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Prolactin and antipsychotics related metabolic disorders

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ABSTRACT *Weight gain is the complex result of ambiental, behavioural, genetic and neurohormonal factors. It was observed that efficient antipsychotics near D2 receptorial antagonism have affinity for other receptors, too. Going on paper related differences among the severity of metabolic disturbances induced by typical (selective blockers of D2 receptor) and atypical (non-selective blockers of D2 receptor) antipsychotics, we studied the metabolic effects of some neuroleptics seeking for their correlation with prolactin levels. Our results evidenced that the prevalence of some components of the metabolic syndrome was significantly higher in patients treated with atypical neuroleptics. Insulin resistance stays on the basis of the metabolic syndrome occuring. Elevated prolactinemia seen after administration of both typical and atypical neuroleptics, showed positive correlation with the body mass index and the severity of insulin resistance, pleading for the important role of D2 receptor blocking effects in the appearance of the metabolic syndrome.*

Background

Obesity is a major contributor to a range of metabolic disorders responsible for morbidity and mortality linked to metabolic syndrome. Adverse events associated with the use of antipsychotics (APs) are thought to be contributory to endocrine side effects constituting metabolic syndrome. Increasing numbers of reports described obesity, diabetes, other carbohydrate metabolism abnormalities and lipid dysregulation in patients treated with APs (Allison et al., 1999; Bergman & Ader, 2005; Haupt & Newcomer, 2001; Newcomer, 2004, 2005; Nihalani, Schwartz, Siddiqui, & Megna, 2011; Réthelyi & Sawalhe, 2011; Riordan, Antonini, & Murphy, 2011; Smith et al., 2009, 2010). The prevalence of metabolic syndrome varies greatley (between 20% and 60%) in adults with schizophrenia (Riordan et al., 2011)

Research on the mechanism by which APs promote body weight gain (BWG) has focused on the direct interaction of these drugs with brain monoamines (such as dopamine, serotonin, histamine, noradrenaline and acetylcholine) involved in feeding regulation. Most authors appear to be agree that the blockade of the serotonin (5-HT1A 5-HT2A,C) and histamine (H1) receptors in the brain is involved in AP-induced BWG (Bishara & Taylor, 2008; Nasrallah, 2008; Nihalani et al., 2011)including greater improvement in negative symptoms, cognitive function, prevention of deterioration, and quality of life, and fewer extrapyramidal symptoms (EPS). An important prolactin (PRL) release appears after D2receptors blockade, as well as after APs. All typical antipsychotic medications are associated with sustained hyperprolactinemia due to their high affinity for the D2 receptor and their slow dissociation from the receptor once bound, but atypicals differ quite dramatically in their propensity to cause prolonged high prolactin levels (Fitzgerald & Dinan, 2008). It is well known that prolactin-elevating drugs suppress gonadal hormone secretion and may enhance autoimmune proclivity, but he relation between prolactin level and weight regulation had received little attention. Beside its role in lactation and reproduction, accumulating evidence suggests that PRL has a crucial impact on energy balance by acting on two key players, the pancreas and the adipose tissue(Carré & Binart, 2014).

The aims of our study were to investigate the prevalence of obesity and other metabolic disorders in patients treated with different antipsychotics and to evaluate the serum prolactin levels correlating them with the anthropometric indexes and metabolic parameters.

Materials and Methods

Patient population: This was a retrospective study including patients treated with APs who were examined in endocrine ambulatory service for obesity. Anthropometric and metabolic data of the outpatients during one year (2012 february -2013 february) treated with different psychotropics were registered and the PRL level was determined.

Study design: The following variables were recorded: age, sex, type of AP medication followed at least for 6 months, body mass index (BMI), waist circumference, triglyceride- and HDL-cholesterol-level, glycemia, HOMA-IR, blood pressure and PRL level.

We assessed BMI (kg/m^2) and waist circumference in cm. Metabolic syndrome criteria were those established by International Diabetes Federation (IDF, 2005), but clinically relevant obesity was defined as a BMI>30kg/m^2. According to the new IDF definition, for persons to be defined as having metabolic syndrome they must have:

- central obesity (defined as waist circumference ≥ 94cm for Europid men and ≥ 80cm for Europid women) plus any two of the following four factors:

- raised triglyceride level: ≥ 150 mg/dL (1.7 mmol/L), or specific treatment for this

- lipid abnormality: reduced HDL cholesterol < 40 mg/dL (1.03 mmol/L) in males and < 50 mg/dL (1.29 mmol/L) in females, or specific treatment for this lipid abnormality.

- raised blood pressure (BP): systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg, or treatment of previously diagnosed hypertension.

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- raised fasting plasma glucose (FPG) ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes.

Serum PRL levels were measured using ELISA kits. Fasting PRL level was measured after 2 hours of waking. Hyperprolactinemia was considered higher than 20 ng/ml values of PRL both in women and men.

Homeostasis Model of Assessment - Insulin Resistance (HOMA-IR) was calculated using the following formula: fasting glucose (mmol/L) x fasting insulin (mU/L) / 22.5

Statistical analysis: For statistical analysis GraphPad Prism 5 trial version was used. Values of data were compared performing Student's t test and for correlation Spearman test was used. The value of P<0.05 was considered significant.

Results

Between patients treated with different psychotropics, 10.89% (63 patients) used chronically APs: 42.85 % (27 patients) was treated with typical APs (TAPs) and 57.14% (36 patients) with atypical APs (ATAPs) at least for 6 month. The used TAPs were: haloperidol and fluphenazine. The used ATAPs were: olanzapine, clozapine, risperidone and amisulpride. The sex distribution was: 92% female, 8% male. The average age ***(±SE)*** in different groups were 44.76±2.13 years in TAPs group and 41.57± 1.76 years in ATAPs group, respectively.

Figure 1 presented the frequency of the different components of the metabolic syndrome. In ATAPs treated patients a higher incidence of dyslipidemia was found (significantly higher frequency of low HDL-cholesterol and of elevated triglyceride level) than in TAPs patients.

In HOMA-IR level no differences were observed between the patients (4.91±0.66 and 4.26 ±0.38 in TAPs and ATAPs group, respectively).

The frequency of association of two elements of metabolic syndrome was 22.22% in the TAPs treated group and 14.44 % in the ATAPs treated group.

The frequency of the complete metabolic syndrome was 22.23% in the TAPs treated group, but significantly higher in the ATAPs group (36.11%, p<0.05).

The frequency of hyperprolactinemia was significantly higher (p<0.05) in the TAPs treated group (44.44 % *versus* 27.77%) than in the ATAPs group.

Considering BMI and HOMA-IR important risk factors for diabetes in metabolic syndrome we looked for the correlation between prolactin levels and BMI, respectively HOMA-IR. Table II and III report the results of this correlation.

Table II: Correlation between prolactin levels and BMI

Patients	r (Spearman)	P
TAPs	0.543	0.003*
ATAPs	0.347	0.05*

* significant values

Table III: Correlation between prolactin levels and HOMA-IR

Patients	r (Spearman)	P
ATAPs	0.682	0.002*
TAPs	0.591	0.03*

* significant values

Discussion

It is well established that AP drugs can induce substantial weight gain, different drugs in greater or lesser extent (Bergman & Ader, 2005; Bou Khalil, n.d.; Goeb et al., 2010; Lieberman, 2004; Newcomer, 2004). There is a growing evidence that treatment of schizophrenia may impair glucose metabolism and increase the risk of diabetes (Bergman & Ader, 2005; Goeb et al., 2010; Haupt & Newcomer, 2001; Newcomer, 2005; Riordan et al., 2011; Smith et al., 2009; F.C.J. Starrenburg & Bogers, 2009). The mechanisms underlying this AP drugs induced metabolic syndrome are likely be multifactorial (Mantzoros, 2009; Nasrallah, 2008; Ruetsch, Viala, Bardou, Martin, & Vacheron, n.d.; F C J Starrenburg & Bogers, 2009). The antipsychotics different receptor affinity and occupancy as well as and their antagonism type could be an important contributing factor for developing metabolic syndrome (Buckley, 2007; Correll, 2010). Antagonism of the serotonin receptor 5-HT2C, for which several APs – particularly ATAPs as clozapine and olanzapine – have high affinity, is a strong candidate as the receptor is known to influence appetite and thereby weight gain (Alvarez-Jiménez et al., 2008; Bou Khalil, n.d.; Newcomer, 2005; Pramyothin & Khaodhiar, 2010; Ruetsch et al., n.d.; Smith et al., 2009). Effects on other receptors, mainly on D2, alpha-adrenoreceptors and particularly the histamine H1receptor have been also implicated (Buckley, 2007; Correll, 2010; Nasrallah, 2008; F C J Starrenburg & Bogers, 2009). In this study where mainly clozapine and olanzapine were chosen between ATAPs, a higher frequency of complete MS and dyslipidemia was found. This is in line with other results (Bergman & Ader, 2005; Bou Khalil, n.d.; Lieberman, 2004; Riordan et al., 2011) in which atypical antipsychotics have been shown to contribute to weight gain, which may well reflect increased body fat deposition.

Endocrine mechanisms, such as activation of the hypothalamus- pituitary - adrenal axis, changes of insulin sensitivity, hyperprolactinemia and gonadal dysfunction may also be involved in APs induced MS. First generation APs are known to induce more important raise in serum PRL concentration (Peuskens, Pani, Detraux, & De Hert, 2014) than atypical APs. This study's results evidenced higher frequency of hyperprolactinemia in TAPs treated than in ATAPs treated group. The majority of the second generation antipsychotics excepting amisulpride and risperidone are considered "PRL sparing" drugs. Now prolactin is considered a metabolic hormone (Carré & Binart, 2014) with important effects on adipocyte function. Further research are needed to investigate the role of PRL and PRL- receptors in psychotropic drug induced metabolic syndrome.

Conclusions

As the results showed in ATAPs treated persons the prevalence of metabolic syndrome is significantly higher than in the TAPs treated group. The most frequent elements of metabolic syndrome in ATAPs treated persons were low HDL-cholesterol and high triglyceride level. Although hyperprolactinemia was more frequent in the TAPs treated persons than in the ATAPs group, the significant positive correlation of PRL level with BMI and HOMA-IR in all of the treated patients suggests that the prolactin release after D2 receptor blockade may be involved in insulin-resistance and developing of metabolic syndrome.

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