. The ROC curve analyse is presented as Fig. 3. A ROC analyse was also conducted for monocyte count between groups but it was not significant.

Table 1
Sociodemographic data of the participants in two groups.

	PBD (n = 38)	Control (n = 37)	Z or χ^2	P
Age	16.3 ± 0.9	16.8 ± 0.6	−1.129	0.25
Sex (male)	10 (26.3%)	10 (27.0%)	0.005	0.57
Bipolar Disorder in Family Members	13 (34.2%)	0	15.312	< 0.0001
Young Mania Rating Scale	2.7 ± 1.3	1.5 ± 0.5	−4.366	< 0.0001

Table 2
Clinical characteristics of the cases with pediatric bipolar disorder.

	Mean	Minimum	Maximum	Median
Age of Onset	13.7 ± 1.9	8 years	16 years	14 years
Age of getting first medical Support	14.3 ± 1.9	8 years	17 years	14 years
Duration of illness	2.9 ± 1.3	6 months	6 years	3 years

Table 3
Peripheral blood mononuclear cells and serum prolidase activity in patient with pediatric bipolar disorder (PBD) and control groups.

	PBD	Control	*Z* or *t*	*p*
Prolidase ng/ml	166.9 ± 21.0	136.7 ± 50.0	−2.172	0.03
Monocytes (× 103/mm3)	562.8 ± 199.7	406.2 ± 112.9	4.166	< 0.0001
Neutrophyl (× 103/mm3)	4140 ± 1542	3778 ± 1262	1.108	0.46
Lymphocytes (× 103/mm3)	2433.6 ± 769.8	2206.2 ± 752.6	1.293	0.86
LMR	4.71 ± 1.7	5.57 ± 1.5	−2.265	0.54
NLR	1.84 ± 0.8	1.80 ± 0.6	−0.307	0.75

LMR: lymphocyte-to-monocyte ratio; NLR: neutrophil-to-lymphocyte ratio.

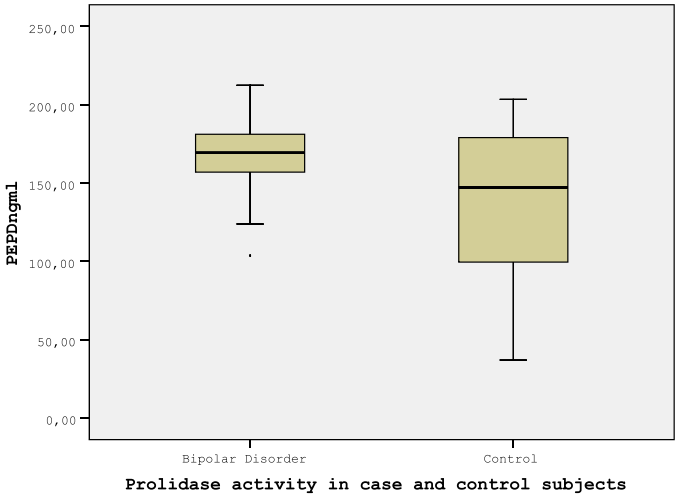

Fig. 1. Prolidase activity in case and control subjects.

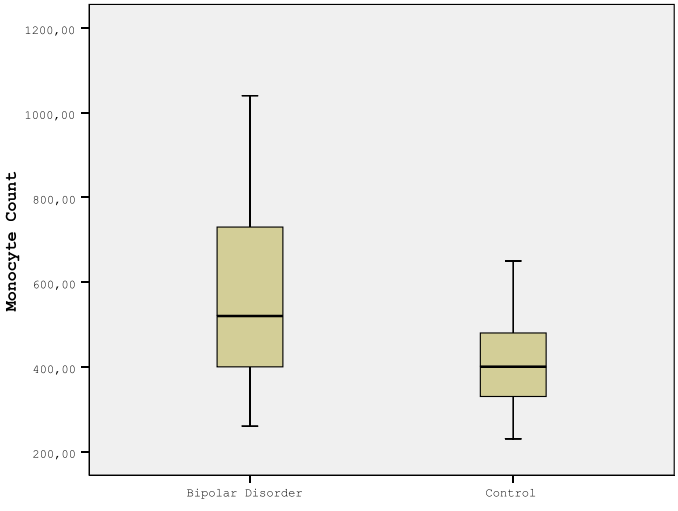

Fig. 2. Monocyte count in patients with bipolar disorder and control subjects.

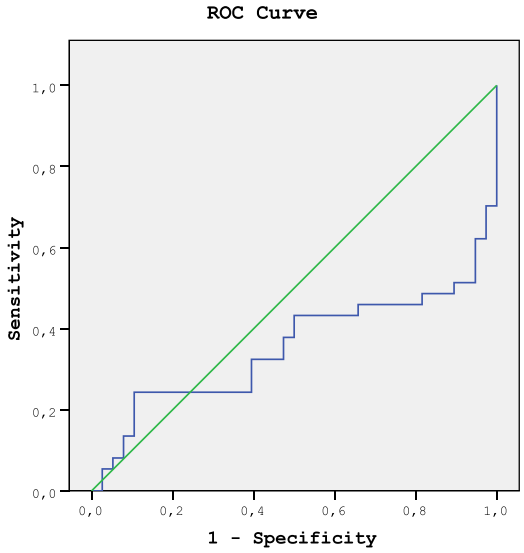

Fig. 3. Receiver operating characteristics curve for prolidase activity between groups.

4. Discussion

The first finding of this study is that patients with PBD exhibited increased prolidase activity than the controls. To the best of our knowledge, this is the first study investigating serum prolidase activity levels in patients with PBD. In another study that evaluated prolidase activity in patients with adult-BD, prolidase activity was found to be higher in adult-BD cases when compared to healthy controls (Selek et al., 2011), which is consistent with our results.

Prolidase is important for the functional metabolism of proline in the brain (Hui and Lajtha, 1978) and proline acts as a neuromodulator in synaptic transmission (Crump et al., 1999). Proline in mammals is synthesized from glutamate by reversal of reactions existing in proline catabolism. Increased proline levels have been reported to cause an increase in glutamate levels and to activate N-methyl D-aspartate (NMDA) receptors (Cohen and Nadler, 1997; Arikanoglu et al., 2013; Delwing et al., 2003). Glutamate is the principal excitatory neurotransmitter in the CNS. In mature brains, it is critically involved in neuroplasticity and, at high levels, neurotoxicity. Increase in glutamate levels activate NMDA receptors and may act in the pathophysiology of BD. Tan et al. (2016) found that glutamate was significantly higher in BD depressive state compared with unipolar depression. Memantine is a non-competitive NMDA receptor antagonist. The manic phase of BD also appears to benefit from memantine (Lu and Nasrallah, 2018). Poletti et al., (2018) suggested that adverse childhood experiences are highly reported in BD and interact with the glutamatergic system in the brain. As a result, dopamine-glutamate interplay dysfunctions have been suggested as pathophysiological key determinants of major psychotic disorders, above all schizophrenia and mood disorders (Tomasetti et al., 2017). We consider that increased prolidase activity causes excessive glutamate levels by increasing proline, and this may result in hyperstimulation of the NMDA receptors.

ROC analyzes in our study indicates the diagnostic value of prolidase activity. Selek et al. (2011) suggested that the prolidase activity may be a trait marker for diagnosing adult-BD. However the increase of the prolidase activity in Selek et al's study was more prominent. As many as 59% of adult patients with BD experience their first episode before the age of 18 (Lish et al., 1994). The significance of the increase in prolidase activity may be associated with the destructive effects of the disorder.

The brain is rich in a fatty acid composition that is highly conducive of oxidation. Therefore, the brain is highly vulnerable to oxidative

stress (Halliwell, 2006). The fatty acid composition of the cell membrane can affect neurotransmitter functioning (Nunez, 1993). Several studies suggested that prolidase activity is increased during oxidative stress (Aslan et al., 2007; Cakmak et al., 2010). Oxidative metabolism is found to be impaired in BD (Savas et al., 2006). Andreazza et al., (2008) meta-analysis suggests that oxidative stress may contribute to the pathophysiology of BD. Selek et al. (2011) reported that prolidase activity is impaired in adult-BD, which may be associated with oxidative stress.

The second finding of our study is that the monocytes are significantly higher in the study group than in the control group. This increase in monocytes may play a role in the etiology of the disorder as an indicator of chronic inflammation. These results points to an immunological dimension of PBD. Immune dysfunction seems to play a major role in the pathophysiology of BD (Rosenblat et al., 2017). However, few studies have evaluated the biochemical basis of immune dysfunction in PBD (Goldstein et al., 2015; Miklowitz et al., 2016). Monocytes are a type of white blood cell, or leucocyte, originating from the bone marrow and circulating in the blood. Some of these cells enter tissues and mature into macrophages (Abbas et al., 2007). Monocytes have an important role in both innate and adaptive immunity. Their effector functions in innate immunity are to phagocytose microbes as mononuclear phagocytes and to produce cytokines that activate other inflammatory cells. They also have an antigen-presenting function in adaptive immunity (Abbas et al., 2007). Increase in monocyte count in PBD is a sign of chronical inflammation and may play a role in the pathophysiology of the disorder. The studies showed that monocyte levels are increasing in psychiatric disorders like autism (Tural Hesapcioglu et al., 2017) and schizophrenia (Uranova et al., 2017) and chronical inflammation may play a role in the pathophysiology of the disorders. The other immunological findings of our study were the absence of significant differences in numbers of neutrophils, lymphocytes, LMR and NLR between the patient and control groups. Likewise, Cevher Binici et al.'s (2018) study which they demonstrated that NLR level was similar in the patient and control group. LMR is a ratio and is affected by the lymphocyte and monocyte counts. LMR levels are lower in the PBD group but it was not statistically significant.

The etiology of BD is multifactorial, resulting from a complex interaction between genetic background and environmental (non-genetic) risk factors (Kerner, 2014). CNS and immune system are systems which are in interaction with each other (Bradstreet et al., 2007). Immune cells and molecules play a crucial role in forming the brain functions by affecting the cognitive and emotional processes (Yirmiya and Goshen, 2011). The immunity might be triggered in the early stages of development for a large number of environmental risk factors such as viral infections (Avramopoulos et al., 2015), toxoplasma gondi (Oliveira et al., 2016), bacterial infections (Benros et al., 2013), and microbiome (Dickerson et al., 2017). As a result, the immune dysfunction may contribute to the development of the disorder via affecting the brain cell functions including synthesis of neurotransmitters and synaptic functions and plasticity. Such as, Winter et al. (2009) found that prenatal immune activation significantly increased the levels of dopamine and its major metabolites.

Serum prolidase activity play a role in physiological and pathological processes like cell migration, tissue resorption and wound healing which are associated with inflammation (Berrier and Yamada, 2007; Hu et al., 2008.). We have previously reported that increased prolidase activity leads to increased glutamate. Microglias are the resident immune cells of the brain. Upon immune activation, microglia release pro-inflammatory cytokines as well as other factors, such as glutamate (Guillemin et al., 2004; Kettenmann et al., 2011). Increased release of glutamate may induce excitotoxicity and contribute to neuronal damage and/or dysfunction (Mechawar and Savitz, 2016). As a result, the increase in PBD prolidase enzyme activity may play a role in the pathophysiology of the disease, contributing to inflammation and glutamate dysfunction.

The third finding of our study we also did not found any correlation between mean prolidase activity and age onset of disease, family history, and disease duration.

The most prominent limitation of this study is the relatively small sample size and we could not evaluate the correlation between disease severity (manic, depressive state) and serum prolidase activity. Other limitations of this study include the lack of glutamate levels along side prolidase activity, and cross-sectional measurements of prolidase activity.

Lai et al. (2018) suggested that there were no significant differences between the acute BD and euthymic BD groups in the biochemical metabolite ratios and executive function. This result is consistent with the DSM classification of BD. In our study the patients in remission period are preferred because of same condition. However, there is a need of studies that compare acute BD, euthymic BD patients and healty controls to understand the biochemical difference of the prolidase activity and monocyte levels.

5. Conclusion

To the best of our knowledge this is the first study evaluating the prolidase activity and leukocyte counts in PBD. These results suggest that the immune system and prolidase activity may be activated in PBD. There is a clinical benefit from the early detection of PBD using serum prolidase activity levels and monocyte counts. Especially, prolidase activity may be a trait marker for diagnosing bipolar disorder. However, further studies are needed to verify this. Our findings may pioneer further clinical biochemical studies on PBD.

Disclosures

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This study was not supported by any company.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.11.066.

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