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Cystinuria Revisited: Presentations with Calcium-Containing Stones Demands Vigilance and Screening in the Stone Clinic

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Abstract

Cystinuria is an inherited disorder resulting in urinary wasting of dibasic amino acids and often the formation of cystine stones. Cystinuria is often complicated by frequently recurring cystine stones which can form staghorn calculi. The clinical features of cystinuria can be extremely variable leading to missed or delayed diagnosis. Indeed, cystinuria may present with "idiopathic" nephrolithiasis and even calcium containing stones and patients presenting with calculi should be screened for this disorder to allow for appropriate medical and surgical management.

Introduction

Cystinuria is an inherited renal disorder resulting in urinary wasting of dibasic amino acids and often the formation of cystine stones. Cystinuria is often complicated by frequently recurring stones, large stones and staghorn calculi, which may result in nephrectomy and renal failure [1]. Cystinuria is caused by mutations in two genes, *SLC3A1* and *SLC7A9*. Cystinuria is often quoted as an autosomal recessive disease, but infact it may be inherited in multiple ways: an autosomal recessive manner, an autosomal dominant manner (often with incomplete penetrance), or in a digenic manner (where mutations are present in both genes). Within *SLC3A1* and *SLC7A9*, point mutations, multi-exon deletions and duplications and genomic rearrangements have all been described, leading to a loss of function of their encoded proteins. *SLC3A1* encodes the accessory protein rBAT [2] whilst *SLC7A9* encodes the catalytic transport protein $b^{0,+}$AT [3]. Together these proteins form a heterodimer that functions as an amino acid transport system known as system $b^{0,+}$, an electrogenic exchanger of extracellular dibasic amino acids and cystine for intracellular zwitterionic amino acids [4,5]. Within the kidney, system $b^{0,+}$ is expressed at the luminal membrane in the renal proximal tubule and mediates reabsorption of cystine, ornithine, lysine and arginine [5].

The clinical features of cystinuria can be extremely variable leading to missed or delayed diagnosis. Clinical variability is mostly seen in patients with heterozygous mutations and a recent study highlights this fact [6]. Here, a genetic screen of 272 renal stone formers and patients with nephrocalcinosis identified 52 likely causative mutations in genes known to lead to monogenic renal stone formation. Surprisingly, within this cohort there were 6 patients in whom known pathogenic heterozygous mutations in *SLC7A9* were detected, where there was no prior clinical suspicion of cystinuria [6]. Three of these patients presented with calcium containing stones (two with *SLC7A9* mutation p.Gly105Arg [7], and the other p.Asn206Glufs*3 [8]) whilst the others were labelled as having idiopathic nephrocalcinosis/nephrolithiasis or hypercalciuria (two with *SLC7A9* mutation p.Ala182Thr [3] and another with p.Gly105Arg [7]).

This observation is a timely reminder that patients with cystinuria may present with "idiopathic" nephrolithiasis and even calcium containing stones. Cystinuria may also be associated with serum biochemical abnormalities including hyperuricaemia [9].

Other descriptions of cystinuria patients forming calcium stones may be found in the literature. Early presentations with calcium containing stones are possible [10]. In contrast, Cupisiti et al. describe a recurrent calcium stone former in whom the diagnosis of cystinuria was delayed until the patient was 72 years of age [11]. Elkoushy and Andonian also describe patients with medium to low levels of cystinuria (presumed to be heterozygous carriers of mutations) with both calcium oxalate and uric acid stone formation [12]. This observation was also corroborated by in vitro data, prompting consideration of cystinuria as a risk factor for calcium stone disease [13]. Consequently, this led to an urge to broadly screen for cystinuria, especially in those patients with unexplained stones [14]. A recent review from St Thomas' Hospital confirmed the fact that even in known cystinuria patients, typical radiolucent cystine stones are not the rule. Here, 16 out of 70 cystinuria patients in this cohort had radio opaque stones [15].

It can be postulated that even with low urinary cystine excretion rates, as seen in patients with heterozygous mutations, cystine crystals form a nidus, which then allows the nucleation of calcium and uric acid crystals. Even once the diagnosis of cystinuria is established and treatment has begun with agents to alkalinise the urine, there may also be a risk of calcium phosphate crystal precipitation [16].

In light of these recent findings by Halbritter et al. [6] and a body of historical reports, we again emphasize the need for biochemical screening of urine for cystinuria for all idiopathic stone formers, where undetected cystinuria patients may be identified [17]. Screening for cystinuria is straightforward and may be performed on a spot urine sample [15,18].

Given that there are 2 underlying genes which lead to cystinuria, whose inheritance patterns and biochemical phenotypes are variable, the detection or clinical suspicion of cystinuria should prompt molecular genetic studies. With the advent of next generation sequencing techniques, these studies will become more accessible and will lead to important correlations between genetic variants and disease presentations and long term outcomes. Renal stone patients deserve a precise diagnosis of their cause of calculi as preventive measures can then be tailored towards the underlying cause.

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