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A randomized double-blind, placebo-controlled study of the effects of supplementation with highly unsaturated fatty acids on ADHD-related symptoms in children with specific learning difficulties

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Abstract

(1) The authors tested the prediction that relative deficiencies in highly unsaturated fatty acids (HUFAs) may underlie some of the behavioral and learning problems associated with attention-deficit/hyperactivity disorder (ADHD) by studying the effects of HUFA supplementation on ADHD-related symptoms in children with specific learning difficulties (mainly dyslexia) who also showed ADHD features. (2) Forty-one children aged 8–12 years with both specific learning difficulties and above-average ADHD ratings were randomly allocated to HUFA supplementation or placebo for 12 weeks. (3) At both baseline and follow-up, a range of behavioral and learning problems associated with ADHD was assessed using standardized parent rating scales. (4) At baseline, the groups did not differ, but after 12 weeks mean scores for cognitive problems and general behavior problems were significantly lower for the group treated with HUFA than for the placebo group; there were significant improvements from baseline on 7 out of 14 scales for active treatment, compared with none for placebo. Group differences in change scores all favored HUFA, reaching conventional significance levels for 3 out of 14 scales. (5) HUFA supplementation appears to reduce ADHD-related symptoms in children with specific learning difficulties. Given the safety and tolerability of this simple treatment, results from this pilot study strongly support the case for further investigations. © 2001 Elsevier Science Inc. All rights reserved.

Keywords: Attention-deficit/hyperactivity disorder; Behavioral problems; Dyslexia; Highly unsaturated fatty acids; Specific learning difficulties

1. Introduction

Behavioral and learning problems in children are a cause of increasing concern; currently attention-deficit/hyperactivity disorder (ADHD) is estimated to affect well over 4% of the school-age population in the United States (Wolraich et al., 1998; Chang and Chuang, 2000), although both diagnostic and treatment issues are a source of ongoing controversy (NIH Consensus Statement, 1998). ADHD shows high comorbidity with several other conditions including specific learning difficulties and the behavioral and learning problems associated with ADHD also occur on a spectrum that extends into the general population.

Certain highly unsaturated fatty acids (HUFAs) of the $n-3$ and $n-6$ series are already known to play an important role in many aspects of physical health, notably in cardiovascular and immune function. The relative lack of these fatty acids in modern Western diets has been highlighted as a potential major health issue and, recently, attention has been focusing on their potential role in a wide range of neurodevelopmental and psychiatric conditions, including ADHD (Taylor et al., 1979; Richardson and Puri, 2000). Two HUFAs of particular importance in neuronal membrane structure are arachidonic acid (AA) and docosahexaenoic acid (DHA), both of which can profoundly influence signal transduction. AA, dihomo-gamma-linolenic acid (DGLA) and eicosapentaenoic acid (EPA) are also crucial to normal brain development and function via their eicosanoid derivatives.

Abbreviations: AA; arachidonic acid; ADHD; attention-deficit/hyperactivity disorder; CPRS-L; Conners' Parent Rating Scale; DGLA; dihomo-gamma-linolenic acid; DHA; docosahexaenoic acid; DSM; Diagnostic and Statistical Manual of Mental Disorders; DSM-IV; Diagnostic and Statistical Manual of Mental Disorders, 4th edition; EPA; eicosapentaenoic acid; HUFA; highly unsaturated fatty acid

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Blood biochemical evidence has suggested that a relative deficiency of certain HUFAs may contribute to some of the behavioral and learning problems central to ADHD (Mitchell et al., 1987; Stevens et al., 1995, 1996a). In the study by Stevens et al. (1995), 53 subjects with ADHD had significantly lower concentrations of key HUFAs in plasma (AA, EPA and DHA) and erythrocyte membranes (AA and adrenic acid) than did 43 control subjects. Moreover, a subgroup of 21 subjects with ADHD exhibiting many symptoms of essential fatty acid deficiency had significantly lower plasma concentrations of AA and DHA than did 32 subjects with ADHD with few essential fatty acid deficiency symptoms.

Furthermore, in a study leaving aside diagnostic issues, behavior, learning and health problems were compared in boys aged 6–12 years who were divided into those with high or low plasma phospholipid total $n-3$ or total $n-6$ HUFAs (Stevens et al., 1996b). Parents reported a greater frequency of physical symptoms indicative of essential fatty acid deficiency for boys with lower plasma $n-3$ or $n-6$ HUFA concentrations than for those with higher levels. A greater number of behavior problems assessed by the Conners' Rating Scale (Conners, 1990b), temper tantrums and sleep problems were reported in subjects with lower total $n-3$ HUFA concentrations. Additionally, more learning and health problems were found in subjects with lower total $n-3$ HUFA concentrations.

Both the $n-3$ and $n-6$ series of HUFAs are important in brain development and function, and the above findings raise the possibility that dietary HUFA supplementation with a combination of $n-3$ and $n-6$ HUFAs might be beneficial for some children with or without an actual ADHD diagnosis. Previous intervention studies that have used only DHA (Voigt et al., 1999) or evening primrose oil (a source of a single $n-6$ HUFA) (Aman et al., 1987; Arnold et al., 1989, 1994) have reported variable but largely unsuccessful results. However, a preliminary report of a study using a combination of $n-3$ and $n-6$ HUFAs does suggest some possible benefits (Burgess, 1998).

ADHD shows particularly strong comorbidity with developmental dyslexia, a syndrome involving (but not identical with) specific reading difficulties. This association appears to be stronger for the predominantly inattentive rather than the hyperactive–impulsive form of ADHD (Dykman and Ackerman, 1991; Hynd et al., 1991), and the high clinical overlap could reflect a common dysfunction of parietal attentional mechanisms (Conners, 1990a). The rate of reading disorder in children with ADHD has been documented as between 25% and 40% (August and Garfinkel., 1990; Semrud-Clikeman et al., 1992), while 15–35% of individuals with reading disorder also meet ADHD criteria (Gilger et al., 1992; Shaywitz et al., 1995; Willcutt and Pennington, 2000). This comorbidity occurs in both clinical and community samples, so it is not simply a selection artifact. Moreover, a recent twin study of the etiology of comorbidity between reading disability and ADHD strongly suggests that common genetic influences predispose children to both reading difficulties and elevations of inattention (Willcutt et al., 2000a,b).

It is therefore interesting that abnormalities of fatty acid metabolism have also been implicated in dyslexia, with suggestions that dietary HUFA supplementation may be beneficial in this condition (Baker, 1985; Stordy, 1995, 2000; Richardson and Ross, 2000; Richardson et al., 1997, 1999). Given the heterogeneity of both dyslexia and ADHD, the question arises of whether fatty acid deficiencies may perhaps particularly characterize a subgroup of individuals who show features of both of these disorders.

A randomized double-blind placebo-controlled trial was therefore conducted to investigate the effects of HUFA supplementation on behavioral and learning problems in children with specific learning difficulties (mainly dyslexia), in which ADHD-related symptoms were the major focus. The prospectively defined hypothesis was that the group of children receiving HUFA supplementation would show reduced ratings for ADHD-related symptoms after 12 weeks compared with the placebo-treated group. This time period must be regarded as close to the minimum for this kind of treatment, because animal studies have shown that it may take over 10 weeks for cerebral membrane HUFA levels to recover following chronic deficiency (Bourre et al., 1988, 1993). However, the study had to fit in with the practical aspects of school academic term lengths.

2. Methods

2.1. Subjects

The planned study population consisted of children aged 8–12 years who were referred to a special school in Northern Ireland for children with specific literacy problems. All had been previously identified by teachers as having unexpected problems in learning to read and write relative to their general ability, and our assessments confirmed that most would meet the usual diagnostic criteria for specific developmental dyslexia, i.e., they showed specific weaknesses on standardized tests of working memory and phonological processing in addition to their specific reading difficulties. None of these children had received an official diagnosis of ADHD or any other psychiatric disorder.

The study was approved by the Queen's University of Belfast Research Ethics Committee and the Local Education Board. After complete description of the study to the children and their parents, written informed consent was obtained from both.

2.2. Inclusion criteria

Inclusion criteria were general ability within the normal range as assessed via the Similarities and Matrices subtests

from the British Ability Scales (BAS) (Elliot, 1983), reading achievements (BAS word reading) more than two standard deviations (below the level expected from this, English as a first language, and endorsement from the child's family doctor. Children were also required to have pretreatment scores, that were above the general population average for their age on three parent rating scales designed to assess ADHD-related symptoms according to DSM-IV criteria: the DSM Inattention, DSM Hyperactive–Impulsive and DSM Combined-type ADHD global scales from the Conners' Parent Rating Scale (CPRS-L) (Conners, 1997).

2.3. Exclusion criteria

Exclusion criteria included the use of fatty acid supplements within the previous 6 months, consumption of oily fish regularly more than twice a week, a history of any other neurological or major psychiatric disorder or other significant medical problems. In particular, none of the subjects was in treatment for ADHD.

2.4. Assignment

The subjects were individually randomized between the two groups. The allocation to parallel groups was double blind and determined by prerandomized codes generated by computer. Coded treatments were allocated sequentially to subjects in strict order of their registration for the trial. There was no direct contact at any stage between the generator and executors of the assignment.

2.5. Active treatment and placebo

For 12 weeks, children in the treatment group received a supplement containing both $n-3$ and $n-6$ HUFAs, to provide the following daily doses: EPA 186 mg, DHA 480 mg, γ-linolenic acid 96 mg, vitamin E (as DL-δ tocopherol) 60 IU, *cis*-linoleic acid 864 mg, AA 42 mg and thyme oil 8 mg. The placebo group received olive oil during this time.

2.6. Measures

At both baseline and 12 weeks, the CPRS-L was used to assess a range of behavioral and learning problems associated with ADHD. This yielded normalized, age-standardized scores (in the form of *t*-scores) for seven subscales assessing individual features of ADHD (Oppositional, Cognitive Problems, Hyperactivity, Anxious/Shy, Perfectionism, Social Problems and Psychosomatic) and seven global scales (Conners' ADHD Index, Conners' Restless–Impulsive, Conners' Emotional Lability, Conners' Global Index, DSM Inattention, DSM Hyperactive–Impulsive and DSM Global Total) (Conners, 1997). Teacher rating scales of ADHD symptoms were not considered appropriate, since all the children were new to the school.

2.7. Masking

Individual children were allocated to receive either the HUFA supplement or an identical-looking olive-oil placebo. Dosage was eight capsules per day for 12 weeks.

Treatment codes were held at a remote location by an independent third party until the trial was completed and all data collated, verified and archived. Sealed envelopes containing the treatment codes had been provided to the trial supervisor and were returned unbroken at study completion.

The analyses were carried out by the trial supervisor, who had minimal involvement in both administration of assessments and contact with participants and who was blinded to the treatment group.

2.8. Statistical analysis

Group comparisons at baseline and 12 weeks were carried out and treatment effect sizes (mean change/baseline S.D.) were calculated for each group. Changes in CPRS-L scores over the 12-week time period were also compared both within and between groups. In many cases, the data were not normally distributed; therefore, nonparametric tests were used. Statistical analyses were carried out using SPSS version 9 (SPSS, 1998).

3. Results

3.1. Demographic data

Forty-one children (mean age 10.25 years, S.D. = 0.74 years) were recruited into the study. In keeping with the selection criteria, their general ability was average (mean intelligence quotient prorated 101.2, S.D. 12.2), but their reading achievement was almost 3 years behind chronological age. Twenty-two children received the HUFA supplement, while 19 received the placebo during the 12-week period. The two groups did not differ with respect to age (active: mean age 10.30 (S.D. = 0.73) years; placebo: mean age 10.19 (S.D. = 0.77) years; $t = 0.44$, $df = 39$, $P = .66$), sex ratio (active: 18 males:4 females; placebo: 17 males:2 females; Fisher's exact probability test, $P = .41$) or any of the baseline psychometric measures. There was no difference in ethnicity between the two groups: all subjects were white Caucasian.

3.2. Participant flow

Of the 41 children who started the trial, 9 (5 active, 4 placebo) withdrew before the end of the 12-week period and were not available for reassessment. The reasons given did not differ between groups (one active and one placebo subject reported digestive upset, one active cited swallowing problems and three per group were noncompliant through

Table 1
Baseline scores (age-standardized with respect to general population norms, in the form of *t*-scores (mean 50, S.D. 10)) on CPRS-L scales (Conners, 1997) for both active and placebo groups

	HUFA supplementation ($N=15$)		Placebo ($N=14$)			
CPRS-L scale	Mean	S.D.	Mean	S.D.	*z*	*P*
ADHD subscales						
Anxious/shy	61.1	13.1	61.9	13.6	0.13	.90
Cognitive problems	62.1	9.6	63.4	7.6	0.44	.66
Hyperactivity	66.4	11.4	64.4	10.2	0.44	.66
Opposition	60.9	12.4	57.5	9.0	0.70	.48
Perfectionism	56.3	15.3	57.0	10.2	0.75	.46
Psychosomatic	64.9	16.8	64.9	15.0	0.18	.86
Social problems	63.0	16.3	57.9	10.3	0.62	.54
ADHD global scales						
Conners' ADHD Index	59.9	11.3	60.1	6.4	0.44	.66
Conners' Restless–Impulsive	63.5	10.0	65.1	9.2	0.46	.65
Conners' Emotional Lability	64.5	13.1	61.4	15.5	0.68	.49
Conners' Global Total	64.9	10.2	65.1	10.7	0.13	.90
DSM Inattention	61.6	10.3	64.7	8.3	1.16	.25
DSM Hyperactivity–Impulsive	67.5	10.6	67.9	9.5	0.28	.78
DSM Global Total	65.7	10.3	67.2	7.7	0.74	.46

apparent lack of interest). Parent CPRS-L ratings at 12 weeks were not available for a further 3 children (2 active, 1 placebo), so analyses of the follow-up data involved 29 children (15 active, 14 placebo); these two groups did not differ significantly with respect to age or sex. Treatment compliance at follow-up was calculated from counts of capsules returned, and did not differ between groups (mean (S.D.): active 90.4% (10.1%), placebo 86.6% (16.4%)).

3.3. Baseline group comparisons

At baseline, scores for the two groups (15 active, 14 placebo) did not differ significantly on any of the 14 CPRS-L scales, as shown in Table 1.

3.4. Analyses at endpoint

The scores for the two groups after 3 months are shown in Table 2. It can be seen that the active treatment group now had significantly lower scores than the placebo group on two global scales — Conners' Global Total and DSM Inattention, and a trend towards lower scores on three subscales — Psychosomatic, Cognitive Problems and Anxious/Shy — as well as the global scale Conners' Restless–Impulsive.

Within the placebo group there were no improvements on any scale at 12 weeks relative to baseline levels (Wilcoxon signed rank test) and, for one global scale, Conners' Index, there was a significant deterioration ($z=2.14$, $P=.03$).

Table 2
Scores (age-standardized with respect to general population norms, in the form of *t*-scores (mean 50, S.D. 10)) at 3 months on CPRS-L scales (Conners, 1997) for both groups

	HUFA supplementation ($N=15$)		Placebo ($N=14$)			
CPRS-L scale	Mean	S.D.	Mean	S.D.	*z*	*P*
ADHD subscales						
Anxious/shy	53.9	14.6	62.1	11.8	1.74	.08
Cognitive problems	57.0	10.4	63.5	9.3	1.79	.07
Hyperactivity	62.0	12.2	62.3	12.3	0.13	.90
Opposition	59.7	9.9	59.8	10.4	0.09	.93
Perfectionism	53.2	12.8	56.1	13.7	0.70	.48
Psychosomatic	53.4	8.9	61.5	12.2	1.93	.05
Social problems	62.1	17.2	60.6	10.1	0.22	.83
ADHD global scales						
Conners' ADHD Index	57.6	6.64	64.2	8.42	2.21	.03
Conners' Restless–Impulsive	58.3	5.22	64.0	8.71	1.69	.09
Conners' Emotional Lability	59.7	9.62	63.7	15.99	0.79	.43
Conners' Global Total	59.7	6.90	65.2	10.51	1.34	.18
DSM Inattention	55.9	9.79	63.6	9.95	1.95	.05
DSM Hyperactivity–Impulsive	64.5	11.20	65.9	11.21	0.50	.61
DSM Global Total	60.5	9.17	65.7	10.16	1.25	.21

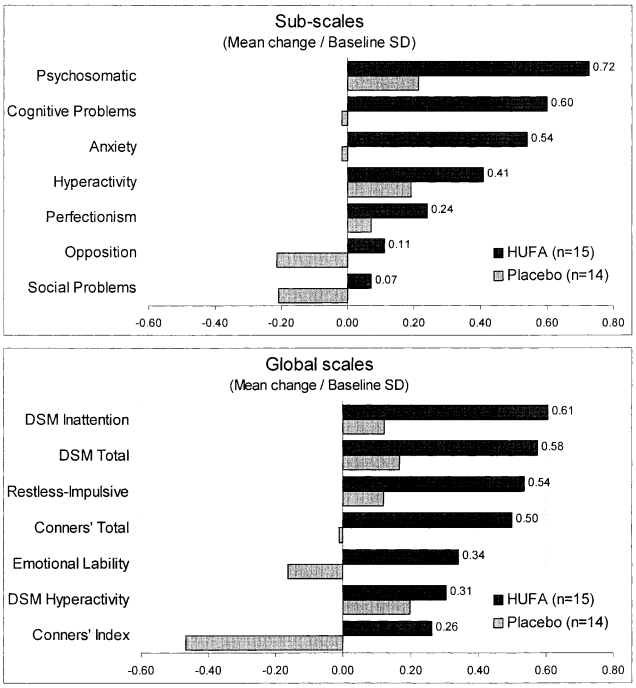

Fig. 1. Treatment effect sizes for each group during the 12-week treatment period.

In contrast, within the active treatment group, significant symptom reductions from baseline were found for three of the seven ADHD subscales: Psychosomatic ($z=2.51$, $P=.01$), Anxious/Shy ($z=2.34$, $P=.02$) and Cognitive Problems ($z=2.29$, $P=.02$) and four of the seven global scales: DSM Inattention ($z=2.59$, $P=.01$), DSM Global Total ($z=2.45$, $P=.01$), Conners' Global Total ($z=1.95$, $P=.05$) and DSM Hyperactive–Impulsive ($z=1.97$, $P=.05$), as well as trend-level improvement in two further global scales, Conners' Emotional Lability ($z=1.77$, $P=.08$) and Conners' Restless–Impulsive ($z=1.68$, $P=.09$).

Improvements were significantly greater for active treatment over placebo (Mann–Whitney test, two-tailed) for the subscales Cognitive Problems ($z=2.45$, $P=.01$) and Anxious/Shy ($z=2.02$, $P=.04$), as well as the global scale Conners' Index ($z=2.25$, $P=.02$), measuring a broader range of behavioral problems. There was also a trend for improvement on Conners' Emotional Lability ($z=1.74$, $P=.08$) to be better on active treatment.

Treatment effect sizes for each group are shown in Fig. 1. For all scales, the changes observed were more favorable for HUFA treatment than placebo.

4. Discussion

Under double-blind conditions, HUFA supplementation was found to be significantly better than placebo in reducing a wide range of ADHD-related symptoms in children with specific learning difficulties. Although statistical power was obviously limited by the small sample size, effect sizes on active treatment exceeded 0.3 for 10 of the 14 scales derived from the CPRS-L, while for the placebo group no positive treatment effects were observed. No adverse side effects were associated with this treatment.

4.1. Diagnostic issues

None of these subjects had been formally diagnosed with ADHD, although parent ratings and clinical impressions indicated that this might well be applicable to some of these children. To our knowledge, this is the first study of its kind in children with specific learning difficulties, although there is mounting evidence for fatty acid abnormalities in dyslexia as well as in ADHD (Richardson and Ross, 2000; Richardson and Puri, 2000). The heterogeneity of each of these conditions is well recognized, as is their high clinical overlap. The results of this pilot study suggest that a specific focus on those individuals with features of both conditions may prove fruitful in future studies of fatty acid metabolism.

4.2. Choice of HUFA treatment

Differences in the composition of fatty acid treatments are another important factor to consider in interpreting these findings in relation to those from previous studies. In ADHD children, one previous large-scale double-blind trial found no benefits from DHA supplementation (Voigt et al., 1999), while another (Burgess, 1998) indicated possible benefits from a supplement containing both EPA and DHA as well as $n-6$ HUFA, as was used in our trial. Earlier studies of $n-6$ supplementation in ADHD gave broadly negative results, so the current balance of evidence raises the possibility that the $n-3$ fatty acid EPA may be the important component in reducing ADHD symptoms. In schizophrenia, treatment with purified EPA alone has been found to be efficacious (Puri and Richardson, 1998; Peet and Horrobin, 2000; Shah et al., 2000), while supplementation with DHA has not (Peet, 1999). Further studies of ADHD, dyslexia and related conditions may therefore do well to explore this possibility.

4.3. Choice of placebo

The choice of placebo is also important in clinical trials of fatty acid supplementation. The use of olive oil as a placebo in this study may be problematic (Puri and Richardson, 2000). Olive oil is a rich source of oleic acid, from which the psychoactive lipid oleamide can be biosynthesized in mammals (Sugiura et al., 1996). Oleamide has a number of important psychoactive actions, such as the induction of sleep and modulation of serotonin receptor-mediated signalling (Cravatt et al., 1995; Thomas et al., 1998; Boger et al., 1998). The use of an inert placebo might therefore have resulted in an even more significant finding.

4.4. Limitations

In this study, practical considerations did not permit blood sampling, although this would obviously have been useful in order to obtain objective measures of fatty acid deficiency. No inferences can therefore be drawn about biochemical mechanisms to explain the improvements observed following HUFA supplementation. However, the fact that subjects were not preselected in any way for low fatty acid status would be expected to weaken any positive effects of HUFA treatment.

Although statistically significant results were obtained, the sample size was relatively small, reflecting the fact that this was a pilot study. In view of the positive results, a larger trial is clearly strongly indicated.

5. Conclusion

HUFA supplementation appears to offer significant benefit in alleviating many ADHD-related symptoms in children with specific learning difficulties (dyslexia). Larger trials are indicated, which should include an inert placebo and objective measures of fatty acid deficiency. The relative contribution of the $n-3$ fatty acid EPA to these effects would appear to merit specific investigation.

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