

Testosterone in first-episode schizophrenia

Eva ČEŠKOVÁ, Radovan PŘIKRYL and Tomáš KAŠPÁREK

Department of Psychiatry, Masaryk University and Faculty Hospital Brno, Czech Republic

Correspondence to: Prof. Eva Češková. MD., PhD.
Department of Psychiatry, Masaryk University and Faculty Hospital Brno
Jihlavská 20, 625 00 Brno-Bohunice, Czech Republic
PHONE: +420 5 3223 2053
FAX: +420 5 3223 3706
EMAIL: eceska@med.muni.cz

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Abstract

OBJECTIVE: Recent neuroendocrinological studies have suggested that gonadal sex hormones play a significant role in the pathophysiology of schizophrenia. Low testosterone is associated with negative symptoms in chronic schizophrenia. The relevance of these findings has not yet been elucidated. The aim of our naturalistic open study was to explore the association between symptoms, drug response and testosterone levels in first-episode schizophrenia to exclude the effects of age, chronic illness, long-term treatment and institutionalization.

METHODS: 68 males, consecutively hospitalised for the first time with first-episode schizophrenia were evaluated using the Positive and Negative Syndrome Scale (PANSS) on admission (before treatment) and at discharge. Further, plasma testosterone was measured. Total testosterone was assayed using chemiluminescent immunoanalysis (CMIA). All patients were treated openly by monotherapy; risperidone being the drug of first choice. Treatment response was defined as delta PANSS (PANSS total on admission – PANSS total at discharge / PANSS total on admission).

RESULTS: On average the total PANSS and PANSS subscales scores significantly decreased during the acute treatment. In contrast to results in chronic schizophrenia, the mean values of testosterone were within the normal range (15.36 and 22.55 nmol/l respectively) both before and after acute treatment. The range of normal values for the method used is given as 5.76–30.43 nmol/l for males <50 years old. On admission only 6 patients had testosterone values lower than 5.76 nmol/l. No significant correlation between negative symptoms (negative PANSS subscale) at the beginning or at the end of acute treatment or between treatment response and testosterone plasma levels was found.

CONCLUSIONS: During the first psychotic breakdown no significant association was observed either between total testosterone plasma levels and symptoms or treatment reactivity. However, schizophrenia is a heterogeneous disease. In some patients with first-episode schizophrenia an alteration of psychoendocrinology parameters has been observed. These patients may be more vulnerable to development of enduring negative symptoms, and pharmacotherapy based on neuroendocrinology profile should be considered.

Abbreviations

PANSS	- the Positive and Negative Syndrome Scale
DHEA	- dehydroepiandrosterone
DHEAS	- dehydroepiandrosterone-sulphate
ICD-10	- The Tenth Revision of the International Classification of Diseases
CMIA	- chemiluminescent immunoanalysis

INTRODUCTION

Recent neuroendocrinological studies have suggested that gonadal sex hormones, including androgens and estrogens, play a significant role in the pathophysiology of schizophrenia [12,13]. Previous studies that have evaluated the relationship between the serum levels of testosterone and schizophrenia have not shown consistent results [15,9,8,18]. However, with respect to the psychopathology of schizophrenia, limited recent studies have shown that there might be a consistent relationship between the serum levels of androgen, especially the level of testosterone, and negative symptoms in male patients with schizophrenia [16,6,1]. The psychobiological role of testosterone in the negative symptoms of schizophrenia might be via modulation of various neurotransmitters and neuropeptides through nongenomic or genomic mechanisms [14].

Negative symptoms in schizophrenia remain a predominant feature in many individuals with schizophrenia and have become a special research interest in the last decade because novel atypical antipsychotics are claimed to have an improved therapeutic efficacy versus older, typical agents against negative symptoms in patients with schizophrenia. The association between symptoms, testosterone levels and drug response in patients suffering from first-episode schizophrenia has not yet been studied. The aim of our naturalistic open study was to explore the association between symptoms, drug response and testosterone levels in drug naïve males hospitalised for the first time with first-episode schizophrenia.

METHODS

Subjects

Males, consecutively hospitalised for the first time (between November 97 and December 2006) with first-episode schizophrenia at the Department of Psychiatry in Brno, who provided written informed consent and who had plasma testosterone assessed were included. ICD-10 diagnoses were made on the basis of a comprehensive assessment of symptoms and history, and all other available information about the patients. The diagnosis was confirmed by a consensus of two psychiatrists during separate interviews.

Clinical assessment

The psychopathology was evaluated using the Positive and Negative Syndrome Scale (PANSS) on admission

(before treatment) and at discharge [10]. Treatment response was defined as Δ PANSS ((PANSS total on admission – PANSS total at discharge) / PANSS total on admission).

Treatment

Most patients were drug-naïve on admission. After a baseline assessment on admission, all patients were treated openly by monotherapy with individually dosed second generation antipsychotics. Risperidone was the drug of first choice; other options were selected according to clinical judgement and drug availability. The only concomitant treatments allowed were benzodiazepines for tension, anxiety and insomnia, and biperidene for extrapyramidal symptoms. The method has previously been described in detail [2].

Testosterone

Total testosterone was assayed by an Abbot machine (Architect) using chemiluminescent immunoanalysis (CMIA). The sensitivity of assay was 0.28 nmol/l (0.08 ng/ml) and the intra-assay coefficient of variation was below 4.5%. Blood samples were taken between 6.00 and 7.00 am under standard conditions before and at the end of acute treatment. Free testosterone plasma levels were not measured in this study. Further, the association between testosterone and PANSS subscales, and treatment effect was evaluated.

Statistical analysis

For statistical analysis descriptive statistics and nonparametric methods (Wilcoxon Matched Pairs Test and Spearman's correlation) were used. The statistical analysis was performed using Statistica software, version 6 (StatSoft, Inc. 2001).

RESULTS

Sample characteristics

68 patients were included. Their average age was 23.8 (SD 4.8) years. The mean duration of the hospitalisation, based on a clinician's judgement of the severity of symptoms, was 44.5 (15.3) days. The mean illness length, determined from the time the patients first exhibited illness-related behavioural symptoms was 3 months (SD 3.0).

Psychopathology

In the entire sample, scores for the total PANSS and all PANSS subscales decreased significantly at discharge (Table 1).

The mean values of testosterone were in the normal range (range of normal values 5.76–30.43 nmol/l). The mild testosterone increase during the treatment was not significant and there was a great variability of values among individual patients at the end of acute treatment. On admission only 6 patients had values under 5.76 nmol/l and 3 patients at discharge (Table 2).

Correlations

No significant correlation between negative symptoms (negative PANSS subscale) at the beginning and at the end of acute treatment or between treatment response and testosterone plasma levels was found (Table 3).

DISCUSSION

Concerning the psychopathology, our results again confirmed the good acute treatment response in first-episode schizophrenia. Further, the results are in agreement with our previous studies concerning psychopathology and its dynamics in first-episode schizophrenia. Negative symptoms were rather prominent and were less influenced by acute treatment than positive symptoms [2].

In our study the mean value of total testosterone was in the range of normal values given by our lab for a corresponding age category, e.g. men under fifty years old. No measurement of free testosterone was performed. However, the results of Ko's study [12] indicated that the serum levels of free testosterone were positively correlated with the serum levels of total testosterone and also estradiol. Six patients had lower values (below the normal range) before acute treatment and 3 of them also at discharge. These patients may be more vulnerable to the development of enduring negative symptoms, and pharmacotherapy based on neuroendocrinology profile should be considered. All the patients are able to continue with a 1-year follow-up study. We are in the process of gathering the data.

Many studies assessing the role of sex hormones, like testosterone, on stress, aggression and impulsivity have been conducted in both healthy individuals and selected populations [11,19]. Several studies have evaluated the relationship between plasma levels of testosterone and other gonadal hormones in patients with chronic schizophrenia [16,6,1]. These studies consistently reported lower testosterone levels in patients than in the normal control [1,16] or significantly lower levels in a patient group with predominantly negative symptoms than in a patient group with predominantly positive symptoms [6]. Further, a significant inverse correlation between negative subscale scores of PANSS and plasma levels of testosterone and free testosterone in the patients with predominantly negative symptoms was detected [1,12].

On the other hand there are very few studies exploring this aspect in patients with first-episode schizophrenia. Huber [7] examined serum hormone levels in 34 men admitted consecutively for an acute exacerbation or first onset of schizophrenia in a blinded prospective design. As compared to matched controls, acutely admitted men exhibited significantly lower serum levels of estradiol, estrogen, testosterone and free testosterone. A correlation of hormone levels with psychopathology was not identifiable. The only study [17] in individuals with a first-episode of psychosis found that baseline dehydroepiandrosterone (DHEA) and dehydroepiandrosterone-sulphate (DHEAS) levels were significantly higher in

Table 1. Mean values of psychopathology.

	Positive PANSS	Negative PANSS	General PANSS	Total PANSS
On admission	23.3 (5.9)	26.3(8.3)	47.5(10.9)	97.1 (10.9)
At discharge	9.4 (2.4)*	19.8 (6.8)*	27.9 (7.3)*	57.1 (15.2)*

* significant difference in relation to baseline values ($p < 0.01$)

Table 2. Testosterone plasma levels in patients with first-episode schizophrenia (n=68).

	Mean value (SD)	Range
On admission	15.36 (6.6) nmol/l	4.7–28.8 nmol/l
At discharge	22.55 (27.55) nmol/l	2.56–101.0 nmol/l

Table 3. Spearman's correlation – r values.

	Testosterone plasma levels
Negative PANSS subscale on admission	0.043666
Negative PANSS subscale at discharge	-0.170267
Delta negative PANSS	0.201184
Delta PANSS	0.179484

schizophrenia patients than in controls. DHEAS levels inversely correlated with the severity of illness and aggressive behaviour. DHEA is a major circulating corticosteroid in man and serves as a precursor of both androgenic and estrogenic steroids [5]. Inspired by these findings, we were additionally looking for an association between aggression and testosterone levels. Aggression was defined using the factor hostile excitement including 4 associated individual items, e.g. hostility, excitement (qualified also as positive PANSS symptoms), poor impulse control and tension (general PANSS symptoms). No significant correlation was found. The authors speculate that a neurosteroid response to the first onset of psychosis may develop which may be associated with a reduction in various adverse clinical features including aggression. Such a putative mechanism may become desensitized with the onset of chronic illness. This idea corresponds to a certain degree to our results and again stresses the importance of the first psychotic episode and the period after it when the positive symptoms are reduced.

Possible limitations of the performed studies are the cross-sectional design and the small sample size. Our study is a little larger; patients seem to be homogenous and a follow-up study is going on. On the other hand, no control group has been used and the study was designed as a natural prospective, open observational study.

Recently, sex hormones such as estrogens and testosterone or its derivatives have been the focus of interest

for treatment of persistent symptoms associated with schizophrenia [4]; however, the results have been inconclusive. Interventional studies using hormone replacement therapy in male psychotic patients with low serum levels of sex hormones could be a future implication.

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