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Original article

Diabetes as a complication of tacrolimus (FK506) in pediatric renal transplant patients

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Abstract. Three cases of insulin-requiring diabetes mellitus associated with tacrolimus (FK506) therapy in pediatric renal transplant patients are presented. New-onset diabetes mellitus has been reported with tacrolimus therapy post liver and kidney transplants in up to 12% of adult patients, but is thought to be rare in pediatrics. Although insulin requirement with tacrolimus therapy has been occasionally reported in adolescent patients post liver transplant, only a single case in a pediatric kidney transplant recipient has been previously documented. These cases illustrate the significant diabetogenic effect of tacrolimus in pediatric renal transplant patients. As the use of tacrolimus becomes more prevalent in pediatric kidney transplantation, pediatric nephrologists should be aware of this potential complication.

Key words: Kidney transplantation – Tacrolimus – Diabetes mellitus

Introduction

Tacrolimus (FK506) is a potent immunosuppressive agent and is a new, promising agent in the management of patients post organ transplantation [1]. Diabetes mellitus has long been a known complication in the post-transplant patient [2–4], primarily attributed to the use of steroids but also associated with immunosuppressive agents such as cyclosporine (CsA) [4]. The diabetogenic effect of tacrolimus has been reported previously in adult transplant patients and pediatric liver recipients [5, 6], but has been reported rarely in pediatric kidney transplant recipients [7, 8]. This report describes three children who received tacrolimus post renal transplant and who, while on relatively low doses of steroids, developed insulin-requiring diabetes.

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Case reports

Case 1

A 16-year-old non-obese white female had end-stage renal disease (ESRD) secondary to an ischemic insult to her kidneys in the neonatal period. She underwent an uncomplicated pre-emptive cadaveric kidney transplant with restoration of normal renal function. In the immediate transplant period, she received methylprednisolone and azathioprine, and was begun on tacrolimus as a primary immunosuppressive agent when the transplanted kidney began to show evidence of function. She was discharged from the hospital on tacrolimus 6 mg p.o. twice daily (b.i.d.) (0.3 mg/kg per day), with levels between 7 and 11 ng/ml, azathioprine 50 mg/day (1.26 mg/kg per day), and prednisone 20 mg/day (0.5 mg/kg per day).

Approximately 1 month post transplant, the patient was noted to have elevated blood sugars in clinic, with serum glucoses ranging between 220 and 420 mg/dl. Attempts were made to manage her hyperglycemia by tapering her prednisone dose to 17.5 mg/day (0.44 mg/kg per day) and decreasing her tacrolimus to 3 mg p.o. b.i.d. (0.15 mg/kg per day), to maintain a low therapeutic level. Although transiently successful, she presented to clinic 2 weeks later with blurred vision. Her blood sugar was 749 mg/dl. She had no evidence of ketonuria or metabolic acidosis. At this time she weighed 39.7 kg (<5% for age) and was on an immunosuppressive regimen of prednisone 17.5 mg/day (0.44 mg/kg per day), tacrolimus 3 mg p.o. b.i.d. (0.15 mg/kg per day), and azathioprine 50 mg/day (1.26 mg/kg per day). Her other medications included furosemide, nifedipine, famotidine, magnesium oxide, and sodium phosphate. Her family history was positive for non-insulin dependent diabetes mellitus (NIDDM) in several adult relatives. Glucose control was achieved with a standard split mix insulin regimen at 0.66 U/kg per day. After the onset of her insulin-requiring hyperglycemia, she continued on a prednisone taper, and her tacrolimus was adjusted to maintain a low therapeutic level. Her hyperglycemia gradually resolved, as did her insulin requirements, and she was off insulin within 4 months. Her current immunosuppressive medications include prednisone 0.23 mg/kg per day, tacrolimus 0.14 mg/kg per day, and azathioprine 1.15 mg/kg per day.

Case 2

An 11-year-old white female underwent a cadaveric renal transplant for ESRD secondary to Henoch-Schonlein purpura. She received methylprednisolone, CsA, and azathioprine immediately post trans-

plant. After an episode of rejection 2 weeks post transplant for which she received OKT3, she began tacrolimus therapy and her CsA was discontinued. After two subsequent episodes of rejection for which she received oral pulses of prednisone, her tacrolimus levels were maintained at approximately 15 ng/ml and she was on a prednisone taper. By 10 weeks post transplant she had stable renal function.

Twelve weeks post transplant she was noted to have a serum glucose of 246 mg/dl at a routine clinic visit. At that time her prednisone and tacrolimus doses were decreased. Despite this, she returned to clinic 5 days later and was found to have a serum glucose of 748 mg/dl. She had no evidence of ketonuria or metabolic acidosis. At that time her weight was 36 kg (25%–50% for age) and she was on prednisone 13 mg/day (0.36 mg/kg per day), tacrolimus 6 mg b.i.d. (0.33 mg/kg per day), and azathioprine 75 mg/day (2 mg/kg per day) for immunosuppression. Her other medications included nifedipine, magnesium oxide, trimethoprim sulfa, acyclovir, and furosemide.

She had a strong family history of NIDDM on both sides of her family. Glucose control was achieved with a standard split mix insulin regimen of 1.1 U/kg per day. Her insulin requirements remained the same for 3 months, but gradually decreased over the next 3 months, and she was off insulin in 6 months, with blood glucose levels ranging from 80 to 120 mg/dl. Her current immunosuppressive regimen includes prednisone at 0.2 mg/kg per day, tacrolimus at 0.23 mg/kg per day, and azathioprine 75 mg/day (2 mg/kg per day).

Case 3

A 16.5-year-old black male received a pre-emptive living-related renal transplant from his mother. He had a history of ESRD secondary to focal and segmental glomerulosclerosis of a solitary right kidney. The patient did well immediately post transplant and was treated with methylprednisolone, azathioprine, and CsA. Despite this immunosuppression, he experienced an episode of rejection 2 months post transplant for which he received methylprednisolone and OKT3. Six months later, another episode of rejection led to initiation of tacrolimus rescue therapy with tapering doses of oral prednisone and discontinuation of his CsA. He was maintained on azathioprine 75 mg/day (1 mg/kg per day), prednisone 15 mg/day (0.2 mg/kg per day), tacrolimus 8 mg b.i.d. (0.23 mg/kg per day), and had levels of tacrolimus between 6 and 10 ng/ml. His serum creatinine again stabilized.

One month later, he was seen in the renal clinic with nausea, vomiting, fatigue, and blurred vision. He also noted a 2-week history of polydipsia and polyuria and a 6-kg weight loss. He had a positive family history of NIDDM in his father. His medications at that time included prednisone 10 mg daily (0.15 mg/kg per day), tacrolimus 8 mg b.i.d., azathioprine 75 mg/day, nifedipine, and trimethoprim sulfa. His urinalysis revealed glucosuria and no ketonuria. His serum glucose was 733 mg/dl with no evidence of metabolic acidosis. His glucose was controlled with a standard split mix insulin regimen at 1 U/kg per day. Over the next 6 months he was tapered to 0.6 U/kg per day of insulin. His current immunosuppressive medications include: tacrolimus 7 mg b.i.d. (0.21 mg/kd per day), prednisone 10 mg every other day (0.08 mg/kg per day), and azathioprine 75 mg/day (0.9 mg/kg per day). His insulin requirements have decreased but persist more than 6 months after the presentation of his hyperglycemia.

Discussion

Diabetes mellitus has long been recognized as a complication of organ transplantation [2]. The use of steroids has been considered the major risk factor, however, other immunosuppressive agents appear to have significant diabetogenic effects [2]. Despite lower doses of steroids with its use, the incidence of CsA-related diabetes in adult renal transplant recipients remains approximately 16% [2].

Since the steroid-sparing effects of tacrolimus are greater than those of CsA, it was hoped that the incidence of post transplant diabetes would decrease with its introduction. However, previous reports document diabetes mellitus as a complication of tacrolimus therapy in adult kidney transplant recipients [9], in pediatric liver transplant patients [10], and in one of eight pediatric renal transplant recipients in a case series [11]. In some studies, hyperglycemia has occurred in up to 31% of adult kidney transplant recipients, with 20% of patients requiring insulin for more than 5 months [6]. Fortunately, reports have indicated the incidences of long-term insulin requirement with tacrolimus in adult liver and kidney transplant recipients are only 12% and 10%, respectively [11]. The incidence in pediatric liver transplant patients is even lower at around 2% [10]. Our report documents new-onset insulin requirements in 3 of our 19 pediatric kidney transplant recipients treated with tacrolimus. In two patients the effect was transient, however, one patient had persistent insulin requirements more than 6 months after presentation.

The pathogenesis of diabetes secondary to tacrolimus is not well understood. The agent has been reported to decrease glucose-induced insulin release at high concentrations from rodent, dog, and human pancreatic islets [10]. Reports conflict on whether the onset of diabetes mellitus in patients on tacrolimus is related to serum levels [12, 13]. History of glucose intolerance, family history of diabetes, obesity [10], and higher steroid doses [2] are clearly risk factors in the adult transplant population. Since all three of the patients reported here had a positive family history of NIDDM and two had received pulses of steroids for rejection, we suspect that the risk factors for tacrolimus-related diabetes mellitus are the same for children receiving kidney transplants as those cited in the adult transplant population.

As tacrolimus is used increasingly in the pediatric renal transplant population, frequent assessment of blood glucose levels and monitoring for glucosuria should be considered an important component of the management in the post-transplant period, particularly in patients with a positive family history of NIDDM. The incidence of diabetes mellitus related to tacrolimus therapy in the pediatric renal transplant population may be higher than the 2% previously reported in pediatric liver transplant recipients. The patients reported here suggest that, as in the adult population, insulin-requiring diabetes mellitus associated with tacrolimus therapy may well be transient. More data are needed to determine the etiology of tacrolimus-related diabetes. Further knowledge of the mechanism causing hyperglycemia in patients receiving tacrolimus may help us to minimize this side-effect of an otherwise promising new therapy.

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Book review

My own country: a doctor's story
Abraham Varghese
Random House and Vintage Books, New York, 1994, pp 432,
US $13, ISBN 0-679-75292-7

Some books make the full circuit and are reviewed in every conceivable venue, from the *New York Review of Books* to *People* magazine. Sometimes this reflects the notoriety of the author or the topic. Occasionally, despite Murphy"s law, this happens because the book is outstanding and has wide appeal. This is the case with Dr. Varghese"s extraordinary chronicle of his experiences as an infectious disease specialist, who, under the pressure of circumstance, became the regional acquired immunodeficiency syndrome (AIDS) doctor in Johnson City, Tennessee.

Dr. Varghese"s tale is straightforward. He went to medical school in India and completed his medical residency in Tennessee. After fellowship training at Boston City Hospital, he returned to Johnson City Medical Center in 1985 and was hired as an attending physician in infectious disease. Over the next 4 years, Dr. Varghese became the primary care provider to all of the AIDS patients in this quiet region of the Smoky Mountains, his own country.

Dr. Varghese's narrative reads like a story by Chekhov. The drag queens, abusive husbands, and the man with transfusion-related human immunodeficiency virus disease who unknowingly infected his wife seem incredible at first reading. Their stories are so poignant and the characters are so brutally open that one wonders how all of these cases were cared for by one doctor. However, the quiet honesty and integrity with which Dr. Varghese reports his turbulent feelings and difficulties within his family force the reader to acknowledge that this is a remarkable writer with the talent and wisdom to record the complexity of life and not simply write about it.

Why review this book for *Pediatric Nephrology*? One reason is that distinguished literature is a rare commodity that should be widely appreciated. However, there are four lessons that pediatric nephrologists would do well to learn from this book. Firstly, it is easy in these days of economical medicine to forget the importance of talking to patients. Cases of chronic renal failure in children are complex, social situations are strained, and it is vital to listen to the patients" own perceptions about their predicament. However, the temptation is to hide behind laboratory data and schedules rather than spend time talking, to cut the conversation short. Dr. Varghese"s stories are so textured because he spent hours letting his patients recount their difficulties in their own words at their own pace. Listening to patients will always be the biggest part of medicine. Secondly, Dr. Varghese could not ignore the social differences between himself and his AIDS-stricken patients. He struggled to overcome this barrier in caring for them. We all deal with patients whose attitudes and world views differ from our own. We can learn a great deal from Dr. Varghese as we try to justify renal transplantation or a course of cyclophosphamide to the parents of children who seem worlds apart from us. Thirdly, the fiduciary responsibility that we assume as doctors and the impact this has on our private lives has been neglected in the face of constant attention to the financial future of medicine. Dr. Varghese reminds us that good medicine is a tough boss that knows no bounds. We must struggle to meet the insistent demands of high-quality medicine while balancing the equally important responsibilities to one"s family and self. Finally, Dr. Varghese vividly illustrates the technological limitations of medical care. He arrived in East Tennessee armed with state-of-the-art knowledge and confident that he could slay any dragon in his path. AIDS relentlessly taught him that was not to be the case. We should not be disheartened by these stark failures and give way to cynicism or self doubt. Instead, like Dr. Varghese, we should struggle to integrate the brains and heart of medicine. Ultimately, Dr. Varghese left East Tennessee and assumed a new job in El Paso, Texas. This extraordinary person had obviously changed a great deal. We should be grateful for the record of that process that he has left for us and hopefully learn from it.

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