REVISTA CHILENA DE PEDIATRÍA
Sociedad Chilena de Pediatría
www.scielo.cl

Rev Chil Pediatr. 2017;88(2):236-242
DOI: 10.4067/S0370-41062017000200007

ORIGINAL ARTICLE

Cardiovascular disease in pediatric patients under chronic peritoneal dialysis

Compromiso cardiovascular en pacientes pediátricos en diálisis peritoneal crónica

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Received: 2-3-2016; Accepted: 26-8-2016

Abstract

Peritoneal dialysis (PD) is the most common renal replacement therapy used in pediatric patients with end stage renal disease. This population has a mortality rate 1,000 times greater compare to pediatric population, mainly due to cardiovascular causes. **Objective:** To characterize pediatric patients on chronic PD in relation to dialysis and cardiovascular outcome. **Patients and Methods:** Cross sectional study. Patients in stable PD according to DOQI criteria were selected. Epidemiological, dialytic, biochemical and cardiovascular variables were registered. Left Ventricular Mass Index (LVMI) was calculated by height/age ($g/m^{2.7}$). Left Ventricular Hypertrophy (LVH) was diagnosed with > 38.6 $g/m^{2.7}$, severe LVH > 51 $g/m^{2.7}$. Data were analyzed using STATA 11.0. continuous variables using ANOVA test and categorical variables were analyzed using χ^2 test or Fisher's exact test. **Results:** 21 patients, 11 males. Mean age 9.2 ± 3.52 years. The most frequent diagnosis was renal dysplasia (52%). Residual and Peritoneal KtV were 0.8 and 1.9 respectively. Fifty-two percent of patients showed LVH, 91% in severe range. A significant relationship between ultrafiltration/m2 and systolic blood pressure was depicted. Also a significant relationship between left ventricular mass index and hemoglobin ($p < 0.05$) was founded. **Conclusions:** The majority of the population showed left ventricular hypertrophy -particularly severe LVH-, which confirms an increased CV risk in this population. Blood pressure and loss of ultrafiltration were founded to be correlated to LVH.

Keywords:
Chronic Kidney Disease;
peritoneal dialysis;
left ventricular Hypertrophy;
left ventricular mass index

Introduction

Peritoneal dialysis (PD) is the most commonly used renal replacement modality in pediatric patients with terminal chronic kidney disease (CKD). The North American Pediatric Renal Trials and Collaborative Studies 2011 (NAPRTCS), showed that among 5,300 patients, 58% used PD as renal replacement therapy (RRT)[1]. In Chile, in 1994, 75% of the pediatric patients on dialysis were on hemodialysis, while in 1999, 75% were on peritoneal dialysis. These figures differ from the adult world, where the prevalence of hemodialysis (HD) patients at August 2008 was 13,613, compared with 594 patients in DP[2].

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Children with CKD on dialysis have a significantly higher mortality rate than the rest of the pediatric population[3-5]. The ANZDATA study reported that the mortality rate is 30 times higher than in pediatric patients without CKD[6]. Among the causes of mortality, cardiovascular disease corresponds to the 50% of the patients deaths on dialysis[7].

Cardiovascular disease is closely linked to volume overload, hypertension, and left ventricular hypertrophy (LVH). According to the International Pediatric Peritoneal Dialysis Network (IPPN)[8], the prevalence of LVH in children in PD reaches 40%. From these, an adequate dialytic control achieves a regression of up to 50%[9].

In pediatrics, the prevalence of LVH in children with end stage renal disease (CKD-5) is not well established. Mitsnefes M. et al (10) reported a figure of 75%, and the IPPN registry showed that only 26% of PD patients had normal heart condition[8]. The NAPRTCS 2008 Registry showed that, from 4,000 patients on dialysis, 57% were with uncontrolled hypertension (> 95%), confirming that in patients with PD, hypertension and cardiac damage are most frequently associated with LVH[7].

The definition of ventricular hypertrophy has been controversial because of factors affecting left ventricular mass (LVM), such as age, gender, surface and body composition. The most commonly used method for defining MVI in adults has been an allometric index that normalizes left ventricular mass to height (2.7), a variable called Left Ventricular Mass Index (LVMI). In adult uremic patients CKD-5, a significant relationship was found between a MVI> 51 g/m$^{2.7}$ and morbidity and mortality, defining this value as LVH. In children, a value of 38.6 g/m$^{2.7}$ corresponds to p95 of LVMI of the healthy pediatric population between 6 and 17 years old[11]. Khoury et al[13] evaluated LVMI in 2,237 healthy and non-obese pediatric patients over 9 years of age, confirming that values > 40 g/m$^{2.7}$ in girls, and > 45 g/m$^{2.7}$ in children, were above the percentile 95. These authors emphasize that in children < 9 years this index varies with age and therefore they suggest correcting LVMI for the size/age variable of the patient.

Until there is more evidence regarding the definition of LVH in the pediatric age, the cut-off values used in most studies correspond to those suggested by the fourth report on the diagnosis, evaluation, and treatment of hypertension in children and adolescents, from the US National Institutes of Health[11].

The aim of the present study was to characterize a group of pediatric patients on chronic peritoneal dialysis from the cardiovascular point of view.

Patients and Methods

Cross-sectional, observational study. Pediatric patients with terminal chronic renal disease on controlled peritoneal dialysis at the Luis Calvo Mackenna Hospital between 2012 and 2014 were evaluated.

Inclusion criteria were considered patients in PD older than 4 months of life at the time of the cut, and at least 3 months of time in peritoneal dialysis. Exclusion criteria were antecedents of structural heart disease.

Anthropometric, clinical, epidemiological, dialytic, biochemical and echocardiographic variables were recorded.

Anthropometric variables

Weight and height, according to Z score/age (ZT/E), Z weight/age (ZP/E), body mass index (BMI) calculated as weight in kg divided by height in square meters and area (ASC), calculated as the square root of weight in kg per size in cm divided by 3600. Clinical variables: systolic and diastolic blood pressure (DBP) expressed in percentiles (> 95 or <p95) according to Age, gender and height, according to reference (11). Biochemical parameters: Hemoglobin (Hb) (mg/dl),

Table 1. Study group characterization

Patients (n = 21)	Gender (%)		Age (average years)		Time in PD (average month)		Anemia (Hb < 11 gr/dl)	iPTH (average pg/ml)	Ca*P (average mg/dl)
	Male Female	48% 52%	9.2 ± 3.5		32.4		Yes 33% No 66%	347.5	58.7
Dialysis	Mode		D/P creat$_2$		D/D Gluc$_2$		Kt/V perit	Kt/V res	anuria
	NIPD CCPD	72% 28%	High-high /average Low-low /average	55% 45%	High-high /average Low-low /average	90% 10%	1.9	0.91	52%
Cardiovascular	HBP(>p95)	48%	LVH (IMVI>p95)	52%	LVMI (g/m^{2,7})	48.43			

PD: peritoneal Dialysis; iPTH: parathyroid hormone; Ca*P: calcium Phosphorus product; D/P creat$_2$: ratio of plasma / creatinine hour 2 ; D/D Gluc$_2$: ratio of dialysate glucose at hour 2 vs hour 0; Kt/V perit: peritoneal Kt/V; Kt/V res: residual Kt/V; HBP: high Blood Pressure; LVI: Left ventricular Hypertrophy; LVMI: Left Ventricula mass Index.

vitamin D (pg/ml), calcium (Ca) (mg/dl), Phosphorus (P) (mg/dl) (Vitros® 4600 Chemistry System), parathyroid hormone (Pg/ml, Immunotopics, San Clemente, CA), FGF23 (pg/ml ELISA, Immunotopics, San Clemente, CA) and Klotho (pg/ml, ELISA, Cusabio, China) during the previous three months To echocardiography. Dialysis variables: dialysis volume/cycle (cc/m^2), dialysis type, peritoneal and residual dialysis dose (Kt V), ultrafiltration ml/24 h (UF), water transport characteristics and solutes of the peritoneal membrane by PET[5].

A cardiovascular evaluation was performed by two-dimensional color Doppler echocardiography performed up to 3 months before the cut. Echocardiography was performed by the same cardiologist at the Luis Calvo Mackenna Hospital. Systolic diameter, end diastolic diameter, interventricular septum thickness and posterior wall thickness were recorded. Left ventricular measurements were corrected for body surface area and expressed on a Z-score scale.

The MVI was calculated as the grams/height index 2.7, according to the Fourth Report of Hypertension in Children and Adolescents of the National High Blood Pressure Education Program Working Group11. HVI was defined as > 38.6 g/$m^{2.7}$, which corresponds to p95 of the LVMI for healthy children and adolescents between 6 and 17 years old. Severe LVH was defined as an MVI > 51 g/$m^{2.7}$, according to the criteria of the International Pediatric Peritoneal Dialysis Network (www.pedpd.org).

Statistical analysis of the data was performed using *STATA 11.0* or *SPS 15.0*. Continuous variables were analyzed by ANOVA and categorical variables using χ^2 or Fisher's Exact Test.

Consent and/or informed consent was requested to all participating patients. The study was approved by the Ethics and Human Research Committee of the Faculty of Medicine of the University of Chile.

Results

Twenty-one patients were included, 11 males, mean age 9.2 ± 3.52 years old. The mean weight and height were 28.3 ± 9.8 kg and 124.8 ± 18.5 centimeters, with a Z average weight of -0.615 and Z average size of -1.92. The average body surface area was 0.98 ± 0.24 m^2 (Table 1).

General characteristics

The most frequent diagnosis was renal dysplasia (11 patients, 52%), followed by three patients with resistant cortical nephrotic syndrome and three patients with atypical hemolytic uremic syndrome. A patient with Alport's syndrome, one with renal polycystic disease, one with reflux nephropathy and one patient with an unrelated etiology.

Dialytic features

Patients were on automated peritoneal dialysis. The mean number of months on dialysis was 32.42 months. Eleven patients did not present residual diuresis, ten showed an average diuresis of 975 cc/m^2/day. The average body surface adjusted ultrafiltration (UF) was 573 cc/m^2. The mean peritoneal Kt V (dialysis dose) was 1.9 and the total Kt V (peritoneal plus residual) was 2.7.

During 2 hours of peritoneal balance test, creatinine D/P creatinine concentration (plasma creatinine hour 2) showed 45% of high average transporters (n = 9) 35% low average (n = 7) a 10 % High transporter (n = 2), and 10% under carrier (n = 2). D/D glucose (ratio of dialysate glucose at hour 2 vs hour 0) showed 50% of medium (n = 1), 40% high (n = 8) and 10% average low transporter (N = 2). A significant relationship was found between total KtV and ultrafiltration, and between D/P creatinine and D/D glucose ($p < 0.05$) (Table 1).

Cardiovascular characteristics

A value of PA> p95 was recorded in ten patients (48%) versus eleven (52%) with PA <p95. The Echocardiography analysis showed LVH in 11 patients (52%), of which 91% corresponded to severe grade. (Table 1).

There was a statistically significant relationship between blood pressure and body surface area, as well as between body surface area adjusted cc/m^2 and SBP, with a similar trend, although without statistical significance with DBP. A significant relationship was found between LVMI and hemoglobin, and between LVMI and calcemia ($p < 0.05$).

The average phosphorus calcium product was 58.70 and the iPTH was 347.5 pg/dl. Only one patient presented PTH < 100, and ten patients showed values > 300 pg/dl. The relationship between iPTH and FGF23 was significant ($p < 0.05$). The mean values of FGF23 and Klotho were 225.7 ± 310 and 126 ± 20 pg/ml, respectively. Seven patients had anemia at the time of the study, with an average Hb of 11.13 mg/dl in the total of the patients. The mean ferritin was 216 mg/dl.

Discussion

LVH has a high prevalence in the pediatric population CKD-510. Associated factors include hypertension, body mass index, type of peritoneal dialysis applied, anemia and hyperparathyroidism, as well as the etiology of CKD other than renal dysplasia[8,14,15].

Among the protective factors are the management of adequate blood pressure, maintaining a euvolemic state, correction of metabolic alterations characteristic of the terminal CKD (calcium phosphorus and base acid metabolism), correction of anemia and management of uremia.

LVH has been associated with 3 groups of factors: with post-load, such as increased systemic arterial resistance, elevated blood pressure and vascular compliance; with preload, such as intravascular volume expansion and anemia; And other independent factors, such as microinflammation and oxidative stress[9].

Various cutoff values have been used for the diagnosis of left ventricular hypertrophy. The most commonly used are adjusted according to the size of the patient[9]. HVI is defined as the LVMI that exceeds p95 for gender and age of normal children and adolescents (Khoury et al)[13]. The International Pediatric Peritoneal Dialysis Network (IPPN) is based on these same recommendations. Values previously estimated by Mitsnefes with a more limited number of patients, found that LVMI was 68-73% in patients in PD[7] and 80-85% in patients in HD[7,16]. The collaborative study published by the IPPN found that the use of height-associated LVMI provides the most prevailing prevalence of LVH in patients with PD[8].

In this study we confirmed the severe cardiovascular compromise of pediatric patients on chronic peritoneal dialysis. Its impact on the medium and long-term survival is paramount, which confirms the importance of a routine monitoring in cardiovascular patients.

Among the objectives in an individualized PD are an adequate UF that prevents hypervolemia, one of its clinical signs being systolic arterial hypertension. Hypertension in PD patients can be managed with volume restriction, leading the patient to its dry weight[18]. Blood purification of solutes should be achieved, not only limited to urea[4,19,20]. In our study, a significant correlation was found between UF and SBP. BP was measured in isolation, without continuous ambulatory blood pressure monitoring. In the study by Mistefens et al[16] it was determined that nocturnal values of SBP greater than p95 had an independent association with the increase in LVMI. In the study by Bircan et al[18], it was shown that random values of PAS > 95 had a sensitivity of 52% and a negative predictive value of 41% for predicting LVH, not in agreement with the criteria of Sorof et al[21], which reports a prevalence of HIV of 47% in patients with PAS values greater than 50%.

The risk of developing LVH is 2 times higher in children with systolic hypertension. In the follow-up of patients in the IPPN collaborative study, SBP was 7 mmHg higher in patients who developed or maintained LVH than in those who returned to LVH and achieved normal LVMI values. Studies have shown that decreasing volume overload and blood pressure over a period of 6 months leads to an improvement in left ventricular mass index values in children with LVH in PD[17].

From the dialysis dose point of view, the KtV is the recommended parameter to evaluate the adequacy of the procedure[4,19,22]. The total KtV (Kt/Vt), expresses the sum of the weekly urea clearance according to the scheduled dialysis indication, called peritoneal Kt/V (Kt/Vp), plus the residual renal function contribution that still maintains the patient through diuresis, called residual Kt/V (Kt/Vr)[23]. In our study, a significant relationship was found between total KtV and total UF. LVH has been inversely related to residual KtV, with higher LVH in anuric patients than in patients with residual diuresis[24,25]. The CANUSA study showed that each 250 ml of urine shows a 36% decrease in overall mortality[26,27]. Patients with residual renal function have better cardiovascular and metabolic profiles than anuric patients; they have less malnutrition, less hypertension, less ventricular hypertrophy, less anemia and lower calcium phosphorus product, with less vascular calcification. All this leads to a better cardiovascular survival in these patients[28]. In our study, there was no significant correlation between LVH and patients without residual diuresis, which may be due to the limited number of anuric patients in the study group. Approximately, a 50% had a KtVr greater than 0.1 and in six of them the KtVr was greater than the KtVp. Wang et al showed that residual renal function is an important independent predictor of LVH and one of the most important factors in adult patient mortality in PD[24].

In patients on dialysis, LVH has been demonstrated without arterial hypertension, which implies that there are other mechanisms involved in the development of LVH in patients in chronic renal replacement therapies[7]. In this sense, hemoglobin values below 11 mg/dl have been associated with mortality and LVH in children on dialysis[17]. Anemia leads to an increase in left ventricular size and ejection volume, possibly increasing cardiac adaptations to volume changes with dialysis[7]. 33% of patients in our study had anemia, with a significant relationship between hemoglobin and total KtV, as well as left ventricular mass index.

There is an observed relationship between anomalies in mineral bone metabolism and LVH[29,30]. PTH has trophic effects on cardiac myocytes by stimulating cardiac fibroblasts and intramyocardial arterial wall thickness, resulting in LVH and intramyocardial fibrosis[31,32]. With Cutoff values of 200 ng/ml of PTH have been shown to be at a 73% risk of LVH, suggesting that PTH cardiotropic actions already appear with moderate values of hyperparathyroidism[33,34]. On the other hand, vitamin D deficiency can activate the Re-

nin Angiotensin Aldosterone system, and active vitamin D supplementation can cause regression of LVH and/or fibrosis. Calcitriol reduces cardiac fibrosis and microvascular remodeling in experimental models of renal failure[41].

The fibroblast growth factor 23 (FGF 23), is a phosphaturic hormone that reduces the activity of 1 renal alpha hydroxylase and also the renal synthesis of 1.25 hydroxy vitamin D, playing a central role in the maintenance of step homeostasis mineral Early stages of the ERC. Different studies, as in this experience, have shown a significant elevation of FGF23 in terminal CKD[35,36]. There are recent experiences linking cardiovascular involvement with plasma levels of FGF 23 in children. Seeherunvong et al demonstrated a strong association between high concentrations of FGF23 and elevated LVMI and that high values of FGF23 are associated with LVH in children and adolescents in HD. They did not find a relationship between FGF23 values and dialysis time, suggesting that the association between LVH and FGF23 could be evident in patients at the onset of HD, showing that the relationship would be present prior to the initiation of dialytic therapy[37].

The FGF 23 of our group was only obtained in twelve of our patients, corresponding to 62% of the group. We did not demonstrate an association between FGF23 and LVH values, probably due to the limited number of patients in whom FGF levels were available[23]. In patients with CKD, FGF23 concentrations progressively increase, as renal function decreases to help maintain serum phosphorus within normal[38], which can lead to very high values of FGF23 correlated with the plasma phosphorus of dialysis patients[39]. Conversely, terminal ERC is considered to be a Klotho deficit state, which has also been evidenced by the values obtained in a subgroup of our patients. Despite not finding a significant association between these 2 hormones of mineral metabolism and LVH, we did observe a significant association between PTHi and FGF values[23].

Conclusion

In this study, values of left ventricular hypertrophy were found to be greater than 50%, corresponding mostly to severe LVH, which evidences the severe cardiovascular involvement of this population. As in this study, the relationship between blood pressure and ultrafiltration have been previously objectified as causal factors of LVH. The importance of cardiovascular monitoring in pediatric patients on dialysis and adjustment of individualized dialysis is reinforced in order to improve the quality of life and survival of these patients.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

Conflicts of Interest

Authors state that any conflict of interest exists regards the present study.

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