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Is attention-deficit hyperactivity disorder increased in patients with celiac disease?

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Abstract

Background: Some studies have shown that neurological and mental disorders in children with celiac disease are higher than in the general population. The aim of this study is to find frequency of ADHD in celiac patients.

Result: The findings of the study showed that the frequency of ADHD in males was 6 cases (22.2%) and 6 cases (18.2%) in females, and although the ADHD score was higher in males, there was no significant difference in sex ($P = 0.697$). The frequency of ADHD in terms of age group also showed that there were no hyperactive children in the age group under 5 years of age; in the age group of 5–9 years old, 8 cases (28.6%); in the age group of 10 to 14 years old, 4 cases (19%); and in the age group of 15 and older, no one was diagnosed with ADHD. The chi-square test showed that the frequency of ADHD in terms of age group was not significantly different ($P = 0.26$). It should be noted that according to Pearson correlation test, there was a reverse correlation between the age and ADHD, but it was not statistically significant ($P = 0.33$).

Conclusions: The frequency of ADHD among boys and girls with celiac disease was 22.2% and 18.2%, respectively.

Keywords: Celiac, Hyperactivity disorder, Attention deficit, Child

Background

Celiac disease is a gluten-sensitive enteropathy, which causes inflammation and destruction of the mucosa of the upper small intestine resulting from gluten ingestion in genetically susceptible individuals [1]. The diagnosis was confirmed according to the results of celiac-specific antibody testing, intestinal biopsy, or HLA testing [2]. The therapy for celiac disease is permanent exclusion gluten from the diet that is associated with total healing of the mucosal lesion.

Although classically a disease of infants, celiac disease now often presents later, and the clinical picture of a child with malabsorption including bulky, foul-smelling, floating stools due to steatorrhea and flatulence is often replaced by the mostly atypical presentation or an asymptomatic presentation [3, 4].

Several non-gastrointestinal manifestations of celiac disease have been described. Atypical presentation with minor symptoms, such as irritable bowel syndrome [5, 6], anemia [7, 8], poor weight gain, and fatigue [9], has become increasingly common. If undetected, celiac disease may progress to significant late complications from malabsorption or secondary autoimmune diseases. Attention-deficit hyperactivity disorder is one of the most common diseases in children and adolescents, and hyperactivity, inattention, irritability, and impulsivity are the most common symptoms of ADHD. The diagnosis of ADHD is demonstrated according to the result of DSM-V (DSM-5) criteria. According to a study in Iran, the prevalence of ADHD among the Iranian population is 10.1% [10]. Most of the studies about relationship between celiac disease and ADHD were carried out in European countries [11]. Limited research was published about frequency of ADHD among patients with celiac disease from Middle East region [12], so the objective of this study was to evaluate the association of ADHD and

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celiac disease in children with a diagnosis of celiac disease in our country.

Methods

In this cross-sectional study, 60 children with a diagnosis of celiac disease were included. The diagnosis is confirmed according to clinical manifestations, serologic and pathologic findings. The place of the study was the pediatric gastroenterology clinic of Shiraz University of Medical Sciences, from 2016 to 2018.

Ethics

The Ethics Committee of Shiraz University of Medical Sciences approved the study, and written consents were obtained from the children's guardians after describing the study in detail.

Diagnosis

The diagnosis of celiac disease was made by a pediatric gastroenterologist according to the criteria of the positive presence of anti-tissue transglutaminase immunoglobulin A antibody (anti-tTG IgA antibody) and total immunoglobulin A (IgA) level, positive biopsy specimens (which were analyzed according to a modified Marsh classification (18), by the following criteria: villous atrophy, elevated IEL count, and hyperplasia of the crypts). They were regularly followed in the pediatric gastroenterology clinic of Shiraz University of Medical Sciences. Patients were assessed for ADHD by an expert pediatric psychiatrist.

Exclusion criteria were severe mental disorders like psychosis and major depression using DSM-5. Also, children with autoimmune disorders, such as diabetes mellitus and thyroiditis, and neurologic diseases, such as epilepsy, were excluded due to the triggering of ADHD-like symptomatology. In our study, there was not any patient to be excluded with the mentioned exclusion criteria.

Measurement

The SDQ questionnaires were used in this study as discussed below. All questionnaires were filled with the help of a medical student due to patients' different educational statuses.

Strength and Difficulties Questionnaire (SDQ)

SDQ includes 5 components as emotional, conduct, hyperactive problems, peer, and prosocial behaviors. The total score of each of these components is categorized into 3 categories: normal as 0–5, borderline as 6, and abnormal as 7–10. For diagnosis of ADHD, all who had the summation of emotional, conduct, hyperactive problems, and peer more or equal to 17 were diagnosed with

ADHD. And then in all cases that were diagnosed, the severity of which of these components is measured. SDQ was assessed by several studies and showed valid outcome measure for use in clinical setting and RCTs [13].

Statistical analysis

Data were analyzed by SPSS version 19. Pearson chi-square was used to examine the results. *P*-value less than 0.05 was considered significant.

Results

In this study, 60 patients (male = 33, female = 27) with celiac disease were studied. The mean age of the patients was 9.75 ± 3.74 years. The minimum and maximum age were 3 and 17 years, respectively. Four (6.7%) patients are under the age of 5 years old, 28 (46.7%) were aged 5 to 9 years old, 21 (35%) were aged 10–14 years old, and 7 (11.7%) at age 15 or more. In Fig. 1, the percentage of patients in the age group is shown.

The mean age of males and female was 10.04 ± 3.65 and 9.52 ± 3.84 years, respectively. According to the *T*-test, the mean age of male and female, there was no significant difference ($P = 0.6$). In Table 1, the mean and standard deviation of the age is shown by gender.

The mean scores of the SDQ questionnaire for ADHD in males and females were 15.52 ± 5.14 and 11.39 ± 7.15 , respectively ($P = 0.015$). The evaluation of SDQ questionnaire score by age showed that the mean of ADHD in children younger than 5 years was 9.75 ± 6.29 , in children aged 5 to 9 was 15.36 ± 6.6 , in children 10–14 years old 11.9 ± 6.99 , and in children aged 15 years and older, 10.86 ± 3.67 . But according to one-way ANOVA, ADHD scores were not significant in terms of age group ($P = 0.13$). The results are shown in Table 2.

The findings of the study showed that the frequency of ADHD in males was 6 cases (22.2%) and 6 cases (18.2%) in females, and although the ADHD score was higher in males, there was no significant difference in sex ($P = 0.697$). The frequency of ADHD in terms of age group also showed that there were no hyperactive children in the age group under 5 years of age; in the age group of 5–9 years old, 8 cases (28.6%); in the age group of 10 to 14 years old, 4 cases (19%); and in the age group of 15 and older, no one was diagnosed with ADHD. The chi-square test showed that the frequency of ADHD in terms of age group was not significantly different ($P = 0.26$). The results are shown in Table 3. It should be noted that according to Pearson correlation test, there was a reverse correlation between age and ADHD, but it was not statistically significant ($P = 0.33$) (Fig. 2).

Out of the 60 patients with celiac disease, 12 (20%) participants were positive for ADHD (6 males, 6 females), and 48 patients were negative for ADHD (21 male, 27

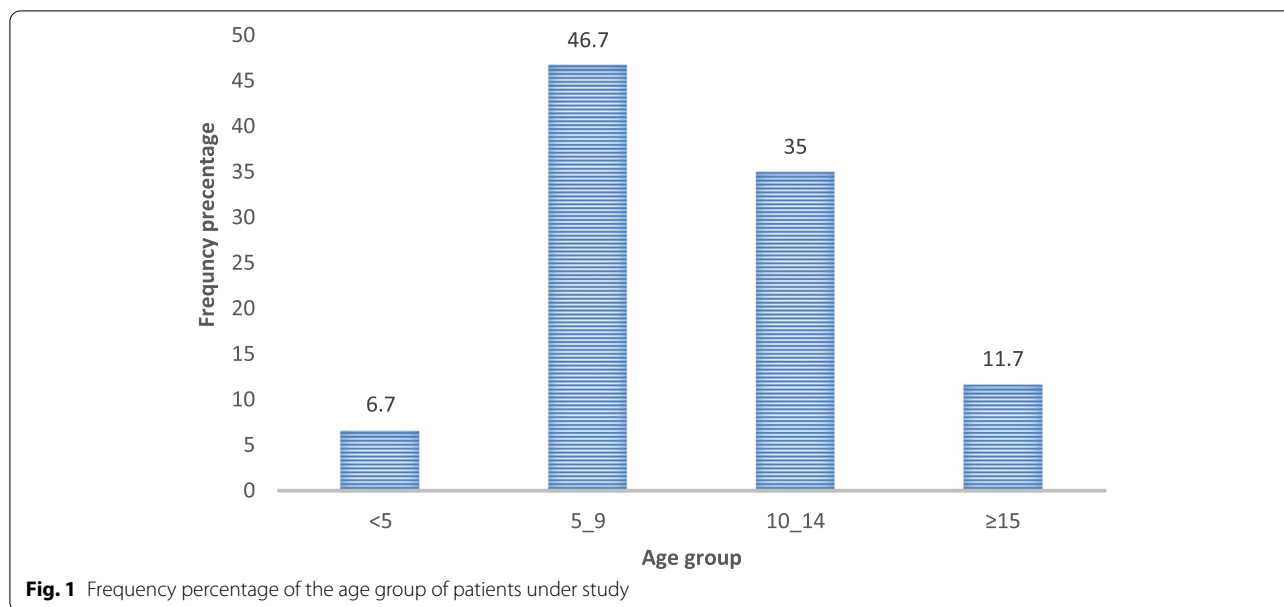


Table 1 Mean and standard deviation of age by gender

Sex	Age	<i>p</i> -value
Male	10.04 ± 3.65	0.6
Female	9.52 ± 3.84	

Table 2 The mean and standard deviation of ADHD score by age and sex

		<i>p</i>	Mean score of ADHD	<i>p</i>
Sex	Male	0.015	15.52 ± 5.14	<i>P</i> = 0.015
	Female		11.39 ± 15.5	
Age group (years)	Less than 5	0.13	9.75 ± 6.29	0.13
	5–9		15.36 ± 6.6	
	10–14		11.9 ± 6.99	
	> 15		10.86 ± 3.67	

Table 3 Frequency distribution of attention-deficit hyperactivity disorder by age and sex

Variable		With ADHD	Non-ADHD	<i>p</i> -value
		Number	Number	
Sex	Male	6 (22.2)	21 (77.8)	0.697
	Female	6 (18.2)	27 (81.8)	
Age group (year)	Less than 5	0	4 (100)	0.26
	5–9	8 (28.6)	20 (71.4)	
	10–14	4 (19)	17 (81)	
	> 15	0	7 (100)	

female). We compared the association of sex with ADHD presentation, and *P*-value was 0.697, and it was not significant. So, sex is not a factor affecting the prevalence of ADHD in patients with celiac disease. In addition, *P*-value was 0.26 for age with ADHD, which there is no substantial relative.

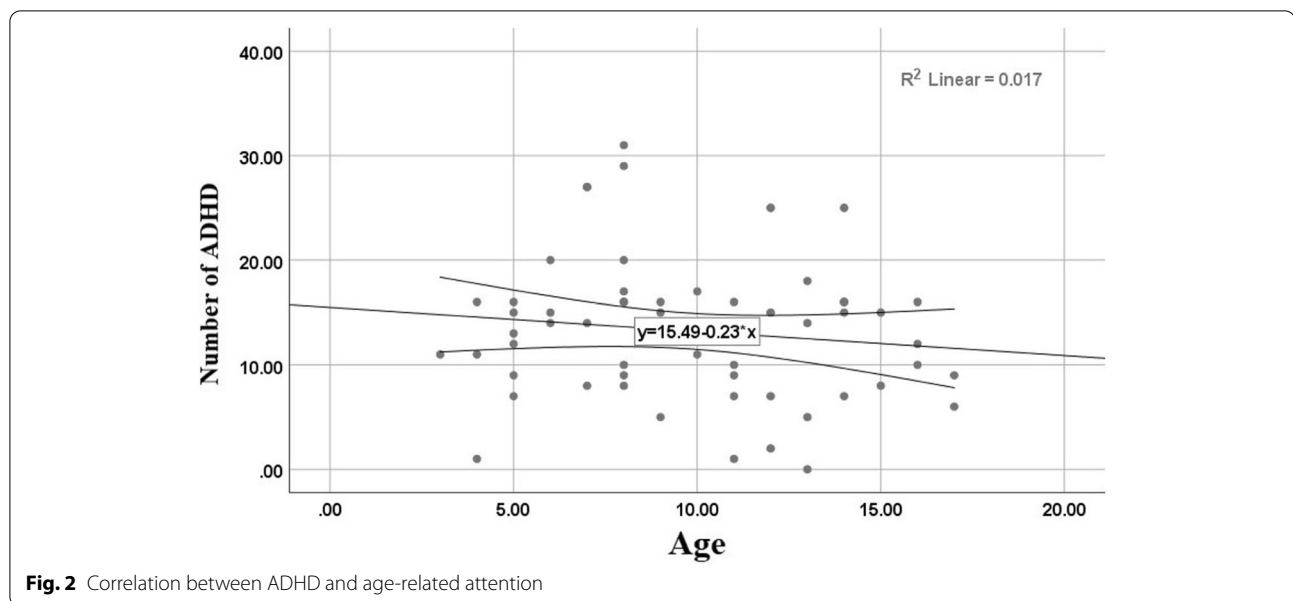
The prevalence of ADHD in celiac disease in our study is 20%, and the prevalence of ADHD in the normal population of schoolchildren in Shiraz was 10.1% [10]. We compared the two populations with Pearson chi-square test; the test statistic was 6.133, and *P*-value was 0.013, and it was significant, so the prevalence of ADHD among patients with celiac is increased.

Among all 12 cases diagnosed with ADHD, we measured the severity of each component including hyperactivity, conduct, emotional, and peer problem, which respectively were 41.6%, 16.6%, 33.3%, and 8.3%.

Discussion

Celiac disease is an autoimmune enteropathy due to gluten sensitivity with mucosal villous atrophy. Celiac disease has both gastrointestinal and non-gastrointestinal manifestations. Gastrointestinal manifestations are called classic or typical celiac disease. Non-gastrointestinal manifestations are dermatitis herpetiform, epileptic seizures, and psychiatric problems including schizophrenia, bipolar disorder, eating disorder, autism spectrum, and ADHD [11].

The prevalence of ADHD in celiac disease in our study is 20%, and the prevalence of ADHD in the normal population of Mashhad was 12.3% [14]. The prevalence of ADHD among normal population of schoolchildren in



Shiraz was 10.1% [10]. The prevalence of ADHD among children and adolescent in another study from Iran was 2.0% [15].

In the current study, the frequency of ADHD among celiac disease was 20% which was higher than the prevalence of ADHD among the Iranian general population. In the study by Butwika et al. 2017, celiac disease is associated with childhood psychiatric disorders including ADHD [16]. In the study by Coburn et al. 2020, anxiety disorder and ADHD were more common in celiac disease than in the general population [17]. Niederhofer and colleagues (2006) found out that the prevalence of definite ADHD in celiac disease is 0.4% and probable ADHD in celiac disease is 2%, and ADHD are overrepresented in nontreated celiac disease, and it could be associated with celiac disease [18]. Ertürk and colleagues (2016) in a meta-analysis suggest that due to inconclusive evidence, assessing ADHD should not be done among patients with celiac disease [19]. In the recent systematic review by Clappison et al., the celiac disease is associated with an increased risk of ADHD [20]. In the study by Coburn et al., the frequency of ADHD among children with celiac disease was significantly higher than general. In the study by Lebwohl et al. (2020), ADHD was increased among children with celiac disease [21]. In a large study among adults, most of the psychiatric disorders increased among patients with celiac disease [22].

In the study by Gungor et al. (2013), there was no difference between the frequency of celiac disease between children with ADHD and the control group [23]. In another study by Kumpersack et al. (2020) on 102 children and adolescents with ADHD, the prevalence of

celiac disease was not higher than the general population [11].

As mentioned above, there was no agreement between studies in terms of the association between celiac disease and ADHD. The sample size was limited in most of the studies. So, multicentric studies are recommended to evaluate the relationship between celiac disease and ADHD.

The main limitation of the current study was sample size and single-center study. The main strength of the study is to use SDQ questionnaire in addition to the clinical assessment of children for ADHD by an expert pediatric psychiatrist.

Conclusions

Frequency of ADHD among children with celiac disease was higher than general population. Another multicentric study with more sample size is recommended.

Limitation

The main limitation of the current study was single-center study and sample size. We used other studies as a control, due to financial limitation.

Abbreviations

Anti-tTG IgA antibody: Anti-tissue transglutaminase immunoglobulin A antibody; ADHD: Attention-deficit hyperactivity disorder; DSM: Diagnostic and Statistical Manual of Mental Disorders; IEL: Intraepithelial lymphocyte; SDQ: Strength and Difficulties Questionnaire; SPSS: Statistical Package for Social Sciences.

Authors' contributions

NH and AG wrote the draft of the manuscript. NH and AG collected the data. RR and MB write the draft of proposal and perform data analysis. AG is

responsible for diagnosis and evaluation of patients with ADHD. HJ reviewed the manuscript and is the corresponding author. All authors read and approved the manuscript.

Funding

None

Availability of data and materials

Data was available with the corresponding author.

Declarations

Ethics approval and consent to participate

This study was approved by the ethical committee of Shiraz University of Medical Sciences

Consent for publication

Nothing.

Competing interests

The authors declare that they have no competing interests.

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Received: 22 February 2022 Accepted: 10 April 2022

Published online: 02 May 2022

References

- Hill ID, Dirks MH, Liptak GS, Colletti RB, Fasano A, Guandalini S, et al (2005) Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 40(1):1–19
- Bannister EG, Cameron DJ, Ng J, Chow CW, Oliver MR, Alex G et al (2014) Can celiac serology alone be used as a marker of duodenal mucosal recovery in children with celiac disease on a gluten-free diet? *Am J Gastroenterol* 109(9):1478–1483
- Rampertab SD, Pooran N, Brar P, Singh P, Green PH (2006) Trends in the presentation of celiac disease. *Am J Med* 119(4):355.e9–14
- Sainsbury A, Sanders DS, Ford AC (2013) Prevalence of irritable bowel syndrome–type symptoms in patients with celiac disease: a meta-analysis. *Clin Gastroenterol Hepatol* 11(4):359–65.e1
- Azami M, Badfar G, Abangah G, Mahmoudi L (2019) Celiac disease in Iranian irritable bowel syndrome patients; a systematic review and meta-analysis. *Gastroenterol Hepatol Bed Bench* 12(2):85–97
- Shayesteh AA, Hajjani E, Hashemi SJ, Masjedizadeh A, Latifi SM, Shayesteh M (2014) Prevalence of celiac disease in Iranian patients with irritable bowel syndrome: a cross-sectional study. *J Dig Dis* 15(1):12–17
- Repo M, Lindfors K, Maki M, Huhtala H, Laurila K, Lahdeaho ML et al (2017) Anemia and iron deficiency in children with potential celiac disease. *J Pediatr Gastroenterol Nutr* 64(1):56–62
- Shahriari M, Honar N, Yousefi A, Javaherizadeh H (2018) Association of potential celiac disease and refractory iron deficiency anemia in children and adolescents. *Arq Gastroenterol* 55(1):78–81
- Skjellerudsveen BM, Omdal R, Grimstad T (2019) Fatigue in celiac disease: a review of the literature. *JGH Open* 3(3):242–248
- Ghanizadeh A (2008) Distribution of symptoms of attention deficit-hyperactivity disorder in schoolchildren of Shiraz, south of Iran *Arch Iran Med* 11(6):618–24
- Kumperscak HG, Rebec ZK, Sobocan S, Fras VT, Dolinsek J (2020) Prevalence of celiac disease is not increased in ADHD sample. *J Atten Disord* 24(7):1085–1089
- Işıkay S, Kocamaz H (2015) The neurological face of celiac disease. *Arq Gastroenterol* 52(3):167–170
- Hall CL, Guo B, Valentine AZ, Groom MJ, Daley D, Sayal K et al (2019) The validity of the Strengths and Difficulties Questionnaire (SDQ) for children with ADHD symptoms. *PloS one* 14(6):e0218518
- Hebrani P, Abdollahian E, Behdani F, Vosoogh I, Javanbakht A (2007) The prevalence of attention deficit hyperactivity disorder in preschool-age children in Mashhad, north-east of Iran. *Arch Iran Med* 10(2):147–151
- Ahmadpanah M, Nazaribadie M, Mohammadi MR, Hooshyari Z, Alavi SS, Ghaleiha A et al (2018) The prevalence of psychiatric disorders in children and adolescents in Hamadan Province, west of Iran. *J Res Health Sci* 18(4):e00432
- Butwicka A, Lichtenstein P, Frisén L, Almqvist C, Larsson H, Ludvigsson JF (2017) Celiac disease is associated with childhood psychiatric disorders: a population-based study. *J Pediatr* 184:87–93.e81
- Coburn S, Rose M, Sady M, Parker M, Suslovic W, Weisbrod V et al (2020) Mental health disorders and psychosocial distress in pediatric celiac disease. *J Pediatr Gastroenterol Nutr* 70(5):608–614
- Niederhofer H, Pittschieler K (2006) A preliminary investigation of ADHD symptoms in persons with celiac disease. *J Atten Dis* 10(2):200–204
- Ertürk E, Wouters S, Imeraj L, Lampo A (2020) Association of ADHD and celiac disease: what is the evidence? A systematic review of the literature. *J Atten Disord* 24(10):1371–1376
- Clappison E, Hadjivassiliou M, Zis P (2020) Psychiatric manifestations of coeliac disease, a systematic review and meta-analysis. *Nutrients* 12(1):142
- Lebwohl B, Haggård L, Emilsson L, Söderling J, Roelstraete B, Butwicka A, Green PHR, Ludvigsson JF (2021) Psychiatric disorders in patients with a diagnosis of celiac disease during childhood from 1973 to 2016. *Clin Gastroenterol Hepatol* 19(10):2093–2101.e13
- Alkhayat M, Qapaja T, Aggarwal M, Almomani A, Abureesh M, Al-Otoom O, Zmaili M, Mansoor E, Abou Saleh M (2021) Epidemiology and risk of psychiatric disorders among patients with celiac disease: a population-based national study. *J Gastroenterol Hepatol* 36(8):2165–2170
- Güngör S, Celiloğlu OS, Özcan OO, Raif SG, Selimoğlu MA (2013) Frequency of celiac disease in attention-deficit/hyperactivity disorder. *J Pediatr Gastroenterol Nutr* 56(2):211–214

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