Pediatr Nephrol (2003) 18:506–510
DOI 10.1007/s00467-003-1139-8

ORIGINAL ARTICLE

Jameela A. Kari · Mohammed Farouq
Hammad O. Alshaya

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis

Received: 18 July 2002 / Revised: 21 January 2003 / Accepted: 22 January 2003 / Published online: 29 April 2003

Abstract Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) is a rare autosomal recessive tubular disorder that is frequently associated with progressive renal failure. The primary defect is related to impaired tubular reabsorption of magnesium (Mg) and calcium (Ca) in the thick ascending limb of Henle's loop. We have studied seven Arab patients with this syndrome who belong to four different families. The mean age at first presentation was 1.5±1.3 years (range 0.1–3 years) and at diagnosis 5.9±4.3 years (range 0.5–12 years). The presenting features were convulsions and carpopedal spasms (5 patients), polydipsia and polyuria (2 patients), rickets (2 patients), and recurrent urinary tract infections (1 patient). Bilateral nephrocalcinosis was observed in all patients. All patients had hypomagnesemia with a mean serum Mg of 0.45±0.09 mmol/l, an inappropriately high urine Mg of 2.07±0.73 mmol/24 h or fractional excretion of 15.3±7.1%, high urine Ca excretion of 4.1±1.2 mmol/24 h or urine Ca to creatinine ratio of 2.6±1.6, and normal serum potassium level of 4.4±0.34 mmol/l. All patients received Mg supplements and thiazide but exhibited slow worsening of their kidney function. After a mean follow-up of 4.4±3.9 years, one patient progressed to end-stage renal failure (ESRF). In conclusion, we report seven Arab patients with FHHNC syndrome. The clinical and biochemical data were similar to previous reports. However, they tend to show a slower rate of progression to ESRF.

Keywords Familial hypomagnesemia with hypercalciuria and nephrocalcinosis · End-stage renal failure · Nephrocalcinosis

J. A. Kari · M. Farouq · H. O. Alshaya
Department of Pediatrics, King AbdulAziz University Hospital, Jeddah, Saudi Arabia

J. A. Kari (✉)
Department of Pediatrics, King AbdulAziz University Hospital, PO Box 80215, Jeddah 21589, Saudi Arabia
e-mail: jkari@doctors.org.uk
Tel.: +996-55677904, Fax: +996-26743781

Introduction

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) is a rare autosomal recessive syndrome that is characterized by severe renal magnesium and calcium loss [1]. Manz et al. [2] reported the first case in 1978, and this was followed by a few additional reports from different parts of the world [1, 3, 4, 5, 6, 7]. It is frequently associated with progressive renal failure, although with variable progression rates [1, 3, 7, 8]. Praga et al. [1] reported that 75% of his eight patients required hemodialysis within a decade of diagnosis, while Weber et al. [8] reported that 36% of their cohort progressed to end-stage renal failure (ESRF) at a median age of 14.5 years. Recently, mutations in paracellin-1 (*PCLN-1*), which encodes the renal tight junction protein paracellin-1 (claudin-16), have been identified as the underlying genetic defect [8].

Homozygous mutations of *PCLN-1* result in a selective defect in paracellular magnesium (Mg) and calcium (Ca) reabsorption in the human thick ascending limb (TAL), with intact sodium chloride reabsorption at this site [9].

FHHNC is different from Gitelman syndrome, which is characterized by hypokalemia, hypomagnesemia, metabolic alkalosis, hypocalciuria, and moderate sodium chloride wasting [10]. It is also different from the isolated familial hypomagnesemia that has an autosomal dominant as well as an autosomal recessive mode of inheritance [10]. The renal Mg threshold is lowered in both forms, but the tubular maximum reabsorption is only reduced in the dominant form.

In this study we present the clinical and biochemical data of seven Arab patients with FHHNC, belonging to four unrelated families.

Materials and methods

Seven patients (4 females and 3 males) with the syndrome of hypomagnesemia, with hypercalciuria and nephrocalcinosis were identified in our department between 1996 and 2002. Their clinical charts were reviewed for clinical presentation, age at first pre-

sentation, age at diagnosis, serum creatinine, Mg, Ca, phosphate, sodium, potassium, chloride, bicarbonate, alkaline phosphatase (ALP), and parathyroid hormone level, and urine Mg, Ca, and creatinine. A complete physical examination, including an ophthalmological study, was performed in every case. Abdominal ultrasonography (US) was performed in all patients and reviewed for evidence of nephrocalcinosis. Mean follow-up between presentation and last visit was 4.4±3.9 years (range 0.5–14 years). Fractional excretion of Mg was calculated when the data for serum Mg and creatinine and urine Mg and creatinine were available at the same time, using the following formula: Urinary Mg×serum creatinine×100/Serum Mg×urinary creatinine. Glomerular filtration rate (GFR) was calculated using the Schwartz formula or diethyenthylene penta-acetic acid scan. Values were expressed as mean±standard deviation.

Results

The mean age at first presentation was 1.5±1.3 years (range 0.1–3 years) (Table 1). However, the mean age at diagnosis was 5.9±4.3 years (range 0.5–12 years). Three patients presented with infantile seizures, while another two patients had seizures later in life. Two patients presented with polyuria, polydipsia, metabolic acidosis, and severe rickets (Table 1). None of the patients had ocular abnormalities detected by an ophthalmologist. Most of the patients had a mild degree of renal impairment at diagnosis with a GFR of 62.8±16.4 ml/min per 1.73 m^2 (Table 2). All patients had a low serum Mg, with a mean of 0.45±0.09 mmol/l (normal=0.7–0.95), an inappropriately high urine Mg of 2.07±0.73 mmol/24 h (normal <1 mmol/24 h) or fractional excretion of 15.3±7.1% (normal <5%), a high urine Ca excretion of 4.1±1.2 mmol/24 h (normal=1.25–3.8) or urine Ca/creatinine ratio of 2.6±1.6 (normal <0.7), and a normal serum potassium level of 4.4±0.34 mmol/l. All patients had medullary nephrocalcinosis. Two patients had their urinary citrate measured and it was low at 50 mg/24 h (normal >150). It was not measured in the other patients because the test was not available in our laboratory. The progression to chronic renal failure was variable.

Family A

Three siblings (2 girls and 1 boy) of seven children were affected. The parents were first-degree cousins. The first affected girl presented at 2 years of age with polyuria and polydipsia. She had rickets and was failing to thrive. Investigations showed Ca of 1.66 mmol/l (normal 2.1–2.6), ALP of 897 U/l (normal <360), and normal phosphate. Because of the presence of metabolic acidosis and nephrocalcinosis, she was diagnosed as a case of distal renal tubular acidosis and was treated with sodium bicarbonate, potassium chloride, and activated vitamin D (1-α drops). However, over the following 18 months, the response to treatment was not as expected. She was lost to follow-up for the following 4 years and presented at 8 years of age with a short stature (both weight and height were below the 3rd percentile). There were no signs of rickets and her Ca, phosphate, and ALP were normal. Despite a very low serum Mg, she had a high urinary Mg and Ca. Urinary citrate was low and she had a moderate renal impairment (Table 2). A diagnosis of FHHNC syndrome was made and she was commenced on Mg citrate and hydrochlorothiazide. Over the next 3 years, she was admitted twice

Table 1 Clinical characteristics

Family (patient)	Sex	Presentation age (years)	Age at (years) diagnosis	Follow-up (years)	Polyuria/ polydipsia	Rickets	Nephro-calcinosis	Ocular abnormalities	Tetany/ convulsions
A (1)	F	2	8	14	+	+	+	–	+
A (2)	F	1.5	1.5	7	+	+	+	–	+
A (3)	M	3	3	0.5	–	–	+	–	–
B (1)	F	0.1	10	5	–	–	+	–	+
B (2)	M	3	9	3	–	–	+	–	–
C (1)	M	0.2	1	1	–	–	+	–	+
D (1)	F	0.4	7	0.5	–	–	+	–	+

Table 2 Biochemical data at diagnosis (*Mg* magnesium, *Ca* calcium, *PTH* parathyroid hormone, *NA* not available)

Family (patient)	Serum creatinine (μmol/l)	Creatinine clearance (ml/min per 1.73 m^2)	Serum Mg (mmol/l)	Urinary Mg (mmol/24 h)	Mg fractional excretion (%)	Urine Ca/creatinine ratio	Urinary calcium (mmol/24 h)	Urinary citrate (mg/24 h)	PTH (mg/24 h)
A (1)	104	42	0.45	3.15			5.71	50	169
A (2)	44	68	0.45	1.08			2.8	50	11.16
A (3)	38	90.5	0.61		7.3	4.25			
B (1)	87	65	0.44	2.18		1.34	3.92		
B (2)	91	58	0.47	1.87	12	2.4	3.81		
C (1)	44	NA	0.32		23.3	4.2			
D (1)	45	53	0.39		18.6	0.88			

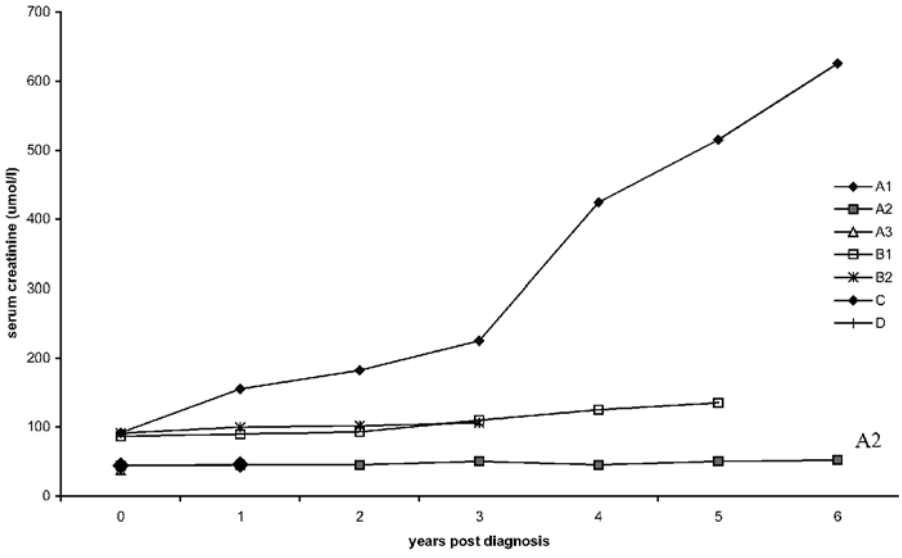

Fig. 1 Renal function expressed as serum creatinine in individual patients. Patients A (3) and patient D had less than a year of follow-up

with carpopedal spasms. Her kidney function worsened over the following years while her serum Mg normalized; Mg at 11 years of age was 0.91 mmol/l and her serum creatinine was 225 mmol/l; this worsened over the next 3 years to 626 mmol/l (Fig. 1). Her GFR was 10 ml/min per 1.73 m^2. Her parents described her as non-complaint with treatment.

The second affected girl presented with polyuria, polydipsia, and rickets at the age of 18 months. She was diagnosed as a case of FHHNC syndrome on the basis of her laboratory tests (Table 2) and the presence of nephrocalcinosis. She was admitted twice with carpopedal spasms and found to have low serum Ca and low Mg. She was treated with Mg citrate and hydrochlorothiazide, with a mild worsening of her kidney function. Her GFR at 9 years of age was 60 ml/min per 1.73 m^2 and her serum creatinine was 52 µmol/l (Fig. 1).

The third affected boy presented at the age of 3 years with gastroenteritis and was found to have metabolic acidosis and nephrocalcinosis. He was diagnosed as a case of FHHNC syndrome as he had a low serum Mg and high urinary Mg and Ca (Table 2). However, he had a normal GFR of 90 ml/min per 1.73 m^2.

Family B

Two siblings of ten children were affected. The parents were second-degree cousins. The first affected girl presented as a newborn with recurrent convulsions. The parents were told that she had a low Ca and calcified kidneys. She was treated with oral calcium and activated vitamin D. She presented to our clinic at the age of 10 years and was diagnosed as a case of FHHNC, on the basis of her laboratory results (Table 2) and the presence of nephrocalcinosis. She was commenced on Mg citrate and hydrochlorothiazide. Her kidney function worsened slowly, and by 15 years of age her serum creatinine was 135 µmol/l and her GFR was 49 ml/min per 1.73 m^2 (Fig. 1).

Her brother presented at the age of 3 years with renal calculi that were treated with shock wave lithotripsy but recurred many times. He was referred to the nephrology clinic at the age of 10 years and the diagnosis of FHHNC was made (Table 2). He was treated with Mg citrate and hydrochlorothiazide; however, he continued to have recurrent renal stones. Analysis of the stone showed that it contained 40% calcium oxalate and 18% tri-calcium phosphate. He had a recurrent urinary tract infection and voiding cystourethrography revealed a grade V reflux on the left side. His GFR was 50 ml/min per 1.73 m^2 and his serum creatinine was 106 µmol/l, 4 years later (Fig. 1).

Family C

There was one affected sibling of two. The parents were second-degree cousins and there was a history of two miscarriages. The male patient presented with recurrent convulsions during the 1st year of life. He was diagnosed (Table 2) and treated with Mg citrate and hydrochlorothiazide. His GFR at 2 years of age was 73 ml/min per 1.73 m^2. The unaffected sibling was screened and found to have normal serum and urine Mg levels.

Family D

There was one affected sibling of seven. The parents were first-degree cousins. The patient had recurrent seizures secondary to hypomagnesemia and hypocalcemia from the age of 4 months, which proved to be difficult to treat with Ca supplements, vitamin D, and carbamazepine. She was diagnosed at the age of 7 years as a case of FHHNC syndrome on the basis of her laboratory tests (Table 2) and the presence of nephrocalcinosis. She was treated with Mg citrate with partial improvement of her seizures. She also suffered from global developmental delay, microcephaly,

and dilated cardiomyopathy. She has two siblings who were developmentally delayed and had frequent seizures. However, they did not have hypomagnesemia, hypermagnesuria, hypercalciuria, or nephrocalcinosis.

Discussion

The clinical and biochemical characteristics of our patients are similar to previously reported cases (Tables 1 and 2). Renal lithiasis, convulsions, carpopedal spasm, polydipsia, polyuria, rickets, and recurrent urinary tract infections were the most common clinical findings. In addition, ocular abnormalities, chondrocalcinosis, and arterial hypertension have been described in other previously reported cases [1, 2, 3, 4, 5, 6]. Most of our patients (71%) had convulsions or tetany, while this was rarely reported previously [1, 2, 3. 4, 5, 7]. Furthermore, one patient in family B had a neonatal convulsion, which is not typical of this condition and could be explained by the concomitant early hypomagnesemia. Ocular abnormalities, including nystagmus, severe myopia, corneal calcifications, and chorioretinitis, have been associated with FHHNC syndrome [1, 7]. However, none of our patients had ocular abnormalities. Polyuria and polydipsia were the main symptoms in most previous reports [1, 2, 3, 4, 5, 6, 7, 8], but were present in only two of our patients (28.6%).

The cardinal biochemical findings of FHHNC syndrome are severe hypomagnesemia, hypermagnesuria, and hypercalciuria. The normal fractional urinary excretion of filtered magnesium is about 5%. In magnesium deficiency in humans, the kidneys can normally reduce the 24-h urinary Mg excretion to less than 1 mmol (24 mg) via unknown mechanisms, and initially without a concomitant fall in the plasma Mg concentration. Renal Mg wasting may be defined as a urinary excretion greater than 1 mmol/day in the presence of hypomagnesemia (plasma magnesium <0.7 mmol/l) [11]. Our patients presented with serum Mg of 0.45±0.09 mmol/l and high urinary Mg, while it would be expected that urinary Mg would be lowered with this degree of hypomagnesemia in a person with adequate Mg handling.

Nephrocalcinosis, which is a fundamental finding in this syndrome, was present in all of our patients. The absence of hypokalemia and metabolic alkalosis and the presence of hypercalciuria excluded Gitelman syndrome [9, 12, 13, 14, 15]. Citrate is a well-known inhibitor of renal lithiasis. However, citrate administration does not appear to have a beneficial influence by limiting the progression to renal insufficiency in FHHNC [1].

We did not study the effect of thiazide treatment on the hypercalciuria. However, all patients had a slow progression to chronic renal failure, except the first patient in family A who progressed to ESRF. She was not compliant with treatment. This leads us to hypothesize that the treatment could delay the progressive deterioration of kidney function. This conclusion is different from that reached by Praga et al. [1] who reported that neither chronic oral Mg administration nor thiazide diuretics normalized serum Mg levels or urinary Ca excretion, or delayed the need for renal replacement therapy. Similarly, Weber et al. [8] and Kuwertz-Broking et al. [3] reported that treatments seemed to have no effect on the progression of the disease. Others [4, 5] reported some delay in the long-term deterioration of renal function and avoidance of rickets by early administration of hydrochlorothiazide. Recently, Stoll and Listman [16] reported nephrolithiasis in a neonate with transient renal wasting of Ca and Mg. After 8 weeks of treatment with Mg and Ca supplementation plus potassium citrate, the hypomagnesemia and hypocalcemia normalized spontaneously, as did the urinary Ca, Mg, and citrate excretion. Interestingly, a year later there was no evidence of nephrocalcinosis on abdominal US.

The biggest reported series is that of Weber et al. [8]. They reported the clinical data and results of *PCLN-1* mutation analysis of 25 FHHNC families with 33 affected individuals. *PCLN-1* mutations were found in all of their patients except three mutant alleles (94%). The gene *PCLN-1*, the claudin 16 gene (3q27), codes for a renal tight junction protein that is involved in the paracellular transport of Mg and Ca in the TAL of Henle's loop, the distal tubule, and the collecting duct [13, 14]. Homozygous mutations of *PCLN-1* result in a selective defect in paracellular Mg and Ca reabsorption in the TAL, with intact sodium chloride reabsorption at this site [9].

Praga et al. [1] showed normal tubular Mg and Ca handling in five transplanted patients with FHHNC, which supports a defect in the Mg and Ca absorption by renal tubules of the native kidneys. We did not investigate unaffected relatives for hypercalciuria. However, this was reported in up to 42% in previous studies [1].

The relatively slow progression to ESRF in our patients compared with previous studies from Europe [1, 3, 8] could be explained by different ethnic backgrounds, as all of our patients were Arabs. Kuwertz-Broking et al. [3] reported two siblings of consanguineous Tunisian parents with FHHNC. After a 32-month follow-up period one commenced hemodialysis at the age of 5 years, whereas his sister showed no decline in renal function. This compares with 75% requiring hemodialysis after 4.3±3.8 years in the case series of Praga et al. [1] from Spain.

The developmental delay in the affected patient of family D can probably be attributed to another metabolic or neurological associated condition, as two of her siblings were developmentally delayed without having FHHNC syndrome.

We conclude that the clinical and biochemical presentation of FHHNC syndrome in Arab patients is similar to other nations. However, the progression to ESRF seems slower.

References

1. Praga M, Vara J, Gonzalez-Parra E, Andres A, Alamo C, Araque A, Ortiz A, Rodicio JL (1995) Familial hypomagnesemia with hypercalciuria and nephrocalcinosis. Kidney Int 47:1419–1425
2. Manz F, Scharer K, Janka P, Lombeck J (1978) Renal magnesium wasting, incomplete tubular acidosis, hypercalciuria and nephrocalcinosis in siblings. Eur J Pediatr 128:67–79

3. Kuwertz-Broking E, Frund S, Bulla M, Kleta R, August C, Kisters K (2001) Familial hypomagnesemia-hypercalciuria in 2 siblings. Clin Nephrol 56:155–161
4. Martin AM, Canals BA, Sanguino LL, Gavilan MC, Flores SJ (2001) Familial hypomagnesemia with hypercalciuria and nephrocalcinosis. An Esp Pediatr 54:174–177
5. Mourani C, Khallouf E, Akkari V, Akatcherian C, Cochat P (1999) Early hypomagnesemia, hypercalciuria and nephrocalcinosis: two cases in a family. Arch Pediatr 6:748–751
6. Evans RA, Carter JN, George CR, Walls RS, Newland RC, McDonnell GD, Lawrence JR (1981) The congenital "magnesium-losing kidney". Report of two patients. QJM 50:39–52
7. Benigno V, Canonica CS, Bettinelli A, Vigier RO von, Truttmann AC, Bianchetti MG (2000) Hypomagnesaemia-hypercalciuria-nephrocalcinosis: a report of nine cases and a review. Nephrol Dial Transplant 15:605–610
8. Weber S, Schneider L, Peters M, Misselwitz J, Ronnefarth G, Boswald M, Bonzel KE, Seeman T, Sulakova T, Kuwertz-Broking E, Gregoric A, Palcoux JB, Tasic V, Manz F, Scharer K, Seyberth HW, Konrad M (2001) Novel paracellin-1 mutations in 25 families with familial hypomagnesemia with hypercalciuria and nephrocalcinosis. J Am Soc Nephrol 12: 1872–1881
9. Blanchard A, Jeunemaitre X, Coudol P, Dechaux M, Froissart M, May A, Demontis R, Fournier A, Paillard M, Houillier P (2001) Paracellin-1 is critical for magnesium and calcium reabsorption in the human thick ascending limb of Henle. Kidney Int 59:2206–2215
10. Rodriguez-Soriano J, Vallo A, Garcia-Fuentes M (1987) Hypomagnesaemia of hereditary renal origin. Pediatr Nephrol 1:465–472
11. Geven WB, Monnens LA, Willems JL (1993) Magnesium metabolism in childhood. Miner Electrolyte Metab 19:308–313
12. Sutton RA, Domrongkitchaiporn S (1993) Abnormal renal magnesium handling. Miner Electrolyte Metab 19:232–240
13. Weber S, Schlingmann KP, Peters M, Nejsum LN, Nielsen S, Engel H, Grzeschik KH, Seyberth HW, Grone HJ, Nusing R, Konrad M (2001) Primary gene structure and expression studies of rodent paracellin-1. J Am Soc Nephrol 12:2664–2672
14. Cole DE, Quamme GA (2000) Inherited disorders of renal magnesium handling. J Am Soc Nephrol 11:1937–1947
15. Rodriguez-Soriano J (1998) Bartter and related syndromes: the puzzle is almost solved. Pediatr Nephrol 12:315–327
16. Stoll ML, Listman JA (2002) Nephrolithiasis in a neonate with transient renal wasting of calcium and magnesium. Pediatr Nephrol 17:386–389