Quebec Cooperative Study
of Friedreich's Ataxia

A Six-Month Phosphatidylcholine Trial in Friedreich's Ataxia

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SUMMARY: *In a six-month open pilot study, pure phosphatidylcholine was administered intravenously (2.5g daily for a month) and orally (5g daily for five months) to sixteen patients with Friedreich's ataxia (FA) and seven patients with other inherited ataxias. Only the oral treatment achieved a mild but significant, 25% improvement, mainly of "central" symptoms in the FA patients at stage 2 of the illness, that is, still able to walk without support and to lead an independent life. However, the drug was ineffective in the more advanced cases. These results are discussed and compared with those obtained with lecithin by other authors.*

RÉSUMÉ: *Nous avons administré la phosphatidylcholine pure par voie intraveineuse (2.5 g par jour pour un mois) et orale (5 gr par jour pour cinq mois) à seize patients avec ataxie de Friedreich (AF) et à sept patients avec autres ataxies héréditaires au cours d'une étude pilote ouverte. Seulement le traitement oral a obtenu une amélioration de 25%, légère mais significative, surtout des symptômes "centraux" des patients avec AF à la phase 2 de la maladie, c'est-à-dire, encore capables de marcher sans aide et de mener une vie indépendante. Le médicament n'avait aucun effet chez les patients en phases plus avancées. Ces résultats sont discutés et comparés avec ceux obtenus avec la lécithine par d'autres auteurs.*

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Recent findings suggest that in Friedreich's ataxia (FA) impaired oxidation of pyruvic acid causes a decrease of acetylcholine synthesis at least in the cerebellar vermis (Reynolds et al, 1976). A similar cholinergic deficiency has been suggested in other inherited spino-cerebellar degenerations (Barbeau, 1978; Legg, 1978). Therapeutic trials with choline chloride in these disorders have given contrasting results. Legg (1978) reported a dramatic improvement in a patient with idiopathic cerebellar degeneration. Philcox and Kies (1979) did not observe any significant improvement in four patients with a dominantly inherited ataxia of late onset. Livingstone and Mastaglia (1979) reported a noticeable improvement in coordination in approximately 50% of eight patients with FA, six with sporadic cerebellar degeneration and six with spastic ataxia. Lawrence et al (1980) studied fourteen patients with a variety of ataxic disorders, one of whom with FA, and observed improved motility only in a patient with idiopathic cerebellar degeneration. Sehested et al (1980) reported no significant changes in six patients with chronic cerebellar ataxia not better classified. These contrasting results may depend on the different cerebellar syndromes considered, on the daily dose of choline chloride (from 4 to 10g), or on the length of treatment (4 days to 6 weeks).

Physostigmine, a cholinomimetic drug that crosses the blood-brain barrier, was also given to fourteen patients with miscellaneous inherited ataxias with a significant improvement (Rodriguez-Budelli et al, 1978). Lecithin, which contains about 20% pure phosphatidylcholine, was found to give more sustained levels of choline than choline chloride (Wurtman et al, 1977). Barbeau (1978 a, b, c; 1979) reported on improvement of about 35% in 10 patients with FA given 7-49 g of lecithin daily, and no clinical change in 6 patients with spastic ataxia. Giovannini et al (1980) observed a significant improvement in 8 patients with a clinical picture of cerebellar atrophy. Chamberlain et al (1980) gave 50-100 g of lecithin daily to 3 patients with FA and one patient with an atypical cerebellar syndrome without significant improvement.

Campania, a region of Southern Italy, has the same prevalence of FA as Western Norway (Skre, 1975) and Iceland (Gudmundsson, 1969), that is 1 x 10^{-5} (Filla et al, 1979); other inherited spino-cerebellar degenerations are also not rare. Furthermore, pure phosphatidylcholine (PC) is commercially available in Italy. We performed an open, six-month trial with intravenous and oral PC in a group of 23 carefully selected patients with inherited ataxia to check the long-term effect of this drug, which is believed to be the main source of choline in lecithin.

PATIENTS AND METHODS

Twenty-three patients were admitted to our study, sixteen with typical FA and seven with other inherited ataxias. The clinical and biochemical pictures of the 16 FA have been thoroughly described together with diagnostic criteria (Campanella et al, 1980; Caruso et al, 1981). The seven patients with other inherited ataxias (OA) included four cases of olivo-ponto-cerebellar atrophy (OPCA), inherited with a dominant (two) or a recessive trait (two), and three cases of the atypical

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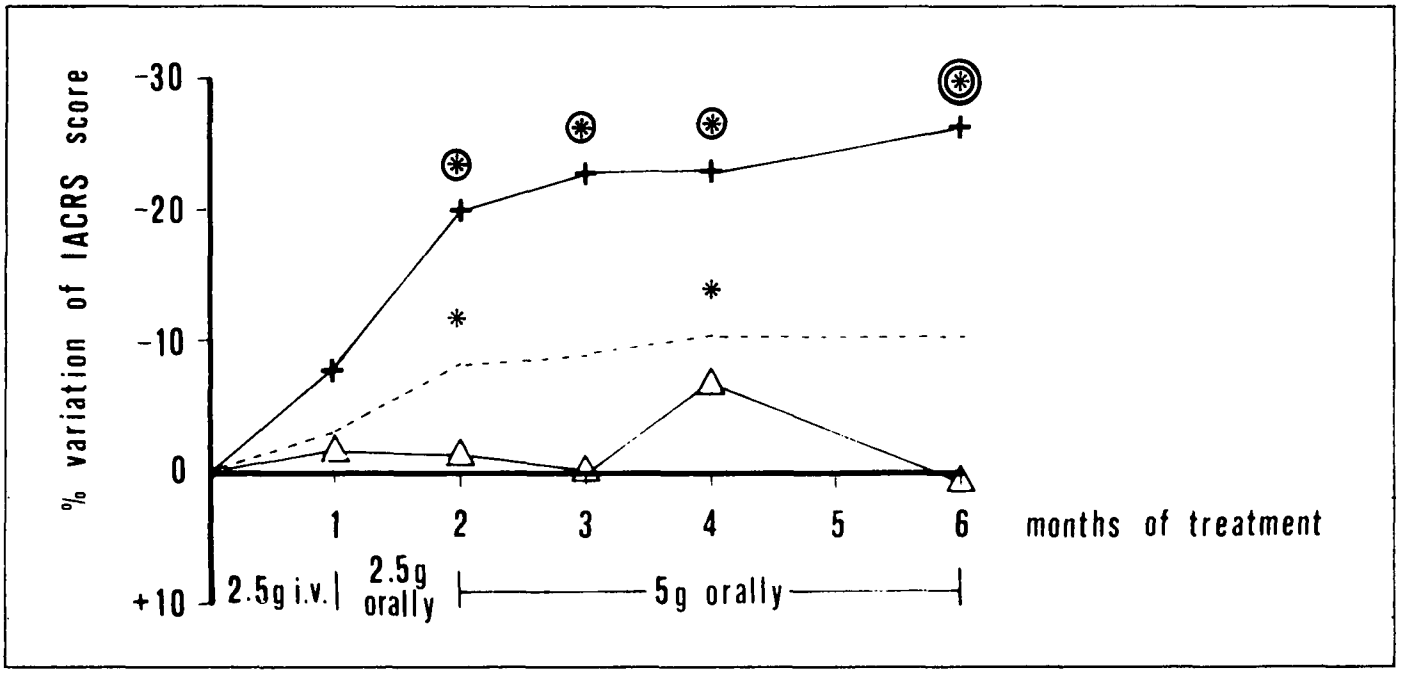

Figure 1 — Phosphatidylcholine trial in 16 patients with Friedreich's ataxia. The dotted line shows the percent decrease of IACRS total score (△IACRS) in all 16 patients. + ——— + △ IACRS in the 6 FA patients at stage 2 of IAPS scale (subgroup 1).△——△△IACRS in the 10 FA patients at stage 3-4 of IAPS scale (subgroup 2). Negative percent variation of IACRS means improvement. Statistical analysis at paired t test: * $p < 0.05$;⊛ $p < 0.02$;◎ $p < 0.01$.

FA of group IIa according to Geoffroy et al (1976).

During the first month the patients received venous infusions of 2.5 g per day of pure phosphatidylcholine (EPL Nattermann) divided in two doses. From the second until the sixth month they received the drug orally: 2.5 g during the second month and 5 g thereafter. The drug was administered divided into three doses at meal times. Clinical and laboratory controls were performed before the trial (baseline) and after the first, 2nd, 3rd, 4th, and 6th month of treatment. At each control the following tests were recorded: IACRS and NUDS clinical rating scales, peg-board, puzzle, cell counter, drawing and handwriting (see Campanella et al, 1980), serum cholesterol, triglycerides and bilirubin, serum lipoprotein pattern (baseline and 4th month). Total scores of rating scales and the data of manual ability and laboratory tests were statistically analyzed by means of paired Student's t test or analysis of variance (Duncan's test).

RESULTS

Here we report the more relevant data from the IACRS scale and cell counter test, which is a manual ability test. A more extensive and detailed paper is in preparation. We analyzed the IACRS scale total score and cell counter counts/10 sec. in the 23 patients overall (group 1) and in the 16 FA patients (group 2). The results in the two groups are similar. The dotted line of fig. 1 shows the percent decrease of the IACRS scale in group 2. After the first month of intravenous therapy a very slight, not significant improvement was seen. From the second to the sixth month a slight, but significant improvement, ranging from 8 to 14%, was observed in both groups. In group 1 paired t test was significant at controls 2-5, in group 2 only at controls 2 and 4. We have recently proposed (Campanella et al, 1980) a simple 4-stage scale to measure the disability and progression of ataxic syndromes (Inherited Ataxias Progression Scale, I.A.P.S.). Stage 1 corresponds to the presymptomatic picture which can be found in a patient's young sibling; stage 2 corresponds to the mild attaint, when the patient is still able to walk without support, stages 3 and 4 correspond to full disability. We also checked the IACRS score variations in the subgroups of patients drawn from IAPS stages. In fig. 1 the continuous lines show IACRS percent variation in the 6 patients at stage 2 (subgroup 1) and in the 10 patients at stages 3-4 (subgroup 2). Looking at the single items of the IACRS scale, we found that dysmetria, gait ataxia, Romberg test, arm-pulling test and hypotonia were favourably modified by the treatment, while other items such as absence of deep tendon reflexes and impairment of vibratory sense remained completely unchanged. We found almost the same results with the cell counter test. In the 23 ataxic patients overall and also in the 16 FA patients (fig. 2, dotted line) a significant improvement (ranging from 9 to 15%) was seen from the third up to the sixth month of treatment. For the FA group, paired t test was significant only at the third month; for all 23 patients it was significant from the second to the last control. In fig. 2 the continuous lines show percent increase of counts/10 sec. also in subgroups 1 and 2.

SIDE EFFECTS

During the intravenous administration of PC almost all the patients presented diarrhea and hypotension. During oral administration, the main side-effects were anorexia (35% of

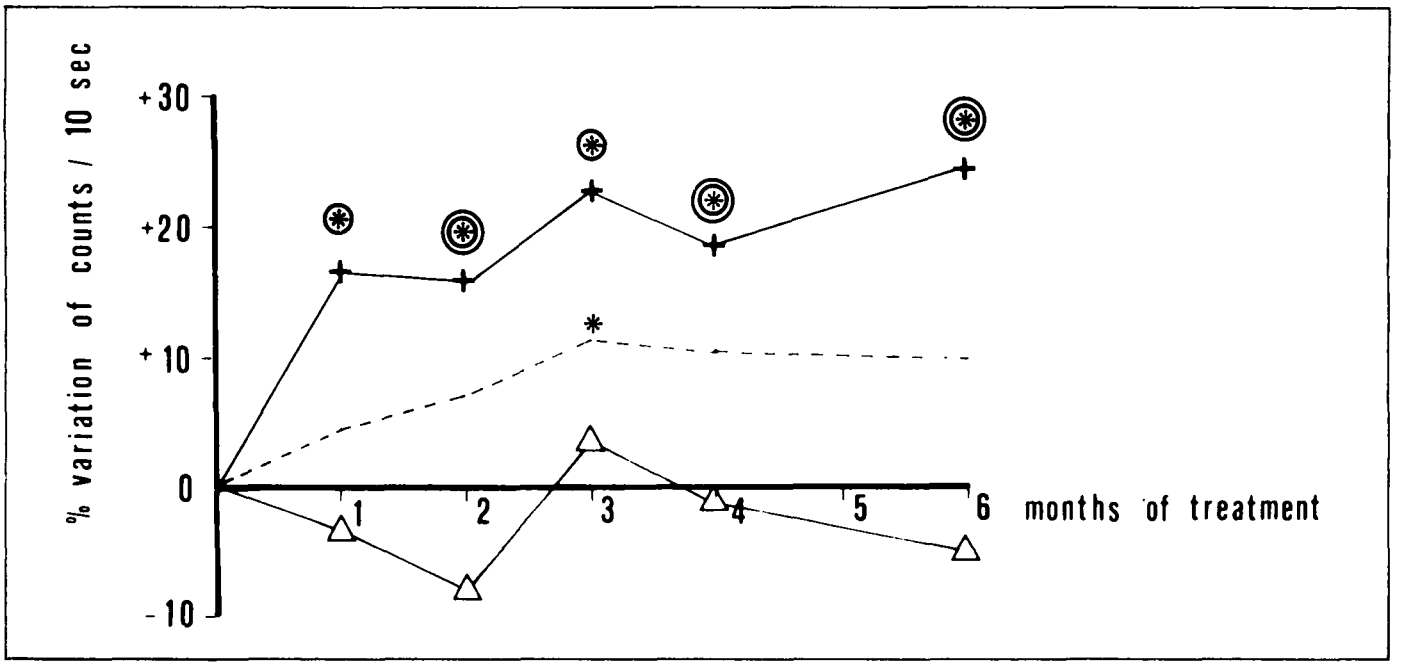

Figure 2 — Phosphatidylcholine trial in 16 patients with Friedreich's ataxia. Percent variation of counts/10 sec (% counts) at the cell counter test (right hand). The dotted line shows △ counts in all 16 patients. + ——— + △ counts in subgroup 1. △ ——— △△ counts in subgroup 2. Positive counts mean improvement. Statistical analysis at paired t test: * $p < 0.01$; ⊛ $p < 0.005$; ◎ $p < 0.001$.

cases), pyrosis (26%), weight variations (17%), facial fibrillations and dystonic movements (13%).

DISCUSSION

It is evident that venous perfusion of PC did not cause any clinical variation. Oral administration on the other hand resulted in a slight but significant improvement, not exceeding 15% in the 23 patients. Dividing the FA patients according to the stage of the illness, we observed that the improvement was exclusively limited to subgroup 1, that is patients at a milder clinical stage of the illness, still capable of walking independently. In this subgroup the improvement reached 25%. In the more advanced cases with overt problems of gait and selfcare, no improvement was observed.

It is unlikely that these results of PC treatment are due to a placebo effect as PC was ineffective when given intravenously, a route known to have a major placebo effect. Moreover, the PC effect lasted unchanged up to the fifth month of oral treatment, whereas a placebo effect would be expected to last less. However, a controlled double-blind trial would verify these preliminary results.

In conclusion, PC shows some effectiveness when given orally in early-stage FA patients. Although this effect is limited to some "central" symptoms, it seems sustained for at least five months and it is not unlikely that the treatment can slow down the course of the illness. However, administration of PC is not a major resource for FA patients, its interest is more theoretical than practical, for the possible mechanism of action of the drug. Our results confirm those of Barbeau (1979) with lecithin in FA, thereby showing that PC (or possibly its linoleic acid content) is the active component of the drug. We cannot draw any conclusion regarding the other seven cases of inherited ataxias, because the group is too small and unhomogeneous.

The mechanism of action of the drug is still unclear. PC could increase acetylcholine synthesis by means of sustained plasma choline levels. In this case its action would be similar to that of physostigmine as reported by Rodriguez-Budelli et al (1978). But the improvement could be also mediated by an action on lipid metabolism, such as an increase of linoleic acid incorporation into membrane PC, as suggested by Davignon et al (1979).

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