Scientific Research Publishing

Open Journal of Nephrology, 2022, 12, 214-221
https://www.scirp.org/journal/ojneph
ISSN Online: 2164-2869
ISSN Print: 2164-2842

A Problem-Solving in a Case of Medullary Nephrocalcinosis

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How to cite this paper: El-Reshaid, K. and Al-Bader, S. (2022) A Problem-Solving in a Case of Medullary Nephrocalcinosis. *Open Journal of Nephrology*, **12**, 214-221.
https://doi.org/10.4236/ojneph.2022.122021

Received: April 9, 2022
Accepted: June 21, 2022
Published: June 24, 2022

Abstract

Medullary Nephrocalcinosis (MNC) is defined as calcium deposition in tubular basement membrane and interstitium of the kidney medulla. It is 20 times more common than cortical one. In this case report, we present a 12-year-boy who presented with persistent nocturnal enuresis for 8 years. Physical examination and routine tests were normal except for microscopic hematuria. Renal ultrasound showed extensive MNC. Twenty-four-hour urine collection revealed normal mineral metabolic screen with low urinary excretion of calcium, phosphorous, magnesium and uric acid yet high for oxalates. Hence, and based on the above-mentioned data, certain metabolic disorders were ruled out: 1) hyperparathyroidism, 2) excessive intake of vitamin D, 3) hypercalcemia, 4) hypercalciuria, 5) hyperuricemia, 6) hyperuricosuria, 7) hypocitraturia, 8) cystinuria, 9) lysinuria and 10) distal renal tubular acidosis were ruled out. Subsequently, urine testing showed high concentration of glycolate with low glycerate and 4-hydroxy-2-oxoglutarates establishing diagnosis of type 1 primary hyperoxaluria (PH I). Further confirmatory tests included: 1) kidney biopsy which showed typical crystals deposition, 2) liver biopsy that confirmed deficiency of the liver-specific peroxisomal enzyme alanine: glyoxylate aminotransferase (AGXT), and 3) full gene analysis that confirmed gene mutation. In conclusion, our case report provides practical algorithm for establishing diagnosis in MNC which is not renal-limited and its prognosis depends upon the underlying etiology.

Keywords

Hypercalcemia, Hypercalciuria, Medullary Nephrocalcinosis, Mutation, Primary Hyperoxaluria

1. Introduction

Contrary to nephrolithiasis in which calcium salts are deposited in the renal tu-

bules, nephrocalcinosis is defined as calcium deposition in tubular basement membrane and interstitium [1]. Nephrocalcinosis is further subclassified into Medullary Nephrocalcinosis (MNC) and cortical one according to the site of calcium salts deposition. Cortical Nephrocalcinosis is associated with vascular diseases of the cortex viz. necrosis/infarction/ischemia, sepsis, hemolytic uremic syndrome and vascular transplant rejection [2]. On the other hand, MNC is associated with: 1) hypercalcemic and/or hypercalciuric states viz hyperparathyroidism, hypervitaminosis D and hypercalcemic states of sarcoidosis and neoplasms, 2) metabolic tubular defect viz. distal renal tubular acidosis (d-RTA) with/without medullary sponge kidney and hyperoxaluria, 3) diseases of the renal pyramids viz. papillary necrosis, sickle cell disease and renal tuberculosis, and 4) furosemide abuse [3]. MNC is 20 times more common than cortical one due to the concentrating effects of the loops of Henle, and the biochemical milieu of the medulla [4]. Prognosis of MNC depends upon the underlying etiology and if untreated, it is a risk factor for end stage renal disease [5]. A practical algorithm for establishing its etiology is laid down in our case report.

2. The Case

A 12-year-old boy presented with frequent micturition and persistent nocturnal enuresis after the age of 4 years. He denied fever, shortness of breath, oedema, abdominal pain, skin rash and joint pains. He did not have past history of significant medical illness, surgery, allergy or chronic intake of medications. There was no family history of renal disease in children or adults < 20 years. On his initial physical examination, the patient was conscious, oriented X3 and without distress of shortness of breath or pain. Blood pressure was 110/70 mm Hg. He was afebrile. He did not have lymphadenopathy, goiter, jugular venous distension or oedema. Systemic examination did not show abnormality. Laboratory investigations showed normal peripheral leucocytic and platelets counts. Hemoglobin was normal with normal MCV. ESR was 20 mm/h. Serum sugar, urea, creatinine, electrolytes and liver functions were normal. Serum cholesterol and TSH were normal. Urine routine and microscopy showed excess RBCs/HPF yet without proteinuria and pyuria. Serum complements (C3 & C4) and protein electrophoresis were normal. ANA, anti-ds DNA, ANCA, RA, hepatitis B surface antigen and anti-HCV antibodies were negative. Chest X-ray and ECG were normal. Abdominal and pelvic ultrasound was normal except for medullary calcinosis in normal-sized kidneys without stones and hydronephrosis (**Figure 1**). Those kidney abnormalities were further confirmed by CT scanning. Serum and urinary mineral as well as metabolic screen are summarized in **Table 1**. It showed normal parathyroid hormone at 7 pmol/L (N: 1.3 - 9.3) and normal 25-OH vitamin D at 78 nmol/L (N: 75 - 125). Twenty-four-hour urine collection revealed normal mineral metabolic screen with low urinary excretion of calcium, phosphorous, magnesium and uric acid yet high for oxalates. Hence, and based on the above-mentioned data, certain metabolic disorders were ruled out: 1) hyperparathyroidism, 2) excessive intake of vitamin D, 3) hypercalcemia, 4) hypercalciuria,

Table 1. Results of mineral metabolic screen for the patient with medullary nephrocalcinosis on normal diet.

Test		Results	Reference range	Assessment
Serum data: *				
Sodium		140	135 - 150	N
Potassium		4	3.6 - 5.1	N
Chloride		106	94 - 115	N
Corrected Calcium		2.3	2.2 - 2.5	N
Phosphrous		1.1	0.97 - 1.68	N
Magnesium		0.8	0.73 - 1	N
Uric acid		370	208 - 428	N
Arterial blood pH		7.4	7.35 - 7.45	N
Bicarbonate		25	24 ± 4	N
Intact Parathyroid hormone		7	1.3 - 9.3	N
25-vitamin		78	75 - 125	N
Anion gab		12	8 - 12	N
24-hour urine data: **				
Volume:		2.1 Litres		
	Creatinine	10280	200 umol/kg	Adequate 24 h-urine collection
	Protein	41	<150	
Electrolytes:				
	Sodium	82	40 - 220	N
	Potassium	28	25 - 125	N
	Chloride	115	110 - 250	N
	Calcium	2.1	2.5 - 7.5	Low
	Phosphrous	7.5	12 - 42	Low
	Magnesium	1.35	3 - 5	Low
	Uric acid	120	150 - 440	Low
	Citrate	3.2	0.6 - 4.8 for males	N
	Oxalate	0.74	<0.50 mmol	High
	Cystine	35	28 - 115	N
	Lysine	159	32 - 290	N

*Range in serum is expressed in mmol/L except for urate in umol/L, protein in g/L, intact PTH in pmol/L and vitamin D in nmol/L. **Range in urine is expressed in mmol except for urate, cystine and lysine in umol and protein in mg.

5) hyperuricemia, 6) hyperuricosuria, 7) hypocitraturia, 8) cystinuria, 9) lysinuria and 10) distal renal tubular acidosis were ruled out. CT scan with contrast excluded medullary sponge kidneys. Subsequently, urine testing showed high concentration of glycolate with low glycerate and 4-hydroxy-2-oxoglutarates establishing diagnosis of type 1 primary hyperoxaluria (PH I). Further confirmatory tests included: 1) kidney biopsy which showed typical crystals deposition (Figure 2), 2) liver biopsy that confirmed deficiency of the liver-specific peroxisomal enzyme alanine:glyoxylate aminotransferase (AGXT), and 3) full gene analysis that confirmed gene mutation. The latter was done using Polymerase Chain Reaction (PCR) Followed by DNA Sequence Analysis and Gene Dosage Analysis by Multiplex Ligation-Dependent Probe Amplification (MLPA) [6]. Subsequently, the patient was placed on the list for combined liver and kidney transplantation.

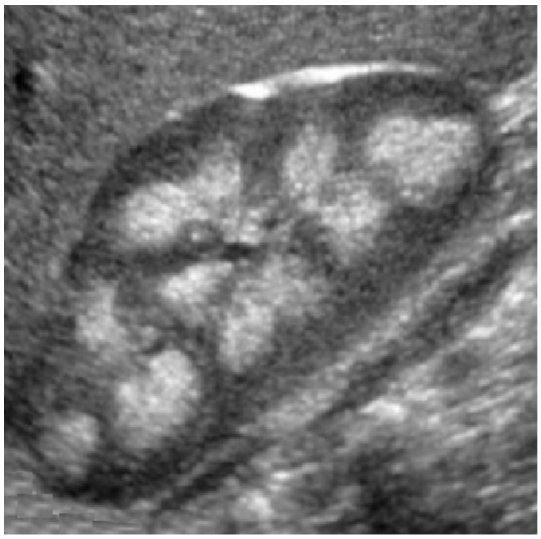

Figure 1. Longitudinal ultrasound view showing extensive medullary nephrocalcinosis.

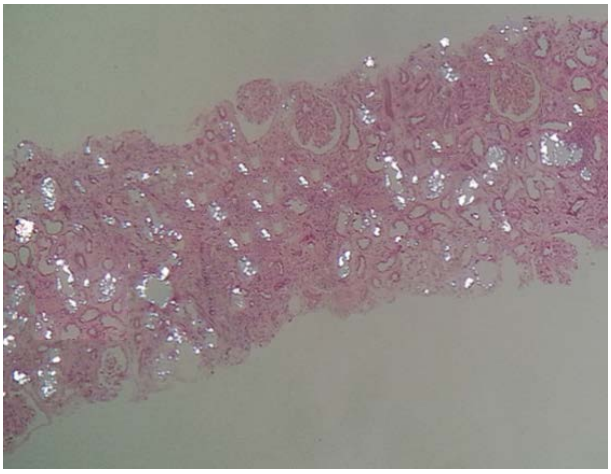

Figure 2. Photomicrograph of kidney biopsy showing extensive deposition of the birefringent calcium oxalate crystals in the tubules and interstitium seen under polarized light microscopy (H and E, ×100).

3. Discussion

Oliver Wrong's sub-divided MNC into being either molecular, microscopic or macroscopic [3]. In clinical practice the term commonly refers to macroscopic nephrocalcinosis that can be detected radiologically as bilateral, symmetrical increased echogenicity within the renal pyramids on ultrasound imaging [7]. Such disorder can manifest with renal colics if associated with nephrolithiasis yet most cases are asymptomatic and diagnosed on routine radiological testing. Ultrasonography is the ideal non-invasive imaging modality for both screening and assessment of disease progression/response to treatment. The latter can be reliably graded (Grade I - III) according to the extent of increased echogenicity affecting the medullary pyramids [8]. CT with/without contrast should be limited to suspected cases of medullary sponge kidney that can be associated with secondary forms of d-RTA and hence MNC [9]. The exact pathogenesis of MNC can be established by assessment of mineral metabolic screen as shown in **Table 1**. The latter should include: 1) adequate urine collection that is confirmed by proper urine creatinine (150 umol/kg for females and 200 for males), 2) serum estimates of electrolytes, pH, and levels of both parathyroid hormone and vitamin D, and 3) urine estimates of electrolytes, citrates, oxalates, lysine and cystine. Hypercalcemic etiologies include: hypervitaminosis D, hyperparathyroidism, immobilization syndromes, chronic granulomatous diseases (sarcoidosis) and infections (tuberculosis) and malignancy [10]. Isolated hypercalciuric states are common risk factor for childhood nephrolithiasis and MNC [11]. The list of etiologies include: genetic disorders viz. autosomal dominant hypocalcemic hypercalciuria (ADHH), which is caused by mutations in the calcium-sensing receptor (CaSR) gene, and genes connected to that receptor pathway (Gα11) [12]. Other genetic diseases resulting in hypercalciuria are familial hypomagnesemia hypercalciuria and Dent Disease. The latter is a rare genetic disorder affecting males since x-chromosomal recessive) and is accompanied by low molecular weight proteinuria and severe hypercalciuria [13]. Secondary hypercalciuria can result from medication (e.g., Furosemide-abuse and vitamin D-intoxication) as well as parenteral nutrition with high daily-intake of protein, sodium, phosphorus, and ascorbic acids that leads to significant increase in urinary calcium and oxalate excretion with low urinary citrates [14]. In our patient, hypercalcemic and hypercalciuric states were excluded by the mineral metabolic screen. Moreover, anatomical defects and medullary sponge kidney were excluded with CT scan. The only significant urinary abnormality in his mineral metabolic screen was hyperoxaluria. He did not have secondary causes for such phenomenon viz. increased intestinal oxalate uptake, due to malabsorptive states such as short bowel disease or chronic inflammatory bowel disease, by increased dietary oxalate intake, or lack of intestinal oxalate degrading bacteria [15]. Moreover, secondary hyperoxaluria is not associated with urine glycolate. The association of hyperoxaluria with glycolateuria is diagnostic for type 1 primary hyperoxaluria. In such patients, kidney biopsy confirms the diagnosis and establishes severity of

the tissue-deposition in a disease with variable phenotypic presentation. On the other hand, histochemical study of liver biopsy and gene analysis confirm the diagnosis. There are three types of genetic hyperoxaluric syndromes: 1) type I (PH I), which is secondary to mutation in the alanine/glyoxylate aminotransferase (AGT) and is characterized by increase urinary excretion of oxalate, glycolate, 2) type II (PH II) which is secondary to mutation in the glyoxylate/hydroxypyruvate reductase (GRHPR) and is characterized by elevated oxalate and l-glyceric acid urinary excretion and type III (PH III), and 3) type III (PH III) which is secondary to mutation in the 4-hydroxy-2-oxoglutarate aldolase (HOGA 1) and is characterized by raised urinary excretion of oxalate and hydroxy-oxo-glutarate and/or hydroxy-oxo-glutamate [16]. PH1 is an autosomal recessive inborn error of glyoxylate metabolism caused by caused by mutations in a gene called AGXT. Such defect leads to deficiency of the liver-specific peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT) which converts glyoxylate to the amino acid glycine [17]. Such high-burden of oxalate-synthesis is beyond the capacity of kidney filtration which ultimately leads to diffuse renal deposition, damage and loss. Moreover, in severe cases, extra-renal deposition, including the myocardium, has been documented and was associated with high-mortality [18]. As stated above, establishing its severity of the PH I is essential in its management since it manifest with variable phenotypic presentation of severity that ranges from early-age of onset and extent of tissue deposition. At present, in severe cases, liver transplantation as a form of enzyme replacement therapy is the only definitive therapy and has been used successfully over the last 10 years [19].

4. Conclusion

The etiology of MNC can be established by mineral metabolic screen that can be confirmed with histochemical and genetic studies with kidney biopsy for disease-severity.

Informed Consent

Written informed consent was obtained from the patient for the publication of this clinical case, there are no images of the patient in this manuscript.

Conflicts of Interest

The authors declare that they have no potential conflicts of interest related to the contents of this article.

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