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Post Renal Transplant Type 2 Diabetes Mellitus in a Case of Familial Juvenile Nephrophthisis

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ABSTRACT

Familial juvenile nephronophtisis, an autosomal recessive tubulointerstitial chronic nephritis, is characterized by progressive renal disease and end stage renal failure, which require kidney transplantation. Post-transplant diabetes mellitus (PTDM) incidence after kidney transplantation varies from 4–25%. Obesity, positive oral glucose tolerance test, metabolic syndromes, and post–transplantation multidrug, high dose, long-term immunosuppressive therapy are the risk factors incriminated.

We present the case of a 15-year-old overweight boy who was diagnosed with familial juvenile nephronophtisis five years before, afterwards progressive renal disease and end stage renal failure. This young patient developed PTDM three years after renal transplantation. His underweight brother, with the same medical history, did not develop PTDM.

Transplantation was mandatory for a child with familial juvenile nephronophtisis.

The case illustrates the risk factors for PTDM.

Keywords: post–transplant diabetes mellitus, end stage renal failure, familial juvenile nephronophthisis

INTRODUCTION

Post-transplant diabetes mellitus (PTDM), a secondary type of diabetes mellitus (DM), is a complication that may occur after a solid organ transplant (1). The PTDM diagnosis is certain when hypoglycemic medication is required in a transplanted patient for at least 3 months. The incidence after kidney transplantation is of 4-25%, and an increase is expected in the next future, as 1.5 million of people around the world are nowadays under dialysis (2).

There are three risk factors categories for PTDM (3):

1. non-modifiable: non-Caucasian race, age >40, male gender for both recipient and donor, family history of DM, cadaver donor, history of acute rejection;
2. potentially modifiable: infections – cytomegalovirus, hepatitis C, impaired glucose tolerance pre-transplantation;

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3. modifiable (Immunosuppressive therapy: Tacrolimus, Sicrolimus, Corticosteroids, Cyclosporine), obesity and metabolic syndrome components.

The corticoids increase peripheral and hepatic insulin resistance, while calcineurin inhibitors (cyclosporine and tacrolimus) have direct toxic effects on β pancreatic cells (4,5). The risk for developing PTDM is 30% for Tacrolimus and 18% for Cyclosporine (6). It is recommendable a maximum plasma concentration of Tacrolimus lower than 15 ng/ml in the immediate post–transplation period (2). A dose of prednisone >1.3 mg/kg/day is associated with a higher risk of developing PTDM. The ideal dose of prednisolone seems to be 5 mg/day (7).

Other modifiable factors (diet, metabolic syndrome) may be ameliorated by life style changes started in the pre–transplantation period.

The American Diabetes Association (ADA) state that oral glucose tolerance test (OGTT) has to be verified before and after transplantation. ADA criteria and guidelines for PTDM diagnosis and treatment are similar to those generally used for diabetes. A normal OGTT on the 5th day after the transplant correlates with a reduced risk of developing PTDM (8). Besides diet and physical therapy, patients should be treated with oral medication, combined oral therapy and insulin, or insulin alone (25%).

Familial juvenile nephrophtisis (FJN) or NHPH1 is a rare condition that progresses almost always to end stage renal failure (ESRF). FJN is an autosomal recessive disorder, characterized by deletions in the 2q12 - q13 region in 70% of the cases (9,10). The rest of the cases are determined by spontaneous mutation or by different genetic defects. The mean age for developing ESRF is 13 years (11,12), sooner for FJN than in other renal genetic disorders. Children with FJN may have the same clinical and histopathological phenotype despite their different genetic defects (13). ❑

CASE REPORT

We present the case of an overweight (G=67 kg >2 SD) 15 years old boy who arrived at the hospital in diabetic ketoacidosis (DKA). He was diagnosed five years before with FJN. Except overweight, he had no remarkable medical history. His physical exam was normal, blood pressure normal, but he presented polyuria. The laboratory tests revealed a mild anemia, elevated serum urea and creatinine. His urine density was 1005 (↓) and he had and elevated urinary Na+.

The renal ultrasound (Figures 1 and 2) revealed small kidneys, with renal dysplasia, hyperechogenic parenchyma, and decreased corticomedullary differentiation. Cysts of different sizes were present at the corticomedullary junction.

The ^{99m}Technetium diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) renal scintigraphy (Figure 3) established his GFR at 58.9 ml/min/1.73 m^2 (stage three renal failure). He received conservative treatment and he was followed-up closely.

FJN progressed to ESRF two years later, in the four stage renal disease, when his glomerular filtration rate (GFR) was 19.4 ml/min/1.73 m^2, on ^{99m}Tc-DTPA renal scan (Fig 4). He was transplanted from a living related donor (mother). Following the transplantation, the induction immunosuppressive triple therapy consisting of Prednisone 1 mg/kg/day + Tacrolimus 5

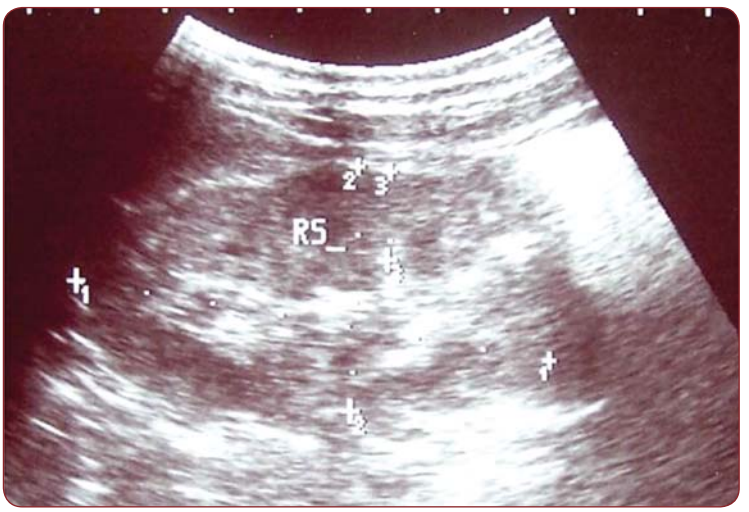

FIGURE 1. Left kidney ultrasound. Renal cystic dysplasia.

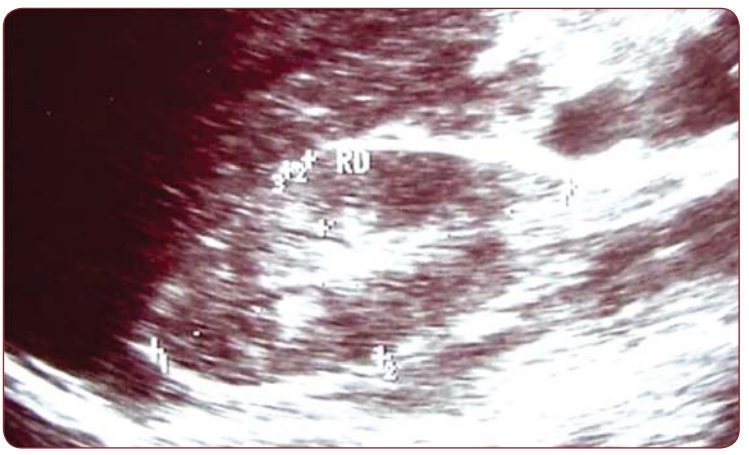

FIGURE 2. Right kidney ultrasound. Renal cystic dysplasia.

mg/day + Mycophenolate Mofetil (MMF) 3 g/day was initiated. After three month of induction therapy, maintenance therapy was started: the prednisone was gradually tapered down to 20 mg/day, the tacrolimus dosage remained the same, and the MMF was tapered down to 1.5 g/day.

Diabetic ketoacidosis (DKA) occurred three years after kidney transplantation. DKA was treated accordingly to the International Society for Pediatric and Adolescent Diabetes protocol. After stabilization, an insulin based schema was unsuccessfully attempted, so he received combined insulin and oral medication, which provided a good control of DM.

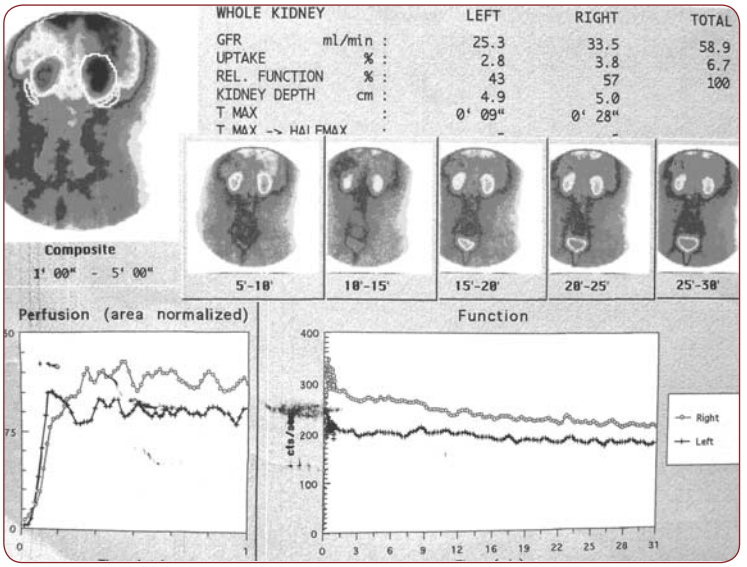

FIGURE 3. ^{99m}Tc–DTPA renal scan. Bilateral small kidneys, poor excretions. GFR=58.9 ml/min/1.73 m^2 (stage 3 renal failure).

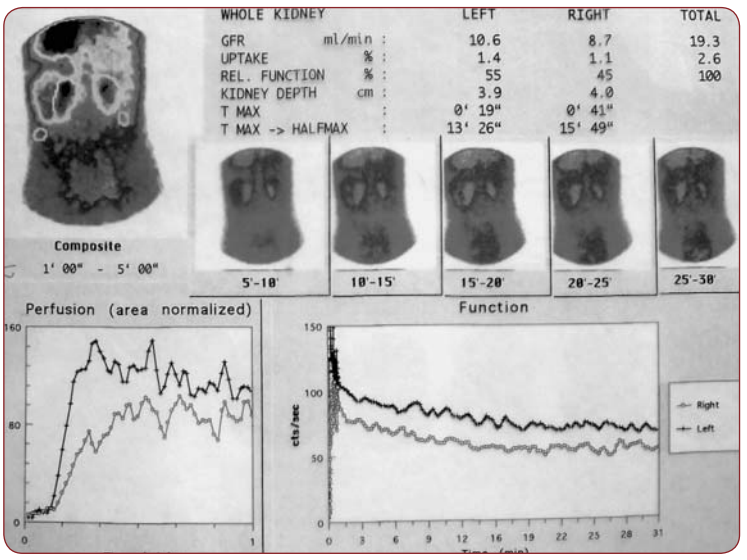

FIGURE 4. ^{99m}Tc–DTPA renal scan (2 years later). Bilateral small kidneys, poor excretion. GFR=19.3 ml/min/1.73 m^2 (stage 4 renal failure).

His clinical exam and laboratory results revealed that the case presented met four out of five metabolic syndrome criteria (high abdominal circumference, elevated "a jeun" glycemia, high cholesterol and high triglycerides).

The presence of four risk factors for PTDM (male gender, obesity, metabolic syndrome components, and immunosuppressive therapy) must be noted.

The first diagnosed with FJN was his younger brother, approximately at the same time.

The ^{99m}Tc-DTPA renal scintigraphy for his younger brother established the 5th stage of kidney failure, according to the Kidney Disease Outcomes Quality Initiative definition and staging. He was transplanted from a living related donor (father) two months after being diagnosed. He followed an immunosuppressive treatment scheme based on prednisone, cyclosporine and MMF. After the induction therapy, the corticosteroid was tapered down and finally withdrawn, so, in this case, a double maintenance immunosuppressive therapy based on cyclosporine and MMF was prescribed. He did not develop PTDM during the first 5 years post-transplantation. In opposition to his brother, he was underweight (no metabolic syndrome components), he was treated according to a different induction immunosuppressive scheme, and he tolerated double maintenance immunosuppressive therapy well.

The younger brother received both conservative and substitutive therapy, while the older one-only conservative therapy, being transplanted 2 years later. ❑

DISCUSSION

All the data – the age of the brothers, the resembling symptoms and physical exams, the similar renal ultrasound findings, and their progressive renal failure in the absence of other renal or urinary abnormalities diagnosed the familial juvenile nephrophtisis.

Considering that no genetic marker is specific for all FJN cases, the following factors are conclusive for the diagnosis:

- a positive familial history (suggestive in 50% of cases);
- decreased capacity to concentrate the urine;
- no signs of nephritic/nephrotic syndrome or abnormality in the urinary tract;
- normal or reduced renal dimensions with ultrasound hyperechogenic parenchyma and poor differentiation between the corti-

cal and the medullar parts. Cysts of different sizes may be present at the corticomedullary junction (14-16);
- histopathological exam confirms the diagnosis. Changes in the tubular basement membranes are highly suggestive of FJN: it may be homogenous, multilayered thicken or, in opposition, disintegrated. Tubular atrophy, cysts and interstitial fibrosis may be present. Periglomerular fibrosis is an early finding and secondary segmental glomerulosclerosis may be seen in advanced disease. Renal biopsy must be performed in order to confirm the diagnosis when the classical genetic deletion it is not present (17).

FJN is the most common (15%) of the genetic disease and 2.4% of all the diseases that progresses to ESRF (18). Clinical manifestations of FJN result from tubular damages, which reduce the urine density and Na^+ excretion. These findings precede the decline of GFR, and can be present in asymptomatic siblings. The progressive decline of the renal function is not apparent and the signs of renal failure develop later on in children. For this reason, a follow up by serial 99mTc-DTPA renal scan is the best method to anticipate and to evaluate the progression of renal failure. Treatment is conservative, but once ESRF develops, the substitutive treatment (dialysis or renal transplantation) becomes mandatory. Tubular damage does not recur in the transplanted kidney. ❑

CONCLUSION

In NHPH disease, as well as in other renal diseases which lead to renal failure, early diagnosis, thorough follow–up and adequate conservative treatment, delay the progress to ESRF.

OGTT has to be performed on the 5th day post-transplantation, as it is one of the predictive factors for PTDM. The immunosupresive therapy may increase the risk of PTDM. Therefore, the medication schedule and doses options may be challenging. Some of the other modifiable risk factors for PTDM (obesity and the metabolic syndrome) may be improved just by recommending some changes in patients' life style and by appropriate therapy.

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