

Is high prevalence of vitamin D deficiency a correlate for attention deficit hyperactivity disorder?

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Abstract The aim of the study was to determine the association between vitamin D and attention deficit hyperactivity disorder (ADHD), and difference in the level of vitamin D in ADHD children and control. This a case-control study carried out in school health and primary health care clinics. A total of 1,331 children and adolescents who were diagnosed with ADHD based on clinical criteria and standardized questionnaires were enrolled in this study and were matched with 1,331 controls, aged 5–18 years old. Data on body mass index (BMI), clinical biochemistry variables including serum 25-hydroxyvitamin D were collected. The study found significant association between ADHD and vitamin D deficiency after adjusting

for BMI and sex (adj. OR 1.54; 95 % CI 1.32–1.81; $P < 0.001$). Majority of the ADHD children were in the age group 5–10 years (40.7 %), followed by 11–13 years (38.4 %). The proportion of BMI <85th percentile was significantly over represented in ADHD group as compared to healthy control (87.8 vs. 83 %; $P < 0.001$, respectively), while on the other hand, BMI >95th percentile was over represented in the control than ADHD group (7.6 vs. 4.6 %; $P < 0.001$, respectively). Mean values of vitamin D (ng/mL) were significantly lower in ADHD children (16.6 ± 7.8) than in healthy children (23.5 ± 9.0) ($P < 0.001$). There was significant correlation between vitamin D deficiency and age ($r = -0.191$, $P = 0.001$); calcium ($r = 0.272$, $P = 0.001$); phosphorous ($r = 0.284$, $P = 0.001$); magnesium ($r = 0.292$, $P = 0.001$); and BMI ($r = 0.498$, $P = 0.001$) in ADHD children. The vitamin D deficiency was higher in ADHD children compared to healthy children.

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Abbreviations

ADHD Attention deficit hyperactivity disorder
BMI Body mass index

Introduction

Attention deficit hyperactivity disorder (ADHD) may affect many aspects of a child's life. It is a common disorder among school-aged children (Barbaresi et al. 2002; American Academy of Pediatrics 2000; Purper et al. 2004), leading to disruptive behaviors and reduced academic

achievement at school (Bener et al. 2008; Sayal et al. 2006). During the last three decades, many articles have raised concerns about the issue of childhood hyperactivity and inattentiveness (Barbaresi et al. 2002; American Academy of Pediatrics 2000; Purper et al. 2004; Bener et al. 2008; Sayal et al. 2006). Attention deficit hyperactivity disorder is most commonly diagnosed behavioral disorder of childhood, affecting 8–12 % of school-aged children (Childress and Berry 2012). The symptoms of ADHD are caused by a neurological dysfunction within the brain and the underlying physiological mechanism which causes ADHD is still not thoroughly understood and remains under scientific study (Bener et al. 2006, 2008).

The pathophysiology of ADHD is complex and not well understood. No specific etiology has been identified for ADHD, and findings are consistent with a multifactorial hypothesis (Childress and Berry 2012; Bener et al. 2006; Swanson et al. 2007; Parisi et al. 2010). Indeed, all neuropsychiatric disorders are thought to be caused by a complex combination of genetic, environmental, and biological factors. Therefore, the proposed etiologies related to prenatal risk factors, genetics, and ADHD neurobiological deficits may all be involved in the pathophysiology of ADHD in different individuals (Biederman 2005; Childress and Berry 2012; Bener et al. 2006). There is limited information about this phenomenon among non-western cultures, in particular in the Arab region (Bener et al. 2006, 2008; Childress and Berry 2012). Prospective studies also indicate that children affected by ADHD are at a high risk of developing comorbid disorders as well as impaired social adjustment (Swanson et al. 2007), epilepsy and EEG anomalies (Parisi et al. 2010), iron deficiency (Parisi et al. 2012), depressive disorders, and learning disabilities (Genizi et al. 2013). In addition, hypocalcemic seizures in vitamin D deficiency has recently been described (D'Eufemia et al. 2012).

Children with ADHD may be at risk of a variety of nutrient deficiencies due to the attentional demands required to obtain adequate levels of nutrient intake as well as the appetite suppressant effects of treatment medication. Vitamin D can boost the levels of the antioxidant glutathione in the brain. Vitamin D deficiency is a major health problem noticed in many parts of the world (Bener et al. 2009). It is not restricted to sunshine-limited regions of the globe. It is still commonly seen in sunshine-rich areas such as Asia-Pacific (Whiting et al. 2007), Indian subcontinent (Bapai et al. 2005), Africa, and Middle East regions (El-Rassi et al. 2009). There are several studies indicating that in the Gulf region, vitamin D deficiency is quite common among people especially in Qatar (Bener et al. 2009a, b, c; Bener and Hoffmann 2010), Kuwait (Majid Molla et al. 2000), UAE (Dawodu et al. 2002), and Saudi Arabia (Al-Mustafa et al. 2007). Sunlight exposure is an important

factor for hypovitaminosis D. Although Gulf countries are sun-rich countries, children are not exposed to sunlight because of the extreme climate and their lifestyle factors such as style of clothing and less outdoor activities. Therefore, higher prevalence of vitamin D deficiency among children in this region could be a possible risk factor for ADHD (Swanson et al. 2007; Bener et al. 2009a, b; Bener and Hoffmann 2010).

The aim of this study was to use a case-control design to investigate whether there are differences in serum vitamin D levels between ADHD and healthy children age 5–18 years old.

Subjects and methods

This is a case-control study which was designed to determine the relationship between vitamin D and ADHD in subjects younger than 18 years in Qatar. The survey was conducted over a period from June 2011 to May 2013. This current study involved a 1,331 ADHD cases and 1,331 age-and ethnicity-matched, control subjects.

To secure a representative sample of the study population, the sampling plan was stratified with proportional allocation. The list of names of government schools was obtained from the Office of Director of General Education, Supreme Council of Education. Government schools were segregated according to the sexes. There were 94,985 children enrolled in government and private primary schools for boys and girls and 38,622 children enrolled in government and private intermediate or preparatory schools for boys and girls and further 34,132 children enrolled in government and private secondary schools for boys and girls in Qatar. To fulfill the objective of the current study, the estimated sample size was 1,750 cases and 1,750 control students.

The study was approved by the Hamad General Hospital, Hamad Medical Corporation. All human studies have been approved by the research ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All the subjects who agreed to participate in this study gave their informed consent prior to their inclusion in the study.

Data collection

Selection of ADHD subjects

The diagnosis of ADHD was based on physician diagnosis. The Conners' teacher scale was used to screen ADHD symptoms among children (Bener et al. 2006, 2008; Parisi et al. 2012). Teacher rating scales (Bener et al. 2006, 2008; Parisi et al. 2012) are also an important part of the evaluation and diagnosis. Teacher rating scales provide necessary

information about the child in the school setting. We used SNAP questionnaire and or Conner's filled by both parents and teachers in addition to the clinical history and school performance. ADHD subjects aged below 18 years were identified from PHC Clinics and School Health as a part of cohort study. A random sample of 1,750 children and adolescents with ADHD were approached. A total of 1,331 gave consent and participated in study with a response rate of 76.1 %. The study excluded the subjects who had calcium supplements or vitamin D intake during the last 6 month before the study; history of epilepsy or anti-epileptic drugs since they affect vitamin D; any history of sunblock use and the pubertal age since we know that behavioral problems and 25(OH) D2 are affected by puberty and use of sunblock.

Selection of controls

Control subjects aged below 18 years were identified from healthy subjects if not ever been diagnosed as ADHD. This group involved a random sample of 1,835 healthy subjects who visited the PHC Centers for any reason other than acute or chronic disease, and only 1,331 subjects were included due to the either refusal of the mother or difficulty in drawing blood from very uncooperative subjects; with a response rate (72.5 %). Healthy subjects were confirmed as non-ADHD children through physician's assessment, SNAP questionnaire, and screening their medical files. The healthy subjects were selected in a way matching to the age, gender, and ethnicity of cases to give a good representative sample of the studied population.

Laboratory investigation

Blood collection and serum measurements of vitamin D
Trained phlebotomists collected venous blood samples, and serum was separated and stored at -70°C until analysis. Serum 25-hydroxyvitamin D (25OHD), a vitamin D metabolite, was measured using a commercially available kit (DiaSorin Corporate Headquarter, Saluggia, Italy). The treated samples were then assayed using competitive binding radioimmunoassay (RIA) technique. Subjects were classified into four categories: (1) *severe* vitamin D deficiency, $25(\text{OH})\text{D} < 10 \text{ ng/mL}$; (2) *moderate* deficiency, $25(\text{OH})\text{D} 10\text{--}19 \text{ ng/mL}$; (3) *mild* deficiency, $25(\text{OH})\text{D} 20\text{--}29 \text{ ng/mL}$; and (4) normal/optimal level is between 30 and 80 ng/mL (Swanson et al. 2007; Bener et al. 2009a, b; Bener and Hoffmann 2010). Some biochemical parameters measured from the serum included vitamin D, calcium, phosphorus, magnesium, urea, parathyroid hormone, bilirubin, albumin, cholesterol, and triglycerides on the basis of previous recommendations (Bener et al. 2009a, b; Bener and Hoffmann 2010; Majid Molla et al. 2000; Holick 2007;

Holick et al. 2011). Serum levels of these biochemical parameters were determined according to standard laboratory procedures.

The questionnaire was designed to meet the objective of this study. The survey was conducted by physicians and based on standardized interviews performed by trained health professionals and nurses. The participants were interviewed by health professionals and nurses concerning their socio-demographic information such as age, gender, place of residence (urban and semi-urban), and monthly income. Height and weight were measured using standardized methods and all the participants wore light clothes and no shoes for this part of the examination. Body mass index (BMI) was calculated as the weight in kilograms (with 1 kg subtracted to allow for clothing) divided by height in meters squared. BMI $<85^{\text{th}}$ percentile was considered normal weight, 85–95th percentile as overweight and $>95^{\text{th}}$ percentile as obese.

Student's *t* test was used to ascertain the significance of differences between mean values of two continuous variables and nonparametric Mann-Whitney test was used. The Fisher's exact test (two-tailed) and Chi-square tests were performed to test for differences in proportions of categorical variables between two or more groups. Pearson's correlation coefficient was used to evaluate the strength of association between variables. The level $P < 0.05$ was considered as the cutoff value for significance.

Results

Table 1 shows the socio-demographic characteristics of the studied children according to ADHD and healthy subjects. Majority of the ADHD children were in the age group 5–10 years (40.7 %), followed by 11–13 years. There was a significant differences observed between ADHD and healthy children in terms of gender ($P < 0.001$), normal weight ($P < 0.001$), obesity ($P < 0.001$), level of education ($P = 0.04$), household monthly income ($P = 0.04$), and consanguinity ($P = 0.02$). Obesity was significantly lower in ADHD children compared to healthy children (4.6 vs. 7.6 %; $P < 0.001$).

Table 2 presents some biochemistry values among ADHD and control children. The study revealed that vitamin D deficiency was considerably more common among ADHD children compared to healthy children. The mean value of vitamin D in ADHD children was much lower than the normal value, and there was a significant difference found in the mean values of vitamin D between ADHD (16.6 ± 7.8 with median 16) versus control children (23.5 ± 9.9) ($P < 0.001$). The mean values of calcium (2.14 ± 0.1 vs. 2.37 ± 0.1 ; $P < 0.001$), phosphorous (1.48 ± 0.3 vs. 1.65 ± 0.2 ; $P = 0.001$), and magnesium

Table 1 Socio-demographic characteristics of studied ADHD and control subject. ($n = 2,662$)

| Variable | ADHD children $n = 1,331$ $n (\%)$ | Control children $n = 1,331$ $n (\%)$ | P value |
|--------------------------------|--|---|---------|
| Age group | | | |
| 5–10 years | 542 (40.7) | 538 (40.4) | |
| 11–13 years | 511 (38.4) | 493 (37.0) | 0.556 |
| 14–18 years | 278 (20.9) | 300 (22.5) | |
| Sex | | | |
| Male | 963 (72.4) | 766 (57.6) | <0.001 |
| Female | 368 (27.6) | 565 (42.4) | |
| Nationality | | | |
| Qatari | 669 (50.3) | 704 (52.9) | 0.175 |
| Non-Qatari | 662 (49.7) | 627 (47.1) | |
| BMI group | | | |
| <85th percentile | 1,168 (87.8) | 1,104 (83.0) | <0.001 |
| 85–95th percentile | 102 (7.6) | 125 (9.4) | <0.110 |
| >95th percentile | 61 (4.6) | 102 (7.6) | <0.001 |
| Level of education | | | |
| Primary | 443 (33.3) | 461 (34.6) | |
| Intermediate | 435 (32.7) | 375 (28.2) | 0.036 |
| Secondary | 453 (34.0) | 495 (37.2) | |
| Household income (\$ US/month) | | | |
| <3,000 | 393 (29.5) | 447 (33.6) | |
| 3,000–6,000 | 520 (39.1) | 514 (38.6) | 0.040 |
| >6,000 | 418 (31.4) | 370 (27.8) | |
| Place of living | | | |
| Urban | 1,206 (90.6) | 1,217 (91.4) | |
| Semi-urban | 125 (9.4) | 114 (8.6) | 0.498 |
| Consanguinity | | | |
| Yes | 514 (37.0) | 432 (32.5) | |
| No | 839 (63.0) | 899 (67.5) | 0.016 |

Table 2 Biochemistry values among ADHD and control subjects

| Biochemistry parameters (units) | ADHD children $n = 1,331$ Mean \pm SD | Control children $n = 1,331$ Mean \pm SD | P value |
|------------------------------------|--|---|---------|
| Vitamin D (ng/mL) | 16.6 \pm 7.8 | 23.5 \pm 9.0 | <0.001 |
| Calcium (mmol/L) | 2.14 \pm 0.1 | 2.37 \pm 0.1 | <0.001 |
| Phosphorous (mmol/L) | 1.48 \pm 0.3 | 1.65 \pm 0.2 | 0.001 |
| Magnesium (mmol/L) | 0.79 \pm 0.12 | 0.88 \pm 0.10 | <0.001 |
| Glucose (mmol/L) | 4.64 \pm 0.8 | 4.36 \pm 0.9 | 0.015 |
| Potassium (mmol/L) | 4.61 \pm 0.5 | 4.50 \pm 0.5 | 0.013 |
| Alkaline phosphate (u/L) | 206.16 \pm 73.6 | 203.71 \pm 73.7 | 0.447 |

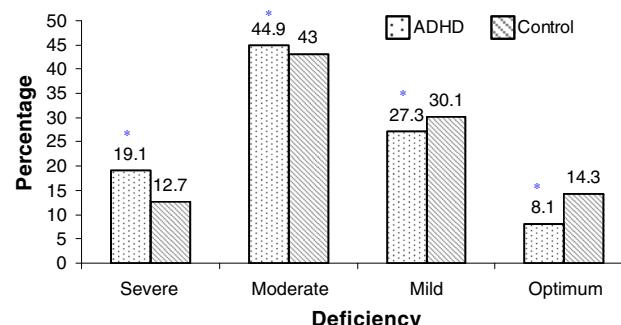
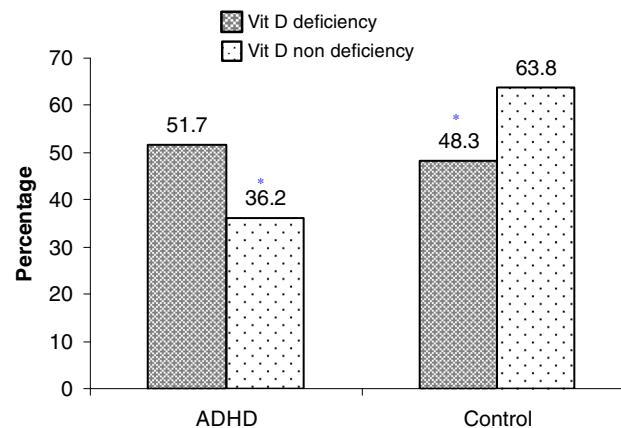
(0.79 ± 0.12 vs. 0.88 ± 0.10 ; $P < 0.001$) were significantly lower in ADHD children than in controls.

There was significant correlation between vitamin D deficiency and age ($r = -0.191$, $P = 0.001$); calcium

Table 3 Multivariable logistic regression for the association between vitamin D deficiency and ADHD

| Variables | Adj. OR (95 % CI) | P value |
|-----------------------|-------------------|---------|
| ADHD | 1.54 (1.32–1.81) | <0.001 |
| BMI percentile groups | | |
| <85 | 1.16 (0.84–1.61) | 0.436 |
| 85–95 | 1.31 (0.87–1.98) | |
| >95 | 1 | |
| Gender | | |
| Male | 1 | <0.001 |
| Female | 1.53 (1.29–1.81) | |

Adj. OR = adjusted odds ratios, outcome variable = vitamin D Deficiency (1 = yes, 0 = no)

**Fig. 1** Serum level of vitamin D among ADHD and control children. *P value < 0.001 as compared to controls**Fig. 2** Vitamin D deficiency and non-deficiency in ADHD and healthy children. *P value ≤ 0.001 as compared to vitamin D deficiency

($r = 0.272$, $P = 0.001$); phosphorous ($r = 0.284$, $P = 0.001$); magnesium ($r = 0.292$, $P = 0.001$); and BMI ($r = 0.498$, $P = 0.001$) in ADHD children. The differences of vitamin D deficiency between ADHD and controls were significant even after controlling for BMI. Multivariable logistic regression analysis showed that ADHD was significantly associated with vitamin D deficiency after

adjusting for BMI and gender (adj. OR = 1.54; 95 % CI 1.32–1.81; $P < 0.001$) (Table 3).

Figures 1 and 2 reveal the distribution of serum vitamin D in children with ADHD and healthy subjects. Severe vitamin D deficiency (<10 ng/mL) was significantly higher in ADHD children (19.1 %) than in controls (12.7 %) ($P < 0.001$). Moderate deficiency (between 10 and 20 ng/mL) was also slightly higher in ADHD children compared with controls (44.9 vs. 43 %; $P < 0.001$). Vitamin D sufficient level (>30 ng/mL) was significantly lower in ADHD children than in controls (8.1 vs. 14.3 %; $P < 0.001$).

Discussion

This case-control study presents, to the best of our knowledge, the first report on association of vitamin D in children with ADHD. The exact etio-pathological changes leading to ADHD are not well defined. The effects of vitamin D on brain development and function, as a neuro-immunomodulatory, leading to behavioral and neuro-psychiatric diseases have recently been reviewed (de Fernandes Abreu et al. 2009; Eyles et al. 2013). It affects the innate and adaptive immunity (Hewison 2011), with diverse effects on various components of immune system particularly T cell, B cells, cytokines, and even T regulatory cells (Urry et al. 2012).

Over the last decade, the association of vitamin D with neuro-psychiatric diseases conditions has been the focus of interest of multiple studies including those on multiple sclerosis (Smolders et al. 2013), schizophrenia (McGrath et al. 2010), Parkinson's disease (Vinh Quoc Luong and Thi Hoang Nguyen 2012), depression and suicide (Umhau et al. 2013), Alzheimer's disease (Annweiler et al. 2013), and cognitive performance in adults (Annweiler et al. 2009).

Various studies indicate that vitamin D is essential for the brain as promotes normal brain development (Eyles et al. 2009), enhances neuroprotection, and modulates matrix metalloproteinases and anti-inflammatory mechanisms (Vinh Quoc Luong and Thi Hoang Nguyen 2012).

Studies on animal models revealed that developmental vitamin D deficiency leads to abnormalities in the brain, large lateral ventricles, poor tissue differentiation, and reduced expression of neurotropic factors (Eyles et al. 2009). In these animals, these resultant brain changes were clinically evident as abnormal behavioral alterations and hyperlocomotion (Groves et al. 2013). This study presents an association, in children, between ADHD with its disruptive behavior and hypovitaminosis D.

Although our study included large sample of participants and it is case-controlled, it has some limitations. Data on the birth month of subjects and parental consanguinity are lacking. As confounding factors, we cannot exclude the

possibility that they have contributed, to some extent, in determining the association of vitamin D with ADHD. Another limitation is the vitamin D source. It is known that vitamin is readily available either by oral intake or by skin biosynthesis through UVB. The study did not include data on children kept on avoidance/restriction diet. It is known that avoidance or restriction diet is one of the modalities of therapy in some case of ADHD and for a relatively short period of time. However, it is unlikely that the majority of ADHD patients in our study were on avoidance diet, or for prolonged time of dietary restrictions as the nutritional parameters (BMI) and laboratory biomarkers (serum albumin, BUN, creatinine) do not indicate evidence avoidance long enough to affect vitamin D status.

Hyperactivity and impulsivity are some of the main characteristic features of ADHD disease in children. In order to avoid injuries, the outdoor physical activity of these children might be restricted in type or limited in duration. As a result, this make them theoretically more liable be deprived from enough exposure to UVB and vitamin D biosynthesis. Data on duration of outdoor activity are lacking, another limitation in our study.

In vitamin D deficient children with ADHD, vitamin D treatment should be initiated. However, whether vitamin D supplementation should be considered as an additional mode of therapy of these children needs further investigation.

What's known on this subject

The data are lacking regarding the association between vitamin D and ADHD in human beings.

What this study adds

The association between vitamin D deficiency and ADHD in children is never been reported. This is the first study to investigate an association between vitamin D and ADHD. The vitamin D deficiency was higher in studied ADHD children than in controls.

Conclusion

The present study revealed that vitamin D deficiency was higher in ADHD children compared to healthy children. Supplementing infants with vitamin D might prove to be a safe and effective strategy for reducing the risk of ADHD, but further genomic and some other relevant tests need to be done.

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Conflict of interest All authors declare that they have no conflicts of interest.

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