[1]H Magnetic Resonance Spectroscopy (MRS) assessment of the effects of Eicosapentaenoic-Docosahexaenoic Acids and Choline-Inositol supplementation on Children with Attention Deficit Hyperactivity Disorder (ADHD)

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Abbreviations:

ADHD: Attention Deficit Hyperactivity Disorder

^{1}HMRS: Proton Magnetic Resonance Spectroscopy

MRI: Magnetic Resonance Imaging

fMRI: functional Magnetic Resonance Imaging

PET: Positron Emission Tomography

SPECT: Single Photon Emission Computed Tomography

Cho: Choline

Cr: Creatine and phosphocreatine

NAA: N-Acetylaspartate

Lac: Lactate

mI: myo-inositol

Glx: Glutamic Acid

Gln: Glutamine

TE: Echo time

TR: Repetition time

RF: Radiofrequency

VOI: Volume of interest

EPA: Eicosapentaenoic Acid

DHA: Docosahexaenoic Acid

LCPUFA: Long Chain Polyunsaturated Fatty Acids

Abstract

This study was carried out to assess the effect of Eicosapentaenoic-Docosahexaenoic Acids (EPA/DHA) and Choline Bitartrate-Inositol (CHO/INO) supplementation on ADHD-children by evaluating their MRS profiles. Basal Ganglia's MRS was performed at the beginning of the study and after 6month EPA/DHA and CHO/INO treatment using a 1.5 Tesla Magnetic Resonance System. The results show a significant increase in the signal intensities of Choline-containing compounds and a significant raise in Choline/Creatine ratio after 6-month-therapy on ADHD-children, which correlate with the improvement of their capacities and abilities. The link between MRS-based EPA/DHA and CHO/INO monitoring and the improvement of the numerical, verbal, visual, hearing and concentration capacities may also provide a fertile ground for developing an EPA/DHA plus CHO/INO based supplementation therapy and predicting its efficacy to upgrade ADHD-children's cognitive abilities.

Introduction

Heinrich Hoffman (1), a physician who wrote books on medicine and psychiatry, first described Attention Deficit Hyperactivity Disorder (ADHD) in 1845. Hoffman realized he could not find suitable readings for his 3-year-old son, so he became a poet. The result was an illustrated book of poems about children and their characteristics. "The Story of Fidgety Philip" was an accurate description of a little boy with ADHD. Yet it was not until 1902 that Still (2) described a group of impulsive children with significant behavioral problems caused by a genetic dysfunction and not by poor child rearing children who still would be easily recognized as having ADHD. Since then, thousand scientific papers on ADHD have been published providing information on its nature, course, causes, impairments, and treatments. Almost 3-5% of the school-age population suffers from ADHD. According to the most recent version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (3) there are three ADHD's patterns of behavior: **predominantly hyperactive-impulsive type** (that does not show significant inattention); predominantly **inattentive type** (that does not show significant hyperactive-impulsive behavior) sometimes called ADHD—an outdated term for this entire disorder; and combined **type** (that displays both inattentive and hyperactive-impulsive symptoms).

The symptoms appear early in the child's life. As many ordinary children may show these symptoms, at a lower level or caused by another disorder, it is important that the child receive a thorough examination and appropriate diagnosis by a well-qualified professional team. Prominent symptoms of this disorder are: poor attention span, inability to complete tasks, hyperactivity, and a tendency to interrupt others. Almost one quarter of children with ADHD also suffer from one or more specific learning disabilities in mathematics, spelling or reading. ADHD's symptoms usually spend many months to appear. Impulsiveness and hyperactivity may precede inattention symptoms, which may not emerge for a year or more. Different symptoms may appear in different settings, depending on the demands the situation may pose for the child's self-control. A child who can not sit still or is otherwise disruptive will be noticeable in school, but the inattentive daydreamer may be overlooked. The impulsive child who acts before thinking may be considered just as a discipline problem, while the passive or sluggish one may be seen as merely unmotivated. Yet both may have different types of ADHD. Sometimes, children are restless; sometimes, they act without thinking and, sometimes, they daydream the time away. When the child's hyperactivity, distractibility, poor concentration, or impulsivity begins to affect its performance in school, social relationships with other children or behavior at home, ADHD may be suspected. However, as the symptoms vary so much across settings, ADHD is not easy to diagnose, especially when inattentiveness is the primary symptom.

Neuroimaging in ADHD

Brain structure's knowledge is helpful to understand the researches scientists are doing looking for ADHD's biochemical basis. Scientists have focused their attention in the brain's frontal lobes, which allow us to solve problems, plan ahead, understand people's behavior and restrain our impulses. Both frontal lobes, right and left, communicate with each other through the corpus callosum (connection nerve fibers). The basal ganglia are the interconnected gray masses located deep in the cerebral hemisphere that link the cerebrum and the cerebellum. Together, basal ganglia, cerebrum and cerebellum, are responsible for motor coordination. The cerebellum is divided into three parts. The middle part is called the vermis. There are several methods available that allow us to look into the brain and imaging it: Magnetic Resonance Imaging (MRI), Magnetic Resonance

Spectroscopy (MRS), functional Magnetic Resonance Imaging (fMRI), Positron Emission Tomography (PET), and Single Photon Emission Computed Tomography (SPECT).

MRI findings on ADHD

Abnormalities in patients with ADHD have been observed in different brain regions (4). Structural neuroimaging studies have shown volumetric abnormalities of the frontal lobes (5-7), basal ganglia (8-9), corpus callosum (8), and parietal lobes (7). Low frontal and striatal volumes found correlate with impaired performance on tasks of response inhibition (9). Recent findings direct the research to cerebellar vermis' lobules suggesting an influence of the cerebellar vermis on prefrontal and striatal circuitry on ADHD (10-11). Durston et.al. (12) reported that volumetric reductions in cortical gray and white matter in subjects with ADHD are also present in their unaffected siblings suggesting that they are related to an increased familial risk for the disorder. In contrast, the cerebellum is unaffected in siblings suggesting that the volume's reduction observed in subjects with ADHD may be more directly related to the pathophysiology of this disorder.

MRS findings on ADHD

Previous results from our research institute demonstrate a decrease in Cho/Cre ratio in frontal lobes on patients with ADHD (13-15). Lactate detection was also reported in 5% ADHD's cases (14). Jin et. al (16) concluded that the striatum was bilaterally involved as revealed by the NAA/Cr ratio, approximately 20–25% neurons in the globus pallidus may have died or may be severely dysfunctional on ADHD-children. The role of Glutamate-Glutamine (Glu-Gln) metabolism in ADHD-patients has also been studied by MRS. Carrey et. al. (17) reported that a striking decrease in the Glu/Cr (mean change 56.1%) of the striatum was observed between 14 and 18 week-therapy on four ADHD-children. In the prefrontal cortex, however, changes in the Glu/Cr ratio were noticed only in subjects who received atomoxetine, not in those who received methylphenidate, suggesting that in vivo MRS measurement has the potential to assess ADHD-children's response to psychopharmacological treatment. Recently, Carrey et. al (18) reported a significant decreased Gln/Glu/GABA to Cr/PCr ratio in the striatum. Other metabolites did not react to the medication used. These findings suggest that Glu may be involved in treatment response on ADHD, especially in the striatum. MacMaster et. al. (19) reported high frontal-striatal Glutamatergic (Glx) resonances on ADHD-children in comparison to Healthy Control subjects without differences in NAA, Cho, or Cr metabolite ratios, suggesting that frontal-striatal Glx resonances may be increased in children with ADHD. Courvoisie et.al. (20) pointed that MRS revealed increased Glu/Gln ratio in both frontal areas, and increased NAA and Cho in the right frontal area on ADHD-subjects. Changes on NAA/Creatine ratio in the right frontal region and mI/Cr ratio in the right and left frontal regions appear to be highly associated with the regulation of sensorimotor, language, and memory and learning functioning in children with ADHD. On the other hand, Yeo et.al. (21) found evidence that suggests sex-specific neurobiological differences in ADHD using MRS.

fMRI findings on ADHD

A fMRI study performed by Chandan et.al. (22) revealed differences between ADHD-children and healthy controls in their frontal-striatal function and its modulation by Methylphenidate during response inhibition. Children performed two go/no-go tasks with and without drug. ADHD-children

had impaired inhibitory control on both tasks. Off-drug frontal-striatal activation during response inhibition differed between ADHD and healthy children: ADHD-children had greater frontal activation on one task and reduced striatal activation on the other task. Drug effects differed between ADHD and healthy children: the drug improved response inhibition in both groups on one task and only in ADHD-children on the other task. The drug modulated brain activation during response inhibition on one task only: it increased frontal activation to an equal extent in both groups. In contrast, it increased striatal activation in ADHD-children, but reduced it in healthy children. The results suggest that ADHD is characterized by atypical frontal-striatal function and Methylphenidate affects ADHD-children's striatal activation differently than healthy children's. Rubia et. al (23) reported mesial hypofrontality on ADHD-adolescents during the performance of two different executive tasks suggesting a task-unspecific deficit in higher-order attentional regulation of the motor output. Lower than normal activation of the right inferior prefrontal cortex and caudate nucleus during the stop task may be responsible for poor inhibitory control on ADHD-patients. Anderson et. al. (24) suggested that further research is needed to clarify the relationship between vermal size, vermal blood flow, stimulant response, and the developmental pathophysiology of ADHD using fMRI.

PET findings on ADHD

During preliminary researches, PET scans of ADHD revealed that ADHD-patients' frontal lobes absorbed less radioactive tracer, which was similar to glucose, than the frontal lobes of patients without ADHD. Zametkin et.al. (25) reported that glucose metabolism, both global and regional, was reduced in adults who had been hyperactive since childhood. The largest reductions were found in the premotor cortex and the superior prefrontal cortex--areas earlier shown to be involved in the control of attention and motor activity.

SPECT findings on ADHD

Amen et.al (26-27) divided ADD into 6 subtypes using SPECT. **Type 1** or **classic ADHD** involves a normal resting brain, but during concentration there are decreases in metabolic activity on the topside (dorsolateral) and underside (orbito-frontal) prefrontal cortex. Thus, reduced brain metabolic activity necessarily equals reduced brain electrical activity and drives neurotransmitter release reducing brain metabolic activity; it also equals reduced brain neurotransmitter activity. **Type 2** or **inattentive ADHD** involves a normal resting brain with reduced metabolic activity in the dorsolateral prefrontal cortex during concentration. **Type 3** is called **over-focused ADHD**. SPECT findings show increased metabolic activity at rest and during concentration in the anterior cingulate gyrus (brain region that connects the prefrontal cortex and limbic system). During concentration, there is also reduced metabolic activity in the orbitofrontal and dorsolateral prefrontal cortex. **Type 4** is **temporal lobe ADHD**. Both, at rest and during concentration, there is decreased (occasionally increased) temporal lobe activity. During concentration, there is typically reduced activity in the orbitofrontal and dorsolateral prefrontal cortex. **Type 5** is **limbic ADD**. SPECT findings include increased deep limbic activity (thalamus and hypothalamus) both, at rest and during concentration, and decreased activity in orbitofrontal and dorsolateral prefrontal cortex. **Type 6** corresponds with **hyperactive ADHD**. SPECT findings include both, at rest and during concentration, patchy increased activity across the cerebral cortex with focal areas of increased activity, especially in the parietal bbes, temporal lobes and prefrontal cortex.

Long Chain Polyunsaturated Fatty Acids (LCPUFA) and ADHD

Stevens' et. al. study (28) first reported in 1995 linked ADHD to a deficiency of certain long-chain fatty acids. Arachidonic Acid (AA), EPA, and DHA are all metabolites of the two essential Fatty Acids, Linoleic Acid (O-6) and Alpha-Linoleic acid (O-3). Some authors (29) are now leaning towards the conclusion that a subclinical deficiency in DHA is responsible for the abnormal behavior of ADHD-children. They point out that supplementation with a long-chain omega-6 fatty acid (evening primrose oil) has been unsuccessful in ameliorating ADHD because ADHD-children need more O-3 acids rather than more O-6 acids (30-42). Researchers also found that children with ADHD were less often breast fed as infants than children without ADHD. Breast milk is an excellent source of DHA. Now, studies are carried out underway to investigate the effect of oral supplementation with DHA on the behavior of ADHD-children. DHA is the building block of human brain tissue and is particularly abundant in the gray matter of the brain and the retina. Low levels of DHA have recently been associated with depression, memory loss, dementia, and visual problems. DHA is particularly important for fetuses and infants.

The DHA content of the infant's brain triples during the first three months of life. Optimal levels of DHA are, therefore, crucial for pregnant and lactating mothers. United States' breast milk's DHA average content is the lowest in the world, due to low fish's comsumption. Therefore, World Health Organization recommended in 1995 that baby formulas should provide 40 mg of DHA per Kilogram of infant's body weight. Postpartum depression, ADHD and low IQs may be all linked to the dismally low DHA intake common in the United States. Other researchers also point out that low DHA levels have been linked to low brain serotonin levels, which again are connected to an increased tendency to depression, suicide and violence (42-44). DHA is abundant in marine phytoplankton and cold-water fish. Nutritionists now recommend people to consume two to three servings of fish every week to maintain DHA levels. Recent results (43-44) report that hyperactive children have lower levels of key fatty acids in their blood than ordinary children do. Analyses showed that boys with ADHD had significantly lower levels of AA, EPA, and DHA acids in their blood. Hyperactive children suffered more from symptoms associated with essential fatty acid deficiency (thirst, frequent urination, dry hair and dry skin) and were also much more likely to have asthma and many ear infections. Researchers conclude that ADHD may be linked to a low intake of omega-3 Fatty Acids (Linoleic, EPA and DHA Acids) or to a poorer ability to convert 18-carbon fatty acids to longer more highly unsaturated acids. As a result, they believe that supplementation with the missing fatty acids may be a useful treatment for hyperactivity (43-44).

CHOLINE and ADHD

Phosphatidilcholine (PCho) and Phosphatidylserine (PS) are natural extracts of lecithin and vital phospholipids for brain cell structure and function. Phospholipids are molecules with an amino acid component and a Fatty Acid component, which are found in every cell membrane in our bodies. ADHD, dyslexia, dyspraxia and autism are now studied as phospholipids disorders because of phospholipids' importance in the natural history, symptoms and prevalence of these conditions within families (45-47). PS plays an important role in neurotransmitter systems, brain metabolism levels and maintaining nerve connections in the brain. PS helps lowering cortisol levels, which are increased in chronically stressed individuals, and improves brain cell membrane fluidity, which helps with dementia and depression (45-47). Despite the experimental data available on using PS for ADHD, its cognitive benefits suggest it should prove extremely helpful (48). A recent study found

that the genetic and structural indicators of poor memory in the brain (called development al instability) correlate with lower concentrations of Cr-PCr and Cho containing compounds, whereas Cre and N-acetyl-aspartate correlate with good memory. These findings may be due to differences in frontal lobe energy metabolism (49) .

Purpose

To assess Choline signal intensity at Basal Ganglia level changes that result from treating children with Attention Deficit Hyperactivity Disorder (ADHD) with Eicosapentaenoic-Docosahexaenoic Acids (EPA/DHA) and Choline-Inositol (CHO/INO) oral supplementation and correlate them with the improvement of the ADHD symptoms.

Methods

ADHD-children and Healthy Subjects

Forty ADHD-children classified according to the DSM-IV criteria were studied after obtaining the written information consent from his parents (31 males and 9 females, mean age 11 ± 4 years). Twenty healthy children (14 male and 6 female, mean age 12 ± 2 years) participated in the study as the Healthy Reference (HR). Four clinical specialists evaluated the children suspected as ADHD-subjects. The first evaluation consisted on a psychological interview where the following tests were applied: Wechsler Intelligence Scale for Children-Revised (WISC-R), Bender Visual Motor Gestalt Test, Harris Test, Wepman Evaluation (Auditory Discrimination), Write and Lecture Examination, Auditive Perception Evaluation and Family Paint Test. A neurologist performed the second evaluation consisting on a physical evaluation and an Electroencephalogram (EEG). These criteria allowed us to exclude any child with neurological compromise. The next step was the psychiatric examination in order to evaluate the child's mental status. The biochemical, pharmacology and neurospectroscopy team, who validated the three previous criteria, carried out the forty interviews.

Magnetic Resonance Imaging (MRI)

Sagittal T1 weighted, Coronal T2 weighted, Axial T2 weighted and T2 Fluid Attenuated Inversion Recovery (FLAIR) images were performed on ADHD and HR subjects and carried out on a 1.5 Tesla system (Magnetom Sonata, Siemens Medical Systems®, Erlangen, Germany) equipped with a standard CP Head coil.

Magnetic Resonance Spectroscopy (MRS)

MRS was performed on each patient before and after the 6-month study. Single voxel proton MR spectra (1.8 cm x 1.8 cm x 1.8 cm = 5.83 cm^3) of each one of both Basal Ganglia in sagittal, axial and coronal images was carried out on a 1.5 Tesla system (Magnetom Sonata, Siemens Medical Systems®, Erlangen, Germany) (Figure 1). MRS data sets were acquired with a Spin-Echo sequence (TR= 1500 msec, TE= 30 msec, 192 averaged acquisitions). N-Acetylaspartate (NAA), Choline (Cho) and Creatine (Cre) intensity signals were detected and NAA/Cho+Cre, Cho/Cre, NAA/Cho and NAA/Cre ratios were calculated, separately, at the right and left Basal Ganglia on ADHD and HR subjects. The results were analyzed with repeated measured Analysis of Variance (ANOVA). Turkey test was applied for multiple comparisons among ratio means with Bonferroni

correction for small samples. Spearman rank correlation coefficients were calculated for Write and Lecture scores and measured metabolite ratios. After the first MRS study was performed, the children started a 6-month supplement consisting on a total daily dose of 50 mg/Kg Choline Bitartrate-Inositol (2000 mg maximum) + Fish Oils 720 mg Eicosapentaenoic Acid (EPA) + 480 mg Docosahexanoic Acid (DHA) (3000 mg maximum).

Results

Figure 1 shows   an spectra performed on a HR subject shows an adequate correspondence between Cho to Cr intensity signal and a very high intensity signal of NAA (Cho/Cr= 0,87).

Figure 2 shows ADHD-patient's MRS profile performed at the beginning of the study (Month 0, Cho/Cr= 0,40).

Figure 3 shows same ADHD-patient's MRS profile performed after 3-month supplementation treatment (Mont 3, Cho/Cr= 0,51).

Figure 4 shows ADHD-patient's MRS profile performed 6 months after receiving EPA/DHA and CHO/INO supplementation treatment (Month 6, Cho/Cr= 0,62).

The results shown in Table 1 demonstrate that Cho/Cr ratio increased in the Basal Ganglia on ADHD-children after 6-month EPA/DHA and CHO/INO supplementation. The Cho/Cre ratio in both sides of Basal Ganglia was 15-16% higher in the second MRS profile than in the first one. NAA/Cho+Cre and NAA/Cre ratios didn't show statistical differences when both studies were compared.

Table 1. MEANS METABOLITE RATIOS' COMPARISON BETWEEN TWO STUDIES PERFORMED ON ADHD-PATIENTS

		NAA/Cho+Cre	NAA/Cre	Cho/Cre
Right Basal Ganglia	Month 0	0.84 ± 0.20 ns	1.48 ± 0.33 ns	0.79 ± 0.27 *
	Month 6 *	0.78 ± -0.25	1.57 ± 0.34	0. 94 ± 0.25
Left Basal Ganglia	Month 0	0.79 ± 0.20 ns	1.41 ± 0.37 ns	0.80 ± 0.26 *
	Month 6 *	0.76 ± 0.24	1.52 ± 0.35	0.95 ± 0.24

* $p < 0.05$. (ns = no significant difference)

Discussion

The previously shown results suggest an increase in the resonance intensity of Choline-containing compounds on ADHD-children after 6-month treatment with oral supplementation of EPA-DHA and CHO/INO. Choline is the precursor of acetylcholine and phosphatidylcholine. Mainly obtained from the diet, Choline constitutes a crucial intermediate in several clinically relevant neurochemical processes. Studies performed on animals demonstrate an increase of Choline metabolites in their brains after oral administration (50-51). Quite a few MRS reports differ from finding similar increases

in human subjects (52-57). In this study, choline-containing compounds in human brain (phosphocholine, glycerol-phosphocholine and choline) were MRS-measured before and after the ingestion of 50 mg/Kg Choline Bitartrate-Inositol in forty ADHD-children. Cho/Cr ratios obtained were compared and referred to HR's basal ganglia Cho/Cr ratios. Substantial and remarkably similar increases in the brain choline resonance occurred, with a nearly 22% rise in the choline resonance observed in ADHD-children (Case No 5 reported in sequence on Figures 2, 3 and 4) after oral supplementation (p < 0.05 versus baseline).

Our data agrees on other authors' reports on the increase of brain Choline levels after Choline ingestion (52-55). Choline metabolites decrease has been observed in basal ganglia, as an age related process (58), and in psychiatric conditions, in which basal ganglia are involved (59). Cho/Cr increased-ratio corresponded with the improvement of the clinical signs of ADHD. Spearman correlation coefficient shows significant statistical association (p<0.05) between the improvement in cognitive abilities of ADHD-children (Verbal/Performance Scales as measured by Wechsler Intelligence Scale for Children-Revised and Visual-motor functioning / Visual-perceptual skills measured by Bender-Gestalt test) and a raise in Cho/Cr ratio. However, our results could be explained on the basis of positive interactions between CHO/INO and EPA/DHA simultaneous administration. The beneficial effects of LCPUFA on ADHD have been brought into focus in the last years. The consistent findings of both clinical signs of fatty acid deficiency and blood biochemical indices of fatty acid abnormalities in a subset of ADHD-children indicate that supplementation with LCPUFA might be helpful in the management of this condition in, at least, some cases. Now, the challenge is to determine what proportion of diagnosed ADHD-children might benefit from such supplementation, and how they may be well identified. Only a few pilot studies about gamma linoleic acid's deficiency effects on ADHD have been published. Two double-blind placebo-controlled trials of gamma linoleic acid (GLA) supplementation gave equivocal results in ADHD-subjects who weren't selected as having low levels of n-6 fatty acids (60-61).

The second study reported modest benefits for GLA supplementation over placebo, although it was less effective than D-amphetamine (61). In addition, the level of serum triglyceride GLA found correlated inversely with Conners' scale scores (62). The GLA's modest benefit is unsurprising. Evidence gathered since then suggests that n-3 rather than n-6 fatty acid deficiency may be more relevant in ADHD. The design of this study and its treatment duration cannot be considered appropriate for the evaluation of fatty acid treatment because second study-subjects were randomly allocated to GLA, D-amphetamine or placebo for 1 month each. Unlike D-amphetamine, fatty acids cannot be expected to act rapidly for changing symptoms or behavior. Rather, recent evidence has shown that LCPUFA levels in the brain may take up to 3 months to recover from a chronic deficiency state (63-64) and this must, therefore, be regarded as an essential consideration in the design of future treatment studies.

A published report on the results from a random, double-blind treatment trial on ADHD-children with clinical signs of fatty acid's deficiency (65) showed its authors' findings that combined-supplementation of DHA, EPA, AA and DGLA (weighted in favor of the n-3 fatty acids) was successful in changing the blood fatty acid profile of ADHD-children. These changes were associated with reductions in ADHD symptoms. In fact, DHA alone may be, indeed, ineffective as other fatty acids (EPA) may account for the benefits detected (65). The differences could be on the basis of subject selection. Further studies are required to determine if the Choline signals raise that we observed is related to the pharmacological combination used, which may suggest a possible

increase either in the brain uptake or in the bioavailability of Choline due to EPA/DHA coadministration. Stoll's data from unstable bipolar disorder patients treated with high-dose omega-3 fatty acid supplementation, previously treated with Choline to attenuate cell signaling through the phosphatidylcholine system (66), agrees on our findings.

The biochemical basis that could possibly support this hypothesis is the evidence that omega-3 fatty acids can also inhibit hydrolysis of membrane phospholipids, such as phosphatidylinositol, and may thus inhibit receptor-linked G-protein signal transduction (66). On the other hand, phosphatidylcholine is also effective in protecting DHA/EPA from free radical oxidative stress. Inositol is a simple polyol precursor in a second messenger system important in the brain. Cerebrospinal fluid Inositol decrease has been reported on depression. Inositol clinically controlled trials are few for patients with depression, panic disorder, and obsessive-compulsive disorder (OCD) (67-70). Positive psychoactive effects on animals (71) clearly strengthen the necessity of further clinical trials and Inositol's potential for general therapeutic use in humans. The possibility of a pharmacological synergism between EPA/DHA, Choline and Inositol on ADHD is already open for further studies.

In conclusion, MRS may provide a useful tool for monitoring ADHD-children's response to nutritional medicine. The link between MRS-based EPA/DHA and CHO/INO monitoring and the improvement of the numerical, verbal, visual, hearing and concentration capacities may also offer a fertile ground for developing an EPA/DHA plus CHO/INO based supplementation therapy and predicting its efficacy to upgrade ADHD-children cognitive abilities.

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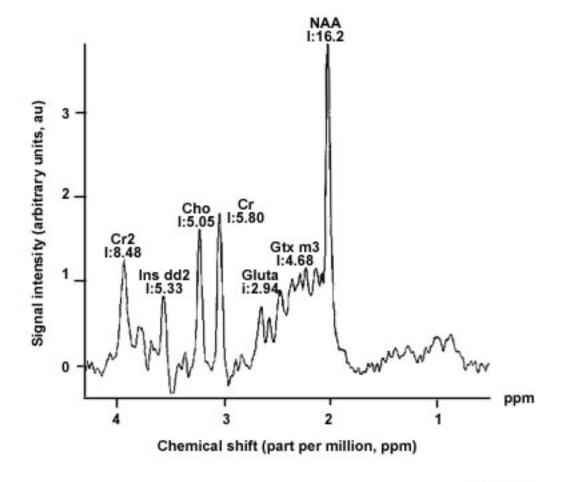
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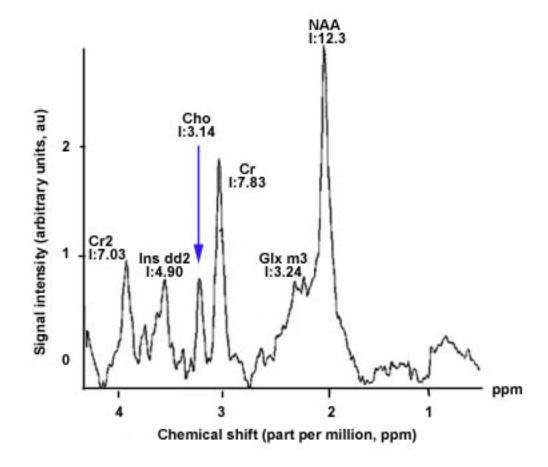
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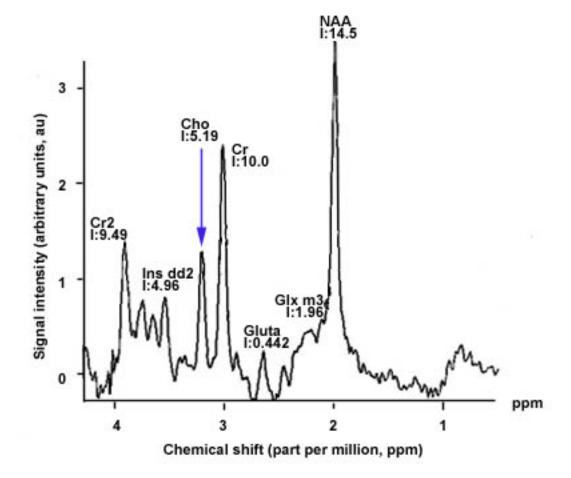
Figure 2

Shows an spectra performed on a HR subject shows an adequate correspondence between Cho to Cr intensity signal and a very high intensity signal of NAA (Cho/Cr= 0,87).

Figure 3

Shows ADHD-patient's MRS profile performed at the beginning
of the study (Month 0, Cho/Cr= 0,40)

Figure 4

Shows same ADHD-patient's MRS profile performed after 3-month supplementation treatment (Mont 3, Cho/Cr= 0,51).
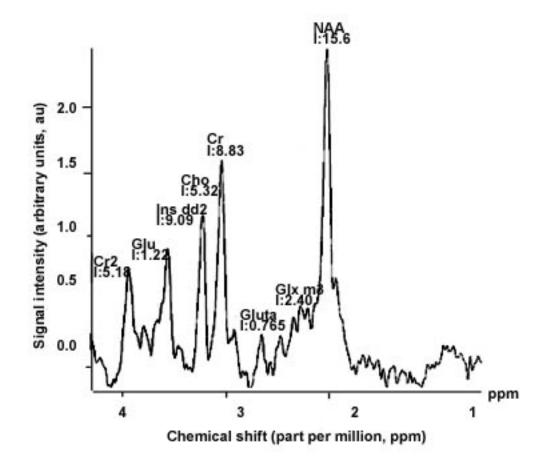
Figure 5

Shows ADHD-patient's MRS profile performed 6 months after receiving
EPA/DHA and CHO/INO supplementation treatment (Month 6, Cho/Cr= 0,62)