Short report

Effect of lecithin on disability and plasma free-choline levels in Friedreich's ataxia

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SUMMARY Four patients with Friedreich's ataxia took part in an open trial, in which they consumed 50–100g/day lecithin granules (containing approximately 22% phosphatidylcholine) for 16 weeks, but no improvement resulted. Several unwanted effects including diarrhoea, nausea, depression, "hot flushes" and weakness were experienced. Resting levels of free-choline in plasma were within the range found in 19 normal subjects. Sixteen other patients with Friedreich's ataxia also had normal free-choline levels. Treatment with lecithin significantly increased plasma free-choline levels, but there was a trend for these to fall towards baseline levels, despite continued ingestion of lecithin.

Because a defect in the pyruvate dehydrogenase complex has been reported in Friedreich's ataxia,^{1,2} and inhibition of this enzyme results in decreased synthesis of acetylcholine (ACh),³ it has been suggested that the neurological deficit in Friedreich's ataxia may be due to impaired central cholinergic mechanisms. Choline, the precursor of ACh, has been reported to raise brain ACh levels in animals,⁴ leading to post-synaptic effects consistent with an increased release of this transmitter.⁵ Treatment with lecithin, a dietary source of choline may therefore, facilitate cholinergic transmission and some improvement has been reported in brief studies of patients with Friedreich's ataxia.^{6,7}

Patients and methods

Two women aged 29 and 18 years (Cases 3 and 4), and a man aged 29 (Case 1) with classical Friedreich's ataxia⁸ beginning between ages 7 and 14 years, and a man aged 56 (Case 2) whose disease was atypical in that it began in the third decade and progressed slowly, took part in the trial.

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These four patients were asked to take lecithin granules 50 g daily with meals for eight weeks and then 100 g daily for a further eight weeks, in an open study which lasted for 20 weeks. In an initial screening session the test procedures were demonstrated and an ECG was performed in order to exclude patients with marked atrio-ventricular conduction abnormalities. The ECG was repeated at intervals during the trial.

Clinical assessment Patients were assessed on the day before starting treatment, then every four weeks during the four months they were taking the lecithin and finally four weeks after stopping treatment. Each assessment consisted of a battery of tests including clinical examination and assessment of the patient's ability to stand from the sitting position, to walk to and fro across the room and sit down again, and to perform tests of finger-nose co-ordination (eyes closed, eyes open) rapid hand patting, and holding the arms outstretched. All these activities were filmed. In addition, a standard task of placing pegs in a pegboard was timed. Speech was assessed using tests of rapid alternating movements of the tongue and jaw, and of repetitively uttered sounds. Tape-recordings of reading aloud and of the patients' descriptions of a picture, and their answers to standard questions were also assessed. On each day of the trial the patients graded their ability in walking and their hand co-ordination, using visual analogue scales. After the trial the six filmed sequences from

each patient were randomised and each sequence from each patient was scored by five neurologists, using a scale of five points: normal, mild, moderate, severe and incapacitating disability (Grade 1-5).

Biochemical studies Routine haematological and blood glucose, cholesterol, triglycerides and liver profile tests were carried out at every assessment. The plasma fatty acids were measured, as a test of compliance; because of the high concentration of linoleic acid in the lecithin granules (62% of the total fatty acids) the ratio of linoleic to oleic might be expected to increase if the patients were taking the treatment. Blood was taken from the four patients in the trial for estimation of free-choline plasma levels at 0, 1, or 2, 4, 8, 12, 16 and 20 weeks. In 20 patients with Friedreich's ataxia, including those participating in the trial, and in 19 controls, baseline plasma free-choline levels were measured after isolation of free-choline by ultracentrifugation.¹⁰

Results

Only one of the four patients (Case 1) was able to complete the trial as planned. A second (Case 2) increased the dose from 50 to 75 g/day during the second eight-week period but a higher dose was found to cause nausea and weakness. The two women (Cases 3 and 4) found that increasing the dose beyond 50 g caused unacceptable diarrhoea and they took 50 g of lecithin throughout the trial. One of these patients (Case 4) became depressed and gained 6 kg weight whilst on the drug and stopped it after 11 weeks (see accompanying figure). All the patients noticed intermittent diarrhoea and two (Cases 2 and 3) felt flushed after taking their daily lecithin dose.

Clinical assessment The results of the six filmed assessments and pegboard tests are shown in the table. For every session, the sums of the scores for the filmed individual tests made by each neurologist were calculated and the means of these five totals are shown in the table. None of the patients reported improvement in their ability to walk or in hand co-ordination. Performance on the pegboard test generally deteriorated during the lecithin treatment but tended to return to the pretreatment score after lecithin was stopped. Similarly, the speech quality deteriorated during the trial and there was decreased ability to carry out rapid tongue movements. The ECG did not change during the trial.

Biochemical studies The pretreatment plasma levels of free-choline in the four patients ranged from 9.0 to 14.0 nM/ml (see figure). These were within the normal range (mean $11.2 \pm \text{s.e. } 0.7$) estimated in the 19 normal subjects. Sixteen other patients with Friedreich's ataxia also had levels within this normal range. The mean baseline value for free-choline in these 16 patients and in the four patients in the lecithin trial was $12.7 \pm \text{s.e. } 0.6$.

In all four patients plasma free-choline levels rose steeply in response to the 50 g dose of lecithin. Plasma levels in three patients at four weeks were 32.0, 34.0, and 42.0 nM/ml. However, in the other patient (Case 3) although a plasma level of 37.0 nM/ml was achieved after one week of treatment, the levels after one month's treatment was only 12.5 nM/ml. This coincided with a period of vomiting and diarrhoea and may thus have been due to malabsorption of the lecithin.

Table Assessment of performance before and during treatment with lecithin

Week	Average total score for filmed assessment				Time taken to transfer pegs (seconds)			
	Case 1	Case 2	Case 3	Case 4	Case 1	Case 2	Case 3	Case 4
0	12.6	12.2	9.2	15.0	220	315	114	254
4	13.6	13.8	9.4	14.4	264	350	129	218
8	—	12.4	8.4	13.2	310	310	112	315
12	11.2	12.6	8.2	13.8*	300	330	125	326*
16	13.0	13.2	8.2	15.4	231	313	125	284
20	12.6	13.2	8.0	—	226	284	140	—

* Week 11

Figure Plasma free-choline levels ●—● and linoleic-oleic acid ratios ◆—◆ before and during lecithin treatment.] indicates normal range of plasma free-choline levels 8.0-17.5 nM/ml, in the group of 20 patients with Friedreich's ataxia.

In the patient who increased the dose to 75 g/day (Case 2), the plasma level of choline reached 62.5 nM/ml after two months on this higher dose. This did not occur in the patient who took 100 g of lecithin (Case 1). In this case the plasma levels fell towards baseline, and faulty compliance probably contributed to this (see figure).

Plasma free-choline levels also dropped towards the baseline value in the two women who remained on the 50 g dose. Both these patients claimed they took the lecithin throughout the trial and their raised linoleic/oleic acid ratios (see figure) seemed consistent with this.

Discussion

There was no obvious improvement in the filmed tests and the patients noted no subjective improvement. Indeed the pegboard test results indicate that lecithin may have led to a deterioration in the patients' performance. Moreover, unwanted effects of lecithin were troublesome. Some of these for example depression, diarrhoea, nausea and weight gain, have been observed in other studies.⁷⁻¹¹ The lecithin used in our trial had a calorific value of approximately 850 calories per 100 g and in view of the immobility of these patients, weight gain was not unexpected.

The finding of normal plasma free-choline levels in our 20 patients with Friedreich's ataxia suggest that there is an adequate supply of choline available for ACh synthesis in this disease. During the trial the plasma free-choline levels rose, indicating that the patients were taking their lecithin. However, the two patients who stayed on the 50 g dose throughout the trial showed declining levels of free-choline during the latter part of the study. Etienne *et al.*, reported a similar trend in a group of patients with Alzheimer's disease who took lecithin for seven weeks.¹² These observations may have implications for long term treatment with lecithin in the ataxias, Alzheimer's disease and in tardive dyskinesia, as trials of lecithin in these conditions have all been of short duration.¹²⁻¹³

Absence of improvement in our patients does not necessarily imply that cholinergic drugs might not be useful in Friedreich's ataxia since lecithin may not be an effective cholinergic agent.¹⁴

In a controlled study some improvement of disability followed treatment with the anticholinesterase drug physostigmine.¹⁵ Further studies of cholinergic drugs should be undertaken to investigate the nature of this pharmacological effect.

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