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

uncommon event in the study of complex disorders (21–23) and can arise from the original result being a false-positive because of bias or chance or from the second result being a false negative because of insufficient power. Such explanations, however, do not seem to account for our conflicting findings. The population of the original study was relatively homogeneous, making the possibility of population stratification remote, and the *P* value for association with type 2 diabetes was highly significant, making chance an unlikely explanation of the association finding. The replication study had close to 100% power to detect the odds ratio observed in the original study. Thus, lack of replication in our study is likely to result from differences in the genetic and/or environmental background of the populations studied, highlighting the need for large, collaborative studies providing sufficient power to investigate gene-gene and gene-environment interactions and their differences among populations.

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Metformin-Induced Pancreatitis

A possible adverse drug effect during acute renal failure

About 2% of episodes of acute pancreatitis are caused by drugs (1). Phenformin was repeatedly associated with acute pancreatitis (1), but only two case reports highlighted a possible causative role for metformin (2,3). In one case, acute pancreatitis occurred for the coexistence of correct metformin treatment and acute renal failure (2); in the other, metformin overdose was deemed responsible (3).

A 61-year-old woman with diabetes and hypercholesterolemia presented after 5 days of vomiting, followed by oliguria and epigastric pain. At home, the therapy of 3 g/day metformin and 80 mg/day fluvastatin was continued, despite symptoms. Laboratory investigations showed metabolic acidosis with normal lactate, creatinine 13 mg/dl, amylase 270 units/l (normal range 30–110), lipase 1,813 units/l (23–300), and white blood cells 9,000/mm^3 (80% neutrophils). Acute pancreatitis was confirmed by computed tomography. No recognized cause of acute pancreatitis was identified (hypertriglyceridemia, hypercalcemia, alcoholism, gall stones, virus, or trauma). Drugs were suspended, and a treatment of insulin and intravenous fluids normalized amylase, lipase, and blood gases. The patient was discharged with stable creatinine levels of 2.7 mg/dl. She was reexposed to fluvastatin for 1 month, but no symptoms were reported.

Available evidence suggests that acute pancreatitis was caused by metformin accumulation, resulting from a combination of drug overdose and acute renal failure, in turn triggered by vomiting in a patient with concealed renal insufficiency. Because renal failure is a contraindication to metformin, rechallenge was performed only for fluvastatin (1), with negative results. In this case, the association drug/event is considered "probable" (4).

In the presence of appropriate doses and normal renal function, metformin-induced acute pancreatitis was never reported. However, when glomerular filtration rate (GFR) is <60 ml/min, metformin accumulates and adverse effects, mainly lactic acidosis, may occur (5,2). Our and previous observations (2,3) suggest to include acute pancreatitis among the possible metformin-induced adverse events precipitated by renal failure.

A GFR <60 ml/min with normal serum creatinine (concealed renal failure) increases the risk of adverse reactions from hydrosoluble drugs in elderly diabetic patients (6). We reanalyzed the data of hospitalized elderly from the Gruppo Italiano di Farmacovigilanza nell'Anziano study (1993–1998). Of 145 diabetic patients given metformin, 28 subjects had concealed renal failure (mean daily dose 808 ± 303 mg), while the other 28 patients had both reduced GFR and increased creatinine values (mean daily dose 686 ± 470 mg). These patients are at risk of acute renal failure, with critical metformin accumulation and ensuing toxicity, including acute pancreatitis.

Metformin is a precious antidiabetic drug (5). Nonetheless, acute pancreatitis can arise in patients with renal insufficiency. GFR should be carefully monitored in older diabetic patients taking metformin.

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COMMENTS AND RESPONSES

Change in HbA_{1c} as a Measure of Quality of Diabetes Care

The Diabetes Quality Improvement Project established performance indicators that were adopted by The National Committee for Quality Assurance in the Diabetes Physician Recognition Program (DPRP) (1,2). The HbA_{1c} (A1C) factors heavily in the scoring system, accounting for 15 of a possible 80 points. To achieve full credit, <20% of a random sampling of patients may have an A1C >9.0% and at least 40% must be <7.0%. This methodology may bias against diabetes consultants who are referred patients in worse control. Improvements in A1C may more readily reflect quality of care. The American Diabetes Association recommends an A1C of <7.0% (3) and in previous guidelines set ≥8.0% as a level whereupon "additional action is suggested" (4). The Diabetes Control and Complications Trial (DCCT) demonstrated that a decline in the A1C of 1% reduced microvascular complications by 30% or more (5). Therefore, poor control and clinically meaningful improvements may be defined by an A1C of ≥8% and −1%, respectively. The purpose of the present study is to evaluate change in A1C as a marker of quality of care.

Patients from one physician were evaluated, and all were referred from other providers. A1C data were collected prospectively in new patients from 1 January 2003 through 31 December 2004.