

Reviewer's report

Title: Fatty acid status and behavioural symptoms of Attention Deficit Hyperactivity Disorder in adolescents: A case-control study

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Reviewer: Barry Sears

Reviewer's report:

General:

Although the data in the article adds some new information in the relationship of dietary intake of omega-3 fatty acids and their blood levels in children with attention deficit hyperactivity disorder compared to normal children, it should be in the form of a letter than an article. It appears that authors were intent on increasing the word count by a somewhat rambling description of attention deficit disorders in the introduction and a lot of speculation in discussion as well as not presenting a complete overview of the current literature using dietary intervention with omega-3 fatty acids.

Introduction:

The authors discuss that EPA and DGLA are critical for brain function without giving supporting evidence. Although they are minor constituents, the eicosanoids derived from them can play a significant role. This should be elaborated since the paper is based on differences in fatty acid compositions in children with ADHD compared to the normal controls.

The authors discuss numerous studies looking differences in fatty acid composition in children with ADHD but only reference one study. A more complete listing of the references would be preferred.

The authors describe intervention trials, but several of their references (21, 22, 26-28) had no information in behavioral changes because they were not done tested.

Experimental Methods:

Because of the dropouts and time constraints, a non-matched number of subjects (11 with ADHD and 8 controls) completed the entire protocol. This would require non-parametric analysis of the data.

The authors should have described in greater detail why they choose using RBC phospholipids over isolated plasma phospholipids. It has been in my experience as well as other investigators (Dr. Bruce Holub at the University of Guelph and one of the leading authorities in omega-3 fatty acid analysis) that more reproducible results are observed using plasma phospholipids versus the RBC phospholipids. Therefore the reproducibility of the RBC results should have been

discussed with CV values.

A t-test is fine for matched numbers of active and controls, but this was not the case in this study. Furthermore it was not discussed whether it was a one-tail or two-tail test. In particular, the non-parametric Friedman test should have been used to assess the changes over time. If the Friedman test was significant, then a Wilcoxon signed ranked test should have been used to confirm the significance. Likewise Spearman correlations should have been used for non-parametric analysis.

Results:

On table 4, I believe the author meant to say dihomo-gamma linolenic acid (DGLA) instead of gamma linolenic acid (GLA) since the levels of GLA are always much lower than DGLA. Also on Table 4 the summation of the total omega-3 fatty acid don't add up for the ADHD or control groups, whereas the total omega-6 fatty acid do.

It is also not clear what the authors mean by fatty acids being reported as per cent of molecular weight. Usually they are reported as per cent of total integrated area of the entire sample.

Discussion:

The lack of reduction of AA levels in this paper compared to the previous work of Burgress and Chen should be discussed in greater detail. If the AA and EPA in both groups are the same and the DHA levels are significantly lower in the ADHD group this would indicate that the activity of the delta 5-desaturase enzyme is equivalent in both groups. Thus the decrease in DHA may be due to increased specific beta oxidation of DHA. Unfortunately this was not discussed nor was the differences of the AA/EPA ratio in other studies. This may be due to using RBC phospholipids as opposed to the isolated plasma phospholipids although Chen et al also observed reduced AA levels and they used RBC phospholipids.

However it is the area of the review of intervention studies that this paper has its greatest deficiency. The authors quote omega-6 intervention studies using the term efamol, which most readers would not understand what that it means. Efamol is commercial trademark for a brand of evening primrose oil that contains 9% GLA. The quoted intervention results with omega-3 fatty acids in ADHD were not mixed, but highly unremarkable in their success. The Voigt study was negative, the Hirayama study was negative, and the Burgress study was unremarkable in that only 2 of the 16 behavioral categories demonstrated any change. The Richardson study, which did give positive results, was not done with children with diagnosed ADHD. Unfortunately the authors appear to be unaware of two recent studies that used high-dose EPA/DHA concentrates and were successful (Germano et al *Nutr Neurosci* 10: 1-9 [2007] and Sorgi et al *Nutr J* 6:16 [2007]). In both these studies more than 20 times the levels of EPA and DHA were used compared to earlier studies and both of these high-dose omega-3 fatty acids observed statistically significant improvement in behavior.

The improvement in behavior was statistically correlated with the change in the AA/EPA ratio. The fact that these references were not discussed is a striking deficiency being relevant with the stated purpose of the paper, and makes the rambling speculative end of the discussion somewhat moot.

Recommendations:

Major Compulsory Revisions: I believe the article is better suited for a letter as it presents new data on the relationship of dietary intake of essential fatty acids and their levels in the RBC phospholipids. Furthermore the relationship of the RBC fatty acid composition and behavior is also useful information. However, the article does not address two published studies that have demonstrated significant improvement of behavior in children once supplemented with high dose EPA/DHA concentrates. Thus the paper gives the reader an incomplete view of the current state of dietary intervention studies.

I would recommend a substantial rewrite of the paper to make it more focused on their experimental data and have far less speculation on the potential causes of the behavioral changes in children with ADHD since it appears that straightforward intervention with adequate levels of EPA and DHA can demonstrate clinical efficacy.

Minor Compulsory Revisions:

I would suggest changes in Table 4 as I discussed above. I would also consider having the authors to look at their data using non-parametric statistical analysis to see how that affects their conclusions.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.