CASE REPORT

Oman Medical Journal [2023], Vol. 38, No. 4: e535

Tuberous Sclerosis Complex with Renal Stones and Distal Renal Tubular Acidosis: Case Report and Literature Review

Anwar Al Omairi[1] and Amna Al Futaisi[2]*

[1]Pediatric Nephrology Unit, Department of Child Health, Sultan Qaboos University Hospital, Muscat, Oman
[2]Pediatric Neurology Unit, Department of Child Health, Sultan Qaboos University, Muscat, Oman

ARTICLE INFO

Article history:
Received: 29 April 2022
Accepted: 17 July 2022

Online:
DOI 10.5001/omj.2023.32

Keywords:
Tuberous Sclerosis Complex; Urinary Stones; Distal Renal Tubular Acidosis; Oman.

ABSTRACT

Distal renal tubular acidosis (RTA) is a common cause of renal stones and nephrocalcinosis in children. Distal RTA can be either acquired or congenital because of a genetic defect. Tuberous sclerosis complex is an autosomal dominant inherited neurocutaneous syndrome with variable renal involvement. We describe a case of a six-year-old boy with tuberous sclerosis complex who developed distal RTA and renal stones.

Renal stones in children, though rare, are associated with identifiable risk factors and carry a higher probability of recurrence than in adults. Children with renal stones require thorough evaluation to identify possible underlying metabolic conditions associated with an imbalance between stone inhibitors and promoters. Distal renal tubular acidosis (RTA) is a common cause of renal stones and nephrocalcinosis in children. Distal RTA usually occurs due to a genetic defect. It can also develop secondary to diseases such as Sjogren syndrome, systemic lupus erythematosus, and medullary sponge kidney disease, or medications such as spironolactone, amiloride, ifosfamide, and acetazolamide.[1]

Tuberous sclerosis complex (TSC) is an autosomal dominant inherited neurocutaneous syndrome with an estimated incidence of nearly 1 in 6000 births and a prevalence of 1 in 7000–20 000 people. This multisystem disorder causes tumors (mostly benign) in the brain, skin, lungs, eyes, heart, and kidneys.[2] Renal manifestations include angiomyolipoma, renal cysts, and less commonly oncocytomas, which may lead to hypertension and chronic kidney disease.[3]

To our knowledge, no previous case report has confirmed a high frequency of renal stones in a patient with tuberous sclerosis. Intractable epilepsy is commonly associated with tuberous sclerosis and often requires treatment with multiple antiseizure medications. Patients using topiramate are at risk for nephrolithiasis because of hypocitraturia and a high urine pH. However, topiramate users are thought to have a low rate of symptomatic stone disease.[4–8]

In this report, we discuss a pediatric case of tuberous sclerosis with co-occurring renal stones and distal RTA and review cases in the literature.

CASE REPORT

A six-year-old boy was diagnosed with TSC in his first year of life. Manifestations included seizures, cortical tubers, facial angiofibroma, retinal astrocytoma, gingival angiofibroma, shagreen patches, and hypopigmented macules. As part of routine surveillance, an ultrasound of the kidneys was conducted which showed a 7 mm renal stone in the interloper region and a 5 mm renal cyst in the right kidney. Owing to the nature of his illness, he had frequent seizures which were well-controlled with topiramate and carbamazepine. Urine cystine, calcium, and uric acid levels were all normal. Tables 1 and 2 list the results of laboratory investigations.

Further serum investigations revealed normal anion gap metabolic acidosis. Urine analysis showed an inappropriately high urine pH (6.5) with a positive urine anion gap, indicating impaired distal tubular acidification of urine. These tests were

*Corresponding author: ✉amnaf@squ.edu.om

Table 1: Serum chemistry.

Lab test	Result	Reference range
Urea	4.0 mmol/L	2.8–8.1
Creatinine	31.0 µmol/L	25–42
Sodium	139.0 mmol/L	135–145
Potassium	4.2 mmol/L	3.5–5.1
Chloride	108.0 mmol/L	98–107
Calcium	2.4 mmol/L	2.15–2.55
Phosphate	1.7 mmol/L	1.05–1.80
PTH	3.1 pmol/L	1.6–6.9
25(OH) vitamin D	64 nmol/L	> 50
pH	7.3	7.35–7.45
pCO_2 (venous)	47.0 mm Hg	34–45
HCO_3	18.0 mmol/L	21.8–26.9
Anion gap	12.0 mEq/L	12 ± 4

PTH: parathyroid hormone; 25(OH): 25-hydroxy; pH: acidity; pCO_2: partial pressure of carbon dioxide; HCO_3: bicarbonate.

Table 2: Urine chemistry.

Lab test	Result
Sodium	150.0 mmol/L
Potassium	53.0 mmol/L
Chloride	191.0 mmol/L
pH	6.5
Beta2-microglobulin	1.6 mg/L
Calcium	3.7 mmol/L
Creatinine	7.4 mmol/L
Calcium/creatinine	0.5
Cystine/creatinine	3.0 µmol/mmol

repeated twice, and the findings were consistent. The child was administered potassium citrate (10 mL twice daily), and the acidosis was corrected.

DISCUSSION

Renal stones in children are associated with identifiable risk factors and carry a higher risk of recurrence than in adults. Therefore, it is the standard of care to evaluate children with renal stones for underlying precipitating factors.[9,10] This child had distal RTA. Whether congenital or acquired, distal RTA may diminish the capacity of the kidney in removing the daily acid load, leading to nephrocalcinosis and renal stones.[11,12] TSC is a multisystemic autosomal dominant disease characterized by the development of numerous benign tumors in different organs. It commonly affects the brain, skin, lungs, and kidneys.[13] There is no known association between TSC and distal RTA. However, two cases of co-occurrence of TSC and distal RTA have been reported. Both patients were women aged 27 and 41 years. Notably, both had significant osteomalacia.[14,15] There has been another report of two Saudi siblings with co-occurring TSC and Fanconi syndrome, a generalized proximal tubulopathy with a proximal RTA.[16]

A diagnosis of distal RTA is established by the presence of normal anion gap metabolic acidosis with the presence of inappropriately high urine pH. The impairment of urine acidification is further confirmed by the presence of a positive urine anion gap. The urine anion gap is calculated by subtracting the level of chloride ions from the sum of the levels of potassium and sodium ions. This enables the estimation of urinary ammonium (NH_4^+) ion levels. For the kidney to secrete protons (H^+), a buffer is required to titrate the gradient and maintain urine pH within a tolerable range. Ammonia, the buffer, is generated by the proximal tubule and converted to NH_4^+ by adding H^+ in the distal tubule. A positive anion gap indicates insufficient NH_4^+ (low secretion of H^+).[17,18]

The mechanism of renal stones in distal RTA is multifactorial. A possible factor is increased absorption of citrate by the proximal tubule driven by acidemia resulting in low urine citrate, a natural stone inhibitor. Other factors include alkaline urine pH and hypercalciuria. The most common type of renal stone in distal RTA is calcium phosphate.[11,19]

The present patient was on topiramate, an antiseizure medication often prescribed for focal seizures and migraine prophylaxis. Several reports have suggested that topiramate can cause RTA by inhibiting carbonic anhydrase, the main enzyme driving bicarbonate absorption in the proximal tubule and H^+ secretion in the distal tubule.[4–8] This may lead to the formation of renal stones.

However, our patient had a renal stone prior to the initiation of topiramate; therefore, his distal RTA was likely caused by a different mechanism. Barone et al,[20] described mice with TSC as having hyperproliferating intercalated cells. The intercalated cells are mainly responsible for H^+ secretion in the distal tubule.[21] The effect of the hyperproliferation of intercalated cells on their function is not yet known. Nevertheless, the presence of topiramate on board probably has an added

effect on the process, increasing the risk of renal stone formation.[22]

Our patient had normal serum potassium, and his metabolic acidosis improved with a small dose of potassium citrate, indicating the mild nature of the disease. Some experts tend to label this spectrum as incomplete RTA, although it is not considered a separate entity.[11] Even if acidosis is mild in nature and subclinical, failure to recognize the condition would result in bone demineralization; therefore, it is recommended to use oral alkalizers to maintain serum bicarbonate levels above 22 mEq/L .[11,18,23]

CONCLUSION

The association between TSC and distal RTA cannot be determined based on available case reports. Distal RTA in children with TSC and renal stones is worth investigating further.

Disclosure

The authors declared no conflicts of interest. A written consent was obtained from the patient's parent.

REFERENCES

1. Kitterer D, Schwab M, Alscher MD, Braun N, Latus J. Drug-induced acid-base disorders. Pediatr Nephrol 2015 Sep;30(9):1407-1423.
2. Islam MP. Tuberous sclerosis complex. Semin Pediatr Neurol 2021 Apr;37:100875.
3. Nair N, Chakraborty R, Mahajan Z, Sharma A, Sethi SK, Raina R. Renal manifestations of tuberous sclerosis complex. J Kidney Cancer VHL 2020 Aug;7(3):5-19.
4. Gupta S, Gao JJ, Emmett M, Fenves AZ. Topiramate and metabolic acidosis: an evolving story. Hosp Pract (1995) 2017 Dec;45(5):192-195.
5. Mirza N, Marson AG, Pirmohamed M. Effect of topiramate on acid-base balance: extent, mechanism and effects. Br J Clin Pharmacol 2009 Nov;68(5):655-661.
6. Warner BW, LaGrange CA, Tucker T, Bensalem-Owen M, Pais VM Jr. Induction of progressive profound hypocitraturia with increasing doses of topiramate. Urology 2008 Jul;72(1):29-32.
7. Sacré A, Jouret F, Manicourt D, Devuyst O. Topiramate induces type 3 renal tubular acidosis by inhibiting renal carbonic anhydrase. Nephrol Dial Transplant 2006 Oct;21(10):2995-2996.
8. Maalouf NM, Langston JP, Van Ness PC, Moe OW, Sakhaee K. Nephrolithiasis in topiramate users. Urol Res 2011 Aug;39(4):303-307.
9. Pietrow PK, Pope JC IV, Adams MC, Shyr Y, Brock JW III. Clinical outcome of pediatric stone disease. J Urol 2002 Feb;167(2 Pt 1):670-673.
10. Tasian GE, Copelovitch L. Evaluation and medical management of kidney stones in children. J Urol 2014 Nov;192(5):1329-1336.
11. Fuster DG, Moe OW. Incomplete distal renal tubular acidosis and kidney stones. Adv Chronic Kidney Dis 2018 Jul;25(4):366-374.
12. Bagga A, Sinha A. Renal tubular acidosis. Indian J Pediatr 2020 Sep;87(9):733-744.
13. Lam HC, Siroky BJ, Henske EP. Renal disease in tuberous sclerosis complex: pathogenesis and therapy. Nat Rev Nephrol 2018 Nov;14(11):704-716.
14. Radó JP, Haris A. Metabolic bone disease (anticonvulsant osteomalacia) and renal tubular acidosis in tuberous sclerosis. Intern Med 1993 Jul;32(7):574-579.
15. Fulop M, Mackay M. Renal tubular acidosis, Sjögren syndrome, and bone disease. Arch Intern Med 2004 Apr;164(8):905-909.
16. Al-Hwiesh AK, Al-Mueilo SH, Saeed I, Barak AH, Al-Muhanna FA. Co-existence of tuberous sclerosis and the Fanconi syndrome in two Saudi male siblings: report on two cases. Saudi J Kidney Dis Transpl 2005 Apr-Jun;16(2):193-197.
17. Hamm LL, Nakhoul N, Hering-Smith KS. Acid-base homeostasis. Clin J Am Soc Nephrol 2015 Dec;10(12):2232-2242.
18. Trepiccione F, Walsh SB, Ariceta G, Boyer O, Emma F, Camilla R, et al. Distal renal tubular acidosis: ERKNet/ESPN clinical practice points. Nephrol Dial Transplant 2021 Aug;36(9):1585-1596.
19. Evan AP, Lingeman J, Coe F, Shao Y, Miller N, Matlaga B, et al. Renal histopathology of stone-forming patients with distal renal tubular acidosis. Kidney Int 2007 Apr;71(8):795-801.
20. Barone S, Zahedi K, Brooks M, Henske EP, Yang Y, Zhang E, et al. Kidney intercalated cells and the transcription factor FOXi1 drive cystogenesis in tuberous sclerosis complex. Proc Natl Acad Sci U S A 2021 Feb;118(6):e2020190118.
21. Giglio S, Montini G, Trepiccione F, Gambaro G, Emma F. Distal renal tubular acidosis: a systematic approach from diagnosis to treatment. J Nephrol 2021 Dec;34(6):2073-2083.
22. Barnett SM, Jackson AH, Rosen BA, Garb JL, Braden GL. Nephrolithiasis and nephrocalcinosis from topiramate therapy in children with epilepsy. Kidney Int Rep 2018 Feb;3(3):684-690.
23. Raphael KL. Metabolic acidosis in CKD: core curriculum 2019. Am J Kidney Dis 2019 Aug;74(2):263-275.