Mass Screening for Celiac Disease Among School-aged Children: Toward Exploring Celiac Iceberg in Saudi Arabia

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See “New Celiac Icebergs Are Spotted, Other Are Slowly Emerging” by Catala on page 661.

ABSTRACT

Objectives: We conducted this mass screening study to determine the prevalence of celiac disease (CD) and characterize the celiac iceberg among Saudi pediatric population in Riyadh, the capital city of Saudi Arabia. Methods: During the study period (January 2014–June 2016), we have conducted a cross-sectional, mass screening, immunoglobulin A-tissue transglutaminase (IgA-TTG-AGA)–based study on 7930 Saudi students from primary and intermediate schools in Riyadh. Students with positive TTG-AGA (>20 U/L) were called in the hospital to undergo a repeat of TTG-AGA; those with borderline positive TTG-AGA (20–60 U/L) and IgA-endomysial antibody (EMA-AGA)–test was performed. Children with TTG-AGA >90 U/L and children with borderline positive TTG-AGA and positive EMA-AGA were advised to undergo upper endoscopy and intestinal biopsy. Results: We identified 221 students with positive TTG-AGA (2.8%) (CD was diagnosed in 110 students (1.5% of the 7177 students) (mean age 11.5 ± 2.4 years), while 25 (3.5%) students had abnormal TTG-AGA for negative EMA (6.6%) and the remaining 51 had transient positive TTG-AGA. We identified 3 clinical patterns in the screening-identified cases with CD: a silent form (37%); a mild symptomatic form characterized by gastrointestinal symptoms in presence of normal growth as overweight/obesity (48%), and gastrointestinal symptoms associated with impaired growth in 15%. Conclusions: Our study provided evidence of a high prevalence of CD among Saudi children (1.5%), a rate that is at least twice the average prevalence rate in Europe and North America.

Key Words: celiac disease, epidemiology, IgA anti-tissue transglutaminase antibodies, IgA endomysial antibodies, mass screening

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What Is Known

• Variation in prevalence rate of celiac disease among different populations is determined by genetic and environmental factors.
• Most of the previously published mass screening studies showed that only one-third of the screening-identified cases with celiac disease were symptomatic.

What Is New

• The prevalence of celiac disease among school-aged Saudi children (1.5%) is at least twice the average prevalence in Western countries.
• Two-thirds of the screening-identified celiac disease cases were asymptomatic with recurrent abdominal pain significantly more frequent among cases with celiac disease.
• The screening-identified cases with celiac disease were significantly more underweight and shorter than nonceliac controls.

Several reports from European countries and the United States suggested that celiac disease (CD) is much more common than previously recognized and claim prevalence rates of 0.5% to 1.5% (1–3). In contrast, there are limited comparable epidemiological studies in Arab population whereas CD is widely perceived as being uncommon. The studies related to CD in Saudi Arabia were either hospital-based, retrospective, and descriptive small studies, or screening studies for children with type 1 diabetes mellitus

IgA was considered positive and invited for repetition of the test in hospital (at stage 2 of evaluation). Normal range for IgA was 0.5 to 2 g/L for ages between 4 and 11 and 0.15 to 1 g/L for children <12 years. Students with TTG-AGA <20 U/L and low total serum IgA were tested for IgG; TTG with IgG >20 U/L were called for repetition of the test.

Stage 2

During this stage of evaluation, all participants with TTG-AGA >200 U/L were invited in the hospital for repetition of the test. Several participants related to CD in Saudi Arabia remain to be answered: What is the prevalence of CD in a mass screening study? What are the epidemiological features and clinical profile of CD iceberg in Saudi Arabia? Is CD a significant health problem in Saudi Arabia? These unanswered questions prompted us to design the first mass screening study in Saudi Arabia to determine the prevalence of CD in children in the capital city, Riyadh.

METHODS

Study Design

The study was a cross-sectional, prospective, population-based study that aimed to identify undiagnosed CD among Saudi students of both sexes attending primary and intermediate schools (ages 6–15 years) in Riyadh, by measuring serum TTG-IgA and serum IgA levels.

Study Population

With an estimated CD prevalence of 1% in school-aged children and recognizing that more than 55% of 5 to 11 years old students attend primary and intermediate schools in Riyadh during the year 2014, a sample size of 4000 children was needed. Considering 30% drop off rate, a total sample size of 5235 children was targeted to estimate the prevalence of 5% in CD.

Recruitment of Students Into the Study

A total of 104 schools were randomly selected using probability proportionate sampling procedure. Of 104 schools, 6 were primary schools (3 male schools and 3 female schools) and 43 intermediate schools (22 male schools and 21 female schools). A health advocate in each school distributed envelopes to all Saudi students. Each envelope contained the following: an educational brochure about CD, an informed consent form, and a questionnaire to collect data on demographics, gastrointestinal (GI) symptoms, and family history of CD. We excluded children with type 1 diabetes mellitus from the study because the pediatric diabetic clinic in Riyadh screen them regularly for CD.

Study Procedures and Interventions

Stage 1

All students whose parents have signed the informed consent underwent CD serology. For each study, a biopsy-confirmed CD 30 to 60 days before an informed consent form, and a questionnaire to collect data on demographics, gastrointestinal (GI) symptoms, and family history of CD. We excluded children with type 1 diabetes mellitus from the study because the pediatric diabetic clinic in Riyadh screen them regularly for CD.

Stage 2

In the stage 1 of the study, all participants with TTG-AGA >200 U/L were invited to undergo upper endoscopy and biopsy from deenutrition (6 biopsies from 2nd to 4th part and 2 biopsies from duodenal cap). Parents who refused refused endoscopy, as recommended by the European society of pediatric gastroenterology, hepatology, and nutrition (ESPGHAN) (1). Cases with CD were interpreted by a dietitian and advised to strictly follow QFD for life and followed up in the clinic every 6 months.

Definitions and Criteria to Start Gluten-free Diet

1. Diagnosis of CD was established if:
   a. Positive serologic test (TTG-AGA, EMA-AGA, or TTG-AGA in the case of low total serum IgA) accomplished by histopatho-logic features consistent with CD (Marsh class ≥3;)
   b. TTG-AGA >200 U/L + positive EMA-AGA + high-risk CD-related HLA genotype in a symptomatic child whose parents refused endoscopy, as recommended by the European society of pediatric gastroenterology, hepatology, and nutrition (ESPGHAN) (1). Cases with CD were interpreted by a dietitian and advised to strictly follow QFD for life and followed up in the clinic every 6 months.

2. "Potential EMA-AGA and inverse classification histopathology grade 0/1 on intestinal biopsies. They have not been started on GFD but
were advised to follow-up closely in the clinic with a repeat of TTG-IgA every 6 months and were offered a repeat of endoscopy should they develop GI symptoms or TTG-IgA titer rises.

3. "Cellic autoimmune" group describes children who had TTG-IgA titer <200 U/L and positive EMA-IgA, but their parents refused upper endoscopy. "Cellic autoimmune" children were advised to start GF and to follow-up closely in the clinic with a repeat of TTG-IgA every 6 months.

4. "Silent CD" defines individuals who were asymptomatic despite having demonstrable characteristic changes of CD on biopsies.

5. Children with GI symptoms were classified as either "oligosymptomatic," if they had only 1 GI symptom; "asymptomatic," if they had no GI symptoms.

Ethical Considerations

The study proposal has been approved by local IRB and ministry of education in Saudi Arabia and the parents of participating students have signed an informed consent.

Statistical Analysis

Data were analyzed using SPSS PC + version 22.0 statistical software (SPSS Inc., Chicago, IL). Descriptive statistics (mean, standard deviation, and percentages) were used to describe the quantitative and categorical study variables. Student t-test for independent samples was used to compare the mean values of quantitative variables. Pearson χ² test and Fisher exact test were used to observe an association between categorical study variables and presence of CD. A P value of <0.05 was considered as statistically significant.

RESULTS

Parents of 7936 of 33,000 students have signed the informed consent and accepted to participate in the study. Six children were excluded: 4 with diabetes mellitus and 2 were known cases of biopsies confirmed CD. Hence, a total of 7930 students of grade 3 to 9 were included (4487 were girls [63%] and 2443 were boys [37%]; mean age 11.22 ± 2.62 years.

Figure 1 shows a flowchart that summarizes the results of serum tests in the 7930 participating students and their outcomes. A total of 7790 students (97.2%) tested negative for TTG-IgA. We have labeled this group as "controls." Of the 7930 students, 221 students tested positive for TTG-IgA (<2.8%) on the first blood specimen collected in school. Further testing to 12 months later hospital revealed that of these 221 students, 115 fulfilled the criteria for upper endoscopy and small-bowel biopsy 92 underwent small-bowel biopsy, whereas the parents of the remaining 23 children (all of whom were positive for TTG-IgA and EMA-IgA) refused endoscopy and were advised to institute GF. Ten of the 23 children were diagnosed according to the new ESPGHAN criteria. One child with IgA deficiency and positive IgG-TTGM had a biopsy-confirmed CD. In summary, the study outcomes were as following: CD was diagnosed in 103 cases (1.3%), another 13 cases had "cellic autoimmune" (both TTG-IgA- and EMA-IgA-positive [0.21%]), 3 cases had potential CD, TTG-IgA was transiently positive in 51 cases (0.64%), and persistent border-line positive TTG-IgA were remaining 53 cases (0.68%). Parents of 5 children in the latter group requested endoscopy and biopsy because their children were asymptomatic; 4 of them had confirmed CD. So the overall prevalence of CD was 1.5% (103 confirmed CD = 1.3% of cellic autoimmune + 2 cases of CD already diagnosed).

General Characteristics of the Cellic Group

The demographic and clinical characteristics of the cellic group are shown in Table 1 and compared with controls. Cellic patients were more significantly overweight as compared to controls (8.2% vs 16.5%, P < 0.003). Also, cases with CD were significantly shorter than controls (height z-score = -1.2, t = 1.46 vs. -0.70, t = 2.34, P = 0.004). Twenty percent of the patients with CD were either overweight or obese (7.8% and 11.7%, respectively). Fifty-five out of the 103 cases with CD (48.2%) were asymptomatic and 16 were oligosymptomatic (15.5%). The remaining 57 cases (36%) had "silent CD."

Histopathology and Serology in the Cellic Group

The frequency of histopathology grading of the 92 intestinal biopsies was as following: 69 cases (75%) revealed a variable degree of villous atrophy (Marsh III c-e), Grade II in 20 cases (22%), and grade I in 3 cases (3%). A positive correlation could be observed between the histopathology grade and the titer of TTG-IgA (Fig. 2) and the symptomatic status (Fig. 2). In 2 cases, histopathological changes consistent with CD (Marsh grade 3a) were observed in biopsies obtained from duodenal cap only (2/93 = 2.15%).

Cellic Autoimmunity Group (n = 13)

The mean age in this group was 10.6 ± 2.5 years (female male = 12 [70.6%]/5 [29.4%]). Other demographic and clinical characteristics of the cellic autoimmune group are shown in Supplemental Digital Content, Table 1, http://links.lww.com/MPG/B494. The mean TTG-IgA titer was 36.6 ± 16.5 U/L in the first serum sample obtained at school visit versus 40 ± 22.2 U/L, 6 to 12 months later, in addition to positive EMA-IgA, which make this group of children probable cases of CD.

Potential Cellic Disease Group (n = 3)

Three cases were labeled as "potential CD" with Marsh grade I, TTG-IgA titers of 26.5, 32.6, and 35.5, and positive EMA-IgA.

TTG-IgA Borderline Group (n = 51)

The clinical characteristics and growth patterns of the children in the TTG-IgA borderline group are shown in Supplemental Digital Content, Table 2, http://links.lww.com/MPG/B494. The mean TTG-IgA titer was 31 ± 10 U/L on the first serum sample obtained at school visit versus 32 ± 9 U/L, 6–12 months later, indicating a persistently positive TTG-IgA over time. All children in this group were EMA-IgA negative.

Transiently Positive Immunoglobulin A-Tissue Transglutaminase Group (n = 51)

The clinical characteristics and growth patterns of the children in the TTG-IgA transiently positive group are shown in Supplemental Digital Content, Table 3, http://links.lww.com/MPG/B505. The mean TTG-IgA titer was 30.4 ± 8 U/L in the first serum sample obtained at school visit versus 10.4 ± 5 U/L, 6 to 12 months later. All children in this group were EMA-IgA negative.

DISCUSSION

To the best of our knowledge, we are dealing with one of the largest mass screening study for CD worldwide. Our study showed several important findings. First, the prevalence of CD among the school-aged children in Riyadh (1.5%) is at least twice the prevalence in North America and Europe. Second, two-thirds of screening-identified children (64%) had ≥1 GI symptoms, which are unlike most of the previously published mass screening studies which showed that only one-third of the screening-identified cases with CD were symptomatic (1–3). Furthermore, another striking finding was that cases with CD were significantly more underweight and shorter than noncontrols.

Many studies reported the prevalence of CD in general population. Most of these studies were conducted in the United States and Europe. Fewer epidemiological studies addressed the prevalence of CD in healthy population in developing countries where the burden caused by CD had been largely underestimated. The highest CD prevalence in the world (5.6%) was reported in an African population originally living in Western Sahara, the Saharan, of Ambi-Barber origin (12). The prevalence of CD in Arab countries in North Africa ranged between 8.5% and 8.0% (13–15). In the Middle East, studies in Iran (16) and in Iran (17) have found CD prevalence in blood donors at 1 in 157 and 1 in 166, respectively. In Turkey, a seroprevalence level of 1.3 per 100 was encountered (18). A variable distribution of CD-predispousing DQ alleles and environmental factors among different populations and ethnicities could explain the variable prevalence of CD that has been reported in different parts of the world. There are only anecdotal reports of CD in Far East countries (19).

On a huge scale of the general pediatric Saudi population, we found a high prevalence of CD in Riyadh (1.5%). To avoid
The demographic and clinical characteristics of the celica group in comparison to the consented group.

<table>
<thead>
<tr>
<th>Cases with CD (n = 13)</th>
<th>Controls (n = 779)</th>
<th>Odds ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean ± SD)</td>
<td>11.49 ± 2.62</td>
<td>11.22 ± 2.67</td>
<td>1.03 (0.94–1.11)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22 (21.4%)</td>
<td>2866 (37.6%)</td>
<td>0.45 (0.281–0.725)</td>
</tr>
<tr>
<td>Female</td>
<td>8 (7.6%)</td>
<td>483 (6.3%)</td>
<td>2.22 (1.38–3.67)</td>
</tr>
<tr>
<td>Weight &lt;3rd percentiles (underweight)</td>
<td>167 (16.3%)</td>
<td>643 (8.3%)</td>
<td>2.17 (1.28–3.67)</td>
</tr>
<tr>
<td>Weight ≥3rd percentiles (short stature)</td>
<td>23 (22.3%)</td>
<td>139 (18.0%)</td>
<td>1.13 (0.818–2.084)</td>
</tr>
<tr>
<td>BMI score (mean ± SD)</td>
<td>0.007 ± 1.77</td>
<td>0.5010 ± 2.00</td>
<td>1.405 (0.759–1.901)</td>
</tr>
<tr>
<td>Height score (mean ± SD)</td>
<td>11.2 ± 1.06</td>
<td>0.70 ± 1.24</td>
<td>0.655 (0.736–1.467)</td>
</tr>
<tr>
<td>Consanguinity</td>
<td>42 (41.2%)</td>
<td>2940 (37.5%)</td>
<td>1.13 (0.864–1.467)</td>
</tr>
<tr>
<td>Family history of celica disease</td>
<td>11 (10.8%)</td>
<td>277 (3.5%)</td>
<td>2.91 (1.52–5.643)</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>11 (10.8%)</td>
<td>385 (5.7%)</td>
<td>0.42 (0.59–1.408)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (5.9%)</td>
<td>435 (5.9%)</td>
<td>2.48 (1.78–2.66)</td>
</tr>
<tr>
<td>Constipation</td>
<td>15 (14.7%)</td>
<td>739 (9.0%)</td>
<td>0.25 (0.105–0.581)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>35 (32.3%)</td>
<td>408 (5.3%)</td>
<td>0.092 (0.01–0.97)</td>
</tr>
</tbody>
</table>

**BMI** = body mass index; **CD** = celica disease; **CI** = confidence interval; **SD** = standard deviation.

**Significant P value.**

The univariate analysis of the prevalence of CD in Saudi Arabia shows a significant association between the two groups. The prevalence of CD in Saudi Arabia is higher than in the control group, with a higher odds ratio of 2.22 (95% CI: 1.38–3.67). The differences in weight, height, and BMI between the two groups were also significant, with higher values in the Saudi Arabia group. The prevalence of family history of celica disease, abdominal distention, diarrhea, and abdominal pain were also higher in the Saudi Arabia group.

**CONCLUSIONS**

Our study provides evidence of a high prevalence of CD among Saudi children and the characteristic of the celica disease in Saudi Arabia. The findings of this study add weight to the evidence that clinically suspected cases of CD account only for a minority of patients and that the majority of cases remain undiagnosed.

**Acknowledgments**

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**REFERENCES**

13. Ben Hazi M, Kelleral未来的研究方向是探讨包括临床和实验室参数在内的一系列因素对CD的预后的影响。这项研究还表明，虽然CD的发病率在儿童中比在成人中高，但其预后在儿童中并未得到充分研究。需要进一步的研究来探讨儿童CD的预后。

**FIGURE 1.** Box plots showing the median values and interquartile range of IgA-TG values of children with celica disease subdivided according to Marshall criteria. These plots were created with the standard deviation of total IgA deficiency of 3.4 mg/dL. The IgA-TG levels were analyzed using the Mann-Whitney U test. **A:** A-clas trimethaphosphate.

**FIGURE 2.** Box blower graph showing the median values and interquartile range of IgA-TG values of children with celica disease subdivided according to Marshall criteria. *Marsh et al.* excluded the students with total IgA deficiency of 3.4 mg/dL. The asterisk indicates a significant difference. IgA-TG = immunoglobulin A-class trimethaphosphate.