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CASE REPORT

Hypocitraturia: a common but not well-known cause of nephrolithiasis

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ABSTRACT

Nephrolithiasis is a frequent problem that can cause serious morbidity. When associated with an underlying metabolic disorder the recurrence rate is higher. Hypocitraturia is estimated to be present in 20-60% of cases. Several secondary causes are known. Potassium citrate is the primary treatment. In the case we present here we emphasise the need for metabolic screening, focussing on hypocitraturia, a less well-known cause of nephrolithiasis.

KEYWORDS

Hypocitraturia, metabolic screening, nephrolithiasis

What was known on this topic?
Nephrolithiasis is a frequent problem that occurs worldwide and can cause serious morbidity. Obstruction, infection and deterioration of kidney function were not uncommon a few decades ago. Although new therapies have been introduced, high recurrence rates still put patients at risk for these complications. When renal stones are the symptom of an underlying metabolic disorder there is a higher risk of recurrence.

What does this case add?
This case underlines the importance of early metabolic screening for patients with recurrent nephrolithiasis, and awareness of the diagnosis of hypocitraturia. This approach will help to predict recurrent stone formation and further complications.

BACKGROUND

Nephrolithiasis is a frequent problem that can cause serious morbidity. Obstruction, infection and deterioration of kidney function were not uncommon a few decades ago. Although new therapies have been introduced, an overall recurrence rate of 50-75% still puts patients at risk for these complications. When renal stones are the symptom of an underlying metabolic disorder there is a higher risk of recurrence.[1] Therefore we emphasise the importance of screening for secondary causes. In this case we demonstrate the need for metabolic screening, with a focus on hypocitraturia, a less well-known cause of nephrolithiasis.

CASE REPORT

A 37-year-old woman was referred by the urologist because of recurrent nephrolithiasis. She has suffered many episodes of nephrolithiasis. In total she had undergone 15 extracorporeal shock wave lithotripsy therapies and two ureterorenoscopies. However, a recent X-ray still showed the presence of four concrements. Because of persistent left-sided lumbar pain and impaired renal function of the left kidney, a nephrectomy was carried out. Urine saturation and stone analysis were not performed. She was on a normal diet and was not taking calcium or vitamin D supplements.

On physical examination she had a blood pressure of 120/80 mmHg. Further examination was unremarkable. Laboratory results revealed a serum creatinine of 66 μmol/l, serum potassium of 3.9 mmol/l, serum bicarbonate of 26 mmol/l and a normal level of serum calcium. The 24-hour urine sample showed a total urine volume of 1455 ml/24 hour, calcium of 3.0 ml/day and

normal levels of uric acid and oxalic acid. However, the 24-hour urine sample revealed a profound hypocitraturia of 0.9 mmol/24 hours (n = 2.2-4.4 mmol/24 hours). Repeated 24-hour urine collection showed similar results. As the other laboratory results were normal, no secondary cause was found for the hypocitraturia.

After treatment with potassium citrate, the urinary excretion of citrate normalised and serum potassium remained within normal values. Since the start of potassium citrate, no new episodes of nephrolithiasis have occurred.

DISCUSSION

Nephrolithiasis is a very common problem in which calcium stones are most frequently found. Recurrence rates among idiopathic stone formers is approximately 40-50% and even higher in the presence of an underlying metabolic disorder.[1] A thorough work-up will assess the aetiology of nephrolithiasis in up to 30-90% of patients.[2,3] Hypercalciuria, hyperoxaluria, hyperuricosuria and hypocitraturia are the metabolic disorders which are most commonly found (*table 1*). Hypocitraturia is estimated to be present in 20-60% if calcium stones are detected.[1,4] Several secondary causes concerning hypocitraturia are known: renal tubular acidosis, malabsorption, potassium deficiency, low intestinal alkaline absorption, low urinary calcium level and low urine volume (*table 1*). In about 50% of the cases, no obvious cause can be found.[5,6] A urine citrate excretion below 1.7 mmol/24 hour in men and 1.9 mmol/24 hour in women is considered to be diagnostic for hypocitraturia.

There are three ways in which citrate normally plays a role in the prevention of calcium stone formation. First, citrate complexes with calcium in the renal tubulus causing a reduction of ionic calcium concentrations in the urine. Second, these citrate-calcium complexes limit calcium supersaturation. Finally, citrate binds to the crystal surface and prevents calcium oxalate and calcium phosphate crystal agglomeration and growth.

When hypocitraturia is found, potassium citrate is the primary treatment with potassium bicarbonate as an alternative.[7] Potassium citrate increases urinary citrate concentration, decreases urinary calcium excretion and enhances the inhibitory function of Tamm-Horsfall proteins on urine crystal growth. Besides the increase of citrate, potassium citrate also induces bicarbonate regeneration, which results in an increase in potassium and urine alkalisation. The latter directly effects distal tubular calcium channels and reduces bone turnover. Together this will diminish urine calcium excretion.[8] The alkalising of the urine has a less beneficial effect for calcium phosphate stone formers, but a beneficial effect for cysteine and uric acid stone formers. Long-term results show an important reduction of the recurrence of nephrolithiasis with potassium citrate treatment.[9]

In case of nephrolithiasis, and when hypercalciuria is present, another option in the pharmacological treatment is thiazide diuretics. These have also shown to be successful in reducing the recurrence rate. Thiazide diuretics enhance the reabsorption of calcium in the proximal and the distal tubule. This effect is most likely caused in two ways. First by stimulation of proximal tubular calcium reabsorption through contraction of extracellular fluid volume, which induces an increase in proximal tubular reabsorption of sodium and hence an increase of reabsorption of calcium. Secondly it is thought to be caused by a direct increase in calcium reabsorption in the distal tubule.[1,10] What is essential is that, in contrast to loop diuretics, thiazide diuretics act distal to the medullary ascending limb so they can enhance secretion of sodium without also increasing that of calcium.

Table 1. *Common metabolic disorders of nephrolithiasis*[1,4]

Hypercalciuria[A]	**Hyperoxaluria**[B]	**Hyperuricosuria**[C]	**Hypocitraturia**[D]
Hyperparathyroidism	High oxalate intake	Myeloproliferative disorders	Renal tubular acidosis
Immobilisation	Bowel pathology	High purine intake	Malabsorption
Metastatic tumours	Increased production of endogenous oxalate	Enzymatic defects	Metabolic acidosis
High dietary salt		Renal leakage	Potassium deficiency
High protein intake		Uricosuric drugs	Hypomagnesaemia
Range of monogenic disorders			Low urine volume
Absorptive hypercalciuria			Low urinary calcium level

[A,B,C,D] **Metabolic disorders and their known aetiologies**

A common side effect of thiazide diuretics is potassium loss. Low serum potassium is known to cause intracellular acidosis, which in turn will lead to hypocitraturia. To preserve the beneficial effect of thiazide it is advised to prescribe potassium supplements.[I]

Next to pharmacological therapy there have been suggestions for dietary adjustments depending on the causative metabolic disorder. Fluid intake over 2 litres/24 hours, limited sodium intake, less than 2 g a day and a moderate protein intake are the most common dietary recommendations.[I,II]

When therapy is only directed at the relief of symptoms, patients with recurrent nephrolithiasis are at risk of kidney function decline. As stated above, a substantial number of the patients have an underlying metabolic disturbance, which in most cases is relatively easy to treat. Unfortunately, nephrectomy had to be performed in our patient. This emphasises the need for early referral to clarify the cause of recurrent nephrolithiasis.

CONCLUSION

This case underlines the importance of early metabolic screening for patients with recurrent nephrolithiasis, and awareness of the diagnosis of hypocitraturia. This approach will help to predict recurrent stone formation and further complications.

DISCLOSURES

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