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

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Abstract

Renal stones are less common in pediatric patients than in adults and are associated with identifiable risk factors and carry a higher risk of recurrence than in adults. 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 (TSC) is an autosomal dominant inherited neurocutaneous syndrome with variable renal involvement including angiomyolipoma, renal cysts, and less commonly oncocytomas. We describe a 6-year-old male child with TSC who developed distal RTA and renal stones. Although, this patient was on topiramate, an antiseizure medication that is linked to renal stones, the renal stone was detected prior to the initiation of topiramate; therefore, distal RTA was likely caused by a different mechanism. The association between TSC and distal RTA cannot be determined based on available case reports; therefore, further studies are required. Nevertheless, distal RTA in children with TSC and renal stones is worth investigating.

Keywords: tuberous sclerosis complex, renal stones, distal renal tubular acidosis, antiseizure medications

Introduction

Renal stones are less common in pediatric patients than in adults. Children with renal stones require thorough evaluation to identify any underlying metabolic conditions that may cause 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 can be primary due to a genetic defect or secondary to other diseases such as Sjogren syndrome, systemic lupus erythematosus (SLE), medullary sponge kidney disease, and medications. The most common medications that cause distal RTA are 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. This multisystem disorder causes (mostly benign) tumors in the brain, skin, lungs, eyes, heart, and kidneys.[2] Renal manifestations include angiomyolipoma, renal cysts, and less commonly oncocytomas, which may lead to the development of hypertension and chronic kidney disease.[3]

No previous report has confirmed an increased frequency of renal stones in patients with tuberous sclerosis. Intractable epilepsy is commonly associated with tuberous sclerosis and often requires treatment with multiple antiseizure medications (ASMs). Patients using topiramate are at risk for nephrolithiasis because of hypocitraturia and a high urine pH. However, TPM users are thought to have a low rate of symptomatic stone disease.[4-8]

In this report, we discuss a child with tuberous sclerosis and cooccurring renal stones and distal RTA and review the described cases in the literature.

Case report

A 6-year-old male child was diagnosed with TSC in his first year of life. Manifestations included seizures, cortical tubers, facial angiofibroma, retinal astrocytoma, gingival angiomyofibroma, shagreen patch, 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 (Laboratory investigations, Tables 1 and 2).

Table 1: Serum chemistry.

Lab test	**Result**	**Reference range**
Urea	4	(2.8 - 8.1mmol/L)
Creatinine	31	(25 - 42 umol/L)
Sodium	139	(135 - 145 mmol/L)
Potassium	4.2	(3.5 - 5.1 mmol/L)
Chloride	108	(98-107 mmol/L)
Calcium	2.39	(2.15 - 2.55 mmol/L)
Phosphate	1.71	(1.05 - 1.80 mmol/L)
PTH	3.1	(1.6 - 6.9 pmol/L)
25 OH vitamin D	64	(>50 nmol/L)
PH	7.28	(7.35-7.45)
PCO2*	47	(34-45) mmHg
HCO3	18	(21.8 to 26.9 mmol/L)
Anion gap	12	

**Venous*

Table 2: Urine chemistry.

Lab test	**Result**
Sodium	150 (mmol/L)
Potassium	53 (mmol/L)
Chloride	191 (mmol/L)
PH	6.5
Beta2-microglobulin	1.62 (0.8 to 2.2 mg/l)
Calcium	3.72 mmol/l
Creatinine	7.4 mmol/l
Calcium/creatinine	0.5 (normal <0.6)
Cystine/creatinine	2.95 umol/mmol (normal 3-11)

Further laboratory investigations revealed normal anion-gap metabolic acidosis. Urine analysis showed inappropriately high urine pH (6.5) with a positive urine anion gap, indicating impaired distal tubular acidification of urine. These labs were repeated twice and the findings were consistent. He 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] Distal RTA is known to be one of the common causes of nephrocalcinosis and renal stones.[11] Distal RTA can be either acquired or congenital because of a genetic defect, resulting in kidney failure to secrete the daily acid load.[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] This child had distal RTA; although there is no known association between TSC and RTA, the coexistence of the two conditions has been described in the literature. To the best of our knowledge, only two cases of TSC associated with distal renal tubular acidosis have been reported.

Both patients were women aged 27 and 41 years old. Notably, both patients 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 chloride from the sum of potassium and sodium. This calculation is used as a means to estimate urinary ammonium. For the kidney to secrete protons (H+), a buffer is required to titrate the gradient and maintain urine pH within a tolerable range. Ammonia is generated by the proximal tubule and converted to ammonium by adding H+ in the distal tubule. A positive anion gap indicates a lack of ammonium (acid).[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]

Topiramate is a widely used antiseizure medication., also used for focal seizures and migraine prophylaxis. There have been several reports suggesting that it can cause renal tubular acidosis by inhibiting carbonic anhydrase in a manner similar to acetazolamide, as both drugs have a sulfonamide group at their active site; carbonic anhydrase is the main enzyme driving bicarbonate absorption in the proximal tubule and H+ secretion in the distal tubule.[4-8]

Our patient had a renal stone prior to the initiation of topiramate; therefore, distal RTA was likely caused by a different mechanism. Barone et al. described mice with TSC as having hyperproliferating intercalated cells.[20] 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 and certainly increases the risk of renal stone formation.[22]

This child 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 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 alkalanizers 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; therefore, further studies are required. Nevertheless, distal RTA in children with TSC and renal stones is worth investigating.

Conflicts of Interest and Financial Disclosures

There are no conflicts of interest to declare.

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