Transient Diabetes Associated With Withdrawal of Lithium Therapy

We describe a patient with bipolar disease who developed diabetic ketoacidosis following discontinuation of long-term lithium treatment. Diabetes resolved completely after 7 months of insulin therapy. Transient diabetes in this patient could have been precipitated by withdrawal of lithium therapy.

A 26-year-old white male was admitted to our hospital with vomiting and abdominal pain. He suffered from bipolar disorder and had been on lithium treatment for 3 years. Six weeks before presentation, he had discontinued lithium due to persistent tremors and 2 weeks afterward developed excessive thirst and polyuria. He had no personal or family history of diabetes and was not receiving any other medications. On arrival, his BMI was 24 kg/m^2 and he was dehydrated and acidotic (pH 7.11), with ketonuria and hyperglycemia (blood glucose 33 mmol/l). We diagnosed diabetic ketoacidosis and treated him accordingly with intravenous fluids and soluble insulin. He rapidly improved and was discharged on twice-daily biphasic insulin. HbA_{1c} (A1C) was 7.2% 1 month later. Subsequently, he experienced repeated hypoglycemic spells, which led to cessation of insulin after 7 months. At this stage, A1C was 5.4% and oral glucose tolerance test was normal, with adequate insulin and C-peptide responses to a glucose load. GAD and islet cell antibodies were negative. After 3 years off treatment, his A1C has remained <5.5%.

We considered several explanations for the unusual profile of diabetes in this patient. The initial presentation was suggestive of type 1 diabetes, but the remitting course makes this diagnosis unlikely. Although prolonged remission may occur in early type 1 diabetes, this honeymoon period is unlikely to last 3 years. Atypical type 2 diabetes, characterized by ketosis at onset and subsequent remission, has been described in African patients but not in whites (1). Nonetheless, the negative antibodies and subsequent insulin independence in this case favor type 2 diabetes as the more likely diagnosis.

The onset of diabetes followed discontinuation of lithium, thus suggesting that lithium withdrawal precipitated diabetes. The effects of lithium on carbohydrate metabolism are complex, and improvement and worsening of glucose tolerance have both been observed in patients receiving lithium (2,3). Studies in rats show that lithium exerts antidiabetic effects by increasing glycogenesis, either through an insulin-sensitizing action or through direct activation of enzymes involved in hepatic glycogenesis (3). An intriguing possibility in this case, therefore, is that diabetes was masked by lithium treatment and precipitated by its withdrawal. To the best of our knowledge, this is the first report of diabetes occurring in association with lithium withdrawal. Clinicians should be vigilant to similar cases that may provide insights into atypical presentations of diabetes.

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Association of hGrb10 Genetic Variations With Type 2 Diabetes in Caucasian Subjects

The genes contributing to type 2 diabetes are mostly unknown (1). Grb10 is an adapter protein that, in target tissues (2,3), interacts with the insulin receptor (3–9), thus affecting downstream signaling (10–12) and insulin action (2,7,10–16). We tested the hypothesis that variants in the Grb10 gene modulate the risk for type 2 diabetes, one of the most frequent outcomes of insulin resistance.

Resequencing of coding and immediately flanking sequences of hGrb10 (17,18) identified six single nucleotide polymorphisms (SNPs), five of which had a minor allele frequency >5%. Based on their physical location and their mutual linkage disequilibrium, these five SNPs (i.e., rs1800504, rs2715128, rs2072235, rs4947710, and rs3807550) could be grouped into two clusters. The rs1800504 and rs4947710 SNPs (each belonging to different clusters) were analyzed for association with type 2 diabetes in 764 diabetic patients and 323 unrelated control subjects from the east coast of central Italy (19,20). No significant association with type 2 diabetes was observed for rs1800504 (data not shown). By contrast, the genotype distributions of rs4947710 (i.e., G/G, G/A, and A/A) were significantly different between case and control subjects (87.2, 12.3, and 0.5% vs. 61.9, 35.8, and 2.3%, respectively, $P < 0.0001$), with A allele carriers showing a reduced risk of type 2 diabetes (unadjusted odds ratio 0.239 [95% CI 0.17–0.33], $P = 0.0001$; age-, sex-, and BMI-adjusted odds ratio 0.235 [95% CI 0.15–0.36], $P = 0.0001$). A potential biological relevance of rs4947710 was suggested by an in silico analysis (ESEfinder; available at http://exon.cshl.edu/ESE/), which indicated that the G-to-A substitution of rs4947710 may cause the disruption of a putative consensus motif for the human Ser/Arg-rich proteins SF2/ASF.

To replicate this association, we studied 731 type 2 diabetic case and 358 nondiabetic control subjects, all being Caucasians from the Boston area (20). In contrast to what was observed in the Italian population, the genotype distributions of rs4947740 were similar in case and control subjects (G/G = 83.9%, G/A = 15.2%, and A/A = 1.0% and G/G = 86.0%, G/A = 14.0%, and A/A = 0.0%, respectively, $P = 0.15$).

In conclusion, a significant association between the hGrb10 rs4947710 SNP (whose biological function on differential splicing is suggested by in silico analysis) and type 2 diabetes was found in Caucasian subjects from Italy but not in those from the U.S. Lack of replication of genotype-phenotype associations is not an