V Edition of the Clinical Cases Contest on

non-surgical clinical management of Kidney Stones

Official template

Title: Pharmacological Management of Recurrent Urolithiais in Sporadic Familial Hypocalciuric Hypercalcemia.

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Key words (3 to 6):

Urolithiasis: urinary calculi.

Whewellite: calcium oxalate monohydrate

Weddelite: calcium oxalate dihydrate

Calcimimetic: a drug that mimics calcium effects on tissues.

1. **Abstract (no longer than 150 words).**

Familial hypocalciuric hypercalcaemia (FHH) is a rare genetic condition commonly inherited in an autosomal dominant fashion; however there are reports of sporadic cases. The condition is grouped into three types FHH1, FHH2, FHH3 depending on the mutation to calcium sensing receptor (CaSR). Most cases are usually asymptomatic but a few may have symptoms of hypercalcaemia and end-organ damage.

This is a case of a 42 year old male who presented with recurrent urolithiasis that was managed by surgery and medical management. He had a total of three episodes of with a high stone burden each time. Complete evaluation was a challenge due to lack of accessibility and expensive cost of some of the investigations. Once the diagnosis was clinched medical management was instituted which he continues with to date. It has controlled the disease with resolution of the urolithiasis.

2. Introduction

FHH is a rare genetic disease which can be inherited or occur sporadically(1). It is caused by mutation of the CaSR gene which causes decreased activity of the CaSR receptor (2). This receptor is important in the metabolism of calcium in the body especially at the level of the parathyroid gland and kidney. CaSR senses elevated levels of serum calcium then decreases PTH secretion with consequent downstream reduction in serum calcium. In the kidney the CaSR leads to decreased reabsorption of calcium by the renal tubules in response to hypercalcaemia. Another important role is the stimulation of osteoblastic activity in bone(1).

The loss of function mutation leads to a failure of the above mechanisms with consequent hypercalcaemia, slightly elevated PTH and hypocalciuria. The hypercalcaemia may cause urolithiasis in some individual especially with FHH1(1,3). The stones are calcium based commonly calcium oxalate.

Management of urolithiasis in the background of metabolic syndrome requires a comprehensive approach including dietary modification, adequate fluid intake, medication as per the metabolic profile and surgery where indicated (4). It is important to appropriately manage urolithiasis so as to avoid some of the long term consequences such as kidney disease(5,6).

3. Clinical Case description

a. Patient information / Medical records

A 42 year old male who presented with bilateral renal colic and a non- contributory medical and family history, his BMI was also within normal. He was diagnosed with bilateral renal and a ureteric calculus on imaging (figure 1) and on basic evaluation he had some no infection in urine but had hypercalcaemia and hyperuricemia.

Bilateral percutaneous nephrolithotomy was done and stone evaluation revealed calcium oxalate and uric acid components. A DASH diet, fluid intake with a target of 3Litres of urine per 24 hours and a short course of febuxostat were given.

Six years later, he had a recurrence of the symptoms, he was found to have developed hypertension, diabetes mellitus and an acute kidney injury (AKI). Medical treatment for the conditions was commenced and to date they are well controlled on drugs, the AKI resolved. Serum chemistries showed high PTH, hypercalcaemia and hyperuricemia. Imaging showed a recurrence of the urolithiasis (figure 2) for which retrograde intra-renal surgery (RIRS) with laser lithotripsy was done. He was advised to continue with medical management. A sestamibi scan was also done and ruled out a parathyroid adenoma (figure 3).

Four months later, he had similar recurrence for which RIRS and laser lithotripsy was done. Imaging and serum evaluation were similar to the previous tests.

b. Diagnostic support studies and results

On all occasions serum chemistry revealed hypercalcaemia, hyperuricemia and high PTH. A serum angiotensin converting enzyme test was done and ruled out occult granuloma and malignant disease.Stone analysis showed 71% whewwllite, 19% weddelite and 10% uric acid stones. Due to financial constrains and unavailabity of test urine 24 hour evaluation was hard to get, when done it showed hypocalciuria of 70mg/24 hours. Urine calcium: creatinine ratio was 0.008.

An initial CT Pyelogram and two none contrast CT- KUB s were the images done to diagnose the stones on the three instances.

Figure 1.

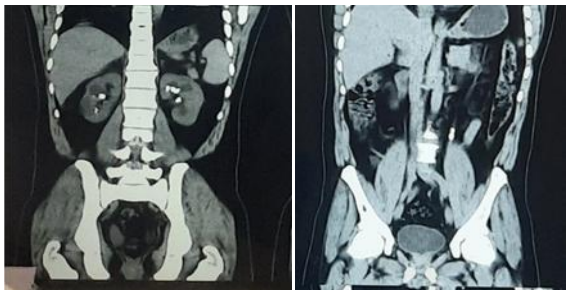


Figure 2.

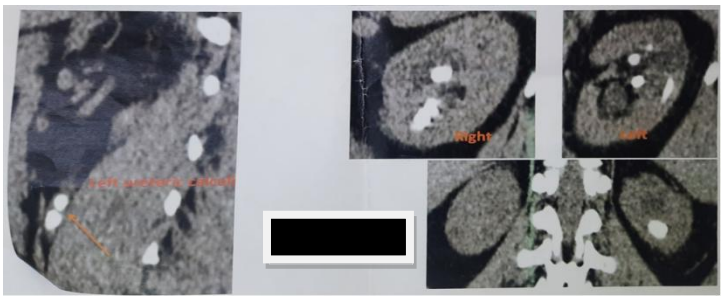
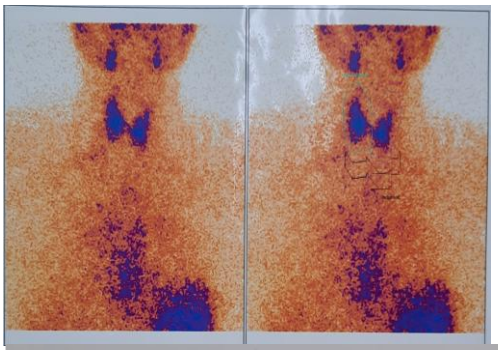


Figure 3.



The Sestamibi image does not reveal any significant change in the findings.

Conclusion

There is no evidence of parathyroid adenoma. However, possibility of parathyroid hyperplasia cannot be ruled out on this scan.

c. Diagnosis

Due to the hypercalcaemia, hypocalciuria and high PTH and low urine calcium: creatinine, a diagnosis of Familial Hypocalcaemia Hypercalcaemia was made.

d. Treatment

He is on dietary management with hydration to a target of 3L/24 hours of urine and low animal protein. He is on lit control PH balance to inhibit the formation of the calcium calculi, cinacalcet a calcimimetic to stimulate the CaSR receptor and allopurinal a xanthine oxidase inhibitor for hyperuricemia.

e. Evolution and progress

Since institution of the medical management he has been stone free and asymptomatic for approximately 1 ½ years now. His serum calcium and uric acid have also been controlled on the medication.

f. Clinical results

The disease is currently under control with normalisation of the metabolic disturbances on medication. He has not formed another stone since his complete evaluation and diagnosis.

4. Discussion

FHH is a rare cause of hypercalcaemia; the cause is a loss of function mutation of CaSR gene. It results in desensitisation of the receptor and in the parathyroid causes increased release of PTH despite high serum calcium levels. It also causes reabsorption of calcium and uric acid in the renal tubules even in the presence of high serum calcium levels. Diagnosis is by serum high normal or slightly elevated PTH and high serum calcium in the background of low 24 hour urinary calcium excretion.

It is one of the causes of hypercalcaemia which is defined as calcium above 2.6mmol/l and is a metabolic cause of recurrent urolithiasis. Patients with metabolic disorders causing urolithiasis are considered high risk stone formers. They should receive a full metabolic evaluation which includes blood chemistry, stone analysis and metabolic urine evaluation. Once the underlying issue has been established, medical management should be instituted; its role is minimising recurrence by correcting the metabolic error. Additional therapies include increased fluid intake and dietary adjustments where appropriate(7).Appropriate surgery is used as necessary.

For FHH hypercalcaemia is controlled by calcimimetics, in cases of hyperuricemia allopurinol is used. Additionally, inhibitors of calcium oxalate stone formation such as phytate, magnesium and phenolos can be used. They inhibit supersaturtion and crystallization of calcium oxalate; additionally they prevent papillary injuries from oxidative stress and reduce free oxalate(8,9). One such combination is lit control Ph Balance.

5. Conclusions and recommendations

Recurrent urolithiasias is a challenge due the financial burden and health costs on the patients. Medical conditions are among the common conditions causing this with hypercalcaemia being a leading contributor. FHH is a rare cause of hypercalcaemia and requires proper evaluation for accurate diagnosis. Some of the diagnostic tests include 24 hour urine evaluation.

In Africa, 24 hour urine evaluation is expensive and not easily available in most 3rd world economies. These impacts on diagnosis and management. Policies should therefore be put in place to change this and make diagnosis and therefore institution of the correct management easier and timely.

Proper medical management or recurrent urolithiasis secondary to metabolic disorders should be started promptly once diagnosis is confirmed. It includes diet, hydration and medication tailored to the disease.

6. Bibliographic references (* of special interest, ** of extraordinary interest)

*1. Lee JY, Shoback DM. Familial hypocalciuric hypercalcemia and related disorders. Best Pract Res Clin Endocrinol Metab. 2018 Oct;32(5):609–19.

2. Nava Suarez CC, Anastasopoulou C, Kathuria P. Familial Hypocalciuric Hypercalcemia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Dec 1]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK459190/

*3. Reddy M, Tanday R, Feeney C, Darko D, Hadjiminas D, Cox J. Renal calculi as a presenting feature in a patient with familial hypocalciuric hypercalcaemia (FHH). Endocr Abstr [Internet]. 2012 Mar 1 [cited 2024 Dec 1];28. Available from: https://www.endocrine-abstracts.org/ea/0028/ea0028p80

*4. EAU Guidelines on Urolithiasis - Uroweb [Internet]. [cited 2024 Dec 1]. Available from: https://uroweb.org/guidelines/urolithiasis/chapter/guidelines

5. Kittanamongkolchai W, Mara KC, Mehta RA, Vaughan LE, Denic A, Knoedler JJ, et al. Risk of Hypertension among First-Time Symptomatic Kidney Stone Formers. Clin J Am Soc Nephrol CJASN. 2017 Mar 7;12(3):476–82.

6. Shang W, Li Y, Ren Y, Yang Y, Li H, Dong J. Nephrolithiasis and risk of hypertension: a meta-analysis of observational studies. BMC Nephrol. 2017 Nov 29;18(1):344.

**7. Jahrreiss V, Seitz C, Quhal F. Medical management of urolithiasis: Great efforts and limited progress. Asian J Urol. 2024 Apr;11(2):149–55.

**8. Grases F, Rodriguez A, Costa-Bauza A. Efficacy of Mixtures of Magnesium, Citrate and Phytate as Calcium Oxalate Crystallization Inhibitors in Urine. J Urol. 2015 Sep 1;194(3):812–9.

**9. FREIXEDAS FG, BAUZÀ AC, ALMIRALL RMP, RODRÍGUEZ AR. Composition containing phytic acid, magnesium and polyphenols for the treatment or prevention of renal lithiasis [Internet]. EP3162376A1, 2017 [cited 2024 Dec 1]. Available from: https://patents.google.com/patent/EP3162376A1/en