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Parental History of Type 2 Diabetes in Patients with Nonaffective Psychosis

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Abstract

Introduction—We attempted to replicate two previous studies which found an increased risk of diabetes in the relatives of schizophrenia probands.

Methods—N=34 patients with newly-diagnosed nonaffective psychosis and N=52 non-psychiatric controls were interviewed for parental history of Type 2 diabetes.

Results—In a logistic regression model that included multiple potential confounders, psychosis was a significant predictor of Type 2 diabetes in either parent ($p < 0.04$).

Discussion—We found an increased prevalence of Type 2 diabetes in the parents of nonaffective psychosis subjects. This association may be due to shared environmental or genetic risk factors, or both.

Keywords

Nonaffective psychosis; Schizophrenia; Type 2 diabetes; Family history; Epidemiology

Introduction

Several lines of evidence suggest people with schizophrenia may have an increased risk of Type 2 diabetes independent of antipsychotic use (Dixon et al., 2000). For instance, studies predating the advent of antipsychotics suggested that impaired glucose tolerance has an increased prevalence within schizophrenia (Braceland et al., 1945; Freeman, 1946; Kasanin, 1926; Langfeldt, 1952; Lorenz, 1922; Meduna, 1942; Robinson, 1940), although these studies lacked details on the subjects' characteristics and did not use any diagnostic criteria. Some more recent studies have suggested that schizophrenia is associated with diabetes, whatever the treatment (Regenold et al., 2002; Wang et al., 2003). Ryan et al. (2003) also found increased

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fasting glucose in antipsychotic-naïve patients with schizophrenia, compared to well-matched controls.

Abnormalities with an increased prevalence in the families of schizophrenia probands include not only psychotic and personality disorders, but also neurological, cognitive, and anatomical abnormalities (Compton et al., 2007; Gourion et al., 2004; Gourion et al., 2003; Ismail et al., 1998; Laurent et al., 2000; Saoud et al., 2000; Sponheim et al., 2006; Thermenos et al., 2004; Wynn et al., 2004; Yazici et al., 2002). Two family studies have also found that the relatives of people with schizophrenia have an increased risk of Type 2 diabetes (Mukherjee et al., 1989; Spelman et al., 2007). The broader category of nonaffective psychosis appears to share family history and other characteristics of schizophrenia (Lichterman et al., 2000). We hypothesized that parents of subjects with nonaffective psychosis would also have an increased prevalence of Type 2 diabetes compared to parents of control subjects.

Methods

Newly diagnosed, antipsychotic-naïve patients at an academic medical center were included if they met DSM-IV criteria for schizophrenia (N=20), schizophreniform disorder (N=7), brief psychotic disorder (N=4), delusional disorder (N=2), or schizoaffective disorder (N=1). Control subjects were recruited by advertisement. All subjects were interviewed using the Structured Clinical Interview for DSM Disorders, version 1. Control subjects did not have a lifetime history of major depression, adjustment disorder, or psychosis.

Subjects were interviewed for a parental history of Type 2 diabetes. A parental history of Type 2 diabetes was scored either “yes” or “no,” based on whether a physician had diagnosed Type 2 diabetes in either the father, the mother, or both. One case of gestational diabetes was rated as “yes.” For nonaffective psychosis subjects, data were confirmed by interviewing the patients’ parents or siblings during a post-discharge follow-up visit. We excluded from further analysis data that was not verifiable due to either adoption or absence of relatives for patients with psychosis. A parental history of Type 2 diabetes among control subjects was obtained by self-report. Some control subjects, however, provided additional information via email after the initial interview.

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, University of Barcelona, the University of Maryland Baltimore, and the Medical College of Georgia.

Results

Table 1 provides demographic information for both psychosis (N=34) and control (N=52) groups. All subjects were Caucasian. Table 2 presents the prevalence of Type 2 diabetes in the parents of psychosis and control subjects. One patient (from the psychosis group) had a positive history of Type 2 diabetes in both parents.

There was a significant association between psychosis and the prevalence of Type 2 diabetes in either parent ($p=0.029$), with a higher prevalence in the psychosis group. The association with nonaffective psychosis, however was not significant for either paternal history ($p=0.053$) or maternal history ($p=0.208$) when these were considered separately.

There were no significant differences between psychosis and control groups based on gender, the proportion recruited from within the catchment area of the Hospital Clinic of the University of Barcelona, and mean paternal or maternal ages at birth. Patients with psychosis were significantly older than controls ($p=0.036$). However, in a logistic regression model that included gender, age, paternal age, maternal age, paternal work status, and presence of

psychosis, only psychosis was a significant predictor of Type 2 diabetes in either parent ($p=0.036$).

There was not a significant difference in the prevalence of a parental history of Type 2 diabetes in subjects with schizophrenia (30%) versus other psychoses (21%).

Discussion

We found an increased prevalence of self-reported Type 2 diabetes in the parents of newly diagnosed antipsychotic-naïve patients with nonaffective psychosis, which supports the results of two previous family studies (Mukherjee et al., 1989; Spelman et al., 2007). The association was significant after controlling for gender, age, paternal and maternal age at birth, and paternal work status in a logistic regression analysis.

An important limitation of our study was that parental history of Type 2 diabetes was obtained by self-report from patients and controls. Though data for the nonaffective psychosis subjects were confirmed by interviewing relatives during a post-discharge follow-up visit, this information was not verified by either obtaining documentation of a doctor diagnosis or laboratory testing for diabetes. Furthermore, some cases of Type 2 diabetes were identified only from the interview with the relatives of psychotic subjects, thereby raising the possibility of a selective recall bias. It might be expected that patients would be less likely than controls to remember a parental history of diabetes because of greater cognitive impairment in psychosis (Harrison, 1999; Meltzer and McGurk, 1999). However, in our study, the psychosis subjects were more likely to report such a history. Some control subjects provided additional information via email after the initial interview, and this may also have introduced a selective recall bias. With regard to biased recall by control subjects, it is somewhat reassuring that the prevalence of parental Type 2 diabetes among control subjects in the study was 7.7%, which is similar to the prevalence of diabetes in Barcelona, Spain (Mata-Cases et al., 2006).

Spelman et al. (2007) found increased glucose intolerance in the first degree relatives of schizophrenia probands compared to the relatives of control subjects, although that study had some limitations with regard to matching between the patients' relatives and the control subjects. Mukherjee et al. (1989), using data from a population registry, also found an increased risk of diabetes in parents and grandparents of subjects with a schizophrenia. The study by Mukherjee et al. (1989) did not use matched controls, but instead compared the prevalence of Type 2 diabetes in relatives of patients with schizophrenia to that in a comparable age group in the general population.

Our results, which would need to be confirmed using glucose tolerance tests, suggest the familial risk of diabetes extends beyond schizophrenia alone to other nonaffective psychoses, although there was a higher prevalence within schizophrenia (30%) than in the other disorders (21%). Our sample size did not allow a robust examination of the significance of this difference. It is possible that if followed prospectively, many of the subjects with either brief psychotic disorder and schizophreniform disorder would subsequently be diagnosed with schizophrenia. Further studies would be needed to determine whether other psychotic disorders, and not just schizophrenia, are associated with a family history of diabetes.

If there is an association between schizophrenia and glucose intolerance, this might occur because diabetes and schizophrenia share some common risk factors. In addition to the two family studies mentioned above, birth and gestational problems may be risk factors for both schizophrenia and diabetes, low birth weight being the most notable example (Kunugi et al., 2001; Wahlbeck et al., 2001; Osmond and Barker, 2000; Ozanne and Hales, 2002). Exposure to prenatal stress during the second or early third trimester of pregnancy appears to confer on the offspring an increased risk of developing schizophrenia later in life, and findings in animals

strengthen this hypothesis (Koenig et al., 2002). Prenatal stress and developmental problems have also become an increasingly important area of research in diabetes and other aspects of the metabolic syndrome (Hales and Barker, 2001; Osmond and Barker, 2000; Ozanne and Hales, 2002; Ravelli et al, 1998). Genetic factors in mothers and their children may account for some of the latter association (Frayling and Hattersley, 2001), but some studies have shown a relationship to the mother's diabetes, but not that of the father (Dabelea and Pettitt, 2001), as well as a relationship between adult glucose intolerance and adverse environmental events during gestation (Roseboom et al., 2001). Twin studies and studies of dietary manipulations during gestation in animals (Delisle, 2002) also suggest shared genes cannot be a complete explanation of the association between low birth weight and adult diabetes.

Another possibility is that there are some shared genetic risk factors for Type 2 diabetes and schizophrenia. Gough and O'Donovan (2005) have described the potential for shared loci between these conditions. The gene for tumor necrosis factor- α (TNF- α), a pro-inflammatory cytokine, is located on chromosome 6p21.3, a region associated with schizophrenia in numerous linkage studies (Zai et al., 2006). There are, however, both positive and negative reports of an association between TNF- α polymorphisms and schizophrenia. The pro-inflammatory effects of TNF- α have also been implicated in the pathogenesis of insulin resistance and Type 2 diabetes (Moller, 2000). Thus, immune system dysregulation and resultant inflammation may be common to the etiology of both diseases. Further investigation of this association is warranted. Our data do not allow us to determine whether the increased prevalence in the parents is due to shared environmental factors or shared genes.

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Table 1

Subject Characteristics

	Psychosis (N=34)	Controls (N=52)	p-value [*]
Mean Age ($\pm$ SD)	31.1 $\pm$ 9.3	27.2 $\pm$ 7.3	0.036
Mean paternal age at birth	32.9 $\pm$ 6.4	32.5 $\pm$ 8.7	0.836
Mean maternal age at birth	28.4 $\pm$ 6.4	29.7 $\pm$ 4.9	0.303
Gender: % Male	70.6	53.8	0.326
% residing in the catchment area	67.6	76.9	0.455

* Gender and residence were analyzed using the Fisher's exact test, two-sided; Student's t-test, two-sided, was used for the other comparisons.

Table 2

Parental History of Type 2 Diabetes

		Psychosis	Controls	p-value[*]
		N (%)	N (%)	
Type 2 diabetes in the father	Yes	6 (18)	2 (4)	0.053
	No	28 (82)	50 (96)	
Type 2 diabetes in the mother	Yes	4 (12)	2 (4)	0.208
	No	30 (88)	50 (96)	
Type 2 diabetes in either parent	Yes	^{**} 9 (27)	4 (8)	0.029
	No	25 (74)	48 (92)	

^{*} Fisher's exact test, two-sided.

^{**} One patient from the psychosis group had a positive history of Type 2 diabetes in both parents.