Prevalence of celiac disease in children with joint hypermobility

Sag E[1], Demir F[2], Sag S[3], Guven B[1], Kalyoncu M[2], Cakir M[1]

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ABSTRACT

Introduction: Generalized joint hypermobility is a clinical feature that is associated with excessive joint laxity, which can occur alone or with various inherited disorders. The term benign joint hypermobility or joint hypermobility is used when presence of musculoskeletal symptoms in subjects with generalized hypermobility in the absence of demonstrable systemic rheumatic disease. In recent studies, it was shown that there is a strong relationship between structural and functional gastrointestinal disorders and joint hypermobility. We aimed to analyze the prevalence of celiac disease in a group patient with joint hypermobility.

Patients and methods: The study included 2 groups of children (i) Group 1; patients with joint hypermobility that were followed in pediatric rheumatology outpatient clinic (n=131). (ii) Group 2; healthy children without known chronic diseases (n=995). Demographic features, clinical findings, accompanying symptoms and anthropometric measurements of all patients were recorded. All cases were screened for celiac disease by serological marker and histopathological examinations if serological marker was positive.

Results: There was no difference between two groups for age , gender, presence of malnutrition and accompanying symptoms (p>0.05). Serology positivity of anti-tissue transglutaminase IgA >20 RU/ml was found in seven patients with joint hypermobility. After histopathological examinations, asymptomatic celiac disease was detected in one (n=1, 0.9%) and potential celiac disease in six patients (n=6, 5.3%). There were six (0.6%) patients with positive serology in the control group. Celiac serology positivity and potential celiac disease were higher in patients with benign joint hypermobility (6.2%, *vs*. 0.6%, OR: 10.9, 95% CI: 3.6-33, p<0.001 and 5.3%, *vs*. 0.4%, OR: 13.9, 95% CI: 3.6--50, p<0.001, respectively), but no significant difference was found on the prevalence of asymptomatic celiac disease (0.9%, *vs*. 0.2%, OR: 4.4, p=0.22).

Conclusion: Our study shows the increased prevalence of potential celiac disease in patients with joint hypermobility. Serological screening of celiac disease is recommended for to rule out organic problems in the presence gastrointestinal symptoms in patients with BJH.

Keywords: Potential celiac disease; organic; joint hypermotility.

INTRODUCTION

Generalized joint hypermobility (GJH) is a clinical feature that is associated with excessive joint laxity, which can occur alone in or with various inherited disorders such as osteogenesis imperfecta, Ehlers-Danlos syndrome (EDS), or Marfan's syndrome (MS) in childhood. The term benign joint hypermobility or joint hypermobility (JH) is used when the presence of musculoskeletal symptoms in subjects with GJH in the absence of demonstrable systemic rheumatic disease, metabolic disease or orthopedic disorder[1]. It was first defined in 1967 by Kirk *et al*. as the occurrence of musculoskeletal symptoms in hypermobile but otherwise healthy persons[2]. Despite the phenotypic overlaps JH with MS, EDS and osteogenesis imperfecta, BJH differs from these disorders with the basis of genetic backgrounds and considered as a more benign form. Environmental factors play the major role for the pathogenesis of BJH and the role of genetic factors is controversial only mutations in the *TNXB* gene, coding the extracellular matrix glycoprotein Tenascin X, has been identified in 5-10% of cases[3]. Prevalence rates vary

1. Karadeniz Technical University, Faculty of Medicine, Department of Pediatric Gastroenterology, Hepatology and Nutrition, Trabzon;
2. Karadeniz Technical University, Faculty of Medicine, Department of Pediatric Rheumatology, Trabzon;
3. University of Health Sciences, Kanuni Education and Research Hospital, Department of Pediatric Surgery, Trabzon

greatly according to race, age, and gender, with higher rates in Asians, younger individuals, and females. In Western adolescent populations, the rate of GJH was found approximately 10-20%[4,5].

In recent studies, it was shown that there is a strong relationship between structural and functional gastrointestinal disorders and JH. Abdominal hernias (≈20-25%), rectal prolapses (≈10% in women), ptosis of internal organs and diaphragmatic hernias are more common in patients with hypermotility syndromes. Functional gastrointestinal disorders including dysphagia, gastroesophageal reflux, irritable bowel syndrome and functional constipation is reported in 30-40% of the patients. Dysautonomia, laxity of peritoneal ligaments and an abnormal connective tissue content within the gut wall leads the gastrointestinal problems in patients with joint hypermobility by influencing pain thresholds and gut motility[6,7].

Decreased gastrointestinal motility and prolonged transit of nutritional antigens within the intestines, secondary changes in intestinal microbiota, changes in the permeability of gut mucosa due to defect of extracellular matrix in the lamina propria may lead the inflammatory gastrointestinal diseases such as inflammatory bowel disease and eosinophilic esophagitis in patients with JH[8-10]. Since prolonged transit time of gluten and increased intestinal permeability are the major factors for the development of celiac disease (CD), the association of JH with CD has been only studied in small series of adult patients[8]. Therefore, we aimed to analyze the prevalence of CD in a group of pediatric patients with JH.

PATIENTS AND METHODS

The study included the 2 groups of children (i) Group 1; patients with JH that were followed in pediatric rheumatology outpatient clinic (n=131). The diagnosis of JH was made by Beighton score (BS) by the pediatric rheumatologists.

We used the Beighton hypermobility score (BHS) as modified by Beighton *et al.* from the Carter-Wilkinson scale for the definition of GJH.[11,12]

- Passive dorsiflexion of the fifth metacarpophalangeal joint over 90 degrees (1 point for each fifth MPJ).
- Passive apposition of the thumb, so that it touches the ventral side of the forearm (1 point for each thumb).
- Active extension of the elbows more than 10 degrees (1 point for each elbow).
- Active extension of the knees more than 10 degrees (1 point for each knee).
- Touching palms to the ground after forward flexion of the trunk with stretched knees (1 point).

A score of ≥5 points in children aged 4–9 years and a score of ≥4 points in children aged ≥10 years were considered as JH[13]. Patients associated with other hypermobility syndromes such as EDS or MS, metabolic diseases or other genetic disorders were excluded (patients were diagnosed as JH after exclusion of other causes of GJH by clinical, laboratory, radiological and/or genetic examinations) (ii) Group 2; healthy children without known chronic diseases, who were admitted to healthy children outpatient clinic aged between 4-17 years old. Children were selected consecutively during study period JH was excluded in all children in group 2 by the pediatric rheumatologists. The number of children in the control group was calculated according to previous population studies on CD[14]. With the assumption that CD is expected to occur in 1% of the population, we calculated that a sample of 1000 healthy children has 95% confidence interval. 1000 healthy children included into the study but due to technical problems such as inadequate peripheral blood samples, 5 children were excluded, and 995 healthy children were included to the study. A roughly age [percentages of participants in each age group (4-7, 8-11, 12-15 and >15 years old) were similar in patients and control group] and gender matching were made between the patients and control group.

Demographic features, clinical findings, accompanying gastrointestinal symptoms (such as presence of chronic constipation, chronic diarrhea, or abdominal pain) and anthropometric measurements of all patients with BJH were recorded. Anthropometric measurements data were presented as Z scores with a cut-off point of two standard deviations (2 SD) as recommended by the World Health Organization. Weight-for-age (WFA), height-for-age (HFA) and weight-for height (WFH) were calculated. SD of z-score <-2 for WFH (WFH z-score) and HFA (HFA z-score) were used to define acute and chronic malnutrition. Obesity was defined as WFH above 2 Z scores[15].

All cases with BJH and control subjects were screened for CD by serological markers. 5 mL of peripheral venous serum samples were obtained from all patients and control subjects. Diagnosis of CD was made based on anti-tissue transglutaminase IgA (tTG-

IgA) antibody positivity and with compatible histopathological findings[16]. IgA deficiency was ruled out in all study group (normal values: 0.15-1.50 g/L). The cutoff level for tTG-IgA defining a positive result was set at 20 RU/mL (the maximum calibrator was 200 RU/mL). Intestinal biopsy was offered to all subjects with positive tTG-IgA levels. Three biopsy specimens were taken from the bulbus and the second part of the duodenum and carefully oriented on filter paper before submersion in 10% neutral buffered formalin. The Marsh classification was used for the histopathological classification[16]. Patients with positive serology but with normal or slightly infiltrated bowel mucosa (Marsh 0-1) were defined as "potential CD". Patients with positive serology and without symptoms or with mild symptoms but had histopathological findings compatible with CD (Marsh 3) were defined as "asymptomatic CD" (such as detected incidentally in screening programs)[17].

The study was conducted in accordance with the principles of the Helsinki Declaration. The study protocol was approved by the institutional Ethics Committee (Ethics Committee no: 2017-35). Informed consent was obtained from patients and/or their parents. The study was supported by Scientific Research Project Coordination Unit of the university.

All calculations in our study were performed using the SPSS 22.0 software, and the continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as percentage (%). Comparison of the quantitative data between the groups was performed using Student t test in the normally distributed variables, and Mann Whitney U test in the non-normally distributed variables. Whereas qualitative data were compared using Chi square test. p value ≤ 0.05 was considered statistically significant.

RESULTS

Demographic and clinical features of the patients with JH and control group were shown in Table I. Mean age of the patients and control group were 9.3 ± 3.1 and 9.1 ± 4.3 years, respectively (p>0.05).

Joint laxity was mostly observed in the thumb (91.2%), knee (88.5%), and elbow (88.5%) in patients with JH. The mean BHS in patients with JH was 6.9 ± 1.1 points (range; 4-9), and in the control group 1.2 ± 0.8 points (range; 0-4) (p=0.001).

Malnutrition was found in 22 patients (19.5%, acute malnutrition in five, chronic malnutrition in 17 patients) with JH. Chronic abdominal pain (n=17, 15%), chronic dyspepsia (n=12, 10.6%) and functional constipation (n=18, 15.9%) were the accompanying gastrointestinal symptoms in patients with JH. Malnutrition was observed in control group in 160 patients (16.1%, acute malnutrition in 45, chronic malnutrition in 115 patients). Chronic abdominal pain (n=112, 11.3%), chronic dyspepsia (n=67, 6.7%) and functional constipation (n=113, 11.4%) were the accom-

TABLE I. DEMOGRAPHIC AND CLINICAL FEATURES OF THE PATIENTS WITH JOINT HYPERMOBILITY AND CONTROL GROUP

Parameters	Patients with JH (n=113)	Control subjects (n=995)	p
Age, mean ± SD, years	9.3 ± 3.1	9.1 ± 4.3	0.700
Age groups, n (%)			
<9 years	71 (62.8)	597 (60)	0.550
9-17 years	42 (37.2)	398 (40)	
Gender, female, n, (%)	51.3	51.9	0.900
Acute malnutrition, n (%)	5 (4.4)	45 (4.5)	0.900
Chronic malnutrition, n (%)	17 (15)	115 (11.2)	0.270
Obesity, n (%)	19 (16.8)	124 (12.5)	0.190
Accompanying gastrointestinal symptoms, n (%)			
Chronic abdominal pain	17 (15)	112 (11.3)	0.230
Chronic dyspepsia	12 (10.6)	67 (10.1)	0.900
Functional constipation	18 (15.9)	113 (11.4)	0.150
Beighton hypermobility score, mean ± SD, points	6.9 ± 1.1	1.2 ± 0.8	<0.001

JH: joint hypermobility

TABLE II. COMPARISON CELIAC SEROLOGY AND CELIAC STATUS OF PATIENTS WITH JOINT HYPERMOBILITY WITH THE CONTROL GROUP

	Patients with JH (n=113)	Control subjects (n=995)	p value	OR (95% CI)
Serology positivity, n, (%)	7 (6.2)	6 (0.6)	<0.001	10.9 (3.6-33)
Potential CD, n, (%)	6 (5.3)	4 (0.4)	<0.001	13.9 (3.6-50)
Asymptomatic CD, n, (%)	1 (0.9)	2 (0.2)	0.18	4.4 0.4-49.3

CD: celiac disease; JH: joint hypermobility

panying gastrointestinal symptoms in control group. No difference was seen in age groups, gender, presence of malnutrition and accompanying symptoms between the groups (p>0.05 for all) (Table II).

Serology positivity (tTG-IgA>20 RU/ml) was found in seven patients (6.2%, 95% CI; 6.08-7.92) with JH, but six of them were less than 200 RU/ml. All of patients underwent endoscopic examination. Histopathological and endoscopic examination revealed subtotal villous atrophy and intraepithelial lymphocyte infiltration (March 3A) in only one patient who had tTG-IgA>200 RU/ml. This patient also had functional constipation and mild short stature (z score for height: -2.04). She was initiated on strict gluten-free diet and, tTG-IgA levels decreased in the 6th month and became negative (tTG-IgA<20 RU/ml) in the 1st year. The other patients had March 0-1 lesions and, they are considered as having potential CD. These patients are followed up with serology 6-month intervals for 1 year. tTG-IgA of three subjects became negative, two decreased and one had elevated (from 22.9 to 45.2 RU/mL) in the 1st year, but control endoscopy remains normal. At the end of the serologic and histopathological examinations of patients with JH, asymptomatic CD was detected in one (n=1, 0.9%, 95 CI; 0.08-1.92) and potential CD in six patients (n=6, 5.3%, 95 CI; 5.08-6.92). There were six (0.6%) patients with positive serology in the control group. 2 of 6 (0.2%, tTG-IgA>200 RU/ml) patients with Marsh 3 lesion on histopathological examination diagnosed as asymptomatic CD and, 4 patients (0.4%) were diagnosed as potential CD.

Comparison of patients with JH and control group was shown in Table 2. Celiac serology positivity and potential CD were higher in patients with JH (6.2%, *vs.* 0.6%, OR:10.9, 95% CI: 3.6-33, p<0.001 and 5.3%, *vs.* 0.4%, OR:13.9, 95% CI: 3.6-50, p<0.001, respectively), but no significant difference was found on the prevalence of asymptomatic CD (0.9%, *vs.* 0.2%, OR: 4.4, p=0.22).

DISCUSSION

In the presence study, we found that the celiac serology positivity and potential CD was more common in children with JH compared to healthy population, but no significant difference was found in the prevalence of asymptomatic CD.

As above mentioned, the prevalence of structural and functional gastrointestinal disorder is increased in patients with JH. In addition, we found the increased rate of celiac serology positivity and potential CD in JH. The association of these two disorders was firstly evaluated by Tinkle *et al*; and no association was found between CD and joint hypermobility syndrome/Ehlers--Danlos syndrome hypermobility type (JHS/EDS-HT)[18]. Then, Danese *et al*. evaluated the CD frequency in 31 patients with JHS/EDS-HT and compared their results with previous population-based study in Italy. They found that the prevalence of CD was 10–20 times more common in JHS/EDS-HT compared to the general population (16.1% *vs.* 1%). Despite the number of patients in their study group was low, they speculate that abnormal collagen synthesis and formation of collagen-gluten crosslinks may facilitate autoimmunity in genetically predisposed subjects[8]. Similarly, Laszkowska *et al*. analyzed Swedish patients with CD for JHS/EDS-HT, and in their subgroup analysis they found a moderately increased risk of prior diagnosed of JHS/EDS-HT in CD patients compared to healthy population, however they speculate this association might be related with high rate of screening celiac serology in patients with JHS/EDS-HT due to high rate of gastrointestinal problems. They do not offer to screen routinely for CD in patients with JHS/EDS-HT if there is

not any other suspicious or indications[19]. Fikree *et al*. found that prevalence of CD was higher in patients with JHS (30.7%) compared to patients with other organic diseases (25.3%), but the results were not statistically significant[20].

It has been reported that the risk of autoimmune disorders such as systemic lupus erythematosus and rheumatoid arthritis is increased in patients with JH. But the pathogenesis of the association of JH with CD seems unclear. Motility disorders in JH may lead to change in intestinal microbiota and intestinal permeability. It may also prolong the transit time of gluten peptides in the small intestines[6]. In recent years, hypermobility syndromes are classified in the group of disorders associated with increased intestinal permeability due to defective collagen synthesis within the intestinal wall[21].

Potential CD is a subgroup of CD associated with positive serology and with normal mucosal architecture. It was reported approximately 20-40% of all patients with positive celiac serology. Most of the patients have associated autoimmune diseases such as type 1 diabetes mellitus and autoimmune thyroiditis or they are first-degree relatives of classical CD patients. They generally have mild symptoms and have HLA typing are similar to CD. They do not recommend a gluten-free diet and approximately 50-70% became seronegative on long-term follow-up[17]. In recent studies, it was shown that over expression of interleukin-15 (IL-15) in the lamina propria, not intestinal epithelium, was associated with development of potential CD[22]. The role of upregulated IL-15 in the pathogenesis of rheumatoid arthritis, type 1 diabetes mellitus, systemic lupus erythematosus has been well defined in previous studies[23,24]. These diseases are associated with increased risk of potential CD. But the role of IL-15 in the pathogenesis of BJH have not been evaluated previously.

On the other hand, an increased incidence of connective tissue diseases in associated with IgA autoantibodies to collagen types I, III, V, and VI have been reported in patients with CD[25]. Specifically, an increased risk of EDS/JHS in patients with CD was found compared to the general population (0.15% *vs.* 0.11%), but not compared to other individuals undergoing small intestinal biopsy in Swedish study[19]. This association between CD and EDS/JHS was much weaker than prior smaller published studies. Oliveira *et al*. found that 7.5% of the patients with CD had rheumatological and connective tissue disorders at the time of initial admission and 41.6% of them were JHS[26].

The only limitation of our study was lack studying CD related-HLA groups in patients with JH and potential CD. It may give more information about the pathogenesis of CD and JH association.

CONCLUSIONS

In conclusion, functional and structural gastrointestinal problems are common in JH. Our study does not support the routine screening CD in patients with JH. However, we propose to screen CD with serological parameters to rule out organic problems in the presence gastrointestinal symptoms. Additionally, further studies should analyze the link between JH and potential CD.

CORRESPONDENCE TO
Murat Cakir
Karadeniz Technical University, Faculty of Medicine
Department of Pediatric Gastroenterology, Hepatology and Nutrition
Turkey/Trabzon
E-mail: muratcak@hotmail.com

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