The Orthomolecular Correction of Metabolic Imbalances Found in Attention Deficit Hyperactivity Disorder: A Retrospective Analysis in an Outpatient Clinic

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Abstract ***Background:*** *Attention deficit hyperactivity disorder (ADHD) is characterized by atypically severe inattentiveness, hyperactivity, and impulsiveness. While its cause is unknown, biological and environmental influences are likely.*

Objectives: *To identify the metabolic imbalances in fatty acid, amino acid, mineral, and pyrrole levels in ADHD patients, and to examine the effectiveness of the nutritional approach in the correction of these imbalances in an outpatient clinic.*

Design: *Medical records of 116 patients with ADHD treated with nutritional approaches were retrospectively reviewed. Demographics were limited to ensure confidentiality. Blood levels of fatty acids, amino acids, vitamins and minerals, hair analysis of heavy metals and urine pyrrole levels were done on all patients. Comparisons with control (i.e., normal values) were made. Improvements following nutritional interventions were measured and compared to controls.*

Setting: *The Riordan Clinic (Wichita, KS), an outpatient complementary and alternative medical clinic. Intervention: Various nutritional interventions (i.e., minerals, vitamins, omega-3 and omega-6 essential fatty acids, flavonoids, probiotics, dietary modifications and chelation of toxic metals by natural substances) were prescribed based on laboratory results.*

Main Outcome Measures: *Serum fatty acid composition, measurements of minerals (normal and toxic) in hair and, in some cases, in red blood cells (RBC), and assessments of vitamins in serum and pyrroles in urine.*

Results: *There was a predominance of below-normal docosahexaenoic acid, eicosapentaenoic acid, and gamma-linolenic acid levels; a high incidence of unfavorable arachidonic acid-to-eicosapentaenoic acid and omega-6-to-omega-3 ratios; deficiencies in zinc, magnesium, and selenium levels; and the presence of toxic metals in above-normal amounts.*

Conclusions: *Our data suggests that at least two of the factors that were the most abnormal, omega-6-to-omega-3 ratios and pyrrole levels, and can in fact improve in subjects undergoing a regimen with nutrient supplementation. While nutritional manipulation did result in improved metabolic profiles in our sample, these results warrant a study of a larger sample, with an attempt to document whether these changes have an effect on improving behavior and cognition in the form of a prospective, controlled clinical study.*

Introduction

Attention deficit hyperactivity disorder (ADHD) is characterized by atypically severe inattentiveness, hyperactivity, and impulsiveness.[1,2] Its cause is unknown, with both biological and environmental influences likely.[3] Molecular and pharmacological studies suggest involvement of the dopaminergic, se-

rotonergic and noradrenergic neurotransmitter systems in the pathogenesis of ADHD.[4-6] Medical approaches for ADHD have used this theory to justify the use of prescription drugs such as methylphenidate which inhibits the reuptake of dopamine (DA) and norepinephrine (NE). The idea that specific nutritional approaches can help behavioral patterns has always been controversial. Some practitioners that study nutrition feel that a global dietary approach is more important than identifying specific moieties such as amino acids.[7] This view has been challenged since the effects of tryptophan or tyrosine depleted-diets affect people in different ways, and can even predict antidepressant response.[8] In fact it is becoming more and more evident that metabolic imbalances in nutrients and minerals affect many neural pathways, and thus may play a role in the expression of ADHD. This would suggest that nutritional therapy may be useful to correcting metabolic imbalances in ADHD.

Nutrients Associated with Improving ADHD Symptoms

Over half of the dry weight of the adult human brain consists of lipids, with the long chain poly-unsaturated fatty acids docosahexaenoic acid (DHA) and arachidonic acid (AA) being prominent. These are synthesized (**Figure 1,** below) from α-linolenic acid (ALA), γ-linolenic acid (GLA) and eicosapentaenoic acid (EPA).

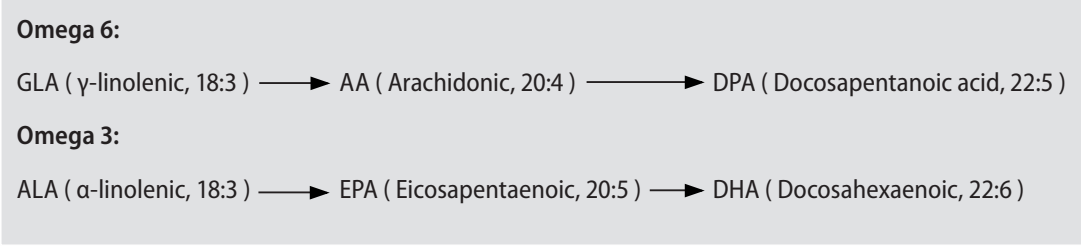
EPA and DHA are important for membrane fluidity, neuron plasticity, neurotransmitter function, and synaptic signal transduction.[9,10] Children with ADHD are reported to have abnormal fatty acid profiles, including EPA deficiency,[11] which may be due to slower conversion of ALA to EPA. Frequency of behavioral problems in ADHD children have been shown to be inversely associated with omega-3 fatty acid levels, DHA levels, and AA levels.[12-20]

Studies have shown that toxic metals such as arsenic, mercury, lead, aluminum, and cadmium can be involved in the onset and progression of ADHD, either by affecting the conformation of specific proteins or by exacerbating local oxidative stress.[21-28] These toxic heavy metals are known to adversely affect brain development in the perinatal period.

Deficiencies in essential minerals may also affect ADHD children. Zinc, for instance, is an important co-factor in the enzymes associated with the metabolism of neurotransmitters and prostaglandins, and is necessary for maintaining brain function.[29,30] Magnesium deficiency is known to cause membrane hyper-excitability with seizures in rodents that can be reversed by magnesium treatment.[31-33] Iron is an important co-factor in the enzymes that help produce DA and NE.

Urinary excretion of pyrroles ("Mauve Factor") is associated with emotional stress. They are present in the urine of acute schizophrenia patients, but disappear when patients recover.[34-41] Pyrroles are elevated in significant percentages of patients with schizophrenia (59%-80%), depression (12%-46%), autism (46%-48%) and ADHD (40%-47-%).[38] It has been suggested that the pyrroles in urine may be the result of an aberration of porphyrin metabolism (in conditions of iron

Figure 1. Pathways of essential fatty acid synthesis.



deficiency, unstable hemoglobin disease, red blood cell/RBC hemolysis, or others).

As a first step in studying the effect of dietary manipulation on ADHD patients, we wanted to document that in fact the parameters most associated with ADHD are amenable to dietary manipulation. With this in mind, ADHD patients at our facility (The Riordan Clinic) are worked up to identify fatty acid, amino acid and mineral deficiencies, as well as pyrrole levels and heavy metal toxicities. According to these results, they are treated with fatty acid supplementation, replenishment of essential minerals, amino acids and, when necessary, remediation of heavy metal toxicity. The present manuscript describes the metabolic changes in nutritional profiles in ADHD patients when given nutritional therapy.

Methods

Inclusionary criteria used were patients with a diagnosis of ADHD that had a nutritional work-up. One hundred and sixteen ADHD subjects that came for treatment at the Riordan Clinic met these criteria. Ages at the beginning of therapy were from 2 through 25 (mean age was 12 years old) and 66 percent of the patients studied were males. No other demographic data was recorded for this study.

The diagnosis of ADHD was made by medical doctors using Diagnostic and Statistical Manual of Mental Disorders-IV criteria based on direct observations plus reports from parents and other care takers. Patient evaluations included measurements of serum fatty acid composition, measurements of minerals (normal and toxic) in hair and, in some cases in RBCs, and assessments of vitamins in serum and pyrroles in urine. These tests were performed by the Bio-Center Laboratory of Riordan Clinic, an accredited clinical laboratory, using standard assay procedures. Mineral analysis in hair was carried out using inductively-coupled plasma-mass spectrometry. All identifying data were deleted from the lab results.

To measure pyrroles levels in ADHD patients, urine samples were collected and ascorbic acid was added (200 mg per 2 mL urine) as a preservative. Pyrroles were detected using the HPL (hydroxyhemopyrrolin-2 -one) assay, a procedure based on extraction of pyrroles from urine with chloroform followed by reaction with Ehrlich's acid aldehyde reagent (50 mL methanol, 2.5 mL sulfuric acid, 0.5 g p-dimethylaminobenzaldehyde) to yield a chromophore with an absorption maximum of 540 nm.

These patients were administered an integrative protocol for ADHD treatment, which has been advocated as an ideal treatment approach for ADHD.[42] This treatment of ADHD involved holistic/integrative medical management, and supplementation with minerals, vitamins, omega-3 and omega-6 essential fatty acids, flavonoids, probiotics, dietary modifications and chelation of toxic metals by natural substances. A list of supplements used, depending upon what deficiencies were found in each individual patient, is given below (**Table 1**, p. 104).

Graphs and curve fits were generated by Kalaidagraph (Synergy Software) and significance tests were carried out using Excel (Microsoft).

Results

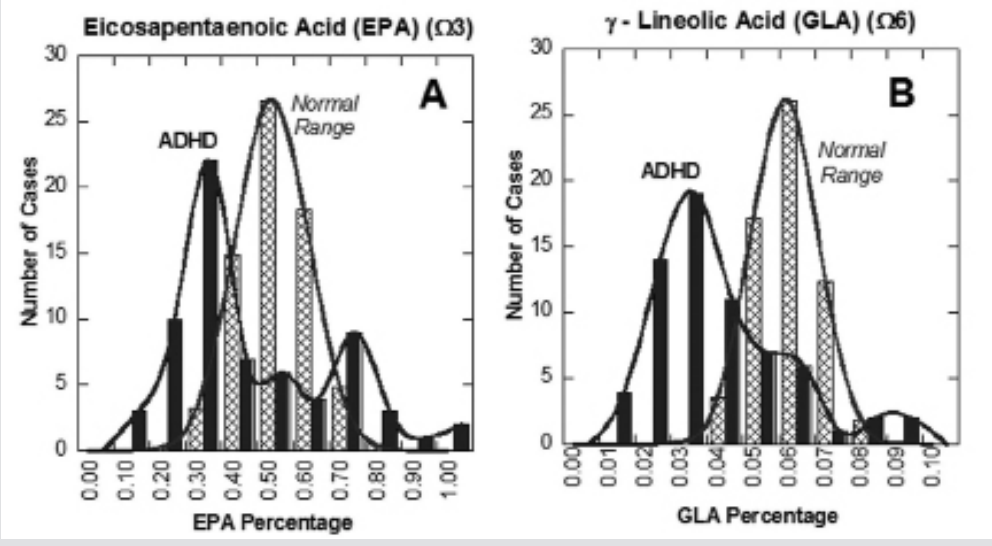
Fatty Acids

Average values for serum fatty acids (percentage of total fatty acid content) for the ADHD patients are given in **Table 2** (p.105). The first column shows the global results of the ADHD patients according to the fatty acid studied. The next three columns consist of a breakdown of the percentages of only those ADHD patients with values above or below the reference range (RR). The RR for all parameters was determined from the analysis of the clinical tests of the same age range subjects without diagnosis of any diseases.EPA and GLA in particular show a high percentage of abnormally low values in these ADHD patients, and have mean values at the lower limit of the RR. Frequency distribution histograms for these two fatty acids are shown in **Figure 2** (p. 104). GLA, despite being omega-6, has anti-inflammatory prop-

Table 1. List of prescribed nutraceuticals. Patients received only some of these supplements depending of their metabolic profile.

Biotin 5000	Pro DHA 1000 Mg	Lecithin	Cod Liver Oil	Phenylalanine 500 mg	Vitamin B2 100mg-100caps,
Glycine	Cal/Mag/Zinc	ProEPA	L-Taurine	L-Tryptophan 500mg	Evening Primrose Oil
Pantothenic Acid 500mg	L-Arginine	Tyrosine/B6)	Digestive Enzymes	D3- 50,000 IU	Methylcobalamin 5000mcg
Currant Seed 500mg	Prodophilus	L-Glutamine	Solar D Gems 4000 IU	Vit. A 10000	MSM Powder
Immuno Pro	Calcium Gluconate	Enzyme Q-10	MG- 100 Caps	DMG	Lutein- 20 Mg-
Potassium Gluc 98mg	Omega-3	Lipoic Acid	Quercetin/Bromelain	Vitamin B1 100mg	Vitamin B6
Borax 100	ProEFA-90 Caps	Selenium-200mcg-	DHA-Junior-250 mg	L-Threonine	Flaxseed Oil Cap,
L Tryptophan 500mg	Captomer 65 Mg	L-Lysine	L-Ornithine- 500	DL-Methionine 500 Mg	NAC 600 Mg
Folic Acid-800 mcg	Niacin 50 Mg	Vitamin D 2000 IU	GABA Caps 750 Mg	Niacinamide 50 mg	Vitamin C 1 Gram
Vitamin E 100 IU	Gentle Iron 25mg	Zinc Sulfate IV 10cc	Zinc Boost	Glucosamine Sulf 500 Mg	

Figure 2. Distributions of EPA (A) and GLA (B) levels in patients with ADHD compared to those expected in healthy subjects (computed from a Gaussian distribution around reference averages and standard deviations).



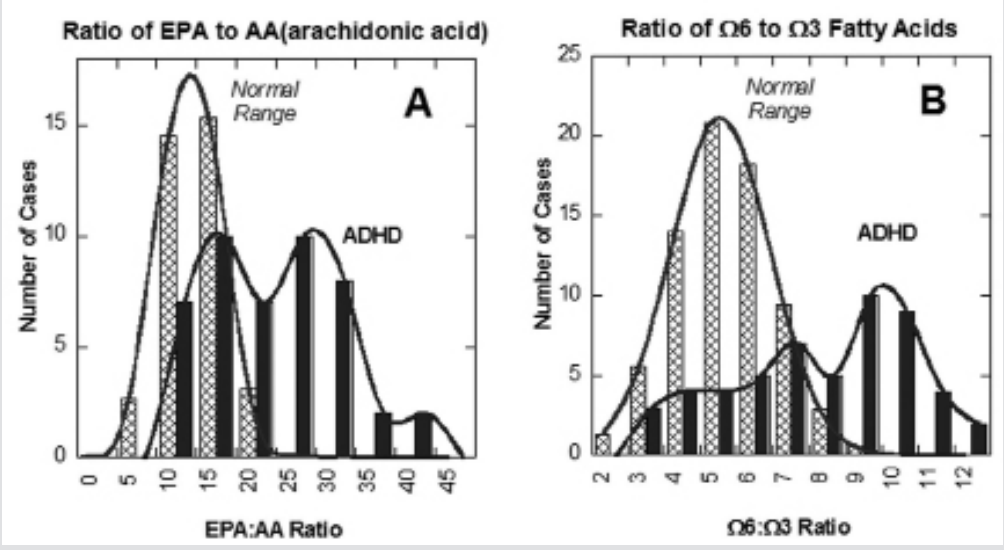
erties, so decreases may lead to increased inflammation.

The AA:EPA ratio, a variable correlated with depression, schizophrenia, dyslexia, dyspraxia, autism and ADHD,[43-47] and omega-6:omega-3 ratios, tend to be higher in ADHD subjects, as shown in **Table 2** and **Figure 3** (p.105). In both ratio parameters, the mean value in ADHD patients is slightly above the reference range.

Table 2. Concentrations of fatty acids in ADHD patients with comparisons to normal ranges.

Fatty Acid Name	ADHD Mean ± SD	Compared to Reference Range % Low	Reference Range	% High
Ω3 Series				
Alpha Linolenic (ALA)	0.15 ± 0.05 %	17 %	0.1 to 0.2 %	None
Ecosapentaenoic (EPA)	0.38 ± 0.21 %	55 %	0.3 to 0.6 %	None
Docosahexaenoic (DHA)	3.0 ± 0.2 %	16 %	2.0 to 5.0 %	None
Total Ω3	3.9 ± 2.0 %	42 %	3.0 to 5.0 %	None
Ω6 Series				
Arachidonic (AA)	14.1 ± 2.0 %	None	12 to 17 %	None
Dihomogamma Linolenic	1.62 ± 0.46 %	None	1.0 to 2.0 %	None
Gamma Linoleic(GLA)	0.047 ± 0.038 %	50%	0.040 to 0.070 %	None
Linoleic (LA)	11.3 ± 1.7 %	-	NA	-
Ratios				
AA/EPA	20.8 ± 13.0	None	5 to 20%	48 %
Ω6/ Ω3	8.1 ± 3.6	None	1.5 to 8.0%	60 %

Figure 3. Distributions of EPA:AA (A) and W3:W6 (B) ratios in patients with ADHD compared to those expected in healthy subjects (computed from a Gaussian distribution around reference averages and standard deviations).



Pyrroles

The frequency distribution of urinary pyrroles levels in ADHD patients is shown in **Figure 4A,** (p. 106). Sixty-five percent of subjects had pyrroles levels above the RR. There were two cases of extremely high levels: 481 ug/dL found in a ten-year-old boy, and 192 ug/dL in a five-year-old girl.

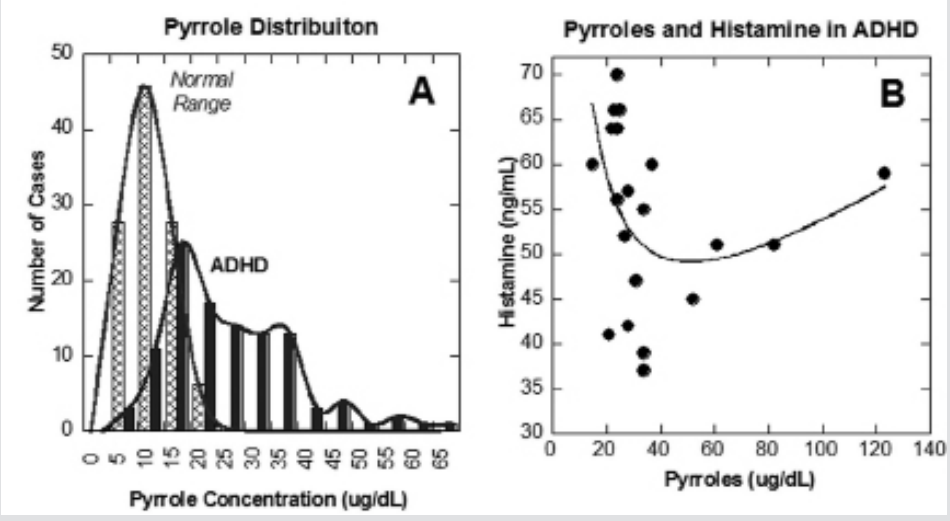
There are correlations between urinary pyrroles excretion and histamine levels.[48,49] Histamine has been shown to be an important brain neurotransmitter, directly or indi-

Table 3. Concentrations of minerals in ADHD patients, with comparisons to reference ranges (for essential minerals) or comparisons with maximum allowable levels (for toxic minerals).

Essential Minerals	ADHD Mean ± SD	Compared to Reference Range % Low	Range	% High
Magnesium (hair)	34 ± 38 ug/g	53 %	25 to 90 ug/g	None
Magnesium (RBC)	5.0 ± 0.7 mg/dL	35 %	4.5 to 6.4 mg/dL	None
Copper (hair)	33 ± 37 ug/g	None	6 to 25 ug/g	37 %
Zinc (hair)	134 ± 37 ug/g	16 %	100 to 180 ug/g	None
Zinc (RBC)	10.3 ± 1.9 mg/dL	28 %	9 to 15 mg/dL	None
Selenium (hair)	2.0 ± 1.4 ug/g	39 %	0.2 to 1.4 ug/g	None

Toxic Minerals	ADHD Mean ± SD	ADHD Maximum Level	Reference Range
Aluminum (hair)	8.3 ± 2.0 ppm	55 ppm	0 to 8.00 ppm
Lead (hair)	1.3 ± 1.5 ppm	9.4 ppm	0 to 1.00 ppm
Mercury (hair)	0.42 ± 0.34 ppm	1.8 ppm	0 to 0.40 ppm
Arsenic (hair)	0.29 ± 0.45 ppm	2.3 ppm	0 to 0.08 ppm
Cadmium (hair)	0.11 ± 0.16 ppm	1.4 ppm	0 to 0.15 ppm

Figure 4. (A) Distributions of pyrroles in patients with ADHD compared to those expected in healthy subjects. (B) Relationship between pyrrole levels and histamine levels in ADHD patients. (Fit to y = 16.9 + 0.28x + 745/x).



rectly influencing other major neurotransmitters, often via inhibition of neurotransmitter release. This fact has been used to explain anxiety, depression, or both. For instance, anxiety may be caused by histamine's inhibition of GABA, a neurotransmitter which is known to alleviate anxiety or by its release of norepinephrine. Half of the ADHD patients had histamine levels above the normal range. **Figure 4B** (above) shows the relationship between pyrroles and histamine in these subjects. At relatively low pyrroles levels, in-

creasing pyrroles correlate with decreasing histamine. As pyrroles levels pass roughly 45 ug/dL, there appears to be a change. At higher pyrroles levels, the increase in pyrroles is associated with an increase in histamine.

Minerals and Toxic Metals

Table 3 (p. 106) shows the mean levels of essential minerals and toxic metals in ADHD subjects. In the case of essential minerals, the reference range and percentages of ADHD subjects above or below reference are given. In the case of toxic metals, maximum observed levels and normal ranges are provided for reference. With the exception of copper, the essential minerals in hair testing tend to be below normal, especially magnesium and selenium levels.

Reduction in selenium combined with elevation of copper would mean less antioxidants availability. The elevated copper levels might be significant because although trace amounts of this mineral are essential, higher than normal levels can be toxic. Elevated copper combined with low zinc has been associated with hyperactivity, attention deficit disorders, behavior disorders, and depression.[50] Excess copper may also induce damage of dopaminergic neurons by allowing oxidation.[51,52]

Toxic metals can substitute for and deplete essential metals. Some ADHD patients in our study showed elevated toxin levels (Table 3). The mean values of aluminum, lead, and mercury were just above the upper "normal" limit, while the mean arsenic level was well above "normal". The maximum levels indicate that some ADHD patients had dramatically high levels of at least one metal. As toxic metals have a synergistic effect, and lead and mercury have higher toxic effects on cells in the body than other heavy metals, the total concentration of heavy metals was estimated by summation of all concentrations, with multiplication of the concentrations of lead, arsenic, cadmium, and mercury by a factor of ten.

According to the data presented in **Figure 5,** (p. 108) high levels of toxic metals resulted in decrease in the level of zinc to copper ratio. Similar trends were observed with selenium (not shown). This would indicate a loss of antioxidant protection.

Effect of Treatment

ADHD patients at the Riordan Clinic were treated using supplementation with minerals, vitamins, omega-3 and omega-6 essential fatty acids, flavonoids, and probiotics (whichever were deficient in a particular subject) as described above Methods. In some cases, we had sufficient data to track changes in pyrroles and omega-6:omega-3 ratios during treatment. Results are shown in **Figure 6** (p. 108).

The omega-6:omega-3 ratio in the subjects, for whom we had data in our database before and after intervention, decreased during therapy. After at least eighty days, all patients saw a reduction in omega-6:omega-3 ratio. The mean omega-6:omega-3 ratio before treatment was 8.9 ± 1.9 (SD) while that after treatment was 4.2 ± 1.0 (SD) (p-value of 0.003 in a paired t-test).

In 24 subjects with pyrrole measurements before and after treatment, the average pyrrole value went down from 40 ± 26 (SD) ug/dL to 21 ± 14 (SD) ug/dL (p-value of 0.001 in a paired t-test). Overall, 21 subjects showed reduced pyrrole levels after treatment while three subjects showed further increases (progression) after treatment.

Deficiencies of zinc and magnesium were also improved by the supplementation. Combined magnesium and zinc uptake for three to twenty-four weeks restored normal Mg and Zn values in hair and red blood cells.

Conclusions

Our data are consistent with reports in the literature that ADHD patients can be deficient in fatty acids and minerals that are thought to be important for maintaining proper neurological function. These data suggest that a significant percentage of ADHD patients have sub-optimal fatty acid levels, which in turn may lead to increased inflammation, poor neural cell health, and reduced production of neurotransmitters such as dopamine and serotonin. In particular, we found:

Figure 5. Relationship between the toxic metal load and zinc to copper ratio in ADHD subjects, based on hair analysis.

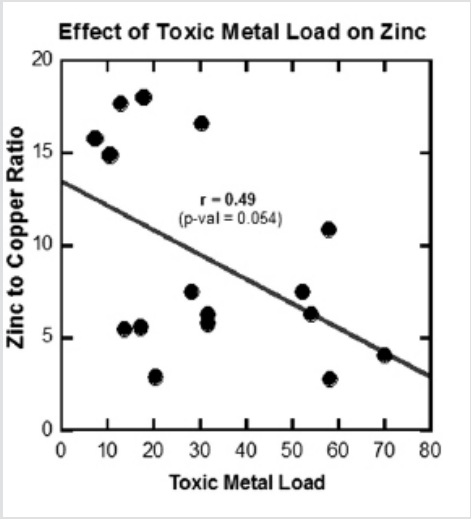
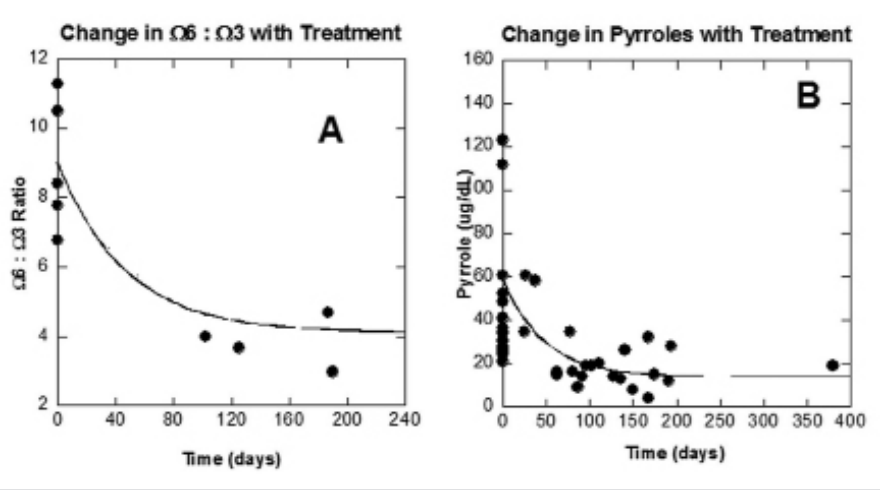


Figure 6. Effects of nutritional therapy on omega-6:omega-3 ratios (A) and pyrroles (B) in ADHD patients. Lines represent least squares data fits to the exponential decay function in Kalaidagraph [$y = \alpha + \beta \exp(-\mu x)$].



1. A predominance of below-normal DHA, EPA, and GLA levels.
2. A high incidence of unfavorable AA:EPA and omega-6:omega-3 ratios.
3. Deficiencies in zinc, magnesium, and selenium.
4. Presence of toxic metals in above-normal amounts.

Furthermore, we found that some ADHD patients have elevated pyrrole levels. As pyrroles are correlated with emotional stress and mental illness, this is an important

observation.

Our data suggest that at least two of the factors that were the most abnormal, omega-6:omega-3 ratios and pyrrole levels, can improve in subjects undergoing a regimen of nutrient supplementation. Thus nutritional manipulation does result in improved metabolic profiles in our sample. The results are robust enough to warrant a study of a larger sample, with an attempt to document whether these changes have an effect on improving behavior and cognition in the form of a prospective, controlled clinical study.

Competing interests

The authors declare that they have no competing interests.

Author Contribution

NM and RH designed the study; NM analyzed the data; all authors contributed to interpretation of data and reviewed the manuscript.

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