Celiac disease in patients with Williams-Beuren syndrome

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Received: 21 July 2015, Revised: 17 November 2015, Accepted: 8 February 2016

SUMMARY: Mıhçı E, Güzel-Nur B, Berker-Karaüzüm S, Yılmaz A, Artan R. Celiac disease in patients with Williams-Beuren syndrome. Turk J Pediatr 2015; 57: 599-604.

Celiac disease is an autoimmune, gastrointestinal disorder characterized by intolerance to the dietary grain protein gluten. An increased prevalence of celiac disease has been reported in Down syndrome and Turner syndrome, but there has been only few previous reports with respect to the association of celiac disease in Williams-Beuren syndrome. The aim of this study was to evaluate the frequency of celiac disease in our 24 Williams-Beuren syndrome patients. Gastrointestinal problems and celiac disease symptoms of patients were noted. All patients were analyzed by the titer of tissue transglutaminases IgA and IgG. HLA genotyping and intestinal biopsy was performed to the patients with positive serology. We also performed gluten free diet in the presence of compatible symptoms, serology, HLA genotyping and intestinal biopsy. In our study, two patients had positive tTG antibodies, but only one had positive biopsy finding for celiac disease. The frequency of celiac disease in patients with Williams–Beuren syndrome was estimated as 1/24 (4.1%). Though the number of participants in this study was limited, the results show that the frequency of celiac disease is higher in Williams-Beuren syndrome compared to the general population. We suggest that a high suspicion and testing for celiac disease should be recommended at certain intervals in all cases with Williams-Beuren syndrome to detect the cause of growth retardation and gastrointestinal problems.

Key words: Williams-Beuren syndrome, celiac disease, tissue transglutaminase antibodies, intestinal biopsy, gluten-free diet.

Williams-Beuren syndrome (WBS) is now recognized to be a multi-system disorder characterized by distinctive facial features, growth delay, mental retardation with typical neurobehavioral profile, cardiovascular anomalies, endocrine complaints including autoimmune disorders, and occasional infantile hypercalcemia[1,2]. Other features include feeding difficulties during infancy, hyperacusis, hoarse voice, joint hyperextensibility, and stellate pattern of iris[3]. The incidence has been estimated 1 in 20,000 live births. The syndrome is mainly sporadic, although there are reports of a few cases following autosomal dominant inheritance[4].

Celiac disease (CD) is defined as a permanent sensitivity to gluten in wheat and related proteins found in wheat and rye. It occurs in genetically susceptible individuals and manifests as an immune-mediated enteropathy. Nowadays prevalence of CD is increasing. Before the serologic screening tests that allow for the identification of silent CD have not become available, the prevalence of CD varied between 1:1,000 and 1:3,000 in Europe. After most modern serologic screening tests, several European studies have shown a population-based screening prevalence for the disease in the order of 1:150 to 1:300[5]. The prevalence of CD is at least 1:212 in healthy Turkish school children[6]. The clinical manifestations of CD range from mild symptoms such as abdominal pain to severe intestinal malabsorption. Some CD risk factors have been determined: early gluten exposure, first degree relatives with CD, several infectious factors, autoimmune or genetic diseases[7]. An increased prevalence of

CD has been reported in some genetic diseases such as Down syndrome, and Turner syndrome with a prevalence between 4.5% and 10.5%, but there has been only few previous clinical study which respect to the association of CD in WBS[8-11]. Because of this, CD has been rarely described in WBS, here we report our own cases with CD screening and manifestations to assess the frequency via the literature.

Material and Methods

Patients

Twenty four patients (12 girls, 12 boys) diagnosed as WBS between 2000 and August 2012 in the Akdeniz University Pediatric Genetics Department were included. The mean age was 9.4 years (24 months-39 years). Two patients had family history of consanguinity. The study protocol was approved by ethical committee of the Akdeniz University and informed consents were obtained from the patients or parents. For obtaining uniform clinical data about family history, gastrointestinal symptoms and physical findings were recorded.

FISH analysis method

All patients had FISH analysis to detect microdeletion of chromosome 7q11.23 region, after clinical assessment by the pediatric geneticist. Initially, chromosome analysis was performed by G-bands by trypsin using Giemsa (GTG) in 72 hours cultured peripheral blood lymphocytes. After the normal karyotypes were revealed from patients, fluorescent in situ hybridization (FISH) was performed using commercial Williams Syndrome Region (7q11.23) probes encompassing ELN. The Cytocell Williams-Beuren 496 kb probe (Cat No LPU 011, Cytocell, USA) consists of three non-overlapping clones from genes FZD9 to GTF21, and contains the chromosome 7 centromere a-satellite D7Z1 probe for control. Images were recorded using a Zeiss Axioplan epifluorescence microscope equipped with a CCD camera and analysed with MacProbe v4.3 software.

All metaphase cells had one red signal (demonstrating for haploinsufficiency of 7q11.23) and two green signals.

Serologic and endoscopic assessments

Celiac disease was diagnosed according to the revised criteria of the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition[12]. As to the gastrointestinal function, particular attention was paid to the features of CD, such as chronic diarrhea, vomiting, delayed growth, and anorexia. Biochemical profile (calcium, urine calcium/creatinine ratio, thyroid functions), IgA tissue transglutaminases (IgA-tTG) and IgG tissue transglutaminases (IgG-tTG) were assessed in all cases. Serum tTG antibodies were assayed by ELISA. Patients were selected for the haplotypes in the human leukocyte antigen (HLA) class II region (HLA DQ), endoscopy and intestinal biopsy performed on basis of tTG antibody positivity. Intestinal biopsies were performed by pediatric endoscopes at the level of the second/third portion of the duodenum.

Statistics

Data analysis was performed using SPSS software version 13.0 for Windows (SPSS, Inc., Chicago, IL, USA). Clinical features were analyzed using descriptive statistics.

Results

Clinical features

In all patients FISH in metaphase spreads and interphase nuclei showed deletion of the elastin gene, and also the karyotypic analysis were normal. Except for three patients, all patients were sporadic. The other three patients had molecularly confirmed familial inheritance. Overall patients presented characteristic facial features of WBS.

Gastrointestinal aspects and celiac disease assesment

The gastrointestinal pathologies and CD symptoms which were seen in our patients include feeding problems and low weight (50%), short stature for normal age matched population (37%), short stature for WBS growth charts (12%), chronic constipation (33%), rectal prolapsus (16%), and enamel defects (4%). Diarrhea was not detected. The gastrointestinal system problems and CD symptoms are seen in Table I.

All patients were negative for tTG antibody except for two children at 1.5 years (patient 1) and 2 years (patient 2) of age. Both of these two children were positivite for tTG antibody with normal total IgA values (Figs. 1 and 2).

Table I. Gastrointestinal Problems and Celiac Disease Symptoms of Patients with Williams-Beuren Syndrome

Gastrointestinal problems and Celiac Symptoms	Number of patients (%)
Feeding Problems and growth retardation	12 (50%)
Chronic constipation	8 (33%)
Rectal prolapsus	4 (16%)
Infantile colic	4 (16%)
Short stature (for WBS growth cards)	3 (12%)
Bloating	3 (12%)
Enemal defects	1 (4%)
Gastroesophageal reflux	1 (4%)
H. pylori infection	1 (4%)
Diverticular disease	1 (4%)

HLA DQ 02 and HLA DQ 05 type detected in patient 1 and HLA DQ 03 and HLA DQ 05 type detected in patient 2. The intestinal biopsy was performed endoscopically and histologically assessed in both of two patients. tTG antibody values during their follow up, gastrointestinal pathologies, CD symptoms, HLA haplotypes, endoscopy, histologic findings of intestinal biopsy and final diagnosis of patient 1 and 2 are seen in Table II.

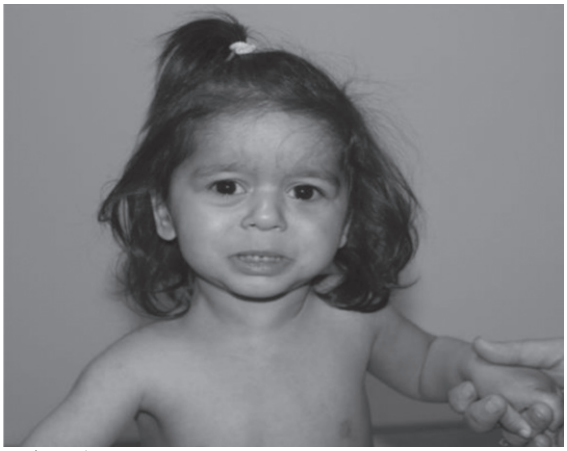
Discussion

Autoimmune pathologies such as CD, thyroid gland disorders, and diabetes mellitus are more common in children with some chromosomal anomalies[13]. A possible association between CD and 22q11.2 deletion has been reported recently but only few previous reports highlighted the prevalence of CD in WBS [14]. First, Castro et al.[8] described a WBS patient with CD in 1986. Shortly after that few sporadic cases have been reported[15]. Furthermore, Giannotti

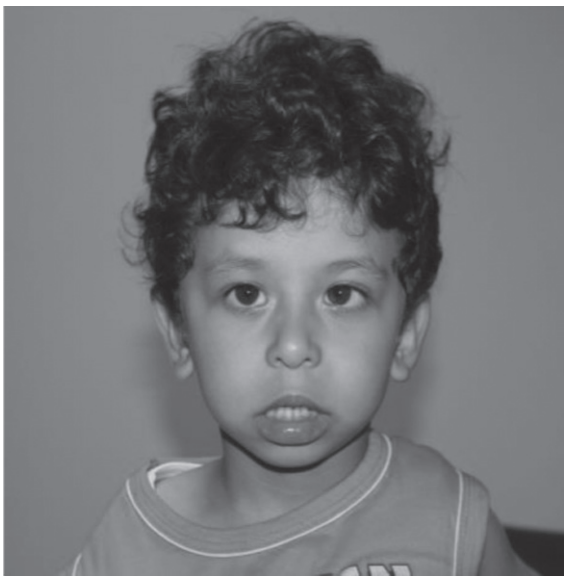
Table II. HLA Haplotypes, Endoscopy, Histology, and Final Diagnosis of Patient 1 and 2.

	Sex	Age (year)	IgA-tTG	IgG-tTG	HLA DQ	Endoscopy	Histology	Gastrointestinal pathologies and Celiac Symptoms	Final Diagnose
Patient 1	F	1.5	positive	positive	DQ2 and DQ8	Atrophic duodenitis	Inflammation and lymphocyte infiltration	Feeding problems and growth retardation, chronic constipation, bloating	Coeliac disease
Patient 1 (After 1 year)		2.5	negative	negative				Absent (increase in weight gain)	
Patient 2	M	2	negative	positive	DQ3 and DQ5	Chronic active gastritis	Mild duodenitis, chronic gastritis	Chronic constipation, rectal prolapsus, bloating	Duodenitis and gastritis
Patient 2 (After 6 months)		2.5	negative	negative				Improved	

F: Female, M: Male
IgA tissue transglutaminases (IgA-tTG) antibody concentrations were positive >5 RIU/ml titers
IgG tissue transglutaminases (IgG-tTG) antibody concentrations were positive >20 RIU/ml titers



Patient 1



Patient 2

Fig. 1. Facial appearance of patient 1 and patient 2

et al.[9] revealed that the prevalence of CD was 9.5% in 63 patients with WBS in Italy. They confirmed the diagnosis with small bowel biopsy from the patients with positive AGA and anti-endomysium antibodies (AEA). In another study the prevalence of CD was reported to be 1.4% in 71 patients with WBS. The investigators confirmed the diagnosis with clinical response to a gluten-free diet in a patient with positive IgG-AGA and IgA-AEA[16].

In our study, two patients had positive tTG antibodies, but they had distinct final diagnosis after the follow-up. In patient 1, in addition to celiac symptoms such as constipation, bloating, weight percentile decrease in growth charts, tTG antibody positivity, and typical HLA haplotype were detected. Intestinal biopsy revealed intraepithelial lymphocyte infiltration, and villous atrophy. She demonstrated clinical response to a gluten free diet and after one year she became seronegative for tTG antibody. In patient 2, chronic constipation, abdominal pain, height percentile decrease in growth charts, and tTG antibody positivity was found. Intestinal biopsy revealed nonspecific findings and after six months negativity for tTG antibody was detected without any diet. He was not diagnosed as CD due to the lack of CD specific antibodies, non-compatible HLA results and nonspecific small-bowel biopsy findings. This discrepancy between two tTG antibody results of patient 2 was attributed to transient gluten hypersensitivity.

Eventually, we show that the estimated prevalence of CD in molecularly confirmed Turkish WBS patients is 1:24 (4.1%). This is significantly high compared to the CD frequency in 0.47% of healthy 20,190 Turkish school children[6]. Our result was consistent with the result of celiac prevalance (%3) in 33 Turkish WBS patients that has been reported recently[17]. Although the number of cases in our study is not high enough to draw a definite conclusion, we showed biopsy-proven CD in a WBS patient. In addition we also confirmed the diagnosis with clinical response to a gluten-free diet.

Celiac disease occurs in genetically susceptible individuals and it is closely associated with genes that code HLA-II antigens. HLA genes are located on chromosome 6 and 95% of patients with CD susceptibility have HLA DQ2 gene and the remaining express HLA DQ8 gene[18]. Consistent with this report we detected HLA DQ2 haplotype in patient 1. It is well known that histologic examination of multiple small bowel biopsy specimens remains the diagnostic gold standard for CD. In addition, AGA, tTG and EMA antibodies are used for serologic screening. tTG antibody positivity which is reported to be a highly sensitive (up to 98%), and specific (around 96%) serologic marker for CD, can be easily determined by an accurate and comparatively cheap technique[19,20]. There have been no report which analysed tTG antibody in WBS. In different studies the frequency of IgA and IgG AGA seropositivity was found to be 11% and 19% in WBS patients, respectively[9,16]. In our study IgA-tTG and IgG-tTG antibody

positivities were found to be 4.7%, and 9.5%, respectively.

The reason of WBS and CD association is still unknown. Celiac disease has a multifactorial inheritance where both genetic and environmental components play crucial roles in the pathogenesis of the disease. Recent evidence of association between CD and WBS suggests 7q11.23 as a candidate region containing non HLA susceptibility genes for CD. However the analysis of ELN17 microsatellite marker in 74 Italian CD families did not lead to the identification of common genetic factors responsible for the association between CD and WBS. Based on this findings, the authors supported the hypothesis that their association may be interpreted as a consequence of a more general metabolic imbalance present in chromosomal disorders such as Down and Turner syndrome[21,22].

Celiac disease has a wide spectrum of gastrointestinal (abdominal distension, chronic or recurrent diarrhea, constipation, abdominal pain, failure to thrive or weight loss, irritability) and extraintestinal manifestations (short stature, enamel defects, iron-deficient anemia, pubertal delay, vomiting, behavioural disturbances). On the other hand, the clinical presentation of CD can be atypical or asymptomatic. For example, in Down syndrome CD can not be detected on the basis of clinical findings alone, because presenting symptoms may be possibly attributed to Down syndrome itself[23]. Similarly, CD symptoms may also be common in WBS. Therefore these patients should be screened for CD if gastrointestinal and extraintestinal manifestations are detected, or growth faltering is observed with specific growth charts for WBS. Asymptomatic patients should also be screened for CD at certain intervals.

In conclusion, this study investigates the association between WBS and CD in Turkish patients. We found a high frequency of CD in molecularly confirmed Turkish WBS patients. Therefore we recommend CD screening at certain intervals in all WBS patients to exclude a treatable cause of gastrointestinal problems and growth retardation in this group. Since the number of cases in our study is not high enough to draw a definite conclusion, future studies with large cohorts including different ethnicities are required to establish associations between WBS and CD more clearly.

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