PAPERS AND SHORT REPORTS

Diuretic-associated hypomagnesaemia

JOHN SHEEHAN, AIDEEN WHITE

Abstract

Clinically suspected hypomagnesaemia was confirmed in 21 patients over 12 months; all patients had been exposed to either short-term vigorous diuretic treatment or moderate-dosage long-term treatment. Magnesium depletion was compounded by a hospital diet surprisingly low in magnesium, a local soft water supply, and, in some patients, high alcohol intake. Common presenting symptoms included depression, muscle weakness, refractory hypokalaemia, and atrial fibrillation refractory to digoxin treatment. The administration of magnesium supplements resulted in prompt improvement of all symptoms particularly in the case of refractory atrial fibrillation.

Chronic low-grade magnesium deficiency from diuretic treatment is more common than published reports suggest. Older patients are at risk, particularly those who have excessive alcohol intake, a diet low in magnesium, or a soft water supply.

Introduction

Diuretics are known to cause magnesium depletion, especially loop diuretics,[1 2] and low concentrations of intracellular magnesium have been reported in various tissues, though concomitant lowering of serum concentrations may not always occur.[2] The documented clinical sequelae of diuretic-associated magnesium depletion tend not to be serious, with the exception of cardiac arrhythmias, which have been reported to be mainly of ventricular origin.[3-5] Sudden death has been reported in patients with hypomagnesaemia, and it has been suggested that there may be a higher incidence of sudden death in patients living in areas with soft water supplies, which are deficient in magnesium.[6 7] Hypomagnesaemia, like hypokalaemia, appears to be a significant risk factor for the development of serious ventricular arrhythmias in acute myocardial infarction.[8-12]

Royal City of Dublin Hospital, Dublin 4
JOHN SHEEHAN, MB, MRCPI, registrar in general medicine
AIDEEN WHITE, MB, senior house officer in general medicine

We attempted to ascertain the magnitude of the problem, to define patients at risk on clinical grounds, and to explore the therapeutic aspects of both acute treatment and prophylaxis.

Patients and methods

Serum magnesium concentrations were measured in patients who had been exposed to short-term intensive diuretic treatment or long-term moderate-dosage maintenance treatment where the clinical background included at least one of the following features: general depression and lethargy disproportionate to degree of cardiac failure; muscle weakness with depressed tendon reflexes; hypokalaemia, especially refractory hypokalaemia; atrial fibrillation rapid or poorly controlled with therapeutic doses of digoxin; high alcohol intake with or without cirrhosis.

Serum total magnesium concentrations were measured in the central laboratory on the Du Pont automatic clinical analyser, which utilises a modification of a methylthymol blue complexometric procedure.[13] All patients were treated with intramuscular boluses of 4-8 mmol of magnesium sulphate in the initial phases followed by oral supplementation with magnesium sulphate salts, diarrhoea being a dose-limiting factor with the salts. Dietary supplementation was attempted in all patients; bananas proved a convenient, palatable, moderately rich source of magnesium. The potassium-sparing diuretic, spironolactone, was used to augment treatment of congestive cardiac failure in six patients; its reported potential magnesium-conserving properties was an added feature.[14 15]

Results

Over the 12-month study period 40 patients satisfied the criteria for measurement of serum concentrations; 21 of these were found to have appreciable hypomagnesaemia. The highest yield was in patients who showed all the outlined screening criteria. Patients with a serum concentration of more than 0·7 mmol/l (1·7 mg/100 ml) were not considered to have clinical features unequivocally related to hypomagnesia and were excluded from the study. Table I summarises the range of clinical features, relevant antecedent diuretic treatment, and serum total magnesium concentrations. The mean serum magnesium concentration was 0·54 mmol/l (1·3 mg/100 ml) (reference range 0·74-0·99 mmol/l (1·8-2·4 mg/100 ml)), the mean age of patients was 67 years, and female to male ratio was 1·6 to 1. The principal clinical diagnosis was congestive cardiac failure, more than half the patients had atrial fibrillation, and frusemide was the most commonly used diuretic, often given intravenously in high dosage. All patients had

TABLE I—*Clinical features, diuretic treatment, and serum magnesium concentrations*

Case No	Age (yrs)	Sex	Depression	Muscle weakness	High alcohol intake	Congestive cardiac failure	Arrhythmia	Digoxin toxicity	Hypokalaemia	Other	Serum magnesium mmol/l	Diuretic treatment		
												Maintenance	Duration (minimum)	Inpatient
1	76	F	Mild	+	+	Mild	Atrial fibrillation				0·58	Frusemide	3 months	Frusemide
2	65	F		+	–	Moderate	Atrial fibrillation				0·65	Frusemide	8 months	Frusemide
3	53	F	Mild	+	–	Moderate	Supra-ventricular tachycardia				0·60	Frusemide	1 year	Frusemide
4	66	F	Mild	+	–	Severe	Atrial fibrillation		3·0		0·63	Frusemide	1 year	Frusemide
5	76	F	Mild	+	–	Moderate	Atrial flutter				0·68	Frusemide	1 year	Frusemide
6	68	F	Mild	+	–	Mild					0·41	Frusemide	6 weeks	Frusemide
7	58	F	Mild	+	–	Moderate					0·65	Metolazone	1 year	Frusemide
8	74	M	Mild	+	–	Mild	Atrial fibrillation	+		Mesenteric embolus—small bowel resection	0·11	Frusemide	1 year	Frusemide
9	49	M		+	–	Moderate	Atrial fibrillation				0·53	Frusemide	6 months	Frusemide
10	76	F	Mild	+	–	Moderate	Atrial fibrillation	+			0·46	Frusemide	1 year	Frusemide
11	70	M		+	–	Mild	Atrial fibrillation	+	3·1		0·21	Bendrofluazide	1 year	Frusemide
12	66	F	Mild	+	–	Moderate	Atrial fibrillation		3·1		0·46	Chlorthalidone	1 year	Frusemide
13	82	M	Mild	+	–	Mild	Atrial fibrillation				0·56	Frusemide	1 year	Frusemide Spironolactone
14	59	M	Moderate	+	+	Moderate	Atrial fibrillation		3·0		0·62	Frusemide	1 year	Frusemide
15	52	M		+	+	Severe					0·52	Frusemide	2 years	Frusemide Spironolactone
16	70	M	Severe	+	–	Mild			3·2	Controlled hypertension	0·49	Metolazone	2 years	Metolazone
17	83	F	Mild	+	–	Mild			3·4		0·65	Chlorthalidone	1 year	Chlorthalidone
18	69	M	Severe	+	+	Moderate			3·2	Ascites: ? alcoholic cirrhosis	0·65	Frusemide	1 year	Frusemide Spironolactone
19	60	F	Severe	+	+	Moderate	Atrial fibrillation		2·9	Ascites; ? alcoholic cirrhosis	0·60	Frusemide	1 year	Frusemide Spironolactone
20	70	F	Mild	+	+	Mild	Atrial fibrillation	+			0·67	Metolazone	6 weeks	Frusemide Spironolactone
21	59	F	Mild	+		Moderate	Atrial fibrillation	+	2·9		0·68	Metolazone	6 weeks	Frusemide

Conversion: SI to traditional units—Magnesium: 1 mmol/l ≈ 2·4 mg/100 ml.

normal serum calcium and albumin concentrations and normal thyroid function. Nine patients had hypokalaemia, full correction of which, with copious oral supplements, proved unsatisfactory before restoration of normal magnesium concentrations. Five patients developed digitalis toxicity, as judged by high serum concentrations during an unsuccessful attempt to control their rapid atrial fibrillation with increasing boluses of digoxin before confirmation and correction of hypomagnesaemia.

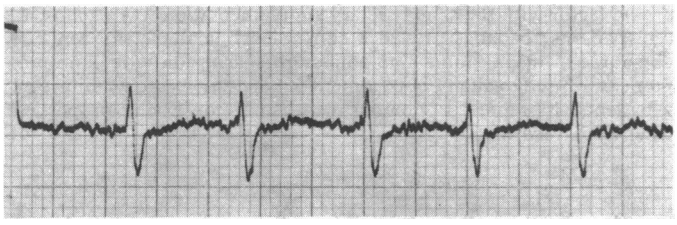

FIG 1—Uncontrolled atrial fibrillation in patient with serum magnesium concentration of 0·21 mmol/l (0·5 mg/100 ml).

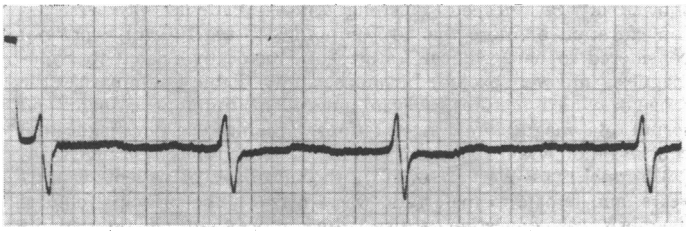

FIG 2—Controlled atrial fibrillation in patient after magnesium repletion (serum magnesium concentration 0·86 mmol/l (2·1 mg/100 ml).

Initial treatment with intramuscular magnesium sulphate resulted in prompt improvement of all symptoms in all cases. Control of atrial fibrillation was achieved within two hours of intramuscular treatment (fig 1) and this was maintained during continued administration and restoration of normal serum concentrations. Intramuscular treatment was continued for at least five days in all cases while normal serum magnesium concentrations were restored. Spironolactone was used in six patients in a dose range of 100-400 mg daily and proved to have useful magnesium-sparing properties. Table II shows the follow-up serum magnesium concentrations at three months with the various treatments.

Discussion

The incidence of diuretic-associated magnesium depletion is now known. Measuring serum total magnesium rather than intracellular magnesium, however, may underestimate the extent of the problem in that intracellular magnesium concentrations may be considerably reduced before there is lowering of serum magnesium concentrations.[2] The documented sequelae of diuretic-associated magnesium depletion, with the exception of cardiac arrhythmias, would not appear serious and respond rather slowly to replacement treatment.[2] The cardiac abnormalities reported generally focus on ventricular arrhythmias, which respond well to magnesium repletion.[3–5] In contrast to findings of previous studies refractory atrial fibrillation was the commonest arrhythmia and responded promptly to magnesium replacement. Digitalis toxicity is a real hazard in patients with hypomagnesaemia in that increasing boluses of digoxin may be administered and the toxicity is enhanced both by the hypomagnesaemia[16 17] and by any concurrent hypokalaemia. The diuretics most commonly implicated in magnesium depletion are the loop diuretics[1] and this was our experience also. The two

TABLE II—*Serum magnesium concentration before and after treatment and at three months*

Case No	Serum magnesium (mmol/l)		
	Before treatment	After acute treatment	Maintenance at 3 months
		Spironolactone	
4	0·63	0·79	0·84
13	0·56	0·76	0·86
15	0·52	0·78	0·80
18	0·65	0·80	0·96
19	0·60	0·82	0·84
20	0·67	0·80	0·88
		Bananas	
1	0·58	0·78	0·79
3	0·60	0·84	0·81
6	0·41	0·82	0·84
7	0·65	0·91	0·88
5	0·68	0·90	0·83
9	0·53	0·80	0·82
10	0·46	0·82	0·81
16	0·49	0·79	0·85
		*Magnesium sulphate**	
2	0·65	0·81	0·86
8	0·11	0·78	0·84
11	0·21	0·86	0·91
14	0·62	0·91	0·88
17	0·65	0·94	0·93
21	0·68	0·91	0·89
		No treatment	
12	0·46	0·86	0·40

* Epsom salts, 2·5 g twice daily.
Conversion: SI to traditional units—Magnesium: 1 mmol/l ≈ 2·4 mg/100 ml.

patients with hypomagnesaemia related to thiazide diuretics alone had concomitant hypokalaemia.

Magnesium depletion was further compounded by the local soft water supply (magnesium content 0·13-0·2 mmol/l (0·3 0·5 mg/100 ml)); the hospital diet, which was found to be low in magnesium and contained on average only 9 mmol/day; and, in six patients, high alcohol intake. The dietary aspect was particularly important as all patients had congestive cardiac failure and a degree of anorexia and thus did not consume the full hospital diet. The therapeutic problem of magnesium administration centres around the poor oral absorption of all magnesium salts and their propensity to cause diarrhoea. In our series all patients were given intramuscular magnesium sulphate in the acute phase and some were later supplemented by dietary manipulation, administration of small amounts of magnesium sulphate orally, and the potassium-sparing diuretic spironolactone, which also has some magnesium-sparing properties.[14 15] Amiloride[18 19] and triamterene[20] have also been reported to have magnesium-sparing properties but were not used in the present study. Bananas proved to be a useful, acceptable, moderately rich source of magnesium and most patients were advised to consume four medium-sized bananas daily, which yielded about 4 mmol of magnesium.

We conclude that chronic low-grade magnesium deficiency from diuretic treatment is more common than the published reports suggest, with older patients living in soft water areas, consuming alcohol to excess, and ingesting diets low in magnesium being the greatest risk.

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ROCKET. In regard the Garden Rocket is rather used as a sallad herb than to any physical purposes, I shall omit it, and only speak of the common wild Rocket. The description whereof take as follows.

The common wild Rocket has longer and narrower leaves, much more divided into slender cuts and jags on both sides the middle rib than the garden kinds have; of a sad green colour, from among which rise up divers stalks two or three feet high, sometimes set with the like leaves, but smaller and smaller upwards, branched from the middle into divers stiff stalks, bearing sundry yellow flowers on them, made of four leaves a-piece, as the others are, which afterwards yield them small reddish seed, in small long pods, of a more bitter and hot biting taste than the garden kinds, as the leaves are also. It is found wild in divers places of this land. It flowers about June or July, and the seed is ripe in August.

The wild Rockets are forbidden to be used alone, in regard their sharpness fumes into the head, causing aches and pains therein, and are less hurtful to hot and choleric persons, for fear of inflaming their blood, and therefore for such we may say a little doth but a little harm, for angry Mars rules them, and he sometimes will be restive when he meets with fools. The wild Rocket is more strong and effectual to increase sperm and venerous qualities, whereunto all the seed is more effectual than the garden kind. It serves also to help digestion, and provokes urine exceedingly. The seed is used to cure the biting of serpents, the scorpion, and the shrew mouse, and other poisons, and expels worms, and other noisome creatures that breed in the belly. The herb boiled or stewed, and some sugar put thereto, helps the cough in children, being taken often. The seed also taken in drink, takes away the ill scent of the arm-pits, increases milk in nurses, and wastes the spleen. The seed mixed with honey, and used on the face, cleanses the skin from morphew, and used with vinegar, takes away freckles and redness in the face, or other parts; and with the gall of an ox, it mends foul scars, black and blue spots, and the marks of the smallpox. (Nicholas Culpeper (1616-54) *The Complete Herbal*, 1850.)