Evaluation of prolactin levels in male patients with first-episode schizophrenia and its correlation with psychopathology

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Background
Prolactin, a polypeptide hormone secreted by lactotroph cells of the anterior pituitary gland, is involved in many biological functions including reproduction, pregnancy, and lactation. A variety of studies over the past four decades have examined other facets of the relationship between prolactin and schizophrenia and call for a reappraisal of this relationship. Some recent studies have found increased prolactin concentrations in antipsychotic-naive psychotic patients, whereas other studies of previously treated but drug-free patients reported concentrations that are normal or lower than those in controls.

Objective
The aim of this study was to determine whether there is a significant rise in serum prolactin in psychotropic drug-naive male patients with first-episode schizophrenia related to disease process and its correlation with psychopathology.

Patients and methods
Thirty male patients with first-episode schizophrenia were included in this cross-sectional study. Patients were drug-free and psychotropic drug-naive. The patients were classified into two groups: those with and those without hyperprolactinemia. Plasma levels of prolactin and demographic and clinical characteristics were compared between these groups. Standardization for control was carried out using 30 control plasma prolactin samples obtained from healthy individuals. Methodology involved assessment by means of radioimmunoassay. For schizophrenic patients, clinical evaluation was carried out by measuring the Premorbid Adjustment Scale (PAS), the Positive and Negative Syndrome Scale, and the Montgomery–Asberg Depression Rating Scale. The scores for these scales were significantly higher in the hyperprolactinemia group than in the nonhyperprolactinemic group.

Results
Serum prolactin level was elevated at baseline in 46.7% of first-episode schizophrenic patients. Duration of untreated psychosis and poor premorbid adjustment (PAS) were significantly higher in the group with hyperprolactinemia than in the nonhyperprolactinemic group. In addition, total Positive and Negative Syndrome Scale scores, negative symptom scores, and Montgomery–Asberg Depression scores in the group with hyperprolactinemia were significantly higher than that in the nonhyperprolactinemic group. There was also a positive correlation between plasma levels of prolactin and duration of untreated psychosis, PAS, negative symptom scores, and Montogomery–Asberg Depression scores.

Conclusion
This study suggests that we should be aware of prolactin levels in first-episode schizophrenic patients, especially when negative and depressive symptoms are prominent. Thus, this finding may change the present pharmacotherapy for negative and depressive symptoms in schizophrenia based on prolactin levels.

Keywords:
first episode, prolactin, psychopathology, schizophrenia

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Introduction

Prolactin plays a vital role in proper functioning of the reproductive system [1]. Prolactin, a polypeptide hormone secreted by lactotroph cells of the anterior pituitary gland, is involved in many biological functions, including reproduction, pregnancy and lactation, and growth and development. Blood prolactin levels could be affected by several variables, including sex, sexual activity, childbirth, stress, smoking, and some medications [2,3].

Prolactin in excess can have effects on fertility in women and sexual function in men [4], which in turn can have a profound effect on an individual. Hyperprolactinemia

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over a long duration has serious negative results on the overall health of the patient. Hyperprolactinemia is associated with a variety of adverse effects: amenorrhea and galactorrhea, an acceleration of osteoporosis in women and a lack of libido and erectile dysfunction in men, and may increase the risk for breast cancer in women.

A variety of studies over the past four decades have examined other facets of the relationship between prolactin and schizophrenia and call for a reappraisal of this relationship. Some recent studies have found increased prolactin concentrations in antipsychotic-naive psychotic patients [5–10], whereas other studies of previously treated but drug-free patients reported concentrations that are normal or lower than those of controls [11–13]. This also applies to the drugs chosen to treat patients. Although atypical antipsychotic agents have a lower incidence for elevating prolactin levels, an increase is still seen. This increase contributes to negative sexual side effects and quality of life, which has a large impact on patient compliance [14]. A look at serum prolactin levels in drug-naive patients offers an opportunity to note any correlation between prolactin levels and psychopathology [15].

In this research, the authors highlight the important findings pertaining to prolactin in antipsychotic drug-naive male patients with first-episode schizophrenia.

Aim

The aim of this study was to determine whether there is a significant rise in serum prolactin level in antipsychotic drug-naive male patients with first-episode schizophrenia and to evaluate whether elevated prolactin is correlated to specific symptoms or dimensions of schizophrenia.

Patients and methods

Design

This work was a cross-sectional study conducted during the period between September 2013 and October 2014.

Setting

The study was conducted at the Department of Psychiatric, Faculty of Medicine, Cairo University, after being approved by the local scientific and ethical committee. Written informed consent was obtained from all patients and/or their care providers.

Participants

This study focuses on first-episode schizophrenia. Patients were chosen on the basis of specific criteria. The study participants included both inpatients and outpatients who were diagnosed with first-episode schizophrenia according to the International Classification of Disease criteria for schizophrenia (International Classification of Disease-10) [16] established on the basis of the Mini International Neuropsychiatric Interview [17]. All were male, between 25 and 35 years of age, had first-episode schizoprenia, and were drug free and drug naive. The study included 30 male patients with a mean (SD) age of 26.2 (9.6). They were divided into two groups: those with and those without hyperprolactinemia. Cutoff points for the plasma prolactin levels were considered to be 16.9 ng/ml. Illness characteristics and demographic data were obtained from clinical interviews and medical records. In addition, 30 healthy controls provided blood samples.

The exclusion criteria were as follows: (a) presence of any other psychiatric morbidity, such as alcohol dependence, which is likely to interfere with diagnosis and follow-up; (b) presence of any concurrent medical or endocrine disorder; (c) clinically significant organic, neurological disorder, or mental retardation; and (d) receiving other medications that are likely to alter prolactin levels.

Nonsignificant differences were identified between patients with hyperprolactinemia and nonhyperprolactinemia with regard to basic demographic data including age, sex, marital state, educational level, and employment. Illness characteristics and demographic data were obtained from clinical interviews and medical records.

Laboratory investigation

Blood samples were taken from patients before any psychotropic drug interventions. All participants were subjected to laboratory investigations; serum glucose, cholesterol, triglyceride, and high-density lipoprotein and low-density lipoprotein-cholesterol levels were measured using photometric methods with an Abbott Architect c16000 Autoanalyzer (Abbott Diagnostics, Illinois, USA). Serum prolactin level was measured using the Chemiluminescent Microparticle Immunoassay method using an Abbott i2000 Autoanalyzer (Abbott Diagnostics). The specimen was taken between 8 and 10 a.m. Blood was collected by means of venipuncture and allowed to clot, and then the serum was separated by means of centrifugation at room temperature and stored at 20°C until used. Twenty-five microliters of each standard, control, and samples was dispensed into appropriate wells. One hundred microliters of enzyme conjugate was dispensed into each well and incubated for 30 min at room temperature, and then the wells were rinsed five times with distilled water. One hundred microliters of substrate solution was added to each well and was incubated for 10 min at room temperature. The enzymatic reaction was stopped by adding 50 µl of stop solution to each well [18].

Clinical assessment

Premorbid functioning was measured with the Premorbid Adjustment Scale (PAS) [19]. We only included participants in their childhood (11 years) and early adolescence (12–15 years) periods for assessment to avoid any possible interference with early symptoms because the onset of prodrome and psychosis usually occurs during late adolescence and early adulthood [20,21]. The Positive and Negative Syndrome Scale (PANSS) [22] was used to evaluate positive and negative symptoms in patients with schizophrenia, as well as general psychopathology associated with schizophrenia; we used the 30-item

PANSS. Each item is rated on a scale from 1 to 7. The sum of 30 items is defined as the PANSS total score and ranges from 30 to 210 points.

The Montgomery–Asberg Depression Rating Scale (MADRS) [23] was used to assess depression.

Statistical analysis

Descriptive statistics were reported as frequencies and percentages for categorical variables and mean ± SD for continuous variables. Distribution of data was evaluated using the one-sample Kolmogorov–Smirnov test. Differences between the two groups were assessed using Student's *t*-test. Correlations between clinical symptom scores and plasma prolactin levels were evaluated using the Pearson correlation test. Differences were considered to be significant when *P*-values were lower than 0.05.

Results

The study enrolled a total of 30 psychotropid drug-naive male patients with first-episode schizophrenia. All patients were divided into two groups, those with and those without hyperprolactinemia. The average age of the hyperprolactinemic patients was 25.2 ± 5.1 ($n = 14$, 46.7%), whereas the nonhyperprolactinemic patients' ($n = 16$, 53.3%) average age was 24.9 ± 4.8 years. No significant differences were identified between patients with hyperprolactinemia and those without hyperprolactinemia with regard to basic demographic data including age, sex, marital status, and educational status. According to the comparison of plasma prolactin levels and clinical features between groups, there were statistically significant differences in PAS ($P = 0.001$), duration of untreated psychosis (DUP) ($P = 0.04$), severity of psychopathology measured using PANSS total score, PANSS-negative scale score, and more severe depressive symptoms (MADRS score) ($P = 0.02$, 0.001, and 0.03, respectively). There was a nonstatistically significant difference in other clinical features between groups. Other comparisons of demographic features and clinical characteristics between groups are shown in Table 1.

Laboratory profile in the groups is presented in Table 2.

Table 3 shows physical parameters.

Patients with hyperprolactinemia had a significantly higher weight and BMI than those in the other group ($P = 0.02$ and 0.001, respectively).

Table 4 presents the correlation between plasma prolactin level and clinical characteristics in schizophrenic patients.

A significant positive correlation was detected between DUP ($r = -0.93$, $P < 0.01$), PAS ($r = -0.94$, $P < 0.01$), the negative subscale scores of the PANSS ($r = 0.73$, $P < 0.001$), MADRS score ($r = 0.78$, $P < 0.01$), and plasma levels of prolactin in patients. We did not find any significant correlation between the other clinical features and biochemical measurements (Table 4).

Discussion

Key findings

We found that (a) antipsychotic-naive male patients with first-episode schizophrenia had significantly increased serum prolactin concentrations compared with controls; (b) Serum prolactin level was elevated in 46.7% of schizophrenic patients; (c) patients with hyperprolactinemia have longer DUP, poor PAS, and more severe psychopathology compared with patients without hyperprolactinemia; (d) our results here do provide further support for an association between plasma prolactin levels and psychopathology in early phases of schizophrenia. There were significantly increased serum prolactin levels in antipsychotic drug-naive first-episode schizophrenia patients versus healthy controls.

Our findings of markedly elevated plasma levels of prolactin in patients in the early stages of the illness are in agreement with most of the previously reported results [5–10,24]. However, the pathogenic mechanism underlying these elevated prolactin levels in schizophrenia is not fully understood. It remains unclear whether higher plasma prolactin levels might be a cause or a consequence of psychosis. Some researchers provide an intriguing explanation for this finding [24]. They suggest that stress leads to an increased level of prolactin, which triggers dopamine release through a feedback mechanism; this increase in dopamine transmission may mediate the link between stress and psychosis. There are several lacunae in this hypothesis: (a) stress or recent life events has not been measured; (b) although raised prolactin may increase dopamine activity in the tuberoinfundibular pathway, it is not known whether it can produce similar changes in the mesolimbic pathway; and (c) this proposal fails to explain why several studies found lower or normal prolactin levels. Despite this, the hypothesis merits further testing, as well as extension to conditions such as acute and transient psychosis, in which the role of stress is much clearer. The finding that patients with schizophrenia have an exaggerated prolactin response to stress may be relevant here. Two recent studies have examined genetic variants in prolactinin patients with schizophrenia. One study examined the frequency of the −1149G/T functional polymorphism of the prolactin gene in 403 patients, compared with 653 healthy controls [25]. They found that the G allele was significantly more common in patients, particularly in male patients, and pointed out that this variation was similar to that reported in autoimmune diseases. Another study examined the association between the prolactin and prolactin receptor genes and both tardive dyskinesia and treatment response but failed to find a significant association in either case [26]. We observed that serum prolactin level was elevated in 46.7% of schizophrenia patients. Other studies assessed the prevalence and severity of hyperprolactinemia in psychotic patients. The rate of hyperprolactinemia was 71% among US inpatients on treatment with antipsychotics, with no important difference between sexes (men 72% and women 68%) [27], whereas in the UK study [28] the rate was considerably lower in outpatients (38%) with a notable difference between sexes,

Table 1 Demographic and clinical characteristics of the patients with elevated and normal plasma prolactin levels

Characteristics	Patients with hyperprolactinemia ($n=14$)	Patients without hyperprolactinemia ($n=16$)	t or χ^2	P
Age [mean (SD)] (years)	25.2 (5.1)	24.9 (4.8)	0.918	0.37
Education [mean (SD)] (years)	9.8 (3.7)	10.1 (4.2)	0.924	0.93
Marital status [*N* (%)]				
Married	8 (57.1)	9 (56.3)	−2.931	0.84
Single	5 (35.7)	6 (37.5)		0.04
Divorced	1 (7.2)	1 (6.2)		0.001
Clinical characteristics				
DUP [mean (SD)] (months)	3.04 (2.3)	1.2 (1.1)	1.393	0.02
PAS [mean (SD)]	0.5 (0.1)	0.3 (0.1)	−0.213	0.68
PANSS [mean (SD)]				
PANSS total score	82.3 (15.3)	80.1 (16.1)	−2.080	0.001
PANSS-positive score	16.3 (5.4)	16.6 (4.6)		
PANSS-negative score	23.9 (5.6)	9.8 (5.2)		
MADRS	12.3 (4.9)		−1.9	0.03

DUP, duration of untreated psychosis; MADRS, Montgomery–Asberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; PAS, Premorbid Adjustment Scale.

Table 2 Laboratory characteristics of the patients with elevated and normal plasma prolactin levels

Variables	Patients with hyperprolactinemia ($n=14$)	Patients without hyperprolactinemia ($n=16$)	Student's t-test	P
Fasting plasma glucose level	86.3 (9.4)	89.1 (8.7)	−1.77	0.08
TC (mg/dl)	176.39 ± 4.66	189.80 ± 43.96	−1.037	0.23
TG↓ (mg/dl)	153.63 ± 84.55	153.63 ± 84.55	0.482	0.16
HDL-C (mg/dl)	48.21 ± 10.38	48.21 ± 10.38	0.437	0.43
LDL-C↓ (mg/dl)	115.63 ± 48.38	115.63 ± 48.38	−1.038	0.18

HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TC, total cholesterol; TG, triglyceride.
There was no statistically significant difference in the other.

Table 3 Physical characteristics of the patients with elevated and normal plasma prolactin levels

Parameter	Patients with hyperprolactinemia (mean ± SD)	Patients without hyperprolactinemia (mean ± SD)	Student's t-test	P
Weight (kg)	81.2 ± 10.6	76.8 ± 11.5	−2.342	0.02
Height (m)	167.2 ± 9.6	168.1 ± 8.6	−0.518	0.6
BMI (kg/m^2)	24.2 (1.1)	21.5 (0.9)	−4.60	0.001

Table 4 Correlation between prolactin and clinical characteristics in schizophrenic patients

	DUP		PAS		PANSS-negative score		MADRS score	
Variables	r	P	r	P	r	P	r	P
Plasma prolactin level	−0.93	<0.01	−0.94	<0.01	0.73	<**0.001**	**0.78**	<**0.01**

DUP, duration of untreated psychosis; MADRS, Montgomery–Asberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; PAS, Premorbid Adjustment Scale.
Bold values are ($P<0.001$ = highly significant); ($P<0.01$= significant).

the rate being twice as high in women as in men (52 vs. 26%). The difference in prevalence may be due to the difference in methodology, a recruitment bias in the retrospective study, or to inpatient versus outpatient status, the lower rate being due to lower compliance with medication among outpatients. The findings of other studies reported in the literature have shown that 38–75% of patients on antipsychotic therapy have hyperprolactinemia [14,29–37].

Relationships between serum prolactin level and symptom profile in schizophrenia patients

In our study, we also conducted correlational analyses between prolactin levels with DUP, PAS, psychopathology (measured using PANSS total score, PANSS positive score, and PANSS-negative score), and depressive symptoms (assessed using MADRS scoring). There were significant positive correlations between baseline serum prolactin and DUP, PAS, PANSS-negative scores, and MADRS scores. The results of this study are similar to those of some previous studies. These studies reported a significant positive correlation between prolactin levels and negative symptoms [4,37–40]. A relation between serum prolactin level and severity of depressive symptoms was concluded by some researchers [41]. Aside from the adverse health effects of hyperprolactinemia, the presence of abnormal prolactin concentrations before antipsychotic treatment is of theoretical interest. It provides further evidence that, as a group, people with schizophrenia and related disorders have anatomical anomalies [42] as well as metabolic abnormalities outside of the brain that cannot be attributed to the effects of antipsychotic treatment [43–46]. Although dopamine exerts a tonic inhibitory effect on the release of prolactin,

serotonin appears to play an important role in the release of this hormone as well [47–50]. The effects of stress and other factors are not necessarily mutually exclusive.

Limitations in the study

Several limitations qualify our findings. First, the sample sizes were small. Second, it cannot be ruled out that our study is susceptible to other confounding factors, such as smoking, drug use, and a measure of stress. Prolactin release may be increased as a part of the stress response [51] and is also partially regulated by thyrotropin-releasing hormone [52] and ghrelin [53], which stimulates prolactin secretion.

Prolactin release may be increased as a part of the stress response [51] and is also partially regulated by thyrotropin-releasing hormone [52] and ghrelin [53], which stimulates prolactin secretion. In a large, general population study, prolactin values were correlated with inflammatory biomarkers [54] and cardiovascular mortality [55] but not with type 2 diabetes mellitus or the metabolic syndrome [56]. In any future studies on prolactin concentrations in antipsychotic-naive patients it would be desirable to examine cortisol, thyroid-stimulating hormone, ghrelin, interleukin-1β, interleukin-6, and tumor necrosis factor-α as well [57–59].

Third, common genetic polymorphisms of the prolactin gene have been reported more frequently in schizophrenic patients [31]. Finally, it is necessary to mention cross-sectional study design limitation. Given the presumed effects of prolactin levels, the need for similar studies in first-episode drug-naive patients, even in at-risk populations, over the life span is warranted to determine the causes of elevated serum prolactin level, the association with genetic polymorphisms, and whether the elevation in serum prolactin level at disease onset determines some aspects of the disease process.

Conclusion

This study indicates that we should assess prolactin levels in patients with first-episode schizophrenia.

Clinicians should ask questions to detect hyperprolactinemia before starting treatment and during follow-up and should give patients relevant information. In conclusion, this study indicates that the assessment of prolactin levels could be an important biological marker for the severity of psychopathology in early phase of schizophrenia and these findings may change the present pharmacotherapy based on the prolactin levels of patients with schizophrenia. A review of the literature on prolactin and schizophrenia suggests that the relationship between them is complex and not confined to the adverse effects of antipsychotics. Although the above interpretations must be regarded as imperfect and tentative, they do call for a reappraisal of the role of prolactin in the various stages of schizophrenia, particularly with regard to its onset and to the development of positive symptoms. Research in this area may lead to an improved understanding of schizophrenia, as well as a better delineation of the effects of prolactin on social behavior and cognition in humans.

Conflicts of interest

There are no conflicts of interest.

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