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Research report

Type 2 diabetes and pre-diabetic abnormalities in patients with bipolar disorders

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ABSTRACT

Background: Abnormalities in the glucose metabolism cause nervous and organic damage and are a cardiovascular risk factor. They could be a main cause for the increased morbidity and mortality rates found in patients with bipolar disorders. The exact prevalence of diabetes and pre-diabetic abnormalities, however, is not clear.
Methods: 85 euthymic outpatients with bipolar disorders from two university hospitals in Germany underwent an oral glucose tolerance test, laboratory screening and clinical measurements. Socio-demographic data, medication, severity of illness, global functioning and life quality were assessed.
Results: Diabetes mellitus was found in 7% of the patients, pre-diabetic abnormalities in 27%. The group of patients with abnormalities in the glucose metabolism had significantly lower quality of life and global functioning. Higher BMI, leptin, triglycerides and CRP levels significantly increased the likelihood for pre-diabetes/diabetes.
Limitations: The low sample size did only allow limited assessment of impact of medication on the results. No healthy controls were assessed.
Conclusions: One-third of the patients with bipolar disorders showed abnormalities in the glucose metabolism and this was associated with impaired global functioning and lower quality of life. Early detection and intervention strategies fitting the needs of patient with bipolar disorder are needed to improve both physical and mental health.

1. Introduction

In patients with bipolar disorders the presence of cardiovascular risk factors is higher than in the general population (Osby et al., 2001). This is a major cause of the increased morbidity and mortality rates that are as high as those in schizophrenic patients (Birkenaes et al., 2007). Type 2 diabetes mellitus (T2DM) is one of the main risk factors for cardiovascular morbidity and is associated with other cardiovascular risk factors such as obesity and metabolic syndrome. Pre-diabetes, based on glycaemic parameters above normal but below diabetes thresholds, constitutes a high-risk state for diabetes with high conversion rates and there is accumulating evidence implying that damage on kidneys and nerves already exists at the pre-diabetic stage (Tabak et al., 2012).

There are data suggesting an up to three times higher risk of T2DM in patients with bipolar disorders compared to the general the population (Cassidy et al., 1999; Lilliker, 1980; McIntyre et al., 2005; Regenold et al., 2002; van Winkel et al., 2008), with, however, a wide range in individual study data.

Different factors are discussed to be responsible for the increased rates of comorbidity of bipolar disorders and T2DM. Long-term medication with mood stabilizers, antipsychotics and antidepressants can have adverse metabolic effects. Medication-induced carbohydrate craving and/or reduced activity levels because of sedation cause weight gain (Elmslie et al., 2001). Especially the use of second generation antipsychotics (SGAs) is associated with glucose dysregulation (Guo et al., 2006; Manu et al., 2012, 2014).

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Additionally, life-style factors and specific psychopathological features could increase the prevalence of T2DM in patients with bipolar disorders. Psychopathological symptoms like hyperphagia, hypersomnia and decreased activity can lead to weight gain and pre-diabetic abnormalities. Patients with bipolar disorders often show disordered sleep rhythms even in euthymic states (Plante and Winkelman, 2008; Ritter et al., 2011). Sleep disturbances have been associated with a reduction in insulin sensitivity, a lack of adequate compensatory insulin release and an increased diabetic risk (Cappuccio et al., 2010).

Alternatively or complementary an intrinsic relationship between abnormal glucose metabolism and bipolar disorders has been discussed (Calkin et al., 2013) with common pathophysiologic processes, like (epi)genetic links, as well as shared neuroendocrine pathways.

To decrease somatic morbidity and mortality in patients with bipolar disorders, early detection of diabetes and pre-diabetes is very important.

2. Methods

2.1. Study design

The study used a cross-sectional approach including retrospective information from patient's medical history.

2.2. Recruitment and subjects

Outpatients treated at the Departments of Psychiatry and Psychotherapy of the University Hospitals Dresden and Würzburg fulfilling the diagnosis of bipolar disorder were asked to participate in the study. All bipolar outpatients were screened for inclusion in the study according to the following criteria: (1) diagnosis of bipolar disorder according to DSM IV (American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th edition ed. Washington, DC: American Psychiatric Association), (2) age ≥ 18 years, (3) Euthymia since at least 8 weeks: Clinical Global Impression Score for Bipolar Disorders ≤ 2 (Spearing et al., 1997), Montgomery Asberg Depression Rating Scale ≤ 12 (Montgomery and Asberg, 1979) and Young Mania Rating Scale ≤ 5 (Young et al., 1978) and (4) no significant medication chances in the last 8 weeks. Exclusion criteria were: (1) pregnancy and breast-feeding, (2) severe somatic disorders and (3) organic affective disorder or bipolar disorder not otherwise specified. After informed consent, clinical, socio-demographic and metabolic data were collected.

2.3. Procedures

Diagnoses were validated based on the Structured Clinical Interview for DSM-IV Axis I Disorders (Wittchen et al., 1997) and a diagnostic panel of two independent psychiatrists. Presence and severity of affective symptoms were rated using the Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) and the Young Mania Rating Scale (YMRS) (Young et al., 1978). The Clinical Global Impressions Scale for Bipolar Disorders (CGI-BP) (Spearing et al., 1997), the Global Assessment of Functioning Scale (GAF) (Jones et al., 1995) and the National Institute of Mental Health's prospective Life Chart Method (NIMH life-chart) (Robins et al., 1981) were used to cover course and severity of illness. For health-related quality of life the Medical Outcome Studies (MOS) short-Form General health Survey (SF-12) (Stewart et al., 1988) and the WHO-Five Well-being Index (WHO-5) (Bech et al., 1996) were used. Patients received a full fasting laboratory screening including blood count, C-reactive protein (CRP), thyroid hormones, glycated hemoglobin (HbA_{1c}) and clinical measurements including Body Mass Index (BMI), abdominal girth and blood pressure. Oral glucose tolerance tests (OGTT) were performed on all patients after an overnight fast with blood samples drawn every 30 min for two hours to monitor glucose, insulin, Pro-Insulin and Lipids.

For the diagnosis of diabetes and pre-diabetic abnormalities the criteria of the American Diabetes Association were used (American Diabetes Association, 2006). Pre-diabetic abnormalities were defined as impaired glucose tolerance (IGT: ≥ 140 and ≤ 200 mg/dl) measured with the OGTT two hours post and/or impaired fasting glucose (IFG: ≥ 110 and ≤ 140 mg/dl) and/or insulin resistance (> 4.65, or > 3.6 in patients with a BMI > 27.5 kg/m^2 using the homeostatic model assessment for insulin resistance HOMA-IR). The presence of a metabolic syndrome was assessed using the adapted ATP-III (National Cholesterol Education Program Adult Treatment Protocol) criteria (waist: male ≥ 102 cm, female ≥ 88 cm; triglycerides: ≥ 150 mg/dl; HDL: male ≤ 40 mg/dl, female ≤ 50 mg/dl; blood pressure: ≥ 130 mmHg/85 mmHg; glucose: ≥ 100 mg/dl). Metabolic syndrome was diagnosed if three of five criteria were met (International Diabetes Federation, 2005).

GAF and the laboratory parameters adiponectin, leptin, ghrelin, homocystein and lipids were only performed in the Dresden sample.

2.4. Statistics

Frequency of diabetes and pre-diabetic changes were assessed using descriptive statistics. To find differences between the group of patients with bipolar disorders and diabetes or pre-diabetic abnormalities and the group of patients without metabolic changes *t*-tests and chi-square tests were used for socio-demographic data and medication (with a $p < 0.05$ considered significant).

One-way analyses of variance (ANCOVA) with post-hoc tests were used to compare the two groups on quality of life and severity of illness. Covariates were age and gender.

Logistic regression analysis was performed assessing the influence of BMI and laboratory data on the likelihood of pre-diabetes/diabetes.

The study was approved by the two local ethics committees.

3. Results

Overall, 85 patients were included into the study (44 in Dresden and 41 in Würzburg). Of these patients, 68 (80%) met criteria for bipolar I and 17 (20%) for bipolar II disorder. The mean age of the patients was 45 years. Most patients had at least a college qualification or professional education and were employed. Only two patients were not treated with any medication, most frequently used medications were mood stabilizers and second generation antipsychotics. Most patients had at least two medications. The rate of psychiatric comorbidities was low. The mean BMI was 29 and 66 (78%) patients were overweight at a BMI > 25. Details on socio-demographical and clinical data are presented in Tables 1a and 1b. No significant differences between the patient groups from Dresden and Würzburg could be found.

Six patients (7%) met diagnostic criteria for diabetes, only in two cases the diagnosis was already known prior to the study. Pre-diabetic abnormalities were found in 23 patients (27%), metabolic syndrome was found in three (3%) patients. Frequency and combinations of pre-diabetic abnormalities and metabolic syndrome are shown in Fig. 1.

Comparing the group of bipolar patients with diabetes or pre-diabetic abnormalities and the group of patients without metabolic abnormalities no significant differences were found in the