Hyperprolactinemia in *drug-naïve* First Episode Psychosis and its positive association with serum BDNF levels at baseline

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BACKGROUND

The relationship between prolactin and schizophrenia has been largely studied and it is widely accepted that hyperprolactinemia is a frequent adverse event of antipsychotic treatment. However, the relationship between hyperprolactinemia and schizophrenia might be more complex, and not only a consequence of antipsychotic treatment.

Studies in drug–naïve first episode psychosis (FEP) show contradictory results in this issue. Whereas some initial studies reported lower or normal serum prolactin levels [1], recent other works have found higher prolactin levels in these patients [2-4] and even in individuals at clinical high risk for developing a psychotic disorder [5].

It is known that brain derived neurotrophic factor (BDNF) has a key role in neural survival and network plasticity and has been involved in the etiopathogenesis of psychotic disorders. Nevertheless, the association between BDNF and prolactin has been poorly studied.

With this study, we want to know how BDNF levels at baseline in *drug-naïve* FEP are influenced by prolactin.

METHODS

Fifty *drug-naïve* FEP treated between April 2013 and July 2017 at the ETEP Program at Hospital del Mar were included. Inclusion criteria were: 1) age 18-35 years; 2) fulfillment of DSM-IV-TR criteria for brief psychotic disorder, schizophreniform disorder, schizophrenia or unspecified psychosis; 3) no previous history of severe neurological medical conditions or severe traumatic brain injury; 4) presumed IQ level > 80, and 5) no substance abuse or dependence disorders except for cannabis and/or nicotine use. All patients underwent an assessment at baseline including sociodemographic and clinical variables (substance use, DUP, PANSS, GAF and CDSS). Fasting blood samples were obtained before administering any medication at baseline and used to determine prolactin levels and BDNF levels. SPSS program was used for statistical analyzes.

RESULTS

In our *drug-naïve* FEP sample (table 1), the 43.5% of patients had hyperprolactinemia (> 530 mcIU/mL) at baseline and prolactin levels showed a significative positive correlation with BDNF levels at baseline (r = 0.521; p = 0.011) (figure 1). Moreover, we did a lineal regression model (STEP-WISE METHOD) that showed that the baseline variables that better predict BDNF levels were prolactin levels, cannabis use and DUP (table 2).

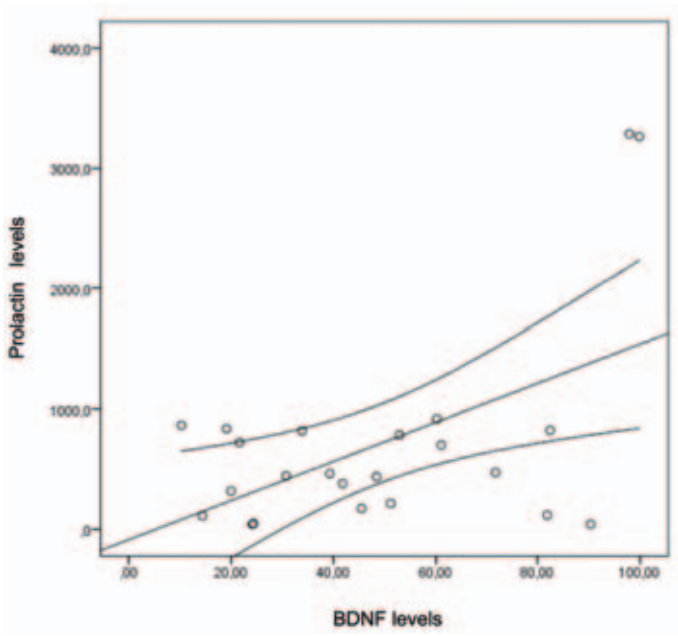

Figure 1. Correlation between BDNF levels and prolactin levels in FEP patients at baseline.

Table 1. Sociodemografic, clinical and neurobiological variables in FEP patients at baseline.

Variable	Patients (N=50)
Age, median (IQR)	26 (24 - 30.25)
Sex, n (% female)	22 (44)
DUP, median (IQR)	31 (8 - 115)
Cannabis use, n (% users)	29 (58)
Tobacco use, median (IQR)	4.5 (0 - 14)
BDNF levels in ng/mL, m (sd)	45.27 (27.14)
Prolactin levels in mcIU/mL, m (sd)	707.36 (863.01)
PANSS P score, m (sd)	24.88 (6.74)
PANSS N score, m (sd)	16.86 (6.65)
PANSS GP score, m (sd)	43.68 (8.27)
PANSS T score, m (sd)	85.24 (15.76)
CDSS score, m (sd)	1.22 (2.02)
GAF score, m (sd)	29.7 (8.89)

Table 2. Lineal regression model (STEP-WISE METHOD) of predictors of BDNF levels in FEP patients at baseline.

Predictor	B	95% CI	p
Prolactin levels	0.14	0.01 to 0.21	0.012
Cannabis use	-1.23	-2.21 to -0.26	0.016
DUP	-0.12	-0.22 to -0.02	0.020

DISCUSSION

Our results suggest that could be a dysregulation of prolactin secretion in *drug-naïve* FEP, thus the frequent hyperprolactinemia in FEP patients would not be only related to antipsychotic treatment.

Moreover, it has been shown that prolactin has extensive effects on the central nervous system, including metabolism of neurotransmitters and neuropeptides, and stress responses [6]. One study [7] found that prolactin could inhibit hippocampal neurons apoptosis in a mouse model of induced depression through the activation of JAK/STAT signaling pathway.

The JAK/STAT signaling pathway is involved in processes such as immunity, cell division and cell death, and it is also activated by BDNF [8]. Taking this into account and our results, we suggest that the prolactin neuroprotective effect could be mediated through the increase of BDNF levels.

Nevertheless, it is also possible that both prolactin and BDNF levels were increased as a stress response. Unfortunately, the nature of this study can't elucidate this fact, and neither if the relationship between BDNF and prolactin is a cause or a consequence. More studies have to be done to clarify this issue.

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**** The authors have no conflicts of interest to declare that are relevant to the content of this study.***

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