Neonatal Diabetes With End-Stage Nephropathy

Pancreas transplantation decision

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OBJECTIVE — To describe the diagnosis of a patient with neonatal diabetes who had been misdiagnosed with type 1 diabetes and referred to our hospital for pancreas and kidney transplantation because of end-stage renal disease.

RESEARCH DESIGN AND METHODS — A diagnosis of neonatal diabetes was made after a molecular genetic study revealed a mutation in exon 34 of the *ABCC8* gene. Pancreas transplantation was ill-advised.

RESULTS — The patient was switched from insulin to glibenclamide 4 months after kidney transplantation, confirming that pancreas transplantation would not have been a good decision.

CONCLUSIONS — This is the first report of a patient with neonatal diabetes who developed diabetic nephropathy that progressed to end-stage renal disease. This report illustrates that careful endocrinological evaluation, including molecular genetic studies, if necessary, is mandatory before a decision to perform a pancreas transplant is made.

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Type 1 diabetes is the main indicator for simultaneous pancreas and kidney transplantation (PKTx) in patients with end-stage renal disease (ESRD). However, from a practical point of view, it is important to consider that patients with diabetes diagnosed at a young age and receiving insulin treatment at the time of the evaluation for PKTx are often assumed to have type 1 diabetes (1). This may lead to unnecessary pancreas transplantation in patients who, without the presence of renal failure, have the capacity to secrete insulin with alternative treatments.

Neonatal diabetes is a very rare condition diagnosed within the first 6 months of life and may be permanent or transient. In transient neonatal diabetes, the disease remits, although the patient may frequently relapse (2,3). Neonatal diabetes may be a consequence of a mutation in the ATP-sensitive K^+ channel (K_{ATP} channel), and ~90% of patients with neonatal diabetes can transfer from insulin to sulfonylurea tablets, achieving good control. Patients with neonatal diabetes can develop diabetes complications, but to date no neonatal diabetic patient with ESRD has been reported.

We report a patient diagnosed with type 1 diabetes and referred to our hospital for PKTx because of ESRD. After a genetic diagnosis of neonatal diabetes, we advised against pancreas transplantation and recommended kidney transplantation alone, with the aim of transferring the patient from insulin to sulfonylurea therapy posttransplant. This case report demonstrates that young people can present forms of insulin-treated diabetes other than type 1 diabetes. Careful endocrinological evaluation and molecular genetic studies are determinant in the evaluation of these patients.

RESEARCH DESIGN AND METHODS

— We report a 28-year-old man, without a family history of diabetes, who was diagnosed with diabetes at 3 months of age and treated with insulin until he was 1 year old. At 13 years of age, hyperglycemia relapsed with overt insulinopenic symptoms, and insulin treatment was reinitiated. He subsequently suffered from brittle diabetes with frequent severe hypoglycemic episodes and mean A1C levels of 10%. He developed proliferative retinopathy, severe autonomic neuropathy with symptomatic gastroparesis, and diabetic nephropathy that progressed to requiring hemodialysis 11 months before the transplant evaluation. His development was normal, and neurological involvement was absent.

On referral to our institution for PKTx, GAD antibodies were negative, free C-peptide concentration was 1.8 ng/ml, A1C was 8.9%, and plasma creatinine was 6.4 mg/dl. He was not obese (weight 60 kg, height 167 cm, and BMI 21.5 kg/m^2), and insulin requirements were 25 units/day (0.41 units $\cdot$ kg^{-1} $\cdot$ day^{-1}). Suspicion of neonatal diabetes led to direct sequencing of the *KCNJ11* genes (K^+ inwardly rectifying channel, subfamily J, member 11 gene) and *ABCC8* (ATP-binding cassette, subfamily C, member 8 gene). *KCNJ11* showed a normal Kir6.2 sequence but with a substitution of arginine by histidine in residue 1379 in exon 34 of the *ABCC8* gene, encoding the sulfonurea receptor (SUR)1 K_{ATP} channel subunit. With the diagnosis of neonatal diabetes, pancreas transplantation was not recommended and renal transplantation alone was proposed.

RESULTS

— Renal transplantation was performed with a kidney from a cadaveric

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Table 1—*Evolution of treatment of diabetes and metabolic control after kidney transplantation*

	Pretransplant	4 months posttransplant	5 months posttransplant	6 months posttransplant
A1C (%)	9.9	11.1	9.1	8
Basal free C-peptide (ng/ml)	1.8	0.3	2.0	2.3
Plasma creatinine (mg/dl)	8.9	1.4	1.2	1.3
Insulin dose (units/day)	25	30	30 to 0	0
Glibenclamide dose (mg/day)	0	0	30 to 45	45

donor. The patient was treated with an initial bolus of antithymocyte globulin followed by prophylactic immunosuppressive therapy with prednisone, tacrolimus, and mycophenolate mofetil. Prednisone was discontinued 4 months after transplant, as the patient was maintaining normal renal function (1.4 mg/dl). At this time, insulin requirements were 30 units/day (0.51 units $\cdot$ kg^{-1} $\cdot$ day^{-1}), A1C was 11.1%, and free C-peptide was 0.3 ng/ml. Transfer from insulin to sulfonylurea therapy was initiated with 30 mg/day glibenclamide, and insulin was withdrawn 1 month thereafter. Two months later, he was on glibenclamide at 0.84 mg $\cdot$ kg^{-1} $\cdot$ day^{-1}. Glycemic control improved, and no hypoglycemic episodes were reported. A1C was 8%, and C-peptide concentration was 2.3 ng/ml. In Table 1, the pre- and posttransplant evolution of A1C, free C-peptide, plasma creatinine level, and insulin and glibenclamide doses are shown.

CONCLUSIONS — One-half of patients with neonatal diabetes are found to have mutations in the *KCNJ11* or *ABCC8* genes, which encode the Kir6.2 and SUR1 subunits, respectively, of the K_{ATP} channel. Most patients with Kir6.2-mutation neonatal diabetes have permanent diabetes; however, in those with the SUR1 mutation, neonatal diabetes is frequently transitory. The K_{ATP} channel of pancreatic β-cells regulates insulin release by linking intracellular ATP production to β-cell membrane potential. On activating *KCNJ11* or *ABCC8* mutations, the response of the channel to ATP reduces, thereby preventing channel closure and consequent insulin secretion. Molecular genetic diagnosis of neonatal diabetes has a dramatic impact on diabetes therapy, because sulfonylureas bind to SUR1 subunits of the K_{ATP} channel and close the channel in an ATP-independent manner (4).

Information regarding the appearance of microangiopathic complications in patients with neonatal diabetes is scarce, being mainly related to retinopathy (5). To our knowledge, no reports have been published on a patient with neonatal diabetes and diabetic nephropathy in ESRD. However, over the years, other patients with neonatal diabetes have probably undergone pancreas transplantation because they have not been appropriately diagnosed.

At present, PKTx is undoubtedly the best therapeutic option for patients with ESRD without contraindications. However, it cannot be forgotten that, compared with kidney transplantation alone, PKTx is associated with slightly greater morbidity (6) and clearly higher costs. On the other hand, the number of pancreata available for transplantation is limited; thus, we are obliged to rationalize their use by implantation in donor recipients in whom the expected benefits are greater than the possible inconveniences. In this case, the dilemma was choosing either PKTx, with the possibility that this was an unnecessary therapy, or carrying out isolated kidney transplantation, risking a possibly unsuccessful transfer to sulfonylurea therapy and losing the advantages of double transplantation. This case illustrates that careful endocrinological evaluation (including molecular genetic studies, if necessary) of candidates for PKTx is mandatory before a decision to transplant is made.

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