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Article · August 2016

DOI: 10.1515/jpem-2015-0473

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Hormone disorder and vitamin deficiency in attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASDs)

DOI 10.1515/jpem-2015-0473
Received December 17, 2015; accepted July 18, 2016; previously published online August 22, 2016

Abstract

Background: The aim of this study was to analyze thyroid hormones and antibodies, ferritin, vitamins B12 and D, adrenal and gonadal steroid levels, and celiac antibodies in children diagnosed with attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD).
Methods: Between February 2014 and July 2014, a total of 77 children and adolescents (31 girls, 46 boys) who were admitted to the Van Training and Research Hospital were included in the study. The study population was divided into three groups including ADHD (n=34), ASD (n=16), and age- and sex-matched healthy controls (n=27). The diagnosis of ADHD was made on the basis of Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5) and DSM-4 Turkish version with the diagnostic interview and Disruptive Behavior Disorder Rating Scale (DBDRS). The diagnosis of ASD was based on the DSM-4 and DSM-5 Turkish version with the diagnostic interview and the Childhood Autism Rating Scale (CARS). The blood samples were obtained between 8:00 and 9:00 A.M.
Results: There was a statistically significant difference in vitamin B12 and D levels and ferritin values among the three groups. The ASD group had the highest ferritin and the lowest vitamins B12 and D levels. Vitamin D levels of the ADHD group were significantly lower compared to the healthy controls.
Conclusions: Our study results highlight the importance of supplementation of vitamins B12 and D in the ASD and ADHD patients.

Keywords: adrenal and gonadal steroids; attention deficit hyperactivity disorder (ADHD); autism spectrum disorder (ASD); thyroid hormones; vitamin B12; vitamin D.

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Introduction

Attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASDs) are two distinct entities, which dramatically change the lives of children. Attention deficit hyperactivity disorder is common in school-age children, which may cause a decrease in school performance in addition to disruptive behaviors [1]. The pathophysiology of ADHD is complex and not clearly understood yet. Although there is no definite identifiable factor, there are several hypotheses that ADHD is multi-factorial [2]. Therefore, prenatal risk factors and genetic properties are the most commonly emphasized in the underlying etiology of the disease [3]. However, ADHD is quite frequent with comorbid conditions such as epilepsy, electroencephalography abnormalities, iron deficiency, depressive disorders, and learning disabilities [4]. However, ASDs are a group of biologically based neurodevelopmental heterogeneous disorders which are related to known risk factors including mutational or variant genes, advanced paternal age, prematurity, and birth complications [5, 6]. Recently, it has been reported that deficiencies of vitamins B12 and D can be present in both groups of diseases and such deficiencies can be included among the risk factors [6, 7].

Additionally, it has been shown that increased androstenedione levels can be a risk factor for ASD in adults [8]. An association of subclinical hypothyroidism and ADHD is also among the other reported risk factors [9]. Therefore, in this study, we aimed to analyze thyroid

hormones and antibodies, vitamins B12 and D levels, ferritin levels, and adrenal and gonadal steroid levels in children with ADHD and ASD in the Van region. To the best of our knowledge, our study is the first to evaluate all these risk factors reported in the literature.

Materials and methods

Between February 2014 and July 2014, a total of 77 children and adolescents (31 girls and 46 boys) who were admitted to the Van Training and Research Hospital were included in the study. The study population was divided into three groups including ADHD (n=34), ASD (n=16), who were admitted to the Pediatric Endocrinology outpatient clinic, and the age- and sex-matched healthy controls (n=27), who were admitted to the Pediatric Endocrinology outpatient clinic for regular developmental visits. The diagnosis of ADHD was made on the basis of Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) and DSM-4 Turkish version with the diagnostic interview and Disruptive Behavior Disorder Rating Scale (DBDRS). The diagnosis of ASD was based on the DSM-4 and DSM-5 Turkish versions with the diagnostic interview and the Childhood Autism Rating Scale (CARS), which was filled out by the parents and teachers.

The body weight and height of all the study population were recorded and the blood samples were obtained between 8:00 and 9:00 A.M. due to the diurnal variation of the hormones. Exclusion criteria were as follows: comorbidities, known genetic or metabolic disorders, head injury or previous history of a surgery, infection on admission, abnormal renal or hepatic test results, chronic diseases, and the use of medication for a chronic condition or any vitamin supplements. The control group included healthy subjects without ADHD or ASD or chronic disease who did not receive vitamin supplements.

Biochemical analysis including serum electrolytes, kidney and liver enzymes, calcitriol, vitamin B12, adrenocorticotropic hormone (ACTH), and cortisol levels was performed at our central laboratory in the Yuzuncu Yil University, Faculty of Medicine using the Architect CI-16200 (Abbott Diagnostics, Abbott Park, IL, USA) and the chemiluminescent method. Ferritin, dehydroepiandrosterone (DHEA), and androstenedione levels were analyzed in the biochemistry laboratory of the hospital using the Immulite® 2000 (Siemens Healthcare Diagnostics, Los Angeles, CA, USA) with the chemiluminescent method.

A written informed consent was obtained from each parent. The study protocol was approved by the Yuzuncu Yil Unviersity, Faculty of Medicine, Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

Statistical analysis was performed using the SPSS v13 software (SPSS Inc., Chicago, IL, USA). The descriptive data were expressed in mean and standard deviation with minimum and maximum values. Normally distributed continuous variables were analyzed using one-way analysis of variance (ANOVA) among the groups. Abnormally distributed non-parametric variables were analyzed using the Kruskal-Wallis H and the χ^2 tests. A p-value of <0.05 was considered statistically significant.

Results

The distribution of the groups according to age and sex is shown in Table 1. There was no significant difference in the age, sex, body weight, and height among the groups.

The distribution of the groups according to thyroid hormone levels and antibody titers ispresented in Table 2. We found no statistically significant difference in the thyroid-stimulating hormone (TSH), free T4 and anti-TPO antibody titers among the groups except one patient in the ADHD group who was diagnosed with autoimmune thyroiditis. This case had normal thyroid hormone levels with an anti-TPO level of 264 IU/mL. In the remaining subjects, thyroid antibody titers were negative. None had selective immunoglobulin A (IgA) deficiency. There was no significant difference in the tissue transglutaminase IgA levels among the three groups. However, the tissue transglutaminase IgA level was high (30 U/L), although the result of the small intestine biopsy specimens obtained by endoscopy was compatible with non-specific duodenitis. In addition, there was no statistically significant difference in the incidence of Celiac disease among the groups ($p>0.05$).

The vitamin levels of all groups are shown in Table 3. There was a statistically significant difference in the vitamin B12 and D levels and ferritin values among the groups. None of the patients had anemia. Although the ferritin levels were found to be normal in both patient groups, the highest ferritin level was in the ASD group, while the lowest ferritin values were found in the control group. However, there was no statistically significant difference in the ferritin levels between the ADHD and ASD groups ($p>0.05$), while a statistically significant difference was found between the patient groups and healthy controls ($p<0.05$ and $p<0.05$, respectively). According to the vitamin B12 analysis in the subjects without anemia, the ASD group had the lowest vitamin B12 levels, whereas the vitamin B12 levels of the ADHD group were significantly lower compared to the controls. In addition, the lowest vitamin D level was found in the ASD group, followed by the ADHD group, while the highest vitamin D levels were detected in the control group. However, there was no correlation between the vitamin D and B12 levels and ferritin values ($p>0.05$).

Adrenal and gonadal hormone levels according to the sex are shown in Table 4. However, due to the small sample size, we were unable to divide patients into groups according to the pubertal age. As we were unable to find any significant differences in the age among the groups, we divided the sample according to their sex to correctly identify the gonadal and adrenal hormone levels. This would

Table 1: Distribution of the groups according to age, gender, body weight, and heights.

	n	Age, years	p-Value	Gender		p-Value	Body weight, kg	p-Value	Height, m	p-Value
		Mean±SDS (min–max)		Girl	Boy		Mean±SDS (min–max)		Mean±SDS (min–max)	
ADHD	34	7.68±3.20 (2–14)	>0.05	11	23	>0.05	28.47±10.21 (12.50–57.00)	>0.05	1.28±0.19 (0.84–1.61)	>0.05
ASD	16	7.88±5.18 (2–18)		6	10		37.46±26.53 (12–82)		1.24±0.32 (0.88–1.70)	
Control	27	9.80±4.01 (3.5–17)		14	13		29.46±14.22 (13.9–59)		1.3±0.23 (0.93–1.67)	

ADHD, attention deficit hyperactivity disorder; ASDs, autism spectrum disorders.

Table 2: Comparison of the groups according to thyroid hormones, thyroid anti-bodies, and tissue transglutaminase IgA levels.

	ADHD	ASD	Control	p-Value
	Mean±SDS (min–max)	Mean±SDS (min–max)	Mean±SDS (min–max)	
TSH, μU/mL	2.27±0.76 (0.91–3.7)	2.03±0.93 (0.61–4.1)	2.61±1.45 (0.07–5.4)	>0.05
T4, ng/dL	1.46±1.71 (1–1.8)	1.11±0.13 (0.8–1.3)	1.13±0.16 (0.64–1.37)	>0.05
Anti-TPO, IU/mL	10.13±47.96 (0.4–26.4)	1.31±0.97 (0.57–4.6)	0.97±0.40 (0.45–2.2)	>0.05
Tissue transglutaminase IgA, U/L	3.89±5.40 (0.0–30.0)	3.15±2.95 (0–10.8)	1.34±0.26 (1.09–1.6)	>0.05

ADHD, attention deficit hyperactivity disorder; ASDs, autism spectrum disorders.

Table 3: Comparison of the groups according to vitamin B12, vitamin D, ferritin, and folate levels.

	ADHD	ASD	Control	p-Value
	Mean±SDS (min–max)	Mean±SDS (min–max)	Mean±SDS (min–max)	
Vitamin B12, pg/mL	371.72±160.63 (156–924)	235.13±68.68 (116–401)	424.04±167.94 (189–900)	0.001
Folate, ng/mL	10.16±2.93 (4–15)	9.17±3.96 (4–16)	8.52±3.75 (2.9–20)	>0.05
25 OH vitamin D, ng/dL	19.49±8.53 (8.1–37.4)	15.11±7.47 (3.9–22.5)	28.73±9.04 (11.6–44.7)	<0.001
Ferritin, ng/mL	39.43±15.00 (16–75)	50.88±31.99 (17–133)	29.14±17.74 (1.5–70)	>0.05

ADHD, attention deficit hyperactivity disorder; ASDs, autism spectrum disorders.

make it possible to compare these hormone levels in each group separately. Furthermore, we found no significant differences in the adrenal and gonadal hormone levels. The 17-OH progesterone level was 3.24 ng/mL (reference range: 0–2 ng/mL) in only one patient, indicating an increased level according to the age of the patient. However, the cortisol response to the standard intravenous therapy in the ACTH test of this patient was normal and the stimulated 17-OH-progesterone level was within normal levels (stimulated 17-OH-progesterone: 4.3 ng/mL). Stimulated 17 (OH) progesterone levels of >10 ng/mL supported the diagnosis of non-classical congenital adrenal hyperplasia.

Discussion

In this case-control study, thyroid hormones and antibodies, adrenal and gonadal hormones, vitamins D and B12 levels, and ferritin values of the patients with ADHD and ASD were analyzed and compared with healthy controls. Although age, sex, body weight, and height were similar among the three groups, there was a statistically significant difference in vitamin D levels. The ASD groups had the lowest vitamin D levels, while the control group had the highest vitamin D levels. There are recent publications in the literature on the relationship between vitamin D deficiency and ADHD. Several studies showed lower vitamin D levels in the ADHD patients compared to the controls, which is also consistent with our study findings [9–11]. In addition, animal studies demonstrated that developmental vitamin D deficiency might lead to abnormalities such as large lateral ventricle, poor tissue differentiation, and reduced neurotropic factor expression [11, 12]. Abnormal behaviors and hyper-locomotion were also observed in animals as a result of alterations in the brain. Therefore, an explanation of the relationship between vitamin D deficiency and ADHD has been attempted in recent studies.

Table 4: Comparison of the groups according to hormone levels.

	Girls	Boys	p-Value[a]	p-Value[b]
	Mean±SDS (min–max)	Mean±SDS (min–max)		
Dehydroepiandrosterone, ng/dL				
ADHD	63.29±83.95 (6.60–288)	58.43±56.92 (5.4–187)	>0.05	>0.05
ASD	125.94±176.27 (3.40–450)	68.22±78.68 (9–33)		
Control	90.51±108.04 (5.20–337.1)	52.47±47.66 (3.2–139.3)		
Androstenedione, ng/mL				
ADHD	0.82±0.78 (0.04–2.1)	0.56±0.49 (0.3–1.86)	>0.05	>0.05
ASD	0.92±0.91 (0.04–2.49)	1.1±1.36 (0.3–3.6)		
Control	1.22±0.96 (0.30–3.20)	1.09±1.30 (0.3–3.45)		
Total testosterone, ng/dL				
ADHD	0.54±0.22 (0.42–1.17)	1.35±3.33 (0.45–16.55)	>0.05	>0.05
ASD	0.57±0.32 (0.42–1.23)	2.66±5.08 (0.45–16.68)		
Control	0.81±0.47 (0.45–1.85)	2.42±5.00 (0.45–17.88)		
ACTH, pg/mL				
ADHD	26.83±5.56 (17.6–37)	25.75±11.79 (13–65)	>0.05	>0.05
ASD	30.66±2.42 (28–35)	30.52±7.01 (20.5–43.2)		
Control	25.43±4.91 (17.6–31)	26.69±6.92 (19.6–36)		
Cortisol, µg/dL				
ADHD	10.34±3.09 (6.7–16)	10.03±3.01 (4.8–19.6)	>0.05	>0.05
ASD	11.28±2.16 (9.33–14)	11.63±2.76 (9.25–18)		
Control	10.85±3.30 (6–16)	10.78±3.14 (6.5–19)		
17 (OH) progesterone, ng/mL				
ADHD	1.08±0.30 (0.66–1.59)	1.06±0.73 (0.37–3.24)	>0.05	>0.05
ASD	0.83±0.49 (0.21–1.45)	1.05±0.33 (0.43–1.52)		
Control	0.94±0.76 (0.30–3.24)	0.77±0.38 (0.16–1.31)		

ACTH, adrenocorticotropic hormone; ADHD, attention deficit hyperactivity disorder; ASDs, autism spectrum disorders. [a]p-Value: comparison of three groups in girls; [b]p-Value: comparison of three groups in boys.

However, there is a limited number of studies explaining the relationship between vitamin D deficiency and ASD. In these studies, vitamin B12 levels were found to be lower in the group with ASD [13–16], which is also consistent with our study findings. The aforementioned pathophysiological mechanism has also been proposed to elucidate the relationship between ASD and vitamin D. A neuroactive hormone, 1,2-dihydroxy-vitamin D, which is an active form of vitamin D, is essential for normal brain hemostasis [16]. Calcitriol plays a role in brain development and cell differentiation, axonal growth, stimulation of neurotrophic factors, modulation of the production of brain-originated reactive oxygen species, and stimulation of glutathione [16]. Calcitriol is a potent anti-oxidant which plays a role in the deoxyribonucleic acid (DNA) synthesis and repair and it downregulates excitotoxicity [16]. Therefore, disruptions in these mechanisms during the neurodevelopmental stage may cause behavioral disorders, such as ADHD and ASD.

In our study, folate and vitamin B12 levels were studied for both disease groups. Vitamin B12 levels were also analyzed and a statistically significant difference was observed among the three groups. However, there was no statistically significant difference in the folate levels.

Vitamin B12 deficiency may cause megaloblastic anemia, atrophic gastritis, glossitis, neuropathy, and demyelination in the central nervous system [17]. Furthermore, the relationship of vitamin B12 deficiency with several neurological and psychiatric disorders has been shown in the previous reports [18–21]. There has been an attempt to explain the relationship between vitamin B12 and ASD by homocysteine metabolism [21]. Vitamin B12 is one of the co-factors of homocysteine metabolism and its deficiency may result in an increase in homocysteine in the body fluids [22]. As homocysteine induces neuronal damage, leading to cell loss and excitotoxicity, it may cause apoptosis [23, 24]. Homocysteine may also lead to ASD, which is a neurodevelopmental disorder, caused by all these events. Chauhan and Chauhan [24] and Suh et al. [25] demonstrated that neuropsychiatric disorders such as ASD might be detected in high homocysteine and oxidative stress states. An explanation of the relationship between ASD and vitamin B12 deficiency has been attempted to a certain extent with all these pathophysiological events.

In our study, the ferritin levels were found to be highest in the ASD group, while healthy controls had the lowest levels. We did not observe ferritin deficiency in the ASD and ADHD groups. This finding is inconsistent with the previous study findings, which examined serum iron and ferritin levels in children with ASD or ADHD [26–30].

In a study including 33 children with autism, Dosman et al. [27] reported lower ferritin levels in this patient population. The authors also found a relationship between the sleep disturbance and iron deficiency in children with ASD. Similar results were reported in another study that was conducted by Youssef et al. [28]. In that study, the authors concluded that children with ASD had significantly lower ferritin levels, compared to the controls. However, despite these findings, controversial results were published by Reynolds et al. and Millichap et al. [26, 29].

Donfrancesco et al. compared serum ferritin levels in a sample of stimulant-naïve children with ADHD and matched controls to assess the possible relationship between serum ferritin levels and ADHD symptom severity, ADHD subtypes, and IQ [30]. The authors showed that serum ferritin did not significantly differ between children with ADHD and controls, as well as among the ADHD subtypes. In our study, we found higher ferritin levels in the patient groups, although the levels were within normal ranges. These findings do not support previous reports suggesting that children with ASD and ADHD were at an increased risk of iron deficiency than the overall population. In addition, these findings do not suggest a causative role for low serum ferritin in ADHD or ASD.

In our study, thyroid hormones and antibodies were also examined among the three groups. We found no significant difference among the groups. Another study including 114 children and adolescents showed increased TSH, suggesting that subclinical hypothyroidism might cause behavioral disorders [9]. The reason for controversial results can be attributed to the small sample size of our study.

Furthermore, Dorn et al. [31] analyzed adrenal and gonadal hormones in children with behavioral disorders. They found that the androstenedione levels were statistically significantly higher in children with behavioral disorders, compared to the controls. Another study showed a correlation between increased androstenedione levels and behavioral disorder severity [32]. Androstenedione, which is a precursor of testosterone, is a weak androgen, which increases in during 6–8 years of age. Since the relationship of testosterone with behavioral disorders has been demonstrated previously, it may cause behavioral disorders by contributing to increased androstenedione testosterone levels. Ruta et al. [8] reported increased androstenedione levels in adults with ASD. El-Baz et al. [33] also demonstrated the correlation between the increased androgens and the severity of the disease in children with ASD. In our study, whose results are consistent with the previous study findings, we examined the adrenal and gonadal androgens in children with ASD and ADHD. Meanwhile, 17-OH progesterone levels, which are used as a screening test for hyperandrogenism and nonclassical adrenal hyperplasia with high androstenedione levels, particularly in females, were also examined. In our study, there was no statistically significant difference in the adrenal and gonadal hormone levels and 17-OH progesterone levels.

Because vitamin B12 and D deficiency can be found separately or together in the ASD and ADHD patients, both patient groups and healthy controls were screened in terms of associated Celiac disease. There are also publications in the literature showing the relationship between gluten enteropathy and neuropsychiatric diseases [34]. Serum IgA levels, which were examined in terms of selective IgA deficiency, were found to be normal in all groups. Serum tissue transglutaminase IgA levels, which have a sensitivity and specificity of >90%, were also examined to screen for Celiac disease. None in the patient and control groups was diagnosed with Celiac disease in our study. Also, there was no statistically significant difference in the antibody titers among the three groups.

In conclusion, this study is the first that evaluated the risk factors for ADHD and ASD, including vitamins B12 and D, ferritin, adrenal androgens, Celiac disease, and subclinical hypothyroidism. Our study results highlight the importance of supplementation of vitamins B12 and D in the ASD and ADHD patients. Furthermore, we recommend increasing the awareness of the public of the vitamin B12 and D deficiencies to prevent these disorders. There is also the necessity of prompting healthcare workers to take preventive measures, such as action on diets, to reduce vitamin B12 and D deficiencies and to encourage the use of supplements.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.
Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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