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Serum DHEA-S concentration correlates with clinical symptoms and neurocognitive function in patients with bipolar II disorder: A case-controlled study

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ABSTRACT

Objectives: Dysregulation of the neuroendocrine system including dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-S), and pregnenolone may play a role in the pathophysiology of bipolar II disorder (BP-II). The aims of the current study are to determine (a) the differences in DHEA, DHEA-S and pregnenolone in patients with BP-II and controls; and (b) the correlation of levels of the above hormones, cognitive function, and clinical symptoms.
Methods: Patients diagnosed with BP-II and healthy controls were recruited from psychiatric department. Blood samples were collected to measure the levels of DHEA, DHEA-S and pregnenolone in all participants, followed by assessment of cognitive function using the Brief Assessment of Cognition in Affective Disorders (BACA).
Results: A total of 32 patients BP-II and 30 healthy control subjects were recruited. The BP-II group was found with significantly elder age, fewer years of education, and lower BACA composite scores compared to the healthy controls. The level of DHEA-S was significantly associated with performance in BACA when controlling for age, gender, years of education and having BP-II ($P = 0.018$). The DHEA-S level was significantly correlated with mania score ($r = -0.498$, $P = 0.010$).
Conclusion: Our findings support that serum level of DHEA-S may be a biomarker representing clinical manic symptoms and cognitive performance.

1. Introduction

Bipolar II disorder (BP-II) is a commonly seen and severe subtype of bipolar disorder (BP). Its clinical presentation includes major depressive episodes and hypomanic episode. BP-II is reported with a prolonged course, mainly with major and minor depressive episodes (Judd and Akiskal, 2003). Although a common subtype of BP, BP-II is frequently under-recognized (Angst et al., 2003a; Benazzi and Akiskal, 2003) because patients usually perceive hypomanic episodes as normal mood status or positive experiences and only seek for treatment during depressive episodes (Angst, 2007). Delayed diagnosis and missed treatment opportunities lead to increased risk for suicide, switched mania, and chronic psychosocial suffering (MacQueen et al., 2003; Rihmer et al., 2001), which add to the burden this disorder places on both patients and society.

In recent years, hormones such as dehydroepiandrosterone (DHEA), has been reportedly involved in regulating mood expression and aggression (Wolkowitz et al., 2001). DHEA, as an adrenal androgen, is an essential substrate for the synthesis of androstenedione and testosterone (Gurnell and Chatterjee, 2001). The DHEA-S, a sulfated form of DHEA, is the most plenty DHEA in humans (Morfin, 2002). DHEA may transform into compounds in the brain, skin, muscle, and reproductive organs. DHEA has been related to depression because it demonstrated ability to modulate neurobiological actions related to mental disorders

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including glutamate receptors, catecholamines, neurogenesis, neuroprotection, and anti-inflammatory properties (Maninger et al., 2009). Dysthymic patients was found with low serum DHEA-S concentrations (Markianos et al., 2007); while DHEA was reported to trigger or precipitate manic symptoms (Kline and Jaggers, 1999; Markowitz et al., 1999). Investigating the DHEA levels in BP has raised much interest in recent years (Marx et al., 2006). One postmortem study found that DHEA level was higher in subjects with BP compared to control subjects (Marx et al., 2006). Another one demonstrated no difference in DHEA levels nor cortisol-DHEA ratio between BP and controls (Gallagher et al., 2007). Furthermore, DHEA is the downstream metabolite of the precursor steroid pregnenolone. Pregnenolone, converted from cholesterol, is involved in the synthesis of steroid hormones as a rate-limiting step. Pregnenolone level was once found higher in BP compared to controls in both parietal cortex and posterior cingulate (Marx et al., 2006). However, the relation between the above neurosteroids and pathogenesis of BP-II warrants further studies, since study on the association of concentration of DHEA and BP, especially BP-II, remains scarce.

Several neuropsychological testing found cognitive deficit in bipolar disorder. Even after the symptoms had been remitted, the damage of cognitive function still remains (Ferrier et al., 1999; Rubinsztein et al., 2000). Martinez-Aran et al. (2004) reported that even in euthymic states, patients with BP still showed poorer ability on executive function and verbal memory than normal controls did, and that there was high correlation between neuropsychological functioning and global assessment of functioning. The decline in cognitive function also influence negatively on patients' drug adherence, treatment effect and prognosis (Summers et al., 2006). Additionally, previous studies even showed changes on intelligence quotient (IQ) and space memory in BP-II (Summers et al., 2006). Glahn et al. (2004) proposed that the deficit of maintaining attention in BP might be related to mood symptoms (trait) instead of a state variable (Quraishi and Frangou, 2002). An inverse correlation between serum DHEA-S levels and cognitive performance has been reported in women (Davis et al., 2008) and elderly (Kalmijn et al., 1998). Therefore, it would be of interest to determine the correlation between these neuroendocrine parameters with cognitive function in BP-II.

To date, there is not yet a reliable biomarker to help diagnosis of BP-II. The diagnosis of BP-II still remains on clinical interview to assess symptom and behavioral, psychological impairment. It is important to identify biomarkers to move beyond symptomatology and nosology for the purpose of refining the diagnosis and treatment. The neuroendocrine system modulates many neurobiological actions such as catecholamine, neuroprotection, and anti-inflammatory properties. Therefore, dysregulation of the neuroendocrine system in patients with BP has gained increasing attention as the pathogenesis of BP. The aim of the current study is to determine whether the association between neuroendocrine parameters (DHEA, DHEA-S, and pregnenolone) with the clinical symptoms and neuropsychological functions of BP-II. The information may serve as an important reference for pathophysiology and benefit the search of potential biomarker for BP-II.

2. Material and methods

The Institutional Review Board for the Protection of Human Subjects at Kaohsiung Veteran's General Hospital reviewed and approved this research protocol and the methods were carried out in accordance with the approved guidelines. Before the study began, a detailed description of the current study was explained to all participants before they signed an informed consent.

Male and female patients with BP-II between 18 and 65 years old were recruited from acute wards and outpatient clinics in psychiatric department at Kaohsiung Veteran's General Hospital. After each patient has been diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) criteria by a senior psychiatrist, they received a structured interview conducted by a clinical psychologist to confirm the diagnoses. The structural interview used, having good inter-rater reliability (Huang et al., 2004), was the Chinese Version of the Modified Schedule of Affective Disorder and Schizophrenia-Life Time (SADS-L) (Endicott and Spitzer, 1978). Patients with any major psychiatric disorders other than BP-II, such as borderline personality disorder, substance abuse or dependence, and cognitive disorders were excluded. Patients having chronic physical illness and metabolic illness were also excluded.

Although DSM-IV-TR criteria require a minimum duration of 4 days of hypomania, current epidemiologic data suggest that a 2-day duration is more prevalent in community samples (Akiskal et al., 1977; Akiskal et al., 1979; Angst, 1998; Angst et al., 2003b; Benazzi, 2001; Judd et al., 2003); therefore, we used the 2-day minimum for hypomania in the diagnosis of BP-II.

All recruited patients were first diagnosed, never received any mood stabilizers or antipsychotics in the past. Symptom severity was assessed after recruitment by the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1967) and the Young Mania Rating Scale (YMRS) (Young et al., 1978). The HDRS contains 17 items to assess the severity of depressive symptoms; the YMRS is consisted of 11-item to rate the severity of mania. From each patient, 20 mL of whole blood was sampled from the antecubital vein of for the purpose of serum DHEA, DHEA-S and pregnenolone concentrations analysis. Serum samples were all collected between 8:00 and 10:00 am after 20 min of rest and after 8 h of fasting. Prior to blood collection, the participants were instructed to refrain from stress or unusual physical activity for a 24 h. Neuropsychological testing was performed upon recruitment.

Thirty healthy volunteers were recruited from the community via poster advertisement in the notice boards in local activity centers. Those with any major and minor psychiatric disorders such as mood disorder, psychotic disorder including schizophrenia, anxiety disorder, personality disorder, alcohol or drug use disorders, or a family history of psychiatric disorder among first-degree relatives were excluded. Those with chronic physical illness and metabolic illness were also excluded. After initial evaluation, the healthy subjects received a one-time blood drawn for the purpose of serum neuroendocrine concentrations analysis. They also received a one-time neuropsychological testing.

The neuropsychological testing, Brief Assessment of Cognition in Affective Disorders (BACA), was used to evaluate objective cognitive functioning in patients with mood disorder (Keefe et al., 2014). This instrument is composed of eight brief assessments including verbal memory (list learning); working memory (digit sequencing); processing speed (verbal fluency; token motor task; symbol coding); reasoning and problem solving (tower of London [TOL]), plus tests of affective interference (emotional distractibility and affective memory) and emotional disinhibition (Keefe et al., 2014). The total time of assessment was around 45 min. The measurement of each domain of BACA was standardized by generating T- or Z-scores. A composite score of BACA was calculated by comparing a patient's performance of each measure to the performance of the subjects of the healthy control group. The composite score is the T- or Z-score of that sum (Keefe et al., 2014). A T-score of 50 means average functioning in regard to the healthy controls with same age and gender; each one standard deviation is represented by every 10 points. This study used T-scores for the composite score for analysis.

All the hormone levels were quantified using luminescence immunoassay (RE62051) (IBL Gesellschaft Für Immunchemie Und Immunbiologie MBH, Hamburg, Germany). Each sample was analyzed in duplicate. The hormone concentration of each sample is determined as average of the duplicates.

SPSS (Version 16.0; SPSS Inc., Chicago, IL, USA) was utilized to analyze the data results. Clinical variables were presented as mean (±standard deviation). In a two-tailed test, $p < 0.05$ was considered statistically significant. Clinical characteristics between BP-II and controls were analyzed using independent *t*-tests. Categorical variables were analyzed