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Gastrointestinal findings in children with Down syndrome: Is there an early sign for Celiac disease?

Down sendromlu çocuklarda gastrointestinal bulgular: Çölyak hastalığı için erken bir belirti var mı?

Halil Kocamaz [1], Sedat Işıkay [2]

Abstract

Aim: To investigate the prevalence of celiac disease (CD) among children with Down's syndrome (DS) and its association with gastrointestinal symptoms and other accompanying diseases.
Methods: The study was consisted of regular trisomy 21 patients who were under follow-up in our department. The age, gender, gastrointestinal symptoms (abdominal pain, constipation, diarrhea, abdominal distension, vomiting, flatulence, and unsatisfactory weight gain/weight loss) and accompanying diseases were recorded. Anti-tissue transglutaminase (anti-tTG) immunoglobulin A (Ig A) levels were analyzed in all cases. Serologically positive patients were referred to a pediatric gastroenterologist for intestinal biopsy.
Results: Totally 98 children with a mean age of 3.2±2.81 years (range: 2-13 years) diagnosed with the DS were included in this study. Among study participants, 46 (46.9%) were female. Among study participants, 3 (3.1%) had positive anti-tTG IgA results and endoscopic biopsies revealed the diagnosis of Marsh type 3b CD in all of them. In correlation analysis, hypothyroidism (p=0.03) and presence of diarrhea (p=0.04) significantly correlated with the CD presence among children with the DS. Diarrhea increased the risk for 1.50 times (0.67-3.34) while hypothyroidism increased the risk for 2.75 times (0.55-13.67) among patients with DS.
Conclusion: Clinicians should be aware of an increased prevalence of CD among patients with DS especially in children with diarrhea and/or hypothyroidism.

Key words: Celiac disease, children, Down syndrome

Öz

Amaç: Down sendromlu (DS) çocuklarda çölyak hastalığının (ÇH) sıklığı ile gastrointestinal semptomlar ve eşlik eden diğer hastalıklarla birlikteliğini saptamak.
Yöntemler: Çalışmaya kliniğimizde takip edilen regüler trizomi 21 olan hastalar alındı. Yaş, cinsiyet, gastrointestinal semptomlar (karın ağrısı, kabızlık, diyare, abdominal distansiyon, kusma, şişkinlik ve kilo alımı / kilo kaybı) ve eşlik eden ek hastalıklar kaydedildi. Tüm olgularda anti-doku transglutaminaz (anti-tTG) immünoglobulin A (IgA) düzeyleri analiz edildi. Çölyak serolojisi pozitif saptanan hastalara, çocuk gastroenteroloji uzmanı tarafından ince bağırsak biyopsisi yapıldı.
Bulgular: Çalışmaya yaş ortalaması 3,2 ± 2,81 yıl (2-13 yıl) olan 98 çocuk alındı. Hastaların 46'sı (% 46,9) kızdı. Hastaların 3'ünde (% 3,1) anti-tTG IgA pozitifliği vardı ve endoskopik biyopsilerin hepsinde Marsh tip 3b ÇH tanısı saptandı. ÇH saptanan DS'lu çocuklarda, korelasyon analizinde, hipotiroidizm (p=0,03) ve diyare (p=0,04) görülmesi anlamlı olarak ilişkili idi. DS'lu hastalarda, ishal ÇH görülme riskini 1,5 kat (0,67-3,34) artırırken, hipotiroidizmin 2.75 kat (0.55-13.67) arttırdığı saptandı.
Sonuç: Klinisyenler, DS'li çocuklarda özellikle diyare ve / veya hipotiroidi varlığında ÇH'nı göz önünde bulundurmalıdır.

Anahtar kelimeler: Çölyak hastalığı, çocuk, Down sendromu

[1] Pamukkale University, Faculty of Medicine, Department of Pediatric Gastroenterology, Denizli, Turkey.
[2] Hasan Kalyoncu University, Health of Sciences, Gaziantep, Turkey.

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Sorumlu yazar / Corresponding author:
Halil Kocamaz

Adres/Address: Department of Pediatric Gastroenterology, Pamukkale University, Denizli, Turkey.
e-posta: drkocamaz@hotmail.com
Tel/Phone: +90 505 5116734

Introduction

Celiac disease (CD) is an immune-mediated systemic disease triggered by gluten in genetically susceptible individuals that is characterized by the presence of specific antibodies. The pathogenesis of CD includes a dominant HLA involvement (DQ2 or DQ8), autoantibodies against transglutaminase and an obviously defined environmental trigger (gluten) [1]. CD has a wide clinical spectrum of gastrointestinal and/or extraintestinal symptoms [2]. Due to its auto immune nature, CD has been associated with other autoimmune diseases including type 1 diabetes mellitus, Hashimoto's thyroiditis and Down syndrome (DS) [3]. Trisomy 21, DS, has been related to high levels of autoantibodies and autoimmune diseases. Autoimmune regulator protein (AIRE) that is located on chromosome 21 has been suggested as the main predisposing factor for autoimmunity in patients with DS [4,5]. There are few study about the association of CD with DS and the prevalence of CD in DS was reported to be between 5-13% in different studies [6-8].

The aim of this study was to investigate the prevalence of CD among children with DS and its association with gastrointestinal symptoms.

Material and methods

Study Design and Patient Selection

This cross-sectional study was conducted between January 2013 and December 2014. The group consisted of regular trisomy 21 patients who were under follow-up in our department. All parents were informed about the investigation. The study was approved by the local Ethics Committee.

Clinical assessment included detailed physical examination, measurement of weight and height plotted on growth carts for DS children followed by an interview of the patients and parents about gastrointestinal symptoms. The age, gender, gastrointestinal symptoms (abdominal pain, constipation, diarrhea, abdominal distension, vomiting, flatulence, and unsatisfactory weight gain/weight loss) and accompanying diseases were recorded.

Venous blood samples (5 mL) were obtained in anticoagulant containing tubes, and anti-tissue transglutaminase (anti-tTG) immunoglobulin A (Ig A) levels were analyzed. The anti-tTG IgA antibodies were investigated through an enzyme-linked immunoassay (ELISA) using human recombinant antigen. Total IgA levels were also studied to determine the IgA deficiency. The patients who has not been introduced gluten are excluded from the study.

Serologically positive patients were referred to a pediatric gastroenterologist for intestinal biopsy. In upper gastrointestinal system endoscopy, three specimens were taken from the duodenal bulb and four from the second part of the duodenum, fixed with 10% formalin and sent to the Pathology Laboratory, where they were processed in paraffin and stained with hematoxylin–eosin. Marsh classification was established for the identification of CD from biopsy specimens [9].

Statistical analysis

Statistical analyses of the data were performed with the SPSS program (Statistical Package for the Social Sciences version 21, Chicago, IL, USA). After testing for normality of the data using Shapiro-Wilk test, one way analysis of variance was used to perform group comparisions. The quantitative variables were described as the mean ± SD and the categorical variables as the frequency and percentage. The study patients with and without CD were analyzed with the descriptive statistics to determine the correlation of accompanying diseases and symptoms with CD and Odd's ratios were calculated for the significantly correlated data. We used Chi-square analysis for to determine relations between variables and Logistic Regression Analysis for to determine Odd's ratio values. A P value <0.05 was considered statistically significant.

Results

Totally 98 children with a median age of 35 months (range= 9 months-156 months) diagnosed with the DS were included in this study. Among study participants, 46 (46.9%) were female. Accompanying symptoms and diseases of the study participants were recorded and 61 (62.2%) of them were having growth retardation, 4 (4.1%) were having recurrent diarrhea, 19 (19.4%) were having constipation. On the other hand, 57 (58.2%) children were having congenital heart disease, 13 (13.3%) of them were having hypothyroidism, 2 (2%) were having biliary stones, 2 (2.0 %) were having undescended testicles, 1 was having ectopic kidney, 3 (3.1%) cases had the history of an operation due to ileus. Two cases were diagnosed with cerebral palsy, and interestingly, epilepsy was determined in 4 (4.7%) of the study participants and 3 of those 4 children were diagnosed with the west syndrome (WS).

Among study participants, 3 (3.1%) had positive anti-tTG IgA results and endoscopic biopsies revealed the diagnosis of Marsh type 3b CD in all of them. None of the patients had IgA deficiency. The general characteristics of these 3 cases are summarized in Table 1.

Table 1: General characteristics of children with Celiac disease

	Case 1	Case 2	Case 3
Age (years)	2	2	3
Gender	Male	Female	Female
Diarrhea	-	-	+
Constipation	-	-	+
Hypothyroidism	+	-	+
Epilepsy	+	-	-
Congenital Heart Disease	+	-	+
Laryngo-malasia	+	-	-
Growth retardation	+	+	+
Iron deficiency anemia	+	+	-

In correlation analysis, hypothyroidism (p=0.03) and presence of diarrhea (p=0.04) significantly correlated with the CD presence among children with the DS, but presence of growth retardation (p=0.25), constipation (p=0.56), congenital heart disease (p=0.59), epilepsy (p=0.14), bile stone disease (p=0.95), ectopic kidney (p=0.95) benign paroxysmal vertigo (p=0.95), Vitamin B12 deficiency (p=0.76), foliate deficiency (p=0.95), and iron deficiency (p=0.74) did not correlate with the CD presence. The odd's ratios for hypothyroidism and diarrhea are summarized in Table 2.

Table 2: Odd's Ratios of Hypothyroidism and Diarrhea

	Odd's ratio	95% Confidence Interval
Hypothyroidism	2.75	0.55-13.67
Diarrhea	1.50	0.67-3.34

Discussion

The prevalence of CD was estimated as 0.47% in healthy Turkish school children [10]. Recently, Kansu et al. [11] reported the overall prevalence of CD as 0.95% in 1047 children with chronic abdominal pain.

The common autoimmune mechanisms in CD and DS propelled the investigators to determine the togetherness of these

2 diseases. Marild et al. [12] reported a 6 fold increased risk of CD in individuals with DS. Nisihara et al. [13] reported the prevalence of CD in patients with DS as 5.6%. Roizen et al. [14] investigated 440 children with DS to determine the frequency of associated medical problems in those patients and reported the prevalence of CD as 5%. Not being too far from these results, we also have determined the prevalence of CD as 3.1% among children with DS. However, Alanay et al. [15] reported that only one patient out of 100 (1%) was detected to be anti endomysial IgA-positive but this child's family refused consent for the biopsy procedure and biopsy could not be performed. Similarly, Pavlovic et al. [16] examined 82 children with DS aged 8 months to 8.6 years for the existence of CD and reported that in 4 children immunoglobulin A and/or immunoglobulin G transglutaminase antibodies were positive, but enteric biopsies showed absence of CD in all cases and the authors suggested not to the screen the children with DS for CD before the age of 8 years. Nevertheless, in our study, all children diagnosed with CD were under the age of 8 years. On the other hand, presence of DS among Celiac patients has also been investigated. In a previous prospective study, we have investigated the neurological findings among celiac patients and reported that 1 (0.3%) out of 297 celiac patients was having DS [17]. Al-Qabandi et al. [18] retrospectively reviewed the records of 47 children diagnosed with CD and reported that 3 (6.4%) of them were also having the diagnosis of DS. Stordal et al. [19] investigated 3006 children with CD for the coexisting conditions and reported that 47 (1.6%) of them were having DS. In general, the prevalence of DS has been reported to be approximately 9-10 Per 10000 live births in Turkey [20] and the prevalence of DS determined in those studies among patients with CD was also rather high.

Interestingly, in another study Bhat et al. [6] reported the prevalence of CD as 7% among 100 children with DS and defined that the pallor and anemia as significant risk factors associated with CD in this group. In this study, for the first time in literature, we have determined that diarrhea or hypothyroidism significantly correlated with the presence of CD among children diagnosed with DS. Diarrhea increased the risk for 1.50 times (0.67-3.34) while hypothyroidism increased the risk for 2.75 times (0.55-13.67) among patients with DS. In fact this finding was not surprising since Hashimoto's thyroiditis is an autoimmune disease that increases the risk of presence of other autoimmune diseases and diarrhea is one of the most common symptoms of CD [21, 22]. Cerqueira et al. [23] reported the prevalence rate of CD as 9.2% in adults with DS.

Remarkably in this study, we have determined that epilepsy was accompanying DS in 4 (4.7%) children and 3 of those 4 children were diagnosed with the WS. In literature, Barca et al. [24] reported that 9 (23%) of 39 children with DS were also having epilepsy and similar with our results in that study the most frequent epileptic syndrome associated with DS was reported as WS. Lack of a control group and low number of patients are the main limitations of this study.

In this study, we have determined an increased prevalence of CD among patients with DS compared with the general population. Moreover, presence of diarrhea and/or hypothyroidism was associated with the CD. In that aspect, clinicians should be aware of an increased prevalence of CD among patients with DS especially in children with diarrhea and/or hypothyroidism.

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