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Glucose abnormalities in the siblings of people with schizophrenia

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Abstract

Background: Some studies suggest that schizophrenia may be associated with an increased risk of diabetes, independently of antipsychotic medications and other confounding factors. Previous studies have also suggested that there is an increased prevalence of diabetes in the relatives of schizophrenia probands.

Method: First-degree siblings of schizophrenia probands ($N = 6$) and control subjects ($N = 12$) were administered a glucose tolerance test. Subjects were matched for gender, age, body mass index, neighborhood of residence, socio-economic status and smoking habits.

Results: The siblings of schizophrenia probands had a significantly increased two-hour mean glucose concentration compared to the control subjects (respective means [SD] were 100.5 mg/dL [27.7] vs. 78.0 [12.3]; $p < 0.03$). Baseline glucose concentrations did not differ.

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BK, MB, EFE, EE, EP, and IC designed the study and wrote the protocol. Authors IC, EE, EFE, BK, AJ, and CG managed the literature searches and analyses. Authors EFE, BK, IC, and CG undertook the statistical analysis, and authors EFE, BK, CG, MB, EP, and AJ wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

Dr. Fernandez-Egea received consulting fees and honoraria from Pfizer.

Dr. Bernardo received consultant fees from Bristol-Meyer-Squibb and Wyeth. He also received honoraria from Janssen-Cilag, Eli Lilly Company, Pfizer, Synthelabo, GlaxoSmithKline and AstraZeneca.

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Dr. Garcia-Rizo and Miss Azucena Justicia have nothing to disclose.

Dr. Kirkpatrick received consulting or speaking fees from Pfizer, Organon, Wyeth, and Solvay.

Conclusions: Although confirmation with larger samples is needed, these results and other studies suggest that diabetes may share familial risk factors with schizophrenia.

Keywords

Schizophrenia; Glucose metabolism; Diabetes; Psychosis; Siblings; Drug-naïve

1. Introduction

Several reports (Ryan et al., 2003; Spelman et al., 2007; Cohn et al., 2006; Venkatasubramanian et al., 2007), although not all (Arranz et al., 2004), suggest that schizophrenia is associated with abnormal glucose metabolism independently of antipsychotic use. A few studies have investigated that diabetes has an increased prevalence in the families of schizophrenia probands. Mukherjee et al. (1989) described an increased prevalence of type 2 diabetes mellitus (T2DM) among first-degree relatives of schizophrenia patients. We have recently replicated this finding (Fernandez-Egea et al., 2008). One study (Spelman et al., 2007) found an increased prevalence of impaired glucose tolerance in an oral glucose tolerance test (GTT) in newly diagnosed, antipsychotic-naïve patients with schizophrenia (10.8%) and their first-degree relatives (18%) compared to healthy controls (0%). However, the relatives and healthy controls were not well matched for age, body mass index (BMI), and smoking habit, which are known risk factors for developing diabetes.

We tested the hypothesis that the first-degree siblings of patients with schizophrenia have abnormal glucose measures on a GTT, compared to matched control subjects.

2. Materials and methods

2.1. Subjects

The relative group consisted of first-degree siblings of patients from a psychiatric service in a general academic hospital (Hospital Clinic of Barcelona). The control subjects come from a sample of 62 healthy volunteers recruited for a study of glucose metabolism in newly diagnosed, antipsychotic-naïve patients with nonaffective psychosis.

Additional inclusion and exclusion criteria for all subjects were: 1) age 18 to 45, 2) no personal history of a major psychiatric disorder, and no psychotic symptoms, 3) no history of diabetes or other serious medical or neurological condition associated with glucose intolerance or insulin resistance (e.g. Cushing's disease), 4) not taking a medication associated with insulin resistance (hydrochlorothiazide, furosemide, ethacrynic acid, metolazone, chlorthalidone, beta blockers, glucocorticoids, phenytoin, nicotinic acid, cyclosporine, pentamidine, or narcotics), and 5) no history of cocaine use in the previous 30 days. All subjects gave informed consent for participation in the study, which was conducted under the supervision of the institutional review boards of the Hospital Clinic of Barcelona, the University of Maryland Baltimore and/or the Medical College of Georgia.

2.2. Matching strategy

This study was part of a larger ongoing study of diabetes in patients with nonaffective psychosis and matched control subjects. For each relative included, 2 control subjects were selected, blind to glucose measures, from the healthy control subjects in that study. The control subjects were recruited during the same time as the sibling group. The control subjects were selected so that they were matched to the siblings with regard to gender, age, BMI, smoking habit (average number of cigarettes per day), and residence in the middle class/upper middle class catchment area (yes/no) of the Hospital Clinic. All of the subjects were Caucasian residents of Spain.

2.3. Metabolic and psychiatric assessment

A two-hour 75 g oral glucose tolerance test began between 8 and 9 AM after an overnight fast. Cortisol blood levels were also recorded at baseline. Body mass index (BMI) was calculated using the formula [weight (kg)/height (m)²]. All subjects were interviewed using the Spanish translation of the Structured Clinical Interview for DSM-IV Axis I Disorders, clinician version (SCID-I). They were also administered the Dartmouth Assessment of Lifestyle Inventory (Rosenberg et al., 1998), which quantifies substance abuse. Socio-economic status (SES) was assessed with the Hollishead–Redlich scale (Hollishead and Rendlich, 1958).

2.4. Statistical analysis

The principal outcome variable was two-hour glucose concentration, as previous studies (Spelman et al., 2007; Cohn et al., 2006), including ours (Fernandez-Egea et al., submitted), have found patient/control differences in that measure but not in fasting glucose. The two groups were compared using the non-paired Student's *t*-test, or the χ^2 test for comparisons of proportions. Statistical tests were performed using version 12.0 for Windows of SPSS (Statistical Package for Social Sciences).

3. Results

The final study sample was composed of 6 siblings (2 women and 4 men) and 12 controls (4 women and 8 men). The two groups were well matched on the variables listed above and residence in the hospital's catchment area in central Barcelona vs. residence outside of that neighborhood (Table 1).

Baseline glucose concentrations were similar (mean [SD]): 86.7 mg/dL (6.6) for the siblings and 80.7 (7.9) for the comparison subjects ($p=0.13$). The values for HbA1c were 4.6% (0.42) vs. 4.4% (0.25; $p=0.243$). However, two hour glucose (2HG) differed significantly between the two groups: the sibling group had a mean concentration of 100.5 (27.7) mg/dL while the control subjects had a mean of 78.0 [12.3]; ($t=2.432$; $d.f.=16$; $p=0.027$). One of the six siblings met criteria for impaired glucose tolerance (2HG between 140 and 200 mg/dL); none of the control subjects had a two-hour value in that range. Both samples were matched ($p>0.4$) for all but one variable (SES; $p=0.16$). For this reason, we also performed a multiple regression analysis using 2HG as the dependent variable and group and SES as independent variables. With this approach, group was still significant (data not shown).

The 12 control subjects were very similar to the other control subjects we had recruited (total $N=54$), with regard to gender, age, BMI, smoking habit, cortisol blood levels, HgbA1c, fasting glucose, 2HG, ethnicity, and residence (data not shown).

4. Discussion

In this small sample, nonaffected siblings of probands with schizophrenia had higher 2HG concentrations than did matched control subjects. These differences could not be attributed to confounding by BMI, gender, age, psychotropic medications, cortisol blood levels, smoking (which in our sample population was correlated with measures of abuse of other drugs, including alcohol; data not shown), socio-economic status, ethnicity, area of residence, or drugs that affect glucose tolerance.

The main limitation of our study was the small sample size. There is also the potential for a survival bias: if there is an increase in diabetes in the families, which is associated with an increased mortality, the relatives of people with schizophrenia are likely to die younger. However, due to the young mean age of both samples, this bias should be very weak. Moreover, such a bias should tend to produce a negative study, rather than a falsely positive study. Despite

the small sample size, the prevalence of impaired glucose tolerance in relatives was similar in our study and that of Spelman et al. (2007), respectively 17% and 18%.

We and others have previously reported increased prevalence of abnormal glucose metabolism (Ryan et al., 2003; Cohn et al., 2006; Spelman et al., 2007; Fernandez-Egea et al., submitted) in newly diagnosed, antipsychotic-naïve patients with nonaffective psychosis. There are also other three reports of an increased family history of diabetes in the relatives of people with schizophrenia or nonaffective psychosis; the subjects of those studies were not administered a GTT (Mukherjee et al., 1989; Gilvarry et al., 1996; Fernandez-Egea et al., 2008). Taken together, these findings suggest that schizophrenia and diabetes share etiological factors that are familial, which may or may not be genetic. Previous studies suggest that diabetes and schizophrenia share risk factors, including low birth weight, prenatal stress, and prenatal famine (Koenig et al., 2002; Barker et al., 1993). Gough and O'donovan (2005) have suggested that they may share genetic risk as well.

The existence of factors that impact the physical health of schizophrenic patients, such as medication side effects, an increased suicide rate, and poorer health care and habit, does not exclude the possibility of a pre-existing vulnerability to diabetes. Our results provide further, albeit indirect, evidence that prior to antipsychotic treatment, schizophrenia is associated with metabolic abnormalities. This underlying vulnerability may increase the impact of the metabolic side effects of antipsychotic medications.

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Table 1
 Characteristics of the relative group and control subjects

	Relatives (N=6)	Control (N=12)	Significance <i>p</i>
Mean age [SD]	30.6 [3.6]	31.2 [5.5]	0.811
Male/female	4/2	8/4	0.694
Mean body mass index [SD]	25.2 [2.5]	24.5 [2.5]	0.615
Mean number cigarettes per day [SD]	7.5 [8.8]	6.8 [9.9]	0.892
Cortisol blood levels (mg/dL) [SD]	20.0 [4.7]	20.7 [5.6]	0.807
Catchment area (yes/no)	4/2	10/2	0.407
Socio-economic status (mean and [SD])	35.0 [13.9]	47.8 [17.8]	0.164