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Metabolic correction for attention deficit/hyperactivity disorder: A biochemical-physiological therapeutic approach

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ABSTRACT

Objective: This investigation was undertaken to determine the reference values of specific biochemical markers that have been have been associated with behavior typical of ADHD in a group of patients before and after metabolic correction.

Background: Attention deficit hyperactivity disorder (ADHD) affects approximately two million American children, and this condition has grown to become the most commonly diagnosed behavioral disorder of childhood. According to the National Institute of Mental Health (NIMH), the cause of the condition, once called hyperkinesis, is not known.

The cause of ADHD is generally acknowledged to be multifactorial, involving both biological and environmental influence. Molecular, genetic, and pharmacological studies suggest the involvement of the neurotransmitter systems in the pathogenesis of ADHD. Polymorphic variants in several genes involved in regulation of dopamine have been identified, and related neurotransmitter pathways alterations are reported to be associated with the disease.

Nutritional deficiencies, including deficiencies in fatty acids (EPA, DHA), the amino acid methionine, and the trace minerals zinc and selenium, have been shown to influence neuronal function and produce defects in neuronal plasticity, as well as impact behavior in children with attention deficit hyperactivity disorder.

Materials/Methods: This study was based on data extracted from our patient history database covering a period of over ten years. We performed laboratory tests in 116 patients 2.7-25 years old with a diagnosis of ADHD. Sixty-six percent (66%) of patients were males. Patients were

followed from 3 month to 3 years. We compared the distributions of fatty acids, essential metals, and the levels of metabolic stress factors with established reference ranges before and after interventions. In addition, we analyzed the association between toxic metal concentrations and the levels of essential metals.

Results: This study was based on data extracted from our patient history database covering a period of over ten years. We performed laboratory tests in 116 patients 2.7-25 years old with a diagnosis of ADHD. Sixty-six percent (66%) of patients were males. Patients were followed from 3 month to 3 years. We compared the distributions of fatty acids, essential metals, and the levels of metabolic stress factors with established reference ranges before and after interventions. In addition, we analyzed the association between toxic metal concentrations and the levels of essential metals. According to these data, the metabolic correction of ADHD by supplementation with minerals, vitamins, essential fatty acids, and amino acids can ameliorate ADHD symptoms. Eighty percent (80%) of children who were treated from several weeks to 1-2 years, demonstrated improvement of metabolic stress level, measured by pyrroles. For these patients the levels of EPA were increased and the omega-6/omega-3 ratio was improved.

Conclusion: In the studied population it was demonstrated that metabolic correction of biochemical disturbances using essential fatty acids, amino acids, and minerals can improve fatty acid profiles and metabolic stress levels. These disturbances or variations from reference values have been associated with behavior typical of ADHD. Further studies need to be conducted with integrative metabolic correction therapy to determine its value in the management of ADHD.

Key words: Attention deficit hyperactivity disorder, metabolic correction, fatty acid composition, essential metals, toxic metals, pyrroles, vitamins and minerals.

BACKGROUND:

According to the National Institute of Mental Health, attention deficit hyperactivity disorder (ADHD) affects approximately two million American children; 3 to 5 percent of the school-age population, and is about four times more common in boys than in girls [1-4]. Over the past several decades this condition has grown to become the most commonly diagnosed behavioral disorder of childhood. According to NIMH, the cause of the condition, once called hyperkinesis, is not known.

ADHD is primarily characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequent and severe than is typically observed in individuals at a comparable level of development [5, 6]. The cause of ADHD is generally acknowledged to be multifactorial, involving both biological and environmental influences [7]. Molecular, genetic, and pharmacological studies suggest the involvement of the dopaminergic, serotonergic, and noradrenergic neurotransmitter systems in the pathogenesis of ADHD. Polymorphic variants in several genes involved in regulation of the dopamine have been identified and related neurotransmitter pathways alterations are reported to be associated with the disease [8-9].

Nutritional deficiencies, including deficiencies in the long chain polyunsaturated fatty acids (PUFA) eicosapentaenoic acid (EPA; 20:5n–3) and docosahexaenoic acid (DHA; 20:6n-3), the amino acid methionine, and the trace minerals zinc and selenium, have been shown to influence neuronal function and produce defects in neuronal plasticity, as well as impact behavior in children with attention deficit hyperactivity disorder. Neurons lacking in plasticity are a factor in neurodevelopmental disorders such as ADHD, autism, and mental retardation. Essential nutrients help maintain normal neuronal plasticity. Among dietary factors, learning and behavior are influenced not only by nutrients, but also by exposure to toxic food contaminants such as lead, mercury, arsenic, and aluminum that can disrupt metabolic processes and alter neuronal plasticity. Toxic heavy metals are found in the air we breathe, the food we eat, and the houses we live in. Toxic metal exposure can result in a wide array of common mental health disorders. The results of studies demonstrate that there are neurochemical and behavioral consequences of heavy metal exposure during brain development.

In addition, nutritional deficiencies and toxic metal exposure have been shown not only to alter neuronal function, but to increase metabolic stress among children with autism. These factors may be directly related to the development of behavior disorders and learning disabilities.

The role of n–3 PUFA's in child mental health has received recent attention related to the treatment of attention-deficit hyperactivity disorder. The association between EFA and hyperactivity was initially hypothesized in the 80's [10]. This hypothesis is compatible with lower blood EFA fractions in children with ADHD compared with matched comparisons. Several recent studies have examined the relation between n–3 PUFAs and children's behavioral problems, depressed mood, and clinical depression [13-16]. The fatty acids that are biologically relevant for mental health include the long-chain n–3 FAs that are present in cell membranes in the brain and neural tissue, namely docosahexaenoic acid and eicosapentaenoic acid. Although the exact mechanisms by which PUFAs, especially DHA and EPA, affect behavioral disorders such as ADHD remain unclear, plausible evidence suggests why DHA and EPA may be involved in these disorders. DHA and EPA are important for both membrane fluidity and neurotransmitter function, especially synaptic signal transduction, particularly during the perinatal period [11, 12]. Summary of studies on blood essential fatty acid (EFA) status in children with attention-deficit–hyperactivity disorder is presented in a review [13]. Cross-sectional studies have reported that the frequency of behavioral problems is inversely associated with n–3 PUFA status [14, 15]. Several case control studies [16-18] have reported low blood concentrations of DHA and arachidonic acid (AA) in children with ADHD compared with age-sex matched control subjects.

Finally, several recent longitudinal studies found a negative association between DHA status early in life and subsequent behavior problems in young children [19-21]. These data suggest children and adolescents with ADHD continue to display abnormal essential fatty acid profiles that are different from normal controls of similar age, and there are metabolic differences in fatty acid handling between ADHD children and normal controls.

One of the hypotheses that link EFA to ADHD is that children with ADHD might suffer from slower conversion of linoleic acid and alpha linolenic acid to long chain PUFA. A recent genetic study supports this direction [22].

Other studies mounted evidence suggesting a central role for transition bio-metals in the etiopathogenesis of ADHD. Indeed, while studying the molecular basis for this heterogeneous

group of diseases, it has become increasingly evident that bio-metals and non-physiological metals [23-30] are often involved in pathology onset and progression, either by affecting the conformation of specific proteins or by exacerbating local metabolic stress. For example, the deficiency of zinc, which is involved in the production and modulation of melatonin, is considered to be a factor in ADHD [31-33]. Zinc is an essential co-factor of more than 100 enzymes, including metalloenzymes, which are necessary in the metabolism of carbohydrates, fatty acids, proteins, and nucleic acids. It is an important factor in the metabolism of neurotransmitters, prostaglandins, and for maintaining brain structure and function.

In a study [34], it was shown that red cell magnesium (Mg) concentrations of ADHD children were below a critical value of 2.2mmol/L. In addition Mg depletion has long been known to cause hyperexcitability with convulsive seizures in rodents [35]. Metabolic disorders and genetic alterations are suspected in this pathology, in which Mg transport and intracellular distribution may be reduced and can be reversed by treatment [36, 37]. In addition, Mg is involved in control of some CNS processes.

Many treatment methods of ADHD have been tried, with the most common approach being psychiatric intervention and use of prescription drugs such as methylphenidate (Ritalin) with mixed results and an array of multiple side-effects.

The purpose of this study is to evaluate if the metabolic correction of pathologic biochemical–physiological disturbances associated with ADHD can be resolved by administering target nutrients.

METHODS:

ADHD diagnosis was made by qualified medical doctors, based on direct observation plus reports by multiple sources (parents and other caretakers).

Laboratory tests were done and analyzed for 116 patients 2.7-25 years old (mean age 12 years old). Thirty-four % of patients were females and 66% males. Patients were followed from 3 months to two-three years.

The protocol for patients with ADHD included evaluations of fatty acid composition, essential metals, toxic metals (in blood and hair), food allergies, levels of urinary pyrroles, and the levels of vitamins before, during, and post treatment.

For all patients, we compared the distributions of fatty acids, essential metals, and the levels of metabolic stress factors with established reference ranges for these parameters. In addition, we analyzed the association between toxic metal concentrations and the levels of essential metals.

Treatment and follow-up

Children and adolescents were administered an integrative protocol for ADHD treatment, similar to a protocol developed by Gant [38-40]. This treatment of ADHD is based on the metabolic correction of biochemical abnormalities associated with ADHD. This safe, evidence based approach gives the patient an opportunity to respond prior to considering more toxic pharmaceutical approaches. The treatment includes supplementation with minerals, vitamins, omega-3 and omega-6 essential fatty acids, flavonoids, probiotics, dietary modifications, and chelation of toxic metals by natural substances.

Statistical methods/data collection

This study was not a controlled experiment, but rather a mining of data from our patient history database covering a period of over ten years.

For statistical analysis Systat software (Systat, Inc) and Kaleidagraph software were used. Variables were presented as mean values ± SD, or as medians with corresponding 25th percentiles. Association between different factors was assessed using linear models and polynomial model. Statistical significance was accepted if the null hypothesis could be rejected at $p \leq 0.05$.

RESULTS:

The analysis of the imbalances and deficiencies found for this group of patients is presented below.

Laboratory tests of patients with ADHD

Essential fatty acids

The fatty acids of interest for our analysis were the n-6 and n-3 PUFA. In particular, the fatty acids linoleic acid (18:3n-6, LA) and alpha-linolenic acid (18:3n-3, ALA) are called essential fatty acids (EFA) as they cannot be synthesized by the human body and, therefore, have to be provided by the diet. The other n-3 and n-6 fatty acids can be synthesized by humans from LA and ALA, respectively.

As it was previously mentioned, the imbalance of fatty acids, reduction in essential metals, increased level of toxic metals, and augmented level of stress are the characteristics and, probably, underlined primary causes of the ADHD condition. Many studies have shown that omega-3 fatty acid deprivation during development results in altered performance in learning tasks, altered activity of membrane receptors and proteins, and altered metabolism of several neurotransmitters including dopamine. Relevant studies suggest that omega-3 fatty acids deficiency decreases the mean cell body size of neurons in the hypocampus, hypothalamus, and cortex [13]. Lower levels of omega-3 fatty acids correlate with a higher score on the behavioral scale for patients with ADHD [18].

Data presented in Table 1 are baseline and show the mean and SD of the percentage of fatty acids, reference range (RR), and percentage of patients with higher and lower level of EFA than reference range.

Analyzed distribution of docosahexaenoic acid (22:6n-3, DHA) for patients with ADHD demonstrated that the 16% of the patients had the levels of this fatty acid lower than reference range (mean-2SD) and for 40% of patients the level of DHA was less than average value of RR.

The DHA has an important structural role: it comprises 10% to 20% of human brain total fatty acid composition, and it is the most predominant *n*-3 fatty acid found in the brain. DHA is important for both membrane fluidity and neurotransmitter function, especially synaptic signal transduction.

Summary of the relative plasma fatty acid composition in patients with ADHD is presented in Table 1.

Table 1. Relative plasma fatty acid composition in patients with ADHD

Relative plasma fatty acid composition in patients with ADHD						
Fatty acid	Mean (%)	Standard Deviation	Double bond	Reference range (% of total)	Higher than RR	Lower than RR
n-3 series						
alpha linolenic	0.15	0.05	18:3n-3	0.1-0.2		17%
Eicosapentaenoic (EPA)	0.38	0.21	20:5n-3	0.3-0.6		55%
Docosahexaenoic (DHA)	3.00	0.25	22:6n-3	2.0-5.9		16%
total omega 3	3.90	1.95		3.0-5.0		42%
omega 6 series						
Arachidonic	14.09	1.98	20:4n-6	12.0-17.0		
Dihomogammalinolenic	1.62	0.46	20:3n-6	1.0-2.0		
Gamma-linolenic	0.05	0.04	18:3n-6	0.04-0.07		50%
Linoleic	11.34	1.70	18:2n-6	9-14		
ratios						
AA/EPA	20.77	13.04		5.0-20	48%	
omega6/omega3	8.14	3.63		1.5-8	60%	

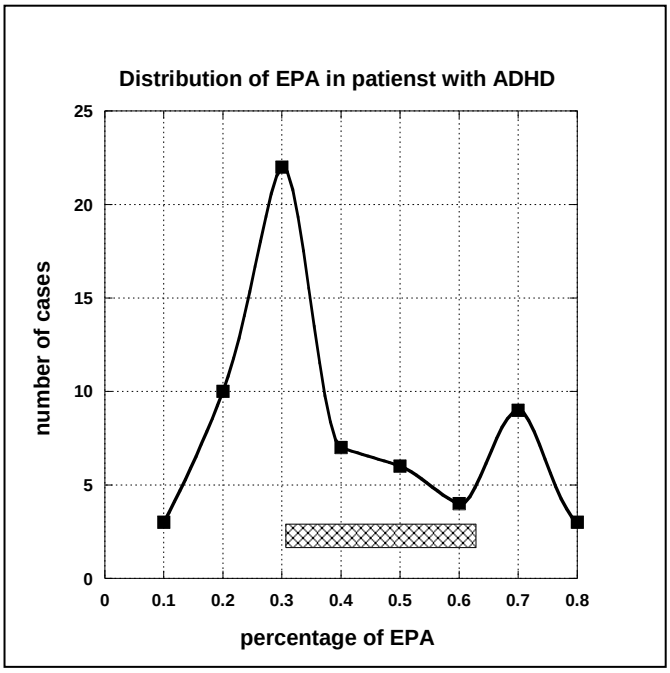
Deficits in the frontal cortex dopamine neurotransmission seen in patients with ADHD could be associated with lower brain DHA concentration. Low DHA status is associated with poor development of visual acuity and low indices of neural development in human infants.

The eicosapentaenoic acid (20:5*n*-3, EPA) is also an *n*-3 long-chain fatty acid that is less abundant in neural (membrane) structures, but has numerous roles in neural, enzymatic, and anti-inflammatory functions. The distribution of this fatty acid in ADHD patients is presented in Figure 1 (bar shows the reference range estimated from the same age population without ADHD). According to these data 50% of patients had a level of EPA lower than reference range.

In addition, the ratio of arachidonic acid to EPA demonstrated the abnormal distribution in patients with ADHD. In the n-6 family, arachidonic acid (20:4n-6, AA) is an important structural lipid in the neural membranes. According to the previous studies, the arachidonic acid to eicosapentaenoic acid ratio in blood correlates positively with clinical symptoms of depression, bipolar affective disorder, and reactive depression.

Our analysis of patients with ADHD demonstrated that there was increased level of this ratio that supports the presence of stress in patients with ADHD conditions. Reference range of the ratio AA/EPA is between 5 and 13. Distribution of this ratio for patients showed that 70% of children and adolescents had ratio levels higher than the normal range. This result provides a basis for the nutritional supplementation of subjects with ADHD, aimed at reducing the AA/EPA ratio.

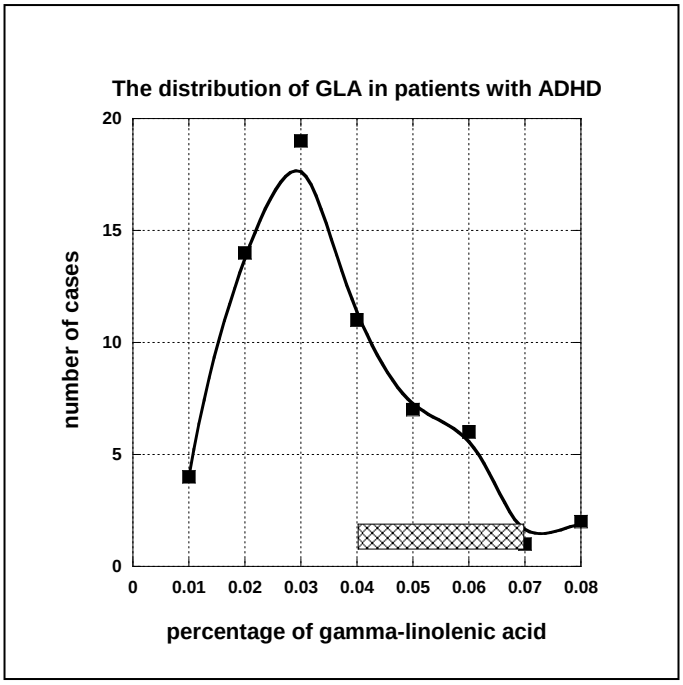
Figure 1. Distribution of eicosapentaenoic fatty acid in plasma of patients with ADHD before treatment.



The analysis of the data of fatty acids in omega 6 series showed that children with ADHD have lower levels of EFAs in omega-6s in addition to omega-3s.

Regarding the omega 6 fatty acids, gamma-linolenic acid (GLA) was significantly lower in patients with ADHD (Figure 2).

Figure 2. Distribution of gamma-linolenic acid in plasma of patients with ADHD before intervention.

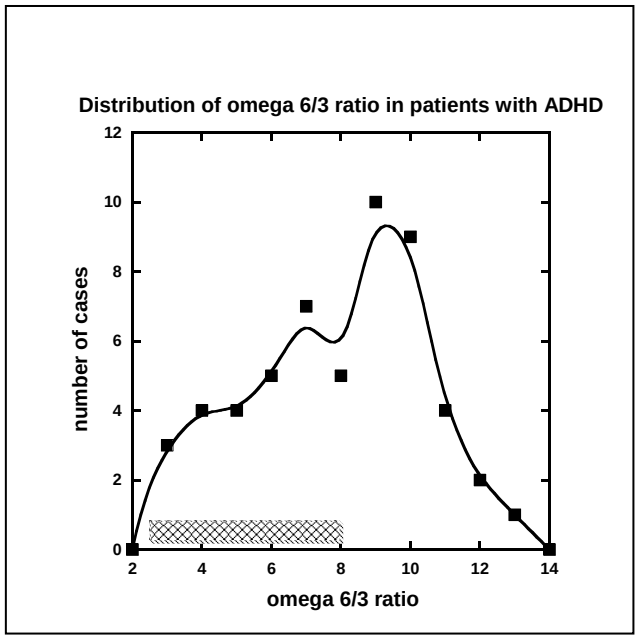


As GLA is an n−6 fatty acid that has anti-inflammatory properties, the decreased level of this fatty acid can lead to increased level of inflammation in patients with ADHD.

Excessive amounts of omega-6 polyunsaturated fatty acids and a very high omega-6/omega-3 ratio was also measured for patients with ADHD.

Our analysis demonstrated that for patients with ADHD there were higher levels of omega 6 and lower level of omega 3 fatty acids (Figure 3). Maximum of the ratio distribution was in the range of 9-10 and 50% of patients had omega6/omega3 levels higher than 8.

Figure 3. Omega-6 to omega-3 ratio measured in plasma of patients with ADHD before treatment.



Urinary pyrroles in patients with ADHD

Pyrroles or "Mauve Factor," a metabolic product of hemoglobin, was first detected in the urine of psychiatric patients by the Hoffer group in 1958 and named for its appearance on paper chromatograms. Irvine extracted the compound from urine, correctly assigned the structure to the pyrrole family, and conferred the common name [40-42]. Hoffer observed that recovery from acute schizophrenia, associated with disappearance of Mauve from the urine, regression with reappearance [43-48]. Large doses of vitamin B6 suppressed Mauve in schizophrenics. Later it became clear that Mauve is not confined to schizophrenia. Mauve elevation is documented in many cognitive, affective, and neurobehavioral disorders. According to the studies [45] elevated levels of pyrroles can be found in patients with schizophrenia (59%-80%), depression (12%-46%), autism (46%-48%) and ADHD (40%-47%). Combined treatment by vitamin B6 and zinc suppressed Mauve and improved symptoms in many neurobehavioral disorders.

Despite that the high level of pyrroles was described in the urine of patients with various mental illnesses, how pyrroles are produced and appear in the urine is still unclear. Pyrrole is from subclass of monopyrroles, well known for biotoxicity, and an elevated level of excretion classically associated with emotional stress. The suggestion is that the pyrroles in urine may be the result of an aberration of porphyrin metabolism (in conditions of iron deficiency, unstable

hemoglobin disease, RBC hemolysis, or others). The test of pyrroles or HPL (hydroxyhemopyrrolin-2-one) assay is based on the extraction of pyrroles from urine with chloroform followed by reaction with Ehrlich's acid aldehyde reagent (0.5 g of p-dimethylaminobenzaldehyde, 2.5 ml sulfuric acid in 50 ml of methanol). This preparation yields a chromophore with an absorption maximum of 540 nm. For this test, urine samples of patients with ADHD were collected and 200-500 mg of ascorbic acid was added as a preservative (2.0 ml of urine for analysis).

The level of pyrroles was measured in 116 patients. Sixty-five % of the patients had a level of pyrroles higher than upper normal limit (20ug/dL). The highest level was measured for a 10-year old boy (481ug/dL). A level of 192ug/dL was found in 5 year old girl and levels of 123ug/dL and 114ug/dL in two boys.

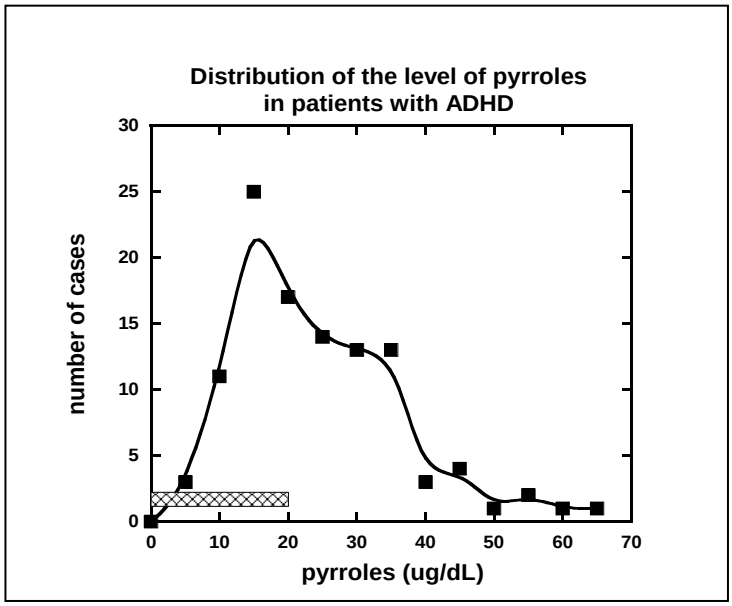
We analyzed a correlation between the levels of pyrroles and histamine. Histamine is an important brain neurotransmitter and neuro-regulator that is present in all nerve cells. Degradation of histamine is through methylation; low histamine levels indicate over-methylation and high histamine level means that the process of re-methylation is overactive. Histamine either directly or indirectly influences all other major neurotransmitters, often via inhibition of neurotransmitter release thus theoretically causing anxiety, depression, or both. The anxiety may be caused by histamine's inhibition of GABA, which slows nerve transmission. Histamine can also release norepinephrine, thus potentially causing anxiety.

Histamine imbalance exists in patients with mental disorders. Patients with a mental disorder may have higher than normal and lower than normal levels of histamine. Histapenia describes the low histamine conditions and histadelia is term for elevated histamine.

The level of histamine was screened for patients with ADHD. Maximum of the distribution of histamine was on the upper level of the reference range (RR), which is 60 ng/ml, and half of the subjects had a level of histamine higher than the upper level of the RR.

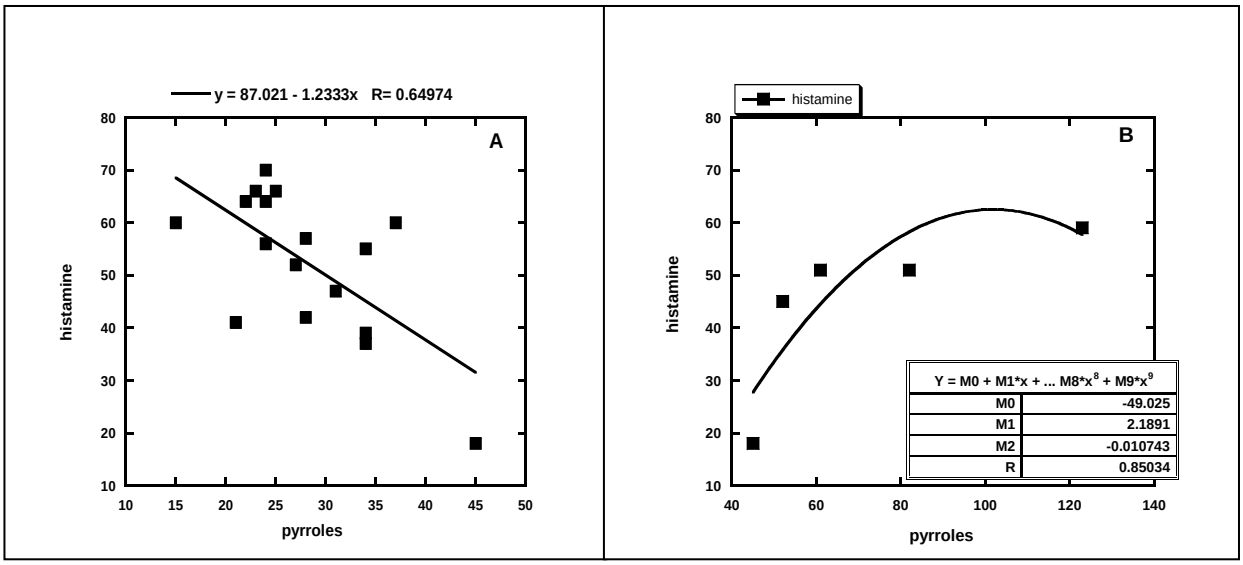
Distribution of the values of pyrroles for patients with ADHD is presented in Figure 4.

Figure 4. Distribution of the levels of pyrroles in urine of patients with ADHD before intervention



We found histamine imbalances in these patients, and two different tendencies in the relations between the levels of histamines and pyrroles. For patients with a mild increase in the level of pyrroles (values less than 45ug/dL), there was inverse association between pyrroles and histamine (Figure 5a). For several patients with very high levels of pyrroles (higher than 45 ug/dL), there was direct correlation between histamine and pyrrole levels (Figure 5b).

Figure 5 (a, b). Correlations between the levels of pyrroles and histamine



ADHD and the levels of essential and toxic metals

The measurements of the levels of the essential metals in plasma, red blood cells, and hair were made by clinical laboratory by inductively-coupled plasma-mass spectrometry. Summary of the data is presented in Table 2.

Table 2. Essential metals in plasma in patients with ADHD

Essential metals in plasma in patients with ADHD							
Essential metals	Number of cases out of reference range	Percentage of patients lower than RR	Mean value	Units	SD	Reference range	Percentage of patients higher than RR
magnesium (hair)	35/68	53%	34.1	ug/g	38.5	25-90	
magnesium (RBC)	26/71	35%	5	mg/dL	0.67	4.5-6.4	
copper (hair)	36/124		33.2	ug/g	37.5	6-25	37% (16 patients) >80ug/g
zinc(hair)	11/68	16%	133.5	ug/g	36.8	100-180	
Zinc (RBC)	17/60	28%	10.3	ug/g	1.9	9-15	
selenium (hair)	41/104	39%	2.0	ug/g	1.4	0.2-1.4	

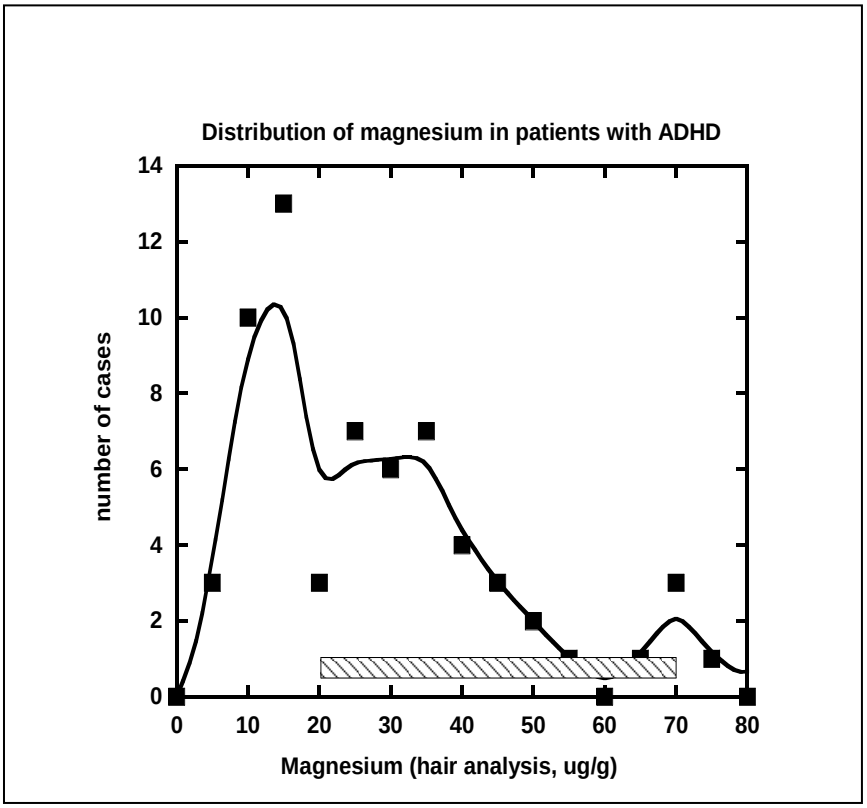
Several minerals were low in ADHD patients. The most pronounced deficiencies were found for magnesium, selenium, and zinc. Data analysis demonstrated that many children with ADHD have lower zinc in relation to reference range (28% of patients had levels of zinc in red blood cells lower than RR).

Our data showed a deficiency of magnesium in patients with ADHD. Magnesium is involved in control of some CNS processes. The prior clinical study has been reported on the effect of Mg supplementation on hyperactivity in children.

Mg deficiencies were indicated by a subnormal concentration of Mg, determined by hair analysis (Figure 6) and red blood cell analysis. Fifty % of patients according to hair analysis and 35% of patients according to RBC analysis had a level of Mg lower than reference range.

Analysis of the distribution of selenium for these patients also demonstrated that 39% of patients had the levels of selenium lower than the reference range. Selenium is an important mineral for maintaining proper antioxidant balances, either directly (as an antioxidant itself) or indirectly (via its incorporation into selenium-dependent enzymes). The latter is evidenced by a number of important enzymes such as the dependence of the important antioxidant enzyme glutathione peroxidase on selenium.

Figure 6. Distribution of the magnesium levels in hair of patients with ADHD



In addition, copper, and zinc participate in SOD enzymatic mechanisms that protect against free radicals, and therefore, serve an important adjunct role in oxidative balance [50]. A diminished level of selenium can indicate an increased level of oxidative stress in these patients.

In addition to the several essential metals mentioned above, a copper imbalance was found in ADHD children and adolescents. Thirty-seven % of patients had a level of copper higher than the upper reference level 25ug/g. Copper interferes with zinc metabolism, affects thyroid activity, and enhances the biogenic amines (the neurotransmitters that stimulate brain activity). Copper appears to have many important functional roles in the body that apparently relate to, among others, the maintenance of the immune function, bone health, and homeostasis [51]. The element is needed in trace amounts, but excess is toxic. It increases lipid peroxidation and depletes glutathione reserves, which makes the organism more vulnerable to oxidative stress. Copper and zinc levels are regulated by metallothionein, a short linear protein composed of 61 amino acid units. When this protein fails to perform its necessary functions, abnormal levels of nutrient metals (such as copper, zinc, and manganese) and toxic metals (such as cadmium, mercury, and lead) can result.

Copper and zinc are in high concentrations in the brain hippocampus. As a result elevated copper and depressed zinc have been associated with hyperactivity, attention deficit disorders, behavior disorders, and depression. It has been suggested that high copper induces damage of dopaminergic neurons through destroying antioxidant defenses, such as it was demonstrated in animal studies by lowering Cu/Zn SOD levels in rats [57, 58].

Our results showed the deficiency of zinc in RBCs of 28% of patients and in hair of 16% of patients. Several other studies have investigated the role of zinc in the etiology of ADHD and have suggested that zinc deficiency is associated with the pathophysiology of the disease [52-

54]. Research has also demonstrated that zinc treatment may be efficacious for ADHD individuals [55].

We analyzed correlation between depressed level of Zn/Cu ratio and increased level of copper in patients with ADHD. The ratio of copper to zinc was chosen as this ratio is clinically more important than the concentration of either of these trace metals. The relationship between Zn/Cu and Cu levels in ADHD individuals showed that the ratios were significantly lower when accompanied by high Cu levels (all values are measured by hair analysis).

Effect of toxic metals on the levels of essential metals

Our analysis demonstrated that toxic metals can substitute and deplete essential metals. The concentration of toxic metals measured in patients with ADHD is shown in Table 3.

Examples of the relations between zinc, selenium and the concentration of toxic metals in hair are presented in Figure 7 (a, b) and show that the increased level of toxic metals results in the depletion of essential metals.

As toxic metals have a synergistic effect and lead and mercury have higher toxic effects on cells in the body than do other heavy metals, the total concentration of heavy metals was estimated by summation of all concentrations with multiplication of the concentrations of Pb and Hg by a factor of ten. According to the data presented in the figures, high levels of toxic metals resulted in a decrease in the level of zinc and selenium. The same inverse correlation was found for the zinc to copper ratio and the levels of toxic metals.

Table 3. Concentration of toxic metals measured in patients with ADHD

Concentration of toxic metals measured in patients with ADHD (hair analysis)			
Toxic metal	Average (ppm)	SD	Maximum level (ppm)
Aluminum	8.32	7.7	55
Lead	1.3	1.5	9.4
Mercury	0.42	0.34	1.8
Arsenic	0.29	0.45	2.3
Cadmium	0.11	0.16	1.4

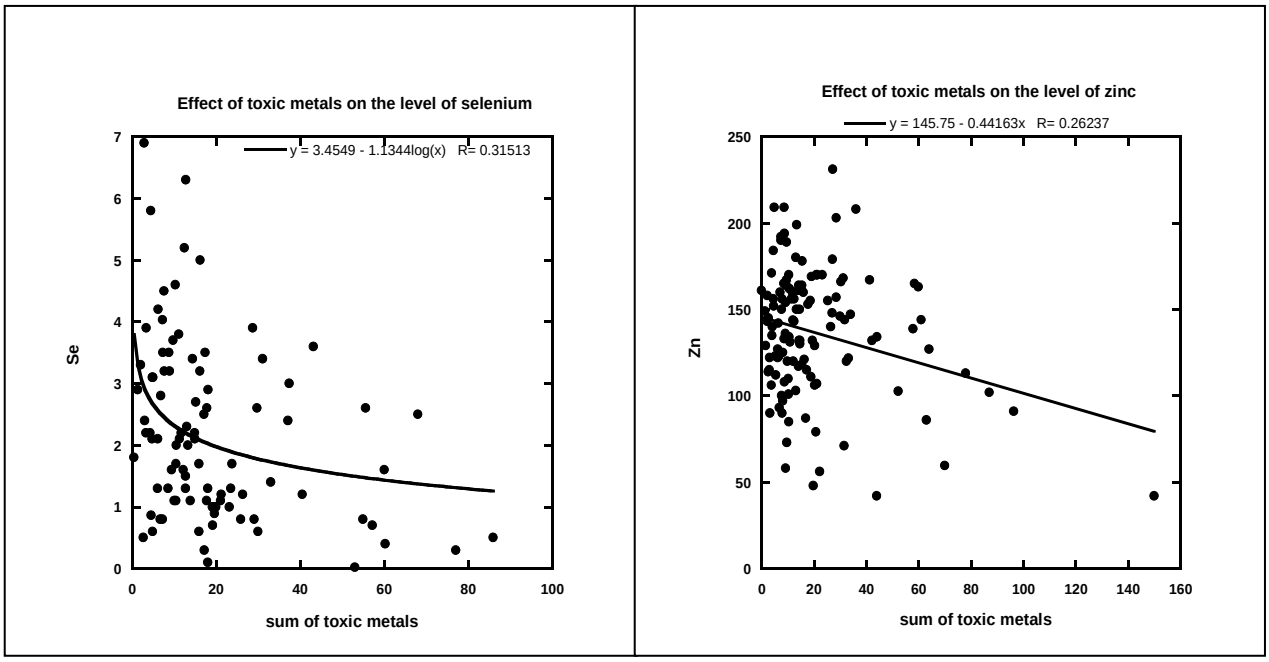


Figure 7 (a, b). Inverse relations between the levels of zinc and selenium in patients with ADHD and accumulated toxic metals in the body

Effect of orthomolecular treatment (metabolic correction) on the level of metabolic stress and fatty acid composition in patients with ADHD

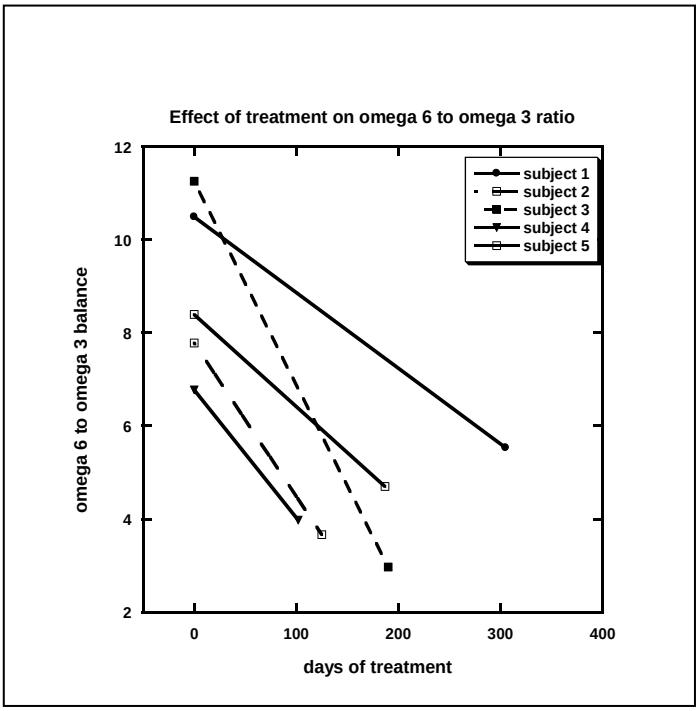
Treatment was performed according to principles of integrative management of this condition, and patients were treated by essential fatty acids, amino acids, minerals, probiotics and vitamins. The list of the medicine (nutraceuticals) that were prescribed in different combination (mixed composition) depending on the laboratory testing of the deficiencies in patients is shown in Table 4.

Table 4. List of prescribed nutraceuticals.
Patients received only some of these supplements depending of their metabolic profile.

Biotin 5000 Mcg #60 Caps	Glycine Sticks 30 Sticks	Pantothenic Acid 500mg- #100
Bk Currant Seed 500mg #90 Softgels	Immuno Pro 10.6 Oz	Potassium Gluc 98mg #100
Borax 100 Tabs	L Tryptophan 60 Caps 500mg	Pro DHA 1000 Mg 60 Tabs
Cal/Mag/Zinc #240 Caps	L-Arginine 500 Mg #100	Prodophilus
Calcium Gluconate IV 1cc	Latero Flora Caps #60	ProEFA-90 Caps 1000mg
Captomer 65 Mg #45 Caps	Lecithin 21 Gr #100 Softgels	ProEPA 60 Count 1000mg
Catemine (Tyrosine/B6) #120	L-Glutamine 500 Mg #90 Caps	ProOmega Liquid-4 Oz
Co Enzyme Q-10 400 Mg 30 Tabs	Lipoic Acid- 100 Mg- 90 Caps	Quercetin/Bromelain #180
Cod Liver Oil 100 Caps	L-Lysine 500 Mg #50	Selenium- 200mcg- #180 Caps
DHAJunior-250 mg- 180 Caps	L-Ornithine- 500 MG- 100 Caps	Solar D Gems 4000 IU 120 Caps
Digestive Enzymes #250 Tabs	L-Taurine #100- 500mg	Solution Of Magnesium 8 Oz
DL-Methionine 500 Mg #250 Caps	L-Threonine 500mg- #100	Vit D3-50, 50,000 IU 100 Caps
DL-Phenylalanine 500 mg #100	L-Tryptophan 500mg #60 Caps	Vitamin A 10000 IU- 100 Softgels
DMG #60 Tabs	Lutein- 20 Mg- 60 Caps	Vitamin B1 100mg #100 Caps
EnteroPro 60 Caps	Methylcobalamin 5000mcg 60 Tabs	Vitamin B2 100mg- 100caps
Evening Primrose Oil #100- 500 Mg Softgel	MSM Powder 200 Gr	Vitamin B6 (Pyridoxine) IV Infusion 1cc
Flaxseed Oil Cap #90 1000 Mg Softgel	NAC 600 Mg 60 Caps	Vitamin C 1 Gram #250
Folic Acid-800 mcg- 100 Caps.	Niacin 50 Mg 300 Tabs	Vitamin D 2000 IU-120 Soft Gels
Gaba Caps 750 Mg-60 Caps	Niacinamide 50 mg #250	Vitamin E 100 IU #250
Gentle Iron 25mg 90 Caps	Zinc Sulfate IV 10cc	Zinc Boost
Glucosamine Sulf 500 Mg- 180 Caps		

As the result of treatment, there were changes in the balance of omega 6 and omega 3 fatty acids. Data in Figure 8 show the examples of the improvement in the ratio of omega 6/omega 3 after treatment.

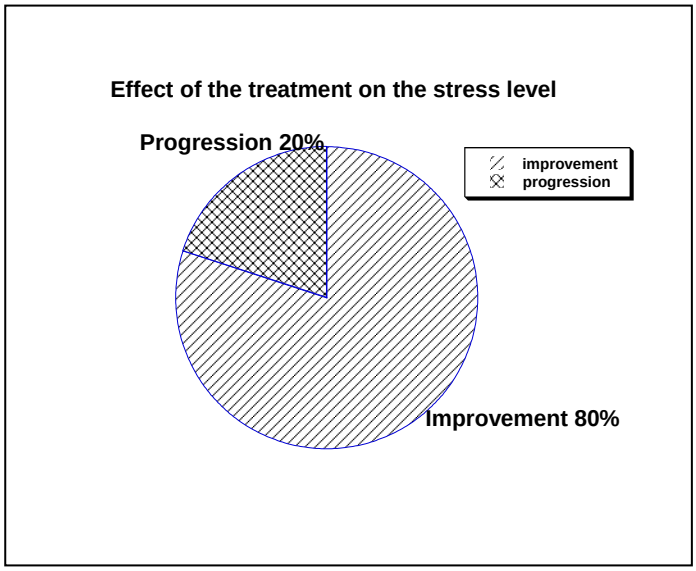
Figure 8. Improvement in the ratio of omega 6 to omega 3 fatty acids after treatment



In addition, for patients who had levels of EPA in plasma at the lower level of the reference range (0.2%-0.3%), these values were increased 2-5 times after 120-500 days of treatment. The level of metabolic stress evaluated by the pyrroles was improved in 80% of patients (Figure 9).

Figure 9. Percentage of patients demonstrated improvement or progression of the stress levels

.



Data of the percentage of improvement in the pyrroles' values (decrease excessive), days of treatment, age and sex of patients are shown in Table 5.

Table 5. Percentage of improvement of the pyrroles' values in patients with ADHD

Age	Sex	Initial value of pyrrole (ug/dL)	Percentage of improvement	Days of treatment	Age	Sex	Initial value of pyrrole (ug/dL)	Percentage of improvement	Days of treatment
9.0	F	48	33.33	167	13.3	M	28	50.00	127
8.5	F	25	40.00	63	15.9	M	26	84.62	167
14.7	F	41	53.66	95	10.2	M	481	92.72	25
9.9	M	34	52.94	80	10.3	M	35	62.86	136
6.0	M	36	27.78	141	18.9	F	28	42.86	63
7.5	M	34	-70.59	37	11.7	M	123	50.41	26
8.5	M	26	65.38	86	11.8	M	61	68.85	102
7.5	M	112	87.50	91	3.4	F	28	67.86	687
5.1	M	25	40.00	63	7.7	M	25	-12.00	193
22.8	M	52	61.54	110	7.9	F	24	66.67	149
10.6	M	21	-66.67	78	22.4	M	30	50.00	174
2.7	M	31	38.71	379	12.8	M	27	55.5	191

Deficiencies of essential metals such as zinc and magnesium were also improved by the supplementation. Combined magnesium and zinc uptake for 3 to 24 weeks restored normal Mg and Zn values in hair and red blood cells.

CONCLUSION:

According to these data, the metabolic correction of ADHD by supplementation with minerals, vitamins, omega-3/omega-6 essential fatty acids, and amino acids can ameliorate ADHD symptoms. After the intervention, 80% of children treated from several weeks to 1-2 years, demonstrated an improvement of metabolic stress level measured by level of pyrroles. For these patients the levels of EPA were increased and the ratio omega6/omega 3 was improved.

Putting all data together, it was demonstrated that after consumption of a combination of fatty acids as well as magnesium and zinc, amino acids, vitamins and probiotics most subjects had a considerable reduction in markers of metabolic stress and reported less emotional problems.

In this study, it was demonstrated that metabolic correction of biochemical disturbances using essential fatty acids, amino acids, and minerals can improve fatty acid profiles and metabolic stress levels. These disturbances or variations from reference values have been associated with behavior typical of ADHD.

Further studies need to be conducted with integrative metabolic correction therapy to determine its value in the management of ADHD.

Competing interests: None of the authors has conflicting interest in this program.

Authors' contribution: NM and RH designed the study; NM, AR, and PT collected and analyzed the data; all authors contributed to interpretation of data and reviewed the manuscript.

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