

Cystinuria: a rare diagnosis that should not be missed

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Cystinuria is a rare autosomal recessive defect causing recurrent urinary tract stone formation. Morbidity from stone formation and repeated urological interventions can be reduced by early diagnosis and adequate medical treatment. In this review, we illustrate these points by discussing three patients with cystinuria and give a brief review of its management.

Introduction

Cystinuria is a rare autosomal recessive defect causing recurrent urinary tract stone formation. We would like to present three patients diagnosed with cystinuria in our unit, who had clinical differences in terms of the timing of their diagnosis, their compliance with treatment, and their outcomes. These features illustrate the importance of recognition of the condition in order to prevent stone recurrence and minimise morbidity. The latest developments and approaches used in the management of cystinuria will also be discussed.

Case reports

Case 1

A 25-year-old man presented with a history of a symptomatic left staghorn stone diagnosed in a public hospital 6 years earlier. The stone was effectively cleared using percutaneous nephrolithotomy (PCNL) and extracorporeal shockwave lithotripsy (ESWL) but was not chemically analysed after removal. He then presented with left loin pain and was found to have a recurrent left staghorn stone. Percutaneous nephrolithotomy was performed and the stone analysis showed cystine. A subsequent urine analysis confirmed the diagnosis of cystinuria. He was put on hyperdiuresis, potassium citrate to alkalinise his urine, and captopril, which was later changed to penicillamine due to symptomatic hypotension. He responded well to treatment maintaining a urinary cystine level below 150 mg/L and has had no stone recurrences during 3 years of follow-up. Family screening detected cystinuria in his sister but she had no history of renal stone formation.

Case 2

A 23-year-old woman presented to our unit complaining of loin pain and was diagnosed with bilateral renal stones. A primary ESWL was planned but this was complicated by steinstrasse (multiple stone fragments in the right ureter), so an open right ureterolithotomy was performed and the stones were cleared. Chemical analysis of the stones suggested cystinuria. Preventive treatment was offered but she defaulted follow-up as she was then asymptomatic. Three years later, she presented with loin pain once again and was found to have recurrent right staghorn and left pelviureteric junction stones. An open right pyelolithotomy, left PCNL and supplementary ESWL were performed to clear all the stones. She was started on preventive treatment again, including hyperdiuresis, urine alkalinisation, and chelating therapy. Stringent control of her urine pH and urine cystine level (190-250 mg/L) over the next 6 years resulted in only minor recurrence—a small (5 mm) asymptomatic right renal stone which was managed conservatively. Family screening detected cystinuria in a sister with an asymptomatic renal stone.

Key words

Cystine; Cystinuria; Treatment outcome;
Urinary calculi

Hong Kong Med J 2008;14:399-401

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Case 3

A 19-year-old man presented with on-and-off bilateral loin pain associated with stone passage. Although imaging just showed multiple small renal stones, his young age and multiple bilateral stones raised suspicions of an underlying metabolic abnormality. Urine and stone analysis was performed and the diagnosis of cystinuria was confirmed. He was started on hyperdiuresis and potassium citrate only. Hyperdiuresis of more than 3 L of urine and adequate urine alkalinisation of pH 6.9-7.7 was achieved. He had no more loin pain and stone passage episodes markedly decreased over the next 2 years but his family

胱氨酸尿症：一種不可掉以輕心的罕見病症

胱氨酸尿症是一種會經常導致尿道結石的罕見染色體隱性遺傳病，及早診斷及適當的藥物治療可以減少結石的形成及影響。本文總結三個胱氨酸尿症的案例以及其治療的重點。

refused screening for cystinuria despite our advice.

A summary of the presentation and management of these three patients is given in the Table. These three patients illustrate the importance of diagnosing and treating cystinuria early. The first two patients suffered from stone recurrence; one due to a delayed diagnosis and the other as a result of non-compliance with preventive therapy. The third case shows that early diagnosis and good compliance with preventive therapy can prevent the development of complications.

Discussion

Cystinuria is an autosomal recessive defect of the reabsorptive transport of cystine and dibasic amino acids including ornithine, arginine, and lysine from the renal proximal tubules and small intestines.¹ This leads to increased urinary excretion of the above four amino acids. Among these, only cystine has low solubility at physiologic urine pH levels (5-7), predisposing it to stone formation.

Cystinuria is rare and affects 1 in 7000 people worldwide, though the prevalence varies from race to race and is less common in Asian populations.² Cystine urolithiasis is the only clinical manifestation of cystinuria, and is responsible for 1 to 2% of urinary stones and 6 to 8% of paediatric urinary stones. The peak age for first stone presentation is during the third decade of life. Although most patients with cystinuria have impaired intestinal cystine absorption, this is not

a clinically significant deficiency as the absorption of short-chain amino acids is not affected.

Cystinuria can be divided into type 1 and non-type 1 (types 2 and 3) diseases. The type 1 form is completely recessive and involves mutations in the gene *SLC3A1* on chromosome 2.³ The non-type 1 forms are incompletely recessive and involve mutations in the gene *SLC7A9* on chromosome 19.⁴ Homozygotes with all three types of cystinuria excrete high concentration of cystine in their urine and are almost always symptomatic stone formers. Heterozygotes with type 1 cystinuria have normal urine cystine excretion and are silent carriers, whereas heterozygotes with type 2 and 3 cystinuria excrete high or moderate amounts of cystine and are at risk of stone formation when their urine cystine levels exceed the stone-forming threshold. The diagnosis is made by analysing urine and stones. Urine microscopy may show typical hexagonal cystine crystals, and the spot urine cystine concentration will be significantly elevated. Quantitative urine amino acid analysis should show significantly high levels of cystine, ornithine, arginine, and lysine. Stone analysis is useful for demonstrating that cystine is the major stone component.

Cystine stones tend to be very hard and need more ESWL shocks for adequate fragmentation. Use of a multimodal approach including ESWL, ureteroscopic lithotripsy, and PCNL is usually necessary for clearing cystine stones. Considering the rapid rate of renal stone recurrences in people with cystinuria, repeated invasive treatment may be needed. Therefore, preventive treatment is the most important part of management.

Preventive treatment relies on a combination of hyperdiuresis, urine alkalinisation, and raising cystine solubility.⁵ Hydration is the cornerstone of treatment, and a hyperdiuresis of 3 L of urine per day is needed to effectively dilute cystine in

TABLE. Characteristics of the three patients with cystinuria*

Characteristic	Case 1	Case 2	Case 3
Age at first presentation (years)	25	23	19
Presenting symptoms and findings	Left loin pain with left staghorn stone	Bilateral loin pain with bilateral renal stones	Frequent stone passage with multiple bilateral small renal stones
Surgical intervention prior to diagnosis of cystinuria	Left PCNL x 3 and multiple ESWL	Multiple ESWL and open right ureterolithotomy	None
Time to diagnosis of cystinuria after presentation (months)	72	19	16
Compliance with preventive treatment	Good	Poor (after first attack) and good (after second attack)	Good
Progress after diagnosis of cystinuria	No new stone formation	Recurrence of stone with multiple treatment done; small recurrence after improved compliance	No more loin pain; markedly reduced frequency of stone passage
Family screening results	One sibling had cystinuria but had no stone	One sibling had cystinuria and asymptomatic renal stone	Refused screening

* PCNL denotes percutaneous nephrolithotomy and ESWL extracorporeal shockwave lithotripsy

urine. Patients are advised to wake at night to drink water to supplement their daytime intake.⁶ Dietary modifications including restriction of methionine (a cystine precursor) and sodium are advocated as these have shown to increase cystine excretion.^{7,8} Potassium bicarbonate/citrate, is often given orally to alkalinise urine. Sodium bicarbonate has been used in the past but this is not advised as sodium increases cystine excretion. In patients who are stone-free, the above measures usually suffice. When the above measures fail to lower urine cystine concentration to less than 250 mg/L and recurrent stone formation occurs, further medical treatment is needed. These include either cystine-binding or cystine-reducing agents that have the ability to dissociate cystine into disulfide moieties with higher solubility than cystine itself. Options include D-penicillamine,⁹ alpha-mercaptopyrionylglycine,¹⁰ captopril,¹¹ and tiopronin.¹²

Barbey et al¹³ reported an average reduction of stone episodes per patient-year from 0.93 to 0.20, and a reduction in urological procedures required per patient-year from 3.0 to 1.5 with proper medical treatment. The urological procedures performed in those having medical treatment were mostly ESWL and other less invasive procedures.¹³ Chow and Streem¹⁴ reported the probability of stone-free survival at 1 and 5 years of treatment as 0.73 and 0.27 respectively, and stone recurrence was independent of pre-intervention urine cystine level, initial stone burden, and type of intervention selected. Stone recurrence and urological procedures required can also be significantly reduced by good compliance with medical treatment.¹⁵ Cystinuric patients are also reported to have poorer renal function and to be

at higher risk for renal loss. Good compliance with proper medical treatment can therefore significantly reduce the morbidity and surgical procedures required to manage cystinuria patients.

The treatment response should be closely monitored by checking urine pH and cystine levels, and using frequent imaging to identify early stone recurrence. Urine pH should be maintained at around 7.0-7.5 to achieve adequate alkalinisation while avoiding the predisposition to calcium phosphate stone formation at pH >7.5.

Conclusion

In patients with urinary calculi, chemical analysis of retrieved stones is mandatory. Knowing the stone composition is essential for guiding subsequent preventive treatment. For young stone formers (<30 years old), especially recurrent stone formers or those with strong family histories of stone disease, urine analysis, including microscopy and quantitative amino acid analysis, should always be done to rule out the possibility of cystinuria. Treatment should be started as soon as cystinuria is diagnosed, and the importance of compliance with treatment, especially the need for hyperdiuresis should be fully explained. After starting treatment, stone prevention relies heavily on meeting treatment targets including appropriate urine pH and urine cystine levels, and must therefore be closely monitored. Measuring urinary cystine levels in family members is helpful for identifying other cystinurics in the family, and can potentially reduce stone formation and invasive urological interventions with the initiation of early treatment.

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