Vitamin D Deficiency in Patients with Attention Deficit Hyperactivity Disorder

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Author’s contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

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ABSTRACT

Objective: This study aimed to investigate the connection between childhood Attention Deficit Hyperactivity Disorder (ADHD) and the level of Vitamin D in the blood.

Materials and Methods: The study was undertaken in 2018 on children in the age group of 4-13 years. Twenty two children diagnosed with ADHD were selected, along with a control group comprising twenty two healthy children showing no symptoms of ADHD or any other neurological disorder or liver or kidney disease or any endocrine problem. Anyone using Vitamin D supplements was excluded from the study. Venous blood samples were acquired from the subjects and serum Vitamin D level was measured.

Results: The mean average level of Vitamin D in the research subjects exhibiting ADHD (18.60±6.33 ng/ml) was found to be lower than the control group (34.34±8.19) (P-value < 0.0005).

Conclusions: This study has shed some light on the role played by Vitamin D in maintaining the antioxidant status of the brain. The study has shown that the Vitamin D is much lower in children diagnosed with ADHD. Vitamin D increases the expression of the enzyme, Gamma-Glutamyl Transf erase (GGT). This enzyme is involved in the metabolism of Glutathione, which is considered an important antioxidant in the brain.

Keywords: ADHD; glutathione; neurological disorder; Vitamin D.

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1. INTRODUCTION

Attention-Deficit Hyperactivity Disorder (ADHD) is a neurological disorder diagnosed on the basis of hyperactivity, inattention and impulsivity. There is no way to detect ADHD by laboratory tests at present and the diagnosis is based on observation of certain behavioral symptoms. It is known from previously published literature that Attention-Deficit Hyperactivity Disorder (ADHD) has a prevalence of 5.3-7.1% among children and adolescents [1]. Before the age of 12, ADHD is characterized by three main symptoms: attention deficiency, impulsivity, and hyperactivity [1,2]. Aggression, anti-social behavior, conflict with peers, and social non adjustment are also clinical symptoms of ADHD [2,3]. At present, the primary treatment method is drug therapy but this has limited success since 30% of patients do not respond to therapy (Fig. 1). Hence, more effective strategies are required [4,5].

ADHD is less common in those parts of the world that receive plenty of sunshine [6]. Exposure to sun and phototherapy are used as treatments for ADHD [7,8]. Numerous studies have investigated the role of nutrition also in the development of ADHD. These studies have found that vitamins and minerals present in breast milk are essential for the newly born child. They protect the child from developing neurological disorders [9-12]. Lately, the attention of researchers has been drawn to the role played by nutrition in the treatment of ADHD as well [10-13]. Many studies have tried to understand the role of micronutrients such as iron [14-16], omega-3 fatty acids [17] and zinc [18,19] in the control and prevention of symptoms of ADHD (Fig. 2). Unfortunately, the role of Vitamin D has been ignored in these studies even when Vitamin D deficiency is known to be associated with various neurological disorders [20-22]. Vitamin D deficiency is common in the Persian Gulf countries despite the easy availability of sunlight. The findings from a previously conducted study have shown that 80% of young girls in Saudi Arabia suffer from Vitamin D deficiency [23].

An important role played by Vitamin D is in the regulation of serum Calcium level in the body. However, it also plays a significant role as signal second messenger in many organs of the body. Hence, it is recommended that Vitamin D levels be checked regularly for pregnant women and newly born babies [24]. The deficiency of Vitamin D, during fetal development, accounts for a number of post-natal neurological disorders [25] (Fig. 3). Additionally, it has been hypothesized that the lack of Vitamin D in both the developing baby and the newly born child adversely affects the development of the brain [25]. The current study was conducted to measure serum Vitamin D levels in children diagnosed with ADHD.

![Fig. 1. Summary of the factors that can lead to ADHD and its current treatment options](image-url)
Fig. 2. Schematic showing the dependence of ADHD on various nutritional factors and metabolites such as the antioxidant, Glutathione.

Fig. 3. The effect of Vitamin D deficiency on the human body.
2. MATERIALS AND METHODS

The study employed 22 children diagnosed with ADHD as research subjects in the age range of 4-13 years and a control group comprising 22 healthy children in the same age group. The demographic data was collected at the time of referral. The diagnosis for ADHD was confirmed using information gathered from personal interviews with the children and their parent(s) and using the criteria described in the Diagnostic Statistical Manual of Mental Disorders (DSM-IV) [26]. Any child suffering from liver or kidney disorder or any other endocrine disease, or anyone using Vitamin D supplements, was excluded from the study. Also excluded were children diagnosed with mental retardation, autism and seizures. Three mL blood samples were obtained from each subject. Vitamin D$_2$ (25-hydroxy cholecalciferol) levels were measured using the DIA source kit and ELISA.

2.1 Statistical Analysis

The data was analyzed using SPSS version-16 (Chicago, IL, USA) by t-test and chi square test and any correlation was considered as significant at α-level ≤0.05.

3. RESULTS AND DISCUSSION

For this study, Vitamin D$_2$ level < 10 ng/mL was classified as being severely deficient (Table 1); Vitamin D$_2$ level in the range between 10-20 ng/mL was classified as being deficient, Vitamin D level in the range between 20-30 ng/mL was classified as being insufficient and a Vitamin D level > 30 ng/mL was classified as being normal. The analysis has shown a difference in serum Vitamin D$_2$ levels between the ADHD and control groups (P-value=0.04) (Table 2). In fact, no research subject in the ADHD group had a normal Vitamin D level. 31.8% of the children in the control group had high serum Vitamin D$_2$ level whereas 61.4% were classified as normal. None of the children in either of the two groups had a Vitamin D$_2$ level high enough that could result in toxicity (Vitamin D$_2$ level >100 ng/mL).

Vitamin D is a neurosteroid and its deficiency results in many neurological disorders [20-22]. Many studies have shown the role played by Vitamin D deficiency in development of neurological disorders [27-33]. Additionally, Vitamin D up-regulates the level of the enzyme, Gamma-Glutamyl Transferase (GGT), also known as Gamma-Glutamyl Transpeptidase. GGT causes the formation of Glutathione, which is an important antioxidant factor in the brain [34]. Lack of Vitamin D during development of the fetus, in the first few days after birth and during childhood, affects nerve differentiation, formation of axon synapses and development of brain structure and function (20).

The results (Table 3) show that children suffering from ADHD exhibited Vitamin D deficiency more frequently than the control group. Additionally, the mean value of serum Vitamin D$_2$ level in the ADHD group (18.60±6.33 ng/ml) was lower than that of the healthy control group (34.34±8.19). This finding confirms the result of a similar study conducted in Turkey where a significant difference (P-value < 0.05) in serum Vitamin D level between ADHD and control groups was demonstrated [35]. Another study reporting 1331 ADHD cases of adolescents less than 18 years of age showed that the Vitamin D level in serum of research subjects was lower than that of the control group. In this study, 8.15% of the ADHD subjects possessed normal serum Vitamin D level [36].

In a study conducted in New Zealand employing 90 ADHD patients over the age of 16, it was found that 27% of the subjects suffered from Vitamin D deficiency. After the use of Vitamin D as a supplement for 8 weeks, many of the subjects reported a lessening of the symptoms of the disease. However, a study in England found no association between ADHD and Vitamin D level [37]. When other supplements such as Zinc, Vitamin B$_{12}$, Iron and Folic acid were investigated, they were found to have no effect [38].

| Vitamin D status      | Blood level (ng/mL) |
|-----------------------|---------------------|
| Severe deficiency     | Less than 10        |
| Deficiency            | 10-20               |
| Insufficiency         | 20-30               |
| Normal                | Other 30            |
| Overdose              | Over 100            |
Table 2. Comparison of serum Vitamin D levels of ADHD patients and control group

| Group     | Severe Vitamin D deficiency | Vitamin D deficiency | Normal Vitamin D level | Total |
|-----------|-----------------------------|----------------------|------------------------|-------|
| ADHD      | 2 (9.1%)                    | 20 (90.1%)           | 0 (0%)                 | 22 (100%) |
| Control   | 0 (0%)                      | 7 (31.8%)            | 15 (38.2%)             | 22 (100%) |
| Total     | 2 (4.5%)                    | 27 (61.4%)           | 15 (34.1%)             | 44 (100%) |

*P*-value < 0.0005

Table 3. Correlation among the various groups

| Group     | Mean | SD  |
|-----------|------|-----|
| ADHD      | 18.6 | 6.3 |
| Control   | 34.3 | 8.2 |
| Total     | 26.5 | 10.8|

*P*-value < 0.0005

4. CONCLUSION

This study has shown that a very high percentage of children exhibiting ADHD suffered from Vitamin D deficiency also. Some of the healthy children in the control group as well exhibited Vitamin D deficiency. It is possible that the low Vitamin D level in children suffering from ADHD causes the expression of the enzyme, Gamma-Glutamyl Transferase (GGT) to become reduced in the ADHD group. GGT is known to produce the antioxidant, Glutathione, which determines the antioxidant status of the brain.

CONSENT

As per international standard, parental written consent has been collected and preserved by the author’s.

ETHICAL APPROVAL

The study was approved by the Ethics Committee of Prince Abdallah Ibn Musaed Hospital (Arar, Saudi Arabia).

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Arnold LE, Hodgkins P, Caci H, Kahle J, Young S. Effect of treatment modality on long-term outcomes in attention deficit/ hyperactivity disorder: A systematic review. PLoS One. 2015;0(2):0116407.
2. Matthews M, Nigg JT, Fair DA. Attention deficit hyperactivity disorder. Curr Top Behav Neurosci. 2014;16:235–66.
3. Gajria K, Lu M, Sikirica V, Greven P, Zhong Y, Qin P, et al. Adherence, persistence, and medication discontinuation in patients with attention-deficit/hyperactivity disorder—a systematic literature review. Neuropsychiatr Dis Treat. 2014;10:1543–69.
4. Brooke SG, Molina Stephen P, Hinshaw L, Arnold E, James M, et al. Adolescent substance use in the multimodal treatment study of Attention-Deficit/Hyperactivity Disorder (ADHD) (MTA) as a Function of Childhood ADHD, Random Assignment to Childhood Treatments, and Subsequent Medication. J Am Acad Child Adolesc Psychiatry. 2013;52(3):250–63.
5. Caye A, Swanson, JM, Coghill D, et al. Treatment strategies for ADHD: An evidence-based guide to select optimal treatment. Mol Psychiatry. 2019;24:390–408.
6. Arns M, van der Heijden KB, Arnold LE, Kenemans JL. Geographic variation in the prevalence of attention deficit/ hyperactivity disorder: the sunny perspective. Biol Psychiatry. 2013;74(8):585–90.
7. Rybak YE, McNeely HE, Mackenzie BE, Jain UR, Levitan RD. An open trial of light therapy in adult attention-deficit/ hyperactivity disorder. J Clin Psychiatry. 2006;67(10):1527–35. [PubMed] [Google Scholar]
8. Hoebert M, van der Heijden KB, van Geijlswijk IM, Smits MG. Long-term follow-up of melatonin treatment in children with
ADHD and chronic sleep onset insomnia. J Pineal Res. 2009;47(1):1–7.

9. Millichap JG. Etiologic classification of attention-deficit/ hyperactivity disorder. Pediatrics. 2008;121(2):358–65.

10. Mimouni-Bloch A, Kachevanskaya A, Mimouni FB, Shuper A, Raveh E, Linder N. Breastfeeding may protect from developing attention-deficit/hyperactivity disorder. Breastfeed Med. 2013;8(4):363–7.

11. Shamberger R. Attention-deficit disorder associated with breast-feeding: a brief report. J Am Coll Nutr. 2012;31(4):239–42.

12. Bener A, Kamal M. Predict attention deficit hyperactivity disorder? Evidence -based medicine. Glob J Health Sci. 2013;6(2):47–57.

13. Millichap JG, Yee MM. The diet factor in attention-deficit/hyperactivity disorder. Pediatrics. 2012;129(2):330–7.

14. Gottfried RJ, Gerring JP, Mithal A, Wahl DA, Bonjour JP, Burckhardt P, Dawson-Hughes B, Eisman JA, et al. Global vitamin D status and determinants of hypovitaminosis D. Osteoporos Int. 2009;20(11):1807–20.

15. Calarge C, Farmer C, DiSilvestro R, Arnold LE. Serum ferritin and amphetamine response in youth with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2010;20(6):495–502.

16. Cortese S, Angriman M, Lecendreux M, Konofal E. Iron and attention deficit/hyperactivity disorder: What is the empirical evidence so far? A systematic review of the literature. Expert Rev Neurother. 2012;12(10):1227–40.

17. Antalis CJ, Stevens Lj, Campbell M, Pazdro R, Ericson K, Burgess JR. Omega-3 fatty acid status inattentive deficit/hyperactivity disorder. Prostaglandins Leukot Essent Fatty Acids. 2006;75(4-5):4–308.

18. Arnold LE, DiSilvestro RA, Bozzolo D, Bozzolo H, Crowl L, Fernandez S, et al. Zinc for attention-deficit/hyperactivity disorder: Placebo-controlled double-blind pilot trial alone and combined with amphetamine. J Child Adolesc Psychopharmacol. 2011;21(1):1–19.

19. Lepping P, Huber M. Role of zinc in the pathogenesis of attention-deficit hyperactivity disorder: implications for research and treatment. CNS Drugs. 2010;24(9):721–8.

20. Eyles DW, Burne TH, McGrath JJ. Vitamin D, effects on brain development, adult brain function and the links between low levels of vitamin D and neuropsychiatric disease. Front Neuroendocrinol. 2013;34(1):47–64.

21. Humble MB, Gustafsson S, Bejerot S. Low serum levels of 25-hydroxy vitamin D (25-OHD) among psychiatric out-patients in Sweden: Relations with season, age, ethnic origin and psychiatric diagnosis. J Steroid Biochem Mol Biol. 2010;121(1-2):467–70.

22. Howland RH. Vitamin D and depression. J Psychosoc Nurs Ment Health Serv. 2011;49(2):15–8.

23. Mithal A, Wahl DA, Bonjour JP, Burckhardt P, Dawson-Hughes B, Eisman JA, et al. Global vitamin D status and determinants of hypovitaminosis D. Osteoporos Int. 2009;20(11):1807–20.

24. Cannel J J, Hollis B W. Use of vitamin D in clinical practice. Altern Med Rev. 2008;13(1):6–20.

25. Dawodu A, Wagner CL. Mother-child vitamin D deficiency: An international perspective. Arch Dis Child. 2007;92(9):737–40.

26. American Psychiatric Association, authors; Diagnostic and statistical manual of mental disorders, fourth edition (DSM-IV) Washington: The Association; 2002.

27. McCue RE, Charles RA, Orendain GC, Joseph MD, Abanishe JO. Vitamin D deficiency among psychiatric inpatients. Prim Care Companion CNS Disord. 2012;14(2).

28. Menkes DB, Lancaster K, Grant M, Marsh RW, Dean P, du Toit SA. Vitamin D status of psychiatric inpatients in New Zealand’s Waikato region. BMC Psychiatry. 2012;12:68.

29. Buell JS, Dawson-Hughes B. Vitamin D and neurocognitive dysfunction: preventing Decline. Mol Aspects Med. 2008;29(6):415–22.

30. Hoogendijk WJ, Lips P, Dik MG, Deeg DJ, Beekman AT, Penninx BW. Depression is associated with decreased 25-hydroxyvitamin D and increased parathyroid hormone levels in older adults. Arch Gen Psychiatry. 2008;65(5):506–12.

31. Berk M, Dodd S, Kauer-Sant’anna M, Malhi GS, Bourin M, Kapczinski F, et al. Dopamine dysregulation syndrome: implications for a dopamine hypothesis of
bipolar disorder. Acta Psychiatr Scand Suppl. 2007;(434):41–9.
32. McGrath JJ, Eyles DW, Pedersen CB, Anderson C, Ko P, Burne TH, et al. Neonatal vitamin D status and risk of schizophrenia: A population-based case-control study. Arch Gen Psychiatry. 2010;67(9):889–94.
33. Mostafa GA, Al-Ayadhi LY. Reduced serum concentrations of 25-hydroxyvitamin D in children with autism: relation to autoimmunity. J Neuroinflammation. 2012;9:201.
34. Hanigan MH. Gamma-Glutamyl Transpeptidase: Redox Regulation and Drug Resistance. Adv Cancer Res. 2014;122:103–141.
35. Goksugur SB, Tufan AE, Semiz M, Gunes C, Bekdas M, Tosun M, et al. Vitamin D Status in Children with Attention Deficit Hyperactivity Disorder. Pediatr Int. 2014;56(4):515–9.
36. Kamal M, Bener A, Ehlayel MS. Is high prevalence of vitamin D deficiency a correlate for attention deficit hyperactivity disorder. Atten Defic Hyperact Disord. 2014;6(2):73–8.
37. Tolppanen AM, Sayers A, Fraser WD, Lewis G, Zammit S, Lawlor DA. The association of 25-hydroxyvitamin D3 and D2 with behavioural problems in childhood. PLoS One. 2012;7(7):40097.
38. Rucklidge JJ, Johnstone J, Gorman B, Boggis A, Frampton CM. Moderators of treatment response in adults with ADHD treated with a vitamin-mineral supplement. Prog Neuropsychopharmacol Biol Psychiatry. 2014;50:163–71.

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