Psychoneuroendocrinology 67 (2016) 70–75

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Abnormal glycemic homeostasis at the onset of serious mental illnesses: A common pathway

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ARTICLE INFO

Article history:

Keywords:
Schizophrenia
Major depressive disorder
Bipolar disorder
Type 2 diabetes mellitus
Mortality
Thrifty psychiatric phenotype

ABSTRACT

Objective: Patients with serious mental illnesses exhibit a reduced lifespan compared with the general population, a finding that can not solely rely on high suicide risk, low access to medical care and unhealthy lifestyle. The main causes of death are medical related pathologies such as type 2 diabetes mellitus and cardiovascular disease; however pharmacological treatment might play a role.
Material and methods: We compared a two hour glucose load in naïve patients at the onset of a serious mental illness ($N = 102$) (84 patients with a first episode of schizophrenia and related disorders, 6 with a first episode of bipolar I disorder and 12 with a first episode of major depression disorder) with another psychiatric diagnose, adjustment disorder ($N = 17$) and matched controls ($N = 98$).
Results: Young patients with serious mental illness showed an increased two hour glucose load compared with adjustment disorder and the control group. Mean two hour glucose values [±standard deviation] were: for schizophrenia and related disorders 106.51 mg/dL [±32.0], for bipolar disorder 118.33 mg/dL [±34.3], for major depressive disorder 107.42 mg/dL [±34.5], for adjustment disorder 79.06 mg/dL[±24.4] and for the control group 82.11 mg/dL [±23.3] ($p < 0.001$).
Conclusions: Our results reflect an abnormal metabolic pathway at the onset of the disease before any pharmacological treatment or other confounding factors might have taken place. Our results suggest a similar glycemic pathway in serious mental illnesses and the subsequent need of primary and secondary prevention strategies.

1. Introduction

Patients diagnosed with a serious mental illness (SMI) exhibit a reduced life expectancy compared with the general population (Druss et al., 2011). An increased suicide risk (Gomez-Duran et al., 2014), unhealthy lifestyle (Brown et al., 1999), low access to medical care or poor health care (Folsom et al., 2005) contribute to the excess risk. However, the leading cause of morbidity and subsequent mortality is medical related pathologies (Nordentoft et al., 2013).

Most studies focus on a specific diagnosis of SMI (Laursen et al., 2013), while only few compare results taking SMI as a group (Druss et al., 2011; Laursen et al., 2007; Nordentoft et al., 2013). In those studies, patients with a diagnosis of schizophrenia had higher mortality risk ratios from natural causes (cancer, endocrine or cardiovascular diseases) than patients diagnosed with affective disorders (which suffered from higher risk ratios of unnatural deaths, such as suicide). Recent studies in North American cohorts reveal a pattern of increased disability and costs (Eaton et al., 2008) and reduced life expectancy (Druss et al., 2011) not only in SMI but also in the general mental health population.

Among the diverse associated pathologies increased in SMI, type 2 diabetes mellitus (T2DM) has historically been a subject of interest. Studies in the pre-antipsychotic era described an altered glycemic homeostasis in mental health patients (McIntyre et al.,

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http://dx.doi.org/10.1016/j.psyneuen.2016.02.001
0306-4530/

2005). Research dates back as far as 1674, when the British physician Thomas Willis discovered (by tasting) that glycosuria was a sign of diabetes and proposed that this disease was caused by "sadness or long sorrow and other depressions"(Willis, 1971). In 1880, the British psychiatrist Henry Maudsley wrote that "diabetes is a disease that often shows itself in families where insanity prevails" (Maudsley, 1880). In his seminal study in 1919, Kooy evaluated psychiatric patients after regular meals, and using plasma glucose levels was able to detect hyperglycemia in melancholia and catatonia.

Pharmacological treatment confounded subsequent studies, as many psychotropic drugs alter biochemical parameters (Charatan and Bartlett, 1955) and increase weight (Allison and Casey, 2001), leading to a high prevalence of metabolic abnormalities (abdominal obesity, blood pressure, lipid and glucose metabolism alterations). Later epidemiological studies reflected a high prevalence of T2DM in schizophrenia (Mitchell et al., 2013), bipolar disorder (Calkin et al., 2013) or major depressive disorder (Roy and Lloyd, 2012) although those results might have been confounded by treatment. However, research in treatment-naïve patients found metabolic abnormalities at the onset of mental disorder, in non-affective psychosis (Fernandez-Egea et al., 2009a; Ryan et al., 2003; Saddichha et al., 2008; Spelman et al., 2007) as well as bipolar (Garcia-Rizo et al., 2014b) or major depression disorder (Garcia-Rizo et al., 2013).

Besides these three major psychiatric illnesses, several other psychiatric diagnoses have been associated with medical pathologies and glycemic abnormalities. Anxiety disorders have received some attention although results have been contradictory (Herva et al., 2006; Hildrum et al., 2009). In a meta-analysis published in 2013 based on 6 studies, post traumatic stress disorder was associated with an increased prevalence of coronary heart disease and cardiovascular mortality (Edmondson et al., 2013). Nevertheless it is important to note that the age of those patients ranged from 36 to 52 years old and so the natural process of ageing might have increased the risk of developing T2DM. Another study reported an association between post traumatic stress disorder and patients who sought help for T2DM (Miller-Archie et al., 2014) even after co-varying by potential confounding factors, such as age and body mass index (BMI). However, in these groups as well, antidepressant or antipsychotic treatments might have confounded these associations. Another potentially confounding factor is stress, which is associated with increased inflammatory and cortisol responses (Carvalho et al., 2015). These are risk factors for glucose intolerance (Kempf et al., 2008).

In the current study, we tested the hypothesis that abnormal glycemic homeostasis is associated with serious mental illness prior to psychopharmacological treatment compared with controls. We also examined adjustment disorder, defined as the development of emotional or behavioral symptoms in response to an identifiable stressor(s) occurring within 3 months of the onset of the stressor(s). Examination of this disorder allowed us to consider the stress response as a confounding factor.

2. Material and methods

2.1. Participants

Patients with a first episode of non-affective psychosis, major depressive disorder or adjustment disorder were recruited at the time of their first lifetime contact with psychiatric services in a general academic hospital (Hospital Clinic of Barcelona). The catchment area for the hospital, Example Esquerre, is a relatively homogeneous middle/upper middle class neighborhood in the center of Barcelona. The psychosis group had a maximum cumulative (lifetime) antipsychotic exposure of 1 week, and no antipsychotic use in the 30 days prior to the study. The major depression and adjustment disorder subjects were enrolled if they had never previously received antidepressant, antipsychotic or mood stabilizing pharmacological treatment. Patients were allowed to receive anti-anxiety medication (lorazepam) the night before blood was drawn, to a maximum of 3 mg, but not on the day of the blood sampling and the oral glucose tolerance test (oGTT). Healthy control subjects were recruited using advertisements. All subjects come from a larger study of diabetes in neuropsychiatric disorders (Fernandez-Egea et al., 2009b) where additional inclusion and exclusion criteria are reported.

Two-hour glucose data has previously been published on 64 patients with psychosis (Kirkpatrick et al., 2012) so 20 additional subjects are now presented. We have published data on 15 patients with depression (Garcia-Rizo et al., 2013), and because of matching, now present data from 12 of those patients. We have previously published a statement of the percentage of 7 patients with bipolar disorder had impaired glucose tolerance (Garcia-Rizo et al., 2014a); here we present two hour glucose values instead. We have not published data on adjustment disorder, so all of those patients are new to publication. As for control subjects 84 were described previously (Kirkpatrick et al., 2012).

All participants gave informed consent for participation in the study, which was conducted under the supervision of the institutional review boards of the authors' institutions and conducted in accordance with the declaration of Helsinki. Seven patients in the non-affective psychosis group ended subsequently received a diagnosis of type I bipolar disorder, consistent with results in the literature (Salvatore et al., 2009), and were considered separately.

2.2. Metabolic and psychiatric assessments

All participants underwent an oGTT which began between 08.00 and 09.00 after an overnight fast. Participants had a fasting blood sample drawn, then were given a 75 mg glucose solution. They rested for 120 min at which point a second blood sample was obtained for measurement of glucose, the two hour glucose load value (2HG). All participants were assessed with the structured clinical interview for axis I DSM–IV psychiatric disorders (SCID–I; First et al., 1999).

The concept of SMI is by definition related with psychotic symptomatology (bipolar disorder, schizoaffective disorder or schizophrenia). However the chronicity and the disability related with major depression disorder, besides the specific characteristics associated with ageing or mortality; allow us to include the diagnosis in between SMI. Sometimes the definition is mixed in research articles so we do include the current paragraph to highlight the concept and the reasons for the inclusion. The US Department of Health and Human Sciences definition of SMI, "a long lasting and severe condition that seriously interferes with a person's ability to take part in major life activities", supports our concept.

Initially two hundred thirty three patients were included in the study. Eighty–eight had a diagnosis of first episode of non affective psychosis, seven of type I bipolar disorder, fifteen of major depressive disorder, nineteen of adjustment disorder, and one hundred four were healthy subjects.

In order to be able to match the samples and to focus on the typical ages of onset of psychosis and bipolar disorder, only patients aged between 18 and 40 years were included in our primary analysis. This sample ($N = 217$) consisted 84 with a diagnosis of non-affective psychosis, 6 with I bipolar disorder, 12 with major depressive disorder, 17 with adjustment disorder, and 98 matched control subjects. The non-affective psychosis group included 49 patients with paranoid schizophrenia, 1 with disorganized schizophrenia, 1 with catatonic schizophrenia, 5 with undifferentiated schizophrenia, 11 patients with brief psychotic