

## Celiac disease in Williams-Beuren syndrome

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Celiac disease was previously reported to be frequent among individuals with Williams-Beuren syndrome; however, this suggestion was not investigated further. The present study was conducted to estimate the prevalence of celiac disease in a group of Turkish individuals with Williams-Beuren syndrome (n=33, age range: 1-24 years) by using anti-tissue transglutaminase immunoglobulin (Ig)A and IgG, anti-endomysium IgA, and intestinal biopsy in individuals with positive serology. The prevalence of celiac disease in this population was compared to its prevalence among healthy Turkish schoolchildren. Of all participants, celiac disease was diagnosed in one patient. Although statistically insignificant (p=0.145), the prevalence of celiac disease was higher among individuals with Williams-Beuren syndrome (3%) than among healthy Turkish schoolchildren (0.47%). We recommend questioning individuals with Williams-Beuren syndrome during routine visits regarding celiac disease symptoms and performing serological screening when consistent symptoms are present. Anti-tissue transglutaminase and anti-endomysial antibodies may help to identify those individuals in whom intestinal biopsy is indicated for the diagnosis of celiac disease.

**Key words:** Williams-Beuren syndrome, celiac disease, anti-tissue transglutaminase antibodies, anti-endomysium IgA, esophagogastroduodenoscopy.

Celiac disease (CD) is an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals. It is characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies, human leukocyte antigen (HLA)-DQ2 or HLA-DQ8 haplotypes, and enteropathy<sup>1</sup>. The prevalence in children between 2.5 and 15 years of age in the general population is approximately 1:300 to 1:80<sup>2</sup>. Serologic screening using anti-tissue transglutaminase (tTG) and anti-endomysial antibodies (EMA) has high (>90%) sensitivity and specificity<sup>3,4</sup> in identifying individuals in whom intestinal biopsy is indicated for the diagnosis of CD. Early diagnosis has important consequences in preventing possible severe complications in the future.

Celiac disease is clinically associated with a number of chromosomal disorders, such

as Down syndrome, Turner syndrome and Williams-Beuren syndrome (WBS). WBS is a multisystem disorder caused by hemizygous deletion of 1.5 to 1.8 Mb on chromosome 7q11.23, which contains approximately 28 genes, such as *ELN*, *LIMK1*, *STX1A*, *FZD9*, *BAZ1B*, *CLIP2*, *GTF2I*, *GTF2IRD1*, and *NCF1*<sup>5</sup>, with an estimated population prevalence between 1 in 10,000-20,000<sup>6,7</sup>. This syndrome is characterized by distinctive facies (Fig. 1), cardiovascular disease, connective tissue abnormalities, intellectual disability, unique personality characteristics, and endocrine abnormalities<sup>4</sup>. The deletion involving *ELN* is responsible for many of the symptoms of WBS, and is demonstrated by fluorescence *in situ* hybridization (FISH) analysis and chromosome microarray studies in 99% of patients<sup>3,8</sup>.

An association between CD and WBS has been documented in several clinical reports<sup>9-11</sup> and

studies<sup>12,13</sup>, with an as yet unknown underlying mechanism, however, it was not validated further. The current study was conducted among a group of 33 Turkish individuals with WBS, in an attempt to determine whether CD prevalence is higher among individuals with WBS than in the general population.

## Material and Methods

### *Patient Population and Clinical Assessment*

A group of 33 individuals with WBS (19 males, 14 females; age range: 1-24 years) were screened for CD during their annual visits to the Pediatric Genetics outpatient clinic between April 2012-April 2013. The diagnosis of WBS was confirmed previously in all patients by FISH analysis using the WSCR probe (Cytocell®, Cambridge, United Kingdom), which discloses hemizygosity of the 7q11.23 region. All parents were informed about the study, and their written informed consents were obtained. The study was approved by the Ethics Committee of Hacettepe University. Clinical assessment included detailed history taking, physical examination and interviews with patients and their parents about gastrointestinal and non-gastrointestinal symptoms.

### *Serologic and Endoscopic Assessments*

Serum samples were collected and tested for immunoglobulin (Ig)A-tTG, IgG-tTG, IgA-EMA, and serum IgA, to exclude a concomitant IgA deficiency. IgA-tTG and IgG-tTG were tested with an enzyme-linked immunosorbent assay kit (Euroimmune GmbH; Lübeck, Germany). The cut-off level for IgA-tTG and IgG-tTG defining a positive result was set at 20 IU/ml (maximum calibrator: 200 RU/ml). Serum IgA-EMA determination using an indirect immunofluorescence method was conducted with a commercial kit (Euroimmune GmbH; Lübeck, Germany) following the manufacturer's instructions. Sera were considered positive in a 1:10 dilution. The total serum IgA level was analyzed with Behring nephelometers (Dade Behring; Marburg, Germany), and serum levels <0.05 g/L were considered as serum IgA deficiency.

Subjects with positive IgA-tTG, IgG-tTG, and/or IgA-EMA results underwent esophagogastroduodenoscopy allowing multiple intestinal biopsies for the diagnosis of CD. Esophagogastroduodenoscopy was performed

with Olympus GIF Q260 videoendoscope (Olympus Optical; Tokyo, Japan). The biopsy samples were taken from the duodenal bulb (at least 1 biopsy) and the second part of the duodenum (at least 4 biopsies), which were then assessed by hematoxylin and eosin (H&E) staining and immunostaining with anti-CD3 monoclonal antibodies for intraepithelial lymphocyte count. All biopsies were evaluated by the same expert pathologist. The Marsh classification was used for the histopathological classification<sup>14</sup>.

### *Statistical Analysis*

Fisher's exact test was used to compare the prevalence of CD in WBS population with previous findings in a published study series<sup>15</sup>. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) software version 11.5 (SPSS, Chicago, IL), and statistical significance was set at a *p* value of <0.05.

## Results

A total of 33 individuals with WBS were screened for CD, including 19 (58%) boys and 14 (42%) girls, with a mean age±SD of 8.3±5.48 years (age range: 1-24 years). None of the participants had IgA deficiency. CD was diagnosed in one (Patient 1) of 33 WBS participants (n=1/33, 3%) using serum levels of IgA-tTG and IgA-EMA and intestinal biopsy (Table I). Patient 1 underwent esophagogastroduodenoscopy and intestinal biopsy, which revealed focal hyperplasia of crypts along with nonspecific findings of duodenitis. A gluten-free diet was not started, however, a second intestinal biopsy was performed after six months, which revealed villous atrophy, crypt hyperplasia and an increase in the number of intraepithelial lymphocytes, consistent with CD Marsh type 3 (Fig. 2). A gluten-free diet was initiated immediately. The prevalence of CD in this population was approximately 3%, which was, although statistically insignificant (*p*=0.145), higher compared to the prevalence of CD in non-WBS Turkish schoolchildren<sup>15</sup>.

## Discussion

The prevalence of CD in this study was, although not statistically significant, higher compared to the prevalence published previously in a series of 20,190 healthy Turkish schoolchildren, aged 6-17 years, who were screened for CD using

**Table I.** Clinical and Serologic Features of the Patient with Williams-Beuren Syndrome and Celiac Disease

|                                                                | Patient 1                                                                                        |
|----------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Gender                                                         | Male                                                                                             |
| Current age (years)                                            | 12                                                                                               |
| Age at diagnosis of Williams-Beuren syndrome (years)           | 5                                                                                                |
| Gastrointestinal symptoms                                      |                                                                                                  |
| Failure to thrive                                              | -                                                                                                |
| Anorexia                                                       | +                                                                                                |
| Abdominal pain                                                 | -                                                                                                |
| Constipation                                                   | -                                                                                                |
| Diarrhea                                                       | -                                                                                                |
| Non-gastrointestinal symptoms                                  |                                                                                                  |
| Dermatitis herpetiformis                                       | -                                                                                                |
| Dental enamel hypoplasia of permanent teeth                    | +                                                                                                |
| Osteopenia/osteoporosis                                        | -                                                                                                |
| Short stature                                                  | +                                                                                                |
| Precocious puberty                                             | -                                                                                                |
| Iron-deficient anemia unresponsive to treatment with oral iron | -                                                                                                |
| Serologic evaluation                                           |                                                                                                  |
| Anti-endomysium IgA                                            | ++++                                                                                             |
| Anti-tissue Transglutaminase IgA (U/ml)                        | >200                                                                                             |
| Anti-tissue Transglutaminase IgG (U/ml)                        | -                                                                                                |
| Endoscopic evaluation                                          | +                                                                                                |
| Pathologic evaluation                                          | Duodenitis*/<br>Villous atrophy, cryptic hyperplasia, increase<br>in the number of lymphocytes** |

\*First esophagogastroduodenoscopy evaluation

\*\*Second esophagogastroduodenoscopy evaluation

IgA-tTG, IgA-EMA and intestinal biopsy<sup>15</sup>. Previously, Giannotti et al.<sup>13</sup> screened 63 children with WBS (mean age±SD: 11.2±7.8 years) for CD using serum levels of anti-gliadin IgA (AGA) and EMA, and diagnosed CD in six patients with characteristic histological findings, with an estimated prevalence of 9.5%<sup>13</sup>. In another study, Santer et al.<sup>12</sup> screened 71 children (age range: 3-50 years; median: 10 years) with WBS for CD by using serum levels of AGA and EMA, and they diagnosed CD in one patient<sup>12</sup>.

Although CD and WBS have different pathogenetic mechanisms, these two diseases share many gastrointestinal symptoms. Gastrointestinal complaints in WBS are due to the

deletion of *ELN*, which results in an abnormality of the elastic fibers<sup>6</sup>. Hypercalcemia, a frequent finding in WBS, may also contribute to the complaints by causing anorexia, abdominal pain and constipation<sup>4</sup>. On the other hand, in CD, gastrointestinal symptoms usually emerge after the introduction of gliadin fractions of wheat gluten and similar alcohol-soluble proteins (prolamines) of barley and rye in the patient's diet. The subsequent immune reaction leads to intestinal inflammation and villous atrophy. However, many symptomatic patients with newly diagnosed CD initially present with non-gastrointestinal manifestations, such as dental enamel hypoplasia of permanent teeth, dermatitis herpetiformis, osteoporosis, short



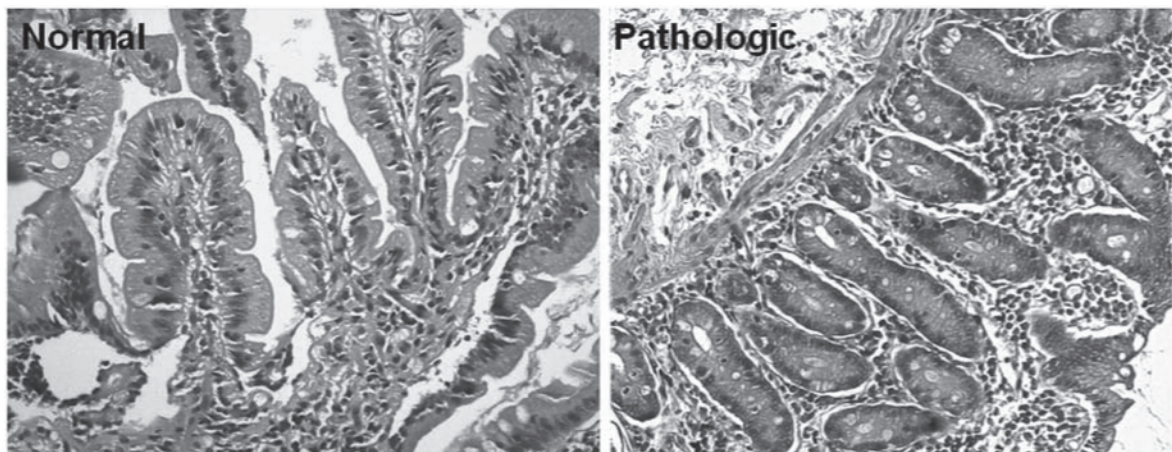
**Fig. 1.** The facial characteristics of the individual with Williams-Beuren syndrome are distinctive. Note the coarse facial features, bitemporal narrowing, periorbital fullness, bulbous nasal tip, malar flattening, full lips, wide mouth, and stellate iris pattern.

stature, delayed puberty, and iron-deficient anemia<sup>2</sup>. Failure to appreciate the variable clinical manifestations of CD leads to a delay in its diagnosis<sup>2,16</sup>. In the present study, the diagnosis of WBS in Patient 1 was established at the age of five years. During the clinical follow-up, he had anorexia and poor weight gain. He also manifested dental enamel hypoplasia of his permanent teeth. However, these symptoms and findings were attributed to his primary

condition, and the diagnosis of CD was not considered until the age of 12 years.

Prompt diagnosis and initiation of a gluten-free diet are desirable for all patients in order to prevent long-term, severe and sometimes life-threatening complications, such as enteropathy-associated T-cell lymphoma, small bowel adenocarcinoma, and other cancers of the gastrointestinal tract<sup>17-20</sup> as well as low bone mineral density and osteoporosis<sup>21,22</sup>. The gold standard for the diagnosis of CD is an intestinal biopsy in all patients<sup>2</sup>. Serological screening tests are frequently used to identify the individuals for whom intestinal biopsy is indicated<sup>2</sup>. Based on the available evidence and practical considerations, including relatively low cost, ease of test performance and reliability, tTG enzyme-linked immunoassay is the universally recommended screening test for CD<sup>2,23,24</sup>. CD is also associated with HLA-DQ2 and -DQ8 haplotypes, and determination of HLA type is considered to be one of the strategies in the diagnosis of CD<sup>2</sup>. However, HLA typing of the patients was not within the scope of the present study.

There is good evidence that the mucosal changes in CD may be patchy in nature and variable in severity<sup>25</sup>. Therefore, it is recommended that multiple biopsy specimens be obtained from the second or more distal part of the duodenum. Patient 1 in the present study had two different histopathological findings on two different occasions at a six-month interval. This may be due to the fact that the mucosal changes were patchy in nature



**Fig. 2.** Duodenal biopsy obtained from Patient 1 demonstrating villous atrophy, crypt hyperplasia and an increase in the number of intraepithelial lymphocytes compared to a normal duodenal biopsy (H&E, original magnification X 200).

and the biopsy specimens were inappropriately oriented; therefore, the diagnostic lesions were missed. Another explanation may be that despite positive serology, diagnostic mucosal changes were still not evident. In addition, the coexistence of villous atrophy with relatively normal adjacent mucosa on histology has been reported in children with newly diagnosed CD<sup>26</sup>. The patient in question may represent one of these newly diagnosed CD patients.

The size of the study population was the limitation of our study. The size of the present study population is smaller than of the previously published European studies<sup>12,13</sup>, and the difference between the WBS and control groups was statistically insignificant. However, this study provides evidence that individuals with WBS may benefit from CD screening and suggests considering CD in individuals with WBS. In addition, the mean age of the participants in the present study was lower compared to the mean age of the participants in the previous European studies<sup>12,13</sup>. Therefore, the number of patients with newly diagnosed CD may increase in time during the follow-up of the individuals with WBS.

In conclusion, we recommend questioning individuals with WBS and their families regarding gastrointestinal and non-gastrointestinal manifestations of CD during their routine visits and performing serological screening with IgA-tTG and IgA-EMA when any symptom suggesting CD is present, in an effort to identify those individuals for whom intestinal biopsy is indicated.

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