Hyperprolactinaemia in first episode psychosis - A longitudinal assessment

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ABSTRACT

Little is known about hyperprolactinaemia (HPL) in first episode psychosis (FEP) patients. We investigated longitudinal changes in serum prolactin in FEP, and the relationship between HPL, and antipsychotic medication and stress.

Serum prolactin was recorded in FEP patients at recruitment and again, 3 and 12 months later. HPL was defined as a serum prolactin level >410 mIU/L (~19.3 ng/ml) for males, and a serum prolactin level >510 mIU/L (~24.1 ng/ml) for females.

From a total of 174 people with serum prolactin measurements at study recruitment, 43% ($n = 74$) had HPL, whilst 27% ($n = 21/78$) and 27% ($n = 26/95$) had HPL at 3 and 12 months respectively. We observed higher serum prolactin levels in females versus males ($p < 0.001$), and in antipsychotic treated ($n = 68$) versus antipsychotic naïve patients ($p < 0.0001$). Prolactin levels were consistently raised in FEP patients taking risperidone, amisulpride and FGAs compared to other antipsychotics. No significant relationship was observed between perceived stress scores ($\beta = 7.13$, $t = 0.21$, df = 11, $p = 0.0.84$ 95% CI −72.91–87.16), or objective life stressors ($\beta = -21.74$, $t = -0.31$, df = 8, $p = 0.77$ 95% CI −218.57–175.09) and serum prolactin.

Our study found elevated rates of HPL over the course of the first 12 months of illness. We found no evidence to support the notion that stress is related to elevated serum prolactin at the onset of psychosis.

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1. Introduction

Hyperprolactinaemia (HPL) is a relatively common, but often unacknowledged side effect of antipsychotic medications. In general, all antipsychotic medication can be associated with HPL, with the propensity for an antipsychotic to cause HPL mainly associated with its degree of D-2 receptor antagonism (Bushe et al., 2008a), and a higher ratio of pituitary to striatal D-2 receptor occupancy (Kapur et al., 2002). The highest prevalence of HPL is seen with amisulpride, risperidone, and paliperidone, even at relatively low doses, followed by the first generation antipsychotics (FGAs) (Bushe et al., 2008b). A recent meta-analysis identified that standardised mean differences compared with placebo for prolactin increase varied from 0·22 for aripiprazole (best drug) to −1·30 for paliperidone (Leucht et al., 2013). Hyperprolactinaemia is important to patients as it has been linked with sexual dysfunction, hypogonadism, (Howes et al., 2007) cancer and osteoporosis (De Hert et al., 2015; Howes et al., 2005; Meaney et al., 2004; Peuskens et al., 2014).

There is a paucity of information on the prevalence of hyperprolactinaemia in early psychosis, particularly among those who are antipsychotic naïve. The largest study in early psychosis identified that 74% of patients treated with risperidone had HPL at some point over a two year period (Schooler et al., 2005), while HPL rates of 71% were identified in the European First Episode Schizophrenia (EUFEST) study, half of those being antipsychotic naïve (Kahn et al., 2008). In two cross sectional studies of antipsychotic naïve FEP patients, 29–39% were identified as having HPL (Aston et al., 2010; Riecher-Rössler et al., 2013). A recent meta-analysis of prolactin in antipsychotic-naïve patients, found significantly elevated prolactin levels in both males and females, though the findings were limited by the small number of identified studies (Gonzalez-Blanco et al., 2016).

The heightened prevalence of HPL, even in antipsychotic naïve FEP patients, does not appear to be attributable to important confounding variables such as sex, smoking status, body mass index (BMI), thyroid stimulating hormone or ghrelin (Garcia-Rizo et al., 2012). This has led some to hypothesise that stress may be causative of HPL, which may in turn be a contributing factor to the emergence of the psychotic episode (Howes and Kapur, 2009; Riecher-Rössler et al., 2013). A postulated mechanism suggests that increased dopamine in psychosis may in part be due to its role as a prolactin-inhibiting factor (PIF), and as part of a regulatory mechanism to down regulate excess prolactin which has been caused by stress (Riecher-Rössler et al., 2013). However, this hypothesis regarding the relationship between stress and HPL has not yet been tested in a FEP group of patients.

1.1. Aims of the study

Given the paucity of longitudinal research investigating HPL in people with early psychosis (Pérez-Iglesias et al., 2012), we set out to investigate the prevalence of HPL during the first year of treatment for psychosis. Specifically, we set out to examine a) the relationship between HPL and antipsychotic medication use, gender, ethnicity, age, smoking and psychopathology at the time of the study recruitment; b) to evaluate any differences in serum prolactin levels and HPL among antipsychotic naïve and antipsychotic treated patients. For the first time, we aimed to elucidate any associations of perceived stress and stressful life events with serum prolactin in antipsychotic naïve patients.

2. Methods

Subjects were recruited in the context of the Physical Health and Substance Use Measures in First Onset Psychosis (PUMP) study, part of the NIHR funded IMPaCT programme. PUMP is a naturalistic longitudinal study assessing the relationship between lifestyle habits and the emergence of cardiometabolic risk over the first year of psychosis. The study was approved by the Joint South London and Maudsley and The Institute of Psychiatry NHS Research Ethics Committee (REC reference number:08/H0807/53).

2.1. Eligibility criteria

Study participants were required to meet the ICD-10 criteria for FEP (codes F20-29 and F30-33) (World Health Organization, 1992) and were aged between 18 and 65. The baseline diagnoses were made from face-to-face interviews and mental health records according to ICD-10 criteria (WHO, 1992) utilising the Operational Criteria Checklists (OPCRIT) (McGuffin et al., 1991). Individuals with comorbid substance use disorders were not excluded. We excluded individuals who met the criteria for organic psychosis (F09) or moderate or severe learning disabilities (as defined by ICD-10, World Health Organization, 1992) (World Health Organization, 1992), who presented with evidence of transient psychotic symptoms resulting from acute intoxication as defined by ICD-10, and who were pregnant.

2.2. Recruitment

Patients were recruited as soon after first presentation as possible and were followed up prospectively over a twelve month period during which they remained under the care of mental health teams. Antipsychotic medication changes were made by the treating psychiatrists as part of routine clinical care over the course of the follow up period.

2.3. Serum prolactin measurement and hyperprolactinaemia definition

There are a variety of reported units of measurement for serum prolactin levels. Studies performed outside of the UK generally report data as ng/ml, whereas most UK data is in mIU/L (the accepted SI unit for prolactin measurement). We measured serum prolactin levels in mIU/L, but have also presented data in ng/ml, calculated on the basis of 1 ng/ml equaling 21.2 mIU/L (Bushe et al., 2008a). All serum prolactin measurements were performed by the same laboratory and a fasting sample was taken in the morning by direct venepuncture without regard to timing of medication in those who were already treated with antipsychotics.

Quantitative determination of prolactin serum levels were evaluated by a direct chemiluminometric method using The ADVIA Centaur® Prolactin assay, which is a two-site sandwich immunoassay. A direct relationship exists between the amount of prolactin present in the patient sample and the amount of relative light units detected by the system. Intraassay and interassay coefficients of variation for serum prolactin are 2.75% and 3.60% (Bayer Diagnostics).

Hyperprolactinaemia was defined in accordance with the hospital laboratory reference range as a serum prolactin level >410 mIU/L (~19.3 ng/ml) for males, and a serum prolactin level >510 mIU/L (~24.1 ng/ml) females. In order to highlight the severity of HPL, we further categorised HPL into those with a serum prolactin above 1000 mIU/L (~47.4 ng/ml) and a serum prolactin level greater than 2000 mIU/L (~94.8 ng/ml). Although arbitrary, this categorisation has been implemented previously in a population with multi-episode schizophrenia (Bushe et al., 2008b), and mirrors previously defined serum prolactin cut offs linked to clinical symptoms, and those commonly used in endocrine practice.

2.4. Antipsychotic medication use

Subjects were interviewed in detail about antipsychotics they were taking at the time of blood sampling. Also, medical records were taken into account to obtain the date when antipsychotic medication was initiated.

Antipsychotic medication doses were standardised as defined daily doses (DDD) based on the dose prescribed at the time of the prolactin measures (WHO Collaborating Centre for Drug Statistics Methodology,