

Complementary and Alternative Treatments of Attention Deficit Hyperactivity Disorder

Dikkat Eksikliği Hiperaktivite Bozukluğunda Tamamlayıcı ve Alternatif Tedaviler

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ABSTRACT

Attention deficit hyperactivity disorder (ADHD) is one of the most common psychiatric conditions estimated to affect 5-10% of the children. It is a chronic condition and frequently persists into adulthood. Approved pharmacological agents for the treatment of ADHD include psychostimulants and atomoxetine. However, non-pharmacological treatment seeking and the use of complementary and alternative medicine are on the rise. Here, the most common complementary and alternative treatments of ADHD will be reviewed. (*Archives of Neuropsychiatry 2011; 48: 94-102*)

Key words: Attention deficit hyperactivity disorder, complementary and alternative treatments, biofeedback (neurofeedback), heavy metal chelation, hyperbaric oxygen therapy, dietary interventions

ÖZET

Dikkat eksikliği hiperaktivite bozukluğu (DEHB) çocukların yaklaşık %5-10 kadarını etkileyen en yaygın psikiyatrik durumlardan biridir. Kronik seyirli bir bozukluktur ve sıklıkla erişkinliğe kadar sürer. DEHB tedavisinde kullanılan onaylanmış farmakolojik ajanlar psikostimülanları ve atomoksetini içerir. Ancak ilaç dışı tedavi arayışları ve tamamlayıcı ve alternatif tıp kullanımı artış göstermektedir. Burada, DEHB'de en sık kullanılan tamamlayıcı ve alternatif tedaviler gözden geçirilecektir. (*Nöropsikiyatri Arşivi 2011; 48: 94-102*)

Anahtar kelimeler: Dikkat eksikliği hiperaktivite bozukluğu, tamamlayıcı ve alternatif tedaviler, biyofeedback (nörofeedback), ağır metal şelasyonu, hiperbarik oksijen tedavisi, diyet uygulamaları

Introduction

Attention deficit hyperactivity disorder (ADHD) is a life-long disorder that comprises inattention and/or hyperactivity and impulsivity (1). It is one of the most common psychiatric conditions estimated to affect 5-10% of all children and predisposes them to impaired academic, familial, social, vocational and emotional functioning if untreated. Contrary to once believed, ADHD does not remit with the onset of puberty alone and at least two-thirds of the teenagers and half of the adults continue to have symptoms of the disorder that cause significant problems in their lives (2).

Several effective treatments have been developed and evidence-based pharmacological and psychosocial interventions have been established for ADHD. Numerous large-scale clinical trials have proven the efficacy of psychostimulant drugs (3-6) and non-stimulant atomoxetine (7, 8). Both psychostimulants and atomoxetine are approved by the US

Food and Drug Administration (FDA) for the treatment of ADHD above the age of 6. Psychostimulants are recommended as the first-line treatment for ADHD, especially when no comorbidity is present (2,9). When clinical response is assessed quantitatively with rating scales and compared to placebo, the effect sizes (ES) were in the large (averaging 1) and moderate to large range (around 0.7) for psychostimulants and atomoxetine, respectively. Although consistently reported to be less effective than pharmacological treatment, behavioral parent training and behavioral school interventions were found efficacious in controlled studies.

Bupropion, tricyclic antidepressants, alpha-agonists are often used in the treatment of ADHD as second-line agents. Even though these drugs were found to be somewhat efficacious in open-label and small controlled trials, they are not approved by the FDA for ADHD. The only exception to this statement is for extended-release guanfacine, which was recently FDA-approved for ADHD, and its clinical effectiveness

has been shown by two randomized double-blind placebo- controlled studies in patients from 6 to 17 years of age (10-12). These agents generally have ES considerably less than those of stimulants and atomoxetine and comparable with the effectiveness of behavior therapy (13). Additionally, side-effect profiles of these drugs such as sedation for guanfacine, seizures for bupropion, cardiotoxicity for tricyclic antidepressants make them less preferred agents. Some open-label studies also showed the benefits of selective serotonin reuptake inhibitors (SSRI) and mixed serotonin-norepinephrine reuptake inhibitors (SNRI), but SSRIs generally were not found for the core symptoms of ADHD and drop-out rates were high for the SNRI, venlafaxine (14).

Although there are some effective treatments for ADHD, many people turn to interventions that claim to be useful but have not been well-studied or shown to be truly effective. Limited number of treatment options, non-responders, apparent or suspected medication side effects, lack of medication-free remission and possibly unwillingness of the parents/children to use drugs brought about the seeking 'novel' treatment options for ADHD. Most of them being introduced decades ago, this kind of treatments are named complementary and alternative medicine (CAM) in the medical literature. Although these two terms are frequently used interchangeably, alternative treatment is described as any treatment which is used in place of conventional approaches – prescription medication and/or standard psychosocial/behavioral treatments for ADHD – and claims to treat the symptoms of ADHD with an equally or more effective outcome. Complementary interventions are not alternatives, but used in conjunction with conventional medicine to improve the outcome or help to decrease the doses of the medication.

Similar to other childhood ailments such as asthma, cystic fibrosis or cancer, parents of children with ADHD are reported to increasingly use CAM (15-17). According to surveys conducted in different parts of the world, CAM use in ADHD varies between 12% and 68% (18). CAM treatments include various approaches such as electroencephalographic (EEG) biofeedback, long-chain polyunsaturated fatty acids (PUFA), trace element and vitamin supplementations, elimination diets, heavy metal chelation, hyperbaric oxygen therapy (HBOT), melatonin, pycnogenol, S-adenosyl methionine, allergy treatment, acupuncture, meditation, homeopathy, chiropractic, ginkgo biloba, hypericum perforatum, L-acetylcarnitine, nicotine, vision therapy, oculovestibular treatment and sound training, all with different efficacy.

Here, we aimed to review the evidence on the use of the most frequently employed CAM treatments, which are electroencephalographic (EEG) biofeedback, heavy metal chelation, HBOT and dietary interventions.

Electroencephalographic Biofeedback (Neurofeedback)

EEG consists of four brain wave frequencies. Delta activity is only observed during sleep and unconsciousness and is out of our interest. Alpha waves are seen in relaxed states when a person is not actively thinking or interacting with the environment, whereas beta waves are increased during concentration, mental activity and interacting with the

surrounding. Lastly, theta waves are increased during times of drowsiness, daydreaming and light sleep but also occur during unfocused states and restless overactivity (19).

Research findings indicate that most children with ADHD show EEG differences when compared to typically developing children. The most well-established results belong to theta activity, which suggests underarousal and decreased cortical activity. Besides increased theta waves in ADHD, increase in theta/beta ratio has also been consistently supported by some studies (19, 20). Results for alpha and beta waves are more variable. Alpha activity is found to be increased, decreased or unchanged in ADHD. Similarly, some studies demonstrate increased beta activity, whereas others do not. Moreover, a small group of children was shown to display an excess of beta activity (21). The differences between studies in gender and age of the participants, sampling and diagnostic procedures as well as EEG processing have been reported to cause the contradictory findings.

Neurofeedback (NF) is described as a neurobehavioral treatment, which aims to help a person to gain self-control over certain brain activity patterns and to use these skills in everyday situations. Theta/beta training and training of slow cortical potentials are two protocols frequently used in children with ADHD (22). NF treatment involves placing electrodes, which are connected to a computer, on a person's head. The computer detects the EEG information and provides a visual or auditory feedback in the targeted frequency band. For example, when the brainwaves are of the desired frequency, the audio beep may inform the patient, or the character in the game will go in the proper direction. At the end of the session, the person gains a reward for earning certain amount of points. After many training sessions, it is hypothesized that having gained increased awareness of one's own physiological processes, the person will be able to produce the desired EEG waves themselves.

NF has been used for the treatment of hyperactivity since 1976 (23) and attentional problems and impulsivity since 1982 (24). After several uncontrolled studies with favorable outcomes, the first controlled study was conducted by Linden et al. in 1996 (25). Most of these controlled studies, which will be reviewed below, suffer from significant methodological weaknesses that make the interpretation of the results and determine the actual effect of EEG biofeedback very difficult. The first, may be one of the most important methodological flaws, is the lack of random assignment of the patients to treatment and non-treatment groups. Treatment groups are often constructed retrospectively from a series of clinical cases that have been previously treated or not with EEG feedback or according to patient/parent preference. Also these studies are generally conducted by clinicians who are being paid for the intervention and published in journals that do not apply strict peer review (19). Another important methodological problem is the lack of appropriate placebo control condition. The effect of patient-therapist time (30-50 sessions, 30-60 min. each), expectations generated by applying electrodes connected to a computer and paying for the treatment, support given to parents, behavioral assignments the child receives

during treatment, relaxation due to respiratory and muscular feedback, all of which are unintended therapeutic mechanisms, may affect the outcomes, rather than the real mediating effects of NF on brain electrophysiology. Also, in many studies, the evaluators are not blind to the treatment received by the cases and EEG changes which are believed to cause the positive results in behavior and cognition are generally not reported.

In the first published controlled study, 18 children with ADHD were randomly assigned to 40 sessions of EEG feedback or to wait-list control groups (25) with equal number of patients in each. The researchers reported significant increase in IQ scores and decrease in parental ratings in inattention but not in hyperactivity and impulsivity in the NF group. Besides strengths of random assignment, wait-list control and no other confounding medications, lack of blindness of the parents and children to treatment, no-placebo control for therapist time, attention and treatment environment were the methodological weaknesses. Also application of variance analysis showed no significant effect for group, but a non-significant trend for time, suggesting that all children showed improvement in time, regardless of whether they were treated or not. However, the small sample size does not allow us to draw reliable conclusions.

The coming three studies aimed to compare the effects of NF with that of stimulants. In the first, Rossiter and LaVaque (1995) assessed 46 subjects with ADHD, aged between 5 and 45 years (26). Equal numbers of patients were assigned to treatment groups according to their preference, insurance coverage for biofeedback or stimulant unresponsiveness. Additional treatment modalities (including additional medication in 5 NF cases) were allowed. Both groups were reported to show significant improvement on the Test of Variable Attention (TOVA), a kind of a continuous performance test assessing inattention and impulsivity, and parent ratings of inattention and hyperactivity and internalizing problems. Although the researchers claim that EEG feedback may be a good choice for medication-resistant cases, lack of randomization, confounding treatments, non-blindness of the subjects, parents and evaluators complicate this conclusion.

Monastra et al. examined 100 children with ADHD all of whom received titrated short-acting methylphenidate (15-45 mg/day), 10-week parenting program with subsequent individualized parent counseling and academic support at school (27). NF was applied as optional along with this comprehensive treatment and 51 of them chose weekly NF sessions for 34-50 weeks. The groups were reported to be equal in the pretreatment scores of IQ, scores of the Attention Deficit Disorders Evaluation Scale, quantitative EEG (qEEG) and TOVA measures, but there was no information on how the additional NF interventions were charged. One year later, the patients were tested with and without their medications. Both groups showed significant improvement on ADHD ratings, the TOVA and qEEG measures, when tested while using their stimulants. However, only those who had received NF sustained these gains when tested off medication. In both groups, the parents who systematically used the strategies taught in the parenting program had

children who displayed fewer attentional and behavioral control problems at home. Large sample size and using the clinical, neuropsychological and EEG measures appear as the strengths of the study, whereas lack of randomization due to self-selection bias, including family resources and inclination to undertake NF, lack of blinding, failure to control for the time spent with a therapist and unequal behavioral interventions applied to the non-neurofeedback group are the major drawbacks of the study.

Fuchs et al. compared 22 children who received NF to 11 children using stimulants and reported that both groups showed comparable improvement in behavioral ratings and TOVA (28). This study, though important for being free from confounding effects of additional treatments, suffer from similar methodological problems of the former two studies of stimulant treatments. Lack of randomization through selecting the subjects according to parent/patient preference confounds the results. In many studies, the financial burden of NF relies on the family, and a family eager enough to pay might report biased results compared to the non-paying group.

Heywood and Beale performed a pilot study with single-subject design to compare the effects of NF with that of placebo condition, involving non-contingent feedback (29). In seven subjects with ADHD, consecutive block sessions of active and sham treatments were delivered and the parental/teacher behavioral ratings and a number of cognitive tests were performed. After controlling for the behavioral trends, active and sham treatments did not result in significant improvements and were not significantly different from each other. The results imply that unintended therapeutic mechanisms such as behavioral techniques could be responsible for the observed improvements of NF which could mistakenly be named as a moderate to large ES.

Drachler et al. conducted a controlled trial to overcome some of these limitations, namely, behavioral techniques integral to NF, respiratory and muscular feedback as a way of relaxation, maturation, change of parental attitudes, etc (30). Thus, they recruited 30 patients with ADHD who were assigned to NF treatment (n=17) or group training (n=13) in a non-random fashion. They found that NF itself improved some behaviors, especially more on parent scales rather than teacher scales, whereas children of both groups showed similar improvements on neuropsychological measures. Also, the advantage of NF training could not be fully attributable to electrophysiological mechanisms in at least half of the subjects, but was rather mediated by unspecific factors such as parental support. Besides strengths of having a control condition with a similar technique (both were behavioral therapies aiming to increase self-awareness and control), duration, time spent in sessions and contact provided to the parents and assessing other factors that might confound the effect of NF, important limitations of this study are the lack of randomization of the groups and the appropriateness of the control condition as it is a group intervention with different settings.

It is difficult, if not impossible, to frame a double-blind design for NF, as it requires both the clinician's and the patient's cooperation, and blinding the clinician would hinder

the procedure. So, although a double-blind randomized placebo-controlled study is the ultimate study design to overcome the limitations listed above, it is not clinically applicable. Instead, Gevensleben et al. conducted a randomized controlled trial with 102 children, where the active study group received NF and the control group received computerized attention skills training (22). To overcome the major limitations of the previous studies, no parental counseling, medication and cognitive skills training were provided, the parents were not overtly told about the treatment the child was receiving and both groups were asked to practice the gained skills in various settings. The response rate, defined as 25% decline in ADHD rating scale in the NF group was reported to be 52%, whereas the control group's was 29%. Improvements in the parent-rated ADHD rating scale were around 25-30% in the NF, and 10% in the control group with significant difference for the total score, inattention and hyperactivity/impulsivity. The calculated ES was 0.60, which corresponds to moderate ES. The improvements in the teacher ratings were significant for total score and inattention but not for hyperactivity/impulsivity, and the ES was calculated as 0.40-0.64. Gevensleben et al. expanded their study to overcome the potential effects of the unintended mechanisms during NF treatment, by showing neural changes after treatment (31). From their original cohort that consisted of 102 patients, 72 were eligible for an EEG study. They stated that in contrast to control training, NF led to a reduction of theta activity. In the 6-month follow-up of the same population, Gevensleben et al. reported that 50% of children in the NF group were still responders and the ES for NF was 0.71 (32).

Arns et al. performed a meta-analysis that included 15 studies with diverse study designs and a total of 1194 subjects and concluded that the ES of NF for inattention, hyperactivity and impulsivity was 0.80, 0.39 and 0.68, respectively (33). Although the results of this meta-analysis seem promising, they should be interpreted with caution as nine out of fifteen studies included patients who also used concomitant psychostimulants.

To sum up, research shows that NF may be seen as a potentially promising treatment option, with one good conducted randomized controlled study by Gevensleben et al. (22). Besides several strengths in the method as random assignment to active or suitable controlled treatments with a reasonable sample size, comprehensive multi-informant evaluations with appropriate blinding and similar expectancies of improvement, the researchers showed that NF was superior to control treatment with ES for between-group comparisons not extending beyond the range of "medium". Pine comments that until the effects of the Gevensleben and colleagues' study are convincingly replicated, child and adolescent psychiatry field is not ready to recommend NF as a therapy for ADHD (34). Besides having much lower ES than conventional stimulant treatments, some factors also limit the application of NF: (a) It requires the patient to sit still for a predefined time period, which might as well be problematic for children with severe hyperactivity; (b) Most NF treatment sessions require approximately 4-6 months for adequate responses and during this time, the child may fall behind his/her peers; (c) It is an expensive treatment modality with around 30-50 treatment sessions and no payback from

government that requires careful utilization and promotion to prevent the readily exhausted family from financial burden; (d) There is paucity of studies on the long-term efficiency and if required, life-long treatment with NF is neither more economic nor more feasible than medication; (e) NF treatment is not free from side effects and was shown to be associated with seizures, manic behavior, anger and irritability, increases in depression, anxiety and agitation, fatigue, sleep disturbance, emotional lability, obsessive compulsive symptoms (OCD) symptoms, tics, somatic symptoms (e.g. headaches, nausea, twitches), decline in cognitive functioning, temporary disorientation or dissociation, enuresis and incontinence (35). Beyond all this, our knowledge of the etiopathogenesis of ADHD rests on mainly dopaminergic systems and brainwaves are not a major contributing etiological factor.

Heavy Metal Chelation

Heavy metals such as lead, mercury and aluminum are neurotoxic, and heavy metal poisoning is known to cause various central nervous system symptoms such as irritability, excitability, shyness and cognitive disability (36). The roles of these metals have been investigated in the etiology of ADHD.

Studies exploring the relationship between ADHD and lead, commonly yielded results that endorsed the association between blood lead level and symptoms of the ADHD. There is evidence that lead alters midbrain/striatal dopamine functioning as well as gene expression in the striatum (37), so the neurotoxic effect of lead on the dopaminergic neurotransmitter system may be implicated in the pathway to ADHD. Wang et al. conducted a study on 630 children with ADHD and 630 controls and correlated ADHD to childhood lead exposure (38). In a study including 1778 children, Ha et al. found that blood lead level was significantly associated with Conners' ADHD score ($p < 0.0001$) and that blood lead levels correlated to the presence of ADHD in a borderline trend ($p = 0.07$). Similar relationship could not be demonstrated for mercury (39). Although the findings suggest that lead might be an etiological factor in the development of ADHD in some patients, the lack of vigorous data in this field holds us back from drawing absolute conclusions.

Nicolescu et al. investigated the effects of heavy metal exposure, namely lead, mercury and aluminum, on ADHD in 83 children in an environment known to be polluted with lead (40). They found borderline to significant association between lead levels and ADHD, but failed to show any association of mercury or aluminum with ADHD. Furthermore, they stated that even levels of lead that are below 10 mcg/dl (which indicates low exposure) are related to ADHD as shown by changes in a neurocognitive test battery and questionnaires structured according to ICD-10 and DSM-IV.

Contrasting with the above-mentioned study, Cheuk and Wong demonstrated that high mercury level was associated with ADHD in 52 children with ADHD and 59 controls (41). They stated that after adjusting for confounding variables, children with blood levels of mercury above 29 nmol/L had 9.69 times (95% CI 2.57-36.5, $p = 0.001$) higher risk of having ADHD, while the suggested treatment threshold for mercury poisoning is 175 nmol/L (42).

These findings led researchers and clinicians to seek for an alternative treatment, namely, chelation therapy. This has

gained significant popularity in the field of autism, regardless of the scientific basis that autism is not related to mercury poisoning. Besides, chelating agents are far less than innocent and are shown to be causing cognitive problems in rats (43). Even more, some serious side effects, such as Stevens-Johnson syndrome (44) and even death (45) has been reported with the use of these agents.

The neurotoxic effects of heavy metals on cells are permanent and irreversible, which further limit the benefits of chelating agents. Yet, any clinical trial aiming to investigate the potential use of chelating agents has been suspended with the claim that it is unethical and carries more than minimal risk and offers no demonstrable benefit (46). Although heavy metal chelation should be avoided, environmental prevention of heavy metal contamination might be promising in the prevention of ADHD and requires further work-up.

Hyperbaric Oxygen Therapy (HBOT)

Although the use of HBOT in ADHD lacks any scientific basis and a literature search including case reports and case studies did not yield any results, its use in ADHD, after autism, is an increasing trend. Its effects on autism are inconsistent (47) and HBOT is not without adverse effects - barotrauma to lungs, paranasal sinuses or teeth, oxygen toxicity, convulsions (48) and even death (47,49).

There is no proof for the use of HBOT in the treatment of ADHD and thus, should be avoided.

Dietary (Nutritional) Complementary and Alternative Treatments

Dietary supplementation and elimination diets are the most commonly applied CAM interventions (50). Supplementation of long-chain polyunsaturated fatty acids (PUFA), zinc, iron, magnesium and vitamins, and elimination diets will be reviewed.

a) Long-Chain Polyunsaturated Fatty Acids

PUFA which include eicosapentaenoic acid (EPA, an omega-3 acid; ω -3), docosahexaenoic acid (DHA, ω -3) and arachidonic acid (ω -6) are important structural components of the neural membranes. They also play critical roles in neural, enzymatic and anti-inflammatory functions (51).

Although the effects of PUFA on brain mechanisms are not clearly defined, some researchers suggested that PUFA deficiency might be important in the etiology of ADHD. First line of evidence for this hypothesis came from studies comparing plasma and/or red blood cell PUFA levels in subjects with ADHD and normal controls. These studies showed lower levels of both ω -3 and ω -6 PUFA in the ADHD group (52-55). Also an experimental study suggested that mesolimbic dopamine pathway was more active and mesocortical dopamine pathway was less active in ω -3 PUFA deficient rats (56). This finding was compatible with dopaminergic hyperactivity in mesolimbic pathways and dopaminergic hypoactivity in the prefrontal cortex observed in ADHD (57). After open-label essential fatty acid supplementation trials in children with ADHD, which usually showed raised PUFA blood levels and improved symptoms, randomized controlled trials were conducted.

The first two placebo-controlled studies tested the effectiveness of ω -6 PUFA (linoleic acid, LA) and gamma-linolenic acid (GLA). In the first, Aman et al. supplemented 31 children in

a double-blind, placebo-controlled crossover study for four weeks each (58). Out of 42 measures including rating scales and cognitive and motor measures, only parent report attention problems score was definitely positively affected by the supplementation. The authors interpreted the results as minimal or no improvements in hyperactive children. In the second study conducted by Arnold et al. in a double-blind placebo-controlled crossover design, 18 boys with ADHD were observed (59). They received 1 month each of placebo, d-amphetamine, and ω -6 PUFA. Parent ratings did not differ, but PUFA effect was between that of placebo and stimulant in only Teacher Conners' hyperactivity factor. Arnold reported that higher behavior problem scores were correlated with lower levels of blood GLA measured after the intervention. Small sample size and relatively short duration of the interventions make this study inconclusive.

The following two studies tested the efficiency of ω -3 supplementation (DHA alone or DHA+EPA) in ADHD in double-blind, placebo-controlled designs. Voigt et al. evaluated 54 children with parental ratings and neuropsychological tests (60). Baseline plasma phospholipids for DHA were particularly low compared to normal children, and at the end of 4-month supplementation, the DHA concentrations increased significantly and were higher than those in the control group. No significant outcomes between groups were observed on behavior and cognition and there was no correlation between PUFA status and treatment outcomes. Hirayama et al. supplemented 20 children with 3600 mg DHA and 700 mg EPA and 20 children received placebo (61). As a result, except for errors of commission in the continuous performance test and visual memory, the two groups were statistically not different, yet interestingly, the placebo group was the one to perform better in the two aforementioned tests. The authors linked these interesting results to a probable learning effect.

Increased number of studies showing co-occurrence of low levels of different PUFAs in blood and relative inability to display anticipated positive results with supplementation with only ω -3 or ω -6 PUFAs led to recent studies which tested the effect of mixtures of ω -3 and ω -6 PUFAs. For this aim, several randomized double-blind placebo-controlled studies have been conducted.

Stevens and colleagues studied 18 children with ADHD, most of whom were under concomitant stimulant medication maintained during the study, except on testing days (62). They found positive results in conduct subscale scores and attention for the 4-month combined PUFA treatment. No positive impact on cognition measures was demonstrated for the PUFA group. Sinn and Bryan compared three randomly assigned treatment groups (PUFA only, PUFA plus micronutrients and placebo) for 15 weeks (63). Both PUFA groups showed significant improvement in parent-rated ADHD symptoms and oppositional behavior as well as a cognitive test measuring ability to switch and control attention.

Some studies revealed that subgroups of children with ADHD benefited more from PUFA treatment. Johnson et al. assessed the effects of mixed ω -3 and ω -6 PUFAs in 75 subjects, half of whom were inattentive type ADHD and the major-

ity had comorbid developmental disorders and found that clinically meaningful response tended to be more frequent in a subgroup with comorbidities such as reading/writing disorders, developmental coordination disorder, borderline intellectual functioning (and autistic symptoms) and was lacking in ODD (64). On the other hand, Gustafsson et al. found that children with comorbid oppositional behavior responded better to EPA supplementation, although behavioral ratings of the whole ADHD group were not statistically different from the placebo group (65). No change in hyperactivity scores was observed.

Although various double-blind, placebo-controlled studies did not yield the anticipated behavioral and cognitive positive results, which were suggested by open-label studies, PUFA treatment still remains to be an economical option, with minor associated adverse effects (e.g. fishy after taste, nausea, diarrhea) and possible efficacy in a minority of patients with ADHD. The results also suggest that supplementation with combination of long-chain ω -3 and ω -6 PUFAs is more promising than with ω -3 or ω -6 alone.

b) Zinc and Iron

As a trace element, zinc is a cofactor to many cardinal enzymes, besides, it is an important modulator of neuronal excitability (66). Most recent findings show that the dopamine transporter is regulated by zinc, which directly interacts with the transporter protein (67). So far, it is well known that zinc deficiency is linked to problems in cognitive development evident by alterations in attention, activity, neuropsychological behavior and motor development (68).

The putative role of zinc in the etiology and treatment of ADHD has led to many research studies, especially after a positive correlation between zinc level and amphetamine response in children with ADHD (69). Also, plasma zinc level was found to be low in children with ADHD when compared to controls (70,71). In order to evaluate the studies testing the effectiveness of zinc supplementation, it is of help to know the recommended daily allowance (RDA) of zinc in children and adolescents. RDA for zinc is around 5 mg for the ages between 4-8 and 8-11 mg for older children. Tolerable upper intake levels of zinc are reported as 12, 23 and 34 mg between the ages 4-8, 9-13 and 14-18 years, respectively (72).

To test whether zinc supplementation was effective in the treatment of ADHD, Bilici et al. designed a placebo-controlled, double-blind trial with 400 patients with ADHD assigned to either placebo or zinc sulfate (40 mg/day elemental zinc) for 12 weeks, but analyzed the results of 193 patients, as more than 50% dropped out of the study (73). The high dropout rate was not related to high levels of zinc as the dropout rates were not statistically different between the placebo and the active treatment group. With the outcome measures being Attention Deficit Hyperactivity Disorder Scale (ADHDS), Conner's Teacher Questionnaire (CTQ), DuPaul Parent Ratings of ADHD, they reported a significant decline in scores in the impulsivity, sociability and hyperactivity subscales of ADHDS and in the conduct and hyperactivity subscales of CTQ. A regression analysis showed that the decline in ADHDS subscales were significantly affected by age, body mass index and baseline free fatty acid and zinc levels, reminding that zinc acts as a

cofactor for in a number of essential fatty acid metabolizing enzymes. As zinc deficiency is endemic in Turkey (74) and zinc deficiency status of the participants was not reported, these finding may as well be interpreted as the correction of zinc deficiency other than the treatment of ADHD and may itself pose little benefit to zinc non-deficient children with ADHD.

Akhondzadeh et al. assigned 44 patients with ADHD to either methylphenidate (MPH) plus zinc or MPH plus placebo in a double-blind, placebo-controlled trial in order to evaluate the effects of zinc as an adjunct to MPH (75). Zinc sulphate group received 1 mg/kg/day MPH plus zinc sulfate (15 mg/day elemental zinc) and the placebo group received 1 mg/kg/day MPH plus sucrose for 6 weeks. At the end of 6 weeks, with 40 eligible patients remaining for analysis, zinc group outperformed the placebo group on measures of both ADHDS scores rated by parents and teachers. This study has the same limitation with the previous one, zinc deficiency is also endemic to Iran (74), and the researchers did not consider the possibility of zinc deficiency in the participants.

Finally, Uckardes et al. evaluated the effects of zinc supplementation on ADHD in low income primary school children in a double-blind, placebo-controlled study (76). Of 226 children, 218 completed the study, and only the zinc levels of 114 children could be measured at baseline. Zinc levels of the ADHD and control groups were not statistically different from each other and the means indicated a non-zinc deficient state. The children were either assigned to placebo or 15 mg/day elemental zinc for 10 weeks and the changes were measured by the parental and teacher Conners' Rating Scales (CRS). At the end of the study, there was no change in teacher-rated scores, while the attention and hyperactivity scores in the zinc and oppositional behavior in the placebo group decreased significantly in the parent-rated scales. This study partially overcomes the previous limitation and suggests that zinc may work in children without zinc deficiency also.

As zinc is an essential ingredient of human diet, and symptoms seen in zinc deficiency such as altered attention, activity and neuropsychological behaviors seem to be related to the symptoms of ADHD, dietary supplementation with RDA of zinc might be of benefit, yet without clear evidence.

Iron is also stated to be of importance in the development of ADHD. Iron deficiency is known to cause attentional problems and decreased cognitive processes as iron is the cofactor of tyrosine hydroxylase, which is involved in the synthesis of dopamine (77). Besides, Erikson et al. investigated the effects of iron deficiency on dopaminergic system in rats and they found a decrease in density of D2 dopaminergic receptors in nucleus accumbens, which is one of the regions known to be affected in ADHD (78). Role of iron in dopaminergic mechanisms led authors to investigate the possible role of iron deficiency in the etiopathogenesis of ADHD (79) and iron supplementation in the treatment of ADHD (80).

Until today only a limited number of studies tested the effectiveness of iron supplementation in the treatment of ADHD. In a preliminary study with no control group and small sample size, Sever et al. reported an improvement in symptoms of ADHD after iron supplementation (0.5 mg/kg/day elemental

iron) in non-anemic children, as measured by parental CRS (81). In the following study, Konofal et al. recruited 23 patients and randomized the patients to either oral iron (16 mg/day elemental iron) or placebo (80). Their results were mixed; they reported a significant decrease in the scores of the ADHDS and in the Clinical Global Impression-Severity scores, but they failed to show a decrease in the parental and teacher CRS. The authors concluded that iron supplementation resulted in improvement only in children with low ferritin levels.

As a conclusion, iron supplementation should not be recommended to all children with ADHD but only to those with concomitant iron deficiency.

c) Vitamins and Magnesium

It is well known that many vitamins play essential roles in the synthesis of the neurotransmitters. To name some, vitamin B6 is the cofactor of the enzyme aromatic amino acid decarboxylase, which takes place in the synthesis of dopamine and serotonin, vitamin C is the cofactor of dopamine beta-hydroxylase, which converts dopamine to noradrenaline, and tetrahydrobiopterine is the cofactor of tyrosine and tryptophan hydroxylases, which take place in the synthesis of dopamine and serotonin, respectively (82,83).

Early interventions regarding vitamin supplementation were composed of mega doses of vitamins, which were proved to be potentially hazardous, leading to hypervitaminosis (84) and elevated transaminase levels and hepatotoxicity (85). Mega doses of vitamins were shown to be at least ineffective (86) and in some cases caused worsening of the symptoms (85).

Further investigations focused on a more specific vitamin, namely vitamin B6, possibly due to its role in the synthesis of dopamine. Trials aiming to test for the effectiveness of vitamin B6 on symptoms of ADHD also included magnesium in their trials given that hypomagnesemia is related to central nervous system irritability, confusion, disorientation and depression. Magnesium alone is shown to be low in children with ADHD also. Kozielc and Starobrat-Hermelin investigated 116 children with ADHD and concluded that 95% were magnesium deficient (87).

Mousain-Bosc et al. conducted a study and concluded that magnesium plus vitamin B6 improved the symptoms of ADHD in a 8-week trial in 40 children (88). Although the children improved, they had a tendency to turn to baseline after the treatment was stopped, which was postulated to be related to decreasing magnesium levels.

As magnesium deficiency shares some symptoms with ADHD and some patients with ADHD are shown to have magnesium deficiency, magnesium is of clinical utility in deficiency states and is observed to correct the associated symptoms of ADHD. The studies using vitamin B6 did not test for the isolated effects of vitamin B6, so the improvements seen in these studies are attributable to neither magnesium nor vitamin B6.

d) Elimination Diets

Dietary elimination of certain foods, additives and ingredients for moderating the symptoms of ADHD has been in the agenda of ADHD long before. One of the most known of these diets is the 'Feingold diet', that relies on the idea that elimination of certain additives, namely salicylates, artificially

added colors, flavors, preservatives would attenuate the symptoms of ADHD. Numerous double-blind studies were unable to show additional benefit of the Feingold diets beyond the normal placebo effect (89). Subsequently, other nutrients including sugars were blamed in the etiology of ADHD and many diets of no use were formed for the treatment.

Studies testing the hypotheses about the effect of diet on ADHD demonstrated efficacy only in subgroups of patients selected for history of food sensitivity or atopic constitution (90). Besides, these kinds of diets put considerable amount of strain on the whole family and are difficult to carry on (91). It is advised to consider elimination diets only in the face of a known or suspected reaction to certain types of food, ingredients or additives.

Conclusion

Although high use rate and thousands of links on the internet to over-the-counter products and CAM treatments that are defined as "definitive cure" for ADHD, there exists very low scientific evidence on the efficacy of these modalities. Further, there is nearly no reports on their long-term effects and side-effect profiles. Despite several drawbacks restricting its use, EEG feedback seems to be a potentially promising agent which needs to be tested with further large, properly controlled, randomized studies. Although results for PUFA supplement are equivocal, especially combined long-chain ω -3 and ω -6 PUFA may be considered for some patients with ADHD. Zinc, iron and vitamin supplementation may be recommended in deficiency states and elimination diets only in the face of a known or suspected reaction to certain types of food. Heavy metal chelation, hyperbaric oxygen and megadoses of vitamins should be avoided.

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