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Association between prolactin serum levels and cognitive function in chronic schizophrenia patients

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ABSTRACT

Introduction. Several studies have explored the relationship between serum prolactin levels, symptomatology, and cognitive dysfunction in individuals at high risk for psychosis and patients with a first psychotic episode. However, the relationship between such variables is poorly understood in the case of chronic patients. **Objective.** To assess the relationship between prolactin levels, neuropsychological impairment, and symptom severity in patients with chronic schizophrenia. **Method.** A total of 31 patients with diagnosis of schizophrenia were evaluated between May and December 2018. The age range was 18 to 60 years, with patients receiving antipsychotic treatment during a month at least. Data was obtained from clinical records, interviews, clinimetry, and with the application of the PANSS and the MCCB battery. For the prolactin measurement, the analysis was performed on a sample of 500 microliters of serum, with a chemiluminescence technique. **Results.** The sample was comprised mostly by men (77.4%), with a mean age of 37.65 years, 13.29 years of formal education, and disease duration of 11.58 years. No correlations were observed between prolactin levels and PANSS components and subscales. Only in male patients is there a negative correlation was found between prolactin levels with the overall combined score of the MCCB battery and cognitive domains of reasoning and verbal learning. **Discussion and conclusions.** Men diagnosed with schizophrenia may be particularly vulnerable to the negative effects of hyperprolactinemia on cognition. These preliminary data have clinical implications for close monitoring of prolactin and cognitive decline in males with schizophrenia. Theoretically, these data are suggestive of a protective effect of hormones in women with this condition.

Keywords: Schizophrenia, cognition, prolactin, men.

RESUMEN

Introducción. Diversos estudios han explorado la relación entre los niveles de prolactina sérica, la sintomatología y la disfunción cognitiva en individuos con alto riesgo de psicosis y pacientes con un primer episodio psicótico. Sin embargo, la relación entre tales variables es poco comprendida en el caso de los pacientes crónicos con esquizofrenia. **Objetivo.** Evaluar la relación entre los niveles de prolactina, el deterioro neuropsicológico y la severidad de los síntomas en pacientes crónicos. **Método.** Se evaluó un total de 31 pacientes. El rango de edad fue de 18 a 60 años, quienes recibieron tratamiento antipsicótico durante un mes como mínimo. Los datos se obtuvieron de entrevistas y de la aplicación de la PANSS y la MCCB. La medición de la prolactina se realizó con una muestra de 500 microlitros de suero, con una técnica de quimioluminiscencia. **Resultados.** La muestra estuvo compuesta en su mayoría por hombres (77.4%), con una edad media de 37.65 años, 13.29 años de escolaridad y una duración de la enfermedad de 11.58 años. No se observaron correlaciones entre los niveles de prolactina y los componentes y subescalas del PANSS. Sólo en los pacientes varones se da una correlación negativa entre los niveles de prolactina con la puntuación global combinada de la batería de MCCB y los dominios cognitivos de razonamiento y aprendizaje verbal. **Discusión y conclusiones.** Los hombres diagnosticados con esquizofrenia pueden ser particularmente vulnerables a los efectos negativos de la hiperprolactinemia sobre la cognición. Teóricamente, estos datos sugieren un efecto protector de las hormonas en las mujeres con esta enfermedad.

Palabras clave: Esquizofrenia, cognición, prolactina, hombres.

INTRODUCTION

The action mechanism of antipsychotic drugs includes the blockage of D2 dopamine receptors, resulting in a reduction of positive symptoms in patients with schizophrenia (Miller, 2009). However, blocking these receptors in the tuberoinfundibular pathway increases prolactin secretion as a side effect (Ajmal, Joffe, & Nachtigall, 2014). For this reason, hyperprolactinemia is a common adverse effect in patients with psychosis who are under pharmacological treatment (Vuk et al., 2019).

In addition to side effects such as weight gain, decreased libido, amenorrhea, galactorrhea, and osteoporosis (Rajkumar, 2014), an increase in prolactin is associated with the onset and maintenance of psychotic symptoms in ultra-high risk population and in patients with a first psychotic episode (Labad, 2019). Labad et al. (2015) proposed that the increase of hormone levels may be a hyper response of the stress biological systems, which led to the hypothesis about the contribution of prolactin to psychosis development in vulnerable individuals.

With regard to cognitive symptoms, studies with high risk for psychosis individuals show a negative correlation between prolactin levels and performance of reasoning, problem solving, and general cognition tasks (Labad, 2019). Moreover, Montalvo et al. (2014) reported a negative correlation between prolactin levels and processing speed tests performance in patients with first episode psychosis. Finally, Yao et al. (2018) described a significant negative correlation between verbal memory and cognitive flexibility performance and hyperprolactinemia in women with schizophrenia. The negative effects of prolactin on cognition mentioned above may have structural correlates with gray matter reduction on the left orbitofrontal cortex, right frontomedial cortex, and bilaterally in the hippocampus (Yao et al., 2018).

Several studies explore the relationship between serum prolactin levels, symptomatology, and cognitive dysfunction in individuals at high risk for psychosis and patients with a first psychotic episode. However, the relationship between such variables is poorly understood in chronic patients. Thus, the aim of the study was to explore the relationship between prolactin, cognition, and symptomatology in patients with chronic schizophrenia.

METHOD

Participants

A total of 50 participants from the schizophrenia clinic from the Instituto Nacional de Psiquiatría Ramón de la Fuente Muñíz (INPRFM), who attended between May and December 2018, were included. The participants met the following inclusion criteria: diagnosis of schizophrenia, age of 18 years or more, minimum schooling of six years, and clinical stability with at least one month under antipsychotic treatment and at least three years with the diagnosis. Participants with delusional disorder, substance induced psychosis, schizoaffective disorder, major neurocognitive disorder or any other serious psychiatric comorbidity, symptoms of catatonia, and active consumption of any substance other than tobacco were excluded.

Measurements

An structured interview was used for clinical and socio-demographic data. Clinical and neuropsychological data were obtained with the following instruments:

- Positive and Negative Syndrome Scale (PANSS). It assesses physical manifestations, interpersonal behavior, cognitive and verbal processing, thought content, affection, behavior, and emotions experienced by subjects with schizophrenia (Kay, Fizbein, & Opler, 1987). In the present study, the adaptation for Mexican population was used. In this version, five main symptomatology domains are identified: positive, negative, cognitive, anxiety/depression, and excitation (Fresán et al., 2005).
- Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB), Central and South America version. It was designed as an initiative of the National Institute of Mental Health, with the aim of homogenizing a measurement instrument that provided a reliable evaluation of the relevant cognitive dysfunctions associated to the diagnosis of schizophrenia and related disorders. This neuropsychological battery assesses seven cognitive domains: processing speed, attention/vigilance, working memory, verbal learning, visual learning, reasoning/problem solving, and social cognition. It consists of 10 tests: Continuous Performance Test – Identical Pairs (CPT-IP), Hopkins Verbal Learning Test (HVLT), Brief Visuospatial Memory Test (BVMT), Brief Assessment for Cognition in Schizophrenia: Symbol Coding (BACS-SC), Verbal Fluency test – Animals (VF), Trail Making Test – A (TMT-A), Wechsler Memory Scale: Spatial Span (WMS-SS), Letter-Number Span (LNS), Neuropsychological Assessment Battery – Mazes (NAB-M), Salovey-Caruso Emotional Intelligence Test: Managing Emotions (MSCEIT-ME).

Procedure

Patients who agreed to participate in the study signed an informed consent letter and were evaluated in a single two-hour session. The application and scoring of neuropsycho-

logical tests was carried out by a clinical neuropsychologist and the application of clinimetry was performed by a psychiatrist. For the prolactin measurement, a blood sample was obtained between 7:30 and 9:00 am. The analysis was performed on a sample of 500 microliters of serum, with a chemiluminescence technique. The measurements are expressed in ng/ml.

Statistical analysis

Descriptive statistics were performed for sociodemographic data, and a Pearson correlation was used for prolactin levels, PANSS subscale scores and MCCB scores.

RESULTS

The final sample consisted of 31 patients, the sociodemographic and clinical characteristics are described in Table 1. The mean age was 37.65 years with a schooling of 13.29 years. All patients evaluated have a chronic course of the disease, with a mean of 11.58 years of evolution.

The monotherapy was the most prevalent pharmacological treatment in 80.6% of the participants. Of these patients, 29% were treated with risperidone, followed by clozapine 22.6%, olanzapine 16.15%, haloperidol 16.15%, aripiprazole 9.7%, sulpiride 3.2%, and trifluoperazine 3.2%. Among those patients that received treatment with two antipsychotic drugs, the most commonly used was aripiprazole 12.9%, followed by sulpiride and quetiapine 3.2%. The 61.3% of the patients were treated with antidepressant medication. Four subjects were treated with long half-life benzodiazepines. The 80.6% of the subjects did not take any type of anticholinergic medication and only six subjects were under treatment with biperidene or trihexyphenidyl; five subjects were taking some mood stabilizer such as magnesium valproate.

A first analysis was performed for the total sample, and in a second phase, the correlations were analyzed according to sex. Results are shown in Table 2.

No significant correlations were observed between prolactin levels and symptomatology. However, in male patients a negative moderated correlation was observed between cognition variables and serum prolactin levels. Such correlations corresponded to reasoning/problem solving, verbal learning, and total MCCB score (Figure 1).

Table 1
Demographic and clinical data

	Variable	*n*	*Percentage*
Sex	Men	24	77.4
	Women	7	22.6
Civil status	Single	28	90.3
	Married	1	3.2
	Divorced	2	6.5
Ocupation	None	17	54.8
	Student	4	12.9
	Home	4	12.9
	Employed	2	6.5
	Professionist	1	3.2
	Skilled trade	3	9.7
	Range	*Mean*	*SD*
Age	23-59	37.65	11.55
Education	9-30	13.29	4.22
Duration of illness	3-38	11.58	7.93

DISCUSSION AND CONCLUSION

In this study, we aimed to explore the correlations between serum prolactin levels with symptomatology and cognitive impairment in patients with chronic schizophrenia.

No correlations were found between prolactin levels and the total score or subscales of PANSS. This finding differs from the one reported by Vuk et al. (2019), who described higher levels of the hormone in more critical patients. The discrepancy can be partially explained considering the sample difference: first the modest number of subjects included in our clinical group limited the analysis; on the other hand, our population was clinically stable and did not showed important differences regarding the doses of antipsychotic treatment. Other variables such as duration, number of hospitalizations, or days of untreated psychosis can also be confusing variables.

Table 2
Correlations between prolactin levels, symptomatology, and neurocgnitive measurements

	Total (n = 31)		
Positive symptoms	-.001		
Negative symptoms	.127		
Cognitive symptoms	.199		
Excitability subscale	.002		
Anxiety and depression subscale	-.045		
PANSS total	.21		
	Total (n = 31)	*Women (n = 7)*	*Men (n = 24)*
Processing speed	-.229	-.194	-.379
Attention/Vigilance	-.072	.146	-.202
Working Memory	.042	.461	-.156
Verbal learning	.009	.141	-.147
Visual learning	-.171	.057	-.417*
Reasoning and problem solving	-.273	-.182	-.449*
Social cognition	.064	-.321	-.197
MATRICS total	-.161	.233	-.448*

Notes: *$p \leq .05$

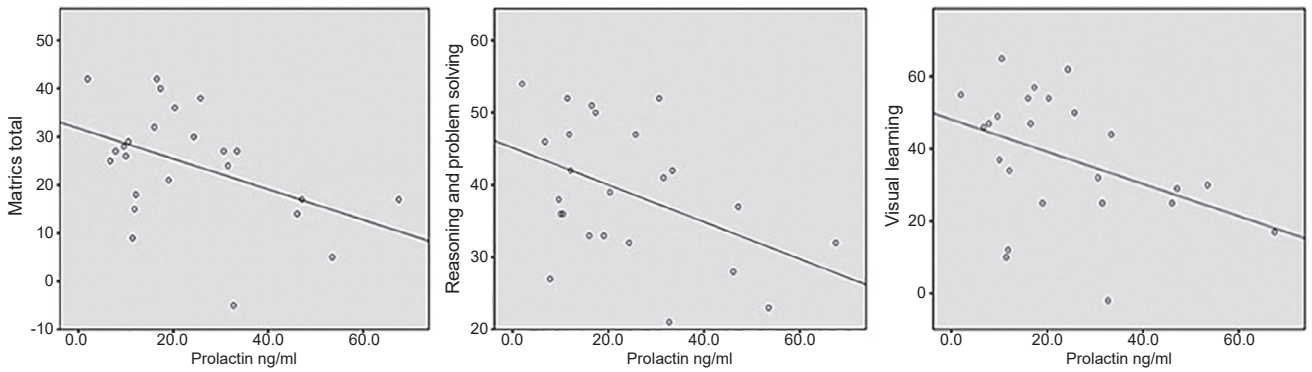

Figure 1. Correlation between cognitive performance and prolactin levels and men with chronic schizophrenia.

Our main finding was the significant correlation between the subdomains of reasoning/problem solving, verbal learning, and MCCB total score with the elevated levels of prolactin observed only in male patients. These results were unexpected. Our first hypothesis implied that the entire group would show a significant correlation between prolactin levels and cognitive performance, considering the evidence that described a generalized effect of the hormone increase with decrease in cognitive scores (Montalvo et al., 2018); in such study, processing speed, working memory, visual learning, and reasoning performance improved after a prolactin decrease in patients with prolactinomas following cabergoline treatment. Consistent findings are described in the work of Degl'Innocenti, Ågren, Zachrisson, and Bäckman (1999) where high levels of this hormone correlated with a decrease in cognitive flexibility scores in patients with major depression. Perhaps, one of the most extreme examples of prolactin's influence on cognition is the work of Brisman, Fetell, and Post (1993) who describe a case of reversible dementia when treating macroprolactinoma.

However, a similar result to our findings is reported by Montalvo et al. (2014). In this study the patients with brief evolution of psychosis displayed a lower cognitive performance associated with the effect of prolactin, especially in men. An important difference with the above study is the years of disease evolution on the studied population. Our patients showed an average of 11 years with the disease, which leads us to assume that male patients with schizophrenia are especially vulnerable to the effects of prolactin independently of the years of evolution and the time of treatment with antipsychotics. However, more studies are needed to test this hypothesis.

What would explain the differential response to prolactin in men and women with this diagnosis? It has been described that the prognosis of schizophrenia shows differences associated to sex. It has been frequently reported that men tend to display an earlier onset of the disease, more relapses, and increased risk of hospitalization. Although the exact mechanism of these differences is unknown, the effect of female hormones as a protective factor in women has been suggested (Bulut, Bulut, & Güriz, 2016). One proposal suggests the protective influence of estrogen, supported by the observation of increased cognitive failure in postmenopausal women. The description of particular cognitive improvement in specific domains like working memory, verbal fluency, and attention after hormonal treatment has been reported (McCarrey & Resnick, 2015).

It is important to mention that prolactin is not the only hormone that can influence cognitive performance. Participation of estradiol, progesterone, follicle stimulating hormone, luteinizing, and testosterone should be considered as they have been related to structural brain changes that could cause cognitive failures (Hoekzema et al., 2017). Moreover, the leading role of cortisol and its implication in the physiopathology of schizophrenia has been studied (Bulut et al., 2016).

More research is needed to elucidate the effect of prolactin on the central nervous system. Recent studies (Cabrera-Reyes et al., 2019) have shown a protective effect of the hormone on the structure and function of the hippocampus, including neuronal plasticity, which opens up a new field of research in psychiatric diseases and in the study of hormones and cognition.

Our results could have clinical implications: considering that male patients are more sensitive to the harmful effect of prolactin on neurocognition, it is advisable to make continuous assessments of the serum levels of this hormone for an early detection of complications.

The most important limitation of this report includes the small sample size we assessed. Increasing the number of patients will allow to explore the influence of other variables such as the type of medication on prolactin levels. Suzuki et al. (2013) reported differences in plasma levels of patients using risperidone or olanzapine monotherapy, total medication time or dose-dependent variations, and body mass index. By studying more defined groups, it would be possible to make more accurate statements about hyperpro-

lactinemia and its relation to cognitive performance in patients with schizophrenia.

The strength of the present work implies its originality as there is only one previous report that relates cognitive measurements to prolactin levels in patients with a brief evolution time, while this work describes the correlation in chronic patients.

Only the male group showed significant correlations between high levels of prolactin and low scores in verbal learning, reasoning/problem solving, and general cognition measured through the MCCB. Our findings lead us to propose the existence of sex-linked differences on the harmful effects of hyperprolactinemia on cognition.

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Conflict of interest

The authors declare they have no conflicts of interest.

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