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RESEARCH REPORT

Mitochondrial Disease in Children: The Nephrologist's Perspective

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Abstract Mitochondrial diseases (MD) are a heterogeneous group of clinical syndromes characterized by the involvement of different organ systems. They constitute the most prevalent hereditary metabolic disease group.
Objective: To review the importance of the kidney in MD from the nephrologist's perspective within the setting of a pediatric tertiary reference center.
Study design: Retrospective study of children (<18 years) with MD followed between 2000 and 2016 at a tertiary Spanish center.
Results: 52 patients were included. The mean age at the time of the study was 10 years (SD ± 5.1). The mean follow-up time was 6.1 years (SD ± 4.7). The median age at diagnosis was 2.5 years (0.3–13.5).

The median number of affected systems was two (range 1–6). The nervous system was the most affected system, with 51 patients (~98%) presenting with neurological involvement. 20 patients (~40%) presented with endocrinological manifestations, 18 (~35%) with vision problems, 16 (~30%) with gastrointestinal symptoms, 5 (~10%) patients developed hearing impairment, and 6 (~10%) cardiac disease.

We detected renal involvement in 13 patients (25%). Eight patients had tubular disease, most frequently hypercalciuria with hypouricemia and five patients had glomerular involvement, with proteinuria and/or decreased glomerular filtration rate as the most frequent symptoms. Only 21 patients (~40%) had been seen by a pediatric nephrologist.
Conclusions: Renal disease was a common occurrence in patients with mitochondrial disease, present in our study in 25% of patients. A regular screening of renal function parameters and the involvement of a nephrologist as part of the multidisciplinary approach to mitochondrial disease appears warranted.

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Introduction

Mitochondrial diseases (MD) are a complex and heterogeneous group of clinical syndromes characterized by secondary multi-organ involvement caused by mitochondrial dysfunction. Enzymatic deficiency in the mitochondrial respiratory chain usually leads to multisystem alterations, predominantly affecting organs with higher energy requirements, such as the brain, skeletal muscle, heart, liver, and kidneys (Darin et al. 2001; Scaglia et al. 2004; Verity et al. 2010). With an estimated incidence of 1 per 5,000 live newborns (Rahman 2012) or 1 in 4,300 adults (Gorman et al. 2015), MD constitute the most prevalent group of hereditary metabolic diseases in children.

No effective curative treatment has been found for MD, thus preventive or supportive measures and early diagnosis of associated complications are the only way to improve the quality of life of these patients (Pfeffer et al. 2012).

This comes at a high medical and socioeconomic cost (McCormack et al. 2017).

Few case series have been published (Martín-Hernández et al. 2005; Broomfield et al. 2015; Hikmat et al. 2017), making it difficult to know the real prevalence of individual organ involvement in patients with MD. The aim of our study was to analyze the extent of organs affected in a pediatric MD population, with particular interest in renal involvement.

Patients and Methods

Study Design

We performed a single-center retrospective study of children (0–18 years old) diagnosed with MD and followed-up at the Children's Hospital Niño Jesús of Madrid, Spain, between 2000 and 2016. Approval from the institutional Ethics Committee was obtained.

Inclusion and Exclusion Criteria

Patients were included if they were aged 0–18 years at the time of diagnosis and if they met at least one of the following criteria: (1) proven deficiency in one or more complexes of the mitochondrial respiratory chain found in muscle biopsy; (2) presence of at least one mutation, deletion or duplication in DNA sequences of mitochondrial or nuclear DNA responsible for the correct functioning of oxidative phosphorylation; (3) clinical compliance with MD defining criteria, including patients with "definite" or "probable" diagnosis according to the most widely accepted criteria (Bernier et al. 2002; Morava et al. 2006). Patients with incomplete records or "possible" rather than definite diagnosis of MD were excluded.

Data Collection

Clinical data were obtained from hospital records. The following disease-related clinical variables were recorded and/or investigated: sex, age at diagnosis, type of first symptom, clinical features (including neurological, cardiovascular, ophthalmological, hearing, endocrine, gastrointestinal, and renal involvement), enzyme assay reports for the mitochondrial respiratory chain complex (MRCC), genetic findings, and syndromic diagnosis. The estimated glomerular filtration rate (GFR) was calculated using the "original" Schwartz formula [GFR (mL/min/1.73 m^2) = K (age-dependent) × height (cm)/Creatinine (mg/dL)] in cases in which the patients' data were old enough; otherwise the modify Schwartz [GFR (mL/min/1.73 m^2) = K (0.413) × height (cm)/Creatinine (mg/dL)] was used (last 4 years). Normal ranges for creatinine, GFR, phosphate, calcium, uric acid, and calcium/creatinine ratios were adjusted for the patient's age are provided. Proteinuria was defined by urinary protein/creatinine (mg/mg) ratio measured in the first morning urine void, and was abnormal when the value was above 0.5 in patients under 2 years old and above 0.2 in patients aged 2 years and above.

Statistical Analysis

Data are summarized as means (Standard Deviation, SD) or as medians (range) when the values do not meet the criteria of a normal distribution. The Kolmogorov-Smirnov test was used to test the normality of distribution of the data. We evaluated differences between means using either the Student's t-test, or the Mann-Whitney U test when the variable data were not normally distributed. Chi square test and Fisher exact test were used to determine the association between qualitative variables. All analyses were performed using SPSS, version 22 (IBM® SPSS® Statistics). P-values <0.05 were considered as statistically significant.

Results

We reviewed 92 patients who had at some point received a provisional diagnosis of MD. In 40 of these patients, the diagnosis was not confirmed; these cases were excluded from our study. The remaining 52 patients met the inclusion criteria. Of the 52, 31 (~60%) were male and 21 (~40%) were female. The mean age at the time of study was 10 years (0.8–18). The mean follow-up time was 6.1 years (0.2–16.4). Nine (9/52; ~18%) patients had died from the time of diagnosis to the time our study commenced, with a mean age of death of 6.3 years (SD ± 4.7). The mean standard deviation of the weight percentile for age and sex was −1.1 (−3.6–1.7) and the mean standard deviation of the height percentile for age and sex was −2.1 (−8.1–1.2).

Initial and Definitive Diagnoses

The median age at diagnosis was 2.5 years (0.3–13.5). The mean age at diagnosis was lower in patients with renal involvement than in patients without renal involvement (2.98 vs 4.09) but this difference was not statistically significant ($p = 0.079$).

Only one (1/52; ~2%) patient had renal symptoms (hematuria) as a first manifestation of disease (Table 1). Neurological symptoms were the most frequent initial symptoms in 36/52 (~70%) patients.

Muscle biopsy was performed in 51 (51/52; ~98%) MD patients. A dysfunction of MRCC was found in 38 (38/52; ~73%) patients (Table 2). Half of these cases (19/38) had isolated complex I deficiency.

Table 1 Initial and multisystem involvement

	First symptom (%) $n = 52$	All patients (%) $n = 52$	Renal damage patients (%) $n = 13$
Neurologic symptoms	*36 (69.2)*	*51 (98.1)*	*13 (100)*
Epilepsy	8 (15.4)	4 (7.7)	0
Motor delay	1 (1.9)	2 (3.8)	0
Psychomotor delay + epilepsy	0	10 (19.2)	2 (15.4)
Encephalomyopathy	0	24 (46.2)	9 (69.2)
– Seizures (first year of life)	10 (19.2)	0	0
– Psychomotor delay or hypotony	17 (32.7)	0	0
Language disorder	0	5 (9.6)	1 (7.7)
Others[a]	0	6 (11.5)	1 (7.7)
Hearing loss	*0*	*5 (9.6)*	*2 (15.4)*
Ophthalmologic symptoms	*2 (3.8)*	*18 (34.6)*	*5 (38.5)*
Ptosis	2 (3.8)	4 (7.7)	2 (15.4)
Squint	0	2 (3.8)	1 (7.7)
Ophthalmoparesis + pigmentary retinitis	0	4 (7.7)	1 (7.7)
Ophthalmoparesis	0	2 (3.8)	0
Visual deficit	0	2 (3.8)	1 (7.7)
Optic atrophy	0	2 (3.8)	0
Myopia magna	0	1 (1.9)	0
Cataracts	0	1 (1.9)	0
Gastrointestinal symptoms	*3 (5.8)*	*16 (30.8)*	*6 (46.2)*
Failure to thrive	1 (1.9)	6 (11.5)	4 (30.8)
Gastroesophageal reflux	0	2 (3.8)	0
Pancreatitis	1 (1.9)	3 (5.8)	1 (7.7)
Liver disease	1 (1.9)	3 (5.8)	1 (7.7)
Vomiting	0	2 (3.8)	0
Endocrinological symptoms	*1 (1.9)*	*20 (38.5)*	*7 (53.8)*
Short stature	0	15 (28.8)	5 (38.5)
Diabetes mellitus	1 (1.9)	2 (3.8)	0
Early puberty	0	2 (3.8)	1 (7.7)
Hypocalcemia	0	1 (1.9)	1 (7.7)
Cardiac symptoms	*1 (1.9)*	*6 (11.5)*	*1 (7.7)*
Rhythm abnormalities	0	3 (5.8)	0
Cardiomyopathy	0	3 (5.8)	1 (7.7)
Sepsis episodes	*3 (5.8)*	N/A	N/A
Renal affectation	*1 (1.9)*	*13 (25)*	*13 (100)*
Unknown	*5 (9.6)*	N/A	N/A

N/A not applicable

[a] Migraine; Ataxia; Leukodystrophy and hemiplegic migraine; Spinocerebellar syndrome; Oculomotor apraxia and myopathy

Nearly one-third of all MD patients (16/52; ~30%) received a syndromic diagnosis. The most frequent diagnoses were Leigh syndrome (10/52; ~20%) and Kearns-Sayre syndrome (4/52; ~8%). One patient was diagnosed with MELAS syndrome and another one with Alpers-Huttenlocher syndrome. The diagnosis was accompanied by identification of molecular genetic alterations in 9 (9/52; ~17%) patients, with mitochondrial DNA depletion in 7 (7/52; ~14%) patients, and FOXRED1 gene mutation in 2 (2/52; ~4%) patients. In 26 (26/52; 50%) patients, the clinical diagnosis was confirmed only by the deficit of one or more MRCC. One patient was diagnosed on the basis of clinical

Table 2 Mitochondrial chain deficits in muscle biopsy ($n = 52$)

	Frequency (%)
Complex I	19 (36.5)
Complex II	1 (1.9)
Complex III	2 (3.8)
Complex IV	8 (15.4)
Deficit of all complexes	1 (1.9)
Other combinations	7 (13.5)
Normal	13 (25)
Not performed	1 (1.9)

manifestations and metabolic and analytical data compatible with MD according to the Bernier and Morava criteria (Bernier et al. 2002; Morava et al. 2006).

Multisystem Involvement

Multisystem involvement is shown in Table 1. Thirteen patients (25%) had renal symptoms directly attributed to the MD.

The median number of affected organs or systems was 2 (SD ± 1.3; 1–6). Patients with kidney disease appeared more likely to have multiple organs affected (three or more) when compared to patients without kidney disease [~54% (7/13) vs ~33% (13/39), respectively]. However, this difference was not statistically significant ($p = 0.18$). No correlations between number of organs affected and age of initial symptom, types of organs involved, each concrete syndrome, MRCC, or the molecular/genetic alteration were found.

Renal Impairment

Of the 52 patients, 13 (25%) (6 males and 7 females) had renal involvement. Eight (8/13; ~62%) patients had tubular alterations and 5 (5/13; ~38%) patients had glomerular involvement; this difference was not statistically significant ($p = 0.4$). The mean age of renal damage was 10.2 years (0.8–17.2), and the mean age at diagnosis was 2.98 years (0.8–8.8) with a mean follow-up time of 6.7 years (0.2–16.4).

Patients with tubular alterations (8/13) are shown in Table 3. One had Kearns-Sayre syndrome and one had Alpers-Huttenlocher syndrome. The most frequent renal dysfunction was hypercalciuria with hyperuricosuria and hypouricemia. Two patients had nephrocalcinosis and one had renal calculi without associated hypercalciuria.

One patient (#6) presented at 3 years of age with repeated pancreatitis and sepsis-like episodes, later developing ptosis. He was seen by a nephrologist from the age of 5 because of acidosis, hypokalemia, and nephrocalcinosis. He was eventually diagnosed with Fanconi syndrome after a study revealing hypercalciuria, generalized hyperaminoaciduria, phosphaturia, proteinuria, and glycosuria leading to chronic renal disease. At 8 years of age, after developing clumsiness and learning difficulties and finding a deletion of mitochondrial DNA, he was finally diagnosed with MD with a Kearns-Sayre phenotype.

Patients with glomerular involvement (5/13) are shown in Table 4. The most common symptoms were proteinuria and decreased GFR with two patients going into chronic renal failure. Two patients had Leigh syndrome, one of them with renal failure. Mean plasma creatinine (Cr) was 0.4 mg/dL (SD ± 0.7; Max. 2) with GFR of 87.6 mL/min/1.73 m^2 (SD ± 44; Min. 25); mean plasma urea was 36 mg/dL (SD ± 80.1; Max. 205) and mean plasma urate was 5.8 mg/dL (SD ± 2.4; Max. 9.7).

Patient #9, a 7-year-old male, with chronic stage G4 kidney disease (KDIGO guidelines 2012), presented with hypotonia from birth with progression to hypotonic-ataxic cerebral palsy, and later with associated hearing loss and visual impairment. MD was suspected in the first year of life, when a muscle biopsy showed a deficiency in complex IV of the mitochondrial respiratory chain. The GFR measured at that time (1-year old) was 50 mL/min/1.73 m^2, with a creatinine of 0.7 mg/dL and urea of 125 mg/dL.

Only one patient (#13) presented with renal symptoms, with an episode of macroscopic hematuria with C4 hypocomplementemia at age 4. This episode was triggered by an infection, but due to the persistence of microhematuria over the following years with no changes in the low C4 levels, the later was considered an isolated low C4 not related to the renal involvement. At age 6, he developed complex partial epilepsy that was difficult to manage and he was diagnosed with MD due to a deficit in complex II with alterations in complexes III, II + III, and I + III. Renal function remained stable, so a biopsy was not performed. Although a definitive diagnosis of his kidney disease has not been reached, there is no other known explanation for his renal symptoms.

Out of the 12 (12/51; 23%) patients who received therapies with known renal side effects, 2 (2/12) had renal involvement prior to commencing those treatments and five (5/12; ~42%) had probable drug-related renal toxicity; only one of them appeared to be in addition to preexisting tubular damage.

Three out of six patients treated with topiramate experienced acidosis. One of them also presented with hypercalciuria. None of the three patients treated with oxcarbamacepin developed side effects. Both patients who received zonisamide developed secondary hypercalciuria; one of them developed transient arterial hypertension after adrenocorticotropic hormone. The other patient treated

Table 3 Patients with tubular damage

	Sex	Age at last follow-up/death (years)	Mitochondrial disease diagnosis	Age at first symptom (years)	First symptom	Age at diagnosis (years)	Multisystem involvement	Age at diagnosis of renal impairment (years)	Renal involvement
1	F	17.2	DMRCC Complex IV + II limit Mitochondrial DNA depletion	0.3	Psychomotor delay Nystagmus	0.8	Encephalomyopathy Nystagmus	17	Hypercalciuria Ca/Cr ratio: 0.43 mg/mg ($N < 0.21$) Proteinuria 0.36 mg/mg ($N < 0.2$) Hypouricemia 1.1 mg/dL (2.8–6) Alkalosis pH 7.48 HCO_3 32.8 mmol/L
2	F	2 (dead)	POLG mutation Alpers-Huttenlocher syndrome	2	Epileptic status	2	Encephalomyopathy Short stature Liver disease	2	Hypercalciuria Ca/Cr ratio: 1.37 mg/mg ($N < 0.21$) Proteinuria 0.53 mg/mg ($N < 0.2$) Hypouricemia 0.9 mg/dL (2–5.1)
3	F	13.8	DMRCC I + II	0.3	Psychomotor delay	4.5	Encephalomyopathy Epilepsy Dysphagia Diabetes mellitus	12	Hypercalciuria Ca/Cr ratio: 0.31 mg/mg ($N < 0.21$) Hypouricemia 0.7 mg/dL (2.8–6)
4	M	11.4	Mitochondrial DNA depletion	0.9	Hypotonia Dystonia	2.5	Encephalomyopathy	11.4	Hypercalciuria Ca/Cr ratio: 0.3 mg/mg ($N < 0.21$) Hypouricemia 1.1 mg/dL (2.8–6)
5	F	15.8	DMRCC IV	0.3	Epileptic seizure	1.7	Encephalomyopathy Epilepsy Early puberty	10	Hypercalciuria Ca/Cr ratio: 0.4 mg/mg ($N < 0.21$) Hypouricemia 1.7 mg/dL (2.8–6) Intermittent proteinuria 0.49 mg/mg ($N < 0.21$) Nephrocalcinosis
6	M	10.1	Mitochondrial DNA depletion Kearns-Sayre syndrome	2.6	Pancreatitis Sepsis-like episode	8.8	Motor clumsiness Hearing loss Ptosis and pigmentary retinitis Pancreatitis Short stature	5.7	Fanconi syndrome

(continued)

Table 3 (continued)

	Sex	Age at last follow-up/death (years)	Mitochondrial disease diagnosis	Age at first symptom (years)	First symptom	Age at diagnosis (years)	Multisystem involvement	Age at diagnosis of renal impairment (years)	Renal involvement
7	F	1 (dead)	DMRCC all	0.1	Epileptic seizure	1	Neutropenia Early onset myoclonic encephalopathy	0.2	Cystinuria (not generalized aminoaciduria)
8	M	15	DMRCC I	0.3	Cardiogenic shock Intrauterine growth restriction	Unknown	Encephalomyopathy Epilepsy Cardiogenic shock Hypocalcemia and hyperphosphatemia	1.2	Nephrolitiasis Hyperuricemia 9.6 mg/dL (2.8–7.2) Metabolic alkalosis pH 7.37 HCO_3 30.8 mmol/L

F female, *M* male, *DMRCC* deficit in the mitochondrial respiratory chain complex, *N* normal range, *Ca/Cr* calcium/creatinine urinary ratio

Table 4 Patients with glomerular damage

	Sex	Age at last follow-up (years)	Mitochondrial disease diagnosis	Age at first symptom (years)	First symptom	Age at diagnosis (years)	Multisystem involvement	Age at diagnosis of renal impairment (years)	Renal involvement	GFR (mL/min/1.73 m^2)	Uric (mg/dL)
9	M	7.7	DMRCC IV	0.5	Hypotony	1	Encephalomyopathy Malnutrition Hearing loss Strabismus	1	CKD	27 ($N > 90$)	9.7 (2–5.1)
10	F	1	DMRCC I + IV Leigh syndrome	0.6	Psychomotor regression	1	Encephalomyopathy	0.8	CKD	57 ($N > 78$)	4.9 (2–5.1)
11	M	8.1	Leigh syndrome	1	Psychomotor delay	2.2	Ataxia Ptosis	8.1	Hyperuricemia	121 ($N > 90$)	5.9 (2–5.1)
12	F	15.6	DMRCC III + IV	1	Psychomotor delay	3.3	Encephalomyopathy Cerebellar atrophy Short stature	15	Low proteinuria Microhematuria	300 ($N > 90$)	5.2 (2.8–6)
13	M	6.7	DMRCC I, II + III	4	Hematuria	6.7	Epilepsy Autism spectrum disorder	4	Hematuria	123 ($N > 90$)	3.3 (2–5.1)

F female, *M* male, *DMRCC* deficit mitochondrial respiratory chain complex, *CKD* chronic kidney disease, *N* normal range

with adrenocorticotropic hormone, with previous tubular damage, developed hypertension as well but no direct nephrotoxicity.

Only 21/52 (~40%) of MD patients in this study were seen by a pediatric nephrologist, mostly in older years.

Discussion

Mitochondria are organelles present in most cells of the organism. They generate energy through ATP production, in a process of aerobic oxidation that takes place in the mitochondrial respiratory chain, which is composed of five enzyme complexes (I, II, III, IV, and V) (Zeviani and Di Donato 2004; DiMauro and Hirano 2005). Dysfunction of the mitochondrial respiratory chain can be caused by genetic mutations in either nuclear or mitochondrial DNA (Moslemi and Darin 2007). Many mutations in mitochondrial DNA have been reported and are collected in online databases (http://www.mitomap.org) (Emma and Salviati 2017).

Due to the ubiquity of the mitochondria, multiple organs are usually involved in MD. In our study, only 14/52 (~27%) patients had a single affected organ/system; the rest had multiple organs affected, with 10/52 (~20%) patients having more than three symptomatic organs. It is therefore necessary to raise awareness to the need of multidisciplinary management and follow-up. The complexity of this disease can only be effectively managed as a joint effort by different medical specialists.

In this regard, multidisciplinary needs can lead to unorganized care, and underestimating comorbidities is a dangerous possibility. In our study, we found that only 40% (21/52) of the patients had ever been seen by a pediatric nephrologist despite 25% of MD patients suffering from renal involvement and several drugs used for MD treatment being nephrotoxic. It is nevertheless encouraging that in recent years increased proportion of patients are being referred to a nephrologist and/or have undergone a complete kidney function screening.

The simplistic unilateral approach to MD that occurs at times in the clinics is also reflected in the literature, with a strong focus on the neurologist perspective (Emma and Salviati 2017). However, although neurological involvement is frequently the guiding symptom, it is remarkable that 21% (11/52) of our patients presented with other affected organs. This heterogeneity is scarcely reflected in the literature, with few published multidisciplinary series (Broomfield et al. 2015; Hikmat et al. 2017) and even fewer series with a focus on renal damage (Lee et al. 2001; Emma et al. 2011; Rahman and Hall 2013; O'Toole 2014).

The kidney is a highly energetic organ, and thus rich in mitochondria, and is particularly susceptible to being affected in MD. A wide range of alterations have been described, from glomerular to tubular and tubulointerstitial damage, and even corticosteroid-resistant nephrotic syndrome in patients with coenzyme Q10 gene mutations (Lee et al. 2001; Emma et al. 2011; Rahman and Hall 2013; O'Toole 2014).

The prevalence of renal involvement in our sample was 25% (13/52). This is notably lower than the 50% (21/42) previously reported in a Spanish cohort (Martín-Hernández et al. 2005), and the 85% (17/20) reported by Broomfield et al. (Broomfield et al. 2015); however, it is higher than the series presented by Hikmat et al., with 11% (3/27) reported renal involvement (Hikmat et al. 2017). This variability could be explained by the heterogeneity of MD, the ascertainment, and the inclusion criteria of these different studies.

Nevertheless, our study has some limitations that may underestimate the prevalence of renal damage. The most important limitation consists of potentially missing data due to the retrospective nature of the analysis. Also, the lack of a pediatric nephrologist assessment in 60% (31/52) of the patients could have resulted in an incomplete renal evaluation, particularly in those patients in which no Ca/Cr and Protein/Cr ratios in urine were performed (48%; 25/52).

Beyond the study limitations, the low detected rate of renal damage may also reflect a lack of awareness of the importance of the kidney in MD. This adds to the fact that renal damage is most frequently asymptomatic in these patients (Martín-Hernández et al. 2005). Our study should raise awareness about the need for renal investigations and adequate renal specialist involvement in the management of children with MD, since it is well known that presymptomatic detection of renal damage and early intervention improve outcome. Exhaustive renal function testing is already recommended for all patients and should be a common practice (Broomfield et al. 2015).

We identified tubular damage in 8/52 patients (~15%). The most prevalent findings in our study include hypercalciuria and hypouricemia secondary to involvement of a single transporter. Only one patient with Kearns-Sayre syndrome presented with renal Fanconi syndrome, the most severe form of tubular involvement, which has been reported in previous studies (Emma et al. 2011; Klootwijk et al. 2014; O'Toole 2014).

Other forms of renal damage include chronic tubulointerstitial nephritis, cystic renal diseases, or glomerular proteinuria, which often progresses gradually and triggers terminal renal failure (Emma et al. 2012; Rahman and Hall 2013; O'Toole 2014). We found glomerular involvement in 5/52 (~10%) patients, out of whom two patients (2/5; 40%) had chronic renal disease. These findings underscore the importance of including MD in the differential diagnosis of patients with renal tubulopathy and/or renal failure

(Rötig et al. 1995; Rahman and Hall 2013; Broomfield et al. 2015).

Our study has important limitations due to its retrospective and mono-centric nature. However, some of its strengths include the diagnosis of specific syndromes in almost one-third of the patients (31%; 16/52), the molecular/genetic confirmation in 17% (9/52) of the patients, and the fact that the center is the most important pediatric reference center in our country. This study adds to the still scarce but much needed literature focusing on kidney damage in MD.

Conclusion

Our data confirm the wide clinical spectrum and multi-organ involvement in MD highlighting the need for a multidisciplinary team. The kidney should be seen as a key disease-susceptible organ, making it essential to monitor renal function in children with MD. Raising awareness and intensive kidney screening strategies performed not only by the nephrologist but also by other concerned specialists will lead to early treatment and improved renal outcome.

In light of our study, we recommend an annual renal evaluation including blood test with electrolytes, blood gases, uric and GFR, and first-morning urine with Ca/Cr and Protein/Cr ratios. A biannual ultrasound for nephrocalcinosis screening is also recommended.

Additional Information Tables: Laboratory Reference Parameters for Children

Table 5 Estimated glomerular filtration rate (GFR) (mean ± SD) (Santos and García Nieto 2006)

Age	GFR (mL/min/1.73 m^2)
1–2 months	64.6 ± 5.8
3–4 months	85.8 ± 4.8
5–8 months	87.7 ± 11.9
9–12 months	86.9 ± 8.4
1–6 years	130.0 ± 4.9
7–10 years	135.8 ± 4.3
>11 years	136.1 ± 6.3

Table 6 Plasma creatinine levels (Hospital's laboratory reference values n.d.)

Age	Range (mg/dL)	
0–21 days	0.32	1.06
21 days–1 year	0.24	0.42
1–2 years	0.16	0.42
2–5 years	0.19	0.51
5–10 years	0.33	0.73
10–18 years	0.4	1.0

Table 7 Plasma uric levels (Hospital's laboratory reference values n.d.)

	Age (years)	Range (mg/dL)	
Female	<1	2.1	6.5
	1–10	2.0	5.1
	10–14	2.8	6.0
	>14	2.8	6.0
Male	<1	2.1	6.5
	1–10	2.0	5.1
	10–13	2.8	6.0
	>13	2.8	7.2

Table 8 Plasma phosphate levels (Hospital's laboratory reference values n.d.)

Age (years)	Range (mg/dL)	
<1	4.8	7.5
1–2	4.5	6.7
2–6	4.5	6.5
6–15	2.7	5.3
>15	2.5	4.5

Table 9 Urinary Ca/Cr ratios (Santos and García Nieto 2006)

Age	Ca/Cr (mg/mg) hypercalciuria
0–6 months	0.8
7–12 months	0.6
<2 years	0.47
>2 years	0.21

Original Scwartz formula: GFR (mL/min/1.73 m^2) = K (age-dependent) × height (cm)/Creatinine (mg/dL). $K = 0.33$ (preterm infants 0–1 year); 0.45 (full-term infants 0–1 years); 0.55 (1–12 years); 0.70 (male >12 years) and 0.55 (female >12 years).

Synopsis

Renal involvement in mitochondrial diseases can affect the different segments of the nephron, leading to a broad spectrum of symptoms; thus, a close follow-up of the renal function is recommended in these children.

Authors Contributions

PP and CdL designed the study; PP, CdL, and MAF conducted the study and wrote the manuscript; TdR contributed to the analysis and reporting of the results; CdL, TdR, CA, and LGS supervised the study and critically reviewed the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest

Paula Pérez-Albert, Carmen de Lucas Collantes, Miguel Ángel Fernández-García, Teresa de Rojas, Cristina Aparicio López, and Luis Gutiérrez-Solana declare that they have no conflict of interest.

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Ethics Approval

This study has been carried out in accordance with the ethical standards approved by the ethical committee of the Niño Jesús Hospital, which is in accordance with the national committee on human experimentation and the Helsinki Declaration of 1975 and the revised version of 2015. For this retrospective study, formal consent was not required by the ethics committee.

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