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Hypomagnesaemia–hypercalciuria–nephrocalcinosis: a report of nine cases and a review

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Abstract

Background. The cardinal characteristics of primary hypomagnesaemia–hypercalciuria–nephrocalcinosis include renal magnesium wasting, marked hypercalciuria, renal stones, nephrocalcinosis, a tendency towards chronic renal insufficiency and sometimes even ocular abnormalities or hearing impairment.

Methods. As very few patients with this syndrome have been described, we provide information on nine patients on follow-up at our institutions and review the 42 cases reported in the literature (33 females and 18 males).

Results. Urinary tract infections, polyuria–polydipsia, renal stones and tetanic convulsions were the main clinical findings at diagnosis. The clinical course was highly variable; renal failure was often reported. The concomitant occurrence of ocular involvement or hearing impairment was reported in a large subset of patients. Parental consanguinity was noted in some families.

Conclusions. The results indicate an autosomal recessive inheritance. The diagnosis of primary hypomagnesaemia–hypercalciuria–nephrocalcinosis deserves consideration in any patient with nephrocalcinosis and hypercalciuria.

Keywords: hereditary diseases; hypercalciuria; kidney diseases; magnesium deficiency; nephrocalcinosis

Introduction

Intestinal malabsorption (including low dietary magnesium) or renal losses cause hypomagnesaemia [1]. Diuretics, cisplatin, aminoglycosides, cyclosporin or amphotericin B mostly account for renal magnesium wasting [1]. Primary renal magnesium wasting is rather unusual [2–4]. Four basic types have been recognized, as given in Table 1. The first basic type, referred to as isolated renal magnesium wasting, is very rare. The nosological classification of isolated renal magnesium wasting currently is controversial [2]. Furthermore, a recent review fails to separate isolated primary renal magnesium wasting from primary intestinal hypomagnesaemia [5], an inborn error caused by a selective defect in intestinal magnesium absorption [6,7]. However, the absence of hypokalaemic alkalosis and nephrocalcinosis distinguishes this basic type of primary renal magnesium wasting from the remaining types, and recent data suggest that in some cases hereditary isolated renal magnesium wasting maps to chromosome 11q23 [8]. The second basic type includes cases of renal magnesium wasting in the context of mitochondrial cytopathies [9]. The third basic type accounts for most cases of renal magnesium wasting. In these patients, renal magnesium wasting is associated with hypokalaemia and alkalosis. Primary renal hypokalaemic alkalosis represents a heterogeneous entity with at least three subsets: Gitelman disease, 'classic' Bartter syndrome and 'neonatal' Bartter syndrome. A unique gene is responsible for Gitelman disease. Conversely, at least three different genotypes have been identified in 'classic' or 'neonatal' Bartter syndrome. Hypomagnesaemia is almost always present in Gitelman disease, occasionally present in 'classic' Bartter syndrome but absent or exceptional in 'neonatal' Bartter syndrome [3,4]. The fourth basic type is the syndrome of primary hypomagnesaemia–hypercalciuria–nephrocalcinosis (PHHN). The cardinal characteristics of PHHN, for which the eponym Michelis–Castrillo has been suggested, include renal magnesium wasting, marked hypercalciuria, renal stones, nephrocalcinosis and sometimes even ocular abnormalities [2]. Very few patients with PHHN syndrome have been described [10–26]. In PHHN, information on renal tubular function and long-term outcome is rather poor. In this report, we provide information on nine patients. We also review the patients with PHHN reported to date in the literature [10–26].

Patients and methods

Nine patients with PHHN syndrome were identified at the Departments of Pediatrics, University of Bern (Switzerland),

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Milan (Italy) and Palermo (Italy) between 1970 and 1997. The cases of patients 1 and 2 have already been published in part elsewhere [26]. The diagnosis of PHHN was based on the repeated demonstration of normal blood pressure, plasma magnesium <0.75 mmol/l (by xylidil blue colorimetric assay [27]), molar ratio of urinary magnesium to creatinine markedly higher than age-dependent lower reference values (children aged 6–24 months: 0.40; children aged 2–10 years: 0.30; children aged 11 years or more: 0.20) [28], molar ratio of urinary calcium to creatinine [28] markedly higher than age-dependent upper reference values (children aged 6–12 months: 2.20; children aged 13–24 months: 1.50; children aged 2–3 years: 1.40; children aged 4–5 years: 1.10; children 6–7 years: 0.80; children aged 8 years or more: 0.70) and extensive medullary nephrocalcinosis (clearly visible on plain X-ray films and confirmed on renal ultrasound). The initial evaluation also included the determination of plasma creatinine, sodium, potassium, chloride, uric acid and calcium, plasma and urinary inorganic phosphate, the blood acid–base balance, proteinuria, glucosuria and aminoaciduria, and the glomerular filtration rate (GFR; by inulin ($n=5$) or creatinine clearance ($n=4$)).

The molar urinary oxalate over creatinine excretion was normal in the patients [29], as compared with age-dependent upper reference values (children aged <6 months: 0.360; children aged 7–24 months: 0.174; children aged 2–5 years: 0.101; children aged >5 years: 0.080).

In four patients (1, 2, 3 and 5), the renal contribution to acid–base balance was assessed after peroral administration of ammonium chloride at a dosage of 3.0 mmol/kg body weight followed by parenteral administration of sodium bicarbonate at a dosage of 1.0 mmol/kg body weight [30]. The urinary excretion rates of bicarbonate and ammonium were plotted against the corresponding concentrations of bicarbonate in plasma. At the crossing point of the two curves, a 'bicarbonate equivalent point' is present, which represents the acid–base equilibrium that the kidney is able to maintain [30]. In six patients (1, 2, 3, 4, 5 and 9), the renal ability to dilute urine following oral water administration and to concentrate following water deprivation for 9–12 h was also assessed.

Results

The history and the initial clinical and biochemical findings of the nine patients (six girls and three boys, age at diagnosis from 0.5 to 12 years), who belonged to five different families, appear in Table 2. The parents of patients 1 and 2 were second degree relatives, those of patients 6, 7 and 8 first degree relatives (patients 6 and 7 were monozygotic twins). The current age of the patients ranges from 10 to 36 years. The patients had been referred for evaluation because of urinary tract infections ($n=7$), renal stones ($n=3$), polyuria ($n=4$), failure to thrive ($n=1$), vomiting ($n=1$) and gross haematuria ($n=1$). Surgical stone management was required repeatedly in patients 1 and 3. One subject (patient 8) was referred because she was the sibling of two recognized patients (twins 6 and 7). Patients 4 and 5 developed nephrolithiasis 7 and 10 years after diagnosis. Pregnancy, delivery and neonatal body weight were normal in the nine patients. In patients 6 and 7 (twins), neonatal body weight was <2.50 kg. Ocular involvement, including myopia, macular colobomata and tapetoretinal degeneration, was present in siblings 1 and 2 (toxoplasmosis initially had been suspected in these patients). Mild bilateral neurosensorial hearing impairment was detected at the age of 17 years in patient 5. Hearing had been found to be normal in this patient 9 years earlier. GFR was moderately decreased in patient 3 and slightly decreased in patient 6. The initial GFR of 75 and 51 ml/(min 1.73 m^2) noted in patients 4 and 5 might well be normal, considering their age of 6 months. Uric acid was slightly increased and GFR consistently decreased at diagnosis in patient 3. Metabolic acidosis was noted in patient 5. Hypomagnesaemia and 'normal' or high urinary magnesium excretion were found in all patients. In patient 9, a normal plasma

Table 1. Biochemical findings in patients with primary hypomagnesaemia, either intestinal or renal

	Urinary magnesium	Urinary calcium	Circulating calcium	Circulating potassium	Acid–base balance
Defective intestinal magnesium absorption (Paunier disease)	Low	Rather low	Low	Normal	Normal
Renal magnesium wasting					
Isolated renal magnesium wasting	'Normal' to high[a]	Rather low	Normal (low)	Normal	Normal
Mitochondrial cytopathies associated with renal magnesium wasting[b]	'Normal' to high[a]	Variable	Variable	Variable	Variable
Hypokalaemic alkalosis with hypomagnesaemia and hypocalciuria (Gitelman disease)[c]	'Normal' to high[a]	Low	Normal (low)	Low	Alkalosis
Hypomagnesaemia–hypercalciuria –nephrocalcinosis (PHHN)	'Normal' to high[a]	High	Normal (low)	Normal	Normal (acidosis)

[a]Inappropriately increased with respect to the concurrent hypomagnesaemia (with negative magnesium balance, the urinary magnesium excretion rapidly falls to very low values unless urinary magnesium wasting is present).
[b]Mostly associated with a generalized dysfunction of the proximal tubule including excessive urinary amino acids, glucose, inorganic phosphate and bicarbonate (so-called de Tonı–Debré–Fanconi syndrome).
[c]Hypomagnesaemia is sometimes present in 'classic' Bartter syndrome (renal hypokalaemic alkalosis with normal or slightly increased urinary calcium excretion).

Table 2. History and clinical and biochemical findings at diagnosis in nine patients with primary hypomagnesaemia-hypercalciuria-nephrocalcinosis (PHHN) with or without ocular involvement

Family	I		II		III	IV			V
Patient	1	2	3	4	5	6	7	8	9
Parental consanguinity	Present		Unknown		Unknown	Present			Unknown
Sex	M	F	F	M	F	F	F	F	M
Age at diagnosis (years)	8	6	2	0.5	0.5	11	11	4	12
Present age (years)	36	31	30	16	21	19	19	10	13
Major initial complaints	Urinary infections Renal stones Polyuria		Urinary infections Renal stones		Urinary infections vomiting, polyuria failure to thrive	Urinary infections gross haematuria	Urinary infections	None	Polyuria
Neonatal body weight (kg)	2.55	2.81	3.52	2.95	4.10	2.15	1.80	3.60	3.21
Ocular involvement	Severe myopia, nystagmus macular colobomata tapetoretinal degeneration		Absent	Absent	Absent	Absent	Absent	Absent	Absent
Hearing impairment	Absent	Absent	Absent	Absent	Absent[b]	Absent	Absent	Absent	Absent
Plasma creatinine[a] (μmol/l)	61	80	160	63	65	92	58	55	71
Glomerular filtration [ml/(min 1.73 m^2)]	81[c]	82[c]	40[c]	75[c]	51[c]	70[d]	129[d]	83[d]	116[d]
Plasma sodium[a] (mmol/l)	136	139	141	140	134	138	142	140	141
Plasma potassium[a] (mmol/l)	4.29	4.44	3.71	4.57	3.49	4.51	4.74	4.96	3.98
Plasma chloride[a] (mmol/l)	104	99	106	107	97	103	102	105	105
Plasma uric acid[a] (μmol/l)	317	389	496	305	250	302	405	273	332
Plasma inorganic phosphate[a] (mmol/l)	1.29	1.22	1.30	1.70	1.85	1.47	1.70	1.60	1.30
Fractional phosphate excretion[a] (10^{-2})	10.2	12.3	24.6	25.8	10.2	14.8	11.9	16.0	9.48
Total plasma magnesium[a] (mmol/l)	0.61	0.63	0.62	0.62	0.65	0.53	0.48	0.52	0.63
Urinary magnesium/creatinine[a] (mol/mol)	0.96	1.05	0.77	1.03	0.83	0.92	1.33	1.38	0.41
Total plasma calcium[a] (mmol/l)	2.52	2.43	2.39	2.40	2.50	2.33	2.34	2.33	2.51
Urinary calcium/creatinine[a] (mol/mol)	1.35	1.71	2.29	2.72	3.01	1.40	1.53	1.88	1.00
Blood pH[a]	7.37	7.36	7.42	7.43	7.24	7.37	7.36	7.37	7.40
Carbon dioxide pressure[a] (mmHg)	44.8	38.2	25.3	21.2	35.8	39.1	40.3	40.9	40.0
Plasma bicarbonate[a] (mmol/l)	25.1	20.9	15.9	13.6	14.9	21.9	22.1	22.9	23.8
Aminoaciduria	Normal	Mild generalized hyperaminoaciduria	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Urinary oxalate/creatinine (mol/mol)	0.019	0.022	0.049	0.078	0.056	0.020	0.026	0.030	0.037
Maximal urinary osmolality (mmol/kg water)	330	283	286	338	305	Not assessed	Not assessed	Not assessed	470
Minimal urinary osmolality (mmol/kg water)	120	82	162	94	78	Not assessed	Not assessed	Not assessed	110
Medical treatment	Thiazides	Thiazides	Thiazides Potassium citrate	Thiazides (for a short time) Potassium citrate Magnesium salts	Potassium citrate Magnesium salts	Thiazides Potassium citrate Magnesium salts	Thiazides Potassium citrate Magnesium salts	Thiazides Potassium citrate Magnesium salts	Potassium citrate Magnesium salts

Mental retardation, arterial hypertension, pathological proteinuria and glucosuria were not demonstrated in the nine patients.
[a]Median of three determinations; [b]detected at the age of 17 years; [c]inulin clearance; [d]creatinine clearance.

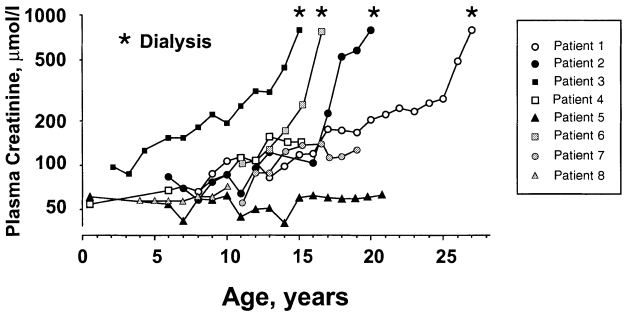

Fig. 1. Long-term course of plasma creatinine in eight patients with primary hypomagnesaemia–hypercalciuria–nephrocalcinosis and a follow-up of at least 5 years.

magnesium level of 0.78 mmol/l had been found at another institution 3 years before diagnosis. All patients presented with normocalcaemic hypercalciuria. Both plain X-ray films and renal ultrasound revealed signs consistent with medullary nephrocalcinosis in the nine patients.

During the neonatal period, patient 7 presented hypocalcaemic seizures, but circulating calcium levels subsequently returned to normal. A mild generalized hyperaminoaciduria was noted in patient 2. The ability to concentrate urine was markedly impaired in the six patients who underwent this examination.

After diagnosis, seven patients (1, 2, 3, 4, 6, 7 and 8) were treated with thiazides, seven (3, 4, 5, 6, 7, 8 and 9) with potassium citrate and five (5, 6, 7, 8 and 9) with magnesium salts.

At follow-up, hypomagnesaemia tended to persist and even to be exacerbated. However, normal plasma magnesium values were sometimes noted in patients when plasma creatinine values were found to be >250 μmol/l.

The long-term course of plasma creatinine in the eight patients with a follow-up of 5 years or more is given in Figure 1. Chronic renal failure followed by terminal failure requiring dialysis was noted in patients 1 (dialysis at the age of 27 years), 2 (20 years), 3 (14 years) and 6 (16 years). Plasma creatinine currently is normal in patients 5 and 9 and slightly increased in patients 4, 7 and 8. Patients 1, 2, 3 and 6 received a cadaveric kidney graft 10–24 months after starting chronic dialysis. Graft failure secondary to chronic rejection occurred in patients 2 and 3. Growth at diagnosis was normal in the nine patients, as indicated by the *Z*-score for height (from $+1.8$ to -1.3). Later on, growth retardation was observed in patient 3, who developed severe renal failure before reaching adult height.

The study of the renal contribution to acid–base balance (Figure 2) demonstrated a reduced urinary ammonium excretion in patient 5. The 'bicarbonate equivalent point' was 21.9, 20.3 and 19.6 mmol/l in patients 1, 2 and 3.

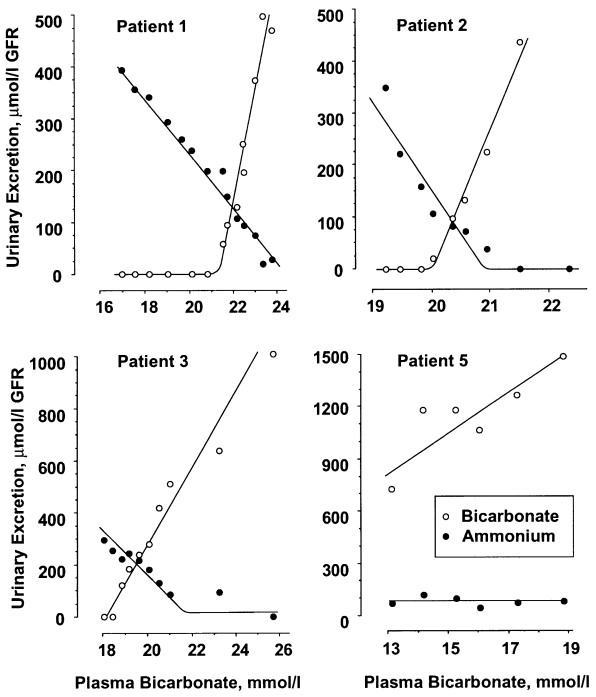

Fig. 2. Renal contribution to acid–base balance in four patients with primary hypomagnesaemia–hypercalciuria–nephrocalcinosis. The urinary excretion rates of bicarbonate and ammonium were plotted against the corresponding concentrations of bicarbonate in plasma. At the crossing point of the two curves, an 'equivalent point' is present, which represents the metabolic acid–base equilibrium that the kidney is able to maintain.

Review of the literature

Apart from the present report, at least 35 families and 42 patients (27 females and 15 males) with PHHN have been described in 16 reports (each containing 1–8 cases) following the first report by Michelis [10–25]. The corresponding clinical data are summarized in Table 3. Urinary tract infections, polyuria–polydipsia, renal stones and tetanic convulsions were the main clinical findings at diagnosis in the patients. Renal failure was often reported.

Renal transplant was not followed by recurrent hypomagnesaemia, hypercalciuria and nephrocalcinosis in 10 patients [13,20,22]. However, a possible post-transplant recurrence was reported in a rather poorly characterized patient [21].

The concomitant occurrence of ocular involvement, first emphasized by Castrillo [14], was reported in 17 of the 42 patients [13–16,20,23,24]. Myopia and macular colobomata were the most common ocular disorders. Hearing impairment was reported in two families with two and one affected members, respectively [13,21]. Parental consanguinity was noted in at least six of the 35 families with PHHN [15,19,22]. None of the parents presented the full blown clinical spectrum of the diseases including renal hypomagnesaemia, hypercalciuria and nephrocalcinosis. However, abnormal renal findings such as isolated hypercalciuria or renal stones were discovered in 16 out of 23 families.

Discussion

Nephrocalcinosis refers to the diffuse deposition of calcium in the kidney and urolithiasis to stones in the

urinary tract, though the two conditions often co-exist [31,32]. Increased urinary calcium, oxalate or urate, low amounts of crystal formation inhibitors (such as citrate and magnesium or some recently described macromolecules) can result in nephrourolithiasis. Also, urine volume and the acid–base status influence the interactions of the aforementioned ions to promote or abrogate crystal formation [31,32]. Increased urinary calcium excretion, magnesium deficiency and urinary acidification disturbances might well account for the tendency towards nephrocalcinosis and urolithiasis in PHHN [10–26].

The biochemical criteria used for the diagnosis of renal magnesium wasting and hypercalciuria in PHHN deserve discussion. The kidney plays a pivotal role in magnesium homeostasis [1]. When magnesium intake is curtailed or when there is intestinal magnesium malabsorption, the normal kidney reduces magnesium excretion to very low values (hypomagnesiuria). Consequently, the concurrent demonstration of hypomagnesemia and urinary magnesium markedly higher than the lower reference value demonstrates renal magnesium wasting [1]. The definition of hypomagnesaemia, as assessed by the xylidil blue colorimetric assay applied in the present study [27], is widely used in the literature [1]. However, other colorimetric assays or flame atomic absorption spectrophotometry sometimes provide different values [2,20]. The definitions of hypercalciuria and hypomagnesiuria used in the present study take into account the fact that in healthy humans the urinary calcium:creatinine and the urinary magnesium : creatinine ratios are elevated in infancy and decline progressively with age [28].

Table 3. Clinical and biochemical data in 42 patients (from 35 families) with primary hypomagnesemia-hypercalciuria-nephrocalcinosis reported in the literature; the nine cases included in the present report are not considered

Consanguineous parents	6 families
Relatives with abnormal renal findings[a]	16/24 families
Hypercalciuria	13 families
Renal stones	7 families
Affected parents	0
Families with more than one affected child	8/35
Female:male ratio	27:15
Age at diagnosis (years)	10 (0.8–40)[b]
Initial clinical presentation	
Urinary tract infections	22/42
Polyuria–polydipsia	31/42
Renal stones	10/42
Tetanic convulsions	8/42
Arterial hypertension	6/42
Rickets	6/42
Muscle weakness	4/42
Muscle cramps	3/42
Arthritic pain	3/42
Lethargy	3/42
Vomiting	3/42
Chondrocalcinosis	2/42
Failure to thrive	3/42
Abdominal pain	2/42
Renal failure	15/42[c]
Renal transplant	11/42[d]
Ocular involvement	17/42
Myopia	17/42
Macular colobomata	4/42
Strabismus	1/42
Chorioretinitis	1/42
Ocular peripapillar depigmentation	1/42
Bilateral keratoconus	1/42
Corneal calcification	1/42
Papillar hypoplasia	1/42
Hearing impairment	3[e]

[a]Information not available in some families; [b]median and ranges; [c]age 19 (14–35) years; [d]age 23 (15–37) years; [e]from two families.

A group of patients concurrently affected by hypomagnesaemia and nephrourolithiasis or nephrocalcinosis reported by a Czechoslovakian group [33] and a girl with renal failure and hypomagnesaemia reported by Chesney and Haughton [34] were not included in our survey, since available information is too scanty.

In PHHN, the cardinal features are rather heterogenous and the renal prognosis rather poor. In addition, extrarenal disturbances not explained by altered salt homeostasis frequently occur. The history of one of our patients is consistent with the assumption that hypomagnesaemia sometimes is not present early in life. The complaints and the findings at diagnosis are variable, including urinary tract infections (probably related to nephrocalcinosis and renal stones), polyuria–polydipsia (related to impaired urinary concentrating ability), tetanic convulsions (related to magnesium deficiency) and muscle weakness or muscle cramps (probably related to magnesium deficiency). The study of the renal contribution to acid–base balance performed in some of our patients with PHHN indicates a disturbed urinary ammonium excretion in some but not all patients. Thiazides, which reduce urinary calcium excretion [38], and potassium citrate or magnesium salts, which inhibit crystal formation [31,32], have been used in patients with PHHN. It is not clear if these pharmacological tools delay the tendency towards renal failure. In our family II, the progression towards renal failure appears delayed in patient 4 as compared with his older sister (patient 3); this might well be related to the fact that treatment with potassium citrate and magnesium salts was started early in life in patient 4. Renal graft is carried out without evidence of recurrence [14,22,23]. This observation argues against a hormonal imbalance of the magnesium and calcium homeostasis and suggests an intrinsic defect in the native kidney tissue. The parents of patients with PHHN are apparently normal but often consanguineous. This fact, taken together with the almost equal incidence in both sexes, strongly indicates an autosomal recessive inheritance. The spectrum of extrarenal disturbances includes ocular disorders such as myopia or macular colobomata in almost half [13–16,20,23,24] and hearing impairment in one-tenth of the patients [13,21]. This report is the first to focus on the occurrence of sensorineural hearing impairment in PHHN. Hearing impairment has already been documented in at least two tubulopathies including classic distal tubular acidosis Albright [35,36] and some cases of neonatal Bartter syndrome [37]. Extrarenal disturbances have probably been underreported in PHHN. In

addition, in PHHN extrarenal signs sometimes present late in life. It would be helpful if the extrarenal signs in PHHN were anticipated.

The renal tubular resorption of magnesium occurs predominantly by paracellular flux in the thick ascending limb of Henle [1,5]. A gene encoding a protein that mediates the paracellular resorption of magnesium and calcium in the tight junction of the thick ascending limb of Henle recently has been identified. Mutations in this gene might cause PHHN [39]. The diagnosis of this rare but intriguing disease deserves consideration in any patient with nephrocalcinosis and hypercalciuria.

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