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RESEARCH ARTICLE

Metabolic Risk Factors in Children with Urinary System Stones

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Abstract

Objective: To diagnose, treat, and prevent stone recurrence, it is important to determine the metabolic risk factors that play a role in developing urinary system stone disease in children. This study assessed children with urinary system stones' clinical, radiological, and metabolic characteristics.

Material and Methods: A retrospective study was conducted on the records of pediatric patients who applied to our pediatric outpatient nephrology clinic for various reasons between February 2018 and December 2023 and were diagnosed with urinary system stones.

Results: Of the 122 patients with a mean age of 4.40±4.16 years (1 month-17 years), 63 (51.6%) were boys and 59 (48.4%) were girls. In 61.4% of the children, a family history was identified. The most common presenting symptom was abdominal/flank pain or restlessness (47.5%). In 25.4% of the patients, the stones were ≤3 mm (microlithiasis), and most stones were in the upper system. One or more metabolic abnormalities have been detected during urine analysis for 58.2% of patients. The most frequent metabolic abnormalities were hypercalciuria (20.5%) and hypocitraturia (17.2%). In 74.6% of patients, the size of stones decreased or completely disappeared with medical treatment based on underlying metabolic abnormalities, and in 17.2%, they did not change at all. Only eight (6.6%) patients required interventional procedures.

Conclusion: Metabolic causes should be investigated first in all children with urinary tract stones. Special medical treatments designed to alter metabolism reduce the need for invasive stone procedures.

Keywords: Childhood, Urinary System Stone, metabolic risk factors, hypercalciuria, hypocitraturia

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INTRODUCTION

Urinary system stones are abnormal mineral accumulations anywhere in the urinary system, especially the kidneys. Although it is less common in children than adults, it is common in all ages, including infancy, and is increasingly prevalent (1). It is influenced by prevalence, age, gender, climate conditions, dietary habits, genetic and socio-economic factors, between 1% and 5% in developed countries and between 5% and 15% in developing countries. In adults, it is more common in males, while in children, there is no pronounced male predominance (2). Our country is in an endemic stone range extending from the Balkans to India.

Stone formation is the formation of crystals due to cell degradation at the tubular level for various physical and biochemical reasons. Some underlying anatomical problems that facilitate the development of stones (such as urinary system constraints and vesicoureteral reflux), infections, endocrine, or some metabolic disorders are detected in 75 to 85 percent of affected children (3,4). The vast majority of stones in children are the result of one or more metabolic disorders. An increase in lithogenic solutes such as calcium, oxalate, uric acid, and cystine in the urine and/or a decrease in factors that inhibit stone formation, such as citrate, magnesium, and pyrophosphate, lead to urinary system stones (5-7).

This study aimed to evaluate the clinical, demographic and radiological findings of children diagnosed with urinary system stones in our center and to determine the metabolic causes that cause stones

MATERIAL AND METHODS

The study retrospectively examined the records of 122 children aged 0-18 referred to our pediatric nephrology clinic for various reasons between February 2018 and December 2023. This study was approved by the Local Ethics Committee (decision no: 114, date: 25.01.2024). It was carried out under the principles of the current Declaration of Helsinki and the principles of good clinical practice. The patient's age, gender, age at diagnosis, complaints, and symptoms at presentation, family history of stones, physical examination findings, medications radiological and laboratory findings were obtained from hospital records. Those with endocrine or metabolic disorders were excluded.

During the application period, the urinary system was evaluated by ultrasonography or plain abdominal radiography, which evaluated the location, size, and any anatomical problems of the stone. Stones >3mm in size were defined as urolithiasis, and hyperechoic structures ≤3mm in diameter in the renal calyces were defined as microlithiasis.

To determine the cause of stones, blood urea nitrogen (BUN), creatinine (Cr), sodium (Na), potassium (K), chlorine (Cl), calcium (Ca), phosphorus (P), magnesium (Mg), uric acid, Parathormone, vitamin D, venous blood gases, complete urine analysis and urine culture results were examined. To determine metabolic risk factors that may predispose to stone development, calcium, uric acid, oxalate, cystine, citrate, magnesium, and creatinine levels in spot urine were evaluated and recorded. The metabolites studied from the spot urine sample were standardized by dividing by the urine creatinine level. The results were evaluated according to the values previously stated in the literature (3,8).

Statistical Analysis

Statistical analyses of the study were performed with the Statistical Package for Social Sciences (SPSS), version 26.0 for Windows (SPSS Inc. Chicago, USA) computer package program. Compliance of continuous variables with normal distribution was evaluated using Kolmogorov-Smirnov/ Shapiro-Wilk tests. Variables with normal distribution were given as mean±standard deviation (SD), and variables without normal distribution were given as median (minimum-maximum). Frequency variables were expressed as number (n) and percentage (%). The statistical significance level was accepted as $P<0.05$.

RESULTS

Of the 122 patients who underwent metabolic analysis with the diagnosis of urinary system stone disease, 51.6% (n=63) were male, and 48.4% (n=59) were female, and it was determined that there was no gender difference between the patients ($p>0.05$). The average age at first detection of the stone was 4.40±4.16 years, the age distribution was 1 month-17 years, and the average age of the study period was 5.44 ± 4 years.

Table 1 presents the patients' demographic characteristics and admission findings. Most of the patients (61.4%) had a family history of kidney stones. The most common reason for admission (47.5%) was abdominal/flank pain or restlessness. While restlessness was the most common reason for admission in patients aged five and younger, it was abdominal and/or side pain in patients older than five

years. Urinary system stones were detected incidentally in 11 patients (9%) who had no symptoms suggestive of stones.

In 25.4% of the patients, the stones were ≤3 mm (microlithiasis), and most stones were in the upper system (Table 2). It was determined that there was a significant relationship between stone size and admission findings, such as hematuria and urinary tract infection ($p<0.05$). It was determined that 68.9% (n=84) of the patients had one stone in their urinary system, and 31.1% (n=38) had more than one stone. In our study, mild biochemical abnormalities were detected in a few patients. Three patients (2.5%) had mild hypercalcemia, two patients (1.6%) had mild metabolic acidosis, and one patient (0.8%) had mild metabolic alkalosis. Metabolic disorder was detected in the urine examination of 58.2% of all patients (n=71)(Table 3). While a single metabolic disorder was detected in 65 patients, six patients had more than one metabolic disorder. The most common metabolic cause in our patients was hypercalciuria (20.5%), the second most common was hypocitraturia (17.2%), followed by hyperoxaluria, hyperuricosuria, cystinuria, and hypomagnesuria, respectively.

With medical treatments in addition to adequate fluid intake and salt reduction, the stones in approximately 74.6% (91/122) of the patients shrank or disappeared completely, and the size of 17.2% did not change (Table 4). Stone sizes at the first diagnosis period in patients whose stones disappeared or decreased in size were smaller than in patients whose stones did not disappear. The most common metabolic disorder in these patients was determined to be hypocitraturia (34.1%).

Extracorporeal shock wave lithotripsy (ESWL) was applied to three patients out of a total of eight patients who developed an increase in stone size and/or obstruction in the urinary system due to stones despite medical monitoring and treatments. Stones were removed surgically in three of the other five patients by endourological methods and in two by percutaneous nephrolithotomy. Calcium oxalate stones were detected in five (62.5%) of eight patients, cystine stones were detected in two (25%), and uric acid stones were detected in one (12.5%) of the eight patients who underwent stone analysis.

Table 1. Demographic characteristics of the patients and admission findings

	Number of patients (n)	Ratio (%)
Male/female	63/59	51.6/48.4
Family history of stones	75	61.4
Age distribution at admission		
<1 year	36	29.5
1-5 years	53	43.5
5-10 years	21	17.2
>10 years	12	9.8
Admission findings		
Abdominal/flank pain/ restlessness	58	47.5
Urinary tract infection	24	19.7
Vomiting	15	12.3
Hematuria	14	11.5
Incidental	11	9.0

Table 2. Radiological findings of patients

	Number of patients (n)	Ratio (%)
Size of stone		
≤3 mm	31	25.4
>3 mm	91	74.6
Location of the stone		
Left kidney	40	32.8
Right kidney	33	27.0
Both kidneys	29	23.8
Ureter	12	9.8
Kidney and ureter	8	6.6
Urinary system anomaly		
Hydronephrosis	11	9.0
Horseshoe kidney	1	0.8
Ectopic kidney	1	0.8
Ureterocele	1	0.8

Table 3. Urinary metabolic abnormalities in patients

	Number of patients (n)	Ratio (%)
Patients with metabolic abnormalities	71	58.2
Single metabolic abnormality	65	53.3
Hypercalciuria	25	20.5
Hypocitraturia	21	17.2
Hyperoxaluria	10	8.2
Hyperuricosuria	6	4.9
Cystinuria	2	1.6
Hypomagnesiuria	1	0.8
Multiple metabolic abnormality	6	4.9
Hypercalciuria + Hyperuricosuria	3	2.5
Hypercalciuria + Hypocitraturia	2	1.6
Hypocitraturia + Hyperuricosuria	1	0.8

Table 4. Treatment and follow-up results of patients

Results	Number of patients (n)	Ratio (%)
Patients with no stones detected	68	55.7
Decrease in stone size	23	18.9
Patients whose stone size does not change	21	17.2
Increase in stone size	10	8.2

DISCUSSION

Although urinary system stone disease is relatively less common in children than adults, its frequency has increased in recent years. While a sedentary lifestyle, changing eating habits and inappropriate vitamin use play an important role in this increase, the widespread use of ultrasonography and increased awareness about stones have made diagnosis easier and more frequent (9).

The frequency, etiology, type, content, and location of urinary system stones are associated with geography. The incidence varies worldwide; It is most frequently seen in endemic regions such as Türkiye and Thailand (10). It has been reported that there is a genetic predisposition to the development of urinary system stones and that half of the children with stones have a family history of stones (11). In this study, a family history of stones was found to have a frequency of 61.4%, consistent with the literature.

Urinary system stones are more common in males in adulthood. Male dominance has also been reported in some child studies (12). However, consistent with our study, it is accepted that there is no gender difference in childhood (13,14). In the present study, 51.6% (n=63) of 122 patients were male, and 48.4% (n=59) were female, and there was no statistical gender difference.

Complaints and findings of the patients at admission vary depending on the age of the patient, the location and size of the stone and whether it causes obstruction, the presence of accompanying urinary tract infection (UTI), and the presence of underlying structural or functional genitourinary anomalies (12-15). The most common symptom in children with urinary system stones is flank or abdominal pain. Infants and young children often cannot express the existence, location, and severity of pain and usually present with nonspecific complaints such as restlessness. Apart from pain or restlessness, these patients may experience hematuria, dysuria, urgency symptoms suggestive of UTI, and nausea/vomiting (16). Fifteen to 20% of children with urinary tract stones are asymptomatic, mainly young children whose stones are detected when abdominal imaging is performed for other purposes (17). In our study, 9% of the patients were children whose stones were detected incidentally while examined for another reason. The most common complaints in our remaining patients were abdominal pain, side pain, or restlessness; clinical findings suggestive of urinary tract infection (or history of UTI); nausea/vomiting; and hematuria. The presenting symptoms of our patients were similar to those in previously reported pediatric studies (13,14,18,19).

Twenty to 25% of children with urinary tract stones have a urinary tract infection or a history of infection. Infection may be the primary cause of a stone or may occur along with an underlying urinary metabolic or structural abnormality. Functional or anatomical obstructions of the urinary tract predispose to stasis and infection, possibly encouraging stone formation. Advances in early detection and repair of obstructive uropathies have reduced the incidence of stones due to infections. In this study, one-fifth of the patients had a history of active or previous urinary tract infections at admission, but no one had struvite stones.

Similar to previous studies, our study observed that most urinary system stones (83.6%) were in the upper urinary system (13,14,18,19). None of our patients had bladder stones.

The decrease in the incidence of bladder stones is attributed to changes in eating habits.

In addition to detecting urinary system stones, ultrasonography provides the advantage of anatomical evaluation. In case series of children with urinary tract stones, structural abnormalities (such as hydronephrosis, double collecting system, posterior urethral valve, and bladder anomalies) have been reported in 10 to 25 percent of patients (14,15). Congenital and structural abnormalities accompanied by urinary stasis are associated with kidney stones. Urine stasis paves the way for crystal and stone formation. This study detected structural urinary system anomalies in 14 children (11.4%). Studies from our country reported 3 to 20% of urinary system anomalies (13,14,18).

Most urinary tract stones in children are associated with one or more metabolic disorders. It is important to reveal the underlying metabolic causes in order to apply an effective treatment method. Metabolic studies consist of blood and urine analyses. Hypercalcemia, hyperuric acidemia, high vitamin D, hyperparathyroidism, metabolic acidosis, or alkalosis can be informative in revealing some diseases that may cause urinary system stones. These results guide the diagnosis, diet, and drug treatments of primary diseases (such as renal tubular diseases).

Metabolic etiology in adults is not as common as in children. For this reason, while metabolic evaluation is recommended only for those with recurrent stones in adults, it is recommended when the first stone is detected in children (7,8). The basis of metabolic assessment is measuring the amounts of solutes in the urine that predispose to stone formation. This is calculated by measuring their amounts in 24-hour urine or by the ratio of each solute to creatinine in spot urine and comparing them with normal age (13,14,18,19). In this study, metabolic evaluations were made by spot urine solute/creatinine measurements.

Two mechanisms explain why metabolic factors cause stone formation. First, increased renal excretion of solutes such as calcium, oxalate, uric acid, and cystine or increased urinary concentrations due to low urine volume. This leads to supersaturation and precipitation of the solute, resulting in the formation of crystals that can aggregate into a stone. Second, natural inhibitors of urinary stone formation are scarce, such as citrate, magnesium, and pyrophosphate. Low levels of these inhibitors, especially hypocitraturia, are associated with kidney stones in adults and children. In two case series of children with kidney stones, approximately 90 percent of the patients had at least one metabolic risk factor (7,20). In some studies from our country, Alpay et al. (18) in 87% of patients, Melek et al. (13) in 69.7%, and Taşdemir et al. (14) in 34.8% detected a metabolic cause. Our study found one or more metabolic disorders in 58.2% of the patients.

The most common metabolic abnormality associated with pediatric stone disease is hypercalciuria (21). In most of the studies conducted in our country, hypercalciuria was found to be the most common cause, while in some studies, hypocitraturia was reported more frequently (13,14,18,22). In our study, a single metabolic disorder was detected in 53.3% of the patients, and nearly half of them (20.5%) were hypercalciuria. The rise in excretion of calcium in the urine can be attributed to three mechanisms: increased intestinal absorption (absorptive hypercalciuria), renal tubular calcium reabsorption defect (renal hypercalciuria), and increased bone resorption (resorptive hypercalciuria) (23). Inadequate fluid intake, immobilization, medications such as diuretics and glucocorticoids, excessive vitamin D, and high-salt diets are environmental factors that can cause hypercalciuria.

Other metabolic abnormalities detected in our study were hypocitraturia, hyperoxaluria, hyperuricosuria, cystinuria, and hypomagnesuria, respectively. Citrate is an inhibitor of calcium oxalate and calcium phosphate crystallization. Hypocitraturia is more common in adult patients with idiopathic kidney stones than in children. Although hypocitraturia is mostly idiopathic, a diet rich in animal proteins and low in potassium and plant foods contributes to a decrease in citrate excretion (24).

In our study, hypocitraturia was the second most common cause of stones and was present in 17.2% of the patients. This rate was similar to that of some child studies in our country (19,25). Furthermore, hypocitraturia (34.1%) was the predominant metabolic abnormality observed in our patients whose stones reduced in size or disappeared.

Oxalate, the end product of glyoxylate and ascorbic acid metabolism, is excreted through the kidneys. In our study, hyperoxaluria was the third most frequently detected metabolic disorder. None of our patients had primary hyperoxaluria, which is a genetic-metabolic disease. Idiopathic hyperuricosuria is thought to result from a defect in renal tubular uric acid excretion, and hyperuricosuria is

detected in 2 to 8 percent of children with urinary stones. Although Elmaci et al. (26) and Kara et al. (19) have reported that hyperuricosuria is the most common metabolic disorder in children in our country, the frequency of hyperuricosuria in our study was found to be in line with the frequency reported in the literature. More than one metabolic disorder may occur together in some children with urinary system stones (14,18). In 4.9% of our patients, we have identified more than one metabolic disorder.

As a result, in this retrospective study conducted in children with urinary system stones, there was no gender difference, family history was common, the most common presenting symptom was abdominal/flank pain or restlessness, stones were generally located in the upper urinary system, microlithiasis was found at a considerable rate, anatomical problems could be detected, the most common presenting symptom was abdominal/flank pain or restlessness. It has been determined that the important predisposing factor is a metabolic disorder and that most of the stones shrink and disappear completely with medical treatment.

CONCLUSIONS

Identifying the cause of urinary tract stones and, in particular, detecting underlying metabolic disorders is a major contribution to preventing new stone formation, as well as planning successful diet and pharmacological therapy. We believe it is possible to reduce or eliminate urinary tract stones and prevent their recurrence with early diagnosis of urinary tract stones in children, identification of metabolic disorders, and effective treatment.

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