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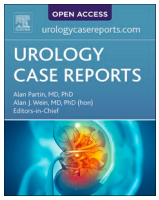

Endourology

First reported magnesium pyrophosphate kidney stone prompts diagnosis of hypophosphatasia

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ABSTRACT

Hypophosphatasia (HPP) is a rare genetic condition associated with poor bone mineralization, low serum alkaline phosphatase, high urinary pyrophosphate excretion, and nephrocalcinosis. Nephrocalcinosis is thought to develop due to the increased filtered loads associated with hypercalcemia and hyperphosphatemia, but the composition of these calcifications is incompletely understood. We report the first ever magnesium pyrophosphate (MgPPi) urinary stone, which prompted the new diagnosis of HPP in a 12-year-old boy. Stone analysis labs should include infrared spectra of PPi salts in their reference libraries to facilitate identification of these rare but clinically important stones.

1. Introduction

Hypophosphatasia (HPP) is a rare genetic condition associated with mutations in the tissue non-specific alkaline phosphatase (TNSALP) gene, resulting in low alkaline phosphatase activity and accumulation of pyrophosphate (PPi) in tissues.[1] The clinical manifestations of this disease vary and may include poor mineralization of the bones and teeth, as well as nephrocalcinosis particularly in young patients. The most severe disease is typically seen in prenatal or infantile presentations, but milder forms of the disease may not be diagnosed until adulthood after repeated fractures. We present here the first report of a magnesium pyrophosphate (MgPPi) urinary stone which prompted the diagnosis of HPP in a child.

2. Case presentation

The patient is a now 12-year-old male who initially presented 2 years ago with right sided flank pain. A renal ultrasound revealed a 6mm right proximal ureteral calculus with upstream hydronephrosis as well numerous bilateral caliceal stones measuring. Urinalysis showed a urine pH of 6, 3 RBCs/hpf and 19 WBCs/hpf and no crystalluria. Serum chemistries were notable for normal electrolytes, normal calcium of 10 mg/dL (normal range: 8.5–10.5 mg/dL), low bicarbonate of 21 mEq/L (normal range: 22–32 mEq/L), and low alkaline phosphatase at 40 IU/L (normal range: 58–234 IU/L). The patient passed the stone and it was submitted to Labcorp (Itasca IL) for compositional analysis by infrared (IR) spectroscopy which revealed a substance not included in the spectral library (Fig. 1). The stone was dissolved in HCl and quantitative chemical analysis was performed. Magnesium was the only cation identified, with no potassium and only trace amounts of calcium present. Ion chromatography was performed to identify the anion component of the stone, revealing that the primary anion component was pyrophosphate with only trace amounts of phosphate. The molar Mg to pyrophosphate ratio was 2.7:1 (higher than the expected 2:1), which suggested that an additional anion such as hydroxyl or carbonate was present but could not be detected by our laboratory.

The patient's past medical history was notable for poor weight gain and febrile seizures in early childhood, both resolved. Dental evaluations have revealed a delay in eruption of the permanent teeth, but no other issues such as early tooth loss. No history of fractures. The boy's father has also had nephrolithiasis of unknown type.

A 24-h urine collection was obtained after this initial stone passage and showed a low urine volume and hypocitraturia without other abnormalities (Table 1). He was treated with high fluid diet and potassium citrate 20 mEq twice daily.

Subsequent renal ultrasounds revealed bilateral non obstructing

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stones with evidence of stone growth. Approximately 18 months after his initial presentation, he again experienced renal colic and was found to have a 10mm left ureteral stone requiring ureteroscopy (Fig. 2). Stone samples were sent for compositional analysis to a different laboratory. However, the specific constituents of the stone could not be determined.

He presented once more while successfully passing an 8mm right ureteral stone. Given the patient's age and MgPPi stone composition, a nephrolithiasis genetics panel was obtained and revealed a heterozygous mutation of the APLP gene, c.1133A > T (p.Asp378Val), associated with autosomal dominant hypophosphatasia. This finding prompted skeletal assessment. Plain films of his wrists revealed very subtle increased sclerosis and irregularity within the distal radial metaphysis bilaterally, which could represent physiologic versus subtle manifestation of hypophosphatasia. Knee X rays were normal.

3. Discussion

Nephrocalcinosis in HPP is thought to be related to hypercalcemia and hyperphosphatemia that occur due to the inability of calcium and inorganic phosphate to be integrated into hydroxyapaptite crystals to mineralize bones and teeth. The increased filtered load can result in hypercalciuria and nephrocalcinosis. Pyrophosphate is also excreted at high levels in the urine of many affected patients.[1] While nephrocalcinosis is classically associated with pediatric variants of HPP, Berkseth et al. reported one patient in their series of 22 adult patients had nephrolithiasis.[2]

Despite the common finding of nephrocalcinosis in patients with HPP, we have been unable to identify sources reporting the chemical composition of stones nor the typical nephrolithiasis-related urine chemistries from patients with HPP other than a previous report from our own laboratory.[3] Potassium magnesium pyrophosphate (KMgPPi) urinary stones have been identified in cats, dogs and an adult man with HPP whose stone was analyzed in our lab.[3] The current case report, however, is the first time a MgPPi stone has been reported in any species and importantly, the stone analysis prompted genetic testing for HPP which confirmed the diagnosis. Of note, the boy in this report did not have hypercalciuria, a finding that will be important to assess in future patients who are found to have pyrophosphate-containing stones in order to better characterize this particular HPP phenotype.

While compositional stone analysis is guideline-recommended, not all urologists order this routinely. However, the identification of rare stones such as those containing various drugs, xanthine, pyrophosphate and others can be invaluable keys to identifying underlying medical conditions. In the case of pediatric HPP, there is now an FDA-approved enzyme replacement, asfotase alfa, that has been shown to improve skeletal mineralization and survival in children with severe forms of the disease.[4] While the initial studies of this medication largely focused on bone mineralization, Whyte et al. reported that "nephrocalcinosis did not progress after the initial 6 months of treatment and it even improved in some patients." We hope future studies of patients prescribed asfotase alfa will better clarify its effect on nephrolithiasis.

Table 1
Urine chemistries obtained when patient was 10 years old.

	Patient value	Age Relevant Male Mean[a]	Age Relevant Male SD[a]
Volume (L/day)	0.6	–	–
Calcium (mg/day/kg)	0.7	2.4	0.7
Oxalate (mg/day/1.73m^2)	20.9	28.9	14.7
Citrate (mg/day/mgCr/d)	79	663	260
pH	5.913	6.38	0.54
Uric Acid (g/day/1.73m^2)	0.43	0.52	0.15
Phosphorus (mg/day/kg)	12	15.5	7.0
Magnesium (mg/day/kg)	0.7	1.7	0.9
SS CaOx	3.49	7	6.2

[a] Age and gender means and standard deviations as provided by the performing laboratory.

Our main impetus for publishing this case report is to draw attention to the existence of this rare but potentially diagnostic category of stones containing PPi salts and provide other labs the reference infrared spectrum. The results obtained with FTIR are only as good as the reference library used by the lab and thus individual labs must constantly seek to improve their independent libraries. In this patient's case, while the initial stone analysis reported by our lab identified MgPPi, a later stone was sent to a different lab that was unable to identify the stone's composition. Given we have found both MgPPi and KMgPPi stones, it stands to reason that other cations such as calcium could also crystallize with pyrophosphate, especially since CaPPi is found in synovial fluid crystals in arthropathy.

4. Conclusion

This is the first report of a MgPPi urinary stone and the second PPi salt stone we have found in our laboratory, with both stone analyses leading to genetic testing for HPP. Stone analysis labs should be aware of this stone type and add these spectra to their IR libraries to improve the chances of making a critical diagnosis.

Consent

Written informed consent and permission to publish the case report was obtained from the child's legal guardian/parent.

COI statement

S.L.B. and J.R.A. are employees of Labcorp. E.S.M. and C.E.A. declare no conflicts of interest.

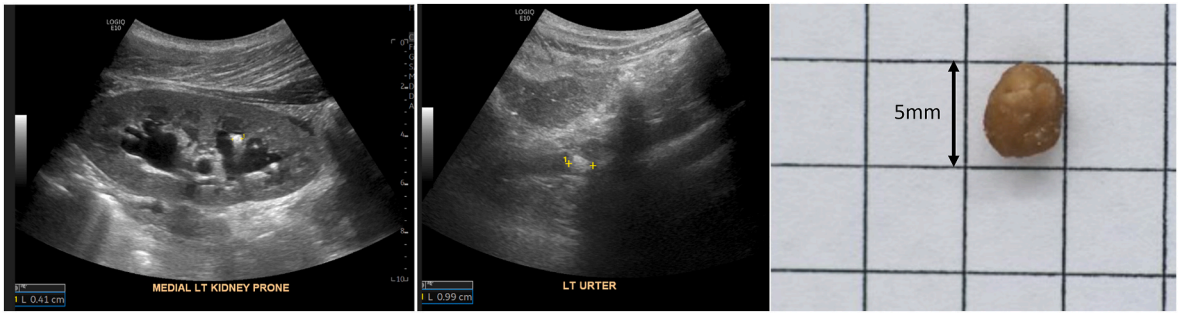

Fig. 1. Infrared spectrum of the patient's kidney stone composed of 100 % magnesium pyrophosphate. The vertical line at 2000 cm-1 denotes a change in the scaling of the x-axis.

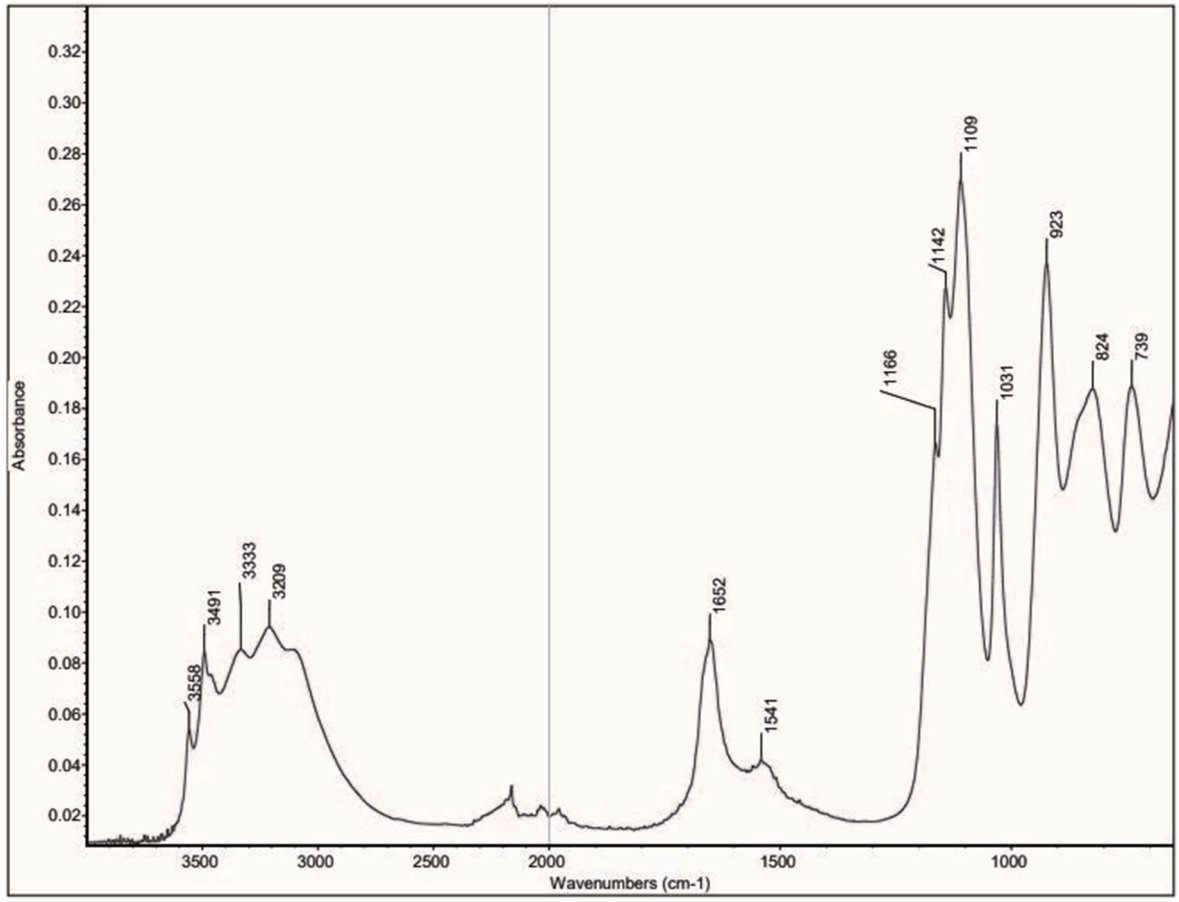

Fig. 2. Renal ultrasound images of the hydronephrotic kidney (left image) and ureteral stone (center), obtained when the patient became obstructed with a 1cm ureteral stone that was ultimately treated with ureteroscopic laser lithotripsy. Right image shows the spontaneously-passed calculus from the patient's earlier initial presentation who stone composition was found to be magnesium pyrophosphate.

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CRediT authorship contribution statement

Carlos E. Araya: Writing – review & editing, Investigation, Data curation. **Erica S. Mercer:** Writing – review & editing, Investigation. **John R. Asplin:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Sara L. Best:** Writing – original draft, Methodology, Data curation.

Abbreviations

HPP	Hypophosphatasia
PPi	Pyrophosphate
MgPPI	Magnesium Pyrophosphate
IR	Infrared

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