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Levels of Zinc, Magnesium and Iron in Children with Attention Deficit Hyperactivity Disorder

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Research Article

Abstract

Background: Attention deficit hyperactivity disorder is a common multifactorial and complex neuro developmental disorder often persisting through adolescence and adulthood. Indications of nutritional treatments with omega-3 fatty acids, and minerals like zinc, magnesium, iron, etc. are gaining importance. We therefore sought to estimate ,and compare the mineral content of zinc, magnesium, and iron in the plasma of ADHD diagnosed children with normal non-ADHD children, and establish a correlation if any with the disorder symptoms.

Methods and findings: Psychiatric evaluation was performed using the Diagnostic and Statistical Manual IV and plasma elemental analysis using atomic absorption spectrophotometry. Low levels of zinc, magnesium and iron were observed in ADHD children when compared to their healthy controls.

Conclusion: Children with ADHD exhibit lower concentrations of plasma zinc, magnesium, and iron as compared to normal controls which could be correlated with the disorder symptoms in ADHD.

Keywords: Hyperactivity; Children; Minerals.

Abbreviations

ADHD: Attention Deficit Hyperactivity Disorder; CPRS: Conner's Parent Rating Scale; TRS: Teacher Rating Scale; Zn: Zinc; Mg: Magnesium; Fe: Iron

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a well-recognized multi-factorial behavioral disorder characterized by hyperactivity, emotional instability, poor co-ordination, short attention span, poor concentration, impulsivity, and problems in conduct and learning. The disorder often persists through adolescence and adulthood. Although the rate of ADHD falls with age, at least half of the children will have impairing symptoms in adulthood [1]. Also though the etiology links ADHD with a complex association of genetic, biological, neurological and environmental factors, a considerable amount of research has been focused upon the nutritional deficiencies too. Epidemiological studies show that the disorder is linked to the deficiency of several micro-nutrients like zinc, magnesium, iron and polyunsaturated fatty acids [2].

Zinc (Zn) affects the metabolism of dopamine indirectly as it serves as a co factor to prostaglandins and neuro transmitters and melatonin [3]. Furthermore the enzyme desaturase requires Zn as a co factor. This enzyme acts on the essential fatty acids linoleic and linolenic acid which are an integral part of the neuronal membranes. About 15% of Zn is found present in the synaptic vesicles, thereby making it crucial for brain development and modulation of synaptic transmission [4]. Its concentration in the body affects the different functions of hormonal metabolism, cell energy requirements, cell stabilization and antioxidant activity. Earlier researches on the pediatric population have explored the distinctive role of Zn which seems to negatively correlate with the severity of their inattention [5]. Experiments on supplementations with Zn sulphate were beneficial as compared to placebo as also one with Zn monotherapy [6,7]. When given in conjunction with stimulants, the benefits to the patient were enhanced and required 37% lower doses of the stimulant as compared to the placebo [8].

Several enzymes of the neurotransmitter metabolism also require Magnesium (Mg) as a cofactor to execute the neuronal functions. ADHD patients on stimulants were benefitted on supplementation with Mg [9]. Retention of brain ammonia content has been shown to lead to inattention, the disposal of which is rendered through Mg. Apart from this it is involved in the generation of ATP and synthesis of the essential fatty acid DHA, required for maintaining the structure and function of neuronal cells. An altered or inefficient memory processing, cognition, concentration, attention span along with intensification in symptoms of aggression, oxidative stress and fatigue have been mainly associated with Mg deficiency. Other observed symptoms include nervousness, irritability and mood swings. As these symptoms overlap with those experienced in ADHD, it has been theorized that ADHD children would also be Mg deficient [10,11].

An earlier research with 52 ADHD children (age 1-15 years), showed that 30 of them had 17-25% lesser concentrations of intracellular Mg when compared to controls [12]. Furthermore these decreased concentrations of Mg were found associated with increase in hyperactivity, shorter attention span accompanied by sleep disturbances [2].

Apart from Zn and Mg, concentrations of iron (Fe) are also implicated in the metabolism of neuro transmitters, thereby proving beneficial in neuro developmental disorders. Fe being a cofactor in monoaminergic neurotransmitter metabolism is considered beneficial in the treatments of neuro developmental disorders. Sleep disturbances in ADHD children makes iron stores to be depleted, and replenishment necessary [9]. Deficiency of Fe in childhood has shown to affect development of the central nervous system, leading to behavioral disorders and mental retardation. Mental retardation, Restless Leg Syndrome (RLS), seizures, breath holding, sleep disturbances and behavioral problems have all been linked to Fe stores in the body. It has been observed that as compared to 18% of controls, a whopping 84% of ADHD children had low deposits of serum ferritin which also correlated with the severity of symptoms in ADHD children. These low levels of ferritin correlated with severity in ADHD symptoms and greater cognitive defects when assessed by Conner's parent rating scale (CPRS) [2,13].

Tyrosine hydroxylase is a crucial enzyme in the synthesis of dopamine which requires Fe as a cofactor. Therefore, both cognition as well as behavioral outcomes could well be related to the deposits of Fe in the body [14]. Earlier studies show that almost 47% of ADHD children who were not anemic also had low serum ferritin levels when compared to controls. This low level also correlated with the severity of ADHD symptoms [15]. An Israeli study on ADHD children shows a significant association with the CPRS though nothing could be attributed to the Teacher Rating Scale (TRS). Studies in France observed greater deficits than in the US counterparts with associations in cognitive deficits too [15]. Low concentrations of serum ferritin not only correlated with the baseline levels of inattention, hyperactivity, and impulsivity but also with the doses of the stimulant amphetamine which would be required for optimization of a clinical response. This makes serum ferritin and supplementation of Fe to be a potential predictor for intervention in optimizing the existing stimulant therapy to ADHD subjects [16].

Our interest laid in the levels of minerals especially Zn, Mg and Fe in the blood of these ADHD children. Though additional studies are warranted, supplementations have proved to be beneficial. We therefore aimed to conduct this study to look at the supposition that trace element deficiencies exist in Indian patients with ADHD which may lead to a deterioration of ADHD symptoms in these children.

2. Materials and Methods

2.1 Subjects

Forty seven ADHD and an equal number of normal non-ADHD children aged 5-12 years belonging to the mid socio economic group were enrolled for the study. This study was conducted at the Bharati Vidyapeeth English Medium School at Dhankawadi, Pune. All children in the study were matched for age and gender and had similar lifestyle and dietary habits belonging to the same geographic region.

2.2 Study design

Of the 47 ADHD children enrolled, only 41 children completed the blood test due to reasons such as fever, drop outs or fear of blood collection by the child. All children underwent a standard clinical assessment comprising a psychiatric as well as clinical psychological evaluation, a structured diagnostic interview, and a medical and personal history evaluation. Parents or legal guardians and teachers responded to oral presentations by the scientist, psychiatrist and clinical psychologist prior to enrolling for the study. All parents/legal guardians gave written consents, and a trained clinical psychologist, assessed the children with the help of Diagnostic and Statistical Manual (DSM IV) as per the guidelines given by American Association of Psychiatry [17]. ADHD rating scale of Du Paul [18] was used to assess hyperactivity of the child. The teacher rating scale to assess the disruptive behavior of the child was done according to the questionnaire by Du Paul et al. [19].

2.3 Ethical clearance

The ethical committee of Bharati Vidyapeeth Medical College approved the study design and protocol.

2.4 Exclusion criteria

Children previously diagnosed with a psychiatric disorder, organic brain disorders, epileptic seizures, current abuse or dependency on drugs or mental retardation were excluded from the study.

2.5 Blood analysis

Blood samples (3-5 ml) of the ADHD as well as normal control group children were collected and plasma stored at -80°C for further analysis. Approximately 1-2 ml of blood was taken for estimating hemoglobin levels. Of the 47 ADHD children, blood collection and analysis could be done for 41 samples due to difficulties in blood withdrawal and other valid reasons. Elemental analysis was done using the automated atomic absorption spectrometry.

2.6 Statistical analysis

We used Paired *t*-test to compare between patients and control as regards plasma Zn, Mg and Fe values.

3. Results

Psychological screening of school students led to the identification of 47 classic ADHD, after a positive result in at least two situations namely school, home or clinical assessment. The demographics of these are given in Table 1. The physical characteristics of height and weight, of all the children of both groups-ADHD as well as the control, were within normal limits for their age. All the children belonged to the middle socioeconomic class. The average hemoglobin concentrations were 12.094 mg/dl for the normal controls and 11.883 mg/dl for the ADHD children. Though not significant, there was an apparent lesser concentration of hemoglobin in the ADHD group as compared to the normal control group. Elemental analysis showed that Mg, Zn, and Fe concentrations were significantly lower in ADHD children when compared to their healthy counterparts with p-values 0.049255, 0.006226 and 0.000131for Mg, Zn and Fe, respectively as seen in Table 2. When measured on aspects of inattentiveness, impulsivity and the teacher rating scale, the control group fared better than the ADHD group (Table 3). The inattentive and impulsivity positive score was higher (14 and 19) for the ADHD children compared to the normal controls (4 and 9). Also the inattentive and impulsivity negative score (9 and 4) was lower for the ADHD children compared to the normal controls (20 and 15). The teacher rating scale too showed a higher value for the ADHD children (18) when compared to the (9) control children.

Table1. Demographic characteristics, and blood hemoglobin of the ADHD and normal children.

	Control	ADHD
Age 5-12 years	171	47
Males	94	36
Females	77	11
Taken for Blood Analysis	41	41
Males	32	34
Females	9	7
Average Hemoglobin	12.094	11.883

4. Discussion

Though many influencing factors have been implicated for the hyperkinetic behavior and inattention in ADHD children, a few nutritional factors have gained attention in the past recent years. Of these food colors, preservatives, poly unsaturated fatty acids (PUFAs) and minerals represent the major nutritional considerations to be looked into [20]. Inappropriate maternal nutrition has been linked to neuronal developmental deficits in the child.

Though our study includes a few samples and dietary intakes of individual elements not taken into consideration, it yet gives us leads towards understanding the problem. Our data adds more credence to the role of nutritional Zn, Mg and Fe in the expression of ADHD symptoms. Significantly low levels of Zn (p value 0.006226), magnesium (p value 0.049255) and Fe (p value 0.000131) were found in ADHD children as compared to their healthy controls as seen in Table 2. Deficits could be well correlated to lower values of hemoglobin concentrations (11.88365 mg/dl) in the ADHD children when compared to their healthy counterparts (12.094 mg/dl). Also lower levels of plasma minerals correlated to the scores of inattention, impulsivity and teacher rating scale Table 3.The positive scores were higher for the ADHD children and lower for the controls. Conversely, the negative scores were lower for ADHD as compared to the controls. Also the teacher rating scores showed that children with ADHD had problems not faced by the controls.

Our results are quite in agreement and compatible with previous reports .Though an association could be established, we cannot attribute a causal relationship for the same. Considering the several injuries, infections, allergies in these children, it could also be considered as an effect rather than the cause [5].

Children taking stimulants and experiencing appetite suppression may have decreased caloric intake and be at an increased risk of insufficient dietary intake of Zn, as well as Mg. The levels of Zn may be lower

Table 2. Elemental analysis in the plasma of ADHD and normal control children.

Element	n	Control	ADHD	p-value
Mg Mean mg/l ± SD	41	23.92683 ± 2.95288	23.20833 ± 3.25483	0.049255
Zn Mean mg/l ± SD	41	0.49829 ± 0.140337	0.463958 ± 0.155094	0.006226
Fe Mean mg/l ± SD	41	1.017073 ± 0.294026	0.952083 ± 0.314872	0.000131

*The concentrations of plasma zinc, magnesium and iron in the ADHD children were significantly lower when compared to non-ADHD children

Table 3. Parent and Teacher rating scores for ADHD and normal control children.

Group	Inattentive Positive Score	Inattentive Negative Score	Impulsivity Positive Score	Impulsivity Negative Score	Teacher Rating Scale Score
ADHD	14	9	19	4	18
Control	4	20	9	15	9

*The control children showed lower scores for inattention, impulsivity and the teacher rating scale in patients with ADHD secondary to differences in dietary intake, differences in absorption, or other mechanisms. Zn deficiency could probably mean a lesser availability of nutrients for pathogens as Zn is known to fight infections and also inflammation, which are elevated in ADHD children. An alternate explanation could involve increased Zn-wasting in the urine of children with ADHD. Earlier researches report only 1% of Mg is located in the extracellular space and one-third of magnesium that is present in bone gets freely exchanged with the plasma. Inadequacy of intakes may therefore go unnoticed, as the mineral concentrations in the plasma or serum may be maintained by bone stores.

Though combined treatments are preferred, one-third of patients yet remain symptomatic. Nevertheless supplementation may complement medication and its response in those with deficiencies [21,22].

But earlier data does not establish a tolerable level of Zn that could be supplemented to ADHD children, making it yet not ready for clinical applications. Also certain cases of gastro-intestinal upsets and toxicity may not put it ready for usage yet. Moreover a combination of Zn, Fe and Mg along with other nutrients may effectively help in alleviating the symptoms of ADHD. When Zn is combined with amphetamine drug used in ADHD, the outcomes were better, re-affirming the role of micronutrients in this disorder [8]. Therefore considering children presenting symptoms with ADHD, for appropriate dietary inclusions could be encouraged by clinicians to help alleviate the symptomatic condition. Presently the current evidence endorses the view that ADHD children receiving mineral supplementation irrespective of their age and the formulation perform psychologically better when compared to a placebo [23].

Certain nutrient deficiencies appear to be observed mostly in certain regions, for example Zn deficits are more pronounced in the Middle East than US. As normal Zn levels in the body do not depict its levels in the CNS, the concentration in hair and urine also needs to be assessed to get a clearer picture [21].

Also in the ADHD children of Arabian Gulf countries, an abnormally low concentration of Fe stores was observed when compared to controls. This has been inversely correlated with poor cognition, instability in psychomotor functions, learning deficits, poor social emotional stability, etc. [24]. Our results are in consistence with this finding.

ADHD children are at a considerable risk for neuro developmental problems in the future. Therefore the association between different elements and their lower concentrations needs to be explored further in longitudinal studies. Other dietary factors inhibiting the absorption of these elements must also be considered to draw logical conclusions [24,25]. The present study indicates that low Fe, Mg and Zn deficiency could be associated with ADHD symptoms and its pathophysiology and therefore should be measured whilst evaluating children with ADHD [26].

5. Conclusion

Our findings though only from a single school may be observed commonly amongst the other populations too. Further well defined randomized placebo controlled studies from different areas may give us hints for future directions. Moreover as the subjects were from a mid-socioeconomic group, the deficiencies could be apparently noted. It is possible that ADHD children from a different socio-economic class may show varied results. Also different genealogies, cultural patterns, food habits and socio-economic backgrounds, together may affect the concentrations of these elements. A future diversity in sampling is therefore called for to interpret findings and give them a generalized logical conclusion. Much research in this area yet needs to be carried out to establish tolerable levels of each element in ADHD in order to make it clinically dispensable. Supplementing these minerals in childhood could in future become a simple, inexpensive, effective, safer and feasible approach for tackling the issue. Nutritional alterations therefore remain a very promising complementary treatment. Combination treatments of critical elements could also be considered.

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