Magnesium in Health and Disease

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Hypomagnesemia and Muscle Electrolytes and Metabolites

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INTRODUCTION

Segmental muscle necrosis has been reported in chronic alcoholism following an intensive alcohol debauche (Douglas et al., 1966; Valaitis et al., 1960; Schnack et al., 1961; Erlenborn and Pilz, 1962; Hed et al., 1962; Perkoff et al., 1966; Lafair and Myerson, 1968). Subclinical chronic forms of alcoholic myopathy, present chiefly as muscle weakness and atrophy, particularly of the proximal muscles (Hed et al., 1962; Ekbom et al., 1964; Douglas et al., 1966; Perkoff et al., 1966; Serratrice et al., 1966; Lafair and Myerson, 1968 and Nygren, 1971). Lowering of isometric muscle strength in chronic alcoholics was cited (Carlsson, 1967; Carlsson et al., 1969). Lower isometric muscle strength in alcoholic and non-alcoholic hypomagnesemic patients than in normomagnesemic alcoholics and normal controls has been reported. The spectrum of alcoholic myopathies has been reviewed by others (Perkoff et al., 1966; Klinkerfuss et al., 1967; Hed, 1970; Nygren, 1971; Stendig-Lindberg, 1973).

The myopathies of chronic alcoholism (in which magnesium deficiency has long been documented (Flink et al., 1954)) morphologically resemble that of experimental Mg deficiency in rats (Lowenhaupt et al., 1950; Mishra, 1960; Heggtveit, 1969). To determine whether Mg deficiency *per se* is a causal factor in myopathy of chronic alcoholism, as well as in other hypomagnesemic conditions, we studied ten patients with muscle weakness and low Mg levels: seven with chronic alcoholism and three with malabsorption.

METHODS

Patients with serum Mg levels of <0.70 mmol/l on first examination were entered into the study (Table 1). Subsequent readings are given in Figures 1 and 2. There were four women (age 44-59) and six men (age 39-64).

Oral Mg therapy was given to patients 5,6,7 and 9: $MgCl_2$ capsules containing 1.88 mmol Mg to case 5; MgO mixture containing 1.20 mmol Mg/ml to cases 6,7, and 9 (Fig.2).

All patients were examined, with special emphasis on their muscular status. Measurement of the isometric maximum voluntary contraction force (MVC) of the quadriceps femoris muscle was done in seven cases by

Table 1. Initial Serum Mg and Quadriceps Femoris Muscle Maximum Voluntary Contraction Force (MVC) in Hypomagnesemic Patients

Patient number	Sex	Age	MVC (kp) Right	MVC (kp) Left	Serum Mg (mmole/liter)	Diagnosis
1	F	44	--	--	0.68	Chronic alcoholism, hepatic cirrhosis, hematemesis, melena (esophageal varices), resection:caudal lobe of liver, porto-caval shunt
2	F	44	--	--	0.65	Chronic alcoholism, hepatic cirrhosis, hematemesis, epistaxis, melena (esophageal varices), spleno-renal shunt + splenectomy
3	M	54	*	34	0.57	Chronic alcoholism, multiple bone fractures, epilepsy, benign essential hypertension, paranoid personality
4	F	50	0.5	1	0.68	Postoperative status: colon diverticulitis + perforated abscess, malabsorption, milk intolerance, psoriasis, arthritis, ostopenia, muscle weakness, diarrhea, polyneuritis, urinary tract infection
5	F	59	14	13	0.63	Jejuno-ileal fistula, malabsorption
6	M	50	26	26	0.57	Chronic alcoholism, pulmonary tuberculosis, pleuritis, proteinuria
7	M	61	26	23	0.42	Chronic alcoholism, essential hypertension
8	M	39	14	19	0.70	Recurrent chronic pancreatitis, status post-gastrectomy + pancreatectomy, malabsorption, past alcohol abuse, epilepsy (tarda?)
9	M	41	--	--	0.65	Chronic alcoholism, epilepsy
10	M	64	27	35	0.71	Chronic alcoholism, epilepsy, atelectasis

* Reading omitted because of residual pain.

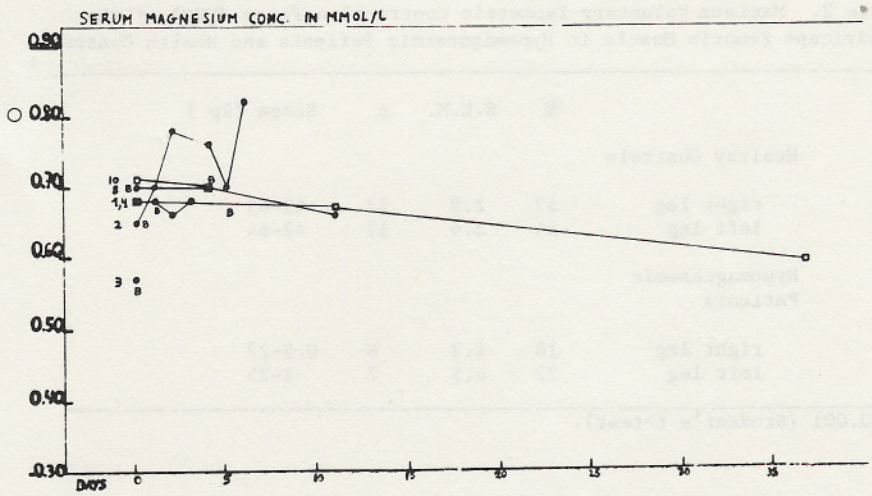

Figure 1. Serum Mg concentration in 6 patients, not treated with Mg supplementation. B = the day of biopsy. Numbers correspond to patient number (see Table 1).

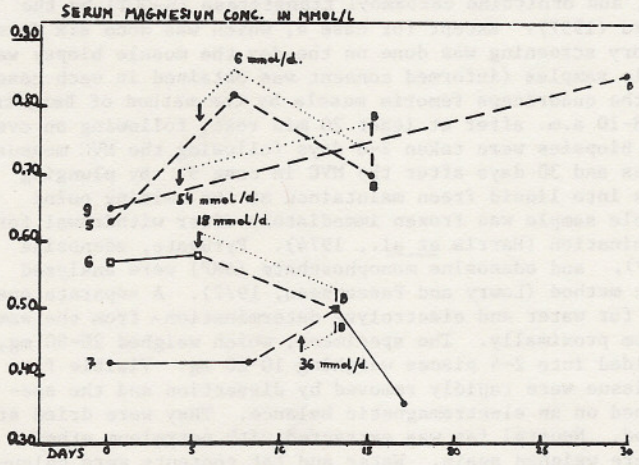

Figure 2. Serum Mg concentrations in 4 patients given Mg supplementation. B = the day of biopsy. The numbers on the left correspond to the patient number (see Table 1.). ↓····1 = duration of Mg supplementation; the individual dosage is expressed in mmole Mg/day.

the modified method of Tornvall (1963) (Table 1). The values were compared with those from 12 healthy normal controls with normal Mg levels, aged 21-56 (Table 2).

Table 2. Maximum Voluntary Isometric Contraction Force (MVC) of the Quadriceps Femoris Muscle in Hypomagnesemic Patients and Health Controls

	$\bar{x}$	S.E.M.	n	Range (kp)
Healthy Controls				
right leg	52	2.8	12	41-65
left leg	54	2.6	12	42-64
Hypomagnesemic Patients				
right leg	18	4.3	6	0.5-27
left leg	22	4.5	7	1-25

$p < 0.001$ (Student's t-test).

Serum Mg was measured by atomic absorption spectrophotometry (AAS) (Perkin Elmer Model 403; Clinical Chemistry Lab.,Karolinska Hospital) and simultaneous serum laboratory screening was performed for all patients. In six cases,serum creatine kinase was estimated by method of Oliver,1955 (see Nygren,1966), and ornithine carbamoyl transferase (S-OCT) by the method of Reichard (1957). Except for case 4, which was done six days earlier, laboratory screening was done on the day the muscle biopsy was taken. The muscle samples (informed consent was obtained in each case) were taken from the quadriceps femoris muscle by the method of Bergström, (1962), between 8-10 a.m. after at least 20 min rest, following an overnight fast. The biopsies were taken 2-8 days following the MVC measurement in five cases and 30 days after the MVC in case 9. By plunging the biopsy needle into liquid freon maintained at the melting point (-150°C) one muscle sample was frozen immediately after withdrawal for metabolite determination (Harris et al., 1974). Pyruvate, adenosine diphosphate (ADP), and adenosine monophosphate (AMP) were analyzed by a fluoremetric method (Lowry and Passonnean, 1972). A separate specimen was taken- for water and electrolyte determination- from the same muscle, but 4-5 cm proximally. The specimens, which weighed 20-80 mg, were equally divided into 2-4 piéces weighing 10-20 mg. Visible fat and connective tissue were rapidly removed by dissection and the specimens were weighed on an electromagnetic balance. They were dried at 90°C and reweighed. Neutral fat was extracted with petroleum ether and the pieces were weighed again. Water and fat contents were calculated. Sodium (Na), potassium (K), and Mg contents were determined by AAS; chloride (Cl) was measured by electrometric titration (Bergström et al., 1973) Tissue water and electrolytes were referred to 100 g fat-free solids.

The determination of extracellular (e.c.) and intracellular (i.c.) water was based on the Cl method. Chloride is freely diffusible across the skeletal muscle fiber membrane and is distributed according to

Nernst's equation (Conway, 1957). Taking the resting membrane potential of muscle in normal man to be 87.2 mV (Bolte et al., 1963), the $Cl_{e.c.}/Cl_{i.c.}$ ratio calculated from Nernst's equation will be 26/1; if the total water and Cl content of the muscle tissue and the é.c.concentration of Cl (obtained by correcting the plasma Cl concentration for a Donnan factor, and a factor for plasma water (Bergström, 1962) are known, e.c. and i.c. water volumes and i.c. electrolyte concentrations can be calculated (Graham et al., 1967; Bergstrom and Bittar, 1969).

RESULTS

There was a significant decrease of the MVC of the quadriceps femoris muscle as compared with normal controls (Table 2). Except for low serum Mg values ($P<0.01$) in all patients, most of the laboratory values were within normal limits. Deviant values were found in the following patients, who had undergone biopsies:

Case 5 increased alkaline phosphatase and decreased serum iron
Case 6 increased S-OCT and decreased total iron-binding capacity (TIBC)
Case 7 decreased serum Ca and TIBC
Case 8 increased S-OCT, decreased TIBC, and borderline low protein
Case 9 increased S-ALAT and decreased TIBC
Case 10 increased S-OCT

The muscle electrolyte determinations showed noted lowered mean Mg content per 100 g fat-free solids ($P<0.001$). The lowest values were found in patients 7 and 9, in spite of Mg treatment of 2 and 11 days duration, respectively, which normalized the serum Mg in case 9. The mean Mg/K quotient (Bergström, 1962) was significantly lowered ($P<0.001$). Mean Na and Cl content and total and e.c. water content per 100 g fat-free solids were significantly raised ($P<0.05$).

Muscle metabolite determinations showed significantly lowered mean creatine phosphate in patients, as compared with controls ($P<0.001$). The mean ADP content was also significantly lower than controls ($P<0.05$). The apparent equilibrium constant for creatine kinase reaction was significantly increased ($P<0.01$).

DISCUSSION

The significantly lowered MVC, confirms earlier findings in hypomagnesemic subjects (Stendig-Lindberg, 1973). Apart from the significantly low serum Mg levels, the laboratory findings were usually within normal limits, although there was a tendency for low TIBC in four patients. Impaired hepatic function activity was indicated by the elevated S-OCT and alkaline phospatase, and in three cases each, of S-ALAT in 1 case and the raised serum bilirubin and ammonia in 2 patients.

Low and normal muscle Mg levels have both been reported in patients with hypomagnesemia (MacIntyre et al., 1961; Dunn and Walser, 1966; Cadell and Goddard, 1967; Lim et al., 1969; Muldowney, 1970; Lim and Jacob, 1972a). We have found that hypomagnesemic patients had only 11% decreased muscle content, both when estimated with reference to fat-free solids and to muscle K content (Bergström, 1962). This is not surprising in view of the fact that only a small fraction of total Mg in muscle is in the free ionized form, the rest being bound as a complex with ATP and other metabolites (Nanninga, 1961). Thus even a substantial decrease in i.c. free Mg might appear only as a very moderate decrease in total Mg provided the bound Mg fraction were unchanged. It

is probable that the free Mg content is an important factor in the neuromuscular excitability of muscle fibres (Chutkow, this symposium) and in electrolyte transport. The increase in total water content per 100 g fat-free solids occurred as a consequence of an increase of e.c. water content, the i.c. water content remaining normal or low.

Sodium and Cl, which are predominantly e.c. electrolytes, also accumulated in muscle tissue. The i.c. Na concentration was low in two and high in one case. Sodium retention with an expansion of e.c. fluid is a common response to trauma and disease and this accumulation is reflected in muscle tissue as well. Since these patients all had a history of chronic disease, these changes cannot be attributed to Mg deficiency alone.

We did find lowering of mean creatine phosphate, which was most marked in case 7, in whom total creatine was also decreased. This patient also had the lowest Mg and the highest Cl content in muscle. This may be a sign of a relative decrease in muscle fiber content in the biopsy specimen, which could be explained by protein calorie malnutrition resulting in net catabolism of muscle protein. Such malnutrition is also known to cause decreased TIBC (Edozien and Udeozo, 1960). and was also observed in cases 6, 7, 8, and 9. A decrease in white muscle fiber protein has also been observed in alcoholism by Kiessling et al., (1975).

Except for the slight lowering of the creatine phosphate and a small decrease in ADP content as well, all metabolites measured showed normal values. These minor changes in metabolite content do not explain the muscle weakness found in patients with hypomagnesemia.

However, it should be pointed out that these findings represent steady state values at rest and cannot portray any possible metabolic alterations which might follow exertion.

SUMMARY

Ten patients (age 35-39) with hypomagnesemia of chronic alcoholism (7 cases) or malabsorption (3 cases) had the MVC of their quadriceps femoris muscle assessed (7 cases) and had laboratory screening (9 cases) and skeletal muscle biopsy analysis for electrolyte and metabolite content (6 cases). The MVC values were significantly lower in hypomagnesemic than in control subjects (Dunn and Walser, 1966). Except for significantly low serum Mg and tests indicative of liver damage (elevated S-OCT (3 cases), alkaline phosphatase (3 cases), S-ALAT (1 case), bilirubin and blood ammonia (2 cases), most laboratory findings were normal. Low serum TIBC, a finding reported in protein calorie malnutrition, was seen in four cases. In comparison with healthy controls, the hypomagnesemic patients had much lower muscle Mg content ($p<0.001$) and increased muscle Na and Cl, as well as e.c. H_2O ($p<0.05$). The apparent equilibrium constant for creatine kinase was increased ($p<0.01$). There was slight lowering of ADP ($p<0.05$) and of creatine phosphate ($p<0.01$). These are interesting findings in view of the lowered MVC and the diminished capacity for sustained muscular effort reported earlier in hypomagnesemic patients.

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