



# Are children with attention-deficit/hyperactivity disorder (ADHD) more likely to develop celiac disease? A prospective study

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## Abstract

**Purpose:** The aim of this study was to evaluate whether the prevalence of celiac among attention-deficit/hyperactivity disorder (ADHD) patients is higher than among the normal population.

**Methods:** The present study was a prospective one investigating ADHD children referred to the Neurology Clinic and Pediatric Ward at Amir Al-Momenin Hospital of Zabol (Sistan and Baluchestan, Iran) in 2019 after their parents' signing of a consent form. All patients underwent Biocard™ Celiac and serology tests. Data were analyzed with SPSS version 21 software.

**Results:** Of all 76 ADHD children undergoing a serum IgA antibodies concentration test, 58 (76%) were male and 18 (23.7%) were female. The mean age of the children was  $6.9 \pm 2.4$ , ranging from 2 years to 12 years. The diagnosis of IgA immunodeficiency was rejected for all children based on total serum IgA antibody results. The overall mean anti-tissue transglutaminase (TTG) level was  $6.8 \pm 5.3$  U/ml, ranging from 0.2 to 37 U/ml. There was no significant difference regarding TTG levels between boys and girls (5.1 vs. 6.0) U/ml. Based on the anti-TTG level results, no celiac case was found among the ADHD patients.

**Conclusions:** There is as yet no evidence suggesting a link between celiac disease and ADHD. Thus, routine celiac disease screening when evaluating for ADHD (and is not recommended). However, the possibility of untreated celiac disease predisposing an individual to ADHD-like behaviors should be considered. Hence, physicians are recommended to evaluate a broad range of physical symptoms, in addition to typical neuropsychiatric symptoms, when evaluating ADHD patients.

**Key words:** attention deficit and hyperactivity disorder, ADHD, celiac.

## INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that affects 5% of school-age children. In most cases, symptoms continue into adolescence and adulthood [1, 2].

ADHD is marked by developmentally improper levels of inattention, hyperactivity, and impulsivity. It seriously interferes with daily activities in various situations (e.g., at home, during education, at work, etc.). It also may increase the risk of other psychological disorders such as oppositional defiant disorder or conduct disorder. In addition, anxiety and mood disorders, learning disorders, sleep disorders, and substance use disorders (SUD) may be diagnosed [3]. The heterogeneity of ADHD reflects the interconnection of multiple factors which all increase the susceptibility of individuals [4]. According to our current knowledge, a wide range of genes with signifi-

cant consequences (including low birth weight, preterm infants, and exposure to maternal smoking in the womb) may be adjusted by environmental factors [5].

ADHD is associated with the presence of certain intestinal disorders of varying intensities [6]. This disorder manifests in many forms: asymptomatic, atypical, and/or associated with clinical signs and symptoms of celiac disease (CD) [5-9]. In addition, some studies point to ADHD as an extra-intestinal and neurological symptom of CD. According to Gujral *et al.* [10], the prevalence of CD is estimated to approximate 0.5-1% in different parts of the world. The only effective treatment for CD is a lifelong gluten free diet (GFD) [10].

Limited research has documented neuropsychiatric symptoms in CD patients, including ADHD. However, data suggesting the prevalence of CD among ADHD patients are lacking and contentious [11].

A systematic review has documented eight studies investigating the potential association between ADHD and CD. However, these studies are difficult to compare, as some have studied patients with learning disabilities [12] and others of those with ADHD-like symptoms [13], in addition to ADHD patients. The same is true for comparing the results, as the authors have not observed the criteria set by the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) for the stepwise diagnosis of CD. The aim of this study is to evaluate whether or not the prevalence of celiac among ADHD patients is higher than the normal population.

## METHODS

This report is of a prospective study investigating ADHD children referred to the Neurology Clinic and Pediatric Ward at Amir Al-Momenin Hospital of Zabol (Sistan and Baluchestan, Iran). The study was approved by the Ethics committee of Zabol University of Medical Sciences (ZUMS). Inclusion criteria were having been diagnosed with ADHD based on the DSM-V as reported by a pediatric neurologist, having no underlying condition, and the informed consent of parents. The exclusion criteria were “refusing to sign the consent form” and “having an underlying disease”.

The sample size needed to illustrate the difference in the CD prevalence rate between ADHD patients (12%) (Nieserhofer *et al.* [14]) and healthy individuals in the Middle East (3%) (Rostami *et al.* [15]) was estimated at 50, using STATA software at a *p*-value of 0.05 (type 1 error) and statistical power of 0.8. Participants were selected through the convenience sampling method. A total of 0.5 ml of blood was sampled from each participant. A step-by-step procedure was also adopted for CD diagnosis based on ESPGHAN protocols. This procedure works by detecting CD-specific antibodies against tissue transglutaminase (TTG2) as the first-line diagnosis method [16].

In all 76 children, tissue transglutaminase IgA (tTg-IgA) antibody was diagnosed in ELISA after eliminating IgA deficiency.

All patients underwent a Biocard™ Celiac Test. This is a rapid test for CD that detects antibodies against tissue transglutaminase in capillary blood. We also evaluated the levels of anti-TTG in the serum. The test was conducted based on the manufacturer's instructions with 97.8% sensitivity and 96.3% specificity. Since none of our patients were suspected after this test there was no need for further testing. Participants had not consumed a GFD during or before the study. This protocol was in accordance with the guidelines of the European society for pediatric gastroenterology, hepatology, and nutrition [17].

## Data analysis

Data were analyzed with SPSS version 21 software. The data frequency was described in terms of descriptive

statistics (as %) and Bayesian histograms. The nominal variable(s) association was also stated by the  $\chi^2$  test. Additionally, the mean of quantitative variables was compared using the independent sample student *t*-test at *p* < 0.05.

## RESULTS

Of all 76 ADHD children undergoing serum IgA antibodies concentration test, 58 (76%) were male and 18 (23.7%) were female. The mean age of the children was  $6.9 \pm 2.4$ , ranging from 2 years to 12 years (Table 1).

A diagnosis of IgA immunodeficiency was rejected for all children based on total serum IgA antibody results. The mean serum value of total IgA was  $138 \pm 63$  mg/dl, ranging from 10 to 337 mg/dl. Generally, IgA immunodeficiency is diagnosed when total serum IgA in a child over 4 years is less than 5-7 mg/dl. However, IgA immunodeficiency was not reported in any of the participants.

The overall mean anti-TTG level was  $6.8 \pm 5.3$  U/ml, ranging from 0.2 to 37 U/ml. There was no significant difference regarding TTG levels between boys and girls (5.1 vs. 6) U/ml. Based on the anti-TTG level results, no celiac case was found among the ADHD patients.

## DISCUSSION

The present study explored CD prevalence in some ADHD children to look for any potential link between these two medical conditions. The aim was to find out if it is plausible to prescribe ordinary CD screening tests and a GFD to ADHD children. This is not merely an academic inquiry, as a GFD is both costly and results in a poorer quality of life [18]. These ultimately lead to various problems, especially in children who are deprived of a normal life due to ADHD.

In the present study, the presence of CD was eliminated in all 76 ADHD patients. The results also rejected the hypothesis suggesting that the prevalence of CD in ADHD children is higher than in normal children.

Based on a recent meta-analysis the prevalence of celiac in the general Iranian population is 3% [19]. There is also

**Table 1.** Total IgA and anti-TTG levels among attention deficit and hyperactivity disorder (ADHD) patients based on their sex

Serologic marker	<i>n</i>	Mean	<i>p</i> -value
Anti-IgA (mg/dl)			
Male	58	132	0.22
Female	18	156	
Anti-TTG (U/ml)			
Male	58	$5.1 \pm 4.3$	0.26
Female	18	$6 \pm 5$	

another study which reported a 0.6% prevalence of celiac among Iranian children [20]. Considering the result of our study in combination with these studies, the hypothesis of a higher prevalence of celiac disease between ADHD children has not been proven. Our results were in line with the those of Kumperscak *et al.*, who evaluated a sample of children and teenagers with ADHD and found no celiac cases among them [21]. Research into the potential link between CD and ADHD is still preliminary. A systematic review has documented only eight studies investigating this issue, of which only three have reported a positive association between these two disorders [11].

CD screening has been conducted with ADHD patients in three studies, with the results being controversial. Lahat *et al.* were successful in diagnosing CD antibodies (AGA, IgA, and EMA) in children with ADHD [22]. On the other hand, Niederhofer *et al.* [14] diagnosed CD antibodies (AGA and EMA) in only 15% of cases. In their study, significant progress was seen in the behavior and functioning of a group of children and adolescents with ADHD after going on a GFD for at least six months, compared with the time period immediately before diagnosis. However, their study had no control group and did not use biopsy for confirming diagnoses. However, Güngör *et al.* in their study showed no difference in CD prevalence between patients with and without ADHD and did not recommend GFD for ADHD patients [23].

The likely underlying mechanisms of the link between attention/learning problems and CD reflect the incremental effects of multiple factors such as those which are nutritional and immunological/inflammatory. However, indirect factors relating to the non-specific impacts of chronic disease could not be rejected [9]. Nutritional factors, micronutrient deficiencies, and anemia are also visible in untreated CD patients [19, 20]. These factors may also play a role in ADHD-like behaviors.

A review by Sonia Gaur suggested that it is better to evaluate the association between ADHD and celiac disease on the basis of different sub-types of ADHD, spe-

cifically in the inattentive type [24]. Another previous study by Efe *et al.*, reported an improvement in inattentive behavior among ADHD patients who received a GFD [25].

Since our study did not find any celiac patients among ADHD ones, we were not able to evaluate the different sub-types of ADHD in association with CD. Some of the previous studies did not report a difference in association based on different subtypes [22, 23]. However, some studies which evaluated the effect of dietary interventions reported an improvement which was present for 12 months among hyperactive subtype patients, while the improvement of symptoms among inattentive subtype patients was observed to last between 8 to 12 months [26-28]. There are also studies which found a significant association between CD and ADHD [29-31]. Alkhayyat *et al.* reported a higher likelihood of different psychological disorders among CD patients. They reported an OR of 1.7 for celiac patients to develop ADHD compared to the normal population [29]. However, most of these studies stated that there is still not enough evidence to support the provision of routine screening for CD among ADHD patients, while psychological consultations are of importance in CD patients [31].

The limitations of the present study included the absence of a control group and the investigation of children only from southeast Iran.

## CONCLUSIONS

There is as yet no evidence suggesting a link between CD and ADHD. Thus, routine CD screening when evaluating for ADHD (and vice versa) is not recommended. However, the possibility of untreated CD predisposing individuals to ADHD-like behaviors should be taken into consideration. Hence, physicians are recommended to evaluate a broad range of physical symptoms, in addition to typical neuropsychiatric symptoms, when evaluating ADHD patients.

### Conflict of interest

Absent.

### Financial support

Absent.

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