Neonatal diabetes and pancreas transplantation

Neonatal diabetes with end-stage nephropathy: pancreas transplantation decision

Enric Esmatjes MD, PhD1,2,3; Amanda Jimenez, MD1; Gonzalo Diaz, MD1; Mireia Mora, MD1
Roser Casamitjana, PhD2,3,4; Guiomar Pérez de Nanclares, PhD5,3; Luis Castaño, MD, PhD5,3
Maria José Ricart, MD, PhD6

1Endocrinology and Diabetes Unit, 4Hormonal Laboratory, 6Renal Transplant Unit Hospital
Clinic Universitari, Barcelona. Spain
2Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
3CIBER de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM)
5Endocrinology and Diabetes Research Group. Hospital de Cruces. Barakaldo, Basque Country,
Spain

Corresponding author
Enric Esmatjes
Email: esmatjes@clinic.ub.es

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available in a future issue of Diabetes Care in print and online at http://care.diabetesjournals.org.
Objective: We describe a patient with a suggestive story of neonatal diabetes (ND) who had been erroneously considered as having type 1 diabetes and was referred to our hospital for pancreas and kidney transplantation because of end-stage renal disease.

Methods: After a molecular genetic study, the diagnosis of ND, due to a mutation in exon 34 of the \textit{ABCC8} gene, was made and pancreas transplantation was ill-advised.

Results: Four months after kidney transplantation the patient was switched from insulin to glibenclamide confirming that pancreas transplantation would not have been a good decision.

Conclusions: This is the first description of a patient with ND who developed diabetic nephropathy which progressed to end-stage renal disease and illustrates that careful endocrinological evaluation, including molecular genetic studies if necessary, of candidates for pancreas transplantation is mandatory before a decision to transplant is made.
Type 1 diabetes is the main indication for simultaneous pancreas and kidney transplantation (PKTx) in patients with end-stage renal disease (ESRD). However, from a practical point of view, this is often simplified on considering type 1 diabetes in patients diagnosed with diabetes when they were young and were receiving insulin treatment at the time of the evaluation for PKTx\(^1\). This conduct may lead to unnecessary pancreas transplantation in patients with the capacity to secrete insulin with alternative treatments which otherwise cannot be used due to renal failure.

Neonatal diabetes (ND) is a very rare condition diagnosed within the first 6 months of life and may be permanent or transient. In the latter case the diabetes remits, although it may frequently relapse\(^2\,3\). ND may be a consequence of a mutation in the ATP-sensitive potassium channel and approximately 90% of patients with ND can transfer from insulin to sulphonylurea tablets achieving good control. Patients with ND can develop diabetic complications, but so far no patient with end-stage renal disease has been reported.

We describe a patient who had been diagnosed with type 1 diabetes and was referred to our hospital for PKTx because of end-stage renal disease. After genetic diagnosis of ND we advised against pancreas transplantation and recommended kidney transplantation alone with the idea of transferring from insulin to sulphonylurea therapy after transplant. The aim of this case report was to point out that young people can present other forms of insulin-treated diabetes than type 1 diabetes. Careful endocrinological evaluation and molecular genetic studies are determinant in the evaluation of these patients.

**CASE REPORT**

A 28-year-old man, without a familial history of diabetes, diagnosed with diabetes at 3 months of age and treated with insulin until he was a one year old is described. 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 HbA\(_{1c}\) levels of 10 %. He developed proliferative retinopathy, severe autonomic neuropathy with symptomatic gastroparesis as well as diabetic nephropathy which progressed to end-stage renal disease requiring hemodialysis since 11 months before. 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, HbA\(_{1c}\) was 8.9 %, and plasma creatinine was 6.4 mg/dl. He was not obese (60 kg, 167 cm, body mass index 21.5 kg/m\(^2\)) and insulin requirements were 25 IU/day (0.41 U/Kg/day). Suspicion of ND led to direct sequencing of the \(KCNJ11\) (potassium inwardly rectifying channel subfamily J, member 11 gene) and \(ABCC8\) (ATP-binding cassette, subfamily C member 8 gene) genes showing 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 SUR1 \(K\_ATP\) channel subunit. With the diagnosis of ND pancreas transplantation was not recommended and renal transplantation alone was proposed.

**CLINICAL EVOLUTION**

Kidney transplantation was performed from a cadaveric 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 maintaining normal renal function (1.4 mg/dl). At this point, insulin requirements were of 30 U/day (0.51
U/Kg/day), HbA1c was 11.1%, and free C-peptide was 0.3 ng/ml. Transfer from insulin to sulfonylurea therapy was initiated with 30 mg/day of glibenclamide and insulin was withdrawn 1 month thereafter. Two months later he was on glibenclamide 0.84 mg/Kg/day. Glycemic control improved and no hypoglycemic episodes were reported. HbA1c was 8% and C-peptide concentration was 2.3 ng/ml. In Table 1 the pre- and post-transplant evolution of HbA1c, free C-peptide, plasma creatinine level and insulin and glibenclamide doses are shown.

DISCUSSION

In individuals with ND, mutations in the KCNJ11 or ABCC8 genes, which encode the Kir6.2 and SUR1 subunits, respectively, of the ATP-sensitive potassium channel (K\textsubscript{ATP} channel) are found in half of the patients. Most patients with Kir6.2 ND have permanent diabetes but in those with the SUR1 mutation, ND is frequently transitory. The K\textsubscript{ATP} channel of pancreatic beta cells regulates insulin release by linking intracellular ATP production to \( \beta \)-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 ND has a dramatic impact on diabetes therapy since sulphonylureas bind to SUR1 subunits of the K\textsubscript{ATP} channel and close the channel in an ATP-independent manner\(^4\).

Information regarding the appearance of microangiopathic complications in patients with ND is scarce, being mainly related to retinopathy\(^5\). To our knowledge, no reports have been published on patients with ND and diabetic nephropathy in end-stage renal disease. However, over the years some other patients with ND have probably undergone pancreas transplantation because they have not been appropriately diagnosed.

At present, pancreas associated with kidney transplantation is undoubtedly the best therapeutic option for patients with ESRD without contraindications. However, it cannot be forgotten that, compared to kidney transplantation alone, there is a slightly greater morbidity\(^6\) and clearly higher costs. On the other hand, the number of pancreas available for transplantation is limited and thus, we are obliged to rationalize their use by implantation in receptors 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 possible unsuccessful transfer to sulfonylurea 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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REFERENCES

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

<table>
<thead>
<tr>
<th>Months Posttransplant</th>
<th>Pretransplant</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<tr>
<td>HbA1c (%)</td>
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<td>11.1</td>
<td>9.1</td>
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<td>0.3</td>
<td>2.0</td>
<td>2.3</td>
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<td>plasma creatinine (mg/dl)</td>
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<td>1.4</td>
<td>1.2</td>
<td>1.3</td>
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<td>insulin dose (U/day)</td>
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<td>30 to 0</td>
<td>0</td>
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<tr>
<td>glibenclamide dose (mg/day)</td>
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<td>0</td>
<td>30 to 45</td>
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