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Celiac disease may be rare among children in South China

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Abstract

Objective: The prevalence of celiac disease (CD) varies geographically and ethnically; however, the prevalence among children in South China remains unknown. We therefore determined the occurrence of CD among Chinese children in South China.

Methods: Serum samples were collected from children and assessed for anti-tissue transglutaminase IgA antibodies (anti-tTG-IgA) and total IgA. Anti-tTG-IgA+ participants underwent human leukocyte antigen (HLA) DQ2/DQ8 determination. Samples with serum total IgA <0.05 g/L were also analyzed for anti-tTG-IgG, and for HLA-DQ2/DQ8 if the values were above borderline. Participants who were anti-tTG-IgA/IgG+ and HLA-DQ2+ and/or HLA-DQ8+ underwent small bowel biopsy.

Results: A total of 8794 children were enrolled, of whom 479 had chronic unexplained abdominal symptoms. Three (0.034%) children were anti-tTG-IgA+ and ten (0.114%) had serum total IgA <0.05 g/L, all of whom were anti-tTG-IgG−. The three positive children were all HLA-DQ2+ and/or HLA-DQ8+. Two underwent gastroscopy, and histopathology of small intestinal biopsy showed duodenal villous blunting in one and increased intraepithelial lymphocytes in the other, neither consistent with a diagnosis of CD.

Conclusion: Our study showed a prevalence of CD autoimmunity of 0.034% and failed to identify any cases of CD, suggesting a low prevalence of CD among children in South China.

Keywords

Celiac disease, China, child, tissue transglutaminase, IgA antibody, HLA-DQ2, HLA-DQ8

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Introduction

Celiac disease (CD) is a chronic systemic autoimmune-mediated disorder characterized by small intestine inflammation and villous atrophy. CD is thought to be triggered by exposure to dietary gluten in genetically susceptible individuals who carry the specific class II human leukocyte antigen (HLA) haplotypes DQ2 and/or DQ8.[1] The classic presentations of CD in children are mostly gastrointestinal, including chronic diarrhea, steatorrhea, bloating, abdominal pain, weight loss, malnutrition, and poor growth. CD was once considered to be a rare disease, but studies have shown an increasing incidence of CD in both pediatric and adult populations.[2]

CD is highly prevalent among individuals of White descent, in whom the frequency of HLA-DQ2 is as high as 25% to 30%. However, although the prevalence of CD in Europe and North America ranges from 0.3% to 3%, it is much lower in the Asia-Pacific region. The presence of CD-predisposing genes, as well as a gluten-rich diet, may contribute to the geographical variations in the prevalence of CD. A recent meta-analysis revealed pooled frequencies of the HLA-DQ2.5 and HLA-DQ8 haplotypes of 3.4% (95% confidence interval 1.3%–5.5%) and 2.1% (0.1%–4.1%), respectively, and HLA-DQ2 and HLA-DQ8 antigen frequencies of 18.4% (15.0%–21.7%) and 8.0% (4.5%–11.4%) in the Chinese population. Significant variations HLA-DQ2 and HLA-DQ8 antigen frequencies were observed among different Chinese regions, from 2.8% in Yunnan province to 22.04% in Xinjiang region.[3] Yunnan is a province in Southern China with a majority Han population and a staple diet of rice, while Xinjiang is located in Northern China and is inhabited mostly by a White population, whose staple food is wheat. This suggests that there are no significant differences in CD-predisposing genes between White and Chinese people.

CD is considered a major health problem affecting approximately 0.7% of the global population and almost 1% of children.[4] In addition, regions once considered to have low rates of CD, such as the Middle East, North Africa, and India, are now thought to have higher prevalences.[5] Recent reports of CD in Chinese populations revealed incidences of about 6.5% in adult patients with chronic diarrhea,[6] and 11.9% in pediatric patients.[7] Kou and his colleagues found a CD prevalence of 2.85% in 246 adult patients with irritable bowel syndrome.[8] These studies suggest that CD may not be a rare disease in China; however, there have been no studies of the prevalence of CD in Chinese children.

Endoscopy and duodenal biopsy showing a characteristic histology is the current gold standard for the diagnosis of CD[9]; however, this method is invasive, and current guidelines recommend non-invasive serological testing for anti-tissue transglutaminase IgA antibodies of (anti-tTG-IgA) as the initial diagnostic screening tool. We conducted a large-scale autoimmunity screening study for CD using anti-tTG-IgA in children who visited our hospital. The overall aim of the study was to determine the possible presence of CD among South Chinese children aged 2 to 18 years of age who visited our hospital.

Methods

Study participants

In this study, we prospectively recruited children with or without chronic unexplained abdominal symptoms who visited the outpatient or inpatient departments at a large tertiary hospital in South China, which acts as the China National Children's Regional Medical Center and handles about 3 million visits annually.

We recruited all children who required blood tests for any reason from May 2018 to May 2020. The inclusion criteria were age 2 to 18 years old, a gluten diet for at least 6 to 8 weeks prior to blood sampling, and patients who agreed to be screened for CD. Children who were taking glucocorticoids were excluded. All of the children's guardians provided signed informed consent prior to blood collection, and both the child and their guardian signed the consent if the child was over 7 years old.

The study protocol was approved by the institutional ethics committee of Guangzhou Women and Children's Medical Center (Approval no.: 2017022905).

Study protocol

The reporting of this study conforms to STROBE guidelines.[10] Blood samples (1 mL) were obtained from eligible children undergoing blood testing for various reasons, after obtaining informed consent. The samples were centrifuged and serum samples were labeled with the patient's name, age, identification number, and diagnostic information, and kept at −80°C in a freezer prior to analysis. Anti-tTG-IgA was detected by enzyme linked immunosorbent assay (ELISA) and total IgA was determined synchronously. Patients who were positive for anti-tTG-IgA underwent genetic testing for HLA-DQ2 and/or -DQ8 haplotypes. Samples with serum total IgA <0.05 g/L were also analyzed for anti-tTG-IgG, and if the values were borderline, also for HLA-DQ2/DQ8. The basic demographics, symptoms, and admitting diagnosis were collected for patients with positive anti-tTG-IgA tests. We also collected blood samples from 100 healthy children who visited the hospital for pre-kindergarten medical check-ups and tested them for HLA-DQ2/DQ8 determination, and children who were positive for HLA-DQ2/DQ8 underwent anti-tTG-IgA testing.

tTG-IgA assay and determination of HLA-DQ2 and DQ8

Serum samples were analyzed for tTG-IgA using an ORG 540A ELISA kit and samples with serum total IgA <0.05 g/L were analyzed for anti-tTG-IgG using an ORG 540G ELISA kit (Orgentec, Mainz, Germany), according to the manufacturer's instructions. The tests had a lower detection limit of 1.0 IU/mL, and 10 IU/mL was used as the cut-off point for a positive result. Blood HLA-DQ2 and/or -DQ8 were detected using a multiplex polymerase chain reaction kit (Super Biotechnology, Tianjin, China).

Small bowel biopsy

At least four biopsies from the distal duodenum and at least one from the duodenal bulb were taken for histology assessment. Biopsy samples were graded according to the Marsh classification. Considering the limited knowledge of CD among the pathologists in our hospital, all the pathological data were also sent to the Department of Pathology, Children's Mercy, Kansas City, USA, to help make the diagnosis.

Data analysis

Categorical data were expressed as percentages and continuous data were expressed as mean ± standard deviation or median.

Results

A total of 8794 children from different clinical sections were enrolled in the study, including 4796 (54.54%) boys and 3998 (45.46%) girls. Of these, 479 patients had chronic unexplained abdominal symptoms. The mean age was 6.04 ± 3.05 (2–18) years.

Three (0.034%) children were anti-tTG-IgA+ with antibody levels of 12.39, 28.4, and 99.5 IU/mL (Table 1), and were

Table 1. Basic demographics, clinical diagnosis, anti-tissue transglutaminase IgA antibodies (anti-tTG-IgA), and human leukocyte antigen (HLA)-DQ2/DQ8 status in three children with positive anti-tTG-IgA.

	Sex	Age (years)	Diagnosis	Anti-tTG-IgA (IU/mL)	HLA-DQ2	HLA-DQ8	Duodenal biopsy
1	M	4.2	Atopic dermatitis	12.39	**Positive**	Negative	Villous blunting
2	F	5.6	Abdominal pain	28.4	**Positive**	Negative	
3	F	7.3	Malnutrition	99.5	Negative	**Positive**	Increased IEL counts

M: male; F: female; IEL: intraepithelial lymphocytes.

diagnosed with atopic dermatitis, abdominal pain, and malnutrition, respectively. Ten (0.114%) children with serum total IgA <0.05 g/L were all negative for anti-tTG-IgG. These three anti-tTG-IgA+ children underwent genetic testing for HLA-DQ2 and HLA-DQ8, of whom two were HLA-DQ2+ and one was HLA-DQ8+. Two of these three patients (with atopic dermatitis and malnutrition, respectively) agreed to undergo gastroscopy. Histopathology of the small intestine biopsies showed duodenal villous blunting but no increased intraepithelial lymphocytes (IELs) in one child, and increased IELs in the other, neither of which were consistent with a diagnosis of CD. We therefore failed to clarify the possible presence of CD in these patients.

In addition, three (3%) of the 100 blood samples from healthy children were HLA-DQ2+, but all three of these were negative for anti-tTG-IgA (Figure 1).

The first patient examined by small bowel biopsy was a 4-year-old boy who was HLA-DQ2+. He was diagnosed with atopic dermatitis, his anti-tTG-IgA level was 12.39 IU/mL, and his cow-milk protein-specific IgE antibody level was 5.8 IU/mL (<0.35 IU/mL). His height and weight were within the normal ranges for his age, and he had a good appetite and no discomfort, such as diarrhea or abdominal pain. Given the absence of an increase in IELS and his medical history of allergy, the pathologist considered that the duodenal villous blunting was a manifestation of his food allergy. The other patient was a 7-year-old girl who was HLA-DQ8+ positive. She was diagnosed with malnutrition and her anti-tTG-IgA level was 99.5 IU/mL. She showed stunted growth, and both her height and weight were at the −2SD level for her age. She had a poor appetite and no diarrhea, but occasionally complained of abdominal pain.

Discussion

Prior to this study, we had never diagnosed a patient with CD in our medical center. In this study, we enrolled 8794 Chinese children of whom only three were positive for anti-tTG-IgA, and all of the positive patients showed low antibody levels. The prevalence of CD autoimmunity was thus only 0.034% in our target pediatric population. Meanwhile, 3% (3/100) of blood samples donated by healthy children were HLA-DQ2+. The prevalence of CD differs among countries and epidemiologic data for CD in China are currently scarce. The present results may reflect a lower prevalence of CD in South China compared with other countries, possibly related to low gluten consumption and a low frequency of CD-susceptibility genes the Southern Chinese population. Southern China, especially Guangdong province, is an area with high rice consumption and low wheat consumption (56.52 kg/person per year vs. 1.11 kg/person per year in urban areas;

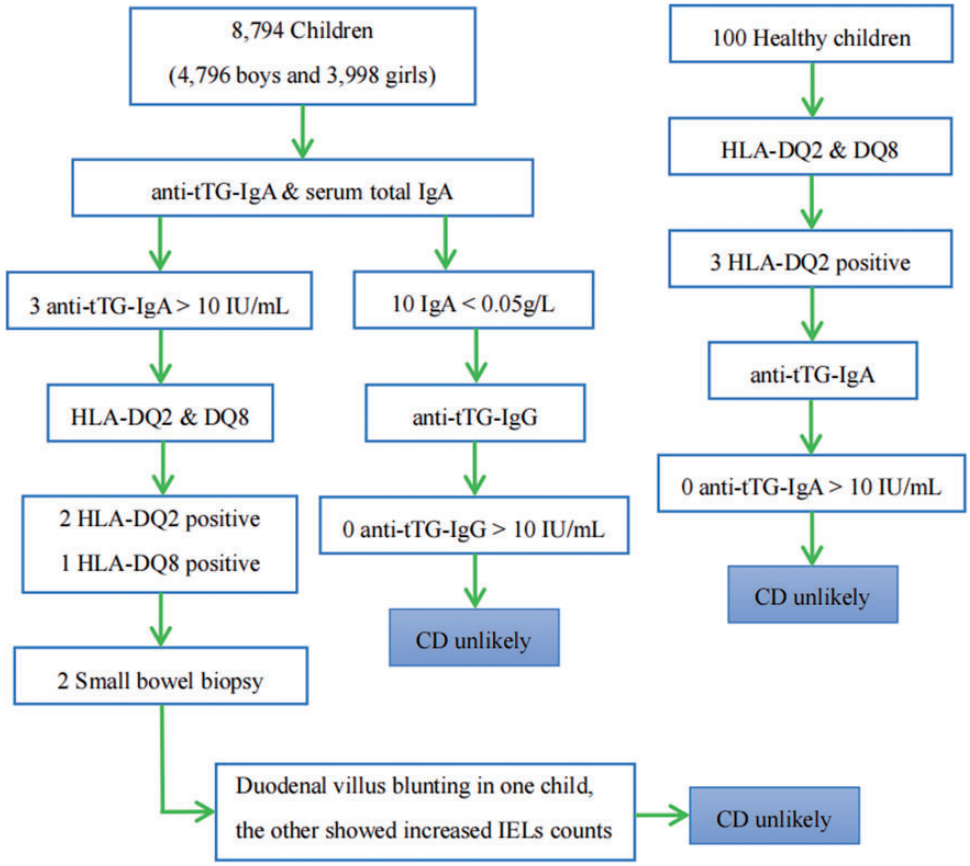

Figure 1. Flowchart of the study. CD: celiac disease; anti-tTG-IgA: anti-tissue transglutaminase IgA antibodies; anti-tTG-IgG: anti-tissue transglutaminase IgG antibodies; HLA-DQ2: human leukocyte antigen-DQ2; HLA-DQ82: human leukocyte antigen-DQ8; IEL: intraepithelial lymphocyte.

187.8 kg/person per year vs. 0.5 kg/person per year in rural areas).[4] Previous research in Thailand[11] found similar results. They assessed the frequencies of HLA-DQB1*02 and DQB1*03:02 alleles and anti-tTG-IgA serology in 46 children with type 1 diabetes mellitus. The allele frequencies HLA-DQB1*0201/02 and HLA-DQB1*0302 were 27% in patients with type 1 diabetes mellitus and 14% in healthy controls, but only one patient was anti-tTG-IgA+ and they were asymptomatic. The prevalence of CD based on positive screening results thus appeared to be negligible in Thai children.[11] Similar results were found by Vietnamese researchers who carried out anti-tTG-IgA-based CD screening in 1961 children and detected no cases of CD.[12] Notably, these Asian countries and regions have similar genetic backgrounds and rice-staple habits.

The anti-tTG-IgA levels in the two positive children in the current study who underwent gastroscopy were 12.39 and 99.5 IU/mL. Histopathology revealed only duodenal villous blunting in one and increased IELs in the other, neither of which was consistent with a diagnosis of CD. However, the minor pathological changes may be associated with low

antibody levels or may reflect the early stage of disease, and the patients should thus be followed up months or years later with repeated small bowel biopsies. The other positive patient who refused to undergo gastroscopy should receive long-term follow up. Our study thus failed to identify any patients with CD.

The study had several limitations. First, we did not perform upper gastrointestinal tract endoscopy and did not obtain intestine biopsy specimens from all anti-tTG-IgA+ individuals. Second, although CD patients have a high specificity and sensitivity for anti-endomysial antibodies, positive patients in this study were not tested for anti-endomysial antibody. Third, we did not collect information about the children's gluten-specific consumption at the time of blood sampling, given that 10 g of gluten per day for 6 to 8 weeks is considered necessary for the production of relevant antibodies in cases of CD.

Conclusions

This analysis of serum samples collected from patients at a large children's hospital found that only 0.034% of children were positive for anti-tTG-IgA, and we thus failed to identify any cases of CD, indicating that the prevalence of CD is low among Chinese children in South China. In addition, although we found three HLA-DQ2+ cases among 100 healthy children (3%), none of these were anti-tTG-IgA+. HLA-DQ2 and/or HLA-DQ8 might thus not be CD-susceptibility genes among Chinese children. Further population-based screening studies are needed to clarify the prevalence of CD; notably, however, there is currently no CD center in China.

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Data availability

Access to the patients' personal data used to support the findings of this study are restricted by the Ethics Committee of Guangzhou Women and Children's Medical Center to protect patient privacy. The general results used to support the findings of this study are available from the corresponding author upon request.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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