

## Celiac disease screening in 100 Turkish children with Down syndrome

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**SUMMARY:** Alanay Y, Boduroğlu K, Tunçbilek E. Celiac disease screening in 100 Turkish children with Down syndrome. Turk J Pediatr 2005; 47: 138-140.

The aim of this study was to screen a group of children with Down syndrome (DS) for celiac disease, and to define future strategies for screening the patients followed at our center. One hundred children over the age of two years with Down syndrome were serologically screened using antiendomysium antibody (EMA) IgA and serum IgA in order to exclude a concomitant IgA deficiency. Clinical assessment included detailed physical examination, measurement of weight and height plotted on growth charts for DS children followed by an interview of the patients and parents about gastrointestinal symptoms. Only one patient out of 100 (1%) was detected to be EMA IgA-positive. The child's family refused consent for the biopsy procedure. None of the patients had IgA deficiency. Abdominal distention was present in 13 (13%) patients, and anorexia in 9 (9%), vomiting in 7 (7%) and alopecia areata in 2 (2%) patients were also noted. Despite the small number of patients in our group, this result yielding 1% EMA-positivity is the lowest yet determined among DS patients. It has led us to discuss whether or not a change in our screening strategy is necessary.

**Key words:** antiendomysium antibody (EMA), celiac disease, Down syndrome.

The strong association between Down syndrome (DS) and celiac disease (CD) has been documented by many studies since the first report by Bentley in 1975<sup>1</sup>. Many studies originating from different centers have reported a prevalence of CD in DS ranging from 4 to 17%<sup>2-4</sup>. The largest group screened in a multicenter study from Italy has shown a prevalence of 4.6%<sup>5</sup>. Studies from the United States have yielded results ranging from 4.8% to 10.3%<sup>6-8</sup>.

The genetic basis of DS is well documented. CD is also known to have a genetic background. The exact mechanism underlying the relation between these conditions is as of yet unclear. The association with autoimmune diseases, including diabetes mellitus type I, thyroid disease, alopecia and vitiligo suggests a common immunologic defect<sup>9-11</sup>.

Serologic testing is the initial step of screening for CD. Serum antiendomysium antibodies [Immunoglobulin (Ig) A] (EMA) have been proven to be sensitive and specific for the diagnosis, as long as IgA deficiency is excluded<sup>8,12,13</sup>. This has been supported by many

other studies<sup>5,14</sup>. Other serological screening methods [antigliadin (AGA) IgA and IgG, tissue transglutaminase (tTG) IgA and IgG] and immunological ones (HLA DQ typing) have also proven to be effective<sup>15</sup>.

The current study was conducted to estimate the prevalence of CD among DS patients attending routine yearly visits at our center. Although the population figures are unknown, this is the largest group of DS children studied in Turkey.

### Material and Methods

#### Patient Population

Celiac disease screening was performed in a group of 100 DS patients (56 male, 44 female) during their routine yearly visit to the Genetics Department at İhsan Doğramacı Children's Hospital, Ankara, Turkey. All patients were over two years of age and had gluten in their diet. The group consisted of regular trisomy 21 patients. All parents were informed of this investigation. The study was approved by the Ethical Committee of Hacettepe University Faculty of Medicine.

### **Clinical Assessment**

Clinical assessment included detailed physical examination, measurement of weight and height plotted on growth charts for DS children<sup>16</sup> followed by an interview of the patients and parents about gastrointestinal symptoms.

All children were serologically screened for EMA IgA and serum IgA to exclude a concomitant IgA deficiency. EMA IgA was performed by direct immunofluorescence assay using monkey esophageal smooth muscle as the antigen (ImmuGI, Buffalo, NY). The assay was considered positive depending on the intensity of the brilliant green network pattern under fluorescence microscope<sup>17</sup>. Serologically positive patients were to be referred to a pediatric gastroenterologist for intestinal biopsy.

### **Results**

The ages of the children ranged from 2 to 14 years, with a mean age ( $\pm$ SD) of  $6.01 \pm 3.04$  years. Abdominal distention was present in 13 (13%) patients, while anorexia in 9 (9%), vomiting in 7 (7%) and alopecia areata in 2 (2%) patients were also noted. Weight and height percentiles of the patients were plotted on growth charts for DS<sup>16</sup>. The number of patients below the 5<sup>th</sup> percentile according to weight and height were 5 (5%) and 6 (6%), respectively. Only one patient out of 100 (1%) was detected as EMA IgA-positive. This patient was a 10-year-old boy, complaining of anorexia. His growth velocity was in the normal range. Unfortunately, the boy's family refused consent for the biopsy procedure. None of the patients had IgA deficiency.

### **Discussion**

Celiac disease screening in DS patients is usually conducted by determination of CD-associated antibodies. The increased rate of false positivity encountered with antigliadin antibodies (AGA) has led investigators to prefer EMA as a more reliable marker<sup>5,8,9,13,15</sup>. The DS population evaluated in this study was determined as older than two years of age according to the revised recommendations of the Health Care Guidelines for individuals with Down Syndrome, 1999 revision<sup>18</sup>. Although the size of the study population is much smaller than the recently published European studies, it is comparable with the prevalence studies conducted in the United States evaluating 97 patients in the study

by Book et al.<sup>6</sup>, and 75 patients in the study by Zachor et al.<sup>19</sup>. Recently, Coğulu et al.<sup>20</sup> have demonstrated 12.7% EMA-positivity, with biopsy proven villous atrophy as 6.3% in a Turkish DS population of 47 individuals in another center.

The result of the current study, yielding 1% EMA-positivity, is the lowest yet determined among DS patients. Considering that weaning practices begin as early as the fourth month, we assume that gluten exposure should be sufficient to cause sensitization. Foods containing gluten are major components of the daily diet in our country, as well as in the other Middle Eastern countries. Therefore, despite the lack of normal population figures, we might have a lower incidence of CD among our DS population.

The multicenter study published from Italy has proven that a long time passes from onset of symptoms to diagnosis. After screening 1,202 DS demonstrating a prevalence of 4.6%. They also calculated that the prevalence would increase to 5.4% when the 10 asymptomatic IgA AGA- and EMA-positive patients were taken into account. Most patients with CD were detected among EMA-positive patients<sup>5</sup>.

The result of our study has led us to question our current screening methodology. What should be the future strategy in our center? Should we increase the number of serological tests used? As a center diagnosing nearly 100 new DS cases yearly, we feel responsible for the early diagnosis of conditions known to be more prevalent in this population. For the last three years we have been following our DS patient population according to the Health Care Guidelines for Individuals with Down Syndrome, 1999 revision<sup>18</sup>. We might consider repeated testing for patients who have demonstrated negative serology in the first screening. Patients with delay in growth according to growth charts, and those with subtle symptoms like anemia or anorexia might also be considered, as well as those with the well known clinical stigmata of CD.

Screening based on AGA IgG is probably irrelevant in DS patients as long as IgA deficiency is excluded. The high prevalence of AGA IgA and IgG in DS patients is thought to be due to their altered immune system<sup>20</sup>. Impaired intestinal epithelial function, causing an overload of food antigens, is thought to alter the antigen-derived maturation of lymphoid

cells in the lymphatic tissues associated with the intestinal mucosa<sup>22</sup>. The risk of false negativity for EMA will probably lead us to use the less specific AGA IgA for screening only patients younger than two years age. A combination of EMA IgA and AGA IgA might be useful for infants who are not IgA-deficient<sup>19</sup>.

Tissue transglutaminase antibodies, especially tTG IgA determined by ELISA (enzyme linked immunosorbent assay), have also been proposed as candidate screening methods for DS patients. Recently, Agardh et al.<sup>15</sup> have demonstrated tTG IgA positivity in a group of patients with positive EMA. The same group was also tTG IgG positive, leading the authors to conclude that tTG IgG may be a useful screening test for IgA-deficient patients<sup>15</sup>.

One other fact to keep in mind is that symptoms of undiagnosed patients may be falsely attributed to DS itself. The fact that identification and treatment of CD improves the quality of life for these children makes it mandatory to consider routine screening. Complications such as malignancy, osteoporosis and anemia seen in untreated patients are significant causes of morbidity.

Despite the lower prevalence rate of EMA positivity in the screened DS population, we believe that asymptomatic screening and repeated screening of symptomatic patients should be considered for children with DS. The most appropriate serological test is yet to be determined, though EMA antibodies are probably the most convincing, and t-TG the most promising. The limited results of this study need to be validated in the future with general population studies along with larger DS groups in our country.

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