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Research paper

Impaired glucose metabolism moderates the course of illness in bipolar disorder

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ABSTRACT

Background: The longitudinal course of bipolar disorder (BD) is highly heterogeneous, and is moderated by the presence of general medical comorbidities. This study aimed to investigate the moderating effects of impaired glucose metabolism (IGM) on variables of illness course and severity in a BD population.
Methods: Fifty-five patients with BD were evaluated. All subjects were evaluated with respect to current and past psychiatric and medical disorders, as well as lifetime use of any medication. Body mass index (BMI) and metabolic parameters were obtained. IGM was operationalized as pre-diabetes or type 2 diabetes mellitus.
Results: Thirty (54.5%) individuals had IGM. After adjustment for age, gender, ethnicity, alcohol use, smoking, BMI and past and current exposure to psychotropic medications, individuals with IGM, when compared to euglycemic participants, had an earlier age of onset (RR: 0.835, p=0.024), longer illness duration (RR: 1.754, p=0.007), a higher number of previous manic/hypomanic episodes (RR: 1.483, p=0.002) and a higher ratio of manic/hypomanic to depressive episodes (RR: 1.753, p=0.028). Moreover, we observed a moderating effect of IGM on the association between number of mood episodes and other variables of illness course, with the correlation between lifetime mood episodes and frequency of episodes being significantly greater in the IGM subgroup (RR: 1.027, p=0.029). All associations observed herein remained significant after adjusting for relevant confounding factors (e.g. age, alcohol and tobacco use, exposure to psychotropic agents, BMI).
Limitations: Cross-sectional design, small sample size.
Conclusions: Comorbid IGM may be a key moderator of illness progression in BD.

1. Introduction

The longitudinal course of bipolar disorder (BD) is highly heterogeneous (Baldessarini et al., 2012; Koenders et al., 2015; Uher et al., 2013). Evidence indicates that while some individuals with BD exhibit a stable episodic course, with good functional recovery and sustained periods of euthymia; other subgroups pursue a chronic and unstable illness (Kessing et al., 1998; Post et al., 2003; Roy-Byrne et al., 1985; Uher et al., 2013; Zis et al., 1980). For many individuals with highly relapse-prone illness, the frequency of episodes, as well as associated observations (e.g. impaired cognitive function), indicate a more progressive illness course (Kessing et al., 1998; Post et al., 2003; Roy-Byrne et al., 1985; Uher et al., 2013; Zis et al., 1980). "Cost-of-illness" as well as "burden of illness" studies indicate that a disproportionate percentage of the overall illness-associated burden and disability in BD is attributed to populations that have highly relapse-prone, chronic, and progressive illnesses (Magalhaes et al., 2012; Post et al., 2003, 2010; Rosa et al., 2012; Tohen et al., 2010).

Several moderators and mediators of illness progression have been reported, including, but not limited to, distal (e.g. childhood adversity) and proximal stressors (e.g. housing instability), as well as comorbidities, such as anxiety disorders and substance and alcohol use disorders (Birmaher et al., 2014; Haro et al., 2011; Post et al., 2003; Uher et al., 2013; Weiss et al., 2015). Accumulating

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evidence indicates that individuals with BD are differentially affected by medical comorbidities (Crump et al., 2013; Gomes et al., 2013; Perugi et al., 2015). Medical comorbidities (e.g. thyroid disorders, migraines, irritable bowel syndrome) have been associated with an unfavorable course of BD, as evidenced by earlier age at onset, multiple mood episodes, chronicity, rapid cycling and increased risk of suicide (Calkin et al., 2009, 2015; Forty et al., 2014; Goldstein et al., 2013; Kemp et al., 2010; McIntyre et al., 2008; Perugi et al., 2015; Ruzickova et al., 2003; Sylvia et al., 2015). A recent study compared different types of medical conditions and its clinical correlates in individuals with BD and documented that metabolic comorbidities were highly associated with early age at onset and chronicity, whilst autoimmune disorders were associated with mood reactivity and instability, suggesting that medical comorbidities may moderate illness trajectory (Perugi et al., 2015).

Although individuals with BD have an approximately 2-fold increased risk of type 2 diabetes (T2DM), relative to the general population (Kemp et al., 2014; Vancampfort et al., 2015), the role of T2DM and impaired glucose metabolism (IGM) on illness progression has been less frequently evaluated. Only two studies to date assessed the relationship between IGM and variables of illness course, with both studies reporting a higher prevalence of chronic course and rapid cycling (Calkin et al., 2015; Ruzickova et al., 2003). Our study sought to replicate and extend results from previous studies by evaluating the impact of IGM on illness trajectory, as well as the effects of multiple confounders (e.g. obesity, psychotropic medications, alcohol and tobacco use). The aim of the present study was to investigate the moderating effects of IGM on variables of illness course and severity in a BD population. We hypothesized that IGM would be associated with illness chronicity, higher episode frequency and non-remitting symptomatology.

2. Methods

2.1. Study population and clinical assessment

Patients (N=55) with BD were recruited from an outpatient unit in São Paulo, Brazil. Psychiatric diagnosis was confirmed with the Structured Clinical Interview for DSM-IV (SCID-I). Manic and depressive symptoms were assessed using the Young Mania Rating Scale (YMRS) and the Hamilton Depression Rating Scale (HDRS), respectively. Functioning was assessed using the Global Assessment of Functioning (GAF) Scale, with low functioning being defined as a score below 70. Demographic and clinical characteristics of the disease, including age of onset, episode frequency, history and number of hospitalizations and suicide attempts, as well as family history of psychiatric disorders were obtained using the same standardized protocol and information from the SCID. All subjects were inquired on medical history, including lifetime use of any prescription medication. We categorized, for the purposes of this study, the currently used psychotropic medications based on potential of drug-induced weight gain, as follows: (1) minimal effect: high-potency first-generation antipsychotics (e.g. haloperidol), selective serotonin reuptake inhibitors, bupropion, aripiprazole, lamotrigine; (2) moderate effect: lithium, valproate/divalproic acid, tricyclic antidepressants, risperidone and (3) marked effect: quetiapine, olanzapine, low-potency first-generation antipsychotics (e.g. chlorpromazine) (Correll et al., 2015; Henderson et al., 2015). Body mass index (BMI) was also measured using the formula BMI=weight (kg)/height (m)^2. Exclusion criteria included presence of unstable or acute medical conditions and current or lifetime alcohol or drug abuse or dependence. This study was approved by the local ethics committee and all subjects provided written informed consent before any study procedure.

2.2. Definition of impaired glucose metabolism

Whole blood samples were obtained from all participants. All samples were collected after a 12-h fasting. Metabolic parameters were measured immediately in a single laboratory with the same assay. IGM was defined as pre-diabetes or T2DM. T2DM diagnosis was based on previous diagnosis by a physician and/or use of antidiabetic medication (e.g. metformin, pioglitazone, insulin). Pre-diabetes was defined according to the ADA criteria: fasting glucose levels between 100 and 125 mg/dL or glycated hemoglobin (Hb1Ac) between 5.7% and 6.4% (Association, 2014).

2.3. Statistical analyses

For statistical analysis, SPSS software for Windows (version 23.0) was used. For the comparison of the demographic and clinical data, the independent samples *t*-test or the Mann-Whitney test were used for quantitative variables; the Chi-square test was used for categorical variables. Generalized linear models were used to assess associations between variables of illness course, as well as to compare subjects with and without IGM. We used linear, Poisson (for count data, e.g. number of episodes) and gamma (for positively skewed distribution, e.g. illness duration) distributions, as appropriate. For dichotomous outcomes we used logistic regression. Interactions between number of mood episodes and IGM were assessed by adding the product term (i.e. IGM*number of mood episodes) to the tested models. Due to the non-linearity of the models, the estimated β coefficients were transformed into rate ratio (RR) estimates. A significance threshold of $p < 0.05$ was used, with no adjustment for multiple comparisons.

3. Results

3.1. Sample characteristics

Forty nine (89.0%) individuals were diagnosed with BD type 1 and 6 (11.1%) with BD type 2. The mean age was 42.85 years (SD 10.77); 46 participants were female (83.6%) and 31 participants (56.3%) were Caucasian. Thirty seven (67.3%) individuals with BD were euthymic at the time of the assessment, the remaining 18 (32.7%) fulfilled criteria for a depressive episode. No subjects fulfilled criteria for a manic or mixed episode. The mean YMRS score was 1.89 (SD 3.08) and the mean HDRS score was 5.67 (SD 5.81). Nineteen participants (34.5%) had a GAF score below 70. Mean number of previously used medications was 5.92 (SD 3.75), 34 subjects (61.8%) were currently using polypharmacy, defined as use of two or more psychotropic medications. Five patients (9.1%) were using medications considered to have a minimal effect on weight, 38 (69.1%) were on agents with moderate drug-induced weight gain and 12 (21.8%) were using medications considered to have a marked effect on weight. Eleven subjects (20.0%) reported use of alcohol, 15 (27.3%) used tobacco. The mean BMI was 28.82 kg/m^2 (SD 5.43). Thirty individuals (54.5%) fulfilled criteria for impaired glucose metabolism.

3.2. Lifetime mood episodes, socio-demographic characteristics and variables of illness course and severity

There was a positive correlation between age and lifetime mood episodes ($r=0.349$, $p=0.008$), but no effect of gender ($p=0.562$) and ethnicity ($p=0.602$). After adjustment for age, gender and ethnicity, a higher number of mood episodes was associated with use of alcohol (RR=1.401, 95% CI 1.156; 1.697, $p=0.001$) and tobacco (RR=1.485, 95% CI 1.252; 1.762, $p<0.001$). Lifetime mood episodes were also higher in participants using