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ORIGINAL ARTICLE

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Pediatric urolithiasis in Armenia: a study of 198 patients observed from 1991 to 1999

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Abstract To study prospectively the risk factors and etiology of urolithiasis in all stone patients aged <15 years admitted from 1991 to 1999 to the Arabkir hospital in Yerevan. Stones were obtained by surgery (64%), extracorporeal shockwave lithotripsy (ESWL) (7%) or cystoscopic extraction (4%); 25% passed spontaneously. All were examined by infrared spectroscopy, and spot urines were analyzed chemically. 198 patients, 180 (68% males) with renal stones and 18 (83% males) with primary bladder stones, were studied. Calcium oxalate (CaOx) was the predominant constituent in 62% of the kidney stones, followed by struvite (17%), calcium phosphate (7%), uric acid (7%), ammonium acid urate (5%), and cystine (2%). Bladder stones contained CaOx in 72%, uric acid in 22% and ammonium acid urate in 6% of patients. Etiology was obviously metabolic in 5% and possibly metabolic in 26%. Twenty percent of stones were infectious, and 19% were endemic (9% bladder and 10% kidney stones); 4% were secondary to urinary stasis with malformation but no infection. Etiology in 26% remained unknown. Stone composition and metabolic etiology are similar to that in central Europe and North America. In contrast, infectious calculi and particularly endemic stones are still common, although becoming less so now. Urolithiasis in Armenia thus reflects the transition from a rural to an urban society.

Keywords Urolithiasis · Kidney stones · Bladder stones · Armenia · Children

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Introduction

Urolithiasis in the pediatric age group, although occurring less often than in adults, causes considerable morbidity [1–4]. Despite its interest, nearly all pediatric series containing data on stone composition and etiology are small, or data are incomplete. To some extent this may be explained by the considerably lower prevalence of pediatric urolithiasis in the Western world as compared to that in certain areas of the Near or Far East, where it may affect considerably more than 1 in 1000 children at risk [4, 5]. In fact, countries such as Armenia where pediatric urolithiasis is common often lack the necessary infrastructure and resources required for the investigation of urolithiasis in children. Armenia, situated at the intersection of Europe and the Near East, appears attractive for the study of stone formation in children. This country underwent a major transition from a rural to a primarily urban population in Soviet times and has since suffered a major economic crisis.

In order to learn more about the etiology and risk factors of stone formation in pediatric patients, a prospective study was begun in 1991 jointly with the Universities of Bonn (Germany) and Zurich (Switzerland). In this paper we report the results of stone analysis of all 198 pediatric patients seen during a period of 9 years and the presumptive etiologies, based on additional urinary analyses performed in the majority of patients.

Patients and methods

One hundred and ninety-eight children aged 4 months to 15 years with urolithiasis were admitted between 1991 and 1999 to the Arabkir Hospital in Yerevan, which is the national referral center for pediatric urology. It is the only place where children with urolithiasis from the whole of Armenia – a country with an approximate pediatric population of 1 million – are being treated. Five additional patients were excluded from the study because the materials provided were artifacts. The stones were obtained by surgery (64%), extracorporeal shockwave lithotripsy (ESWL) (7%) or cystoscopic extraction (4%); 25% passed spontaneously. Calculi were examined by infrared spectroscopy at the Laboratory of Experimental Urology in Bonn and were classified according to the prevailing constituent exceeding 50% of the whole stone mass examined.

Urine samples from the second (fasting) voiding in the morning were obtained in 179 patients, one in 32, two in 121 and >2 in 26 patients. The samples were transferred into two tubes containing either 0.2 ml 6 M HCl (for oxalate, calcium, citrate and creatinine) or thymol crystals (for pH, uric acid and creatinine). Urine samples were kept frozen until analysis at the Laboratory of Biochemistry of the University Children's Hospital of Zurich, Switzerland. Oxalate and citrate were measured by ion chromatography, calcium with a colorimetric cresolphthalein-complexon method, uric acid by uricase and creatinine by the standard kinetic Jaffé procedure [6]. Interpretation was based on ratios (*x* over creatinine) derived from healthy Swiss children [7–9]. Briefly, the upper limits of normal (mol/mol) used for the age groups 1–3/3–5/5–7 and >7 years were, for calcium 1.4/1.1/0.8/0.7, for oxalate 0.12/0.08/0.07/0.06, for uric acid 1.3/1.1/0.8/0.55, and for citrate (lower limit) 0.12/0.12/0.08/0.08, respectively. If more than one specimen was obtained, the average ratio was used. Ratios exceeding *twice* the upper limits of normal were considered *strongly* abnormal.

Results

Clinical findings

Data from 198 patients with documented urolithiasis were evaluated. In 163 patients (82%), calculi were located in the *upper* urinary tract (in 121 in the kidney and in 42 in the ureter), in 26 patients in the *bladder*, and in 7 in the *urethra.* The origin remained unknown in 2 of the 50 patients with spontaneous stone passage; in the remaining 48 it was the upper urinary tract as evidenced by the clinical and ultrasonographic findings. Bilateral stones were found in 37 patients. In those with unilateral stones, there was a slight preponderance of the right side with 70 (56%) vs 56 (44%) on the left system.

Eighteen of the 26 patients with vesical calculi were considered to have *primary bladder stones* because of the large size (>15 mm in diameter) and the absence of lithiasis or gross anomalies of the upper urinary tract. These 18 patients were considerably younger (median 5.5; range 2–14 years) than those with kidney stones (median 7.8; range 0.4–15 years) (Fig. 1). In fact, 61% were less than 5 years old in contrast to only 29% of those with renal stones. There was a clear male preponderance both in the group of patients with kidney stones (68%) and in the group with primary bladder stones (83%) (Fig. 1). The main symptoms at presentation were abdominal or flank pain (49%), gross hematuria (25%), and dysuria (27%) isolated or in combination. Ten (5%) only presented after spontaneous passage of stones. Minor symptoms (nausea and vomiting) were noted in 6% of children. Urinary tract infections were diagnosed in 37% of all patients.

Stone composition

Calcium oxalate (CaOx) was the predominant constituent of the *kidney stones* in 112 (62%) patients, followed by struvite in 32 (17%), calcium phosphate in 12 (7%), uric acid in 12 (7%), ammonium acid urate in 9 (5%), and cystine in 3 (2%) (Fig. 2). The proportion of CaOx stones increased with age from 50% in patients <5 years and 63% (age 5–10 years) to 73% (10–15 years). Of the 18 *primary bladder stones*, 13 (72%) contained CaOx, 4 (22%) uric acid and 1 (6%) ammonium acid urate.

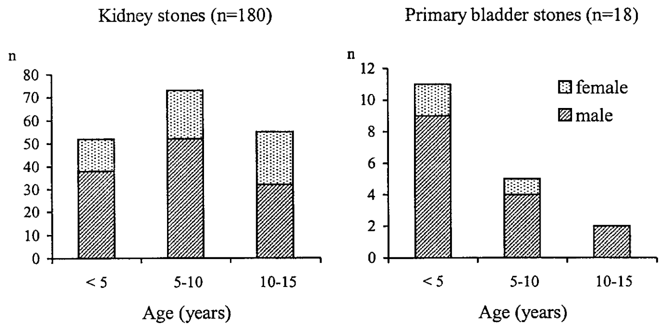

Fig. 1 Age distribution and gender of patients with kidney stones (*left*) and primary bladder stones (*right*). Note different scale

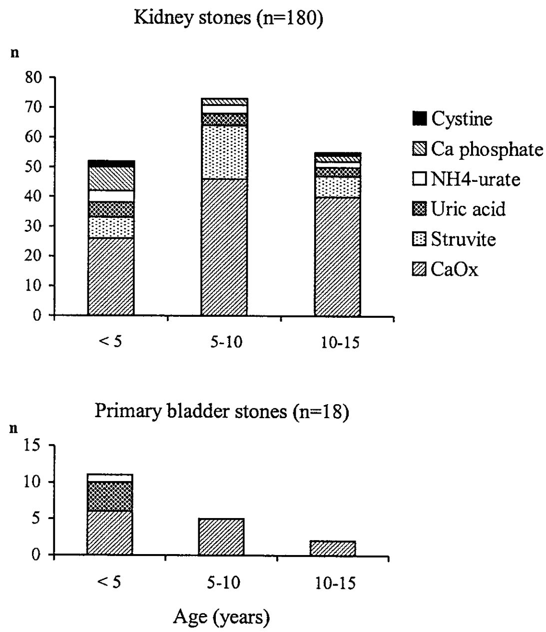

Fig. 2 Stone composition according to age in 180 patients with kidney stones (*upper panel*) and 18 patients with primary bladder stones (*lower panel*)

Etiology

Based on the results of stone and urine analysis, an etiology of urolithiasis was determined in 147 patients (including the 18 patients with endemic bladder stones), whereas in 51 (26%) the cause of stone formation remained unknown (in 13 due to incomplete data) (Fig. 3). An obvious *metabolic* origin (confirmed by 24-h urine collection) was found in ten patients (5%): Six had se-

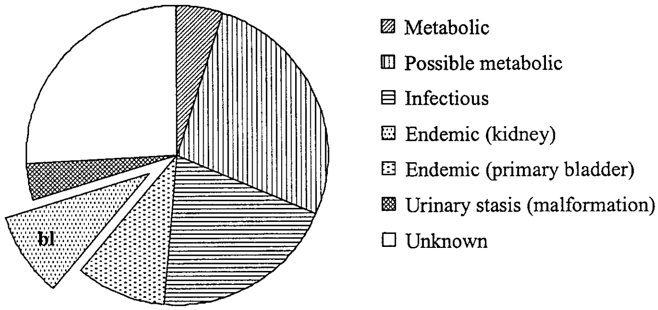

Fig. 3 Etiology of stone formation in 198 pediatric patients with urolithiasis [*bl* primary (endemic) bladder stones]. Stones listed under urinary stasis associated with malformation of the urinary tract were not of infectious origin

vere hypercalciuria based on *strongly* abnormal ratios, three had cystinuria and one had primary hyperoxaluria type 1. In 52 (26%) further patients the CaOx stones were of possible metabolic origin: Eight patients had elevated calcium/creatinine ratios suggesting idiopathic hypercalciuria, 16 had elevated oxalate/creatinine ratios, 12 had low citrate/creatinine ratios and 16 had a combination of these abnormalities (7 hypercalciuria/hyperoxaluria; 2 hypercalciuria/hypocitraturia, 4 hyperoxaluria/hypocitraturia, and 3 patients with all three anomalies).

Infectious stones were found in 40 (20%) of patients. They were composed of struvite in 27 patients, of calcium phosphate in 12, and of ammonium acid urate in 1. The etiology of struvite stones in five additional patients remained unknown as they had no evidence of previous or current urinary tract infection. All five had ultrasonographic findings of urolithiasis and clinical symptoms, i.e., gross hematuria (2), abdominal pain (2), and dysuria (1); three of them passed large amounts of struvite gravel (up to 5 g/week).

Urinary stasis secondary to a urinary tract anomaly in the absence of infection led to formation of stones (all containing CaOx) in eight patients (4%): Three had a three pyeloureteric junction obstruction, two had ectopic kidneys, and one each had posterior urethral valves, vesicoureteric reflux and primary megaureter.

Endemic stones

Nineteen patients (10%) had *kidney* stones considered to be of *endemic* origin based on the following arguments: Eleven had uric acid stones in the absence of hyperuricosuria and eight had ammonium acid urate stones without evidence of a urinary tract infection. The former 11 patients had normal variations of the urinary pH, i.e., no fixed pH <5.8 at the time of the examination. An additional 18 patients (9%) had *primary (i.e., endemic) bladder* stones. The majority of them (13) had calcium oxalate stones: four had slightly abnormal urinary ratios, either for oxalate (2), calcium (1) or citrate (1). The remaining five patients, four with uric acid and one with ammonium acid urate stones, had normal uric acid/creatinine ratios at the time of workup.

Discussion

The prevalence of urolithiasis varies widely among geographic regions [4]. Stones appear to be particularly common in children living in Armenia, and this is one of the largest studies on urolithiasis in the pediatric age group [4]. The well-known male preponderance, especially in the younger age group, has again been confirmed [1, 4, 5, 10–13]. The majority of stones were located in the upper urinary tract (i.e., renal pelvis and ureter). Stones in the present study were still mainly removed by open surgery, as no adequate lithotriptor was available. However, this situation is now changing.

The etiology of pediatric urolithiasis is influenced not only by the geographic area, but also by the extent of workup and the definitions adopted [4]. In contrast to most other studies, classification was based on analysis not only of stones in all, but of urine in the great majority of patients. However, the stone nucleus was not analyzed separately [10]. *Metabolic* abnormalities and infectious stones prevail in most series [1–3, 13, 14]. Contrary to our expectations, metabolic stones were found more frequently than infectious ones. This finding differs from studies in the neighboring countries Turkey and Iran, where infectious stones were seen in 32%–45% [1, 11], or even in the majority of cases [14]. However, metabolic stones prevailed in two recent studies from Turkey [12, 13].

Apart from the obvious metabolic diseases found in a minority (5%) of patients, there were several minor metabolic disturbances such as mild hypercalciuria, hyperoxaluria and hypocitraturia, either isolated or in combination. The relative significance of each of these abnormalities in stone formation is still a matter of debate: although hypercalciuria traditionally has been considered to represent the main risk factor for CaOx-urolithiasis in pediatric patients, as discussed elsewhere [4], there is some evidence that hyperoxaluria and (to a lesser degree) hypocitraturia may be more important [6, 15–17]. Pediatric stone formers in a recent Turkish study had statistically lower urinary citrate excretion than controls [16]. However, the significance of this finding in terms of hypocitraturia is not clear, particularly as the cutoff value chosen for normal daily citrate excretion was set at a very high level (1.67 mmol = 320 mg/1.73 m^2), thus leading to overestimation of this condition. Indeed, 7 of their 24 control children were also classified as hypocitraturic [16]. Although we could not confirm the frequent simultaneous occurrence of hypocitraturia and hyperoxaluria they reported [16], we observed either anomaly more often than hypercalciuria. However, the limits of normal used in our study are not based on children living in Armenia, and we had – with few exceptions – no 24-h urine collections.

Infectious stones, found in 20% of patients, made up the second largest group. It is generally accepted that struvite (i.e., ammonium-magnesium phosphate or triple phosphate) urolithiasis does only occur in the presence of infection by urease producing microorganisms such as *Proteus* species. Interestingly, we observed five patients with struvite stones who had no documented urinary tract infection (however, the possibility of covert infection is not entirely ruled out). The etiology and clinical implication of these findings remain unclear, as there exist no reports on non-infectious struvite stones in men. Accordingly, these five stones were classified as being of unknown origin. The growth of calcium phosphate stones is facilitated by infection and a high urinary pH. All 12 patients indeed had a urinary tract infection, whereas none had evidence for another cause such as immobilization or renal tubular acidosis. However, as stones in half of them contained 10%–20% calcium oxalate, it is likely that these were not primary infectious stones. Although 37% of all patients were considered to have had a urinary tract infection, in fact only 20% had infectious stones. However, not all infections contribute to stone formation, and some patients may have been misdiagnosed because of similar symptoms and urinary findings. This underscores the need for careful investigations in this population.

Urinary tract anomalies with *stasis*, but no infection, leading to CaOx stones accounted for only 4% of urolithiasis, which is less than in other series, with figures up to 30% [11, 13].

Altogether, *endemic stones* (10% originating from the upper urinary tract and 9% from the bladder) constituted an important etiological group. We have used the term endemic (or of dietary origin) for all primary bladder stones and for a subgroup of kidney stones. Indeed, most endemic *renal* stones consisted of uric acid, a constituent rarely found in pediatric patients living in the Western world – in contrast to the situation in adult patients [18]. We were unable to demonstrate hyperuricosuria in any of our patients, based on their normal uric acid/creatinine ratios when compared with those obtained in healthy Swiss children [9]. In contrast, Bedouin children with urolithiasis living in Israel, having a considerably higher prevalence of stone formation than Jewish children living in the same area, showed a higher uric acid excretion index than the Jewish patients [5]. However, stone analysis was available only for a few of them. We assume that in our patients a low and fixed urinary pH at the time of stone formation, coupled with a low urine volume, was the responsible mechanism [4, 19], although this could no longer be demonstrated later on. A similar mechanism (low urinary pH and low fluid intake) has recently been shown to be present in children on a ketogenic diet – who are prone to form stones – with over half of the calculi being composed of uric acid [20]. The pathogenesis of the ammonium acid urate stones – found in eight of our patients with endemic renal stones but rarely seen in children in the Western world in the absence of infection and struvite – is also related to an unbalanced diet that contains little phosphate which leads to a high urinary pH [21].

Primary bladder stones, once very frequent in children [22], have almost disappeared in the developed world, probably as a result of a balanced nutrition [4, 23]. According to studies performed in 1930–1933 in Armenia, the great majority of stones in adults were then located in the bladder (R. Eolian 1930; S. Aydinian 1933; unpublished data); this proportion decreased to 32% in 1973 (A. Egiazarian, dissertation; Yerevan 1973). The same trend is noted in children, as bladder stones accounted for 62% in 1968 (I. Melkumiants, dissertation; Yerevan 1968) versus 9% in the present study. Nevertheless, primary bladder stones still constitute an important group in some regions, accounting for one-fourth to one-third of all pediatric stones in Tunisia [10] and Turkey [12] and for more than half in Cameroon [24] and India [25]. The main bladder stone components were also calcium oxalate [12, 22, 25], uric acid [22] and ammonium acid urate [10, 24].

In 26% of patients the cause of the stone formation remained unknown, sometimes due to incomplete data. This figure is in accordance with other studies [3, 4].

In conclusion, the metabolic risk factors, accounting for nearly one-third of all calculi, and the stone composition were similar to those in the Western world. In contrast, infectious calculi, and particularly the endemic stones were more common, each being found in one-fifth of the patients. However, infectious stones were less frequent than in some neighboring countries, and the endemic stones had considerably decreased in Armenia, as compared to older studies. Thus, urolithiasis in Armenia reflects the transition from a rural to a mainly urban population, with dietary factors and an insufficient fluid intake presumably playing important roles. Last but not least, we think studies like this one, carried out despite considerable logistical problems, are much needed and could serve as examples of successful cooperation between countries that differ greatly in terms of infrastructure and available resources.

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LITERATURE ABSTRACTS

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Hepatitis C virus in blood and dialysate in hemodialysis

Am J Kidney Dis (2001) 37:38–42

The prevalence of hepatitis C virus (HCV) positivity among hemodialysis patients remains high compared with that of the healthy population, and thus the issue of safety and environmental protection must be addressed. The purpose of this study is to evaluate the dynamics of prehemodialysis and posthemodialysis blood HCV levels and HCV escape to spent dialysate. Because heparin has an inhibitory effect on the reverse-transcription polymerase chain reaction (RT-PCR) assay, a serine protease inhibitor (nafamostat mesilate) was used as the anticoagulant for hemodialysis. High-flux polysulfone membrane dialyzers were used; dialyzer reuse was not performed. Multicyclic RT-PCR was performed for the quantitative detection of HCV. To elucidate HCV escape to spent dialysate, a portion of total spent dialysate was continuously extracted in a sterile fashion using a minutely adjusted syringe pump. No HCV extravasation to spent dialysate was found, although HCV copy numbers were reduced to a statistically significant level in postdialysis blood compared with predialysis levels ($P<0.05$; $n=20$). The need to establish standards for risk management in dialysis centers is evident. The data obtained in this study strongly suggest that to minimize the risk for HCV transmission, lower transmembrane pressure (TMP) should be used in the hemodialysis of HCV-positive patients, with fresh polysulfone dialyzers and dialysis settings of 180 to 250 mL/min for blood flow, 500 mL/min for dialysate flow, and less than 18.72 mm Hg for TMP.

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Does a high concentration of calcium in the urine cause an important renal concentrating defect in human subjects?

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The objective of this study was to evaluate the hypothesis that a high concentration of ionized calcium in the lumen of the medullary collecting duct causes an osmole-free water diuresis. The urine flow rate and osmolality were measured in normal human subjects, as well as in patients with a history of nephrolithiasis who excreted more than 5 mmol of calcium per 24 h. There was an inverse relationship between the concentration of calcium in the urine and the 24 h urine volume both in normal subjects and in patients with a history of nephrolithiasis. When the concentration of calcium in the urine was greater than 5 mmol/l, the urine volume was less than 1 litre per day in the majority of subjects. After 16 h of water deprivation, when the concentration of calcium in the urine was as high as 17 mmol/l (ionized calcium 7.4 mmol/l), urine osmolality was 1258 mOsm/kg of water and the urine flow rate was 0.30 ml/min. We conclude that, although a calcium receptor may be present in the lumen of the medullary collecting duct in human subjects, an extremely high concentration of urinary total and ionized calcium does not cause a clinically important defect in the renal concentrating process.