ORIGINAL ARTICLE

Vitamin B status in patients with chronic fatigue syndrome

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J R Soc Med 1999;**92**:183–185

Some patients with chronic fatigue syndrome say they benefit from taking vitamin supplements. We assessed functional status for the B vitamins pyridoxine, riboflavin and thiamine in 12 vitamin-untreated CFS patients and in 18 healthy controls matched for age and sex. Vitamin-dependent activities—aspartate aminotransferase (AST) for pyridoxine, glutathione reductase (GTR) for riboflavin, transketolase (TK) for thiamine—were measured in erythrocyte haemolysates before and after *in-vitro* addition of the relevant vitamin.

For all three enzymes basal activity (U/g Hb) was lower in CFS patients than in controls: AST 2.84 (SD 0.62) *vs* 4.61 (1.43), $P<0.001$; GTR 6.13 (1.89) *vs* 7.42 (1.25), $P<0.04$; TK 0.50 (0.13) *vs* 0.60 (0.07), $P<0.04$. This was also true of activated values: AST 4.91 (0.54) *vs* 7.89 (2.11), $P<0.001$; GTR 8.29 (1.60) *vs* 10.0 (1.80), $P<0.001$; TK 0.56 (0.19) *vs* 0.66 (0.08), $P<0.07$. The activation ratios, however, did not differ between the groups.

These data provide preliminary evidence of reduced functional B vitamin status, particularly of pyridoxine, in CFS patients.

INTRODUCTION

Chronic fatigue syndrome (CFS) is characterized by profound physical and mental fatigue and exhaustion after minimal physical activity[1,2]. It is commonly associated with other somatic symptoms, including myalgia and disorders of mood and sleep, and theories of its causation include viral infections, immunological and neuroendocrine disturbances, and social or psychological dysfunction. As yet, no firm evidence has been provided to support any of these[3,4].

Vitamin–mineral supplements have been recommended in CFS[5–7] on the basis of anecdotal claims that sufferers have recovered after taking large doses of one or more vitamins[6]. The most commonly recommended vitamins include vitamin C, the B vitamins (especially B_6, B_{12} and folic acid), vitamin A and β-carotene[5–8].

The aim of the present study was to assess the B-group vitamin status of CFS patients. The activities of three erythrocyte vitamin-dependent enzymes—thiamine-dependent transketolase, riboflavin-dependent glutathione reductase, and pyridoxine-dependent aspartate aminotransferase—were assayed before and after *in-vitro* addition of the relevant vitamin. This approach assesses the functional vitamin status of these cells.

METHODS

Patients and controls

King's College Hospital has established a unit specializing in the assessment and management of CFS. Patients are referred to the service from other specialists, primarily in internal medicine, and from general practitioners. All consecutive referrals over 12 months were considered for this study. The criteria for inclusion were fulfilment of the Oxford criteria for CFS[2], and abstinence from any vitamin preparation since the start of the illness.

Of the 101 patients potentially suitable, only 17 had not taken any vitamin preparation during their illness (confirming the popularity of vitamin supplementation in CFS[9]). All 17 agreed to participate in the study, but analytic problems meant that specimens from only 12 could be analysed.

The 12 patients were typical of those attending specialist CFS clinics. Disability was high and only 2 were in full-time employment. The mean (SD) age of the 8 female patients was 43.8 (9.5) years, range 24–52 and of the 4 males 36.3 (15.3), range 19–51. The controls were 18 healthy age and gender matched volunteers (11 women, 7 men) whose specimens were analysed in parallel with the patient samples. The mean age of the control group was 37.2 (9.4), range 21–51.

Haemolysates and assays

Venous blood (10 mL) was withdrawn and transferred to lithium-heparin tubes. Before assay of the vitamin-dependent enzymes, the samples were centrifuged at 4 °C for 10 min at 1000 *g* and plasma and buffy coat were removed. The erythrocytes were washed three times with an equal volume of 0.15 mol/L NaCl, lysed with an equal volume of distilled water, mixed thoroughly and, to ensure complete haemolysis, frozen at −70 °C and thawed at room temperature three times. Samples of the haemolysates

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were stored at −70 °C before assay. Haemoglobin was determined in the haemolysate with a commercial kit (Sigma) measuring conversion to methaemoglobin[10].

Enzyme assays were performed as described by Williams[11]. *In-vitro* addition of vitamins and calculations of the results were as described previously[12]. All reagents were obtained from Sigma Chemical Co, Poole, Dorset, unless otherwise stated.

Statistical analyses

The group results are expressed as mean (SD). Comparison of the means between the two patient groups and the control group was by ANOVA with Bonferroni correction following log transformation of the data. Probabilities of differences less than 0.05 were regarded as statistically significant.

RESULTS

Table 1 shows the mean enzyme activities before and after addition *in vitro* of the relevant vitamin. There was no difference for males and females in either group and therefore the data are pooled. For all three enzymes the basal and activated enzyme activities are lower in the CFS patients than in the controls. The differences are most striking for aspartate aminotransferase (pyridoxine); individual data points are shown in Figure 1. This indicates a functional deficiency of the B vitamins, particularly pyridoxine, with normal levels of apoenzyme and holoenzyme protein.

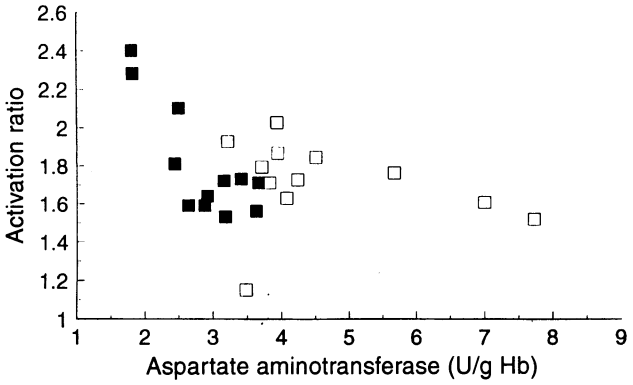

Figure 1 **Enzyme activation ratios plotted against basal erythrocyte aspartate aminotransferase activities for controls and patients with chronic fatigue syndrome (CFS).** (■=CFS, □=controls)

DISCUSSION

Jacobson *et al.*[13] found that CFS patients, in common with those infected with certain viruses or mycoplasmas, had a 50% prevalence of subnormal serum folate; they did not assay red-cell folate as a measure of tissue levels. Regland *et al.*[14], however, did not confirm these findings in 24 Scandinavian CFS patients though they did find raised homocysteine levels in cerebrospinal fluid (which they attributed to low B_{12} levels in the fluid). In an interesting recent paper Baldewicz *et al.*[15] describe evidence of pyridoxine deficiency in recently bereaved homosexual men, related to a measure of psychological stress.

Studies of tissue vitamin functional status are more relevant than serum levels of the free vitamins, and the data

Table 1 **Erythrocyte enzyme activities in patients with chronic fatigue syndrome (CFS) and healthy controls**

	CFS n=12	*Control n=18*	*P*
Aspartate aminotransferase			
Basal activity (U/g Hb)	2.84±0.62	4.61±1.43	<0.001
Activated activity (U/g Hb)	4.91±0.54	7.89±2.11	<0.001
Vitamin effect (%)	42.2±5.0	41.6±1.6	0.6
Activation ratio	1.81±0.29	1.73±0.19	0.4
Glutathione reductase			
Basal activity (U/g Hb)	6.13±1.89	7.42±1.25	0.04
Activated activity (U/g Hb)	8.29±1.60	10.0±1.80	0.001
Vitamin effect (%)	26.1±1.2	25.8±1.0	0.5
Activation ratio	1.41±0.26	1.38±0.24	0.3
Transketolase			
Basal activity (U/g Hb)	0.50±0.13	0.60±0.07	0.04
Activated activity (U/g Hb)	0.56±0.19	0.66±0.08	0.07
Vitamin effect (%)	10.7±1.3	9.1±1.0	0.4
Activation ratio	1.12±0.35	1.10±0.06	0.5

Data show mean and standard deviation for subjects in each group.

from the present investigation are consistent with functional deficiencies of pyridoxine, riboflavin and thiamine. The most striking deficiency, that of pyridoxine, if present in the central nervous system, might account for the depressive features of CFS. These deficiencies are unlikely to reflect low dietary intake or malabsorption since CFS patients are typically well nourished; moreover, a recent dietary survey yielded no evidence that such patients had low intakes of pyridoxine, riboflavin, thiamine or various other vitamins and micronutrients[16]. It is possible that subnormal vitamin activities at a cellular level are responsible for the observed findings.

Excessive losses, catabolism or vitamin requirements by this group of patients are postulated. More detailed studies of functional vitamin status in relation to clinical features of CFS (particularly central nervous signs such as depression and memory impairment) are clearly indicated. A placebo-controlled double-blind study[17] of a polynutrient supplement including pyridoxine, riboflavin and thiamine has shown significant improvements, particularly fatigue scores, after six weeks' treatment. Other studies showed no apparent benefit from folic acid and vitamin B_{12}[18] or from a polyvitamin–mineral mixture[19]. A controlled study of vitamin B monotherapy would be of interest in this group of patients, since most of the studies to date have been poorly controlled and have employed polytherapy. But clearly, many patients with CFS are currently taking vitamin and other supplements with little evidence of benefit.

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