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ÇOCUKLARDA ÜRİNER TAŞ HASTALIĞI VE RENAL MİKROLİTİYAZİS: TEK MERKEZLİ BİR ÇALIŞMA

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Özet

Nefrolitiazis, çocuklarda görülme sıklığı giderek artan yaygın bir hastalıktır. Renal mikrolitiazis (ML), üriner ultrasonda 3 mm'den küçük renal hiperekojenik odak olarak tanımlanır. Pediyatrik popülasyonda ML'nin klinik önemi halen tartışmalıdır. Bu çalışma, çocuklarda renal ML ve aşikar nefrolitiazisli çocukların demografik verileri ve metabolik anormalliklerindeki farklılıkları değerlendirdi. İki grup arasında lateralite, taş sayısı, taş çapı, idrar yolu enfeksiyonu, ağrı ile prezentasyon, rastlantısal olarak saptanan böbrek taşı, idrar yoğunluğu, hiperkalsiüri, spot idrar ürik asit/kreatinin oranı, idrar sodyum/potasyum oranı, ve potasyum sitrat tedavisi alma ($p = 0,02$, $p = 0,03$, $p<0,001$, $p = 0,02$, $p = 0,04$, $p = 0,01$, $p = 0,04$, $p = 0,02$, $p<0,001$, $p = 0,03$, $p = 0,041$ ve $p = 0.013$, sırasıyla) açısından anlamlı fark saptandı. ML, aşikar nefrolitiazisin gelişimindeki ilk basamak olabilir. Bu nedenle, ürolitiazis saptanan tüm hastalar taş boyutuna bakılmaksızın hastalığın komplikasyonlarını önlemek amacı ile takip altına alınmalı ve ML'nin yönetimini ve doğal seyrini değerlendirmek için daha ileri çalışmalar yapılmalıdır.

Anahtar Kelimeler: Çocuk, mikrolitiyazis, nefrolitiyazis

URINARY STONE DISEASE AND RENAL MICROLITHIASIS IN CHILDREN: A SINGLE CENTRE STUDY

Abstract

Nephrolithiasis is a common disorder with increasing prevalence in children. Renal microlithiasis (ML) is defined as a renal hyperechogenic focus smaller than 3 mm in diameter on urinary ultrasound. The clinical importance of ML remains controversial in the pediatric population. The current study evaluated the differences in the demographic data and metabolic abnormalities between children with renal ML and those with overt nephrolithiasis. There were statistically significant differences between the two groups in terms of laterality, number of stones, stone diameter, urinary tract infections, pain at presentation, incidental kidney stones, urine density, hypercalciuria, spot urine uric acid/creatinine ratio, urine sodium/potassium ratio, and potassium citrate therapy ($p = 0.02$, $p = 0.03$, $p <0.001$, $p = 0.02$, $p = 0.04$, $p = 0.01$, $p = 0.04$, $p = 0.02$, $p <0.001$, $p = 0.03$, $p = 0.041$, and $p = 0.013$, respectively). ML may be the first stage in the development of overt nephrolithiasis. Therefore, all patients with urolithiasis, regardless of stone size, should be followed up to prevent complications of the disease and further studies should be performed to assess the management and natural course of ML.

Key Words: Children, microlithiasis, nephrolithiasis

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INTRODUCTION

Nephrolithiasis (NL) is a common health problem in which a solid foreign body of urine components precipitates and aggregates within the urinary tract and kidney (Cao et al., 2023). Stone formation occurs due to the oversaturation of urine by crystals, depending on decreased water intake, increased pro-lithogenic factors, such as calcium and oxalate, and reduced anti-lithogenic factors, such as citrate and magnesium in urine (Injeyan et al., 2023). Pediatric nephrolithiasis is a multifactorial disease with varying features depending on climatic, metabolic, dietary, and genetic factors (Önal et al., 2021). In the last decade, the incidence of renal stones in children has been reported to increase to 6-10% (Reusz et al., 2020). Although this rate is still lower than in adults, pediatric urolithiasis should not be underestimated due to the significantly higher underlying metabolic risk factors and recurrence rate when compared to adults (Marra et al., 2019). Renal microlithiasis (ML) is defined as renal calyceal, pelvic, or ureteral hyperechogenic deposits smaller than 3 mm in diameter on urinary ultrasound (USG) (La Manna et al. 1998, Fallahzadeh et al., 2016). The clinical presentation, importance, metabolic predisposing factors, and prognosis of ML remain controversial; therefore, there is a need for further studies in pediatric kidney stones and ML. The current study aimed to evaluate and compare the demographic and clinical data and risk factors between children with ML and those with overt NL in our geographical region.

METHOD

Research Model

A retrospective, descriptive study.

Universe-Sample (Research Group)

The medical records of 108 patients admitted to the Pediatric Nephrology Unit between October 2021 and October-2022 were retrospectively included in the study after receiving institutional ethical approval. Demographic, clinical, laboratory, and imaging data, and treatment modalities were evaluated, and the patients with ML and overt NL were compared according to these variables. All subjects with missing data were excluded.

Kidney stones were detected on urinary USG, and the diagnoses of ML and overt NL were made based on echogenic shadows being <3 mm and ≥3 mm, respectively. On USG, nephrocalcinosis was defined as an increased echogenicity of the kidneys. A mid-stream clean catch urine sample with at least >100,000 colony-forming units/milliliter (CFU/mL) of a

microorganism was defined as a urinary tract infection (UTI) for the children with sphincter control. In patients without sphincter control, urine specimens were collected via urethral catheterization, and the growth of at least >1,000-50,000 CFU/mL was defined as a UTI (Stein et all., 2015).

Blood tests (blood urea nitrogen, creatinine, sodium, potassium, chlorine, calcium, phosphorus, magnesium, venous blood gas, and parathormone), urinalysis, urine culture analysis, and spot urine metabolite analysis (calcium, uric acid, magnesium, creatinine, sodium, and potassium) were performed. Parathormone and 25-hydroxy-vitamin D were examined in patients with hypercalcemia or hypercalciuria. Hypercalciuria, hyperuricosuria, and hypomagnesuria were diagnosed based on levels above the upper limit of the spot urine solute/creatinine ratio (Baştuğ et al., 2012).

High fluid intake and a sodium-restricted diet were recommended to all patients. The patients who had metabolic risk factors, such as hypercalciuria, hyperuricosuria, and multiple stones, were treated with potassium citrate.

Data Collection Tools

Hospital medical records were reviewed for each patient retrospectively.

Data Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows, v. 22 (IBM SPSS Inc. Chicago, USA). A p-value of <0.05 was considered statistically significant. The normality of the distribution of variables was checked using the Kolmogorov-Smirnov and Shapiro-Wilk tests and histograms. Quantitative data were presented as mean ± standard deviation or median values as appropriate, while categorical data were obtained as numbers and percentages. The differences between the groups in terms of continuous variables were examined using Student's t-test or the Mann-Whitney U test. The $\chi 2$-test was used to assess categorical data.

RESULTS

A total of 108 patients with kidney stones were enrolled in this study. The demographic, clinical, and laboratory parameters of the patients are presented in Table 1. Fifty-seven (53%) of the patients were female, and 20 (18.5%) were under one year of age. Two patients had urolithiasis due to distal-type renal tubular acidosis with nephrocalcinosis, one due to D vitamin intoxication and the other due to hyperparathyroidism. UTIs were detected in 50 (46%) patients. Potassium citrate was administered to 34 (31%) patients. Eighteen (17%) patients with overt

NL required surgical intervention. Seven (39%) of these patients underwent extracorporeal shock wave lithotripsy, nine (50%) underwent ureterorenoscopy, and 2 (11%) required open surgery. Stone composition data were available for 15 patients, of whom 12 (80%) had calcium, two (13%) had uric acid, and one (7%) had struvite stones.

Table 1. Demographic, clinical, and laboratory variables of the patients

Variables	Patients (n = 108)
Age (median, min-max, year)	4 (2.75-16.5)
Age at diagnosis (median, min-max, year)	3 (0.5-15.5)
Gender (male/female)	51/57
Family history of kidney stones (n, %)	61 (56%)
Laterality (unilateral/bilateral)	56/52
Number of stones (single/multiple)	55/53
Diameter of stones (mm)	4 ± 3
Hypercalcemia (n, %)	5 (4.6%)
Hypercalciuria (n, %)	10 (9%)
Hypomagnesuria (n, %)	15 (14%)
Hypouricemia (n, %)	8 (7.4%)
Acidosis (n, %)	2 (1.8%)
Nephrocalcinosis	2 (1.8%)
Vitamin D intoxication (n, %)	1 (1%)
Hyperparathyroidism (n, %)	1 (1%)

n: number, min: minimum, max: maximum

The patients were divided into two groups according to their stone diameters: ML (<3 mm) and overt NL (≥3 mm). The comparison of the two groups is presented in Table 2. There were 52 (48%) patients with ML and 56 (52%) patients with overt NL. Statistically significant differences were found between the two groups in terms of laterality, number of stones, the stone diameter, UTIs, pain at presentation, incidental kidney stones, urine density, hypercalciuria, spot urine uric acid/creatinine ratio, urine sodium/potassium ratio, and potassium citrate therapy ($p = 0.02$, $p = 0.03$, $p < 0.001$, $p = 0.02$, $p = 0.04$, $p = 0.01$, $p = 0.04$, $p = 0.02$, $p < 0.001$, $p = 0.03$, $p = 0.041$, and $p = 0.013$, respectively). However, the groups did not significantly differ in relation to age at diagnosis, gender, family history of kidney

stones, other presenting symptoms (hematuria, irritability, or dysuria), blood phosphorus, urine pH, urine calcium/creatinine, or urine magnesium/creatinine.

Table 2. Demographic, clinical, and laboratory variables of the study groups

Variables	Microlithiasis (n = 52)	Overt nephrolithiasis (n = 56)	p-value
Age at diagnosis (median, min-max, year)	2.75 (0.3-15.5)	4.5 (0.3-16.5)	0.1
Gender (male/female)	26/26	25/31	0.5
Family history of kidney stones (n, %)	25 (48%)	36 (64%)	0.1
Laterality (unilateral/bilateral)	35/17	21/35	**0.02***
Number of stones (single/multiple)	32/20	23/33	**0.03***
Stone diameter (median, min-max, mm**)**	1.75 (0.5-2.9)	4.5 (3-15.5)	**<0.001***
UTI	15 (29%)	35 (62%)	**0.02***
Presenting symptoms			
-Pain (n, %)	25 (48%)	30 (54%)	**0.04***
-Hematuria (n, %)	4 (8%)	12 (21.4%)	0.23
-Irritability (n, %)	3 (6%)	2 (3.5%)	0.3
-Dysuria (n, %)	6 (11%)	7 (12.5%)	0.96
-Incidental (n, %)	14 (27%)	5 (9%)	**0.01***
Blood calcium levels	10.4 ± 0.6	10 ± 0.5	**0.04***
Blood phosphorus levels	4.9 ± 0.8	4.7 ± 0.7	0.2
Urine density	1012 ± 8	1016 ± 10	**0.02***
Urine pH	6.2 ± 0.4	6.3 ± 0.5	0.5
Hypercalciuria (n, %)	1 (2%)	9 (16%)	**<0.001***
Hypomagnesuria (n, %)	6 (11.5%)	9 (16%)	0.08
Hypouricemia (n, %)	3 (6%)	5 (9%)	0.06
Spot urine calcium/creatinine	0.24 ± 0.13	0.26 ± 0.19	0.3
Spot urine magnesium/creatinine	0.26 ± 0.13	0.23 ± 0.17	0.4
Spot urine uric acid/creatinine	1.1 ± 0.7	0.8 ± 0.4	**0.03***
Spot urine sodium/potassium	1.1 ± 0.6	1.8 ± 1	**0.041***
Potassium citrate therapy	13 (25%)	21 (37.5%)	**0.013**

n: number, min: minimum, max: maximum, UTI: urinary tract infection, *p < 0.05 was excepted as significant and marked bold

DISCUSSION

Although pediatric kidney stone disease is less common than in adults, its incidence is increasing worldwide. The diagnosis of kidney stones may be challenging due to the variety of

symptoms related to stone localization and size in children, and delays in diagnosis can cause complications such as UTIs, urinary tract obstruction, renal parenchymal injury, and renal failure (Cao et al. 2023, Kokorowski et al., 2010). Renal ML was first defined by La Manna et al. in 1998. Since then, only limited data have been presented on the diagnosis, outcome, and clinical importance of this condition. In the current study, the differences between ML and overt NL in terms of demographic, clinical, and laboratory data and metabolic risk factors were investigated in our geographical region.

In this study, the mean age of the patients with urolithiasis was similar to the literature (Dinçel et al. 2012, Taşdemir et al. 2017), and the patients with overt NL were found to be older than those with ML. Stone size may grow over time, it is important to follow up patients with ML. In many adult studies, male dominance has been reported in pediatric stone disease. However, in the pediatric sample of the current study, the number of male and female patients with kidney stones was nearly equal (Alpay et al. 2009, Bilge et al. 2013). A family history of stones in children was reported to be 54.7% by Dursun et al. (2008), which is consistent with our result (56%). In the current study, the patients with overt NL had a higher incidence of family history and a higher frequency of multiple and bilateral stones. In contrast, Fahimi et al. (2016) reported these rates to be similar between ML and overt NL groups, which may be due to the younger age of their patients.

UTI is one of the main presenting symptoms and a significant cause and/or complication of renal stones in children. However, its effect on ML has not yet been clarified. In the current study, 29% of the patients with ML had UTIs, which is similar to the rates ranging from 18 to 34.6% in the literature (Bilge et al. 2013, Fahimi et al. 2015). Comparable to the present study, UTIs are reported to be significantly higher in the overt NL group than in the ML group (Fahimi et al. 2015). This may be because larger renal stones in overt NL cause urinary stasis, which is a known predisposing factor for UTIs.

In this study, pain and dysuria were the main presenting symptoms in both ML and overt NL groups. However, asymptomatic cases in which stones were detected incidentally were more common in the ML group, seen at a rate of 27%, which is consistent with previous studies (Bilge et al. 2013, Fahimi et al. 2015). Patients with ML tend to be asymptomatic. In addition, most radiologists may not consider ML to be important enough to be reported. Furthermore, considering the difficulties in the diagnosis of ML, the actual incidence of ML may be underdiagnosed.

Similar to Yüksel et al. (2015), we determined hypomagnesuria and hypercalciuria to be the most common metabolic risk factors for kidney stones. Although rare, previous studies have

stated controversial results regarding metabolic risk factors in ML versus overt NL groups. Yilmaz et al. (2020) reported hyperoxaluria and Fahimi et al. (2006) reported hypercalciuria to be more common in patients with overt NL than in those with ML. Among the metabolic risk factors evaluated in the current study, hypercalciuria was found present at a statistically significantly higher rate in the patients with overt NL. However, there were no significant differences between the ML and overt NL groups in terms of calcium/creatinine levels. On the other hand, the spot urine uric acid/creatinine ratio was significantly lower, and the sodium/potassium ratio was significantly higher in the patients with overt NL. Hypouricosuria and higher urine sodium/potassium levels are known to be associated with nephrolithiasis (Cirillo et al. 1994, Sankar Raj et al. 2020, Yilmaz et al. 2020); however, there are no data concerning ML. Potassium citrate therapy is reported to be effective in preventing the growth of ML (Fallahzadeh et al. 2016, Unno et al. 2017). In our study, 25% of the patients with ML were treated with potassium citrate.

The main limitations of our study are the small sample size and the retrospective design. Another limitation is the absence of data on spot urine citrate, cystine, and oxalate levels, which are not analyzed in our hospital. There is a need for prospective studies with larger sample sizes to investigate the etiology, follow-up, and outcomes of ML and overt NL.

In conclusion, in recent years, the increasing frequency of ML in children may be due to the increasing rates of USG screening and the improvements in the imaging technique allowing for the detection of smaller foci of calculi. Although the clinical outcomes of ML remain controversial, ML seems to be associated with underlying metabolic risk factors that are similar to those observed in overt NL. Furthermore, ML may be the first stage in the development of overt NL. Therefore, all patients with urolithiasis of any size should be followed up to prevent complications of the disease.

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Conflict of interest: The authors declare no conflict of interest.

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