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Magnesium supplementation in children with attention deficit hyperactivity disorder

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KEYWORDS

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Abstract *Background:* Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder with associated mineral deficiency.

Aim: To assess magnesium level in ADHD children and compare it to the normal levels in children. Then, to detect the effect of magnesium supplementation as an add on therapy, on magnesium deficient patients.

Methods: The study was conducted on 25 patients with ADHD and 25 controls. All subjects had magnesium estimation in serum and hair. ADHD children were further assessed by Wechsler intelligence scale for children, Conners' parent rating scale, and Wisconsin card sorting test. Then magnesium deficient patients were assigned into 2 groups, those who received magnesium, and those who did not. The difference between the studied groups was assessed by Conners' parents rating scale and Wisconsin card sorting test.

Results: Magnesium deficiency was found in 18 (72%) of ADHD children. The magnesium supplemented group improved as regards cognitive functions as measured by the Wisconsin card sorting test and Conners' rating scale. The patients reported minor side effects from magnesium supplementation.

Conclusion: Magnesium supplementation in ADHD, proves its value and safety.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common, early-onset and enduring neuropsychiatric disorder characterized by developmentally inappropriate deficits in attention, hyperactivity, increased impulsivity and emotional deregulation, resulting in impairments in multiple domains of personal and professional life [1].

Evidence for dietary/nutritional treatments of attention-deficit/hyperactivity disorder (ADHD) varies widely; however recommended daily allowance of minerals and essential fatty acids is an ADHD-specific intervention [2].

Magnesium is the fourth most abundant mineral in the body and is essential for good health [3]. Its biological importance evolves from being an essential trace mineral involved in over 300 metabolic reactions including cellular

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energy generation, nucleic acid production (DNA, RNA), and protein synthesis. Magnesium (Mg^{+2}) is, also, the most abundant intracellular divalent cation [4].

The mineral magnesium is necessary for sufficient brain energy and aids smooth transmission of communications through the central nervous system, calms the central nervous system and is an important component in the making of serotonin [5].

Magnesium deficiency is typified by a number of reductions in cognitive ability and processes, and in particular a reduced attention span along with increased instances of aggression, fatigue and lack of concentration [6]. Other common symptoms of magnesium deficiency include becoming easily irritated, nervousness, fatigue and mood swings [6].

Given the nature of these symptoms and the significant amount of overlap that they share with ADHD, this led many experts involved in the treatment and care of ADHD to hypothesize that children who suffer from ADHD also have magnesium deficiency as well.

In the current study, magnesium level in children with attention deficit hyperactivity disorder (ADHD) will be compared to normal children, in both serum and hair. Then, the effects of magnesium supplementation in magnesium deficient patients will be assessed.

2. Subjects and methods

This study is a case-control prospective interventional comparative study. It was conducted on 25 patients with ADHD and 25 age and sex matched controls.

2.1. Participants

Patients were considered ineligible for the study, if they fulfilled criteria of ADHD according to DSMIV, their age range was between 6 and 16 years and their IQ above 70. Ineligibility for the study included presence of other medical conditions as significant anemia, chronic illness, hearing or vision impairment, medication side effects which may result in hyperactivity and impaired sleep rhythm.

Twenty five healthy children recruited from the sibs of the ADHD group were included in the study as a control group.

Both patients and healthy controls were recruited from Children's hospital and institute of psychiatry, Ain Shams University, Cairo, Egypt. The work has been carried out in accordance with the code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

2.2. Study design

Patients were recruited from the clinic randomly. After explaining the purpose of the study, written consents from parents and the acceptance of the ethics committee of Ain Shams University were obtained. Data were collected through the administration of the predesigned questionnaires to the parents.

Each patient in this study was subjected to the following; Full detailed medical history including presence of organic or psychological diseases, perinatal and developmental history, family history of similar cases, and the previous treatment which was received.

Clinical Examination included; body measurements, physical examination and neurological examination.

2.3. Investigations

Serum magnesium level was assayed by auto analyzer [7].

Hair magnesium level (Fresh, clean hair sample) was subjected to Inductively Coupled Mass Spectroscopy (ICP-MS) which has been cited as currently the most sensitive and comprehensive technique available for multi-element analysis of trace elements to measure hair magnesium in both cases and controls [8].

2.4. Scales

DSM (IV) to confirm the diagnosis of ADHD in cases and to exclude concomitant psychiatric disease [9].

Conners' parent rating scales using an Arabic version for detection of the severity of ADHD [10]. Items are scored on 14 subscales but in our study we used only the hyperactivity, inattention, oppositional and impulsivity scores.

Wisconsin's card sorting test (WCST) is a neuropsychological test of "set-shifting", i.e. the ability to display flexibility in the face of changing schedules of reinforcement. It's a measure of executive function. We used computerized versions of the task (Microsoft Windows-compatible version 4.0). It has the advantage of automatically scoring the test, which was quite complex in the manual version [11].

Wechsler intelligence scale for children (WISC) using the Arabic version for IQ assessment [11].

We compared the ADHD group (25 patients) with the matched control group (25 children) as regards different variables mainly the hair and serum magnesium. The ROC Curve (Receiver Operating Characteristics) was used for the diagnosis of decreased magnesium level in hair among ADHD children as there is no available reference in Egypt for hair Magnesium in this age group. Using ROC Curve,

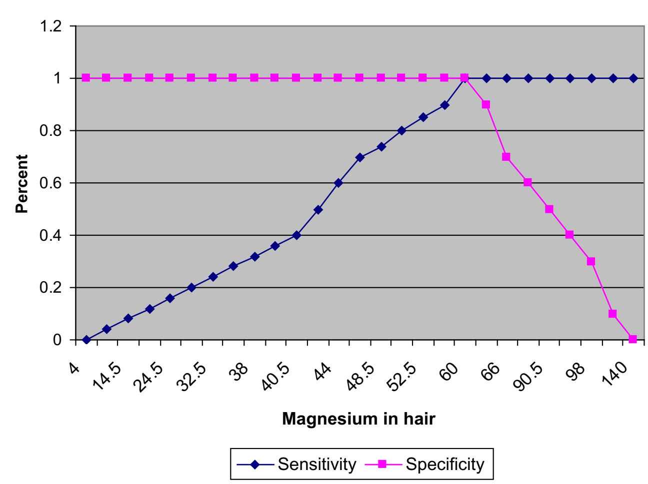

Figure 1 Using ROC Curve the cut off value for deficient magnesium level in hair was equal or less than 60.

the cut off value for deficient Magnesium level in hair was equal or less than 60 as shown in Fig. 1. And according to this cut off value; the magnesium deficient ADHD patients were found to be 18 (group B) and the ADHD cases with normal hair magnesium were 7 cases (group A).

The magnesium deficient children were randomly assigned into 2 equal groups. The first group received magnesium supplementation in a dose of 200 mg/day as an add on therapy to the standard medical treatment. The second group received standard medical therapy alone. After 8 weeks the 2 groups will be compared with Conners' parent rating scale and Wisconsin card sorting test.

2.5. Statistical analysis

The collected data were revised, coded, tabulated and introduced to a PC using Statistical package for Social Science. Data were presented and suitable analysis was done according to the type of data obtained for each parameter.

I. *Descriptive statistics*: mean, standard deviation (±SD), minimum and maximum values (range) for numerical data and frequency and percentage of non-numerical data were applied.
II. *Analytical statistics*: included The ROC Curve (*receiver operating characteristic*) which provides a useful way to evaluate the sensitivity and specificity for quantitative diagnostic measures that categorize cases into one of two groups. *Student t test* was used to assess the statistical significance of the difference between the two study group means. *Correlation analysis (using Pearson's method)*: To assess the strength of association between two quantitative variables. The correlation coefficient denoted symbolically by "r" defines the strength and direction of the linear relationship between two variables. *Chi square test:* was used to examine the relationship between two qualitative variables. *Fisher's exact test*: was used to examine the relationship between two qualitative variables when the expected count was less than 5 more than 20% of cells. *Paired t-test* was used to assess the statistical significance of the difference between two means measured twice for the same study group.

3. Results

In the current study, there was no significant difference regarding the age and gender among normal children (control) and ADHD patients Table 1. i.e the two samples were homogenous (P value > 0.05).

There was a significant difference between cases and controls as regards hair magnesium level but there was no significant difference as regards serum magnesium level Table 2.

Magnesium deficiency was more common in males than in females, otherwise the other characteristics showed no significant difference (Table 3).

Also, there was no statistically significant difference as regards attention, memory loss, fear, restlessness, insomnia, tics, cramps and dizziness between the two groups.

Table 1 Comparison between cases and controls regarding personal characteristics.

		Type				P^*	Sig
		Cases $N = 25$		Controls $N = 25$			
			%		%		
Sex	Male	20	80.0	19	76.0	0.107	NS
	Female	5	20.0	6	24.0		
Age	Mean ± SD	7.74 ± 1.48		7.40 ± 1.35		0.534**	NS

NS = non significant; Sig = significance.
* Chi square test.
** Student's t test.

Table 2 Comparison between cases and control as regards serum and hair magnesium level.

	Type				P	Sig
	Cases $N = 25$		Controls $N = 25$			
	Mean	±SD	Mean	±SD		
Serum Mg (mg/dl)	2.23	0.13	2.32	0.28	0.366	NS
Hair Mg (mg/kg)	54.48	16.65	109.20	26.34	0.0001	HS

SD = standard deviation; NS = non significant; HS = highly significant; Sig = significance.

At the beginning of the study there was no statistically significant difference between the two groups as regards the different psychiatric scales Table 4.

However, when we correlated hair magnesium level to the different psychiatric scales among children with ADHD we found a significant correlation between hair magnesium and total IQ and an indirect significant correlation between hair magnesium and the hyperactivity components of Conners' scale Table 5.

The magnesium deficient patients (18 patients) were then randomly divided into two groups; Group B 1 (9 patients) received magnesium supplementation, Group B 2 (9 patients) received their standard medical treatment without magnesium supplementation.

Comparison between the psychiatric scales at baseline and at follow up among magnesium treated ADHD cases who had low hair magnesium level (group B1) showed that there was a highly significant improvement in hyperactivity and impulsivity, and also a significant improvement in inattention, opposition and conceptual level Table 6.

While, comparison between the psychiatric scales at baseline and at follow up among untreated low hair Magnesium ADHD cases showed that there was no such improvement Table 7.

Percentage of improvement of the psychiatric scales at follow up among magnesium treated (group B1) and untreated (group B2) Fig. 2.

Percentage of change in Categories completion, Conceptual level, Oppositional and impulsivity components of Conners' scale although showed improvement at follow up in

Table 3 Comparison between cases with normal (group A) and low hair magnesium (group B) as regards personal and medical characteristics.

		Mg in hair diagnosis				*P*	Sig
		Normal Mg (group A) $N = 7$		Decreased Mg (group B) $N = 18$			
		N	%	N	%		
Sex	Male	3	42.9%	17	94.4%	0.012	S
	Female	4	57.1%	1	5.6%		
Age	Mean ± SD	7.8 ± 1.2		7.7 ± 1.6		0.917	NS
Maternal age at conception	Mean ± SD	25.7 ± 3.3		25.3 ± 5.1		0.836	NS
Number of sibling	Mean ± SD	1.6 ± 1.3		1.7 ± 0.7		0.700	NS
Order of birth	Mean ± SD	1.9 ± 0.9		1.8 ± 0.9		0.840	NS
Consanguinity	Negative	6	85.7%	14	77.8%	0.999	NS
	Positive	1	14.3%	4	22.2%		
Socioeconomic	Unprivileged	6	85.7%	11	61.1%	0.362	NS
	Privileged	1	14.3%	7	38.9%		
Family history	Non	4	57.1%	12	66.7%	0.434	NS
	ADHD	0	0.0%	3	16.7%		
Mother's occupation	Negative	5	71.4%	14	77.8%	0.739	NS
	Positive	2	28.6%	4	22.2%		
Perinatal asphyxia	Negative	3	42.9%	15	83.3%	0.066	NS
	Positive	4	57.1%	3	16.7%		
Development	Delayed	1	14.3%	7	38.9%	0.362	NS
	Normal	6	85.7%	11	61.1%		
Medical treatment	Ritalin	6	85.7%	12	66.7%	0.341	NS
	Atomoxetine	1	14.3%	6	33.3%		
Serum Mg (mg/dl)	Mean ± SD	2.2 ± 0.1		2.3 ± 0.1		0.081	NS

Table 4 Comparison between cases with normal (group A) and low hair magnesium (group B) as regards different psychiatric scales.

			Mg in hair				*P*	Sig
			Normal Mg (group A) N = 7		Decreased Mg (group B) $N = 18$			
			Mean	±SD	Mean	±SD		
Wechesler scale	Verbal skills	Comprehension	9.6	1.5	9.9	2.8	0.676	NS
		Arithmetic	7.7	2.5	8.7	3.7	0.541	NS
		Similarities	11.1	2.5	10.2	3.7	0.490	NS
		Digit span	5.9	2.0	7.6	2.9	0.158	NS
	Performance skills	Picture completion	8.9	2.5	8.7	2.7	0.908	NS
		Block design	9.0	2.1	8.6	2.5	0.677	NS
		Digit symbol	8.0	3.6	8.9	3.0	0.577	NS
	Total IQ	Verbal IQ	96.6	8.6	99.2	17.4	0.712	NS
		Performance IQ	95.1	13.5	96.9	14.1	0.779	NS
		Total IQ	95.9	10.5	97.7	15.6	0.775	NS
	Wisconson's card sorting test	Categories completion	3.5	2.1	2.9	2.0	0.643	NS
		Conceptual level	48.8	33.0	41.4	27.0	0.672	NS
	Connors'	Oppositional	67.7	8.4	67.8	11.8	0.978	NS
		Inattention	75.9	9.1	71.2	12.4	0.381	NS
		Hyperactivity	78.6	11.3	79.4	9.0	0.859	NS
		Impulsivity	82.7	11.4	78.2	9.2	0.308	NS

magnesium treated patients of group B1 rather than untreated patients of group B2. However these changes were not statistically significant (60%, 60%, 55.6% and respectively).

However, the percentage of change in the inattention as well as hyperactivity components of Conners' scale showed a statistically significant improvement (77.7% and 88.9% respectively).

As regards the side effects of magnesium supplementation in our patients (group B1) 22.2% experienced adverse effects in the form of mild abdominal pain and diarrhea Table 8.

4. Discussion

In the current study, there is a robust finding of decreased hair magnesium in 18 (72%) of children with ADHD, while serum hair magnesium is normal. This could be explained on genetic and metabolic basis. Metabolically, Mg^{2+} transport may be reduced without change in serum MG^{2+} concentrations. This supports the finding of low hair follicle Mg^{+2}, while serum Mg^{2+} is normal. Furthermore, abnormalities in TRPM6 genes, which regulates the entry of magnesium into

Table 5 Correlation between magnesium hair and serum levels and the psychiatric scales among children with ADHD.

		Total IQ	Categories completion	Conceptual level	Oppositional	Inattention	Hyperactivity	Impulsivity
Hair Mg	r	0.749	0.028	0.105	−0.173	−0.311	−0.663	−0.086
Mg/kg	P^*	0.0001	0.939	0.773	0.493	0.210	0.003	0.734
	Sig	HS	NS	NS	NS	NS	S	NS
Serum Mg	r	0.097	0.651	0.565	0.996	0.370	0.704	0.946
Mg/dl	P^*	0.340	0.133	0.168	−0.001	−0.187	0.080	−0.014
	Sig	NS	NS	NS	NS	NS	NS	NS

R = correlation coefficient; NS = non significant; HS = highly significant.
* Pearson correlation test.

Table 6 Comparison between psychiatric scales at baseline and at follow up among magnesium treated cases (group B1).

		Mean	N	±SD	P	Sig
Categories completion	Before treatment	3.40	5	2.074	0.061	NS
	After treatment	5.80	5	0.447		
Conceptual level	Before treatment	49.20	5	30.376	0.038	S
	After treatment	81.00	5	10.173		
Oppositional	Before treatment	64.44	9	12.022	0.024	S
	After treatment	52.78	9	10.022		
Inattention	Before treatment	69.89	9	13.797	0.012	S
	After treatment	53.44	9	8.918		
Hyperactivity	Before treatment	79.22	9	9.066	0.001	HS
	After treatment	55.33	9	10.380		
Impulsivity	Before treatment	77.44	9	8.705	0.001	HS
	After treatment	56.44	9	10.608		

SD = standard deviation; NS = non significant; HS = highly significant; S = significant; Sig. = Significance.
*Paired t test.

epithelial cells and controls Mg^{2+} urinary excretion could be a putative factor in the previous finding [12].

The results gives us the clue that the total serum magnesium concentration is not the best method to evaluate the magnesium status; as changes in serum protein concentrations may affect the total concentration without necessarily affecting the ionized fraction or total body magnesium status, since about 30% of serum magnesium is bound to proteins [13]. For this reason, we used both serum and hair magnesium to assess magnesium status.

Magnesium interacts with noradrenergic and dopaminergic system [14]. The role of noradrenergic and dopaminergic system in the pathophysiology of ADHD has been extensively studied. In addition, stimulants and atomoxetine act through adrenergic and dopaminergic receptors [15]. Thus, magnesium deficiency could be related to the pathophysiology of ADHD.

In agreement with our results came a study done by Kozielec [16] who observed low magnesium level in ADHD children; where Magnesium deficiency was found in 95 percent of ADHD patients examined, most frequently in hair (77.6 percent), in red blood cells (58.6 per cent) and in blood serum (33.6 percent) indicating that magnesium deficiency in children with ADHD occurs more frequently than in healthy children.

Mousain-Bosc et al. [17] reported that, intraerythrocytic magnesium were lower in children with ADHD, while serum magnesium was normal.

Similar results were obtained also from another Egyptian study, where serum ferritin, zinc and magnesium levels were lower in ADHD children than controls ($p = 0.001$) [18].

We can speculate that magnesium deficiency in ADHD due to behavioral manifestation related to the core pathology of ADHD [19]. Children with ADHD may suffer from feeding problems owing to their stubbornness and unexpected reactions to the parent's orders [20]. They lack the attention required to sit through a meal to obtain adequate levels of nutrient intake, as well as the appetite suppressant effects of treatment medication [21].

In the current study, magnesium deficiency was more prevalent in males than in females. Also, no significant difference was observed regarding serum magnesium and sociodemographic data. This finding was supported by previous study, where magnesium levels were higher in girls with ADHD [22]. This gender difference seen in our studies, could be partly due to the hormonal difference between males and females where estrogen secretion is responsible for the better magnesium utilization by young female adolescents (it may slow the metabolic rate and hence increases the magnesium level in hair) [23].

At the beginning of the study there was no significant difference among cases with normal (group A) and cases with low hair magnesium (group B) as regards the different psychiatric scales. This could be explained by the fact that ADHD is largely a heterogeneous disorder stemming from genetics and environmental factors [24] and, small sample size in the current study. For that reason also not all the patients who received the magnesium supplementation improved at follow up.

However, there was a significant correlation between hair magnesium and total IQ, and an indirect significant correlation between hair magnesium and hyperactivity score. Previous studies demonstrate that magnesium deficiency was associated with deficient cognitive function and low academic achievement in adolescent girls. Moreover, familial hypomagnesemia was related to inattention, mental retardation and speech problems [25].

Table 7 Comparison between the psychiatric scales at baseline and at follow up among untreated ADHD cases with magnesium who had low hair magnesium levels (group B2).

		Mean	*N*	±SD	*P*	Sig
Categories completion	Baseline	2.40	5	2.074	0.063	NS
	Follow up	3.60	5	1.517		
Conceptual level	Baseline	33.60	5	23.891	0.066	NS
	Follow up	43.00	5	21.966		
Oppositional	Baseline	71.22	9	11.300	0.018	S
	Follow up	66.89	9	10.994		
Inattention	Baseline	72.56	9	11.588	0.237	NS
	Follow up	70.56	9	11.970		
Hyperactivity	Baseline	79.67	9	9.500	0.201	NS
	Follow up	76.44	9	8.805		
Impulsivity	Baseline	78.89	9	10.093	0.062	NS
	Follow up	71.78	9	8.941		

SD = standard deviation; NS = non significant; S = significant; Sig. = Significance.
*Paired *t* test.

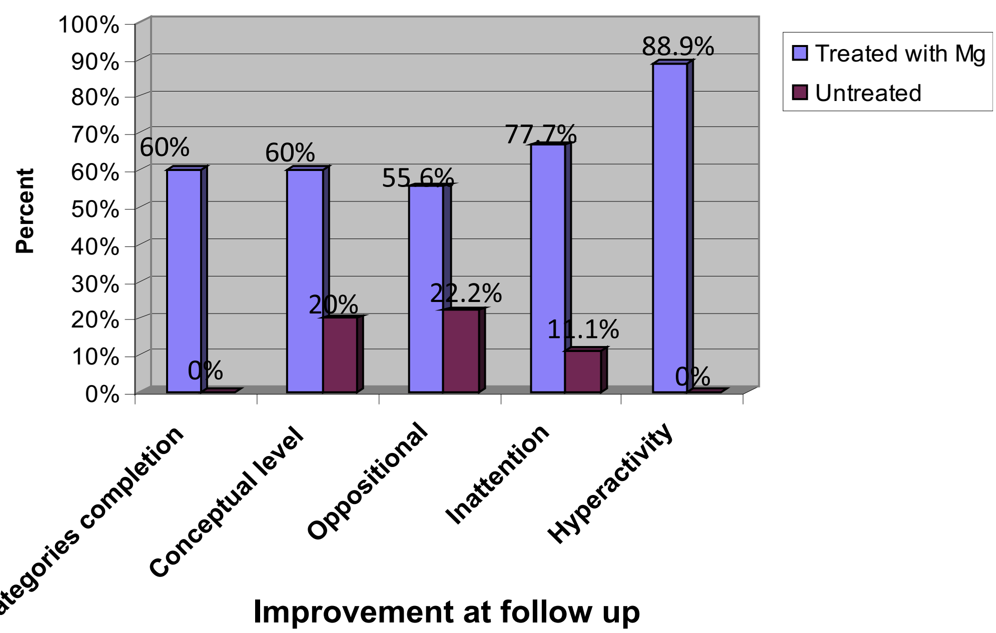

Figure 2 Improvement of psychiatric scales at follow up among treated (group B1) and untreated group (group B2).

Table 8 Adverse effects among magnesium treated cases (group B1).

Adverse effect	(Group B1) *N* = 9	%
Negative	7	77.8
Positive	2	22.2

In phase 2 of the current study, magnesium deficient patients were randomly assigned into two groups; those who received magnesium supplementation and those who did not. On follow up; in the magnesium supplemented group, Conners' parents rating scores sub items improved, with a highly significant improvement in the hyperactivity ($p = 0.001$) and the impulsivity domain ($p = 0.001$). Other sub items improved, but the improvement was not statistically significant. The highly significant improvement seen in hyperactivity could be due to the fact that magnesium is needed for relaxation at the neuromuscular junctions [26]. Similarly, follow up of cognitive function using Wisconsin card sorting test, showed significant improvement in the category completion ($p = 0.061$) in the conceptual level ($p = 0.038$).

In the current study; despite the general improvement of Conners' scores in group B1 compared to group B2 after supplementation, this improvement pushed the patient from one category of the rating scale (obtained at beginning of the study) to another only in the change in inattention ($p = 0.05$), and the hyperactivity ($p = 0.001$) sub items of Conners' scale; otherwise the changes in the other components were not statistically significant.

On the other hand, follow up of the magnesium unsupplemented group showed that the cognitive function and Conners' rating scale sub items did not improve, except for the oppositional scale, as parents of this group were assigned to behavioral therapy.

Our results match with those obtained by Nogovitsina [27] where analysis was done after 30 days of magnesium supplementation to ADHD patients and showed improvement in the form of significant decrease in the total point scores on all scales ($p < 0.05$; $p < 0.001$) There was also a significant decrease in point scores on the ‘‘anxiety’’ and ‘‘impairment of attention and hyperactivity’’ scales. In another study, supplementation of ADHD patients with Mg-B6 regimen for at least 2 months significantly modified the clinical symptoms of the disease: namely, hyperactivity and aggressiveness were reduced, school attention was improved. When the Mg-B6 treatment was stopped, clinical symptoms of the disease reappeared in few weeks [17]. Similar results were obtained by other studies [27,28].

These results suggest that magnesium supplementation, or at least proper amounts of magnesium in the diet, may prove to be beneficial for children with ADHD. Further research is needed to help to identify the etiology, impact, and possible therapeutic implications of low micronutrient status in ADHD, given the essential nature of these micronutrients in the production of the neurotransmitters involved in ADHD.

Regarding the side effects of supplementation, we found that 22% of the cases given the treatment suffered from mild attacks of abdominal pain or diarrhea. This is consistent with Jaing [29] who reported that oral magnesium supplementation can cause mild side effects, such as diarrhea and abdominal cramps.

Although, our study is limited by small number of cases, but it has an advantage on other studies in that we used magnesium without B6 in treatment of ADHD, the use of sibs as a control group and the use of objective scales (Wisconsin card sorting test) in the assessment of response to magnesium treatment.

5. Conclusion

Mg supplementation for few weeks significantly reduced the clinical symptoms of ADHD. Further studies on larger samples and over longer periods of time are needed to generalize the study.

Conflict of interest

The authors declare no conflict of interest. There is no financial and personal relationship with other people or organizations that could inappropriately influence their work.

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