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RESEARCH LETTER

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Immunological characteristics of diabetes in schizophrenia

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Abbreviations IA2: insulinoma antigen 2 · LADA: latent autoimmune diabetes of adults

To the Editor

In 1899, Henry Maudsley, the first psychiatrist to link diabetes to psychiatric illness, wrote that "diabetes is a disease which often shows itself in families in which insanity prevails" [1]. With this observation, Maudsley suggested that patients with schizophrenia are genetically predisposed to diabetes. The introduction of chlorpromazine (in 1953) and, more recently, the atypical antipsychotics was followed by an increase in the number of cases of new-onset diabetes and the worsening of glycaemic control in cases of existing diabetes in patients with schizophrenia [2]. These findings suggest an iatrogenic, rather than a genetic, origin of diabetes in schizophrenia, in the form of antipsychotic-induced weight gain. However, this debate has not, as yet, been settled.

In general, diabetes associated with schizophrenia is classified as type 2 diabetes. However, there are two arguments against this classification. The first argument is the rapid onset of schizophrenia-associated diabetes: over 80% of patients who develop diabetes do so within 6 months of initiating antipsychotic therapy [2]. With such a rapid onset, weight gain is unlikely to be the main stimulus for the development of the diabetes. A prospective randomised trial comparing the classical antipsychotic haloperidol with the three atypicals clozapine, olanzapine and risperidone found no relationship between glucose change and weight gain at endpoint, thereby confirming the independence of these two measures [3]. The second argument is the dramatic clinical presentation of diabetes in schizophrenia. There is an enhanced risk of metabolic complications, such as ketosis, acidosis and ketoacidosis, which are associated with a mortality rate of 26.5% [4–6]. These features are suggestive of type 1 diabetes or latent autoimmune diabetes of adults (LADA) rather than type 2 diabetes.

Type 1 diabetes and LADA are characterised by diabetes-related antibodies, i.e. antibodies against insulin, GAD and insulinoma antigen 2 (IA2), which are found in over 80% of type 1 diabetic subjects and in fewer than 5% of the general population [7, 8]. The aim of this study was to determine the prevalence of the three diabetes-related antibodies in schizophrenic patients, thereby establishing whether autoimmune phenomena play a role in diabetes associated with schizophrenia.

Patients (81 men [68.1%], 38 women [31.9%]; mean age 41.5 years [SD=10.9, range 19–65]) gave informed consent to participate in the study, which was approved by the Ethics Committee of the University of Utrecht. The psychiatric diagnosis was based on the shortened version of the

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Table 1 Prevalence of type 1 diabetes antibodies

	Schizophrenic patients		General population	*p* value [a]	Type 2 diabetic patients	*p* value [b]
	n	% (95% CI)	% (95% CI)		% (95% CI)	
Anti-GAD antibodies	3	2.52 (1.08–3.96)	1.0 (0.09–1.93)	0.10 (NS)	3.5 (1.82–5.18)	0.56 (NS)
Anti-IA2 antibodies	0	0.0	0.08 (–0.18 to 0.35)	0.75 (NS)	2.5 (1.07–3.93)	0.08 (NS)
Anti-insulin antibodies	3	2.52 (1.08–3.96)	2.0 (0.72–3.28)	0.68 (NS)	–	–

[a] Schizophrenic patients vs general population; [b] schizophrenic patients vs type 2 diabetic patients

Structured Clinical Interview for DSM-IV Axis I Disorders (MINI-SCID) and the available medical records. After fasting overnight, patients underwent a standardised OGTT. Autoantibodies against GAD, IA-2, and insulin were measured in serum by RIAs [7–9]. Patients with pre-existing diabetes were exempt from the OGTT, but had blood samples taken for determination of autoantibodies. Differences between groups were analysed using *z*-statistics.

The results indicated that diabetes was present in 17 patients (14.3%): 11 patients (9.2%) had existing diabetes and six patients (5.1%) were diagnosed by OGTT. Compared with the 1.5% prevalence of all cases of diabetes (type 1 and type 2) among the general Dutch population of the same age group [10], both the prevalence of existing diabetes and the overall prevalence of diabetes were significantly increased ($p<0.0001$) in the study population.

The results of the antibody analyses are shown in Table 1. Three patients tested positive for GAD antibodies, no patients tested positive for IA-2 antibodies and three patients tested weakly positive for insulin antibodies. Thus, the prevalence rates of antibodies against GAD, IA2 and insulin in the study population are not significantly different from those for the general population [7–9] or those for a population of patients with type 2 diabetes [11, 12]. Moreover, antibody-positive patients were not diagnosed with diabetes, and none of the subjects tested positive for more than one antibody, a result that is generally considered to be highly predictive of type 1 diabetes.

Our results demonstrate that, while the prevalence of diabetes is increased, confirming previous findings [13], the prevalence rates of antibodies against GAD, IA2 and insulin are not statistically different from those observed in the general population or in patients with type 2 diabetes. It is generally assumed that antibodies to GAD remain present long after the diagnosis of diabetes and represent one of the most sensitive antibodies for the identification of type 1 diabetes in adults (LADA). Therefore, we assume that the observed prevalence of anti-GAD antibodies is representative of the prevalence of autoimmunity in patients with schizophrenia, unless other, completely different, antigens are targeted. The low prevalence of anti-IA2 and anti-insulin antibodies further supports this assumption. Several case reports on the presence of antibodies against GAD, IA2 and islet cells in antipsychotic-induced disturbed glucose metabolism have reported negative results; however, to the best of our knowledge, our data from a large sample are the first to show that diabetes in patients with schizophrenia is unlikely to be autoimmune mediated (i.e. type 1 or LADA). This is in line with earlier epidemiological data from a large cohort study, which reported a negative association between juvenile-onset diabetes and schizophrenia [14].

The question of why the course of diabetes mellitus is more severe in schizophrenia remains to be answered.

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