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ORIGINAL RESEARCH

Secondary hyperparathyroidism is a risk factor associated with graft survival in pediatric patients with renal transplantation: a single-center study.

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Abstract

Introduction: Kidney transplantation in pediatrics is the treatment of choice for end-stage renal disease (ESRD) and has widely proven advantages over dialysis treatments. The aim of the present study was to determine the risk factors related to global and graft survival in a group of pediatric kidney transplant patients treated at a national referral hospital with observation of factors associated with secondary hyperparathyroidism.

Methods: The present observational, retrospective study was carried out in the Hospital Metropolitano de Quito, Ecuador, from January 1, 2010, to June 30, 2013. We studied mortality and graft survival, presence of hyperparathyroidism before transplantation, and demographic and clinical variables (compatibility). The Kaplan Meier method was used for analysis, and relative risks are presented.

Results: 33 patients aged 12 ± 3.8 years entered the study. There were cadaveric donors in 21 cases (63.6%) and living donors in 12 patients (36.4%). 18 were men (54.5%). The etiology of ESRD was indeterminate in 63.6%, nephropathies in 24.2%, and uropathies in 12.1%. there was cute rejection in 1 patient and late rejection in 10 patients. Variables with significance in graft survival were hyperparathyroidism (RR = 6.0 (95% CI = 1.078-45.902) P = 0.032), not receiving complete immunosuppression (RR = 14.5 (95% CI = 3.807-55.225) P <0.001), and the need for post-transplant dialysis in the first week and early biopsy (RR = 15 (95% CI = 3.9-57.2)).

Conclusions: This study demonstrated that secondary hyperparathyroidism is a negative risk factor for kidney graft survival in pediatric transplant patients.

Key words: Kidney Transplantation; Critical Care; Child; Prognosis; Cause of Death; Parathyroid Diseases.

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Introduction

Kidney transplantation is the treatment of choice for children with end-stage chronic kidney disease (ESRD) because it improves neurodevelopmental, psychological, and quality of life far more than available dialysis procedures [1-3]. The medical and surgical care of ESRD and kidney transplantation in children presents unique changes [3]. At present, due to the development of transplantation and research centers specialized in pediatric care, the improvement in the preparation and selection of donors and recipients, improvement of the surgical technique, and new immunosuppressive schemes, pediatric patients have a graft survival similar to that of that reported in adults. In fact, children under 10 years of age have achieved the best kidney transplant survival of all age groups [4].

In addition, kidney transplantation represents the optimal modality for the management of ESRD since it allows for recovery in varying degrees from severe complications of uremia, especially growth retardation, in addition to being a cost-effective procedure from the first year of transplant. Multiple factors negatively intervene in the overall survival and graft survival of a transplanted patient, among which are the nutritional status prior to transplantation, compatibility, the presence of bone-metabolic complications triggered by chronic phosphorus retention, and the presence of secondary hyperparathyroidism. Therefore, an observational study was planned to measure survival and its relationship with these factors. The hypothesis was that secondary hyperparathyroidism is a risk factor in patient survival.

Population and methods

Design of the investigation

This is a longitudinal observational study with a retrospective source.

Venue and study period

The study was carried out in the Pediatric Surgery area of the "Hospital Metropolitano de Quito" (HMQ), Ecuador. The observed period of exposure was between the dates of January 1, 2010, and June 30, 2013. The period in which the study was carried out was January 1, 2015, to June 30, 2015.

Sample size

The sample was a non-probabilistic census-type sample of all possible cases that attended the institution on the specified dates.

Participants

Patients under 18 years of age admitted to the surgery service for kidney transplantation from a related living donor or cadaveric donor were included.

Variables

Sociodemographic variables such as age, sex, weight, height, and body mass index were recorded at the time of transplantation, as well as one year and two years after the procedure. Mortality was recorded in each case. Parathyroid hormone (PTH) levels were recorded in the intact fraction.

Data sources and measurements

The statistics department was requested to list patients treated with a diagnosis of pediatric kidney transplantation during the proposed research period. Through a manual review, a definitive list of cases was finally determined, and a double check of the separate records of pediatric surgery and pediatric nephrology was performed.

Avoidance of bias

The information was always taken by the same main researcher (Luis Moreno Sánchez), and the data were curated and validated by the study director. Supervision was carried out by the study director. A single computer was assigned with a password administered only by the principal investigator.

Statistical methods

Descriptive statistics were used to describe the characteristics of the population by obtaining the mean, maximum, and minimum. Survival statistics were applied with the Kaplan Meier method to measure overall and graft survival. A study of risk and protective factors with Relative Risk (RR) is presented. A result is considered statistically significant when the complete RR interval exceeds or is less than 1 with a P value < 0.05. We used the statistical package SPSS 22.0 for Windows (IBM Corp. Released 2013. Armonk, NY).

Ethical criteria

The protocol for this research was approved by the Bioethics Committee of the International University of Ecuador. The data-use authorization was granted by the teaching department of the HMQ.

Results

33 patients aged 12 ± 3.8 years entered the study. There were 18 men (54.5%) and 15 women (45.5%). 26 cases were mestizo-Hispanic (78.8%), and 7 cases (21.2%) were indigenous. The median weight was 26 kg.

Clinical history

Weight and height are described in Table 1. 27 patients (81%) had high blood pressure prior to transplantation. 15 patients (45.5%) had secondary hyperparathyroidism prior to transplantation. The etiology of renal failure was not identified in 21 patients (63%), while it was nephropathies (glomerulonephritis + tubulointerstitial nephritis) in 8 patients (24.3%) and uropathies in 4 patients (12.1%). The median hemodialysis treatment time was 7 months.

Table 1 Clinical characteristics of the study patients.

Variable	At transplant	1 year	2 years
Weight (Kg)	26	34.2	40.4
Height (cm)	129	134.2	139
GFR-LD(ml/min/1.73 m2)	85*	63	64
GFR-CD(ml/min/1.73 m2)	78*	79	70

GFR: glomerular filtration rate. LD: living donor. CD: Cadaveric donor. * Values were taken one month after transplantation

Immunology

Blood types were ORh + in 24 patients (72.7%), Arh + in 4 patients (12.1%), BRh + in 4 patients (12.1%), and Orh- in 1 patient (3%). 3 patients (2 BRh + and 1 Orh-) received ORh + type grafts. Pretransplant blood transfusions were done in 27 patients (81.8%). In 6 cases, the transfusion was in the last semester of the transplant, and in 10 cases, it was between 6 months and more than a year after the procedure. The antibody reactive panel was negative in 9 patients (27.3%), and 2 patients (6.1%) had a strong positive panel greater than 50%. 1 case (3%) had a moderate positive panel between 20 and 50%.

The compatibility of the human leukocyte antigen in patients with a living donor had a median of 58%, and in patients with a cadaveric donor, it was 39%. Treatment in the first year was with calcineurin inhibitors + mycophenolate + prednisone in 31 cases (93.9%). In the second year, calcineurin inhibitors (CNI) + mycophenolate (MMF) + prednisone (PDN) were used in 10 cases (30.3%). CNI + MMF in was used 13 cases (39.4%), and M-TOR inhibitors (IMTOR) + MMF + PDN were used in 5 cases (15.2%). In the third year, we used tacrolimus + MMF in 36.4% (12 patients), IMTOR + MMF in 7 patients (21.2%). MMF + PDN in 2 cases (6.1%), CNI + MMF + PDN in 4 cases (12.2%), and IMTOR + MMF + PDN in 1 patient (3%).

Perioperative data

There were 21 cases (63.6%) with a cadaveric donor and 12 patients with a living related donor (36.4%). The median age of donors was 24 years (minimum 2, maximum 53 years). The median days of hospitalization were 8 days with a minimum of 5 and a maximum of 17 days. Surgical time was 222.5 minutes with a minimum of 140 and a maximum of 440 minutes.

The type of ureteral implant was intravesical in 18 cases (54.5%) and extravesical in 14 cases (42.4%). In 1 case, it could not be defined in the clinical history. As early surgical complications, 2 cases (6.1%) had pneumothorax, 1 case (3%) had perrenal hematoma, 1 case (3%) had lymphocele, 1 case (3%) had urinary fistula, 1 case (3%) had venous thrombosis, 1 case (3%) had arterial thrombosis, 1 case (3%) had arterial thrombosis with urinary fistula, and 1 case (3%) had arterial thrombosis + venous thrombosis.

As late surgical complications, 4 patients (12.1%) had urinary stenosis, and one (3%) had intestinal obstruction. Cold ischemia time in a cadaveric donor was 12 hours with a minimum of 8 hours and a maximum of 36 hours. There was acute rejection in 1 patient and late rejection in 10 patients.

Graft survival

At the end of the observation period, grafts survived in 28 patients (84.8%).

Overall survival

Overall survival to the third year was 29 cases (87.9%). Survival was greater for patients with a living related donor than in patients with a deceased donor (Fig.1).

Relative risk studies

The variables with significance in graft survival were hyperparathyroidism (RR = 6.0 (95% CI = 1.078-45.902) *P*= 0.032) and patients who did not receive immunosuppressive medication complete (RR = 14.5 (95% CI = 3.807-55.225) *P*= 0.001; Figure 2). The need for post-transplant dialysis in the first week (RR = 15 (95% CI = 3.9-57.2) *P*= 0.007) was a factor associated with mortality, as was the need for kidney biopsy at the 1st month (RR = 14.9 (95% CI = 3.932- 57.223 *P*= 0.001).

No statistical significance was found in the following variables: concordance of blood group, organized household, family support, personal pathological history, family pathological history, previous hospitalizations, previous hospitalization reason, number of previous hospitalizations, pre-transplant transfusions, number of pre-transplant transfusions, transplant, last transfusion prior to transplant, arterial hypertension, dialysis period, etiology of ESRD, weight at transplant, days of hospitalization, other surgery after transplantation, type of ureteral implant, need for biopsy the first year after transplantation, acute rejection, rejection chronic, rejection treatment, number of infection episodes, living donor recipient ratio, time in intensive care of the cadaveric donor, double creatinine after extraction, infection before extraction, use of vasopressors before extraction, percentage of histocompatibility, antibody reagent panel before transplantation, immunosuppressive treatment in the first, second, and third years, and finally, the change of institution for follow-up.

Discussion

This study reports that secondary hyperparathyroidism is a strong predictor of graft dysfunction in pediatric patients with kidney failure who underwent kidney transplantation with living donors as well as cadaveric donors. Most reports observe that hyperparathyroidism persists after transplantation and has negative effects on the graft and the patient [5-7]. Hypercalcemia is a frequent finding in patients with a functioning kidney transplant, with a prevalence that ranges between 5% and 66% depending on the series, although severe hypercalcemia (total calcium > 12 mg / dl) is quite exceptional. These differences in prevalence are due to several factors, such as considering different cut-off values as diagnoses of hypercalcemia or considering the serum value of ionic calcium or total calcium, regardless of correction by albumin [5, 7, 8].

Another factor to take into account is the period of time considered since the prevalence of hypercalcemia decreases as time passes since kidney transplantation [7-9]. The pathophysiological mechanism suggested as responsible for post-transplant hypercalcemia is greater tubular reabsorption of calcium due to the action of PTH. The results of different studies are disparate; while some show a decrease in the fraction

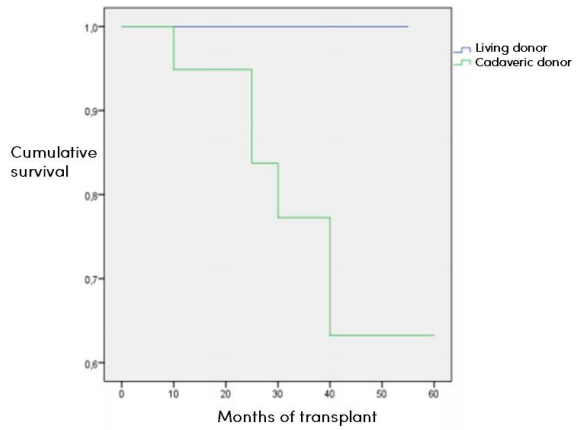

Fig. 1 Kaplan Meier graph according to the type of donor, patient survival function

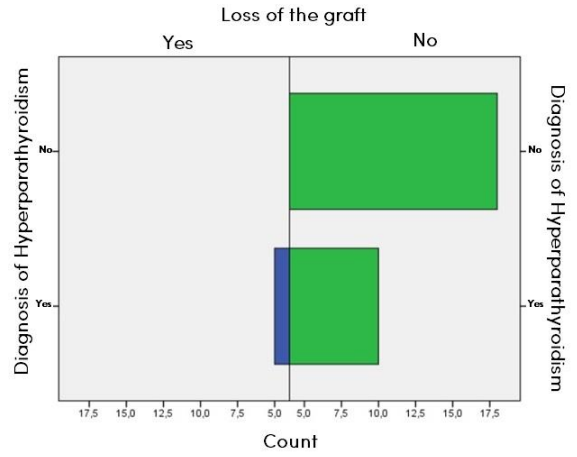

Fig. 2 Blue box indicates patients who had a diagnosis of hyperparathyroidism and lost the graft (5 patients); green boxes: patients with (10 patients) and without (18 patients) a diagnosis of hyperparathyroidism who did not lose the graft; RR = 6.0 (95% CI = 1.078-45.902).

of calcium excretion, others report greater urinary calcium excretion. It seems that the effect of PTH increasing tubular calcium reabsorption would be more evident in the long term and less evident in the immediate post-transplant phase.

There is a greater intestinal absorption of calcium due to an increase in serum calcitriol values caused by the increase in its synthesis due to the stimulation of PTH. Serum calcitriol values gradually recover in most patients after transplantation, and it has been observed that this is related to the rapid and progressive decrease in serum levels of Fibroblast Growth Factor 23 (FGF23). However, there have been no studies that have shown differences in calcitriol values between patients with hypercalcemia and normocalcemia [5].

Increased bone resorption of calcium is mediated by PTH. Significantly higher serum alkaline phosphatase values are observed in patients with hypercalcemia than in patients with normocalcemia, suggesting increased bone turnover [5]. Through a vasoconstriction mechanism, hypercalcemia can impair the functionality of the kidney graft both acutely and chronically. It can also cause tubulointerstitial calcifications that could negatively influence long-term graft survival [5]. Other effects have also been described, such as cases of pancreatitis in kidney-transplant patients with hypercalcemia due to HPT. It has also been shown to increase the risk of calcifications in soft tissues and the development of vascular calcification.

Epidemiological studies have shown that abnormalities in mineral metabolism are independently associated with higher rates of these adverse outcomes. Furthermore, the presence of alterations in mineral metabolism is often used clinically as an indicator of chronicity and severity of kidney disease [10]. A study published in 2008 [11] reported an association between time on hemodialysis, graft functionality, and the presentation of HPT. This suggests that a short duration of hemodialysis and a functional graft are the main predictors of correction of hyperparathyroidism after of kidney transplantation [11-13]. The statistically associated factors were determined as "not receiving complete immunosuppression" (RR = 14.5 (95% CI = 3.807-55.225) $P<0.001$) and the need for post-transplant dialysis in the first week and early biopsy (RR = 15 (95% CI = 3.9-57.2). These factors are considered epiphenomena as a consequence of post-transplant kidney failure or graft dysfunction.

Implications for clinical practice

Hyperparathyroidism should be controlled prior to performing a kidney transplant in order to reduce morbidity and mortality in this group of patients.

Strengths of this study

This study was a census-type study in which the entire possible population of a third-level national reference center was included.

Limitations of this study

Among the limitations of the present study was that data were not available for some variables, such as calcium levels. Another limitation is the retrospective design of the study. More studies in the future should include a prospective assessment with data on the osseous-metabolic area, which allows for observation of the impact on mortality.

Conclusions

This study demonstrated that secondary hyperparathyroidism is a negative risk factor for kidney graft survival in pediatric transplant patients.

Abbreviations

LD: Living Donor. CD: Cadaveric donor. GFR: glomerular filtration rate. HPT: Hyperparathyroidism. CNI: calcineurin inhibitors. MTOR: M-TOR inhibitors. MMF: mycophenolate. .PDN: prednisone. RR: relative risk.

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Authors' contributions

Luis Moreno Sánchez: Conservation of data, Formal analysis, Acquisition of funds, Research, Resources, Software, Writing - original draft, Writing: review and edition.
Paúl Astudillo Neira: Data preservation, Formal analysis, Fund acquisition, Research, Resources, Software, Writing - original draft, Writing: review and editing.
Freud Cáceres Aucatoma: Conceptualization, Project Management, Supervision, Validation, Visualization.
Fernando Jiménez: Methodology, Validation.
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Availability of data and materials
The data sets generated and / or analyzed during the current study are not publicly available due to the confidentiality of the participants, but are available through the corresponding author upon reasonable academic request.

Ethical statements
Protection of people
The authors declare that the procedures followed were in accordance with the ethical standards of the responsible human experimentation committee and in accordance with the World Medical Association and the Singapore Declaration.

Declaraciones éticas
Protección de personas
Los autores declaran que los procedimientos seguidos se conformaron a las normas éticas del comité de experimentación humana responsable y de acuerdo con la Asociación Médica Mundial y la Declaración de Singapur.

Data confidentiality
The authors declare that they have followed the protocols of their work center on the publication of patient data without identification.

Publication consent
It is not required for retrospective studies, the protocol was approved and the institution does not require it for a study of medical records as a primary source.

Conflicts of interest
The authors declare not to have any interest conflicts.

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