Case Report

Transient diabetes mellitus and peripheral insulin resistance following Tacrolimus intoxication in a child after renal transplantation

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Introduction

Tacrolimus (FK 506) has been demonstrated to be a potent immunosuppressive agent in organ transplantation [1]. The drug is now available as rescue therapy for steroid resistant rejection in organ transplantation. Diabetes mellitus as a complication of the use of Tacrolimus has been reported in adult [2] and paediatric [3] renal transplant patients. The pathogenesis of diabetes mellitus secondary to Tacrolimus is not well understood, and there is controversy as to whether a correlation of this complication to Tacrolimus serum levels [4] does exist. We report on a case which documents a correlation between a high Tacrolimus trough level and onset of insulin requiring diabetes mellitus.

Case report

A now 13-year-old girl with end-stage renal failure and chronic persistant hepatitis C was successfully transplanted with a maternal graft in May 1989. The underlying renal disease was histologically proven xanthogranulomatous pyelonephritis. There was no family history of diabetes mellitus. Immunosuppression after transplantation consisted of ATG, cyclosporine (CsA) and steroids. The maternal graft had one match each on HLA A, B and D, and there was rhesus incompatibility. Two rejection episodes were treated with steroids, and serum creatinine subsequently was 130 μmol/l.

An acute rejection episode was diagnosed in January 1996 with a rise of serum creatinine to 230 μmol/l, doubling of kidney volume and rise of resistance index by more than 10%. There was no response to a 6-day intravenous therapy of 10 mg/kg methylprednisolone. A renal biopsy revealed acute tubulointerstitial rejection and no evidence for CsA toxicity. Immunosuppression was switched to Tacrolimus rescue therapy, and serum creatinine fell to 180 μmol/l within 1 month. Tacrolimus trough levels were between 8.8 and 11.3 ng/ml measured by IMx (Abbott).

Ten weeks after initiation of rescue therapy, the patient developed polydipsia, nausea, headache, blurred vision, and weakness. A urine test revealed glucosuria, and the patient was admitted to hospital. There was no ketonuria. On examination, the patient showed a 5% weight loss, a dry mouth, and a mild tremor. A blood sample showed a serum glucose of 41.2 mmol/l, and a C-peptide of 11.4 ng/ml. A second C-peptide measurement was 9.2 ng/ml while still on insulin injections, suggesting increased endogenous insulin production (normal value after 12 h of fasting <3.5 ng/ml). Unfortunately, no information is available on insulin concentrations available prior to commencing insulin infusion. Autoantibodies against insulin and islet cells were negative. IGF-1 was 429.1 ng/ml, and 1 week later declined to 347.8 ng/ml (normal range 240–696 ng/ml for 12–17 year-old girls). Serum creatinine had increased from 190 to 256 μmol/l.

Acidosis was absent. One week before admission, Tacrolimus trough level had been >15 ng/ml, and on admission Tacrolimus trough level was at 36.5 ng/ml (therapeutic range: 6–11 ng/ml).

The patient was treated with intravenous and subcutaneous insulin injections. Blood glucose level control was difficult. Despite insulin doses of 75 units per day (i.e. 1.8 units per kg), it was not possible to achieve normoglycaemia. It is noteworthy that the patient was remarkably well with blood glucose levels of up to 40 mmol/l.

Tacrolimus was discontinued, and Tacrolimus levels were 24 ng/ml after 12 h, 10.6 ng/ml after 24 h, and 7.7 ng/ml after 48 h, respectively. Serum creatinine decreased to 208 μmol/l. Tacrolimus was discontinued and the patient was switched back to CsA. One day later the patient was normoglycaemic receiving 67 units of insulin. Insulin dosage was tapered down to achieve normoglycaemia within 8 days. Thereafter, no further
insulin injections were needed. Two weeks after onset of diabetes mellitus C-peptide was still elevated at 9.6 ng/ml, and insulin was also elevated at 50.0 μU/ml.

HbA1c was 5.4% 2 months before the onset of diabetes, 9.6% 1 week after onset of diabetes, 7.5% 2 weeks later, and 5.1% at the latest follow-up 3 months after the event. An intravenous glucose tolerance test was performed 4 weeks after onset of diabetes and showed a normal k-value of 1.63. Early insulin secretion was 91.3 μU/ml at 1 min and 84.6 μU/ml at 3 min after intravenous glucose load. The sum of the first and third minute insulin values was normal at 175.9 μU/ml. The $10^{-60} - 60$ integral in this patient was 2113 μU/ml/min (normal second phase insulin production ranges from 400 to 2520 μU/ml/min in pubertal adolescents). Results of the glucose tolerance test are summarized in Figure 1. C-peptide was high prior to the test and increased to a maximum of 15.9 ng/ml. A second glucose tolerance test was performed 9 weeks after the onset of diabetes, and this time C-peptide was normal for the degree of renal failure at 4.85 ng/ml. Normal values of C-peptide in our laboratory are 0.78 ± 0.54 ng/ml in normal children (n = 5), 0.96 ± 0.48 ng/ml in children with Turner syndrome (n = 11), 2.58 ± 1.62 ng/ml in children with a reduced GFR and a serum creatinine below 100 μmol/l (n = 6), 3.12 ± 1.47 ng/ml in children with a serum creatinine between 100 and 200 μmol/l (n = 4), 4.26 ± 2.67 ng/ml in children with a serum creatinine above 200 μmol/l (unpublished data). The second glucose tolerance test was completely normal (figure 2).

Discussion

Diabetes mellitus is an important complication after organ transplantation. Steroids and other immunosuppressive agents have been identified as major risk factors [4]. Despite the use of low dose steroids, Tacrolimus has been associated with the onset of diabetes mellitus in one of eight paediatric renal transplant recipients [5]. In paediatric liver transplantation, an incidence of 2% diabetes mellitus has been reported [6]. In a recent communication, 3/19 paediatric renal transplant patients treated with Tacrolimus developed diabetes mellitus. All of them had a positive family history of non-insulin dependent diabetes mellitus [3].

Few data are available on insulin secretion and C-peptide in Tacrolimus induced diabetes. Three children developing diabetes mellitus on Tacrolimus after liver transplantation were reported with elevated C-peptide [7]. It was argued that the absence of ketonuria in the face of significant hyperglycaemia supports the hypothesis that there is no insulin deficiency involved in the development of Tacrolimus induced diabetes mellitus. Our patient also showed absence of ketonuria. Even in non-diabetic liver transplant recipients on Tacrolimus, C-peptide concentrations were found to be significantly increased when compared to healthy controls. C-peptide concentrations were also increased in liver transplant recipients on cyclosporin based immunosuppression. C-peptide response in glucose tolerance tests was increased in patients on Tacrolimus compared to patients on CSA, and the proportion of patients with impaired glucose tolerance was greater in the Tacrolimus treated group. C-peptide can be increased after renal transplantation because of renal insufficiency. In fact, graft function in our patient was impaired. For comparison, we have obtained C-peptide values from children with varying degree of renal insufficiency without renal transplantation. It is noteworthy, that the patient had an increased basal C-peptide 4 weeks after onset of diabetes if compared to the degree of renal insufficiency. Nine weeks after transplantation C-peptide was within the range of children with comparable renal insufficiency.

The data demonstrate that glucose tolerance was impaired in our patient on high Tacrolimus trough levels. The increased C-peptide blood levels suggests that there was increased endogenous insulin production. Glucose tolerance impairment ceased immediately following cessation of Tacrolimus, however, increased blood C-peptide were found up to 4 weeks after onset of diabetes mellitus. Only 9 weeks after onset C-peptide was normal for the degree of renal failure at 4.85 ng/ml. Normal values of C-peptide in our laboratory are 0.78 ± 0.54 ng/ml in normal children (n = 5), 0.96 ± 0.48 ng/ml in children with Turner syndrome (n = 11), 2.58 ± 1.62 ng/ml in children with a reduced GFR and a serum creatinine below 100 μmol/l (n = 6), 3.12 ± 1.47 ng/ml in children with a serum creatinine between 100 and 200 μmol/l (n = 4), 4.26 ± 2.67 ng/ml in children with a serum creatinine above 200 μmol/l (unpublished data). The second glucose tolerance test was completely normal (figure 2).

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returned to normal. We postulate that diabetes mellitus in paediatric renal transplant recipients on Tacrolimus may be due to peripheral insulin resistance and that hyperglycaemia in these patients is not due to insulin deficient diabetes mellitus. We recommend measurement of C-peptide regularly after renal transplantation. Measurement of this marker could serve as an early indicator for development of glucose intolerance in paediatric renal transplant recipients on Tacrolimus. Further evaluation on the mechanism of peripheral insulin resistance are required.

References


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