Early hyperprolactinaemia in acute psychiatric inpatients: a cross-sectional study

Iperprolattinemia precoce in pazienti ricoverati in SPDC: uno studio trasversale

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Summary

Objectives

Hyperprolactinaemia is an important adverse effect of many drugs. Few naturalistic studies have compared rates of hyperprolactinaemia across psychotropic medications, especially antidepressants. In this cross-sectional study, we aimed to: 1) assess the prevalence and severity of hyperprolactinaemia in a sample of individuals with severe acute psychiatric illnesses, and 2) identify the demographic and clinical factors that might influence levels of prolactinaemia.

Methods

225 individuals were consecutively recruited. Individuals with any medical conditions and other not psychopharmacological drugs known to induce hyperprolactinemia were excluded. Blood samples were collected prior to breakfast and medication administration. Prolactin levels were measured by an electrochemiluminescent immunoassay.

Results

About 2 in 3 individuals treated with antipsychotics had hyperprolactinaemia. Treatment with antipsychotics, particularly risperidone ($p = 0.002$), and young age ($p<0.005$) were associated with hyperprolactinaemia. We did not find any association between antidepressants and hyperprolactinaemia ($p = 0.07$).

Conclusions

Hyperprolactinaemia is a common and early phenomenon among individuals treated for acute psychiatric disorders, especially in younger patients and women.

Key words

Early hyperprolactinaemia • Psychotropic medications • Psychiatric disorders

Introduction

Hyperprolactinaemia (HP) refers to an elevation of the level of the hormone prolactin (PRL) in the blood and is a frequent adverse effect of psychopharmacological treatment. HP may have clinical consequences that are more detectable in the short term (reproductive and sexual dysfunction) than in the long term (osteoporosis, weight gain, cardiovascular disorders and an increased risk of breast or endometrial cancer) [1 2]. Antipsychotics which are known to be the most common cause of pharmacological HP have different propensities to induce HP [3 4]. Several mechanisms by which antipsychotics cause HP have been proposed [5]: 1) strong binding to D_2 receptors (expressed by K-off) [6]; 2) $5HT_2/D_2$ receptor antagonism, which exerts a balanced effect on PRL release [7]; 3) permeation of the haematoencephalic barrier [8]; and 4) partial agonism of D_2 receptors [9].
Additionally, antidepressants, mainly tricyclics, monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs), may cause HP although to a lesser degree. Most studies have focused on these three antidepressant categories [10 4]. Pharmacodynamic mechanisms such as serotoninergic receptor modulation [11] and GABAergic stimulation [12] have been suggested.
Few naturalistic studies have compared the rates of HP across psychotropic medications. Most studies have examined antipsychotics [13] whereas there are few and weak data on antidepressants which are from small samples or case reports/series [10]. The results are also difficult to compare because of methodological differences in the units of measurement of PRL, definition of HP (categorical or continuous, different cut-offs), sampling, sample size and a lack of information about pharmacological treatment (add-on medications, dosages) [14]. Given these assumptions, in the present study, we sought to: 1) measure the prevalence and severity of HP in a sample of acute psychiatric patients, and 2) identify the demographic and clinical factors that might influence the elevation of PRL levels.

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Methods

Study population

Between 2010 and 2011, 225 DSM-IV-diagnosed patients were included in this cross-sectional study. The participants were consecutively recruited in the Psychiatric Unit at the University-Hospital of Padua, Italy. The inclusion criteria were: i) age of 18 years old or greater and ii) same duration of treatment (1 week ± 1 day) with antipsychotics, antidepressants or mood stabilizers, either in monotherapy or in combination. The patients were excluded if they had medical conditions or were receiving medications known to cause HP.

Written informed consent was obtained from all patients, according to the local institutional policy. Medications were administered by nursing hospital staff to ensure adherence.

To compare dosages across different antipsychotics, daily dosages were transformed into haloperidol equivalent doses [15]. All patients received a routine laboratory assessment (including PRL serum level testing). Blood samples were collected from the patients between 8:00 a.m. and 8:30 a.m., prior to breakfast and medication administration. PRL levels were measured by an electrochemiluminescent immunoassay (ECLIA Cobas 6000).

Our laboratory set serum PRL above the upper limit of normal to 25 ng/mL for women and 15 ng/mL for men. The degree of HP was also considered in terms of severity (> 47 ng/mL), based on other studies [13 16].

Statistical analysis

The Kolmogorov-Smirnov method was used to test for the normality of variables. A Student's t-test and Mann-Whitney U test were used for normally distributed and ordinal variables, respectively. For categorical variables, a chi square test was used. To identify the truly independent risk factors for the presence of HP, logistic regression was performed, and variables significantly related to the presence of HP in the univariate analyses were included in the model. The significance level was set at $p<0.05$.

Results

Demographic and clinical characteristics

The characteristics of the sample are presented in Table I. Most patients (56.8%) had PRL blood levels above the upper limit of normal (15 ng/mL for men and 25 ng/mL for women). The mean PRL level was 32.7 ng/mL (SD ± 31.9; range 0.6-183.8).

Univariate analysis

HP was significantly more prevalent in younger (mean age 44.4 ± 16.2 years) than in older (52.45 ± 16.1 years) individuals ($p < 0.005$), in men (73%, N = 75) than in

TABLE I.
Demographic and clinical characteristics of patients (N = 225).
Caratteristiche demografiche e cliniche dei pazienti (N = 225).

	N (%)	Mean ± SD
Gender		
Men	102 (45.4)	
Women	123 (54.7)	
Age (years)		
Men		44.4 ± 16.2
Women		50.6 ± 15.5
Menopausal status		
Premenopausal	64 (52)	
Postmenopausal	59 (48)	
Diagnoses		
Psychotic Disorders	121 (53.8)	
Depressive Disorders	47 (20.9)	
Bipolar Disorders	32 (14.2)	
Personality Disorders	18 (8)	
Others Disorders	7 (3.1)	
Duration of illness (years)		14.6 ± 3.5
Medications		
APs	167 (74.2)	
FGAs	31 (13.8)	
Haloperidol	17 (7.6)	
Perphenazine	6 (2.7)	
Promazine	8 (3.6)	
SGAs	119 (52.9)	
Olanzapine	36 (16)	
Risperidone	33 (14,7)	
Quetiapine	28 (12.4)	
Aripiprazole	10 (4.4)	
Clozapine	12 (5.3)	
2 APs (FGA + SGA)	17 (7.5)	4.98 ± 3.03
APs dosage (mg/day)		
ADs	70 (31.1)	
SSRIs	40 (17.8)	
SNRIs	24 (10.7)	
Other ADs	6 (2.7)	
APs + ADs	43 (19.1)	
MSs	81 (36)	
Lithium	15 (6.7)	
Valproate	60 (26.7)	
Other MSs	6 (2.7)	
Prolactin level (ng/mL)		32.7 ± 31.9
Range		(0,6 – 183,8)
Hyperprolactinemia	128 (56.8)	
Men (> 15 ng/mL)	75 (33.3)	
Women (> 25 ng/mL)	53 (23.5)	
HP severity	≤ 47 ng/mL	> 47 ng/ml
All	83	45
Men	61 (81,3%)	14 (18,7%)
Women	22 (41,5%)	31 (58,5%)

women (43%, N = 53) ($p < 0.005$) and in premenopausal (53%, N = 34) than in postmenopausal (32%, N = 19) women ($p = 0.020$). Among women, 58% (N = 31) had PRL levels above 47 ng/mL ($p < 0.005$). HP was significantly more prevalent in patients with diagnosis of psychosis (71.9%) ($p < 0.005$) and in individuals treated with antipsychotics (65%, N = 108) ($p < 0.005$). HP was also associated with a higher daily antipsychotic dose (mean haloperidol equivalent daily dose 5.33 ± 3.05 mg/day vs. 4.33 ± 39 mg/day, $p = 0.02$). When the severity of HP was considered, women showed significantly higher levels of HP than men ($p < 0.005$).

Other variables were not associated with HP (particularly, the combination of two antipsychotics or one antipsychotic and antidepressants; $p = 0.34$).

Prevalence and degree of HP according to the type of single antipsychotic are shown in Table II. Risperidone showed the highest prevalence of HP (90.9%) ($p = 0.002$), and 16 of 30 risperidone-medicated patients showed PRL levels above 47 ng/mL ($p < 0.03$). Among other second generation antipsychotics (SGAs), HP was under 47 ng/mL in the vast majority of cases. The combination of antipsychotics and antidepressants/mood stabilisers was also not significantly associated with HP ($p = 0.07$).

We found HP in 20 patients not treated with antipsychotics; only two of 20 cases were treated with antidepressants.

Multivariate analysis

Variables significantly related to HP in univariate analysis (age, gender, diagnosis and antipsychotic treatment) were used as independent variables in a multivariate logistic regression. All variables except diagnosis were significantly associated with HP, and the regression function predicted 71% (95% CI 65-77%) of all cases of HP.

Discussion

In our sample, the overall prevalence rate of HP was high (57%), and was even higher among patients treated with antipsychotics (65%). Our rates were similar to those values reported in previous studies, in which HP was present in 28% [2] to 69% [17] of patients on antipsychotic treatment.

Younger age was associated with HP for both genders. This result is frequently reported in the literature [18]. We found higher rates of HP in men than in women. This result is not in accordance with the findings of other studies which showed higher rates of HP among women [19,20]. This discrepancy may be related to different laboratory criteria for defining HP and the different duration of treatment.

When the severity of HP was considered, women presented a more severe degree of HP, in agreement with the results of other studies [21].

Our study confirmed that HP was more prevalent in premenopausal than in postmenopausal women, in accordance with the findings of other studies [18]. In women, reproductive age has been associated with a more pronounced risk of HP due to oestrogens having an indirect stimulating effect on PRL release by inhibiting hypothalamic dopamine synthesis and a reduction in the number of pituitary D_2 receptors [22].

Our study confirmed the strong association between HP and the use of antipsychotics [4,23]. We did not ob-

TABLE II.
The prevalence of hyperprolactinaemia according to the type of pharmacological treatment. *La prevalenza dell'iperprolattinemia a seconda del tipo di trattamento farmacologico.*

Drug	HP (>15/25 ng/mL)		HP (≤ 47 ng/mL)		HP (> 47 ng/mL)	
	N	%	N	%	N	%
APs	108	64.7	70	64.8	38	35.2
FGA monotherapy	22	70.9	17	77.3	5	22.7
SGA monotherapy	73	61,3	45	61.6	28	38,4
Risperidone	30	90,9	14	46.7	16	53.3
Olanzapine	22	61.1	14	63.6	8	36.4
Quetiapine	10	35.7	7	70	3	30
Clozapine	7	58.3	7	100		
Aripiprazole	4	40	4	100	-	-
2 APs (FGAs + SGAs)	13	76.4	8	61.5	5	31.5
MSs and/or ADs	20	34.5	13	65	7	35

HP: hyperprolactinemia; APs: Antipsychotics; FGAs: First Generation Antipsychotics; SGAs: Second Generation Antipsychotics; MSs: mood stabilisers; ADs: antidepressants.

serve significant differences when antipsychotics were administered in monotherapy or in combination with another antipsychotics or antidepressants. We also found that a higher dosage may exert an influence on elevating PRL levels, consistent with the findings of previous studies [17].

It is noteworthy that the association of first-generation antipsychotics (FGAs) with high rates of HP has been confirmed [17 21]. Olanzapine, clozapine, aripiprazole and quetiapine were also associated with HP, even though these drugs have been known to induce only transient and milder PRL elevation by different pharmacodynamic properties [24 25]. Aripiprazole, can even reduce HP [26]. Risperidone was confirmed to be the most PRL-elevating medication [14 16]. This drug has been reported to induce an early and persistent rise in PRL levels, even if tolerance occurs in the long term [27].

Interestingly, we did not find any association between HP and antidepressants. This result confirms that antidepressants may exert only an occasional PRL-elevating effect [10]. Out of 128 subjects with HP, 20 were not treated with antipsychotics.

These HP patients were taking mostly mood stabilisers and antidepressants in only two cases. This result may be explained by other, unmeasured factors such as recent antipsychotics which were mostly not available for retrospective quantification, hospitalisation or environmental stress. In fact, stress is a condition known to induce HP [3 23]. Further studies may include tools such as rating scales to measure these factors.

Lastly, in the present study, detection of HP was performed by PRL sampling after one week of pharmacological treatment, regardless of clinical symptoms. Our results are consistent with the findings of previous naturalistic cross-sectional studies that used different (mostly longer) times for the stabilisation of pharmacological treatment [19 28].

Clinical guidelines do not provide precise recommendations on measuring PRL which is suggested only in the presence of clinical symptoms [29 30]. Our study seems to indicate that systematic and early examination of PRL serum levels might be a preliminary tool to identify HP and to more promptly manage emergent HP side effects in acutely treated patients.

Conclusions

These preliminary findings suggest that during the early stage of pharmacological treatment HP is very frequent in patients who are younger, women of reproductive age and undergoing treatment with risperidone. Future prospective studies examining these factors are needed to evaluate the causal relationship with HP and its clinical symptoms in both the short and long terms.

Conflict of interests

None.

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