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The relationship between sex hormone profiles and symptoms of schizophrenia in men

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Abstract

Aim: Recent studies have shown that sex hormones play a role in the development of schizophrenia and the severity of disease symptoms. However, study results have been inconsistent. This study compares the relationship between severity of disease symptoms and levels of estradiol, progesterone, testosterone, DHEA-S, prolactin and cortisol in male schizophrenia patients and a matched group of healthy controls.
Methods: The study sample included 38 men diagnosed with schizophrenia according to DSM-IV TR criteria, and matched by age with 38 healthy controls. All subjects were between 18 and 55 years old, 22 of them had been treated with olanzapine and 16 with quetiapine. Their symptom severity was evaluated by administering the Scale for the Assessment of Positive Symptoms (SAPS) and Scale for the Assessment of Negative Symptoms (SANS). Hormone levels for schizophrenia patients and healthy controls were evaluated using a chemiluminescence immunoassay method. The hormone profiles of schizophrenia patients and healthy controls were compared statistically. We examined the relationship between subjects' and controls' hormone levels and their scores on the SANS and SAPS scales.
Results: This study found statistically significant elevated levels of serum DHEA-S, cortisol, and prolactin ($p = 0.012$, $p = 0.009$, and $p = 0.021$ respectively), in schizophrenia patients as compared to a control group. Subjects' serum estradiol and progesterone levels ($p = 0.005$ and $p < 0.001$ respectively), were significantly lower than controls' levels. There was a positive correlation between subjects' SANS scores, estradiol ($p = 0.001$) and progesterone levels ($p = 0.027$). No relationship was found between subjects' hormone levels and their SAPS scores.
Conclusion: There may be a relationship between progesterone, estradiol, cortisol and DHEA-S, and the pathophysiology of schizophrenia. These hormones can be used as biological markers for the disorder of schizophrenia. More studies with larger sample sizes are needed to confirm these findings.

1. Introduction

Schizophrenia is a mental disorder that negatively impacts mental and social functioning in affected patients and is associated with positive and negative symptoms [1]. Despite the fact that the prevalence of schizophrenia is the same in both males and females, female schizophrenia patients have a better prognosis than males. For men, treatment with medication provides less benefit, they show more frequent relapses and a greater rate of hospitalization, and fewer cases go into remission. But while the exact pathophysiology of these differences is not understood, it is likely that sex hormones play an important role [2].

We know that estrogen hormones in women protect their cognitive functioning and decrease psychotic symptoms independent of the effects of metabolization of medicine. Moreover, this effect is not related to testosterone [3]. Studies comparing male schizophrenia patients showing lower levels of testosterone than a healthy control group did not identify a difference in severity of symptoms. Also female schizophrenia patients have been found to have higher levels of testosterone than healthy controls [4].

It has been known for some time that DHEA and its sulfide ester DHEA-S are produced in the adrenal glands as precursors to sex steroid synthesis. More recently, it has become clear that these chemicals have neurobiological effects on the central nervous system and brain functions. These hormones are thought to act as facilitators for repair

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functions like neuroprotection, neurogenesis, neuronal survival, anti-oxidant and anti-inflammatory processes [5]. Knowledge of these hormonal effects in schizophrenia has stimulated study of similar effects in other neuropsychiatric disorders like depression, anxiety disorders, post-traumatic stress disorder and dementia.

Neuroendocrinology studies suggest that the hypothalamic–pituitary–adrenal (HPA) axis may play a role in the pathophysiology of schizophrenia [6]. Abnormal flows on the HPA axis may result in higher cortisol levels in schizophrenia patients. Thus, increased levels of cortisol may be the result of abnormalities on this axis in addition to the effects of stressful situations, anger and withdrawal symptoms, or the use of antipsychotic medications in treating this illness [7]. It has been argued that these changes in cortisol levels are related to schizophrenia symptoms and cortisol levels may have significant effects on symptom severity [8] and cognitive functioning [9] in affected individuals. On the other hand, studies that have examined the relationship between cortisol levels and psychosis, as with studies that examined other neurosteriods [10,11], have found contradictory results. It has been written that neuroactive steroids like pregnenolone, allopregnenolone and dehydroepiandrosterone (DHEA) play a role in the pathophysiology of schizophrenia; they may have a role in the treatment of schizophrenia as well [12]. It has been demonstrated that there is a relationship between DHEA and cortisol, and that DHEA's antiglucocorticoid antagonist effect results in protection of hippocampal neurons against cell die off [13].

We do not yet fully understand what role reproductive hormones and cortisol play in schizophrenia. Studies to date have been limited and have shown inconsistent results. The aims of this study were to compare levels of sex hormones and cortisol in male schizophrenia patients and healthy controls and to identify any relationship between their hormone levels and symptom severity. We aim to determine if there is a relationship, and whether using these hormones as biomarkers in diagnosis and treatment could affect treatment approaches.

2. Materials and methods

2.1. Subjects

This study included 38 male patients 18 to 55 years old admitted to an outpatient clinic who met the criteria for schizophrenia according to DSM-IV TR [14]. Patients included in this study had been using olanzapine or quetiapine for at least one year. In addition, they had not been treated with any other antipsychotics, mood stabilizers, benzodiazepines or anticholinergic medications. They met the Andreasen criteria [15] scoring ≤2 on SANS and SAPS subscale scores for at least 6 months of remission. Patients undergoing an acute psychotic episode were excluded from the study because they could not cooperate effectively.

Individuals were also excluded according to the following criteria. A diagnosis of alcohol or substance dependence, organic mental disorders, learning disabilities, neurological or endocrine disorders. Patients and healthy controls with prior hormone therapy history were excluded as well. When these exclusion criteria were applied to 64 admissions, 38 subjects participated in the study. 12 subjects were excluded due to comorbid Axis 1 diagnoses, 5 subjects due to neurological disorders, 7 subjects due to alcohol usage and 2 due to endocrine disorders.

Thirty-eight age matched controls with no diagnosed major psychopathology were recruited. They reported no relevant current or past psychiatric or physical illness.

This study was approved by the local ethics committee. All subjects provided written informed consent for participation in the study after the study procedure had been fully explained.

2.2. Clinical assessment

A socio-demographic data form was administered to participants who met the study criteria to obtain information on their height, weight, age, marital status, duration of illness, duration of antipsychotic use and antipsychotic dosage. The dosages of antipsychotics used by these patients were calculated in terms of chlorpromazine equivalent doses [16] and antipsychotic medication dosages used were compared based upon chlorpromazine equivalent dosages.

All patients were administered the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS). The Turkish versions of these scales were found to be reliable by Erkoç et al. [17,18].

2.3. Hormone assays

Serum levels of FSH, LH, cortisol, DHEA-S, progesterone and testosterone were measured with a chemiluminescence immunoassay method using a DXI 800 (Beckman-Coulter) hormone analyzer. Plasma estradiol and prolactin levels were determined with a commercially available immunoassay kit produced by Modular Analytics E 170 (Elecsys module) system.

Venous blood samples for patients enrolled in this study were drawn between 08:00 and 10:00 AM, placed in anticoagulant tubes and then serum was separated by centrifugation for 10 min 3000 rpm/min. Sera was stored at −80 °C. When the complete series of patient samples had been collected, sera were studied all at one time in a hormone laboratory. For males, prolactin levels of 2.5–18 ng/mL, estradiol levels of 11–44 pg/mL, FSH levels of 1.3–13.6 mIU/mL, LH levels of 1.2–10 mIU/mL, progesterone levels of 0–0.2 ng/mL, DHEA-S levels of 90–492 μg/dL, testosterone levels of 2.4–9.5 mg/mL and cortisol levels of 5–23 μg/dL were considered within normal limits.

2.4. Statistical analysis

Statistical analyses were performed using SPSS software version 23.0 (SPSS, Chicago, IL). Descriptive analyses were