



The Relationship Between Attention Deficit Hyperactivity Disorder and Functional Constipation in Patients Referred to Pediatric Gastrointestinal Clinic of the Hospitals of Khorramabad City, Iran

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Abstract

Objectives: Both Functional constipation and attention deficit hyperactivity disorder (ADHD) have a high prevalence among children. The aim of this study was to determine the relationship between functional constipation and ADHD.

Materials and Methods: In this case-control study, 4-12-year-old children who were diagnosed with functional constipation were included in the case group and children with no functional constipation were included in the control group. Diagnosis of functional constipation was performed according to ROME III criteria. All participants were interviewed for ADHD using the Persian version of Conners' Parent Rating Scale (short form). Statistical analysis was performed by Chi-square test for investigating the relationship between functional constipation and ADHD.

Results: A total of 100 children with functional constipation and 147 children without constipation were selected. Among the functional constipation group, 27 (27%) had a high score for ADHD and among the group without functional constipation, 16 (10.0%) had a high score for ADHD. The odds ratio was 3.028 (95% confidence interval = 1.532-5.986; *P* value = 0.001). There was no statistically significant relationship between constipation and ADHD considering the age and gender.

Conclusions: Functional constipation has a relationship with ADHD. The chance of having ADHD is 3 times higher in children with functional constipation. Further studies, particularly cohort studies, are recommended to assess the incidence of ADHD symptoms in infants with functional constipation in the future. Further studies on the possible pathophysiology of the digestive system and bacterial intestinal flora, especially in early childhood and infancy, are suggested for investigating the development of behavioral disorders and ADHD.

Keywords: ADHD, Functional constipation, Case-control study

Introduction

Functional gastrointestinal disorders are very commonplace in children. One of the most common types of these disorders is functional constipation which is characterized by infrequent and painful defecation. This disorder can cause psychological complications and physical stress in children and their families (1). The mechanism of constipation in children is multifactorial and has not yet been fully understood (2). In about 90% of patients referred for constipation, no specific organic cause is found and therefore they are diagnosed as functional constipation (3). Its prevalence in North and South America is 10%-25% while in Europe, it is 0.7-12%. In Asia, its prevalence is 0.5%-29.6% (4). During breastfeeding, the prevalence of constipation is between 0.5 and 39.3%, however, according to the consensus of experts, its prevalence is estimated to be approximately 15% (5). In adult population, constipation

is more common in women; however, data on the gender differences in infants and children are unclear (6). Many factors account for the differences in the prevalence of constipation in children in different reports, which include differences in the definition of constipation, age groups included, or methodologies used (7). The most important mechanism of developing functional constipation, especially in young children, may be behavioral state and fear of painful defecation (8). The stool stays in the rectum and the mucosa of the rectum absorbs water, making the stool too hard to excrete. Many children with previous functional constipation have a positive family history of functional constipation; therefore, genetic factors seem to play a role. However, no specific mutations have so far been discovered (8-13). The relationship between parental child-rearing attitudes and functional constipation has also been reported. Nutritional factors (inadequate intake of dietary fiber, fruits, and vegetables, as well as cow's milk

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Key Messages

- ▶ Functional constipation is associated with ADHD in children.
- ▶ Prediction of ADHD from constipation during infancy may be possible in future.

protein allergy), obesity, inactivity, living in war-affected areas, low economic levels, and low parental education levels have also been reported (14-17). Some psychological factors such as physical and sexual abuse, anxiety, and depression have been identified as contributing factors to constipation (18). Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental and behavioral disorders in childhood which is characterized by inattention, hyperactivity, impulsive behaviors, and concentration difficulty (19). The prevalence of this disorder is about 3%-10% in children (20,21) and has increased since 2003 (19). The prevalence of the disorder in school-aged children is 5%-12% (22). Much research has been done on the etiology of ADHD and the impact of various biological, environmental, and psychological factors on the development of this disorder has been discussed. Additionally, it has been established that neuroanatomical and neurochemical systems are involved in the development of this disorder (23). In one study with a very large population ($n = 742939$), the prevalence of ADHD was estimated to be 4.4%, and the prevalence of constipation was significantly higher in these patients than in the healthy population (4.1% vs. 1.5%) (24). The mechanism of the association between ADHD and functional constipation has not yet been elucidated, but certain issues such as sensory processing disorder or lack of attention to sensory stimulation in ADHD patients may interfere with the process of toilet training in these children. These patients do not sit on the toilet for an adequate period of time due to hyperactivity and lack of concentration. In other words, the intestine does not allow excretion with active peristalsis (25). Recently, studies have suggested that intestinal bacterial flora can cause gastrointestinal symptoms, such as constipation, and that biochemical changes in the blood may be a cause of hyperactivity syndrome.

Therefore, based on previous studies, we decided to investigate the relationship between functional constipation and ADHD given that early treatment of each may be effective in controlling the other. However, the main goal of our study is to examine the association between functional constipation and the development of hyperactivity. This study investigated the odds of developing ADHD in children with functional constipation compared with children without functional constipation. In addition, sometimes the diagnosis of ADHD in children is delayed until school-age, which causes behavioral and learning problems. Therefore,

the symptoms of constipation in such children (if the hypothesis is confirmed) can be an important warning for ADHD.

Materials and Methods

In the present case-control study, the cases were children with functional constipation and the controls were children without functional constipation. The inclusion criteria included being 4-12 years old, having clinical symptoms of functional constipation based on ROME III criteria, not having psychotic disorders, and having parental consent to participate in the study. The exclusion criteria included being under 4 years of age and over 12 years of age, having other gastrointestinal disorders, and avoiding referral to a psychiatrist. The target population consisted of children aged 4 to 12 years who referred to the clinics of Shahid Rahimi and Madani educational hospitals of Khorramabad city, west of Iran. All children aged 4 to 12 years with functional constipation who referred to the pediatric clinics during the year 2018 and the first half of the year 2019 were included as cases if they fulfilled inclusion criteria and did not have the exclusion criteria. The control group was also selected from children of the same age group who did not have functional constipation. Children or their parents were given necessary explanations about the study and written consent to participate in the study was obtained from them before inclusion in the study. All children were evaluated based on clinical symptoms of functional constipation based on ROME III criteria. After recording demographic characteristics including age and gender in pre-prepared questionnaires, Conners' Parent Rating Scale (attached form) was completed by parents through an interview with a psychiatrist. The minimum sample size was estimated for both case and control groups according to the following formula:

$$n_1 = n_2 = \frac{(p_1(1-p_1) + p_2(1-p_2))(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2}{(p_1 - p_2)^2}$$

Considering $P_1 = 20\%$, $P_2 = 40\%$, type I error rate of 5%, and type II error rate of 20%, the sample size for each group was estimated to be 79 people, and therefore, at least a total of 160 individuals were considered to be enrolled in the study.

Procedure

Both case (with functional constipation) and control (without functional constipation) groups were randomly selected from children referred to the pediatric gastrointestinal clinic. Clinical and paraclinical data of case and control groups were recorded in pre-prepared data collection forms. Diagnosis of functional constipation was made by a pediatric gastroenterologist based on a final evaluation. The Conner's Parent Rating Scale (short form) was filled out for both groups. This questionnaire is used

to measure ADHD (hyperactivity), which was reported to have a reliability of 0.9 according to Conners in 1997 (26). In the study of Alizadeh et al in 2005, the Persian version had a reliability of 0.85 (27). The questionnaire has 27 items, each of which is scored from 0 to 3.

A mean score of above 1.5 indicates attention deficit disorder. The higher the score, the more severe the disorder. Finally, cases with scores above 1.5 were examined for ADHD by a psychiatrist.

Data Analysis

The data were expressed as mean and standard deviation (mean \pm SD) for the quantitative variables and as percentages for the qualitative variables. Independent *t* test was used to compare the quantitative variables whereas chi-square test was used to compare the qualitative variables. A *P*-value of less than 0.05 was considered statistically significant. The SPSS version 22.0 (IBM, Chicago, US) was used to do statistical analysis.

Ethical Issues

Before the beginning of the study, all patients were informed about the objectives of the study. Only patients with full consent to participate in the study who signed the informed consent form (the parents) were included in the study. The information was kept confidential (the patients' names and surnames were not recorded in the questionnaires but were coded).

Results

In the present study, 100 children with functional constipation and 147 children without functional constipation were evaluated for ADHD. The mean age of children with functional constipation was 7.56 ± 2.6 years and the mean age of children without functional constipation was 7.95 ± 2.7 years. The difference was not

statistically significant according to the results of the independent *t* test ($P = 0.273$). In addition, of the children with ADHD, 50% were girls and 50% were boys. This rate was 55.1% and 44.9% in children without functional constipation, respectively. According to the results of chi-square test, there was no statistically significant difference in gender distribution between the case and control groups ($P = 0.43$). Besides, the difference in the frequency distribution of age between the case and control groups was not statistically significant ($P = 0.311$) (Table 1).

According to the results of Table 2, 27 (27%) children with functional constipation had ADHD, and 16 children (10.9%) in the control group had functional constipation (Figure 1), indicating a statistically significant difference ($P = 0.001$) according to the results of Chi-squared test. In addition, the odds ratio of ADHD was 3.082 times higher in children with functional constipation than in children without functional constipation (95% confidence interval: 1.532-5.986).

Table 3 represents the frequency distribution of ADHD in children with functional constipation by gender. In total, 12 (24%) girls with functional constipation had ADHD, and 15 (30%) boys with ADHD had functional constipation, without any statistically significant difference ($P = 0.499$).

Discussion

Our study demonstrates the association between functional constipation and ADHD. The frequency of functional constipation is higher in children with ADHD, and an odds ratio of approximately 3 represents that the development of functional constipation increases the risk of ADHD by three times. In our study, no differences in gender and age were found between children with and without functional constipation. Almog et al studied 62 children with ADHD and 57 controls for investigating

Table 1. The Frequency Distribution of Demographic Characteristics of Children With and Without Functional Constipation

Functional Constipation	Age			<i>P</i> Value ^a	Gender			<i>P</i> Value ^a
	8-12 years No. (%)	4-7 years No. (%)	Total No. (%)		Boy No. (%)	Girl No. (%)	Total No. (%)	
Has it	45 (45%)	55 (55%)	100 (100%)	0.43	50 (50%)	50 (50%)	100 (100%)	0.311
Does not have	77 (52.4%)	70 (47.6%)	147 (100%)		66 (44.9%)	81 (55.1%)	147 (100%)	

^a Chi-square test.

Table 2. Frequency Distribution of ADHD in Children With and Without Functional Constipation

Functional Constipation	ADHD			OR (95% CI)	<i>P</i> Value ^a
	Has it No. (%)	Does not have No. (%)	Total No. (%)		
Has it	27 (27%)	73 (73%)	100 (100%)	3.028 (1.532-5.986)	0.001
Does not have	16 (10.9%)	131 (89.1%)	147 (100%)		

^a Chi-square test.

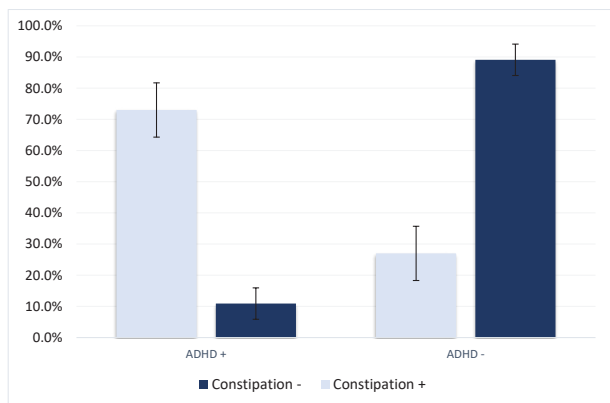


Figure 1. Distribution of Functional Constipation Among Children With and Without ADHD. The error bars indicate 95% confidence interval.

the symptoms of gastrointestinal disorders including abdominal pain, diarrhea, constipation, and food allergies. Their study showed that food allergy was more common in children with ADHD than in controls; however, this difference was not statistically significant (28). In a study by Duel et al, urinary tract infections were investigated in 28 children with ADHD and 22 children without ADHD. Urinary tract infections included daytime urinary incontinence, nocturia, burning sensation, and frequent urination, as well as constipation. The study used a rating scale called DVSS (dysfunctional voiding symptom survey). Children with ADHD have higher scores than those without ADHD (29).

Mckeown et al conducted a prospective cohort study on 742939 children aged 4-12 years with ADHD and without ADHD from the beginning of 2005 to the end of 2007. The prevalence of constipation was 4.1% in the ADHD group and 1.5% in children without ADHD and the prevalence of ADHD was higher in boys than in girls (24). Some studies have been done on the association between functional constipation and ADHD. In a study by Yousefichaijan et al in Arak, 100 children with ADHD were selected as cases and 100 children without ADHD were selected as controls. The prevalence of functional constipation was 9% in the ADHD group and 4% in the group without ADHD but the difference was not statistically significant and the study failed to show a relationship between ADHD and functional constipation (30). One of the reasons for the differences between the results of our study and these studies is the

consideration of diagnosis of ADHD for the selection of case and control participants, while our study is based on functional constipation. In the study of Yousefichaijan et al, many criteria were considered in the methodology for the selection of case and control participants, which may have led to selection bias. For example, parents were to have at least a high school diploma in some studies, while both functional constipation and ADHD were reported to be associated with the economic status and education levels of parents. Recent studies have suggested the role of intestinal flora in the development of constipation and behavioral disorders such as autism (31,32). If functional constipation is considered a sign of ADHD in the future, the symptom should be taken more seriously, because ADHD is not usually diagnosed in infancy, and it is diagnosed immediately after the child exhibits abnormal behaviors at school or has difficulty concentrating and learning. Given that the rate of functional constipation is higher in children with ADHD than in the healthy population, attention should be directed to this issue especially in children with prolonged constipation. Perhaps one of the reasons for the lack of response to conventional treatments in children with constipation is the presence of ADHD in these children, and it may therefore be helpful to identify children with ADHD in these children. Given the inconsistency in the results of some studies that have confirmed the association of functional constipation with ADHD and others that have rejected this hypothesis, further studies are needed. Usually, after descriptive studies provide a higher frequency of an event, a case-control study is carried out to confirm the causal relationship. The advantage of case-control studies is the short time required to conduct these studies, while their disadvantage is that the obtained relationship cannot be definitively established. Besides, prospective cohort studies are more robust to suggest a causal relationship, although it may take a long time. To determine the relationship between functional constipation and ADHD, it is suggested that a cohort study should be conducted on infants with and without functional constipation and these infants be examined for symptoms of ADHD a few years later at preschool and school ages.

Limitations of the Study

The notable limitations of the present study were the lack of parents' cooperation to refer a psychiatrist and their

Table 3. Frequency Distribution of ADHD among Children With Functional Constipation by Gender

Functional Constipation	ADHD			OR (95% CI)	P Value ^a
	Has it No. (%)	Does not have No. (%)	Total No. (%)		
Girl	12 (24%)	38 (76%)	50 (100%)	1.375 (0.559-3.295)	0.499
Boy	15 (30%)	35 (70%)	50 (100%)		

^a Chi-square test.

denial of having a child with mental disorders. Case-control design was another limitation.

Authors' Contribution

SA and SS: concept and design. ZZ and AH: data collection and interpretation of the data. ZZ and AH: performing of the study and writing of the draft. KA: performing statistical analysis and interpretation. All authors read and approved the study.

Conflict of Interests

None declared.

Ethical Issues

This study was approved by the Ethics Committee of Lorestan University of Medical Sciences (IR.LUMS.REC.1398.080).

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References

- Rasquin A, Di Lorenzo C, Forbes D, et al. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology*. 2006;130(5):1527-1537. doi:10.1053/j.gastro.2005.08.063
- Rajindrajith S, Devanarayana NM. Constipation in children: novel insight into epidemiology, pathophysiology and management. *J Neurogastroenterol Motil*. 2011;17(1):35-47. doi:10.5056/jnm.2011.17.1.35
- Rajindrajith S, Devanarayana NM, Benninga MA. Children and adolescents with chronic constipation: how many seek healthcare and what determines it? *J Trop Pediatr*. 2012;58(4):280-285. doi:10.1093/tropej/fmr096
- Mugie SM, Benninga MA, Di Lorenzo C. Epidemiology of constipation in children and adults: a systematic review. *Best Pract Res Clin Gastroenterol*. 2011;25(1):3-18. doi:10.1016/j.bpg.2010.12.010
- Vandenplas Y, Abkari A, Bellaiche M, et al. Prevalence and health outcomes of functional gastrointestinal symptoms in infants from birth to 12 months of age. *J Pediatr Gastroenterol Nutr*. 2015;61(5):531-537. doi:10.1097/mpg.0000000000000949
- Lewis ML, Palsson OS, Whitehead WE, van Tilburg MAL. Prevalence of functional gastrointestinal disorders in children and adolescents. *J Pediatr*. 2016;177:39-43.e3. doi:10.1016/j.jpeds.2016.04.008
- Boccia G, Manguso F, Coccorullo P, Masi P, Pensabene L, Staiano A. Functional defecation disorders in children: PACCT criteria versus Rome II criteria. *J Pediatr*. 2007;151(4):394-398. doi:10.1016/j.jpeds.2007.04.011
- Tabbers MM, DiLorenzo C, Berger MY, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. *J Pediatr Gastroenterol Nutr*. 2014;58(2):258-274. doi:10.1097/mpg.0000000000000266
- Mugie SM, Di Lorenzo C, Benninga MA. Constipation in childhood. *Nat Rev Gastroenterol Hepatol*. 2011;8(9):502-511. doi:10.1038/nrgastro.2011.130
- Gibas-Dorna M, Piątek J. Functional constipation in children - evaluation and management. *Prz Gastroenterol*. 2014;9(4):194-199. doi:10.5114/pg.2014.45099
- Knowles CH, Farrugia G. Gastrointestinal neuromuscular pathology in chronic constipation. *Best Pract Res Clin Gastroenterol*. 2011;25(1):43-57. doi:10.1016/j.bpg.2010.12.001
- King SK, Sutcliffe JR, Ong SY, et al. Substance P and vasoactive intestinal peptide are reduced in right transverse colon in pediatric slow-transit constipation. *Neurogastroenterol Motil*. 2010;22(8):883-892. e234. doi:10.1111/j.1365-2982.2010.01524.x
- Peeters B, Benninga MA, Hennekam RC. Childhood constipation; an overview of genetic studies and associated syndromes. *Best Pract Res Clin Gastroenterol*. 2011;25(1):73-88. doi:10.1016/j.bpg.2010.12.005
- Samsam M, Ahangari R, Naser SA. Pathophysiology of autism spectrum disorders: revisiting gastrointestinal involvement and immune imbalance. *World J Gastroenterol*. 2014;20(29):9942-9951. doi:10.3748/wjg.v20.i29.9942
- Mazurek MO, Vasa RA, Kalb LG, et al. Anxiety, sensory over-responsivity, and gastrointestinal problems in children with autism spectrum disorders. *J Abnorm Child Psychol*. 2013;41(1):165-176. doi:10.1007/s10802-012-9668-x
- van Dijk M, de Vries GJ, Last BF, Benninga MA, Grootenhuys MA. Parental child-rearing attitudes are associated with functional constipation in childhood. *Arch Dis Child*. 2015;100(4):329-333. doi:10.1136/archdischild-2014-305941
- Sehhatti F, Hughes C, Mirghafourvand M, Anjoman Azari Z. The effect of short-term foot reflexology in improving constipation symptoms during pregnancy: a two-armed, randomized controlled trial. *Int J Womens Health Reprod Sci*. 2020;8(3):303-310. doi:10.15296/ijwhr.2020.49
- Haug TT, Mykletun A, Dahl AA. Are anxiety and depression related to gastrointestinal symptoms in the general population? *Scand J Gastroenterol*. 2002;37(3):294-298. doi:10.1080/003655202317284192
- Wolraich M, Brown L, Brown RT, et al. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*. 2011;128(5):1007-1022. doi:10.1542/peds.2011-2654
- Pineda D, Ardila A, Rosselli M, et al. Prevalence of attention-deficit/hyperactivity disorder symptoms in 4- to 17-year-old children in the general population. *J Abnorm Child Psychol*. 1999;27(6):455-462. doi:10.1023/a:1021932009936
- Amiri S, Fakhari A, Golmirzaei J, Mohammadpoorasl A, Abdi S. Tourette's syndrome, chronic tics, and comorbid attention deficit/hyperactivity disorder in elementary students. *Arch Iran Med*. 2012;15(2):76-78.
- Connor DF. Preschool attention deficit hyperactivity disorder: a review of prevalence, diagnosis, neurobiology, and stimulant treatment. *J Dev Behav Pediatr*. 2002;23(1 Suppl):S1-9. doi:10.1097/00004703-200202001-00002
- Biederman J, Spencer T. Attention-deficit/hyperactivity disorder (ADHD) as a noradrenergic disorder. *Biol Psychiatry*. 1999;46(9):1234-1242. doi:10.1016/s0006-3223(99)00192-4
- McKeown C, Hisle-Gorman E, Eide M, Gorman GH, Nylund CM. Association of constipation and fecal incontinence with attention-deficit/hyperactivity disorder. *Pediatrics*. 2013;132(5):e1210-1215. doi:10.1542/peds.2013-1580
- Johnston BD, Wright JA. Attentional dysfunction in children with encopresis. *J Dev Behav Pediatr*. 1993;14(6):381-385. doi:10.1097/00004703-199312010-00004
- Conners CK. *Conners Rating Scales-Revised: Technical Manual*. North Tonawanda, New York: Multi-Health Systems; 2001.
- Alizadeh H. A theoretical explanation on attention deficit/hyperactivity disorder: behavioral inhibition model and nature

- of self-control. *J Except Child*. 2005;5(3): 323-348. [Persian].
28. Almog M, Gabis LV, Shefer S, Bujanover Y. [Gastrointestinal symptoms in pediatric patients with attention deficit and hyperactivity disorders]. *Harefuah*. 2010;149(1):33-36.
29. Duel BP, Steinberg-Epstein R, Hill M, Lerner M. A survey of voiding dysfunction in children with attention deficit-hyperactivity disorder. *J Urol*. 2003;170(4 Pt 2):1521-1523. doi:10.1097/01.ju.0000091219.46560.7b
30. Yousefichaijan P, Salehi B, Shekholeslami H, et al. Is attention deficit hyperactivity disorder more prevalent in children with functional constipation? *Sch J Appl Med Sci*. 2015;3(1C):209-213.
31. Liu S, Li E, Sun Z, et al. Altered gut microbiota and short chain fatty acids in Chinese children with autism spectrum disorder. *Sci Rep*. 2019;9(1):287. doi:10.1038/s41598-018-36430-z
32. Srikantha P, Mohajeri MH. The possible role of the microbiota-gut-brain-axis in autism spectrum disorder. *Int J Mol Sci*. 2019;20(9):2115. doi:10.3390/ijms20092115

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