Management of urolithiasis associated with tuberous sclerosis complex

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Abstract

The most common renal symptoms of tuberous sclerosis complex (TSC) are angiomyolipomas (AMLs) and renal cysts; however, some patients with TSC also develop urolithiasis. In this study, we evaluated the incidence, risk factors and clinical courses of TSC-associated urolithiasis. We analyzed a total of 102 patients who met the diagnostic criteria for TSC, of whom 15 (14.7%) had urolithiasis. We compared urinary specific gravity, urine pH, serum calcium, intact parathyroid hormone and the use of antiepileptic agents of the urolithiasis and non-urolithiasis groups. The urine specific gravity and urine pH were higher in the urolithiasis group than in the non-urolithiasis group ($P = 0.005$, $P = 0.042$, respectively). No significant difference was found between the two groups with regard to the serum corrected calcium and intact parathyroid hormone levels. The antiepileptic drugs topiramate and zonisamide were more frequently administered to the urolithiasis group than the non-urolithiasis group ($P < 0.001$, $P = 0.039$, respectively). Four patients in the urolithiasis group underwent surgery. Three patients could not receive extracorporeal shock wave lithotripsy due to the risk of bleeding from the AML, and therefore underwent transurethral lithotripsy. If urolithiasis is comorbid with TSC-associated AML, the treatment options are more limited in cases with multiple AMLs around the stone due to an increased risk of hemorrhage. Prevention and early detection of urolithiasis are beneficial to patients with TSC.

Background

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder in which hamartomas develop throughout the body, and is associated with various organ disorders¹. TSC arises from a mutation of either the *TSC1* gene on chromosome 9 or the *TSC2* gene on chromosome 16, which encode hamartin and tuberin, respectively^{2,3}. Anomalies in the *TSC1* and *TSC2* genes, which are important regulators of the mammalian target of rapamycin pathway, results in the development of benign and/or malignant tumors in multiple organs⁴. In Japan, the incidence of TSC is estimated to be one in 7,000–10,000 persons, and the total number of patients is estimated to be 15,000, which is equivalent to the frequency in the US⁵. The number of TSC patients without symptoms is increasing⁶.

The most common renal manifestations of TSC are angiomyolipomas (AMLs), which are observed in up to 80% of the patients⁷. Renal cysts are another frequent kidney lesion in TSC, and are observed in 14–32% of the patients; however, the incidence of urolithiasis in TSC is unknown⁸. Since both urolithiasis and rupture of renal AML cause severe pain and hematuria, discrimination between them is very important for the management of TSC. However, there have been few reports on urolithiasis associated with TSC. Furthermore, carbonic anhydrase inhibitors such as topiramate and zonisamide are commonly used as a treatment for epilepsy, and these drugs can induce metabolic acidosis in some patients. It has been reported that long-standing metabolic acidosis promotes urolithiasis⁹. In the present study, we retrospectively investigated the incidence, risk factors and treatment of urolithiasis associated with TSC.

Methods

Patients and study design

TSC was diagnosed according to the ITSCCG diagnostic criteria after consultations with an internist and a dermatologist. Of the 102 patients who met the diagnostic criteria, 15 had urolithiasis on CT examination. Eighty-seven patients without urolithiasis were used as controls. The CT apparatus was used the Optima CT660 (GE Healthcare, Tokyo, Japan). The CT settings were as follows: scanning time, 0.7 seconds/rotation; tube voltage, 120 kV; tube current, automatic exposure control; slice thickness, 3.75 mm; reconstruction clearance, 3.75 mm. All images were evaluated by specialists in diagnostic radiology.

Urine specific gravity, urine pH, serum calcium, and intact parathyroid hormone were analyzed in the urolithiasis and non-urolithiasis groups. A BioMajesty JCA-BM6070 biochemical analyzer (JEOL, Tokyo, Japan) was used for the analysis. When the serum albumin level was ≤ 4 mg/dL, the serum calcium levels were corrected using the formula: $\text{calcium} + (4 - \text{“serum albumin”})$, and designated as corrected calcium.

In the urolithiasis group, the stone size, location, and treatment were analyzed. The information on the treatment status of epileptic seizures and the use of antiepileptic agents of all patients was obtained by interviews. This study was approved by the ethics committee of JR Tokyo General Hospital. All patients gave informed consent.

Exclusion Criteria

The following patients were excluded: those with poor respiratory conditions as a result of lung lymphangioleiomyomatosis, those with swallowing disorders, pregnant patients, and those taking vitamin D3 or calcium.

Statistical analyses

Patient characteristics and laboratory findings were assessed using Student's *t*-test or the Wilcoxon signed-rank test. *P* values of <0.05 were considered to indicate statistical significance.

Results

Patient characteristics

We analyzed a total of 102 patients with TSC, 15 of whom (14.7%) had urolithiasis (Table 1). No significant differences in age or sex were found between the two groups. The incidence of mental retardation in the urolithiasis group was higher than in the non-urolithiasis group ($P = 0.048$). Epileptic seizures were observed in $>80\%$ of cases in both groups, and the patients were treated with antiepileptic agents. Topiramate and zonisamide were more frequently administered in the urolithiasis group than in

the non-urolithiasis group ($P < 0.001$, $P = 0.039$, respectively). Thirteen of the 15 cases in the urolithiasis group were treated with topiramate or zonisamide. No patients took both agents. The median periods of antiepileptic treatment were longer than 80 months in both groups. No significant differences were found between the two groups with regard to the administration rates of other antiepileptic agents, the treatment period, or the incidence of manifestations of TSC in the kidney, skin, brain, and other organs.

Laboratory findings

Table 2 shows the urinary and serum findings in both groups. The urine specific gravity and urine pH were higher in the urolithiasis group than in the non-urolithiasis group ($P = 0.005$, $P = 0.042$, respectively). No significant differences were found between the serum corrected calcium and intact parathyroid hormone levels of the two groups.

Characteristics of the stones and treatments of the urolithiasis group

Table 3 shows the characteristics of the stones and treatments of the urolithiasis group. Thirteen patients had symptoms and two had no symptoms. Four cases had bilateral urolithiasis. The median stone size was 8 mm; 8 were renal and 11 were ureteral stones. No patients had stones ≥ 20 mm in diameter. The stone treatments included oral medication ($n = 7$), surgery ($n = 4$) and active surveillance ($n = 4$). Three of the 4 patients who underwent surgery had multiple AMLs around the stone. Because of the risk of bleeding from AML, these patients could not undergo extracorporeal shock wave lithotripsy (ESWL); thus, transurethral lithotripsy (TUL) was performed. All 4 patients who received surgery became stone-free. Three of the 7 cases treated with oral medication had spontaneous stone expulsion. The stone composition was pure calcium oxalate in one case and mixed calcium phosphate and calcium oxalate in six cases. A typical case is shown in Figure 1. The subject was a 25-year-old man. He had a subependymal giant cell astrocytoma in the brain, multiple AMLs in the bilateral kidneys, and multiple angiofibroma on the face. He visited our hospital in June 2017 due to macrohematuria. Abdominal plain CT showed a 13-mm stone in the right kidney. ESWL was difficult because AMLs surrounded the stone. Thus, TUL was performed and the stone was completely removed.

Discussion

In Japan, the estimated annual incidence of first-episode upper urinary tract stones was 137.9 per 100,000 population in 2015¹⁰. In our study, the incidence of TSC-associated urolithiasis was much higher than in the general population. The incidence of epileptic seizures was 80–90% in TSC patients^{11,12}. Refractory epileptic seizures are often observed in TSC, and it is not uncommon to take three or more antiepileptic agents^{11,12}. Topiramate and zonisamide have been widely used as antiepileptics. However, it has been reported that those drugs are associated with the development of acidosis and urolithiasis^{13,14}.

In some patients, topiramate and zonisamide lead to renal tubular acidosis through the inhibition of carbonic anhydrase in the renal tubules, which influences systemic metabolic acidosis and alkaline urine pH with a low urine citrate concentration. These metabolic changes result in calcium phosphate stone formation^{13,14}. A study by Maalouf et al. showed that the prevalence of symptomatic urolithiasis among adult topiramate users was 10.7 %¹⁵. The median daily dose of topiramate was 300 mg and the median treatment period was 48 months¹⁵. Faught reported that the incidence of kidney stones associated with zonisamide was 2.7 % (15 of 549)¹⁶. Most patients with refractory epileptic seizures need to take anti-epileptic agents for a long period. Longer administration of topiramate and zonisamide might result in a higher incidence of urolithiasis. In our study, the median antiepileptic treatment period was >80 months in both groups. We discontinued both drugs for all patients who had urolithiasis and switched to other agents.

In the urolithiasis group, the incidence of mental retardation and the urine specific gravity were higher than in the non-urolithiasis group. Patients with mental retardation are susceptible to dehydration because they cannot keep themselves hydrated. Thus, the daily urine volume decreased and the urine specific gravity increased. Increased urine specific gravity may promote stone development. We recommend to TSC patients and their families to drink >2 liters of water a day.

Medical expulsive therapy is recommended for urinary stones <10 mm in size¹⁷. Alpha blockers promote the spontaneous expulsion of urinary stones¹⁸. On the other hand, urinary stones $\geq$ 10 mm in size are not expelled spontaneously. Thus, surgical treatments such as TUL, ESWL, and percutaneous nephrolithotomy (PNL) are recommended¹⁹. AMLs are often comorbid with TSC^{20,21}. Unlike sporadic AML, TSC-associated AML develops at multiple sites on the bilateral sides.⁷ It develops at a younger age, and tends to exhibit a much faster growth rate over time than sporadic AML^{22,23}. When urolithiasis is comorbid with TSC-associated AML, ESWL and PNL cannot be performed because of the risk of bleeding from the AML. On the other hand, TUL does not damage the renal parenchyma and can be performed safely. Surgical options for the treatment of urolithiasis in patients with TSC-associated AML are limited. Furthermore, topiramate and zonisamide lead to the development calcium phosphate stones in some cases. In the present study, only one stone was composed of pure calcium oxalate; six were composed of mixed calcium phosphate and calcium oxalate. Urinary stones containing calcium phosphate are harder than calcium oxalate stones²⁴. Otsuki et al. reported that stones containing calcium phosphate require more laser energy and a longer operating time, and that they are associated with a higher rate of perioperative complications²⁴. Thus, prevention and early detection of urolithiasis are beneficial to TSC patients.

The present study has several limitations. First, this was a retrospective study and the urolithiasis group consisted of only 15 patients. The incidence of urolithiasis associated with TSC in this study does not reflect the overall prevalence of TSC in Japan. In addition, our hospital manages a large number of patients with refractory epileptic seizures; thus, the treatment period of patients receiving antiepileptic agents may be longer than in other medical institutions. Second, the urinary calcium and citrate

concentrations were not measured in this study. The urine calcium to creatinine ratio and urine citrate to creatinine ratio change with diet and exercise. Spot urine examinations during early morning fasting, and 24-hour urine collection are difficult in TSC patients with mental retardation. There were no patients with hyperparathyroidism in the urolithiasis group.

Conclusions

Urolithiasis is more likely to develop in TSC patients receiving long-term treatment with topiramate or zonisamide. Periodic blood, urine, imaging tests and appropriate use of antiepileptic drugs are necessary for those patients. When hematuria or severe abdominal pain is observed in patients with TSC-associated AML, urolithiasis should be considered in addition to rupture of the AML. If urolithiasis is comorbid with TSC-associated AML, the treatment options are more limited in cases with multiple AMLs around the stone due to an increased risk of hemorrhage. Prevention and early detection of urolithiasis are beneficial to patients with TSC.

Abbreviations

AML: angiomyolipoma; ESWL: extracorporeal shock wave lithotripsy; PNL: percutaneous nephrolithotomy; TSC: tuberous sclerosis complex; TUL: transurethral lithotripsy

Declarations

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Authors' contributions

Study design: TH, KE, Data acquisition: TH, YI, KM, JM, KE, Data analysis and interpretation: TH, YI, KM, JM, Drafting the manuscript: TH, KE, Critical revision of the manuscript for scientific and factual content: MT, SE, Supervision: SE. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the ethics committee of JR Tokyo General Hospital. All patients gave informed consent.

Consent for publication

Not applicable.

Competing interest

The authors declare that they have no competing interest.

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Tables

Table 1. Patient characteristics

Characteristics	Urolithiasis group (n=15)	Non- urolithiasis group (n=87)	<i>P</i> value
Median age (range)	27 (17-51)	26 (16-56)	0.609
Sex			
Male/Female	8/7	46/41	1.000
Mental retardation	12 (80%)	44 (51%)	0.048
Epileptic seizure	14 (93%)	70 (80%)	0.461
Antiepileptic agents			
Carbamazepine	9 (60%)	36 (41%)	0.260
Zonisamide	7 (47%)	16 (18%)	0.039
Topiramate	6 (40%)	3 (3%)	<0.001
Sodium valproate	5 (33%)	25 (28%)	0.763
Levetiracetam	4 (27%)	19 (22%)	0.740
Clobazam	3 (20%)	12 (14%)	0.459
Median treatment period with antiepileptic agents (months) (range)	102 (40- 184)	84 (26-240)	0.245
kidney			
angoimyolipoma	13 (87%)	59 (68%)	0.220
cyst	5 (33%)	16 (18%)	0.187
Skin			
Facial angiofibromas	13 (87%)	70 (80%)	0.731
Hypomelanotic macules	7 (47%)	49 (61%)	0.579
Shagreen patch	5 (33%)	27 (31%)	0.756
Brain			
Cortical tubers	14 (93%)	75 (86%)	0.686
Subependymal nodules	10 (67%)	53 (61%)	0.779
Subependymal giant cell astrocytoma	2 (13%)	10 (11%)	0.689
Others			
Lung lymphangiomyomatosis	4 (27%)	19 (22%)	0.740

Retinal hamartoma	3 (20%)	9 (10%)	0.378
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Table 2. The laboratory findings in the urolithiasis and non-urolithiasis groups

	Urolithiasis group	Non-urolithiasis group	<i>P</i> value
Urine specific gravity	1.026±0.007	1.017±0.005	0.005
Urine pH	7.4±0.6	6.9±0.5	0.042
Serum corrected calcium (mg/dl)	9.3±0.5	9.7±0.5	0.086
Serum intact PTH (pg/ml)	44.3±19.5	40.8±12.9	0.781

PTH: parathyroid hormone

Table 3 The characteristics of the stones and treatments of the urolithiasis group

Symptoms	
Abdominal pain	5
Back pain	4
Macrohematuria	3
Microhematuria	2
No symptoms	2
Stone side	
Right/Left/Bilateral	6/5/4
Size	
<10 mm	12
10-20 mm	3
>20 mm	0
Location	
R2/R3	6/2
U1/U2/U3	5/2/4
Treatment	
Anticholinergic agents	7
Alpha 1 blocker	3
Transurethral lithotripsy	4
Active surveillance	4

Figures

Figure 1

Axial CT of the kidney. A) A 13 mm stone can be seen in the right kidney. Multiple AMLs are observed around the stone. B) The stone was completely removed after transurethral lithotripsy.