

ATTENTION DEFICIT HYPERACTIVITY DISORDER AND VITAMIN D IN CHILDREN...IS THERE A RELATIONSHIP?

By

Reham M. El-Hossiny*, Farida M. El-Baz*, Amira I. Hamed**, Tareq A. Mohamed*
and Batoul M. Abd El-Raouf*

*Pediatric Dept., Faculty of Medicine, Ain Shams University, Cairo, Egypt

**Clinical pathology Dept., Faculty of Medicine, Ain Shams University, Cairo,
Egypt

*Correspondence to: Batoul Mohamed Abd El-Raouf Mohamed Hassan

Address: Ain Shams University, Children's Hospital, Abbassiah Square, Cairo,
Egypt

Mobile: 02-01113778353, E-mail: drbatoul@med.asu.edu.eg

ABSTRACT

Background: A frequent, early-onset, chronic developmental problem in children and adolescents is attention-deficit/hyperactivity disorder (ADHD). ADHD's etiopathogenesis is unknown. Low vitamin D levels have been linked in several studies to a variety of illnesses and neuropsychiatric conditions. Therefore, this study aimed to investigate the association between serum vitamin D levels in paediatrics and ADHD.

Methods: This is a case-control study conducted in a child psychiatry clinic, Ain shams children's hospital involving a total number of thirty ADHD patients diagnosed according to DSM-V criteria and thirty apparently healthy controls were included in the study during the period from June 2016 to January 2017, they were selected by simple random method. The age of both groups ranged from 6-16-year-old. Serum 25-OH-vitamin D level was evaluated in both groups.

Results: Serum 25-OH-vitamin D was significantly lower in children with ADHD than in healthy controls.

Conclusion: This study has evidenced a significantly low serum vitamin D level in children with ADHD. There is an association between lower 25-OH-vitamin D concentration and ADHD in childhood. Therefore there is a need for the treatment of patients with vitamin D deficiencies.

Key words: ADHD; Children; Neurodevelopmental; 25-OH-Vitamin D.

INTRODUCTION

One of the most common mental health conditions affecting children and adolescents is attention deficit hyperactivity disorder (ADHD) (Arnold et al., 2015). Before the age of twelve, the disease can be identified by three key symptoms: difficulty paying attention, hyperactivity, and impulsivity (Arnold et al., 2015, Matthews et al., 2014). Aside from these primary symptoms, other clinically significant secondary symptoms include aggression, lack of social skills, peer conflict, and anti-social behaviour (Matthews et al., 2014, Gajria et al., 2014). Genes and prenatal risk factors are believed to have a major impact on the pathophysiology of ADHD (Kian et al., 2022). According to several studies, ADHD is one of the neurodevelopmental diseases with the highest heritability rate, with inheritance accounting for between 54% and more than 70% of the causes of the condition (Eilertsen et al., 2019). ADHD is more common in boys than in girls, despite research showing different male-to-female ratios. (Tarver et al., 2014).

ADHD has a profound effect on how young people operate and develop, as well as how it affects other people, including family

members, friends, and teachers (Wehmeier et al., 2010), and it is a major factor in both low academic performance and turbulent behavior in schools (Bener et al., 2014). Additionally, ADHD has been related to long-term detrimental effects on social-emotional growth, professional success, and intellectual capacity (Wehmeier et al., 2010). ADHD has also been connected to a higher risk of accidents in youth. (Lahat et al., 2011).

A severe health problem that has been reported throughout the world is vitamin D deficiency, It is not just found in places with little sunlight; it can also be found in places with lots of sunshine. (Holick et al., 2012). The precise reasons for such high rates are either unclear or not well understood. Children may have inadequate vitamin D levels due to vitamin D deficiency during pregnancy, inadequate oral vitamin D supplementation during childhood, and little sun exposure. (Bener et al., 2013). Recent studies have connected vitamin D insufficiency to several illnesses, including neuropsychiatric disorders (Goksugur et al., 2014).

Significant public health repercussions would result from the identification of a causal relationship between vitamin

deficiencies and suboptimal brain performance. Numerous micronutrients are known to be lacking in significant portions of the world's population, especially the impoverished (**Holick et al., 2012**). A vast amount of evidence demonstrates that a dietary deficiency in one or more critical micronutrients, such as vitamin D, can impair mental function. Supplementing with Vitamin D, multivitamins, and minerals has also been shown to improve cognitive function in several trials (**Polivka et al., 2012**). The relationship between vitamin D insufficiency and ADHD in young children has rarely been covered in the literature.

AIMS OF THE WORK

The purpose of this study was to investigate the link between ADHD in children and serum vitamin D levels.

PATIENTS AND METHODS

Ethical considerations:

- A written informed consent was obtained from patients or their legal guardians.
- Approval by the local ethical committee of the pediatric department and faculty of medicine, at Ain Shams University was obtained before the study.

- The authors declared no potential conflicts of interest concerning research, authorship, and/or publication of the article.
- All the data of the patients are confidential and the patients have the right to keep it.
- The patient has the right to withdraw from the study at any time.
- The researcher explained the aim of the study to the patients and their guardians.

Sample size:

Using EPI INFO sample size calculator; with 0.05 alpha error, confidence interval of 0.95 and power of the study of 0.80. The minimum sample size calculated to detect the prevalence of vitamin D deficiency among ADHD patients comparing them to controls is 60 cases.

Inclusion criteria: Children who were diagnosed with ADHD using DSM-V criteria.

Exclusion criteria: Patients with any psychiatric disease, intellectual handicap, or chronic significant medical or neurological disorders were excluded.

Study design:

This is a case-control study that includes two groups:

Group I (ADHD): involved thirty children who were diagnosed with ADHD using DSM-V criteria (DSM-V, 2013). They were chosen by simple random method from the paediatric department of Ain Shams Hospital's child psychiatry clinic, and their ages varied from 6 to 16.

Group II (Controls): involved thirty apparently healthy youngsters who were recruited from the outpatient clinic, they were chosen to be age and sex-matched.

All studied groups underwent:

- A thorough history taking including Personal history, prenatal history, developmental history and family history, dietary history, history of bony aches, and factors causing vitamin D deficiency.
- Physical examination, to detect any organic disease as well as neurological examination.
- Psychological evaluation, which included an IQ test using the Wechsler Intelligence Scale for Children (WISC), and Conner's Parent Rating Scale.
- Laboratory investigations using an ELISA technique to estimate the serum level of human 25 hydroxyvitamin D.

Psychological tests:

Conner's Parent Rating Scale-revised; long version (CPRS-L): It assists with assessing children and adolescents for attention deficit/hyperactivity disorder (ADHD). The items on the test show a high degree of face validity and are quite similar to the DSM-IV criteria for diagnosing ADHD. It is used to determine the subtypes and severity of ADHD as well as to score co-morbid cases in order to compare cases with co-morbid ADHD and bipolar illnesses to those with ADHD alone. It can be used by parents of children and teenagers ages three to seventeen. The Long Form contains 80 items and can be completed by most parents/guardians in approximately 20 minutes; On each form, the parents/guardians rate how often their child or adolescent engages in the behaviours listed on a form based on a four-point scale. The scale ranges from Not True at All (Never) to Very Much True (Very Often) (Conners, 1998).

The scale is plotted on hand-scored profiles to obtain the raw scores and T scores of the child according to their ages: five age groups namely ages 3-5,6-8,9-

11,12-14,15-17 years old. Two profiles are available according to the child's gender: a profile for males and a profile for females. T scores of the patients are obtained by plotting the raw scores of inappropriate profiles from rows and columns.

T score guideline is as follows:

- 1- Average, typical score is 45-55.
- 2- Slightly atypical, borderline 56-60.
- 3- Mildly atypical, possible problems 61-65.
- 4- Moderately atypical, evident significant 66-70.
- 5- Markedly atypical, significant problem > 70.

The revised Arabic versions of Conner's rating scale, long versions, and parent form used in this study were translated and validated through previous research conducted by **El Sheikh et al., 2002** at the institute of psychiatry, Ain Shams University.

Wechsler Intelligence Scale for Children: An individually given intelligence test designed for children between the ages of six and sixteen and 11 months. Indicators of human intelligence are assessed using verbal and nonverbal (performance) skills by the WISC. The WISC comprises

exercises such as general knowledge questions, classic math problems, vocabulary exercises, maze completion, and block and picture constructions. The scale's certified Arabic version was used in this investigation (**Melika, 1984**).

Measurement of 25 hydroxyvitamin D using commercial ELISA kits:

To test the serum 25-hydroxyl vitamin D level using the enzyme-linked immunosorbent assay (ELISA) method, venous blood samples (5 ml) from each patient and control participants were taken under sterile circumstances. When the 25(OH)D level is below 10ng/ml, it is considered to be deficient, when it is between 10 and 30ng/ml, it is considered to be insufficient and when it is between 30 and 100ng/ml, it is considered to be sufficient (**Holick, 2009**).

Statistical analysis:

Statistical Package for Social Science (**IBM Corp. Released, 2011**) was used to edit, code, tabulate, and import the acquired data onto a computer. Armonk, New York: IBM Corp., IBM SPSS Statistics for Windows, Version 20.0. Data were presented, and the type of data obtained for each parameter was appropriately analysed. P-value: level of significance (P>0.05: Non-

significant (NS), $P < 0.05$: Highly significant (HS)).
 Significant (S). and $P < 0.01$:

RESULTS

The results of our study will be demonstrated in the following tables and figures:

Table (1): Demographic characteristics of the studied groups

	Cases			Controls			P	Sig
	Mean	\pm SD	Median(IQR)	Mean	\pm SD	Median(IQR)		
Age (years)	9.94	\pm 2.41	9.5(9-11)	8.93	2.86	8.5(6-12)	.148 [‡]	NS
Birth order	2.10	\pm 1.47	2.0 (1-3)	1.83	.99	2(1-2)	.608 [‡]	NS
Sex	Male	23	76.7%	21	70.0%		.232*	NS
	Female	7	23.3%	9	30.0%			
Consanguinity	-ve	21	70.0%	25	83.3%		.222*	NS
	+ve	9	30.0%	5	16.7%			
Sun Exposure duration	<30min	3	10.0%	3	10.0%		1.0**	NS
	>30min	27	90.0%	27	90.0%			
WT (kg)	33.68	9.03		30.97	14.30		.383	NS
HT(cm)	135.47	12.30		128.1	20.82		0.101	NS
B.M.I.	18.14	3.51		17.78	2.56		0.657	NS

[‡]Student T-Test, ^{‡‡}Mann-Whitney test, *Chi-Square test, **Fisher exact test.

Table (1) shows that there was no significant difference between the two groups as regards Demographic data.

Table (2): Comparison between cases and controls regarding vitamin D levels

Variable	Cases			Controls			P	Sig
	Mean	\pm SD	Median(IQR)	Mean	\pm SD	Median(IQR)		
Vitamin D(ng/ml)	14.50	11.32	8.5 (7-20)	39.20	27.62	35(20-50)	.001 ^{‡‡}	HS

^{‡‡}Mann-Whitney test

Table (2) shows that cases have significantly lower vitamin D levels compared to controls.

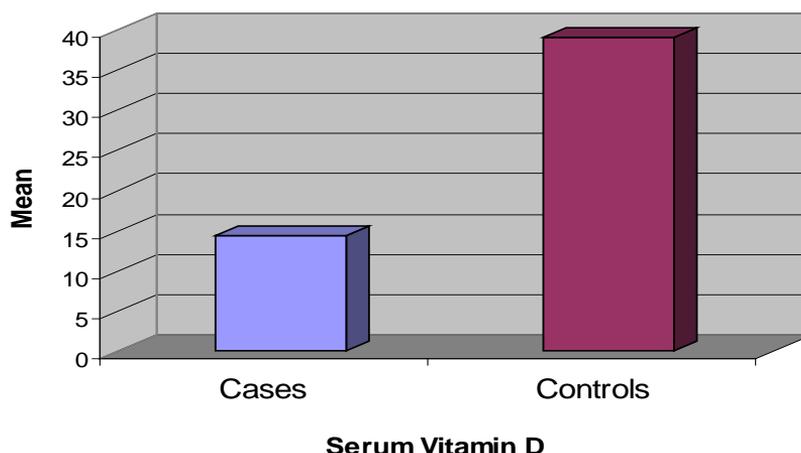


Figure (1): Comparison between cases and controls regarding vitamin D levels

Figure (1) shows that cases have significantly lower vitamin D levels compared to controls (14.50 ± 11.32 Vs 39.20 ± 27.6).

Table (3): Relation between personal and medical data and vitamin D among cases

Variable		Vitamin D			P-value	Sig
		Mean	\pm SD	Median		
Sex	Male	14.22	11.26	9(7-20)	.882	NS
	Female	15.43	12.35	8(6-28)		
Consanguinity	-ve	15.00	12.56	9(7-20)	.964	NS
	+ve	13.33	8.23	8(7-20)		
Sun exposure	<30 min	5.67	2.31	7(3-7)	.001	HS
	>30 min	15.48	11.51	9(7-20)		

Table (3) reveals that there is no significant association between sex, consanguinity, or FH regarding vitamin D levels,

but Long-term sun exposure and vitamin D levels are positively and statistically significantly correlated.

Table (4): Description of disease characteristics and treatment received among group I

		Mean	±SD
Age of onset in years		4.70	2.16
ADHD subtypes	Inattentive	3	10.0%
	Hyperactivity	12	40.0%
	Combined	15	50.0%
Behavioural therapy	-ve	16	53.3%
	+ve	14	46.7%
Speech therapy	-ve	25	83.3%
	+ve	5	16.7%
Drugs	-ve	2	6.7%
	+ve	28	93.3%

Table (4) shows that the mean age of onset in years among cases was 4.70 ± 2.16 . ADHD subtypes: the combined (n=15, 50.0%) and Hyperactivity subtypes (n=12, 40.0%) were the most prevalent

followed by the inattentive type (n=3, 10%). Cases subjected to behavioural therapy (n=14, 46.7%), while cases receiving speech therapy (n=5, 16.7%) and those receiving medications (n=28, 93.3%).

Table (5): Description of IQ and Conner's Parent Rating scale scores among cases

	Mean±SD	Minimum	Maximum	significance
IQ	89.60±11.36	75.00	108.00	Markedly elevated
Oppositional	69.83±10.02	48.00	87.00	Markedly elevated
Cognitive	72.70±9.96	44.00	90.00	Markedly elevated
Inattentive	72.29±10.23	45.00	90.00	Markedly elevated
Hyperactivity	79.80±8.67	61.00	90.00	Markedly elevated
Emotional	74.31±12.86	44.00	90.00	Markedly elevated
Hyperactivity-impulsivity	76.63±9.85	52.00	90.00	Markedly elevated

Table (5) shows that the mean IQ, Oppositional, Cognitive, Inattentive, Hyperactivity, Emotional, and hyperactivity/impulsivity score

was 89.60 ± 11.36 , 69.83 ± 10.02 , 72.70 ± 9.96 , 72.29 ± 10.23 , 79.80 ± 8.67 , 74.31 ± 12.86 , 76.63 ± 9.85 respectively showing Markedly elevated significance.

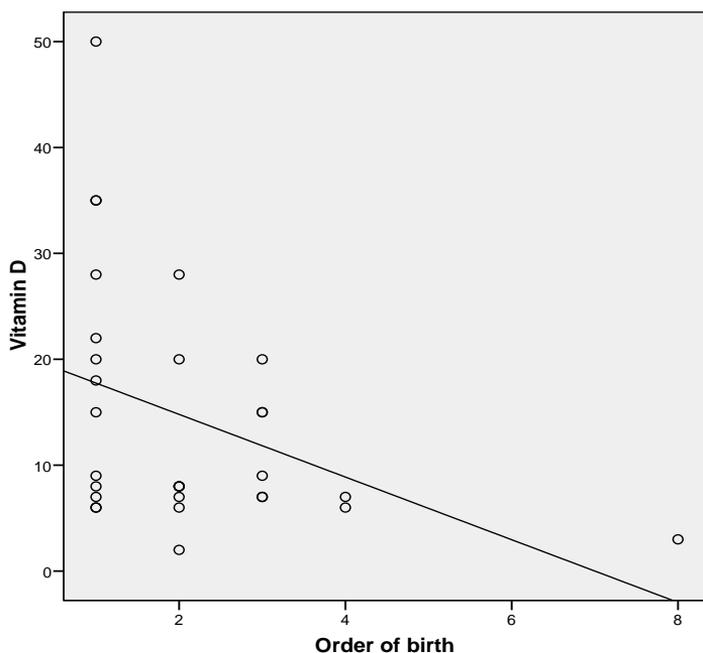


Figure (2): Correlation between the order of birth and vitamin D levels among ADHD cases

Figure (2) shows a birth order and vitamin D levels in cases have a significant negative association.

Table (6): Correlation between vitamin D level and each IQ and Conner’s scale among ADHD cases

		IQ	Oppositional	Cognitive	Inattentive	Hyperactivity	Emotional	Impulsivity
Vitamin D (ng/ml)	r	.296	-.080	-.394	-.233	.147	.159	.022
	P	.112	.676	.031	.272	.437	.410	.909
	Sig	NS	NS	S	NS	NS	NS	NS

*Spearman correlation

Table (6) reveals that there is no significant difference between cases in terms of vitamin D and each of the IQ and Conner's scale characteristics (oppositional,

inattentive, hyperactivity, and impulsivity), however, there is a significant negative link between vitamin D and cognitive score only.

DISCUSSION

Little research has been done on the relationship between vitamin D deficiency and ADHD in children. The goal of our research is to determine vitamin D levels in children with ADHD and how they relate to the severity of the condition.

In this study, serum vitamin D levels in the ADHD group were lower than in the control group, with the following values: The mean Vitamin D levels in the cases was 14.50 ± 11.32 ng/ml, with a median of 8.5. Vitamin D deficiency is found in about 57 per cent of cases. Controls had a mean vitamin D level of 39.20 ± 27.62 ng/ml, with a median of 35. 6.7 per cent of controls have vitamin D deficiency. This finding is consistent with those of a related study that was carried out in Turkey among children aged 7 to 18, where it was discovered that there was a significant difference ($P < 0.05$) in the mean serum vitamin D levels between the cases (20.9 ± 19.4 ng/ml) and controls (34.9 ± 15.4) (Yeşiltepe-Mutlu et al., 2020). Backed with our finding (Sharif et al., 2015) A study of 1331 ADHD cases and the same number of healthy people under the age of 18, showed that the mean range blood

vitamin D level of ADHD children ($16.6-7.8$ ng/ml) was lower than the control group ($23.5-9.9$ ng/ml), which also found a noticeably low serum vitamin D level in kids with ADHD. This recommends that serum vitamin D levels should be monitored regularly, and patients with vitamin D deficiency should be treated. (Li et al., 2020) stated that vitamin D deficiency in children with ADHD was increased in comparison with that in Healthy controls and recommended that Attention should be paid to regular testing of vitamin D levels in children with ADHD. Furthermore, 8.15 per cent of ADHD sufferers showed normal vitamin levels in their blood (Kamal et al., 2014).

Our study shows a highly significant positive relationship between sun exposure duration and vitamin D levels. Meanwhile, there was no significant difference between cases and controls as regards sun exposure duration. Our findings were backed up by (Al-Othman et al., 2012), who wanted to see if the prevalence of vitamin D deficiency is related to the amount of physical activity and sun exposure among seemingly healthy Saudi children and adolescents, and found that

serum vitamin D levels increased with increasing sun exposure. Exposure to sunlight produces 10,000 to 20,000 IU when 30% of the body's surface area is exposed to sunlight for 15 to 30 min a day (**Bouvard et al., 2011**).

Our study reveals that there is a strong negative association between case birth order and vitamin D, but no correlation between case age and vitamin D. In terms of vitamin D levels, there was no significant difference between sex, consanguinity, or family history of ADHD. The negative relationship between case birth order and vitamin D could be explained by maternal vitamin D deficiency during multiple pregnancies and births, according to (**Taylor et al., 2010**), who discovered that A considerable proportion of children are in danger of insufficient and deficient vitamin D levels, especially those born to women who have a history of repeated pregnancies, which has persuaded paediatricians to give infants vitamin D supplements. Furthermore, there are strong links between children's vitamin D levels and maternal vitamin D status (**Nichols et al., 2015**).

Although, we found no correlation between age, sex and vitamin D levels among cases, on the contrary (**Al-Horani et al.,**

2016) declared that vitamin D levels are affected by many factors such as gender, sex, BMI, physical activity, and lifestyle.

It is well known that Vitamin D is one of the micronutrients that improve neurodevelopmental function, especially in the first 1000 days of life. In terms of vitamin D and each of the IQ and Conner's scale features (oppositional, inattentive, hyperactivity, and impulsivity), there is no significant difference between cases; nevertheless, there is a substantial negative link between vitamin D and cognitive score solely. Our findings of cognitive impairment due to vitamin D insufficiency are confirmed by a cross-sectional study conducted in Egypt, which found that school-aged children with vitamin D levels of 37.5 to 77.5 nmol/L had higher neurodevelopmental status than children with levels of less than 27.5 nmol/L (**Nassar et al., 2012**). Vitamin D, being one of the micronutrients that increase neurodevelopmental function, has an impact on early childhood neurocognitive development (**Schwarzenberg et al., 2018**). Low blood 25-OH-vitamin D is also linked to an increased risk of cognitive impairment in the elderly, according to another study (**Llewellyn et al., 2011**). On the

contrary, (**Chowdhury et al., 2020**) found no correlation between vitamin D status and any of the mental outcomes or steady growth, and they refute the notion that low vitamin D status in a young life is a necessary barrier to cognitive development and linear growth. A recent study in India found no link between vitamin D insufficiency and cognitive-developmental status in children aged 12 to 36 months (**Chowdhury et al., 2017**). Furthermore, a case-control study in the United States found no link between vitamin D deficiency and neurodevelopmental status (**Windham et al., 2017**).

CONCLUSION

We suggest an association between 25-OH vitamin D concentration and ADHD in childhood.

RECOMMENDATIONS

Children with ADHD have low levels of serum vitamin D, which suggests that serum vitamin D levels should be regularly checked. ADHD children should have adequate amounts of vitamin D supplements and sun exposure.

LIMITATIONS OF THE STUDY

Our study limitations may be attributed to the small sample size the short period of data collection and the nonavailability of funding sources.

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