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Magnesium: An Intervention for Attention Deficit Hyperactivity Disorder

Laura Terrazas*

Department of Nutritional Sciences, Rutgers University 310 W Hamilton Ave Campbell, CA. 95008, USA

***Corresponding author:** Laura T, Department of Nutritional Sciences, Rutgers University 310 W Hamilton Ave Campbell, CA. 95008 USA, Tel: +831-334-3938; E-mail: lauraterrazas2@gmail.com

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Abstract

This article reviews magnesium as a potential intervention for treatment of comorbid anxiety, depression, emotional dysregulation and increase memory and learning in students with Attention Deficit Hyperactivity Disorder (ADHD). 72% to 96% of those diagnosed with ADHD are magnesium deficient. Deficiency has been linked to excitability in N-methyl-D-aspartate (NMDA) receptors which may increase depression and anxiety and decrease working memory; traits common in ADHD. ADHD is frequently compounded by mood disorders such as anxiety and depression. Magnesium has been successfully used to treat depression and anxiety. Research is needed to determine if magnesium is an option to treat ADHD.

Introduction

In 2011, Attention Deficit Hyperactivity Disorder (ADHD) affected 11% of children in the United States, 42% increase since 2003 and encompasses nearly one in ten children [1-4]. Worldwide rates are cited slightly lower, between two and five percent, possibly due to the differences between the International Classification of Diseases, Tenth Edition (ICD-10) and The American Psychiatric Association's Diagnostic and Statistical Manual (DSM) [2,5,6]. ADHD is frequently undiagnosed as the presentation has significant variability amongst individuals and is often considered invisible [4,7]. The DSM is used to diagnose inattentive, hyperactive-impulsive or combined ADHD. One manifestation that is common in those diagnosed with ADHD, yet is not a sign or symptom in the DSM-5, is emotional dysregulation. [6,7] Approximately 30-50% of those with ADHD are diagnosed with comorbid mood disorders of depression and/or anxiety which may lead to chronic mild stress (CMS) [6-8].

Working memory, which is at the heart of cognitive control, explains almost 50% of ADHD [9]. When impaired, attention lessens, learning decreases and stress in social situations increases [7,10,11]. Those with ADHD often present as typically developing students compared to their peers. Their actions can be mistaken as immature, disrespectful or irritating to others and create poor peer relations [6,12,13]. This may create a domino effect within a person with ADHD, leading to an emotional outburst, which further decreases working memory, creates behavioural problems, internalization issues and decreases verbal and spatial working memory [7,8,11,14]. As working memory decreases, the ability to self-regulate decreases and this is thought to lead to high rates of anxiety and depression associated with ADHD [11].

Financial impact of ADHD

ADHD has an annual childhood financial impact of $50 billion in the United States. Of that, $530 million is spent on the juvenile justice system and $22 billion on health care issues.2 Although ADHD is traditionally considered a childhood disorder, there is a rate of four to five percent that continues into adulthood. The annual adult cost approaches $130 billion, with $4 billion per year used to support the 15%-40% of adults with ADHD who are incarcerated [1,15,16]. Those with ADHD also have more missed school days, a higher dropout rate, higher healthcare needs and costs, more sick days from work and lower paying jobs [1,6,10]. This disorder has a significant impact on the person, the parents, the household and society.

Current method of treatment

The American Academy of Paediatrics recommend stimulant medication such as methylphenidate and amphetamines to decrease symptoms of ADHD [2,3,17,18]. These prescribed medications stimulate the prefrontal cortex which in turn reduces cognitive load and frees up working memory but have known side effects such as behaviour problems, aggression, nervousness, and loss of sleep [17,19]. In 2011, six percent of children in the United States were taking medication for ADHD [3]. Those diagnosed with ADHD had an average medication rate of 69% with some areas reaching 86% [3]. There is a low compliance rate for those who have comorbid disorders due to side effects such as anxiety and depression and at times stimulants are contraindicated [7,17].

In a yearlong study of adults with ADHD, to determine treatment efficacy, side effects and comorbidity of psychiatric disorders, Fredriksen et al. found that comorbid anxiety and bipolar disorder were less effective with medication [17]. Approximately one third of adults discontinued the medication noting side effects such as mood instability, nausea, agitation and anxiety [17]. Additionally, in a four-year study Fleming etal. found higher dropout rates; absenteeism; special education rates and health need costs, as well as lower academic achievement, for those diagnosed with ADHD and taking medication compared to those who were not treated with medication [20].

Magnesium in the body

Magnesium plays a ubiquitous role in the body and has important effects in the brain, nervous system, heart and skeletal muscles. It is involved in over 300 known functions including mood regulation, carbohydrate metabolism, pulmonary smooth muscle function and protein synthesis [21-23]. It is a necessary cofactor in over 600 enzymatic reactions, 325 of which occur in the brain [8,22].

Magnesium is currently used to treat pre-eclampsia, bronchial spasmodic asthma and cardiac dysrhythmia disease [24-28]. Adequate magnesium stores in the body are essential for normal brain function and its deficit may account for many neurological diseases [22,29-31].

Approximately 60% of the US population is deficient in magnesium and 68% do not consume the recommended daily allowance (RDA) for Magnesium see (Table 1) [21,22,29]. This is due to low magnesium levels in soil, water filtration, increased amounts of consumed processed foods, foods that block absorption, decreased supplementation, disease states, profuse sweating, and stress [22,23,32]. Refining and processing foods, result in the loss of 80-90% of magnesium and the promulgation of the Western Diet has increased the number of people who are deficient in magnesium worldwide [22,29,32].

Gender	Magnesium intake per day
Adult Males	420
Adult Females	360
Boys 14-18 years old	410
Girls 14-18 years old	360
Youth 9-13 years old	240
Children 4-8 years old	130
Children 1-3 years old	80

Table 1: The Recommended Daily Allowance (RDA) for Magnesium mg/day [21].

Assessing magnesium in the body

Evaluating magnesium in the body is challenging and magnesium values are not part of routine blood panels. Normal plasma serum levels are 1.5-1.9 mEq/L or 0.75-0.95 mmol/L but may not accurately reflect total body stores [21,22,32]. An equilibrium is maintained in the blood by resorbing magnesium from the bone stores. Approximately 0.3% of total body magnesium is present in serum with 50-60% in boney stores [22,33]. Homeostasis is ensured with resorption from these stores and when serum levels are low [22,23,33-35]. When total body magnesium is significantly depleted it may take weeks or years to replenish [32,35].

As serum magnesium levels don't always reflect total body magnesium stores, an easy and accurate method that more closely measures total body magnesium is needed. Several studies have suggested a more appropriate way to measure red blood cell magnesium levels or perform magnesium load testing [22,23,32,33,36]. A more recent comparison study looking at serum, red blood cell and hair magnesium measurements found that hair levels are a better surrogate for total body magnesium stores [37]. In a further study by El Baza et al. it was shown that using Coupled Mass Spectroscopy (ICP-MS), to measure hair magnesium levels correlated most closely with total body stores. Unfortunately, this test is only offered in limited locations and is not cost effective [38].

Discussion

Influence of magnesium on learning disabilities and mental health

Magnesium is a crucial mineral and appropriate levels in the body are essential for normal cognitive function and mental health [22,29,39]. This is true for all people but may be more so for those who suffer from ADHD. Seventy-two to 96% of those diagnosed with ADHD have been found to be significantly deficient in magnesium [37,38]. Studies have shown that in these patients, supplementation with magnesium improves attention and working memory and decreases anxiety, depression and emotional dysregulation [14,17,22,29,38-42]. El Baza et al. has suggested that magnesium deficiency may be at the root of the behavioural manifestations seen in patients with ADHD [38]. This may be multifactorial and related to the fact that magnesium's inhibitory role neuromuscular junction [31,38]. Magnesium deficiency may also lead to dysfunction of the amygdala, which may increase anxiety and depression and in turn lead to hypothalamic dysregulation and the ability to process information, further decreasing working memory. This is thought to be mediated by magnesium's effect at the level of the N-methyl-D- aspartate (NMDA) receptors [8,22,31,38-40,43].

N-methyl-D- aspartate (NMDA) is a common receptor that has both inhibitory and excitatory function in different regions of the brain [22,39,43]. It is also involved in controlling synaptic plasticity, mood, learning and memory. The interplay between different receptors in the brain is mediated by ion fluctuations and low magnesium levels play a role [8,22,42,43]. When magnesium stores are low, γ-aminobutyric acid (GABA) receptor function is inhibited and may lead to the behavioural inability to calm one's self efficiently [22,43]. This chain of events this thought to cause a decrease in neural plasticity, learning and memory, as well as depression and anxiety [22]. Eby notes that 60% of clinical depression is considered treatment resistant and sites the imbalance of the NMDA receptor as a possible cause [29]. In addition, NMDA may create an over-excitability in the synaptic transmission and lead to the formation of reactive oxygen species (ROS) to form which may cause neuronal death [22,29,43,44]. Mechanisms which inhibit this over-excitability of NMDA receptors may induce neuroprotection [22,44]. In traumatic brain injury (TBI), ROS formation is common and in rat studies magnesium supplementation is thought to be neuroprotective and has been shown to improve both cognitive and motor function but these results could not be reproduced in human studies [22,44].

In 1921, magnesium was first used to treat depression [22,41] Jorgensen et al. showed that magnesium restriction led to depression in as little as six weeks [30]. Additionally, Ghafari et al. found altered NMDA receptor function not only cause depression but reduced the ability of the amygdala-hypothalamic receptors to receive information and impaired learning and spatial memory. They felt this was mediated by elevated glutamate levels [31]. Pochwat et al. found magnesium supplementation alleviated generalized depression and depression from CMS [8]. Those with ADHD are in a constant state of CMS which may lead to depression. Through these mechanisms magnesium therapy may be a solution to decrease depression and anxiety and increase learning ability, without the negative side effects of traditional medications and at significantly lower cost.

Implications for practice and research

While stimulant drugs do help reduce some of the symptoms of ADHD, though these drugs may not be targeting one of the main problems which is low magnesium. Stimulant medications excite the prefrontal cortex and increase working memory. This can decrease symptoms of ADHD. These drugs increase other disorders within the body though, some of which may be mediated by magnesium deficiency [7,20]. No research had been found on this and therefore this is an area of need.

There are very few studies that assess both behavioural and cognitive function associated with magnesium treatment [38]. A large, randomized, controlled study is required to investigate whether magnesium supplementation can decrease the symptoms of ADHD, mitigate the negative behaviours and increase learning. Additionally, investigation is required to determine an accurate, cost effective means to measure magnesium status in the body. Finally, clarification of the dosage and most bioavailable form of magnesium treatment is needed. With any future research, treatment compliance rates should also be measured especially for those with comorbid psychiatric disorders. Magnesium may be a better solution than stimulant drugs to decrease the symptoms of depression and anxiety and increase learning ability, without the negative clinical side effects at significantly lower cost.

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