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Original Article

Composition of urinary tract stones formed by children in two populations in the Uyghur region of China

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Abstract

Background: To retrospectively compare the composition of urinary tract stones formed by Uyghur children from the southern (Kashgar) and northern (Urumchi) parts of the Xinjiang region.

Methods: The chemical composition of urinary tract calculi formed by 855 Uyghur children from the two regions in Xinjiang (366 Kashgar and 489 Urumchi) was compared retrospectively. Stone composition was determined by infrared spectroscopy. Factors that might have been of relevance for the findings such as age, gender, stone location and geographic region were also considered.

Results: Kashgar children were younger than Urumchi children (2.8 ± 2.7 vs. 4.3 ± 3.7 years, $p < 0.001$). Although ammonium urate was the dominant stone component in the whole population, calcium oxalate was most common in children from Urumchi. The mean occurrence of ammonium urate, calcium oxalate and uric acid differed significantly between stones formed by Kashgar and Urumchi children (52.5% vs. 29.2%, 18.9% vs. 29.4%, 12.3% vs. 20.9%; respectively, $p < 0.001$). Renal stones were less frequently recorded in Kashgar children than in Urumchi children (65.8% vs. 91.6%, $p < 0.001$). Interestingly, bladder stones were more common in children from Kashgar (28.4% vs. 3.7%; $p < 0.001$).

Conclusion: Uyghur children from the southern part of Xinjiang apparently had a more serious form of stone disease than children from the northern part and the occurrence of stones dominated by ammonium urate stones was extremely high in children from the southern part of the region.

Keywords: Ammonium urate; Pediatrics; Stone composition; Urolithiasis

1. Introduction

Urinary tract stone formation is a common pathological condition afflicting the population worldwide. Previously published reports have shown that stone disease is particularly common in the Xinjiang Uyghur Autonomous Region, which is located at the northwest border of China,[1−4] far away from the sea. This is a region suffering from long annual periods of sunshine with little precipitation.[5,6] The people in Uyghur

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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lives in a particular cultural and geographical environment, with special dietary habits and life style.[2] Urinary tract stone disease comprises is a significant health problem for the children in this part of China.[3] The youngest children afflicted by urolithiasis in this region were only 3 months old[4] and the growth and health of these children are seriously affected by this pathology. The causes of the high prevalence of stone formation in Xinjiang Uyghur children are, however, complex and poorly understood. Environmental factors, age, dietary habits, metabolic disorders, and socioeconomic conditions are acknowledged as a nexus to the frequent occurrence of urolithiasis.[7−9]

Accurate analysis of stone composition plays a critical role for identification of possible risk factors and for decision on how to design recurrence prevention and treatment of these children. Previous reports have shown that stone composition was different in both children and adults, when Uyghur and Han patients were compared.[4,10] There is, however, a paucity of reports dealing with urinary stone composition in Uyghur children from Xinjiang. A retrospective study was therefore carried out with the aim of comparing stone composition between children from the southern (Kashgar) and northern (Urumchi) parts of Uyghur in Xinjiang. Attempts were made to relate the findings of stone composition to etiological factors such as metabolic abnormalities and with the ultimate goal to formulate a proper strategy for stone treatment and recurrence prevention.

2. Methods

The chemical composition of stones formed by Uyghur children younger than 13 years old, between March 2009 and October 2016, were retrospective reviewed. The data were available from two institutions: the First people's Hospital of Kashgar Erea, localized in Kashgar, southern part of Xinjiang and the First teaching hospital of Xinjiang Medical University, localized in Urumchi, northern part of Xinjiang. These two regions were considered representative of the northern and southern parts of Xinjiang. The geographic difference between the two regions is determined by the Tianshan Mountains. The average annual temperature of northern Xinjiang is < 10 °C, with annual precipitation of ~150−270 mm. Southern Xinjiang suffers from a much drier climate. The annual temperature is ~10−13 °C, with an annual rainfall of only ~40−80 mm.[5,10]

The stones either had passed spontaneously, been removed by shock wave lithotripsy, endoscopic or open surgery. Patients were excluded from the study if information on age, gender, stone location, or stone composition were missing. Stone composition was analyzed by infrared spectroscopy. Stones were classified according to the predominant stone component recorded. Stone specimens were first dried after which approximately 1 mg of the sample was evenly mixed with 200 mg of potassium bromide, powdered, compressed into a small tablet and scanned by Fourier transform infrared spectroscopy.[4] According to the principles of classification of stone components recommended in the European Association of Urology guidelines,[11] calcium oxalate (CaOx), calcium phosphate (CaP) and uric acid (UA) were classified as non-infection stones. Stones composed of ammonium urate (AUU), magnesium ammonium phosphate (MAP) and/or carbonate apatite (CA) were classified as infection stones. In view of the rarity of cystine in Xinjiang children,[4] such stones were referred to as "other stone component" together with xanthine, 2,8-dihydroxyadenine and other substances. The children were divided into three age groups: age < 3 years old (age level 1), 3 ≤ age < 7 years old (age level 2), and 7 ≤ age < 13 years old (age level 3).

Continuous variables were expressed as means ± standard deviation (SD). Categorical variables were recorded as frequency and percentage. Independent-sample Student's t-test and Chi-square test were used for group comparison. A *p*-value less than 0.05 was considered statistically significant. The whole statistical analysis was conducted by using SPSS 16.0.

3. Results

Information on stone composition was available for 855 Uyghur children including 366 (42.8%) from Kashgar and 489 (57.2%) from Urumchi. There were 591 (69.1%) male and 264 (30.9%) female children with a mean age of 3.5 ± 3.9 years, ranging between 2 months and 12 years. AUU (39.2%) was the dominating component for the majority of stones formed by children in the Uyghur region. Following stratification of stone composition according to the children's age, both the proportion of CaOx and the kidney stone, respectively, increased with age ($p < 0.001$). In contrast, the percentage of AUU, UA and bladder stones decreased ($p < 0.001$). The characteristics of stone composition for all Uyghur children are presented in Table 1.

In the further evaluation findings were compared between the Kashgar and Urumchi children (Table 2). Kashgar children

Table 1
Characteristics of Uyghur children with urinary tract stone.

Characteristics	Total	Age level 1	Age level 2	Age level 3
Number (%)	855	461 (53.9)	237 (27.7)	157 (18.4)
Mean age, (years)	3.5 ± 3.9	1.2 ± 0.5	4.0 ± 1.2	9.8 ± 1.7
Sex, n (%)				
Males	591 (69.1)	327 (70.9)	165 (69.6)	99 (63.1)
Females	264 (30.9)	134 (29.1)	72 (30.4)	58 (36.9)
Component, n (%)				
CaOx[a]	213 (24.9)	56 (12.2)	76 (32.1)	81 (51.6)
CaP	70 (8.2)	40 (8.7)	13 (5.5)	17 (10.8)
MAP	63 (7.4)	36 (7.8)	17 (7.2)	10 (6.4)
AUU[a]	335 (39.2)	213 (46.2)	93 (39.2)	29 (18.5)
CA	14 (1.6)	8 (1.7)	6 (2.5)	0
UA[a]	147 (17.2)	100 (21.7)	30 (12.7)	17 (10.8)
Others	13 (1.5)	8 (1.7)	2 (0.8)	3 (1.9)
Stone location, n (%)				
Kidney[a]	689 (80.6)	347 (75.3)	201 (84.8)	141 (89.8)
Ureter	44 (5.2)	27 (5.9)	12 (5.1)	5 (3.2)
Bladder[a]	122 (14.3)	87 (18.9)	24 (10.1)	11 (7.0)

CaOx = calcium oxalate; CaP = calcium phosphate; MAP = magnesium ammonium phosphate; AUU = ammonium urate; CA = carbonate apatite; UA = uric acid.

[a] $p < 0.001$ by χ^2 test.

Table 2
Characteristics in pediatric urolithiasis children from the Kashgar and Urumchi.

Characteristics	Kashgar (n = 366)	Urumchi (n = 489)	*p*
Mean age, (years)	2.8 ± 2.7	4.3 ± 3.7	<0.001
Range, (years)	0.25–12	0.17–12	
Sex, n (%)			
Males	260 (71.0)	331 (67.7)	0.294
Females	106 (29.0)	158 (32.3)	
Age groups, n (%)			
Age level 1	234 (63.9)	227 (46.4)	<0.001
Age level 2	96 (26.2)	141 (28.8)	0.400
Age level 3	36 (9.8)	121 (24.7)	<0.001
Component, n (%)			
CaOx	69 (18.9)	144 (29.4)	<0.001
CaP	33 (9.0)	37 (7.6)	0.444
MAP	20 (5.5)	43 (8.8)	0.065
AUU	192 (52.5)	143 (29.2)	<0.001
CA	4 (1.1)	10 (2.0)	0.278
UA	45 (12.3)	102 (20.9)	0.001
Others	3 (0.8)	10 (2.0)	0.147
Stone location, n (%)			
Kidney	241 (65.8)	448 (91.6)	<0.001
Ureter	21 (5.7)	23 (4.7)	0.412
Bladder	104 (28.4)	18 (3.7)	<0.001

CaOx = calcium oxalate; CaP = calcium phosphate; MAP = magnesium ammonium phosphate; AUU = ammonium urate; CA = carbonate apatite; UA = uric acid.

were significantly younger than that of Urumchi children (2.8 ± 2.7 vs. 4.3 ± 3.7 years; $p < 0.001$). The highest percentage of children in both Kashgar and Urumchi were recorded at age level 1. Moreover, the percentage of Kashgar children at the age level 1 was markedly higher than that of Urumchi children (63.9% vs. 46.4%; $p < 0.001$). A significantly lower percentage of Kashgar than Urumchi children was observed at age level 3 (9.8% vs. 24.7%; $p < 0.001$). The majority of Kashgar children had stones composed of AUU (52.5%). However, CaOx (29.4%) was the most common stone component for Urumchi children. The percentage of AUU was significantly higher for Kashgar children (52.5% vs. 29.2%; $p < 0.001$), while the percentage of CaOx and UA was higher in stones formed by Urumchi children (CaOx, 18.9% vs. 29.4%, $p < 0.001$; UA, 12.3% vs. 20.9%, $p = 0.001$). Although most stones were located in the kidney in both groups, the percentage was lower in Kashgar than in Urumchi children (65.8% vs. 91.6%; $p < 0.001$). The percentage of bladder stone was significantly higher in the Kashgar group (28.4% vs. 3.7%; $p < 0.001$).

When the children from Kashgar and Urumchi were further stratified according to stone composition and age (Table 3), the results showed that AUU was the major stone component at age levels 1 (55.6%) and 2 (53.1%) in Kashgar children, while CaOx (41.7%) was the most common stone type at age level 3. Moreover, CaOx was the major stone component at age levels 2 (35.5%) and 3 (54.5%) in Urumchi children, whereas AUU (36.6%) was the major component at age level 1.

Although the percentage of AUU decreased with age in both groups (Fig. 1; Kashgar children, $p = 0.018$; Urumchi children, $p < 0.001$), the prevalence of AUU was higher in Kashgar children than in Urumchi children irrespective of age. In contrast, CaOx stones showed an opposite trend with increased percentage in older children (Fig. 1; Kashgar, $p < 0.001$; Urumchi, $p < 0.001$).

The Kashgar group had a higher percentage of bladder stone than the Urumchi group at age level 1 (34.2% vs. 3.1%; $p < 0.001$) and age level 2 (19.8% vs. 3.5%, $p < 0.001$). To the contrary, renal stones were less common in Kashgar children than the Urumchi children of corresponding age groups 59.4% vs. 91.6%, respectively at age level 1 ($p < 0.001$) and 76.0% vs. 90.8%, respectively ($p = 0.002$) at age level 2 (Table 3). Interestingly, Kashgar children showed a downward trend in occurrence of bladder stones with age (Fig. 2, $p = 0.001$) but

Table 3
Characteristics in pediatric urolithiasis children from the Kashgar and Urumchi according to age.

Characteristics	Age level 1		*p*	Age level 2		*p*	Age level 3		*p*
	Kashgar (n = 234)	Urumchi (n = 227)		Kashgar (n = 96)	Urumchi (n = 141)		Kashgar (n = 36)	Urumchi (n = 121)	
Mean age, (years)	1.2 ± 0.5	1.3 ± 0.5	0.276	4.1 ± 1.2	4.2 ± 1.2	0.476	9.3 ± 1.8	10.0 ± 1.6	0.027
Sex, n (%)									
Males	171 (73.1)	156 (68.7)	0.303	68 (70.8)	97 (68.8)	0.738	21 (58.3)	78 (64.5)	0.504
Females	63 (26.9)	71 (31.3)		28 (29.2)	44 (31.2)		15 (41.7)	43 (35.5)	
Component, n (%)									
CaOx	28 (12.0)	28 (12.3)	0.903	26 (27.1)	50 (35.5)	0.175	15 (41.7)	66 (54.5)	0.175
CaP	22 (9.4)	18 (7.9)	0.575	5 (5.2)	8 (5.7)	0.877	6 (16.7)	11 (9.1)	0.330
MAP	13 (5.6)	23 (10.1)	0.830	6 (6.2)	11 (7.8)	0.650	1 (2.8)	9 (7.4)	0.538
AUU	130 (55.6)	83 (36.6)	<0.001	51 (53.1)	42 (29.8)	<0.001	11 (30.6)	18 (14.9)	0.033
CA	3 (1.3)	5 (2.2)	0.689	1 (1)	5 (3.5)	0.433	0	0	1.000
UA	35 (15.0)	65 (28.6)	<0.001	7 (7.3)	23 (16.3)	0.040	3 (8.3)	14 (11.6)	0.808
Others	3 (1.3)	5 (2.2)	0.689	0	2 (1.4)	0.516	0	3 (2.5)	1.000
Stone location, n (%)									
Kidney	139 (59.4)	208 (91.6)	<0.001	73 (76.0)	128 (90.8)	0.002	29 (80.6)	112 (92.6)	0.760
Ureter	15 (6.4)	12 (5.3)	0.607	4 (4.2)	8 (5.7)	0.828	2 (5.6)	3 (2.5)	0.702
Bladder	80 (34.2)	7 (3.1)	<0.001	19 (19.8)	5 (3.5)	<0.001	5 (13.9)	6 (5.0)	0.141

CaOx = calcium oxalate; CaP = calcium phosphate; MAP = magnesium ammonium phosphate; AUU = ammonium urate; CA = carbonate apatite; UA = uric acid.

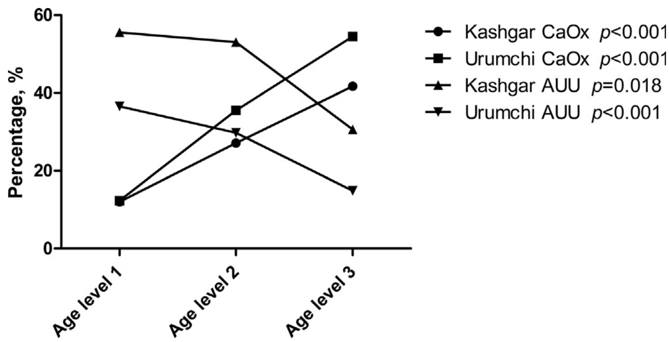

Fig. 1. Association of age distribution with stone composition. CaOx: calcium oxalate, AUU: ammonium urate.

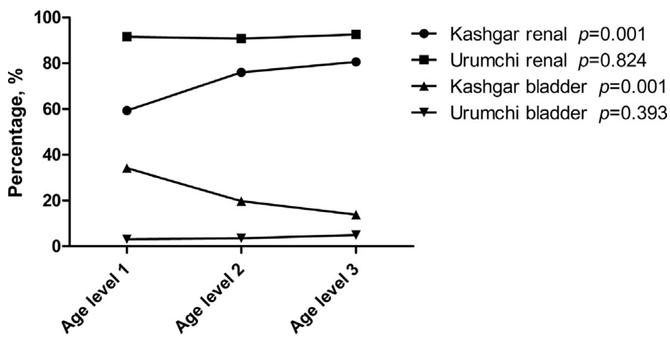

Fig. 2. Association of age distribution with stone site.

an upward trend in stones located in the kidney (Fig. 2, $p = 0.001$). A corresponding observation was not made for Urumchi children.

When the children from Kashgar and Urumchi were stratified according to stone composition and stone locations, the AUU composition of both renal stone and bladder stone in Kashgar group were significantly higher than Urumchi group (53.1% vs. 29.2%, 52.9% vs. 16.7%; respectively, $p < 0.01$), while both the CaOx and UA composition of renal stone were lower (17.4% vs. 29.0%, 11.2% vs. 21.0%; respectively, $p < 0.01$), which was shown in Table 4.

4. Discussion

The prevalence of urinary tract stone disease is so high in Xinjiang that it is necessary or at least highly desirable to reduce the potential risk of this pathology and to come up with some strategy for effective recurrence prevention. However, to the best of our knowledge, reports rarely have focused on regional differences in terms of composition of stones formed by children from Xinjiang. In this study, we retrospectively reviewed the data of Uyghur pediatric urolithiasis from the Kashgar and Urumchi parts of Xinjiang. The observations disclosed significant differences between children from the two regions. There are well recognized differences in economic conditions, geographical environment, diet and lifestyle between the two districts Kashgar and Urumchi of Xinjiang. Results from our study showed that Kashgar children with urolithiasis were younger than those from Urumchi. Moreover, the proportions of AUU and bladder stones were significantly more common in Kashgar children. There is, however, no clear explanation of the fundamental differences between the two regions and further investigations seem important in order to increase the understanding of the pathology with the aim of formulating an appropriate stone preventive strategy.

Age is one basic feature for understanding the epidemiology of a disease and in the present study, results indicated that stones in Xinjiang children were most frequent at an age below 3 years in both the Kashgar and Urumchi regions. This observation was similar to that previously recorded by Wang et al.[2] According to their report, the largest percentage of children with stone disease in Uyghur was observed in children with an age between 1 and 3 years. These authors argued that a potential cause might be a disturbed balance between dietary demand and growth that occurred after the period of lactation.[2] Cillo et al.[12] observed higher urinary excretion of calcium, oxalate, and urate in artificially than in breastfed infants. Co-incidentally, panada, a characteristic diet in Xinjiang,[13] was frequently given to Uyghur infants as an artificial food, particularly common for Kashgar children. Moreover, Uyghur infants were normally fed with dairy milk.[2] Calcium, phosphate, and other minerals occur at higher concentrations in cow milk than in human milk. Accordingly it might be difficult for infants to tolerate these milk components. Excessive and long-term intake of dairy milk might thus result in increased absorption of calcium and phosphate,[14] leading to an imbalance in calcium and phosphate metabolism. Such an imbalance can promote the development of urolithiasis in infants.

Table 4
Distribution of stone composition in different stone location.

Characteristics	Renal stone (n = 689)		*p*	Ureteral calculi (n = 44)		*p*	Bladder stone (n = 122)		*p*
	Kashgar (n = 241)	Urumchi (n = 448)		Kashgar (n = 21)	Urumchi (n = 23)		Kashgar (n = 104)	Urumchi (n = 18)	
Component, n (%)									
CaOx	42 (17.4)	130 (29.0)	0.001	5 (23.8)	6 (26.1)	0.862	22 (21.2)	8 (44.4)	0.068
CaP	24 (10.0)	37 (8.3)	0.454	3 (14.3)	0	0.201	6 (5.8)	0	0.590
MAP	17 (7.1)	40 (8.9)	0.394	0	1 (4.3)	1.000	3 (2.9)	2 (11.1)	0.157
AUU	128 (53.1)	131 (29.2)	<0.001	9 (42.9)	9 (39.1)	0.802	55 (52.9)	3 (16.7)	0.004
CA	2 (0.8)	8 (1.8)	0.505	0	1 (4.3)	1.000	2 (1.9)	1 (5.6)	0.383
UA	27 (11.2)	94 (21.0)	0.001	2 (9.5)	6 (26.1)	0.302	16 (15.4)	2 (11.1)	0.843
Others	1 (0.4)	8 (1.8)	0.246	2 (9.5)	0	0.222	0	2 (11.1)	0.021

CaOx = calcium oxalate; CaP = calcium phosphate; MAP = magnesium ammonium phosphate; AUU = ammonium urate; CA = carbonate apatite; UA = uric acid.

AUU was the most common stone composition in children from Kashgar. Although CaOx, similar to a previous report,[4] was the main component of stones formed by Urumchi children, results showed that AUU stones were most frequent at age level 1 in Urumchi children. This finding is in accordance with observations made by Alaya et al.[15] These authors showed that the proportion of AUU stones was higher in younger children in Tunisia. It is of note that the composition of stones formed by Uyghur children was significantly different from that recorded in Han children in China, who had formed stones mainly comprising CaOx.[4,16] Furthermore, the average age of Uyghur children with urolithiasis was younger than the Han children.[4] This observation indicates a specific severity of stone disease in Uyghur children.

The formation of AUU occurs in hyperuricosuria and ammonium-enriched urine.[17,18] The etiology of hyperuricosuria is mainly related to the intake of purine rich food, low fluid intake, loss of water and a diet with a high acid load.[19] A diet with a high content of protein and purine-rich food stuffs such as animal offal, beef, mutton and pickled products are common components of the Uyghur diet.[3] This kind of diet is likely to increase the excretion of urinary calcium, oxalate and urate, and to decrease the excretion of citrate.[20] Moreover, Uyghur women preferred high-protein food stuffs rather than fruits and vegetables during pregnancy and lactation. The same supplementary diet was also used for infants.[3] Furthermore, Kashgar is a much poorer district than Urumchi. Kashgar children may suffer from a more imbalanced diet with insufficient quantities of proteins and phosphate due to the barely satisfactory economy. A diet deficient in milk and rich in cereals given to children in the underdeveloped areas is acidic and has a low concentration of phosphate, which is closely linked to endemic lithiasis, especially the occurrence of bladder stone.[17,21] Another cause for ammonium-enriched urine is infection, low fluid intake, small urine volume and hypophosphatemia.[17] The insufficient supply of drinking water[5,6] and poor sanitary conditions in Xinjiang is likely to increase the occurrence of infection. Though information on infection was not available for the group that were studied, Wumaner et al.[3] showed that the percentage of urinary tract infections reached a level of 42.3% in Uyghur children with urolithiasis. Also, groundwater in Xinjiang is generally hard, fresh to brackish, high in saline and with a low content of alkali.[22] These factors indicate how important groundwater quality is for living and drinking.

The age of onset of stone formation was lower in Kashgar children than in Urumchi children. This phenomenon was closely linked to the problematic environment of southern Xinjiang, with the dry climate and poor living conditions. As stated above the annual temperature is ~10−13 °C, with annual rainfall of not more than ~40−80 mm.[5,10] Additionally, southern Xinjiang is subjected to much more weather problems. Periods of drought, sand storms, cold spells and hot-arid winds are examples of weather conditions that cause difficult living conditions for the residents and give rise to huge economic damage. Children living in this environment suffer from a sustained state of dehydration, exhibit less urine production, contributing to highly concentrated urine with increased risk of crystallization and stone formation. In addition, synthesis of vitamin D is promoted by more sunshine, a situation that leads to increased absorption of calcium.[23,24]

According to EAU guideline,[25] pediatric bladder stones are the common problems in underdeveloped areas of the world and are usually AUU and UA stones, strongly implicating dietary factors. The higher occurrence of bladder stones in Kashgar children compared with that in Urumchi children is most likely an effect of poor socioeconomic conditions. A large proportion of the Kashgar population subsists on a monotonous diet of panada, a diet that mainly comprises wheat flour. This kind of panada also is a substitute or given as supplementary food to the infants. Ansari et al.[26] showed that such a diet pattern with meals composed of excessive quantities of cereals and insufficient quantities of protein, lays the ground for development of bladder stones.

There are several limitations of this report regardless of the sizable sample. This study lacked baseline characteristics of the children such as diet and urine composition. There was no information on urinary tract infection. Therefore, the outcomes only reflect superficial information and the results are of course not sufficient to prove the stone etiology. Nevertheless, the observations are unique in as much as they compare two different populations of stone forming children in Xinjiang Uyghur.

This is the first study that compares differences in urinary stone composition between Kashgar and Urumchi children from Xinjiang, China. Significant differences of stone characteristics between these two regions were observed. Kashgar children obviously suffer from a more serious stone disease than Urumchi children.

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