

Letter to the Editor

Double-Blind, Placebo-Controlled Study of L-Acetylcarnitine for the Treatment of Hyperactive Behavior in Fragile X Syndrome

To the Editor:

The fragile X syndrome, considered the most common cause of inherited mental retardation, comprises long narrow face, large and prominent ears, macroorchidism, mental retardation, language deficit, autism, and behavioral disturbances [Chudley and Hagerman, 1987]. Hyperactivity is a significant problem for almost all young fragile-X males [Hagerman et al., 1985; Levitas et al., 1983; Mattei et al., 1991; Finnelli et al., 1985]. Attention deficit disorder (ADD) is frequently diagnosed [Fryns et al., 1984; Hagerman et al., 1985].

Treatment of fragile X syndrome patients is a critical issue for the families because intellectual handicap and behavior problems may create difficulties in social relations [Chudley and Hagerman, 1987]. To date, no specific treatment has been found, although rehabilitative and symptomatic interventions may be helpful [Levitas et al., 1983]. Medical treatment has focused on improving the behavior problems, particularly the ADD and hyperactivity. Central nervous system stimulants were reported to be effective for the treatment of these problems [Hagerman et al., 1988]. However, their use is controversial in retarded patients. The prevailing opinion is that stimulants are not effective in the moderately and severely retarded patients because these drugs further decrease the already limited attention capacity [Aman and Singh, 1982]. The aim of the present preliminary study is to evaluate the efficacy of L-acetylcarnitine (LAC) in improving the behavior of fragile-X patients.

LAC is an acetyl derivative of carnitine detectable in various brain regions from an early stage of development and is required for the transport and use of fatty acids and in energy metabolism. LAC treatment has proven particularly effective in experimental animals (rats) with learning deficits and hyperactivity [Dell'Anna et al., 1997]. In vitro, LAC was shown to inhibit the

cytogenetic expression of the fragile site FRAXA in lymphocytes of fragile-X patients [Pomponi and Neri, 1994].

Twenty fragile-X boys ages 6–13 years (mean age 9.2 years) were evaluated in a double-blind study designed to compare the benefits of LAC and placebo treatment. Informed consent was obtained from parents before enrollment in the study. LAC (Nicetile®, Sigma Tau S.p.A., Pomezia, Italy) at a dose of 50 mg/kg twice a day and a similarly administered placebo were assigned randomly for a 1-year period. Three patients stopped the treatment after 1 month; 17 completed the study (8 of these were treated with LAC and 9 with placebo).

Neuropsychological testing was performed by a psychologist before treatment (T0), 1 month (T30), 6 months (T180), and 12 months (T365), respectively, after the beginning of treatment. Subjects were evaluated with the following tests: the Wechsler Intelligence Scale for Children-Revised (WISC-R); the Bender Gestalt test; and the Conners Abbreviated Parent-Teacher Questionnaire [Conners, 1973].

All patients included in the trial tolerated well the administration of LAC, and no side effects were noted.

Statistical evaluation of the results was as follows. On the 17 subjects who completed the study (8 LAC, 9 placebo), a linear discriminant analysis was performed, using treatment as grouping variable and all possible differences of measured scales (value at 365 days minus baseline value at 0 days) as predictors. A nonparametric Wilcoxon independent-sample test was used to evaluate the significance of difference.

The results of Wechsler Scale testing showed that the patients' IQs, ranging from < 30 to 69, did not change after the treatment (< 30 to 71 at T365).

The Bender Gestalt test shows visual-perceptive and graphic functions related to the extent of mental retardation, and no statistically significant differences between LAC-treated and placebo-treated patients could be demonstrated.

The Conners Abbreviated Parent-Teacher questionnaire completed by parents showed a significant reduction ($P = 0.0065$) of hyperactive behavior in the testing

*Correspondence to: Dr. M.G. Torrioli, Cattedra di Neuropsichiatria Infantile, Policlinico A. Gemelli, Università Cattolica del S. Cuore, Largo A. Gemelli 8, 00168 Roma, Italy.
E-mail: mgtorrioli@pcg.it

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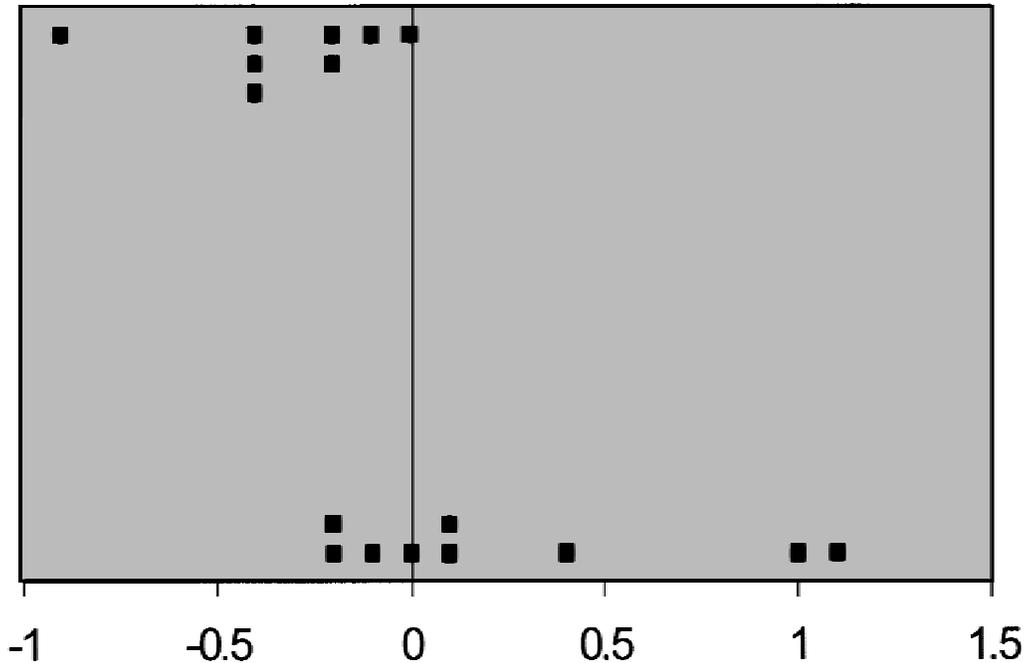


Fig. 1. Subjects treated with LAC appear in the upper part of the figure; subjects treated with placebo in the lower part. For each subject, the horizontal scale expresses the variation in the Conners parents' score obtained after 1 year of treatment.

performed at T365 compared with T0 in LAC-treated subjects. Placebo subjects increased ($+0.244 \pm 0.164$) and LAC subjects decreased (-0.325 ± 0.098) their score over a 1-year period (Fig. 1). Modifications were not observed in intermediate testing at T30 and T180.

The Conners questionnaire completed by teachers did not show any significant differences between treated and untreated subjects. The discrepancy between parents and teachers may be related to differences in compilation. In fact, Italian school legislation provides mentally retarded students with a support teacher, even within the classroom. It is well known that the child's hyperactive behavior can be minimal or absent in a strict one-to-one relationship [DSM IV, 1994]. Therefore, support teachers are likely not to have seen substantial modifications in the children's behavior during the trial.

Thus, our results, although preliminary, demonstrate the efficacy of LAC treatment on the hyperactivity of fragile-X boys. Our finding suggests the use of LAC in a larger group of patients to determine if there may be effects on other aspects of behavior and cognitive development.

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M.G. Torrioli*
S. Vernacotola
P. Mariotti
E. Bianchi
Cattedra di Neuropsichiatria Infantile
Facoltà di Medicina "A. Gemelli"
Università Cattolica
Roma, Italy

M. Calvani
Sigma-tau S.p.A.
Pomezia, Italy

A. De Gaetano
Centro di Fisiopatologia dello Shock
Consiglio Nazionale delle Ricerche
Roma, Italy

P. Chiurazzi
G. Neri
Istituto di Genetica Medica
Facoltà di Medicina "A. Gemelli"
Università Cattolica
Roma, Italy