SHORT COMMUNICATION

Hyperprolactinaemia in early psychosis – not only due to antipsychotics

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Abstract

Hyperprolactinaemia is often found in patients with schizophrenia and usually considered a consequence of antipsychotics. Prolactin levels were measured in 43 At-Risk Mental State individuals (ARMS) and 26 patients with First Episode Psychosis (FEP). Hyperprolactinaemia was found in 25.6% of ARMS and 46.2% of FEP. Within 60 antipsychotic-naïve ARMS and FEP, hyperprolactinaemia was found in 26.7%. Hyperprolactinaemia may be pre-existing in a subgroup of patients with schizophrenia.

Keywords: antipsychotics, At-Risk Mental State, prolactin, psychosis, schizophrenia

Abbreviations:

FEP, First Episode Psychosis

ARMS, At-Risk Mental State

FEPSY, (***F***rüh***E***rkennung von ***PSY***chosen) study on the early recognition of psychosis at the University Psychiatric Outpatient Department, Basel

HPG, hypothalamic-pituitary-gonadal

BSIP, Basel Screening Instrument for Psychosis

EUFEST, European First Episode Schizophrenia Trial

1 Introduction

Hyperprolactinaemia has often been found in patients with chronic schizophrenia. It can be an adverse effect of conventional, but also many atypical antipsychotics (Bushe and Shaw, 2007; Kinon et al., 2003), for reviews see (Bushe et al., 2008; Montejo, 2008; Riecher-Rössler et al., 2009) and seems to be related mainly to the D2-receptor affinity of antipsychotics (Montejo, 2008).

Hyperprolactinaemia can have many adverse clinical effects (Riecher-Rössler et al., 2009). It can not only lead to galactorrhoea, but also suppresses the activity of the hypothalamic-pituitary-gonadal (HPG) axis and thereby gonadal function, leading to reduced physiological production of estrogens and testosterone (Dickson et al., 2000). This can cause amenorrhoea and menstrual irregularities in women and erectile dysfunction, ejaculatory problems and reduced spermatogenesis in men. In both genders it can be associated with loss of libido, orgasmic dysfunction, infertility and emotional lability (Haddad and Wieck, 2004; Miller, 2004). When chronic, it can cause osteopenia and osteoporosis (O'Keane and Meaney, 2005) and increase the risk of bone fractures (Howard et al., 2007).

However, there are indications that hyperprolactinaemia in schizophrenic patients might, in some cases, not be due to antipsychotics but a pre-existing condition. Hypoestrogenaemia in women with schizophrenia has been described long before the introduction of antipsychotics (Diczfalusy and Lauritzen, 1961; Riecher-Rössler and Häfner, 1993). This has been hypothesized to be a consequence of stress-induced hyperprolactinaemia (Riecher-Rössler and Häfner, 1993). Unfortunately, prolactin was not examined in those patients and there are few recent studies on prolactin levels in antipsychotic-free or -naïve patients with schizophrenia, with contradictory results showing increases, decreases or comparable concentrations in

schizophrenic compared to healthy subjects (Kahn et al., 2008; Meltzer, 1987; Segal et al., 2004).

In individuals with an At-Risk Mental State for psychosis (ARMS), to our knowledge prolactin levels have not been investigated up to now. We therefore performed a small study on prolactin levels in ARMS individuals and FEP patients, most of whom were antipsychotic-naïve.

We hypothesized that hyperprolactinaemia can occur in neuroleptic-naïve FEP patients, and even in ARMS individuals.

2 Materials and Methods

Subjects were recruited in the context of the ***FEPSY*** study, a prospective study on the early recognition of psychosis (***F***rüh***E***rkennung von ***PSY***chosen) at the University Psychiatric Outpatient Department, Basel. The inclusion and exclusion criteria have been described in detail elsewhere (Riecher-Rössler et al., 2007). Briefly, the Basel Screening Instrument for Psychosis (BSIP) was used to identify ARMS, corresponding to the criteria described by Yung et al. (1998).

Exclusion criteria were age <18, insufficient knowledge of German, IQ <70, psychosis clearly due to organic brain disease or substance abuse (except cannabis).

2.1 Subjects

Subjects were recruited from 03/01/2000 to 02/29/2004, 234 individuals were screened in our specialised clinic. For details see Riecher-Rössler et al. (2007). Prolactin measurements could be obtained from 43 ARMS and 26 FEP.

Subjects were interviewed in detail about any antipsychotics they had ever taken in the past (lifetime) and about all medication they were taking at the time of blood sampling. Also, medical records were taken into account, especially concerning the precise date any neuroleptic medication was initiated. All psychotropic medication was categorised into three groups: high-potency neuroleptics, antidepressants and tranquilizers (see Table 1).

The study was approved by the Ethics Committee of Basel, Switzerland, and all individuals included in the study gave written informed consent.

2.2 Prolactin measurement

The Elecsys Prolactin assay, an electrochemiluminescence immunoassay, Ref Number 03203093 190, Roche Diagnostics GmbH D-68298 Mannheim, was used to measure prolactin levels. The method has been standardized against the 3rd IRP WHO Reference Standard 84/500. The lower and upper reference limits were calculated as the 5th and 95th percentiles. Hyperprolactinaemia was defined as a prolactin level above the 95th percentile.

3 Results

Table 1 shows the socio-demographic characteristics of the individuals, their medication, and prolactin values.

Insert *Table 1*

Hyperprolactinemia was found in 11 (25.6%) of 43 ARMS, one of the 11 had been taking low dose olanzapine for behavioural control for 1.5 months, the other 10 were antipsychotic-naïve at the time the blood sample was taken. Amongst FEP patients, hyperprolactinaemia was found in 46.2% (12/26). Half of those (6/12) were antipsychotic-naïve, the others had been taking low-dose

olanzapine or risperidone for less than 3 months. Thus, 10 of the neuroleoptic-naïve ARMS (23.8 %) and 6 of the neuroleptic-naïve FEP (33.3 %) had hyperprolactinaemia.

Figure 1 shows the prolactin serum values of the neuroleptic-naïve patients.

Insert *Figure 1*

4 Discussion

In this study we found hyperprolactinaemia in about 20% of the neuroleptic-naïve ARMS individuals and in about 30% of the neuroleptic-naïve FEP patients.

Our findings indicate that hyperprolactinaemia in schizophrenia is not necessarily only caused by antipsychotic treatment, but might already be present in neuroleptic-naïve FEP and even in prodromal stages. There was a gender effect with mean prolactin values elevated only in female ARMS and FEP.

In this context it is interesting to note that hypoestrogenaemia and irregular menstrual cycles, the main consequences of hyperprolactinaemia, have also been described in many unmedicated schizophrenia patients (Riecher-Rössler, 2005; Riecher-Rössler et al., 1998; Häfner and Riecher-Rössler 1993). This could well be due to previously often undiagnosed hyperprolactinaemia, as prolactin can suppress gonadal function and physiological estrogen production. Early clinicians such as Kraepelin (1909) or Kretschmer (1921) reported that many schizophrenic women showed physical signs indicating “insufficient functioning of the sexual glands” with “hypoestrogenism”. In the 1930s, studies analysing estrogen levels in blood and urine confirmed these observations. Researchers found decreased estrogen blood levels in most of the schizophrenic inpatients they examined (Diczfalusy and Lauritzen, 1961). As at the time neuroleptic therapy had not

been introduced, the observed abnormalities cannot be interpreted as side effects of neuroleptics. Prolactin levels, unfortunately, were not measured in those days.

Segal et al. (2004) and also Mazure et al. (1997) found prolactin levels within or close to the normal range in unmedicated patients with schizophrenia.

However, just recently in the EUFEST study, investigating 498 FEP patients, hyperprolactinaemia was found in 71% of FEP, most of whom were neuroleptic-free (Kahn et al., 2008).

Our finding of hyperprolactinemia could be caused by general stress associated with the illness experience, as stress can induce hyperprolactinaemia (Biondi and Picardi, 1999).

There also is evidence for increased pituitary volume in antipsychotic-free FEP patients (Garner et al., 2005; Pariante et al., 2005). This could indicate an increased pituitary activity associated with prolactin production (MacMaster et al., 2007). Recently, Mondelli et al. (2008) found enlarged pituitary volumes even in unaffected relatives of patients with schizophrenia.

Dopaminergic transmission is well known to be increased in psychosis. We also know that dopamine is the most important prolactin inhibiting factor. The reciprocal relationship between prolactin and hypothalamic dopamine secretion has been confirmed in many studies (Grattan and Kokay, 2008). Thus it could well be that stress induces hyperprolactinaemia and that the increase of dopamine in psychosis is – at least partly - a regulatory mechanism in order to down-regulate prolactin.

A limitation of our study is the small sample size and results need to be confirmed in larger samples before definite conclusions can be drawn.

5 Conclusions

Our findings support that prolactin should be measured in FEP patients before introducing antipsychotics. If serum prolactin levels are already increased, clinicians should consider choosing prolactin sparing neuroleptics.

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Table 1

Sample characteristics and prolactin values[a]

	FEP[b]	ARMS[c]	p
n (men / women)	26 (19 / 7)	43 (23 / 20)	χ^2=0.203, p=0.653
mean age (± SD)	30.5 (7.4)	25.7 (7.6)	U-Test=344.5, p=0.008
n patients on high-potency neuroleptics (%)	7 (28.0)	1 (2.3)	χ^2=9.564, p=.002
n patients on antidepressants (%)	4 (16.0)	9 (20.9)	χ^2=0.249, p=.618
n patients on tranquilisers (%)	12 (48.0)	9 (20.9)	χ^2=5.427, p=0.02
Prolactin values [d,e]			
men: prolactin mean (± SD)	18.3 (11.8)	13.5 (8.2)	U-Test =164.5, p=0.172
men: prolactin median men[3]	16.0	12.2	
women: prolactin mean (± SD)	157.1 (333.2)	30.55(34.9)	U-Test =42.0, p=0.13
women: prolactin median	31.4	21.8	
Prolactin values in the subgroup of antipsychotic-naive patients [d,e]			
n (men/women)	13/5	23/19	
men: prolactin mean (± SD)	16.5 (11.8)	13.5 (8.2)	U-Test =124.5, p=0.415
men: prolactin median	15.9	12.2	
women: prolactin mean (± SD)	26.9 (14.1)	30.6 (35.9)	U-Test =37.0, p=0.489
women: prolactin median	24.1	21.7	

[a] Prolactin serum levels are given in µg/l

[b] FEP: First Episode Psychosis; one missing for medication at time of blood test
[c] ARMS: Individuals with an At-Risk Mental State
[d] Reference prolactin serum level, men: 4.1–18.4 µg/l
[e] Reference prolactin serum level, women: 3.4–24.1 µg/l

Supplementary Table 2: Patients with hyperprolactinaemia - prolactin values at the time of blood sample

1. ARMS			
	Prolactin value µg/l	**High-potency neuroleptic treatment (duration)**	**Other psychotropic medication (*)**
male	20.9	none	none
male	23	none	none
female	24.9	none	none
female	41	none	none
male	44.3	none	none
female	46.2	none	none
female	54.7	none	none
female	166	none	none
female	48.8	none	chlorprothixen
male	19	none	chlorprothixen
female	29	olanzapine (1.5 months)	paroxetine
2. FEP			
male	22.2	none	none
female	31.4	none	none
male	46.8	none	none
male	21.1	none	none
female	47.5	none	chlorprothixen
male	29.6	none	chlorprothixen
male	25	olanzapine (2 days)	chlorprothixen
male	26	olanzapine (3 months)	venlafaxine, chlorprothixen
female	912	olanzapine (1 month)	missing
male	39.3	risperidone (2 days)	none
female	53.5	risperidone (1 day)	none
male	26.8	risperidone (missing)	fluoxetine

(*) with potential effect on prolactin levels

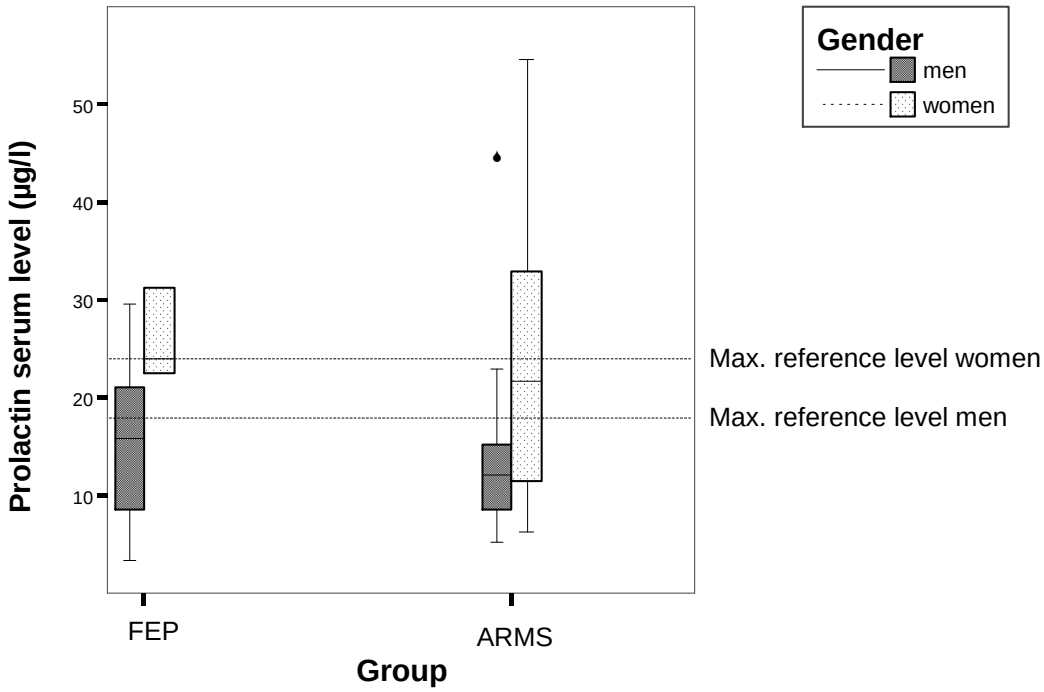

Fig. 1. Prolactin serum levels in neuroleptic-naïve patients according to group and gender. Reference prolactin serum levels: men 4.1-18.4 µg/l, women 3.4-24.1 µg/l. One outlier (*) in the male ARMS group.