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Evolution of metabolic risk factors over a two-year period in a cohort of first episodes of psychosis

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ABSTRACT

Patients with a first episode of psychosis (FEP) display a broad range of metabolic risk factors related to the development of diverse medical comorbidities. Initial stages of these disorders are essential in understanding the increased vulnerability of developing cardiometabolic disturbances, associated with a reduced life expectancy. This study aimed to evaluate the metabolic profile of a cohort of patients with a FEP and its evolution during a two year follow-up, as well as the factors that influence the changes in their metabolic status.

16 participating centers from the PEPs Project recruited 335 subjects with a FEP and 253 matched healthy controls, aged 9–35 years. We investigated a set of anthropometric measures, vital signs and laboratory data obtained from each participant over two years in a prospective, naturalistic study.

From the beginning of the study the FEP group showed differences in the metabolic profile compared to the control group, together with a progressive worsening in the major part of the analyzed variables during the follow-up period, with higher rates of obesity and metabolic syndrome. Certain risk factors were related to determinate clinical variables such as male gender, the presence of affective symptoms or an early onset or to treatment variables such as the use of antipsychotic polypharmacy, antidepressants or mood stabilizers.

Our results highlight the extremely high risk of patients at early phases of schizophrenia and other psychotic disorders of developing cardiovascular comorbidity and the fast worsening of the metabolic profile during the first two years.

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1. Introduction

Patients with a first episode of psychosis (FEP) display a wide array of metabolic disturbances (Fleischhacker et al., 2013), which over time might predict the development of diverse medical conditions, such as metabolic syndrome (MetS) or cardiovascular diseases (CVD). Those medical co-morbidities seem to underlie the increased mortality in those patients detected even at the onset of a mental disorder (Laursen et al., 2013; Nordentoft et al., 2013). Part of this increased risk might also be related to the metabolic side effects of antipsychotics, already present after few weeks of treatment (Fernandez-Egea et al., 2011; Tek et al., 2016).

Initial stages of psychotic disorders are essential in understanding the increased risk of developing metabolic disturbances (Fernandez-Egea et al., 2009; Perez-Iglesias et al., 2014). Two meta-analyses reflect that the risk for MetS is low in FEP but increases over time (Mitchell et al., 2013; Mitchell et al., 2011), with high prevalence in chronic patients (Arango et al., 2008). The determination of MetS rates at initial stages might underscore the risk of developing CVD, so further analysis must be implemented (Garcia-Rizo et al., 2017). At initial stages, glucose abnormalities are the most replicated findings (Rajkumar et al., 2017; Garcia-Rizo et al., 2016; Greenhalgh et al., 2016; Perry et al., 2016; Pillinger et al., 2017; Ryan et al., 2003; Spelman et al., 2007). Besides, other CVD risk factors have been assessed: (i) blood pressure, through increased pulse pressure (Fernandez-Egea et al., 2009); (ii) lipid profile has been reported to be altered (Keinanen et al., 2015) or subclincal (Misiak et al., 2017), while other studies did not find differences(Kirkpatrick et al., 2010); and (iii) abdominal obesity (Ryan et al., 2004), but other studies failed to replicate (Fernandez-Egea et al., 2009; Keinanen et al., 2015). In this context, the study of the population with a FEP is of great interest because it avoids the effect of confounding variables, such as somatic comorbidities, prolonged antipsychotic treatment or chronicity (Bernardo and Bioque, 2014; Bernardo et al., 2013).

The PEPs Project was a multicenter, prospective, longitudinal, naturalistic study, conducted in 16 research sites in Spain designed to follow a cohort of 335 subjects with a FEP, matched with 253 healthy controls (Bernardo et al., 2013; Bioque et al., 2016). The aim of the present study was to evaluate the metabolic profile of patients at the FEP and its evolution during the two year follow-up, aiming to identify the factors that influence in these early changes. This study offers a unique opportunity to extend previous research by investigating the prevalence of metabolic abnormalities in a real-world cohort of patient with a FEP treated with commonly-used drugs during a follow-up of two years.

2. Methods

2.1. Subjects

During the recruitment period (2009–2012), every patient who met the inclusion criteria that was attended at the PEPs project participating sites facilities was invited to participate in the study, either inpatient or outpatient. The rationale and the complete clinical protocol used in the PEPs project were previously published (Bernardo et al., 2013) (free text available both in English and Spanish).

The inclusion criteria for patients were: presence of a FEP in the last 12 months, age between 7 and 35, and speak Spanish correctly. The Spanish translation of the K-SADS-PL (Kaufman et al., 1997) was used to assess current and past psychopathology in children and adolescents according to DSM-IV criteria (American Psychiatric Association (Washington), 1994), and the SCID-I & II, with a Spanish translation available, for adults (First et al., 1994, 1999). In order to retrospectively characterize and date the initial symptoms of a psychotic illnesses the Symptom Onset in Schizophrenia (SOS) inventory was used (Perkins et al., 2000).

The exclusion criteria for patients were: (1) mental retardation according to DSM-IV criteria (American Psychiatric Association (Washington), 1994), (2) history of head trauma with loss of consciousness and (3) presence of an organic disease with mental repercussions.

Healthy controls were matched by age (±10%), gender and parental socio-economic status (SES), measured by the Hollingshead-Redlich scale (±1 level). They also had to speak Spanish fluently. The exclusion criteria for controls were the same as for patients plus having a personal antecedent of psychotic and/or major affective disorder and having a first degree relative with psychotic disorder history.

With the above mentioned criteria, a cohort of 335 subjects who have suffered a FEP within the previous 12 month and 253 healthy controls were included in the PEPs Project, with an age between 9 and 35 years. 198 patients and 158 control subjects were kept in the study until the two year follow-up final visit.

Being a naturalistic study, there were no specific guidelines for treatments, so patients received antipsychotic treatment based on the clinician's choice. Dosing, co-medications or treatment changes were based on clinical necessity. Following the inclusion/exclusion criteria, treatment with antipsychotics did not exceed 12 months at study entry, with a mean duration of untreated psychosis (DUP) of 106.21 days (Bernardo et al., 2017). As the majority of the participating centers were tertiary university hospitals a large majority of the patients included in the study were recruited during their first hospitalization, when the first antipsychotic treatment was indicated. The major part of the patients (n = 304, 90.7%) were under antipsychotic treatment by the time they were included in the study, with a mean of 54.08 days taking antipsychotic treatment (Bioque et al., 2016). Only a small proportion (n = 49, 14.6% of the sample) had been taking antipsychotic for more than three months before the inclusion. A previous report gave a full description of the psychopharmacological treatment used in this study (Bioque et al., 2016).

The study was approved by the investigation ethics committees of all participating centers and informed consent was obtained from all participants or legal guardians.

2.2. Study assessments and biochemical determinations

At baseline, a complete medical history was taken. Body weight, blood pressure and waist circumference were assessed at baseline and at 2, 6, 12 and 24 months visits. Laboratory data was obtained at every visit in patients and at baseline and at 24 months in controls. In all the participating sites, blood glucose, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, and triglycerides (TG) were directly analyzed by enzymatic procedures with an Automatic Chemical Analyzer. Glycated hemoglobin was analyzed by high-performance liquid chromatography (HPLC). The reference values at each site were recorded in a common database called GIDSAM, where individual values were homogenized and included (Bernardo et al., 2013).

2.3. Metabolic and cardiovascular risk assessment

Taking each individual's anthropometric measures, vital signs and laboratory data, the presence of MetS and/or obesity was established for each participant at baseline and 24 month's visit. As subjects included in the PEPs project were aged from 9 to 35, both conditions were defined with available criteria which have different definitions for underage and adult. Thus, the presence of Mets was defined using the International Diabetes Foundation (IDF) criteria (Alberti et al., 2005; Zimmet et al., 2007). In subjects aged 10 to 16 years, the MetS criteria were abdominal obesity ≥90th percentile (or adult cut-off if lower), fasting glucose ≥100 mg/dL, triglycerides ≥150 mg/dL, HDL cholesterol <40 mg/dL and blood ≥130/85 mmHg. In subjects ≥16 years the criteria were abdominal obesity >94 cm in men and >80 cm in women, fasting glucose ≥100 mg/dL, triglycerides ≥150 mg/dL, HDL cholesterol <40 mg/dL in men and <50 mg/dL in women and blood pressure ≥ 130/85 mm Hg, or being under pharmacological treatment for any of

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