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MULTIPLE SCLEROSIS: DECREASED RELAPSE RATE THROUGH DIETARY SUPPLEMENTATION WITH CALCIUM, MAGNESIUM AND VITAMIN D

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ABSTRACT

A group of young patients having multiple sclerosis was treated with dietary supplements containing calcium, magnesium and vitamin D for a period of one to two years. The experimental design employed self-pairing: the response of each patient was compared with his/her own case history as control. The number of exacerbations observed during the program was less than one half the number expected from case histories. No side effects were apparent. The dietary regimen may offer a new means of controlling the exacerbation rate in MS, at least for younger patients. The results tend to support a theory of MS which states that calcium and magnesium are important in the development, structure and stability of myelin.

INTRODUCTION

We report here on clinical trials with a group of patients having multiple sclerosis (MS). These patients were treated over an extended period with dietary supplements furnishing quantities of calcium, magnesium and vitamin D.

The rationale for this approach is provided by a theory of the underlying causes of MS published by one of us (PG), (1, 2). This theory states that, in a genetically predisposed group, a requirement exists for higher than normal intake of calcium, magnesium and vitamin D. Failure to supply this requirement during the development of the central nervous system results in myelin of abnormal lipid composition and myelin instability. In such cases of unsatisfied nutritional dependency, breakdown of myelin

occurs in adulthood with the appearance of signs and symptoms of MS. Conversely, MS is prevented when the nutritional dependencies are satisfied.

According to the theory, the critical period for supply of the nutrients is before and during adolescence. Nevertheless, we reasoned that MS patients might be helped by a regimen supplying the crucial nutrients because myelination is an on-going process, at least into the third and fourth decade of life (3, 4) and hence myelin repair might be possible.

Protocol

We followed the protocol advanced by Schumacher for testing new therapies in MS (5). According to this plan, patients serve as their own controls. For each patient, the experience during the test period is compared with the case history.

Young patients (22 - 37 years) were selected who (i) were diagnosed as definite cases of MS and (ii) exhibited unambiguous symptoms (exacerbations) within 12 to 24 months prior to the start of the trial. This selection led to a test group with a higher than normal exacerbation rate. However, we considered this necessary in order to develop a valid statistical interpretation in view of the short time planned for the test (about one to two years) and the small size of the group.

Sixteen patients (6 males, 10 females) were chosen from our practices. They were supplied with calcium and magnesium in the form of dolomite tablets, sufficient to furnish 10 mg of magnesium per kilogram of body weight daily. This dosage also furnishes 16 mg per day of calcium/kg of body weight, amounts which, at least for normal subjects, insure states of positive balance for both magnesium (6) and calcium (7). Vitamin D, which promotes absorption of the minerals, was taken in the form of cod liver oil at the rate of 5,000 i.u./day (about 20 g of oil per day). Without confinement of patients, it was not possible to verify that all supplements were ingested as required. However, the patients reported good compliance, which we had no reasons to doubt.

Patients were examined quarterly. At each visit serum calcium, magnesium and phosphorus were determined to insure that no imbalances were created by the regimen. Initially, and again at 6 months, serum levels of 25-hydroxy vitamin D metabolite were measured (normal range: 15-80 ng/ml). This precaution was taken because of the use of a relatively high dose of vitamin D. No abnormalities were found during the course of the study.

We initially aimed for a one-year trial, with the option of continuing for a second year if the results, and agreement by the patients, permitted. Of the sixteen who started, ten finished approximately one year or more.

The effectiveness of the regimen was judged by comparing the number of exacerbations during the trial with the number expected from patient histories. In these calculations, all exacerbations (mild and severe) were given equal weight. We personally observed about 65% of the exacerbations in the histories, and all bouts during the trial. We took as our definition of an exacerbation a period of not less than 24 hours in which there is worsening of an existing symptom or group of symptoms, provided that the course of the disease had been stationary or improving during the previous month.

Materials

The dolomite tablets were from the Hudson Pharmaceutical Corp., West Caldwell, N.J., and contained nominally 94 mg magnesium and 155 mg calcium per tablet. We verified these potencies by independent chemical analyses. Patients consumed about 5 - 8 tablets/day, the exact number determined by body weight.

The cod liver oil was from Marine Products Co., South Boston, MA, and was chosen to have a potency of 250 i.u. vitamin D per gram. The vitamin D concentration was verified by independent assay at the WARF Institute, Madison, WI, using the rat line test, and by chromatagraphic analysis. The patient took 20g/day for a total of 5,000 i.u. To make the oil more palatable, a "tasteless" form was furnished. Despite this, several patients found the oil objectionable and elected to leave the program.

Results

Table 1 gives the exacerbation record before and during the trial for the ten patients who participated for eleven months or more (the "long-term" group). For each patient an exacerbation rate (the "initial rate" in Table 1) was computed from the historical data. In all cases except one (patient RC) the rate was the total number of exacerbations experienced since onset divided by the duration at the time the test began. For patient RC we used only recent experience for calculation of the rate because of a long quiescent period in his history.

Table 1

Historial and Experimental Data for Long-term Group

	BEFORE					DURING	
Patient	no. exac.	no. months	init. rate (exac/yr)	theor. final rate	aver. rate	no. exac.	no. months
GB	6	54	1.33	1.02	1.18	1	24
JC	5	49	1.22	0.90	1.06	2	24
MM	5	26	2.30	1.66	1.98	0	19
KO	9	52	2.07	1.61	1.84	1	12
RP	9	84	1.29	1.09	1.19	1	24
LV	4	25	1.92	1.63	1.78	1	11
RC	2	13	1.85	1.55	1.70	0	24
DS	10	96	1.25	1.06	1.16	1	24
HS	8	105	0.91	0.79	0.85	1	24
RT	8	140	0.68	0.61	0.65	1	24

Uncorrected rate:

No. exacerbations expected = 25
No. exacerbations observed = 9 Ratio 2.7
Significance $p < .005$

Corrected rate:

No. exacerbations expected = 22
No. exacerbations observed = 9 Ratio 2.4
Significance $p < .01$

The exacerbation rate is believed to decrease spontaneously during the course of the disease (8). If this is so, then the declining rate must be taken into account in estimating the expected number of exacerbations. We do this by employing a lower rate, the "theoretical final rate" (see Table 1). The numerical method used to calculate the theoretical final rate is based upon the data of Müller (9). Table 2 shows the number of bouts per year over a 20 year span computed by converting the cumulative data of Müller into units of bouts/year. Table 1 gives the theoretical final rate, i.e. the rate each patient would have had (taking duration into account) if his rate spontaneously declined according to the pattern of Table 2.

We next compute an average rate (i.e. the average of the initial and theoretical final rates; see Table 1). From this average rate and the period of treatment for each patient, we estimate that, according to the null hypothesis,

the patient group should have experienced 22 exacerbations; 9 were observed (ratio = 2.4). According to the X^2 test, this decrease is significant; $p < .01$.

Table 2

Change in relapse rate with time after on-set
(adapted from data of Müller (9))

Time after on-set (years)	Rate (bouts/yr)	Relative Rate (percent)
2	1.16	100
5	0.60	51.7
10	0.40	34.5
15	0.30	25.9
20	0.25	21.5

An alternative view of accounting for the effect of elapsed time on exacerbation rate (and hence on the expected number of relapses) comes from the data of Thygesen (10). In his study, Thygesen presents values for rate (attacks/year) *vs.* duration for patients divided according to age. For 15 patients under the age of 40, the data appear scattered; no downward trend is obvious, as can be seen for example, in the results of Müller (Table 2). If the initial rate is used, the expected number of exacerbations is 25. Comparing this with 9 observed, we find a ratio of 2.7; $p < .005$.

The actual improvement afforded by the treatment is probably somewhat greater than the factor of 2.4 - 2.7 recorded here for the long term group. During the test period we personally observed all exacerbations. Only a fraction of the historical exacerbations (65%) were observed by us, the remainder being drawn from medical records. A number of episodes may have been missed during the historical period.

Six patients voluntarily dropped out of the trial. Table 3 shows the data for the group of drop-outs and the reasons for leaving. This group experienced 5 exacerbations in 39 patient-months, with 7.5 expected. If these are added to the data of Table 1, the total number of exacerbations expected becomes 32 and the number observed 14 (ratio 2.3). The decrease for the treatment period is still significant by the X^2 test; $p < .005$.

Table 3

Historical and experimental data for drop-outs

	BEFORE			DURING	
Patient	no. exac.	no. months	init. rate (exac/yr)	no. exac.	no. months
MF	5	40	1.50	0	8
JK	3	25	1.44	2	8
PK	6	26	2.76	1	8
JM	3	63	0.57	1	4
JO	3	10	3.60	1	3
CS	5	15	4.00	0	8

Reasons for dropping out:

JK	Changed neurologist
PK	Had exacerbation: objected to taste of oil
JM, MF, CS	Stopped taking supplements
JO	Had exacerbation, became pregnant

The factor by which the exacerbation number is decreased by the regimen is therefore 2.3 - 2.7, depending upon the assumption used to estimate the number expected.

CONCLUSIONS

The results reveal a beneficial (i.e. negative) effect of the supplements on the number of exacerbations experienced by the ten patients who participated full term. There are several reasons that may explain why the treatment was not more effective in reducing the number of exacerbations. First, the daily dose of calcium and magnesium was selected from studies on normal subjects. It is possible that the requirement by MS patients for these minerals to insure positive balance is substantially greater than that for normal individuals. Studies of mineral balance with MS subjects would be necessary to remove this uncertainty.

Second, the theory upon which this study is based holds that nutritional inadequacy during development is crucial. In this study we have attempted to supply the critical substances well after the disease process began. It may not be possible to reverse completely demyelination in the adult patient.

Despite the failure to eliminate all exacerbations, the experimental regimen has resulted in a significant reduction in the number of relapses. We are unaware of any other study demonstrating long term improvements in MS patients under comparably controlled conditions, without side effects.

The results are important for two reasons. First, the regimen employed may be regarded as a therapeutic means for controlling the relapse rate in MS, at least for younger patients. (Although we treated a few patients with the progressive form of the disease, the number was too small to draw any meaningful conclusions.)

Second, the favorable results tend to support the theory which states that calcium, magnesium and vitamin D are important in the etiology of MS.

In this study, cod liver oil supplied the require level of vitamin D. This oil is, however, a complex substance that contains other species of importance to the structure of the central nervous system, e.g. eicosapentaenoic acid and docosahexaenoic acid. While we have placed emphasis on vitamin D as the active ingredient, it is possible that consumption of these two fatty acids could have played a part in the favorable therapeutic effects observed.

The positive findings suggest that a larger trial may be of value to determine if the regimen should be widely applied as a treatment for MS. In the event a broader test is undertaken, we would recommend modifications of the protocol used here. (1) A double-blind scheme should be employed. In addition to the many benefits of this method, the ambiguity attending the occurrence of drop-outs would be minimized. (2) Vitamin D should be supplied in the form of a concentrate rather than from cod liver oil. The consumption of cod liver oil over an extended period would be unacceptable to many patients, no matter how promising the benefits or how tasteless the oil. Also, the use of a vitamin D concentrate in place of the oil would clarify the role and importance of the vitamin as opposed to other constituents present in the oil. (3) A study of the requirements in MS patients to achieve positive balance for both calcium and magnesium should be made tc set the required dose level.

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