Short reports

Hypomagnesaemic tetany

I J Ramage, M Ray, R D Paton, R W Logan, T J Beattie

Abstract

Hypomagnesaemic tetany (hypomagnesaemic tetany with secondary hypocalcaemia) is a rare inherited form of hypomagnesaemia. Initial reports involved affected males only; however, affected females have also been reported. The case of a child with hypomagnesaemic tetany is described, the biochemical and genetic aspects of this condition are reviewed and the importance of the assessment of renal magnesium excretion in patients presenting with hypomagnesaemia is highlighted.

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Hypomagnesaemic tetany (hypomagnesaemic tetany with secondary hypocalcaemia) results from relative malabsorption of magnesium in the presence of a normal intraluminal concentration, but is responsive to oral supplementation. First described in 1968,¹ hypomagnesaemic tetany was initially thought to have an X-linked inheritance, but subsequent reports have suggested an autosomal recessive inheritance.

Here, we describe a four year old girl who presented with hypomagnesaemia, hypocalcaemia and tetany and review the biochemical and genetic aspects of this condition.

Case report

A four year old girl, the second child of unrelated white parents, was referred with a history of seizures. Twenty four hours before admission, she developed abnormal behaviour which consisted of failing to recognise the familiar characters on her favourite video and increasing agitation. Her general practitioner observed nystagmus, rhythmic blinking, and shaking of her hands.

Her past medical history included two episodes of apparent febrile convulsions precipitated by viral respiratory infection at ages nine months and two years. The birth and neonatal period were normal, she was fully immunised and her development was normal apart from expressive speech and language delay for which she was receiving speech therapy. There was no significant family history and no history of drug or substance ingestion.

On admission the patient was agitated, apparently hallucinating and eating and drinking voraciously. She was normotensive, general physical examination was normal and her height and weight lay on the 90th percentile. There was no specific neurological deficit apart from the finding of an unsteady gait.

Initial results on plasma (table 1) revealed hypocalcaemia, subnormal parathyroid hormone (PTH) concentrations and profound hypomagnesaemia. Serum thyroxine and thyroid stimulating hormone concentrations were normal. Routine urinalysis revealed no proteinuria or glycosuria and urinary aminoacid chromatography showed a normal pattern. The urinary calcium:creatinine ratio was 0.085 mmol/mmol and the urinary magnesium:creatinine ratio was less than 0.025 mmol/mmol. Renal tubular reabsorption of magnesium and phosphate was 97% and 92%, respectively.

The patient's electroencephalogram, cranial computed tomography scan, and forearm and hand x ray films were normal. A renal ultrasound scan showed no evidence of nephrocalcinosis. The results of a PTH stimulation test (table 2) revealed a normal plasma cyclic AMP and phosphate response to the exogenous PTH, thus excluding pseudohypoparathyroidism.

Department of
Medical Paediatrics,
Royal Hospital for
Sick Children,
Yorkhill NHS Trust,
Glasgow G3 8SJ

I J Ramage
M Ray
T J Beattie

Department of
Biochemistry
R D Paton
R W Logan

Correspondence to:
Dr I J Ramage, Department
of Medical Paediatrics,
Renal Unit, Royal Hospital
for Sick Children,
Yorkhill NHS Trust,
Glasgow G3 8SJ.

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Table 1 Plasma electrolytes before and after treatment

Analyte	Presentation	On magnesium glycerophosphate	Reference ranges (age related)
Sodium (mmol/l)	144	138	136-145
Potassium (mmol/l)	3.5	3.6	3.5-5.6
Chloride (mmol/l)	104	104	98-106
Bicarbonate (mmol/l)	24	22	18-25
Urea (mmol/l)	1.9	4.5	2.5-6.0
Creatinine (μmol/l)	34	37	35-106
Calcium (mmol/l)	1.47	2.67	2.19-2.51
Phosphate (mmol/l)	1.97	1.73	1.3-1.75
Total protein (g/l)	73		59-78
Albumin (g/l)	39		35-52
PTH (pmol/l)	0.7	1.6	1.0-6.5
Glucose (mmol/l)	4.6		3.3-5.5
Magnesium (mmol/l)	<0.10	0.67	0.6-0.95

Table 2 PTH stimulation study

Analyte	Time (minutes)				Reference ranges
	0	5	10	30	
Calcium (mmol/l)	2.55	2.52	2.48	2.46	2.19-2.51
Phosphate (mmol/l)	1.72	1.63	1.59	1.58	1.3-1.75
Magnesium (mmol/l)	0.45	0.43	0.42	0.42	0.6-0.95
cAMP (nmol/l)	80	108	1130	940	16-32
PTH (pmol/l)	0.7	0.55			1.0-6.5

The patient was treated initially with intramuscular and later oral magnesium sulphate; however, this preparation resulted in diarrhoea and was later replaced with magnesium glycerophosphate. She required 20–28 mmol daily of supplemental magnesium to maintain a normal plasma concentration. Following adequate magnesium replacement her plasma calcium and PTH concentrations returned to normal (table 1).

The patient's behaviour normalised following treatment. Her speech problems also showed improvement, in keeping with published data indicating a high prevalence of hypomagnesaemia in children with speech delay.² Plasma calcium and magnesium concentrations in her parents and sibling were normal.

Discussion

The relation between hypomagnesaemia and PTH secretion is well documented,³ although knowledge of the precise mechanism of the interaction is incomplete. PTH enhances renal tubular magnesium reabsorption and is secreted in response to a mild reduction in plasma magnesium concentrations.

In profound hypomagnesaemia (plasma magnesium <0.35 mmol/l), however, a combination of impaired PTH secretion, 1,25 dihydroxy vitamin D3 formation and end organ resistance to PTH results in secondary hypocalcaemia.³ These effects are not apparent in mild hypomagnesaemia and may explain reports of normocalcaemic hypomagnesaemia.⁴

Hypomagnesaemia occurs most frequently as an acquired entity secondary to inadequate dietary intake, chronic gastrointestinal disease or following bowel resection and secondary to increased urinary excretion.⁵ Inherited forms of hypomagnesaemia may be associated with either disordered renal tubular or intestinal transport of magnesium.

Three types of hypomagnesaemia associated with disordered renal tubular reabsorption of magnesium are recognised.⁶ Familial hypomagnesaemia secondary to isolated renal tubular wasting of magnesium may be asymptomatic or present with tetany or generalised convulsions. Both autosomal dominant and recessive forms have been proposed. Familial hypocalcaemia/hypomagnesaemia (Gitelman's syndrome) is inherited as an autosomal recessive trait and the hypomagnesaemia is accompanied by hypocalcaemia, metabolic acidosis, hypocalciuria, and moderate sodium chloride wasting. Familial hypomagnesaemia/hypercalciuria is also inherited as autosomal recessive condition and hypomagnesaemia is always associated with hypercalciuria and nephrocalcinosis. The final form of inherited hypomagnesaemia, hypomagnesaemic tetany, results from an isolated defect in carrier mediated intestinal magnesium transport. The non-carrier mediated transport remains intact,

as demonstrated by the correction of hypomagnesaemia with oral supplementation.⁵

Assessment of renal magnesium excretion should permit differentiation between the renal and intestinal transport defects. In a number of published reports, however, the distinction between isolated renal tubular magnesium wasting in particular and hypomagnesaemic tetany has not been made.⁷

The genetic aspects of hypomagnesaemic tetany are complex. Initial reports were almost exclusively in affected male patients resulting in an X-linked inheritance pattern being accepted. However, affected females were subsequently reported and various authors have now proposed an autosomal recessive transmission.⁸

The finding of a balanced translocation in a female child 46XX, t(9;X)(q12;p22) with microcephaly, dysmorphic features and psychomotor retardation⁹ has been quoted as evidence of the gene defect for hypomagnesaemic tetany having a chromosomal location of Xp22.¹⁰ The occurrence in this case may be explained by postulating the Lyon hypothesis, with the active X chromosome bearing the mutant allele and the normal X chromosome being selectively inactivated, as occurs in most balanced X-autosome translocations.

The relative paucity of reports of affected females may be explained by genetic heterogeneity, whereby the severity of the disease reflects tissue expression of the mutant allele on the active X chromosome similar to that described in ornithine carbamoyl transferase deficiency. An alternative explanation may be that there is an autosomal gene coding for a defect modulated by a gene on the short arm of the X chromosome. Further clarification of the genetic basis of this condition, however, must await accurate localisation and ultimate cloning of the gene defect.

In summary, although inherited forms of hypomagnesaemia are rare, this case highlights the discriminatory value of renal magnesium excretion in the assessment of these patients.

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