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Záznam: 1

Titul:	Red blood cell magnesium and chronic fatigue syndrome.
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Zdroj:	Lancet; 3/30/1991, Vol. 337 Issue 8744, p757, 4p, 3 Charts
Typ dokumentu:	Article
Tématické termíny:	*CHRONIC fatigue syndrome
Abstrakt:	Investigates whether patients with chronic fatigue syndrome have low red cell magnesium concentrations and whether treatment with magnesium improves their well being. These hypotheses were tested in a matched case-control study and a double-blind,randomized, placebo-controlled trial.
Počet slov plného textu:	3795
ISSN:	00995355
Přírůstkové číslo:	9104291881
Databáze:	Academic Search Complete

Část: ORIGINAL ARTICLES

RED BLOOD CELL MAGNESIUM AND CHRONIC FATIGUE SYNDROME

The hypotheses that patients with chronic fatigue syndrome (CFS) have low red blood cell magnesium and that magnesium treatment would improve the well-being of such patients were tested in a case-control study and a randomized, double-blind, placebo-controlled trial, respectively. In the case control study, 20 patients with CFS had lower red cell magnesium concentrations than did 20 healthy control subjects matched for age, sex, and social class (difference 01 mmol/l, 95% confidence interval [CI] 0.05 to 0.15). In the clinical trial, 32 patients with CFS were randomly allocated either to intramuscular magnesium sulphate every week for 6 weeks (15 patients) or to placebo (17). Patients treated with magnesium claimed to have improved energy levels, better emotional state, and less pain, as judged by changes in the Nottingham health profile. 12 of the 15 treated patients said that they had benefited from treatment, and in 7 patients energy score improved from the maximum to the minimum. By contrast, 3 of the 17 patients on placebo said that they felt better (difference 62%, 95% CI 35 to 90), and 1 patient had a better energy score. Red cell magnesium returned to normal in all patients on magnesium but in only 1 patient on placebo. The findings show that magnesium may have a role in CFS.

Lancet 1991; 337: 757 60.

Introduction

Chronic fatigue syndrome (CFS) (formerly myalgic encephalomyelitis) has received much interest in the past decade, but has probably been endemic for centuries. In the second century, Galen described a disease complex similar to CFS, and in this century, outbreaks

of "neurasthenia", abortive poliomyelitis, Icelandic disease, Akureyri disease, Royal Free disease, and even hypochondriasis have been reported, all of which have the typical features of CFS.(n1) The cause is unknown, though the disorder has been attributed to mass hysteria., Lately, a viral basis of infection, especially due to Epstein-Barr virus (EBV) or Coxsackie B virus, has been considered. Findings of raised EBV antibody titres have proved to be poorly reproducible; moreover, the coincident increased amounts of other viral antibodies point to generalized immune activation rather than direct implication of EBV.(n3, n4) The role of Coxsackie B virus is equally unclear. Two studies have demonstrated an increase in Coxsackie B virus antibody,(n5, n6) and in another study Coxsackie B virus was recovered from the gut in a substantial proportion of patients.' By contrast, Miller and colleagues,(n8) using assays for Coxsackie B virus IgM and IgG, failed to distinguish between patients with CFS and control subjects. A useful review of published work has been given by David et al.(n9) Treatment remains inadequate and depends largely on rest and education. Although antidepressants may help the associated depression and anxiety, they may be counterproductive because they reinforce the idea to the patient that his or her physician regards the condition as psychogenic in origin. The desperation of patients, who believe that they have a physical illness, leaves the way open for bogus remedies and "food" supplements, such as germanium and tryptophan (banned in some countries). Immunotherapy, so far, seems to offer the only clinically significant benefit.(n10)

The study reported here was started for three reasons. Firstly, one of us (D. D.) had noticed that some practitioners were using magnesium to treat CFS, with good results in some patients when given parenterally. Secondly, many of the symptoms of CFS are similar to those of magnesium deficiency--ie, anorexia, nausea, learning disability, personality change, weakness, tiredness, and myalgia. Finally, in a pilot study (unpublished) we found that patients with CFS had subnormal red blood cell magnesium concentrations.

Thus, we decided to see whether patients with CFS have low red cell magnesium concentrations and whether treatment with magnesium improves the well-being of such patients. We investigated these hypotheses in a matched case-control study and a double -blind, randomized, placebo-controlled trial, respectively.

Patients and methods

Patients

Patients in both the case-control study and the clinical trial were defined as having CFS according to the following criteria proposed initially by Abraham and Lubran(n12) and revised by Holmes et al(n13) (Australian criteria): (1) generalized chronic persisting or relapsing fatigue (exacerbated by very minor exercise) causing substantial disruption of usual daily activities, and lasting over six months; (2) neuropsychiatric dysfunction including impairment of concentration (difficulty in completing mental tasks that were easily accomplished before onset of the syndrome) and/or onset of short-term memory impairment; (3) at least five of myalgia, localized muscle tenderness, arthralgia,

headaches, depression, tinnitus, paraesthesia, insomnia for more than 6 months with no other cause, lymphadenopathy, and pharyngitis (on two or more occasions after the initial illness).

These criteria assume a normal physical examination and exclusion of other chronic infections and immunological disorders.

Red blood cell magnesium measurement

Clinical trial--Blood samples were taken by venepuncture (`Vacutainer' needles) and collected into heparinised tubes (vacutainer 606484). 2 ml of the sample was transferred to a tube that was free of trace elements, spun for 15 min at 1200 g ('Multex Centrifuge', MSE, UK), and the supernatant was then separated. 2 ml of whole blood was also taken from the sample for analysis. Specimens of both plasma and whole blood were diluted 1/50 with lanthanum chloride ($LaCl_3$) in HCl and nebulised directly into an air/acetylene flame for atomic absorption measurements at 285.2 nm. Continuous source background correction was used. The diluent used was 0 1% (weight/volume) $LaCl_3$ in 1% (volume/ volume) HCl. A stock of standard magnesium solution (10 mg/ml) was also prepared (1 ml of concentrated standard [1000 mug/ml] diluted to 100 ml [volumetric flask] with I ml concentrated HCl and water). Samples of either re-suspended red cells or plasma were diluted in duplicate with 2000 lll of diluent in plain polycarbonate tubes, stoppered, mixed, and then analyzed with an atomic absorption spectrophotometer (Perkin-Elmer). Atomic absorption peak heights for standards and specimens were measured. Standard peak heights were used to construct a calibration curve against which sample peak heights were calculated. Serum magnesium concentration is a poor predictor of magnesium status,(n11) whereas an erythrocyte intracellular concentration is more accurate.(n12) Therefore, we calculated red cell magnesium concentration (R) as follows:(n12)

$$R = P + (100[W-P]-H)$$

where P = plasma magnesium, W = whole blood magnesium, and H = packed red cell volume (%).

Case-Control study--Plasma and whole blood magnesium concentrations were measured by Biolab Medical Unit, London. The methods were essentially the same as above with the exception that a Pye-Unicam PU 9000 atomic absorption spectrophotometer was used. The instrument, sample preparation, and standardization procedures were those recommended by the manufacturers.(n15)

Case-control study

From October to December, 1989, cases were recruited consecutively from patients attending the Centre for the Study of Complementary Medicine, Southampton, and who satisfied the above criteria. A control group was chosen from our colleagues and from people having routine blood tests in the department of hematology. Individuals attending for routine blood tests and who were suspected of having a disease that might cause

hypomagnesaemia were excluded. Red cell magnesium was measured in cases and controls.

Randomized controlled trial

Between January and June, 1990, patients were recruited from the Centre for the Study of Complementary Medicine and from general practitioners (GPs) in the Southampton area. A letter was sent to 140 GPs, of whom 60 replied; 20 referred patients for the clinical trial. The trial was approved by the local ethical committee. No patient included in the trial had been recruited in the case-control study. Each patient referred was assessed by D. D. and patients entered the trial only if they satisfied the Australian criteria and if duration of illness was greater than 6 months and less than 18 months. Based on a 15% placebo response and 50% treatment response, we tried to recruit 50 patients to give an 80% power to achieve significance at 5%.

Patients were randomly allocated with a computer generated random log to one of two treatment groups. Each patient was told that he or she would be given one of two treatments--namely, an "active" treatment or an "alternative" treatment. The full therapeutic regimen was described to patients in detail and they were then asked whether they would like to take part in the trial. Those who wished to do so were asked to sign a consent form. It was also explained to the patients that if, at the end of the trial, they were found to have been given the alternative treatment, they would be able to receive the active treatment if they so wished. The treatment groups were labelled A and B. Group A received 50% magnesium sulphate (1 g in 2 ml), whereas group B received placebo (2 ml injectable water). To ensure that the trial was double-blind, both sets of ampoules, which were the same size, were masked in white sticky paper, and labelled A or B. Both solutions are clear, so that neither those giving the treatment nor the patients knew which one was being administered. The therapeutic regimen consisted of an intramuscular injection, given in the gluteal region, every week for 6 weeks. After the first injection, patients were given the choice of either attending the centre for the remaining five rejections or having their own GP administer the injection. Most patients chose to receive the remainder at the centre. The exceptions were those who had to travel far.

Before the first injection and a week after the last, patients were asked to complete the Nottingham health profile,(n16) which contains questions in six categories--ie, energy, pain perception, sleep patterns, sense of social isolation, emotional reactions, and physical mobility. The scores are weighted so that in each category the minimum score is 0 (for someone with no complaints) and the maximum score is 100 (for someone who answers yes to all questions). After treatment, subjects were asked "Do you feel you have benefited from treatment?", and if so, to describe the benefits briefly.

Also, before the first injection and a week after the last, a sample of blood was taken for analysis of erythrocyte magnesium level and for red cell folate index. Red cell magnesium was measured at the department of clinical biochemistry, Southampton General Hospital, as described above. Erythrocyte folate index was measured to exclude the possibility that

the patient had a generalised malabsorption syndrome, which might have affected magnesium absorption in the small intestine and thus contributed to hypomagnesaemia.

Results

Case-control study

The cases were 18 women and 2 men (mean age 36 2 years [range 18-71]).11 cases were in social classes I/II and 9 were in social classes III-V.20 control subjects were matched for age, sex, and social class. The mean age of control subjects was 36.5 (range 18-72). Mean red cell magnesium for cases was 1.60 mmol/1, whereas that for control subjects was 1.70 mmol/1 (difference 0.10 mmol/1, Student's paired t test = 4.62, df= 19, $p < 0.001$, 95% confidence interval [CI] for the difference 0.05-0.15).

Clinical trial

Owing to time constraints, only 38 patients were recruited to the trial, of whom 4 were excluded before because they did not satisfy the diagnostic criteria for entry. No patient withdrew when the trial was explained to them.(n2) group A patients dropped out of the trial: a generalised rash, which might have been a side-effect of treatment, developed in 1 female patient, and 1 male patient could not obtain the cooperation of his GP, who wanted to know what treatment he was on. Since we believed that to inform his GP would have jeopardised the double-blindness of the study, we withdrew the patient from the study. Thus, 15 patients were randomised to group A and 17 to group B. The two groups were similar with respect to baseline characteristics (table I). Red cell magnesium concentrations were lower than normal in both groups. Mean Nottingham health profile scores have been given(n16) for patients with various conditions. In the categories energy, pain, emotional reactions, sleep, social isolation, and physical mobility, patients with minor nonacute illnesses scored 24.2, 15.9, 14.7, 18.7, 5.1, and 7.3, respectively, whereas patients with osteoarthritis scored 63.2, 70.8, 21.3, 48.7, 12.5, and 54.8. Our patients with CSF had higher scores for all categories than did patients with minor illnesses. Scores were lower with respect to pain, sleep, and physical mobility but higher with respect to energy, emotional reactions, and social isolation, than those in patients with osteoarthritis.

Table II shows the changes in the Nottingham health profile scores after treatment or placebo. Reduction in scores for energy, pain, and emotional reactions was significantly greater in group A than in group B. The overall score was also highly significantly improved for group A. 12 group A patients (80%) claimed to have benefited from treatment, compared with only 3 group B subjects (18%) (Chi 2= 10.1, df= 1, p =0.0015, difference=62%, 95% CI 35-90). Before treatment, 11 group A patients scored the maximum of 100 for energy and of these, 7 scored the minimum of 0 after treatment. By contrast, 14 group B patients scored 100 before treatment and of these, 1 had a reduced score after treatment.

The changes in magnesium concentrations and packed red cell volume are shown in table III. There was a pronounced rise in both whole blood magnesium and red blood cell

magnesium concentrations in group A patients that was not matched by a corresponding rise in group B subjects. Before treatment only 1 person in group A had a red cell magnesium concentration within the normal range compared with none in group B. After treatment, red cell magnesium was within the normal range in all group A patients but in only I group B patient.

Discussion

One of the difficulties in investigating CFS is that the disease is largely not recognised by the medical profession.(n17, n18) Of the 60 GPs who replied to our letter, 40 made it clear that they did not believe there was such a disease, and would therefore not forward patients for the trial. Although the remaining 20 GPs were sympathetic and did refer patients for the study, many of them seemed not to know of any specific criteria of diagnosis, and the condition was a medical enigma to them. Diagnosis of CFS is difficult and it is important that other organic causes are excluded. In our study the Australian criteria of diagnosis provided a systematic method of screening patients.

In the case-control study, the difference in erythrocyte magnesium concentrations between patients with CFS and control subjects was statistically significant, but quite small. Previous unpublished studies (D. Dowson and S. Davies, personal communications) have also repotted low magnesium in patients with CFS. Furthermore, all but 1 of our patients recruited to the trial had red cell magnesium concentrations below the normal range. We cannot compare directly the data from the case-control study with those from the clinical trial because the magnesium measurements were done in different laboratories under slightly different conditions. Since magnesium slowly leaches out of red cells into the plasma when stored, care was taken in the clinical trial to ensure that the delay between the taking of blood and analysis was a short as possible; however, this does not explain the differences between laboratories, since the delay was greater in the case-control study. That plasma magnesium concentrations were all within the normal range (0.8-1.0 mmol/1) before and after the trial confirms the finding of Alfrey et al(n11) that plasma magnesium is a poor predictor of the body's magnesium status.

Why should magnesium benefit patients with CFS? The improvement in the emotional reaction scores of the Nottingham health profile in the magnesium treated group is in accordance with the findings of investigators who have used magnesium to treat conditions such as anxiety and insomnia and organic mental disorder.(n19) One of the clinical features of magnesium deficiency is psychiatric disturbance; neuropsychiatric dysfunction is one of the cardinal symptoms of CFS. However, the basis for the therapeutic action of magnesium is unknown. What causes low magnesium? One suggestion is that low physical acivity, or perhaps stress, rather than the disease itself, can lead to abnormal biochemical status. CFS patients are often very stressed and anxious because they are isolated and because friends and relatives are unsympathetic. Stress anxiety and nervousness can lead to hypomagnesaemia.(n20, n21) Magnesium seems also to affect energy status. We showed an improvement in energy status after magnesium treatment, which accords with other studies in which magnesium supplementation was used to treat tiredness.(n22, n23) Johansson(n24) has reported

benefit of magnesium for muscle cramps and mylagia. Additionally, magnesium deficiency was found in a group of competitive swimmers;(n25) those on magnesium supplementation had lower blood lactate concentration and lower oxygen consumption, despite higher glucose utilisation during a race.

We have shown that patients with CFS have slightly lower magnesium levels than healthy controls and that treatment with magnesium seems to benefit patients, especially with respect to their energy and emotional status. However, we realise that our trial was small and that follow-up was only 6 weeks; therefore, the results should be viewed with caution. There are some unresolved questions. Would the benefit that we have recorded be maintained and for how long? Should magnesium be given by injection, or taken orally? We hope that our findings will stimulate more GPs to take an interest in the disease.

We thank the patients who volunteered for this study; Dr G. Lewith and Dr J. Kenyon for referring patients for the clinical trial; Maureen Smith and Helen Wilson at the Centre for the Study of Complementary Medicine, Southampton, for doing the injections; Dr H. T. Delves, Mrs S. Draper, Mr C. Fellows, and Mr B. Suchak for help with the laboratory work; Dr S. Davies and Dr J. Howard, Biolab Medical Unit, for analysing blood samples; Dr G. P. Weavind, Mr R. D. Hyde, and Mr Bill Fairfield for help with analysis for blood samples and biochemistry; Dr A. J. Pelosi for commenting on the script and Lindsey Izzard for typing it. This research was funded by the ME Action Campaign.

TABLE I--BASELINE CHARACTERISTICS

Characteristic	Group A (n = 15)	Group B (n = 17)
Sex (M/F)	5/10	5/12
Mean age (range) (yr)	35.7 (18-56)	37.1 (22.51)
Mean packed red cell volume (SD)	0.39 (0.037)	0.39 (0.033)
Mean Nottingham health profile score (SD)		
Energy	85.8 (28.3)	93.2 (15.1)
Pain	28.9 (28.1)	24.8 (33.3)
Emotional reactions	62.8 (22.4)	46.2 (30.1)
Sleep	35.2 (31.0)	27.4 (28.1)
Social isolation	49.6 (36.8)	36.3 (29.9)
Physical mobility	22.5 (15.7)	33.1 (22.6)
Overall	248.9 (71.5)	261.1 (91.6)
Mean (SD) magnesium concentration (mmoll/l)		
Plasma	0.80 (0.082)	0.81 (0.058)
Whole blood	0.99 (0.070)	1.00 (0.046)
Red blood cell(*)	1.29 (0.079)	1.28 (0.067)

(*) Normal range 1.41-2.09 mmol/l

TABLE II--CHANGES IN NOTTINGHAM HEALTH PROFILE SCORES

Nottingham health profile category	Change in score after treatment: Group A	Group B	Change between group	CI	p value
Energy	-15.04	-4.47	-46.57	-76.16 to -16.98	0.002
Pain	-19.63	2.65	-22.28	-39.16 to -5.39	0.011
Emotional reactions	-33.32	-7.38	-24.93	-43.90 to -5.96	0.013
Sleep	-13.61	-7.04	-6.58	-19.12 to 5.97	0.278
Social isolation	-17.80	-4.86	-12.95	-35.20 to 9.31	0.237
Physical mobility	-9.11	-3.65	-5.46	-16.49 to 5.57	0.336
Overall	-143.51	-24.74	-118.76	-184.56 to -118.76	0.001

CI = confidence interval.

TABLE III--CHANGES IN MAGNESIUM LEVEL AND PACKED RED CELL VOLUME

--	Change after treatment: Group A (n=14)(*)	Group B (n=17)
Magnesium (mmol/l)		
Plasma	0.091 (0.093)	0.080 (0.072)
Whole blood	0.29 (0.091)	0.037 (0.048)
Red blood cell	0.57 (0.192)	-0.018 (0.059)
Packed red cell volume	0.006 (0.20)	-0.003 (0.025)

Values are means (SD). (*) 1 person refused to give blood.

REFERENCES

(n1.) Kendell RE. Chronic fatigue, viruses, and depression. Lancet 1991; 337: 160-62.

(n2.) Ramsay AM. Encephalomyelins simulating poliomyelitis and hysteria. Lancet 1957; ii: 1196-1200.

(n3.) Editorial. EBV and persistent malaise. Lancet 1985; i: 1017-18.

(n4.) Jones JP, Ray G, Minnich LL, Hocks MJ, Kiblet R, Ineas DO. Evidence for active Epstein-Barr virus infection in patients with persistent unexplained illness: elevated early antigen antibodies. Arm Intern Med 1985; 201: 1-7.

(n5.) Fegan KG, Behan PO, Bell EJ. Myalgic encephalomyelias: report of an epidemic. J R Coll Gen Pract 1983: 33: 335-37.

(n6.) Calder BD, Warnock PJ. Coxsackie B infection in a Scottish general practice. J R Coll Gen Pract 1984; 34: 15-19.

(n7.) Youseff G. Chronic enterovirus infection in patients with post-viral fatigue syndrome. Lancet 1988; i: 146-50.

(n8.) Miller NA, Carmichael HA, Calder BD, et al. Antibody to Coxsackie B virus in diagnosing postviral fatigue syndrome. Br Med J 1991; 302: 140-43.

(n9.) David AS, Wessely S, Pelosi AJ Postviral fatigue syndrome: time for a new approach. Br Med J 1988; 296: 696-99.

(n10.) Lloyd AR. Intravenous immunoglobulin therapy and immunotherapy with transfer factor in patients with chronic fatigue syndrome. The Cambridge symposium on myalgic encephalomyelitis (9 12 April, 1990). Nightingale Research Foundation Circular--The Nightingale, Spring 1990: 1.

(n11.) Alfrey AC, Miller NL, Butkus D. Evaluation of body magnesium stores. J Lab Clin Med 1974; 84: 153-62.

(n12.) Abrabam GE, Lubran MD. Serum and red cell magnesium levels in patients with premenstrual tension. Am J Clin Nutr 1981; 34: 1264-66.

(n13.) Holmes GP, Kaplan JE, Gantz NM, et al. Chronic fatigue syndrome. A working case definition. Ann Intern Med 1988;108: 387-89.

(n14.) Lloyd AR, Wakefield D, Broughton C, Dwyer J. What is myalgic encephalomyelitis? Lancet 1988; i: 1286-87.

(n15.) Milner A, Whiteside PJ. Introduction to atomic absorption spectrophotometry. Cambridge: Pye Unicorn Ltd, 1984: 78-82.

(n16.) Hunt SM, McEwen J, McKenna SP. Measuring health status: anew tool for clinicians and epidemiologists. J R Coll Gen Pract 1985; 35: 185-88.

(n17.) McEvedy CP, Beard AW. Royal free epidemic of 1955: a reconsideration. Br Med J 1970;1: 7-11.

(n18.) McEvedy CP, Beard AW. A controlled follow-up of cases involved in an epidemic of benign myalgic encephalomyelitis. Br J Psychiatry 1973 122: 141-50.

(n19.) Webb WL, Gehi M. Electrolyte and fluid imbalance: neuropsychiatric manifestations. Psychosomatics 1981; 22:199-203.

(n20.) Abraham AS, Shaoul R, Shimonovitz S, Eylath U, Weinstein M. Serum magnesium levels in acute medical and surgical conditions. Biochem Med 1980; 24: 21-26.

(n21.) Devane J, Ryan MP. Postoperative changes in lymphocyte potassium and magnesium. Irish J Med Sci 1980;149: 73-76.

(n22.) Seelig M. Review article: magnesium deficiency in the pathogenesis of disease. New York: Plenum Press, 1980.

(n23.) Bastien S. Patterns of neurophychological abnormalities and cognitive impairment in adults and children. The Nightingale Research Foundation Circular--The Nightingale, Spring 1990 (1)3: the Cambridge Symposium on Myalgic Encephalomyelitis (9 12 April 1990).

(n24.) Johansson BW. Magnesium infusion in decompensated hypomagnesaemia patients. Acta Pharmacol Toxicol (Copenh) 1984; 54:125-28.

(n25.) Schmidt M. The effects of a magnesium supplementation on the energy metabolism in competitive swimmers. Magnesium Res 1989; 2: 281-83.

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