Familial hypomagnesemia with hypercalciuria and nephrocalcinosis in 2 sisters

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ABSTRACT

نقص المغنيسيوم في الدم و المصاحب لزيادة الكالسيوم في البول وتكلس الكلى العائلي (FHHNC) هو مرض وراثي نادر ذو صفة متنحية لها علاقة بالأنابيب الكلوية. يتميز هذا المرض بهدركلوي للمغنيسيوم والكالسيوم ويؤدي في النهاية إلى فشل كلوي. وقد تم في الآونة الأخيرة ربطه بطفرة في الجين المسمى بكلودين 16 (CLDN 16) والتابع للبروتين الرابط المسمى بالباراسيلين– 1 (PCLN-1) هذا التقرير يتحدث عن أختين مصابتين بمرض (FHHNC) راجعت الأختان المستشفى في وقت مبكر من العمر إلا انه في البداية تم تشخيص الأولى بأن لديها نقص في إفرازات الغدد جارات الدرقية، أما المريضة الثانية فقد تم تشخيصها بأثر رجعي بعد تشخيص أختها. تطورت حالتهما إلى فشل كلوي مزمن خلال السنوات التالية. يهدف هذا التقرير إلى زيادة وعي الكادر الطبي بهذا المرض الجيني النادر آملين أن يؤدي ذلك إلى التشخيص والعلاج المبكر.

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) is a rare autosomal recessive tubular disorder characterized by excessive renal magnesium and calcium wasting, eventually, progressing to renal failure. It has been recently attributed to a mutation in the Claudin 16 (CLDN 16) gene of the Paracellin-1 (PCLN-1) tight junction protein. Herein, we report 2 sisters with FHHNC. Both sisters presented at an early stage with hypomagnesemia and hypocalcemia. The first patient was initially mislabeled and treated as a case of hypoparathyroidism, while the second patient was diagnosed retrospectively after the diagnosis of her sister. The 2 patients developed end stage renal disease.

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Primary magnesium wasting disorders are relatively rare conditions. In the last 4 decades, many reports on inherited magnesium disorders have been published, mainly because of a better understanding of the underlying genetic defect. Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) is an autosomal recessive inherited disease characterized by excessive renal magnesium and calcium wasting, frequently associated with bilateral nephrocalcinosis and progressive renal impairment.[1] The primary defect is related to impaired magnesium and calcium reabsorption in the thick ascending limb (TAL) of the loop of Henle. The FHHNC is caused by a mutation in the Claudin 16 (CLDN 16) gene of the Paracellin-1 (PCLN-1) protein, recently identified as a tight junction protein predominantly expressed in the TAL.[2,3] Affected patients usually present during childhood with recurrent urinary tract infection, polyuria/polydipsia, hematuria, or nephrolithiasis. The course of FHHNC is highly variable, symptoms may be mild at the beginning of the disease.[4] In this report, we present 2 sisters with FHHNC who have been mislabeled for many years. The objective of this report is to increase the awareness of the medical community of such a rare genetic disorder aiming for an early diagnosis and management.

Case Report. *Patient One.* A 19-year-old Saudi female who had normal milestone development. She presented to the medical care for the first time at the age of 6 years after she was noticed by the family to have attacks of abnormal hand movements. Documented physical examination was unremarkable apart from horizontal nystagmus. Serum biochemistry revealed: blood urea nitrogen (BUN) 23 mg/dL (normal range [NR] 7-22), creatinine (Creat) 0.8 mg/dL (NR 0.5-1.0), calcium (Ca) 10.1 mg/dL (NR 8.5-10.2), magnesium (Mg) 1.1 mg/dL (NR 1.8-2.4), phosphorus (PO_4) 4.4 mg/dL (NR 2.5-4.9). Brain CT scan was normal and EEG revealed the presence of generalized epileptic discharges with

focal accentuation in the centro parietal region. She was labeled to have tics and planned for observation only. She remained asymptomatic until the age of 11 when she presented again with one attack of carpopedal spasms. Physical examination was unremarkable, and laboratory investigations revealed: BUN 18 mg/dL, Creat 1.4 mg/dL, sodium (Na) 137 mEq/L (NR 135-148), potassium (K) 4.4 mEq/L (NR 3.8-5), chloride (Cl) 100 mEq/L (NR 95-109), carbon dioxide (CO_2) 22 mEq/L (NR 24-32), Ca 6.4 mg/dL, Mg 0.6 mg/dL, PO_4 5 mg/dL, pH 7.32, alkaline phosphatase (Alk Phos) 538 U/L (NR 43-277), and albumin 3.6 g/dL (NR 3.5-4.8). At this time she was diagnosed to have hypoparathyroidism and was treated by calcium carbonate and activated vitamin D. During follow-up, she was labeled to have hypocalcemia with mild renal impairment but no specific diagnosis was given. The doses of Ca and vitamin D were adjusted, and later on Thiazide diuretic was added. She was not regular on follow-up and was non-compliant to medication. At the age of 12 years, she was seen at the adult endocrinology clinic. Further history was taken and revealed that she had no history of urinary tract infection, polyuria, polydipsia, hematuria, abdominal pain, or renal stones. Family history was positive for chronic renal failure (CRF) in one of her sisters. Her father died suddenly at the age of 40 years of unrecognized cause. Her mother, one sister, and 2 brothers were healthy. The parents were first-degree cousins. Physical examination was unremarkable apart from nystagmus and myopia. Pertinent results of tests requested or taken from the patient's records revealed: BUN 28 mg/dL, Creat 1.8 mg/dL, Ca 7.5 mg/dL, PO_4 6.0 mg/dL, Mg 0.6 mg/dl, albumin 2.9 g/dL, Alk Phos 243 U/L, uric acid 7.1 mg/dL (NR 3-6), parathyroid hormone (PTH) 77.0 pmol/L (NR 1.3-7.6). Twenty-four hour urine, protein 1065 mg/24^0 (NR 0-165) creatinine clearance 64.19 ml/min/1.73 m^2 (NR 75-115), urine Ca 214 mg/24^0 (NR 40-350) or 4.39 mg/kg/day, urine PO^4 519.8 mg/24^0 (NR 400-1300), urine Mg 119 mg/24^0 (NR 12-192) (**Table 1**).

Table 1 - Laboratory and radiology findings.

Test	Patient-1	Patient-2	Normal value
Serum level			
Calcium mg/dL	6.4	6.1	8.5-10.5
Phosphorus mg/dL	5.0	5.9	2.5-4.9
Magnesium mg/dL	0.6	1.0	1.8-2.4
Albumin mg/dL	3.6	3.4	3.5-4.8
Blood urea nitrogen mg/dL	18	34	7-22
Creatinine mg/dL	1.4	2.0	0.5-1.0
Sodium mg/dL	137	141	135-148
Potassium mg/dL	4.4	4.8	3.8-5.0
Chloride mg/dL	100	108	95-109
Bicarbonate mg/dL	22	22	24-32
pH	7.32	NA	7.35-7.45
Uric acid mg/Dl	7.1	4.6	3.0-6.0
Parathyroid hormone pmol/L	77	41.7	1.3-7.6
Alkaline phosphatase U/L	538	168	43-277
25-OH-vitamin D	NA	NA	
Urine			
pH	6.0	5.5	5.0-8.0
Glycose uria	Negative	Negative	
Protein mg/dl	30	100	
Citrate	NA	NA	
24-urine			
Magnesium mg/24^0	119	NA	12-192
Calcium mg/24^0 (mg/kg)	214 (4.39)	NA	40-350 (<4.0)
Phosphorus mg/24^0	519.8	NA	400-1300
Protein mg/24^0	1050.6	1089	0-165
Creatinine clearance ml/min/1.73 m^2	64.19	26.0	75-115
Radiology			
Abdominal ultrasound	Nephrocalcinosis	Nephrocalcinosis Nephrolithiasis	

NA - not available, 24^0 - 24 hours

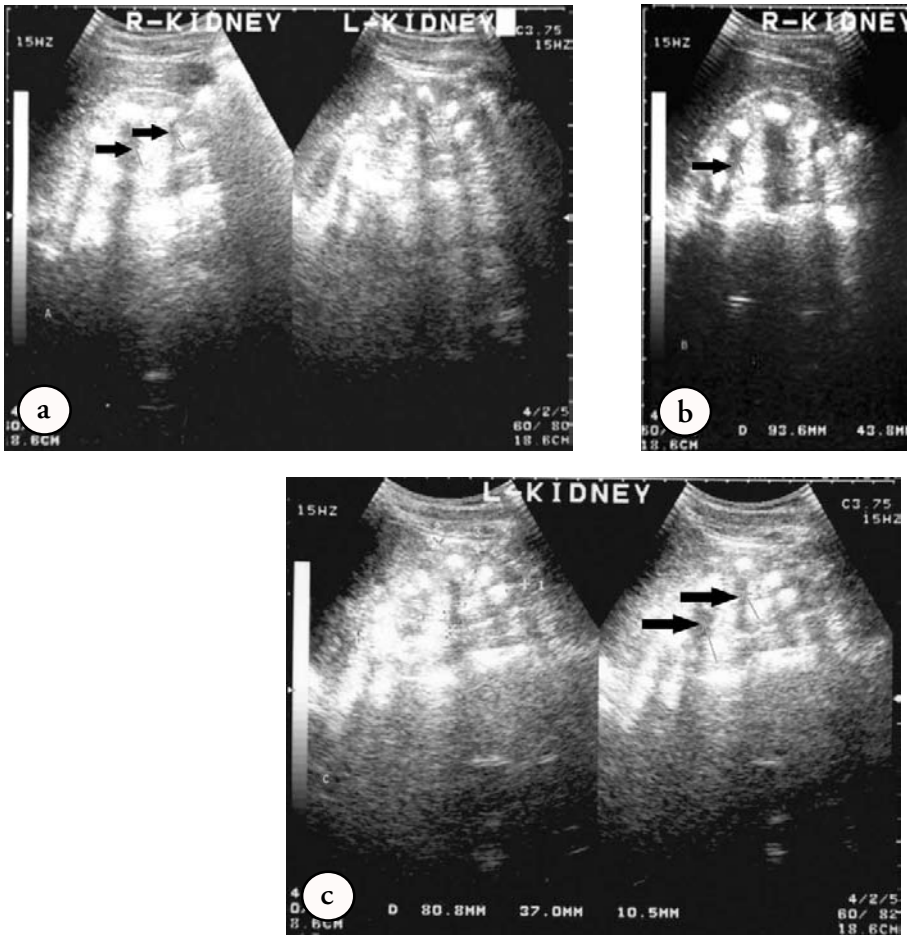

Figure 1 - Ultrasound for patient - 1, showing, **a**) both kidneys, **b**) right kidney, **c**) left kidney. All showing strong shadowing consistent with nephrocalcinosis as indicated by the arrows.

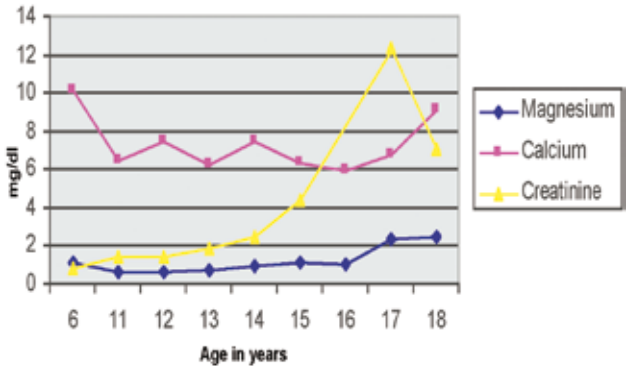

Figure 2 - Change in serum magnesium, calcium and creatinine over time for patient - 1.

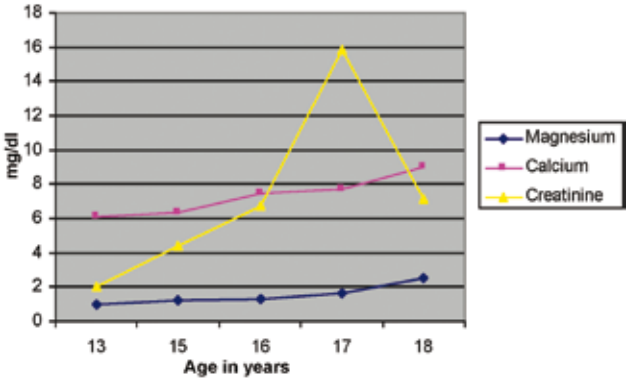

Figure 3 - Change in serum magnesium, calcium and creatinine over time for patient - 2.

Abdominal ultrasound was consistent with bilateral nephrocalcinosis (**Figure 1**). Audiogram revealed mild to high frequency sensory neuronal deafness of the left ear and ophthalmological evaluation documented the presence of bilateral horizontal nystagmus, myopia, ocular peripapillary depigmentation, and questionable corneal calcification. Based on the above, she was diagnosed to have FHHNC. Magnesium salt and Allopurinol were added to the medications. She continued to be non-compliant and although she remained asymptomatic in spite of persistent hypomagnesemia with hypocalcemia, her kidney function worsened over the following years (**Figure 2**). By the age of 17, she presented with symptoms of uremia. Her BUN was 252 mg/dL and Creat was 11.0 mg/dL. The serum Mg level normalized to 2.4 mg/dL. She was started on regular hemodialysis and planned for renal transplant.

Patient 2. The affected sister is currently 24 years old. Her first presentation was at the age of 6 years when she was evaluated by the ophthalmology team for decreased vision. She was documented to have bilateral horizontal nystagmus and myopia. At the age of 13, she presented with abdominal pain with no other significant symptoms. Physical examination was unremarkable apart from the ophthalmological findings. The biochemical profile revealed: BUN 34 mg/dL, Creat 2 mg/dL, Na 141 mEq/L, K 4.8 mEq/L, Cl 108 mEq/L, CO_2 22 mEq/L, Ca 6.1 mg/dL, PO_4 5.9 mg/dL, Mg 1.0 mg/dL, albumin 3.4 g/L, PTH 41.7 pmol/L, uric acid 4.6 mg/dL, Alk Phos 168 U/L, 24^0 urine protein 1089 mg/24^0 and creatinine clearance 26 ml/min/1.73 m^2 (**Table 1**). Abdominal ultrasound was consistent with bilateral nephrocalcinosis and nephrolithiasis. She was labeled to have renal tubular acidosis with chronic interstitial nephritis versus medullary sponge kidney and was treated with calcium carbonate in addition to activated vitamin D. She was not regular on follow-up. She remained asymptomatic, however, her kidney function deteriorated over time (**Figure 3**). By the age of 17 years, she was diagnosed to have end stage renal disease and started on hemodialysis. She developed one attack of seizure during dialysis and was treated with anticonvulsant therapy. She had successful live-unrelated kidney transplant one and half years later.

Discussion. Magnesium homeostasis is dependent on the balance between intestinal absorption and renal excretion. Hypomagnesemia can result from decreased dietary intake, malabsorption, or renal loss.[5] In the normal adult kidney, approximately 80% of the total serum magnesium is filtered at the glomeruli and more than 95% of the filtered magnesium is reabsorbed (50-60% in the cortical TAL, 20-25% in the proximal tubule, and 5-10% in the distal convoluted tubules). Thus, only 5% of the filtered magnesium is excreted in the urine.[6] Loss of function mutation in the PCLN-1/CLDN 16 gene results in a selective defect in paracellular magnesium reabsorption in the human TAL and leads to profound hypermagnesuria and hypomagnesemia. Since calcium and magnesium transport systems are frequently linked, the defect in renal magnesium handling is associated with a high rate of Ca excretion resulting in nephrocalcinosis and renal failure.[3] The FHHNC, which is linked to a mutation of the PCLN-1/CLDN 16 gene was first described by Michelis et al in 1972 (Michelis-Costrillo syndrome).[7] The cardinal features are hypomagnesemia, hypercalciuria, and nephrocalcinosis. It usually progress to end stage renal disease and may have extrarenal manifestations, mainly ophthalmic and auditory abnormalities. Our index patient (Patient 1) was documented to have hypomagnesemia with lowest magnesium level of 0.6 mg/dL (**Figure 2**), hypermagnesuria defined as daily excretion of more than 10-30 mg in the presence of hypomagnesemia,[8] hypercalciuria defined as urine Ca excretion of more than 4.0 mg/kg/day[9] and nephrocalcinosis identified by ultrasound (**Figure 1**). The second patient was also found to have hypomagnesemia with lowest Mg level of 1.0 mg/dL and nephrocalcinosis documented by ultrasound. Urine electrolytes study was not carried out (**Table 1**). The Mg level normalized in both patients after the development of end stage renal disease (**Figures 2 & 3**). The first patient presented with muscular tetany while the second patient was discovered during evaluation for abdominal pain. In a study of 25 families with FHHNC by Weber et al,[4] muscular tetany and abdominal pain were the initial presentation in 7% and 10%. In spite of the hypercalciuria, the serum Ca level in patients with FHHNC usually remains within the normal range.[2] An important observation was the fact that both of our patients had severe biochemical hypocalcemia with lowest corrected Ca level of 5.4 mg/dL for the first patient, and 6.0 mg/dL for the second patient. The presence of hypocalcemia may be related to vitamin D deficiency, which is common in this part of the world,[10] or related to the renal impairment. Unfortunately, vitamin D assay was not available at our institute and was not carried out. Both patients had a high parathyroid hormone level in spite of severe hypomagnesemia, which may reflect a chronic Ca depletion.[2] Both sisters had nephrocalcinosis while nephrolithiasis was found only in patient 2. Nephrolithiasis was the fifth common presenting complaints in the study of Weber et al.[4] Differential diagnoses that should be considered include isolated dominant hypomagnesemia with hypercalciuria, isolated recessive hypomagnesemia with normocalciuria, hypomagnesemia with secondary hypocalcemia, and

autosomal dominant hyperparathyroidism.[11] The 2 sisters have ophthalmic manifestations in the form of myopia and bilateral horizontal nystagmus. Patient 1 was also found to have ocular peripapillary depigmentation and questionable corneal calcification. Ocular involvement was reported in 30.3-40.5%.[4,12] Patient 1 has unilateral mild to high frequency sensory neuronal deafness; unfortunately, patient 2 had no audiogram evaluation. Hearing abnormalities were found in 3/42 patients reported by Benigno et al.[12] Interestingly, both patient's first evaluation was at the age of 6 years and both needed hemodialysis by the age of 17. Most patients with FHHNC progress to renal failure, which usually occurs in the second or third decade. The reported renal function deterioration rate is variable. Some suggested that the rate of disease progression is genetically determined. Kari et al[13] reported 7 Arab patients (of Saudi national-personal communication), with slow progression to end stage renal diseased contributed to ethnic background. The rate of progression in our 2 patients is similar to that reported in the literature. Patient 2 had successful renal transplant, and patient 1 is planned for kidney transplant. In general, renal transplant corrects the tubular disorder.[4]

The diagnosis of patient 1 was delayed for at least 6 years and the initial finding of low Mg level was ignored, while patient 2 was diagnosed retrospectively after the presentation of her sister. The reported delay of the diagnosis of such patients is up to 10 years.[13,14] Early diagnosis and start of medical therapy may not influence the natural history of the disease; however, it may improve the growth and final height of the patients.[15] Another important benefit of early diagnosis is family planning since parental consanguinity was found in the families studied.[4] The parents of our patients are first-degree cousins. Family members of our patients were invited for evaluation, however, they were reluctant to come. Although, genetic testing would be helpful, particularly in the presence of ophthalmic manifestations, it was not performed due to lack of resources.

In conclusion, the diagnosis of FHHNC should be considered in all patients presenting with hypomagnesemia especially in the presence of positive family history or renal impairment. Putting disease components together will help in the early diagnosis and management.

References

1. Praga M, Vara J, González-Parra E, Andrés A, Alamo C, Araque A, et al. Familial hypomagnesemia with hypercalciuria and nephrocalcinosis. ***Kidney Int*** 1995; 47: 1419-1425.
2. Weber S, Hoffmann K, Jeck N, Saar K, Boeswald M, Kuwertz-Broeking E, et al. Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis maps to chromosome 3q27 and is associated with mutations in the PCLN-1 gene. ***Eur J Human Genet*** 2000; 8: 414-422.
3. Simon DB, Lu Y, Choate KA, Velazquez H, Al-Sabban E, Praga M, et al. Paracellin-1, a renal tight junction protein required for paracellular Mg2+ resorption. ***Science*** 1999; 285: 103-106.
4. Weber S, Schneider L, Peters M, Misselwitz J, Rönnefarth G, Böswald M, et al. Novel paracellin-1 mutations in 25 families with familial hypomagnesemia with hypercalciuria and nephrocalcinosis. ***J Am Soc Nephrol*** 2001; 12: 1872-1881.
5. Mouw DR, Latessa RA, Hickner J. Clinical inquiries. What are the causes of hypomagnesemia? ***J Fam Pract*** 2005; 54: 174-176.
6. de Rouffignac C, Quamme G. Renal magnesium handling and its hormonal control. ***Physiol Rev*** 1994; 74: 305-322.
7. Michelis MF, Drash AL, Linarelli LG, De Rubertis FR, Davis BB. Decreased bicarbonate threshold and renal magnesium wasting in a sibship with distal renal tubular acidosis. (Evaluation of the pathophysiological role of parathyroid hormone). ***Metabolism*** 1972; 21: 905-920.
8. Agus ZS. Hypomagnesemia. ***J Am Soc Nephrol*** 1999; 10: 1616-1622.
9. Tasic V, Dervisov D, Koceva S, Weber S, Konrad M. Hypomagnesemia with hypercalciuria and nephrocalcinosis: case report and a family study. ***Pediatr Nephrol*** 2005; 20: 1003-1006.
10. Al-Jurayyan NA, El-Desouki ME, Al-Herbish AS, Al-Mazyad AS, Al-Qhtani MM Nutritional rickets and osteomalacia in school children and adolescents. ***Saudi Med J*** 2002; 23: 182-185.
11. Konrad M, Weber S. Recent advances in molecular genetics of hereditary magnesium-losing disorders. ***J Am Soc Nephrol*** 2003; 14: 249-260.
12. Benigno V, Canonica CS, Bettinelli A, von Vigier RO, Truttmann AC, Bianchetti MG. Hypomagnesaemia-hypercalciuria-nephrocalcinosis: a report of nine cases and a review. ***Nephrol Dial Transplant*** 2000; 15: 605-610.
13. Kari JA, Farouq M, Alshaya HO. Familial hypomagnesemia with hypercalciuria and nephrocalcinosis. ***Pediatr Nephrol*** 2003; 18: 506-510.
14. Tajima T, Nakae J, Fujieda K. Two heterozygous mutations of CLDN16 in a Japanese patient with FHHNC. ***Pediatr Nephrol*** 2003; 18: 1280-1282.
15. Wolf MT, Dötsch J, Konrad M, Böswald M, Rascher W. Follow-up of five patients with FHHNC due to mutations in the Paracellin-1 gene. ***Pediatr Nephrol*** 2002; 17: 602-608.