Clinical presentation and outcome in primary familial hypomagnesaemia

Hanna Shalev, Moshe Phillip, Aharon Galil, Rivka Carmi, Daniel Landau

Abstract
The clinical presentation and long term outcome (mean follow up eight years, range 0.25 to 21) of 15 patients with autosomal recessive primary familial hypomagnesaemia is described. The most common (67%) presenting events were generalised hypocalcaemic-hypomagnesaemic seizures at a mean (SD) age of 4.9 (2.5) weeks. Thirteen infants, treated soon after diagnosis with high dose enteral magnesium developed normally. Their serum calcium returned to normal concentrations but serum magnesium could not be maintained at normal concentrations (0.53 (0.12 SD) mmol/l; normal >0.62). Delay in establishing a diagnosis led to a convulsive disorder with permanent neurological impairment in two infants. Reported complications of prolonged hypomagnesaemia such as renal stones, hypertension, arrhythmias, sudden death, or dyslipidaemia were not observed.

(*Arch Dis Child* 1998;**78**:127–130)

Keywords: hypomagnesaemia; hypocalcaemia; genetics; tetany

Primary ("congenital") hypomagnesaemia with secondary hypocalcaemia is a rare genetic disorder characterised by recurrent tetany or convulsions in early infancy, or both, which are refractory to calcium supplementation but respond to magnesium treatment. In most patients primary hypomagnesaemia is caused by a selective defect of magnesium absorption in the small intestine,[1 2] but the basic underlying mechanism of this disease is unknown. Primary hypomagnesaemia has been previously described in at least 30 patients and is thought to be inherited as an autosomal recessive disease.[3–6]

Magnesium is a critical cofactor for numerous enzyme systems and its deficiency may result in varied clinical manifestations. In adults chronic magnesium depletion has been linked with hypertension,[7] arrhythmias,[8] atherosclerotic vascular disease,[9] and metabolic bone disease.[10] However, since these complications can result from other chronic illnesses in adults, the exact role of hypomagnesaemia is undefined. Children with primary hypomagnesaemia are commonly reported as presenting with tetany or convulsions, or both. Only a few reports are available regarding long term outcome. We studied 15 patients with primary hypomagnesaemia, most were studied since early infancy. We describe the clinical and biochemical data of these patients at presentation as well as long term follow up evaluation of their clinical and biochemical disease course.

Patients and methods
Medical records of 15 patients with primary hypomagnesaemia who were diagnosed and followed up at the paediatric nephrology clinic of the Soroka Medical Center in the past 20 years were reviewed. Diagnosis of primary hypomagnesaemia was established by the presence of low serum magnesium in spite of normal renal magnesium excretion (fractional excretion <5%).[11] There was no history of magnesium depleting drugs intake and all patients had to be supplemented with high doses of oral magnesium. Two patients (numbers 6 and 7 in family 1, fig 1) were the subject of a previous report.[12] All patients belong to two extended Arab-Bedouin families in which a high rate of consanguinity exists (fig 1). Thirteen of the 15 patients were invited for reassessment of their clinical and biochemical status. One patient (number 8 in family 1) was still too young (<6 months) for long term evaluation, and another patient (number 2 in family 2) was institutionalised out of the region and could not be approached. A neurodevelopmental examination was done in two apparently healthy patients using the Beery developmental test of visual motor integration and the Goodenough-Harris drawing test.[13 14] An electroencephalogram was obtained in 13 of the 15 patients. General laboratory screening included: serum electrolytes: sodium, potassium, magnesium, calcium, and phosphorus; analysis of serum lipoproteins (high density lipoprotein (HDL), low density lipoprotein (LDL), and very low density lipoprotein (VLDL), and triglycerides. Normal general enteral absorption was established by performing a standardised xylose absorption test and measuring serum carotene concentrations, serum albumin, and total proteins. Bone status was assessed by measuring total alkaline phosphatase, N-terminal parathyroid hormone, and vitamin D metabolites (25 hydroxycholecalciferol and 1,25 dihydroxycholecalciferol). Bone age was determined using a radiograph of the patient's left wrist. Bone densitometry was done in two patients using a Norland XR-26 (Norland Sciences Instruments, Fort Atkinson, WI, USA) and compared with published age related norms.[15]

Results
The patients belonged to six nuclear families. Three families, of which seven boys were patients, belonged to one extended Arab-

**Soroka Medical Center and Faculty of Health Sciences,
Ben Gurion University of the Negev,
Beer Sheva, Israel:
Department of Pediatrics**
H Shalev
D Landau

Paediatric Therapeutic and Diagnostic Day Care Centre
M Phillip

Zusman Child Development Centre
A Galil

Genetics Institute
R Carmi

Correspondence to:
Dr Daniel Landau,
Department of Pediatrics,
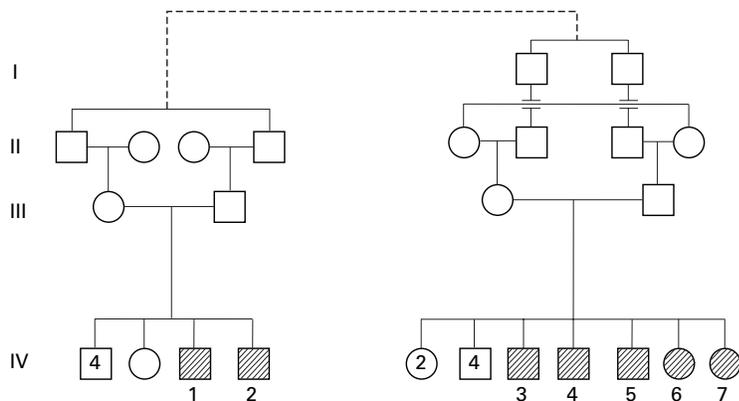Soroka Medical Center, PO
Box 151, Beer Sheva 84101,
Israel.

Figure 1   Pedigree of kindred 1.

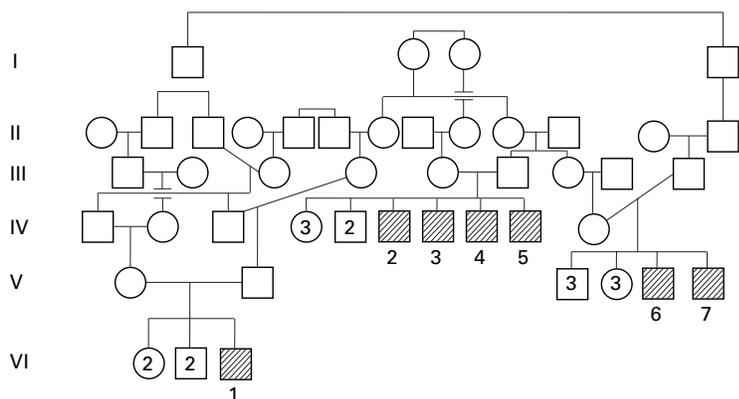*Figure 2   Pedigree of kindred 2.*

presented with generalised seizures, two with restlessness, and two with carpopedal spasms without loss of consciousness. One patient (number 5, family 2) was found to be hypomagnesaemic when screened shortly after birth because of a family history of primary hypomagnesaemia in older siblings. All patients except the one ascertained by screening were hypocalcaemic and hypomagnesaemic on presentation. The mean (SD) serum magnesium at that time was 0.24 (0.11) mmol/l and total serum calcium was 1.64 (0.41) mmol/l. Patients were treated during the acute stage of their disease with recommended doses of parenteral calcium and magnesium. When switched to oral magnesium supplements an average (SD) dosage of 38 (22) mg elemental magnesium/kg/day (table 2) was necessary to maintain normal blood magnesium. This dosage was much higher than the recommended maintenance daily supplementation (4–10 mg/kg/day).[16 17] Diarrhoea, the main side effect of enteral magnesium supplementation, occurred in four patients. Convulsive episodes, which are associated with hypomagnesaemia and hypocalcaemia, were the most prominent clinical feature of some patients during an average (SD) follow up period of 8(6) years (range: 0.25 to 21). Two patients (number 7 in family 1 and number 2 in family 2) had more than 10 such episodes during infancy, which resulted in psychomotor retardation and an epileptic disorder that necessitated chronic anticonvulsive treatment. Eight other patients had less than 10 hypomagnesaemic-hypocalcaemic seizure attacks and the other three patients were free of convulsions after initiation of supplemental magnesium. All of them had normal psychomotor development.

Current clinical and biochemical evaluation showed that an oral magnesium dosage (18–87 mg/kg/day or 0.7–3.5 mmol/kg/day of elemental magnesium) kept the patients free of symptoms (table 2). This was sufficient to maintain normal total serum calcium concentrations. Serum magnesium concentrations, however, remained subnormal (mean (SD) serum magnesium: 0.53 (0.12) mmol/l) despite normal

Bedouin kindred where all parents were closely related (fig 1). The other eight patients—six boys and two girls—were also products of consanguineous mating and were distributed in two nuclear families which descended from common ancestors (fig 2). None of the parents had any episode of tetany or hypomagnesaemia.

Table 1 summarises clinical and laboratory data at presentation. All 15 patients (13 boys and two girls) were diagnosed at an average (SD) age of 4.9 (2.5) weeks. Ten (67%)

Table 1   Clinical and laboratory data at presentation

Kindred	Patient No	Sex	Presentation age (weeks)	Clinical presentation	Serum calcium (mmol/l)	Serum magnesium (mmol/l)
1	1	M	8	Restlessness, tremor	1.61	0.21
1	2	M	3	Convulsions	1.91	0.25
1	3	M	10	Convulsions	1.54	0.25
1	4	M	4	Restlessness	1.81	0.25
1	5	M	4	Convulsions	1.59	0.29
1	6	F	4	Carpopedal spasms and stridor	1.41	0.25
1	7	F	2	Carpopedal spasms and stridor	1.31	0.2
1	8★	M	6	Convulsions	1.54	0.13
2	1	M	2	Convulsions	1.57	0.08
2	2	M	6	Convulsions	0.93	0.21
2	3	M	3	Convulsions	1.49	0.46
2	4	M	3	Convulsions	2.60†	0.46†
2	5	M	2	Asymptomatic	2.47	0.33
2	6	M	8	Convulsions	1.34	0.04
2	7	M	8	Convulsions	1.54	0.21
Mean (SD)			4.9 (2.5)		1.58 (0.33)	0.24 (0.11)
Normal					2.12–2.70	0.62–1.08

★ Patient not shown on pedigrees (figs 1 and 2).
†Value after one bolus of parenteral magnesium sulphate.

Table 2   Current clinical and biochemical status

Kindred	Patient No	Age (years)	Height SD score	Weight SD score	Oral magnesium dosage (mg/kg/day)	Serum magnesium (mmol/l)	Serum calcium (mmol/l)	Fractional excretion of magnesium (%)
1	1	8.5	0.98	4.88	36	0.63	2.68	1.0
1	2	6.5	−2.58	−1.02	47	0.42	2.30	0.2
1	3	10	−0.76	−0.35	27	0.46	2.42	0.3
1	4	3.25	0.74	0.97	28	0.5	2.45	0.3
1	5	8.25	0.06	0.37	22	0.5	2.35	0.05
1	6	21	−3.38	1.17	17	0.54	2.35	1.4
1	7	20	−2.56	1.17	44	0.46	2.35	0.4
1	8	0.5	NA	NA	58	0.75	2.58	1.6
2	1	1.5	NA	−1.7	40	0.38	2.5	0.8
2	2	13	NA	NA	NA	NA	NA	NA
2	3	8.5	−1.38	−0.83	11	0.46	2.52	0.6
2	4	5.5	−1.33	−0.92	18	0.5	2.60	0.4
2	5	0.6	−0.13	1.05	20	0.83	2.75	NA
2	6	9	−2.58	−0.42	72	0.5	1.89	0.3
2	7	4.5	−2.14	−0.79	90	0.46	2.42	1.3
Mean (SD)		8.03 (6)	−1.26 (1.44)	0.28 (1.69)	37.9 (22)	0.53 (0.12)	2.44 (0.2)	0.67 (0.49)
Normal					4–10	0.62–1.08	2.12–2.70	<5

NA = data not available.

renal magnesium fractional excretion (< 5%).[11] No evidence for malabsorption of other elements or nutrients was found and the patients' average weight standard SD scores for age were normal. Standardised xylose absorption tests as well as serum carotene and total proteins were normal. Serum parathyroid hormone concentrations, at a time when serum calcium was normal and serum magnesium abnormal, were within the normal (SD) range (16.2 (4.8) pg/ml; normal: 10–55). Serum electrolytes (sodium, potassium, and chloride) were normal. Serum triglycerides, total cholesterol, and its fractions (HDL, LDL, and VLDL) were all normal. In view of reports on the function of urinary magnesium as an inhibitor of lithiasis, renal sonography was performed in all patients.[18] There was no evidence of calcification or of kidney stones. Electrocardiograms did not show any conduction abnormalities (for example, prolonged QT interval) or arrhythmias. There was no history of sudden death or syncope in any of the patients and blood pressure was normal for age in all.

Patients' height and weight SD scores were calculated (table 2). Mean weight and height SD scores were 0.28 (1.69) and −1.26 (1.44) respectively. The high variability in height and weight SD scores was compatible with the midparental height variation in the families studied. No significant delay in bone age was noticed in any of our patients. Analysis of bone radiographs and bone densitometry disclosed no evidence of osteoporosis.

Discussion
We describe here the clinical phenotype and follow up evaluation of 15 patients with primary hypomagnesaemia belonging to two large Bedouin kindreds. The high rate of consanguinity suggests that the mechanism of inheritance in these families is autosomal recessive. Male predominance, as observed in previous reports,[3–5 16 19] was present in our families (13 boys out of 15 patients). X linked recessive inheritance as initially proposed for primary hypomagnesaemia was based on different pedigrees in which only affected boys were reported.[20 21] The finding by Meyer et al of a female patient manifesting primary hypo-

magnesaemia in addition to dysmorphic features and mental retardation and carrying a de novo chromosome translocation 46X, t(X;9)(p22;ql2) was thought to be consistent with this type of transmission.[22] Moreover, the later finding by Chery *et al*[23] of a hybrid cell line containing the der (X) chromosome of this patient led the authors to the conclusion that the gene locus for the disease resided in a 3.4 cM interval on Xp22.2. On the other hand several other reports described primary hypomagnesaemia in females, suggesting an autosomal recessive inheritance.[12 24 25] In an attempt to resolve the issue of inheritance in this disorder a model of an autosomal disease gene, the expression of which is modulated by an X linked gene, has been proposed.[26]

Our families clearly show the overrepresentation of boys among affected individuals. However, analysis of the pedigrees reveals findings which are more consistent with autosomal recessive inheritance. Firstly, all nuclear families with affected siblings are consanguineous. Secondly, one kindred (number 1, fig 1) contains two affected girls with normal 46, XX karyotypes. Thirdly, while two of the nuclear families in the kindred with affected boys only are indeed related through the female line, as expected for X linked transmission, the third nuclear family is not. It seems more likely therefore that the mode of inheritance of primary hypomagnesaemia in our families is autosomal recessive. Indeed, recent linkage analysis studies done using DNA samples from our patients have found a linkage to the long arm of chromosome 9.[27]

The clinical manifestations of primary hypomagnesaemia in our patients are similar to those reported previously in sporadic cases.[4 5 12 21] Firstly, the early tetanic convulsions responded to treatment with parenteral magnesium. Subsequently, a good neurodevelopmental outcome could be achieved in those children who were treated with the appropriate long term dosage of enteral magnesium. Failure of early diagnosis of primary hypomagnesaemia or non-compliance with treatment recommendations can be detrimental causing permanent neurological damage (as shown in two of our patients) and even

death.[5] [21] Treatment with high doses of enteral magnesium was successful in keeping our patients symptom free and normocalcaemic, but it did not fully normalise serum magnesium concentrations: blood magnesium concentrations could be raised from less than 50% of the normal lower limit to only about 75% of the low normal concentration. The mechanism leading to hypocalcaemia in hypomagnesaemia is controversial. Several factors have been proposed such as end organ unresponsiveness to parathyroid hormone (PTH)[28]; impaired synthesis and/or release of PTH[29]; and impaired formation of 25-dihydroxyvitamin D_3.[30] Hypomagnesaemia can impair calcium release from bone in a PTH independent mode.[31] Hypocalcaemia has been found to be associated with dementia in adults.[32] Thus our experience as well as that of others indicates that hypocalcaemia is neurologically detrimental through repeated uncontrolled seizures and non-seizure related mechanisms.[5] [19] [33]

A variety of other morbid manifestations have been reported to be associated with chronic hypomagnesaemia, even when only subclinical (for example, decreased intracellular) magnesium concentrations occur.[7–10] In the group of children described here, however, who have usually frank hypomagnesaemia, none of those complications was observed. In fact reports regarding other chronic hypomagnesaemic states in childhood, such as Gitelman's syndrome and familial hypomagnesaemia and hypercalciuria commonly describe only weakness and tetany (with or without nephrocalcinosis, depending on the existence of associated hypercalciuria) as long term complications of this biochemical abnormality.[34] [35] This, combined with our data, further supports the hypothesis that the morbidity associated with hypomagnesaemia in adults may have additional aetiologies and that long term mild hypomagnesaemia in children and adolescents does not necessarily cause long term complications.

1 Nordio S, Donath A, Macagno F, *et al*. Chronic hypomagnesemia with magnesium-depended hypocalcemia. I. A new syndrome with intestinal magnesium malabsorption. *Acta Paediatr Scand* 1971;**60**:932–4.
2 Milla PJ, Aggett PJ, Wolff OH, *et al*. Studies in primary hypomagnesaemia: evidence for defective carrier-mediated small intestinal transport of magnesium. *Gut* 1979;**20**:1028–33.
3 Yamamoto T, Kabata H, Yagi R, *et al*. Primary hypomagnesmia with secondary hypocalcemia. Report of a case and review of the world literature. *Magnesium* 1985;**4**:153–64.
4 Dudin KI, Teebi AS. Primary hypomagnesaemia. A case report and literature review. *Eur J Pediatr* 1987;**146**:303–5
5 Abdulrazzaq YM, Smigura FC, Wettrell G. Primary infantile hypomagnesaemia: report of two cases and review of literature. *Eur J Pediatr* 1989;**148**:459–61.
6 Arnold JD, Oldfield RK, Pollard AC, *et al*. Primary hypomagnesaemia: a case report. *Aust Paediatr J* 1983;**19**:45–6.
7 Dyckner T, Wester PO. Effect of magnesium on blood pressure. *BMJ* 1983;**286**:1847–9.
8 Ramee SR, White CJ, Svinarich JT, *et al*. Torsade de pointes and magnesium deficiency. *Am Heart J* 1985;**109**:164–7.
9 Rayssiguier Y, Gueux E. Magnesium and lipids in cardiovascular disease. *J Am Coll Nutr* 1986;**5**:507–19.
10 Heroux O, Peter D, Tanner A. Effect of a chronic suboptimal intake of magnesium on magnesium and calcium content of bone and on bone strength of the rat. *Can J Physiol Pharmacol* 1975;**53**:304–10.
11 Sutton RAL, Domrongkitchaiporn S. Abnormal renal magnesium handling. *Miner Electrolyte Metab* 1993; **19**:232–40.
12 Garty R, Alkalay A, Bernheim JL. Parathyroid hormone secretion and resposiveness to parathyroid hormone in primary hypomagnesemia. *Isr J Med Sci* 1983;**19**:345–8.
13 Beery KE. *The developmental test of visual motor integration*. 3rd Ed. Toronto: Modern Curriculum Press, 1989.
14 Harris DB. *The Goodenough-Harris drawing test*. Los Angeles: Harcourt-Jovanovich, 1963.
15 Tsukahara H, Nakashima T, Yoshimoto M, *et al*. Evaluation of lumbar bone mineral density by dual energy x-ray absorptiometry. *Acta Paediatr Jpn* 1991;**33**:459–66.
16 Geven WB, Monnens LAH, Willems JL. Magnesium metabolism in childhood. *Miner Electrolyte Metab* 1993;**19**:308–13.
17 Seelig M. Magnesium requirements in human nutrition. *Magnesium Bull* 1981;**3**:26–47
18 Johansson G, Backman U, Danielson BG, *et al*. Magnesium metabolism in renal stone disease. *Invest Urol* 1980;**18**:93–6.
19 Stromme JH, Steen-Johnsen J, Harnaes K, *et al*. Familial hypomagnesemia—a follow up examination of three patients after 9 to 12 years of treatment. *Pediatr Res* 1981; **15**:1134–9.
20 Skyberg D, Stromme JH, Nesbakken R, *et al*. Congenital primer hypomagnesemia, an inborn error of metabolism. *Acta Paediatr Scand* 1967;**56**:26–7.
21 Vainsel M, Vandevelde G, Smulders J, *et al*. Tetany due to hypomagnesaemia with secondary hypocalcemia. *Arch Dis Child* 1970;**45**:254–8.
22 Meyer M, Mattei JF, Viallard JL, *et al*. Hypocalcemie magnesodependante par trouble specifique de l'absorption du magnesium associee a une anomalie chromosomique. *Rev Fr Endocrinol Clin* 1978;**19**:101–8.
23 Chery M, Biancalana V, Philippe C, *et al*. Hypomagnesemia with secondary hypocalcemia in a female with balanced X/9 translocation: mapping of the Xp22 chromosome breakpoint. *Hum Genet* 1994;**93**:587–91.
24 Becker K, Lombeck I, Bremer HJ. Primaere hypomagneseiaemie. Klinischer verlauf, diagnostische und therapeutische untersuchungen bei drei kinder. *Monatsschr Kinderheilkd* 1979;**129**:37–42.
25 Henneckam RCM, Donckerwolcke RA. Primary hypomagnesemia, an autosomal recessive inherited disease? *Lancet* 1983;**i**:927.
26 Mettey R, Hoppeler A. Les deficits magnesien de l'enfants. *Arch Fr Pediatr* 1982;**39**:837–44.
27 Walder RY, Shalev H, Brennan TMH, *et al*. Familial hypomagnesemia maps to chromosome 9q, not to the X chromosome: genetic linkage mapping and analysis of balanced translocation breakpoint. *Hum Mol Genet* 1997;**6**:1491–7.
28 Rude RK, Oldham SB, Singer FR. Functional hypoparathyroidism and parathyroid hormone end-organ resistance in human magnesium deficiency. *Clin Endocrinol (Oxf)* 1976; **5**:209–24.
29 Anast CS, Winnacker JL, Forte LR, *et al*. Impaired release of parathyroid hormone in magnesium deficiency. *J Clin Endocrinol Metab* 1976;**42**:707–17.
30 Fatemi S, Ryzen E, Flores J, *et al*. Effect of experimental human magnesium depletion on parathyroid hormone secretion and 1,25 dihydroxyvitamin D metabolism. *J Clin Endocrinol Metab* 1991;**73**:1067–72.
31 Grabe ML, Schulman J. Hypomagnesemic hypocalcemia independent of parathyroid hormone. *Ann Intern Med* 1986;**104**:804–5.
32 Eraut D. Idiopathic hypoparathyroidism presenting as dementia. *BMJ* 1974;**i**:429–30.
33 Guillard O, Mettey R, Lecron JC, *et al*. Congenital hypomagnesemia: alternative to tissue biopsies for monitoring body magnesium status. *Clin Biochem* 1992;**25**:463–5.
34 Rodriguez-Soriano J, Vallo A. Familial hypokalemia-hypomagnesemia (Gitelman's syndrome). *Pediatr Nephrol* 1990;**4**:C22.
35 Praga M, Vara J, Gonzalez-Parra E, Andres A, *et al*. Familial hypomagnesemia with hypercalciuria and nephrocalcinosis. *Kidney Int* 1995;**47**:1419–25.