

Insufficient awareness of celiac disease in China: population-based screening is needed

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Celiac disease (CD), once considered a gastrointestinal condition, is now known as a systemic autoimmune disease initiated by exposure to dietary gluten mainly in human leukocyte antigen DQ2 (HLA-DQ2) or HLA-DQ8 carriers. The classic presentations of CD include intestinal manifestations such as chronic diarrhea, bloating, abdominal pain, constipation, weight loss, or poor growth in children. Iron-deficiency, osteoporosis, and neuropathy attributable to vitamin B12 deficiency is also frequently seen in celiac patients. Immune responses spreading to tissues apart from the intestine cause dermatologic conditions such as dermatitis herpetiformis, and even increased risk of miscarriage in women.

CD was first described in 1887 by Samuel Gee, and until a few decades ago, CD was considered as an uncommon enteropathy mainly affecting individuals of European ancestry. But according to a systemic review published in 2018, CD has already emerged as a major health problem, affecting approximately 0.7% of the general population worldwide.^[1] However, information about celiac patients in China appears to be rare enough that they exist occasionally in case reports or case series. Thus, it is likely that what we see is only the tip of the “celiac iceberg.”^[2]

An Emerging Disease in China

Very few studies about CD in China are available through the Medline/Pubmed database, but it is now believed that CD in China is not so rare as previously thought.^[3] A recent study recruiting 19,778 Chinese adolescents and young adults showed a prevalence of CD autoimmunity reaching 2.19%.^[4] And in provinces where wheat is the staple food, positive serology rates were found to be higher.^[4] Some other studies explored the prevalence of CD among certain clinical settings. Wang *et al* found a seroprevalence of

1.77% (7/395) among patients with diarrhea-predominant irritable bowel syndrome (IBS), and four out of these seven cases were eventually diagnosed as CD according to duodenal histology.^[5] Another group reported a seroprevalence reaching 22% among patients with type 1 diabetes mellitus and autoimmune thyroid diseases.^[6] Unfortunately, in most studies, seropositive individuals did not undergo biopsy for confirmation of CD diagnosis.

CD-predisposing HLA haplotypes have been shown to be necessary for the development of CD. Among the Caucasian population, approximately 25% to 30% are HLA-DQ2 carriers,^[7] while the proportion of HLA-DQ2 or HLA-DQ8 carriers from the Chinese population has been believed to be low. However, a meta-analysis conducted by Yuan *et al* revealed a 3.4% and 2.1% frequency of HLA-DQ2.5 and HLA-DQ8 haplotypes respectively in the Chinese population.^[2] Prevalence of HLA-DQ antigens was higher, reaching 18.4% and 8%, respectively for HLA-DQ2 and HLA-DQ8.^[2] Therefore, in spite of the slightly lower percentage of HLA-DQ2 or HLA-DQ8 carriers from the Chinese population, the current rareness of CD in China could not be explained.

Per-capita wheat composition is another important determinant of CD prevalence. It has been believed that low exposition to wheat products may prevent the prevalence of CD in China. In fact, wheat has been the major food in China for more than 4000 years, and it has been a dominant cereal in the northern part of China for centuries. In particular, Chinese people even consume a product called “mianjin,” which is mainly constituted of gluten. Also, as our diets are becoming more and more westernized, it is predicted that higher incidences of CD is likely to occur in the future.

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More Clinical Awareness for CD

Undiagnosed and untreated CD could lead to severe malabsorption and higher risks of lymphoma, which is associated with a nearly four-fold increased risk of death.^[8] It is thus important to increase awareness of CD among clinicians, therefore to promote active case-finding.

Patients with evidence suggestive of malabsorption, such as chronic diarrhea, bloating, post-prandial abdominal pain, are recommended to be tested for CD.^[9] Also, clinicians should be aware that the frequency of CD is elevated in many common clinical scenarios, such as unexplained iron-deficiency anemia, unexplained elevation of liver enzymes, and type I diabetes mellitus.^[10] Testing for CD in these patients is also reasonable, as studies have shown that related symptoms or abnormal lab tests tend to normalize or improve after initiation of gluten-free diet.

There is a considerable overlap in symptoms between CD and IBS. It has been shown that 20% to 50% of celiac patients fulfilled the Rome criteria.^[11] Presumably, some patients could be mislabeled as IBS, leading to delayed diagnosis of CD. A recent meta-analysis showed that pooled prevalence of biopsy-proven CD in patients with IBS reached 3.3%, with an odds ratio of 4.5, showing a significant higher prevalence of CD in people with IBS-type symptoms.^[12] A study conducted in Shandong Province also confirmed this presumption in the Chinese population. Kou *et al* found that 2.85% of their patients with IBS were diagnosed with CD.^[13] Thus, to pursue the diagnosis of CD more aggressively in patients with suspected IBS might facilitate future identification of celiac patients in China.

A Standardized Diagnosis of CD

To establish a diagnosis of CD, there should be a combination of evidence including a reasonable medical history, physical examination, positive serology, and a characteristic duodenal biopsy histology.^[9,14] Immunoglobulin A anti-tissue transglutaminase (tTG) is the preferred test for detection of CD with a sensitivity about 95% and specificity at 95% or greater, but this single test is not sufficient for diagnosis.^[9] Also, it is worth noting that positive serology tests are dependent on ingestion of gluten, while gluten-free diets could lead to false-negative results. Multiple biopsies of the duodenum showing increased intraepithelial lymphocytes, crypt hyperplasia, and villous atrophy still remains the central component of the diagnosis of CD.^[15] Additionally, histological response after gluten-free diet could help confirm the diagnosis of CD.

Anti-gliadin antibodies (AGAs) have been frequently used in Chinese studies about CD. However, evidence has shown that AGAs are accurate only when pre-test prevalence of CD is high or in children less than 2 years of age.^[16] While endomysium antibodies and antibodies against human tTGs are serology tests that are considered truly celiac-specific.^[9] Therefore a popularization of highly sensitive and specific screening tests in China is also necessary.

Standardized tissue acquisition and histological description is another problem that we should pay attention to. Villous atrophy of the duodenum can be patchy in celiac patients; thus it is recommended to acquire one to two biopsies of the bulb and at least four biopsies of the distal duodenum for histological evaluation.^[9] Modified Marsh classification is commonly used for CD, while some clinicians would prefer a more accurate description. Evaluation of villous height: crypt depth ratio (normal ratio: 3:1) derived from properly oriented specimens could provide better guidance in the follow-up phase.^[17] Also it is important to be aware that many other conditions such as common variable immunodeficiency syndrome, AIDS, enteropathy-associated T-cell lymphoma, and many autoimmune diseases, could also cause villous atrophy in duodenal biopsies.

Conclusions

The epidemiological burden of CD in China has not been clearly evidenced yet, probably attributing to poor awareness of this disease among clinicians and limited access to diagnostic procedures. Therefore, there is urgent need for population-based screening studies on the prevalence of CD. Yet it is important to be aware that seroprevalence cannot be equated with prevalence of biopsy-confirmed CD. Thus to conduct duodenal biopsy in seropositive patients is necessary to rule out false-positive seropositive individuals. If the screening studies confirm a serious under-diagnosed situation of CD, to promote the availability of gluten-free food products in China will be the major challenge before this disease emerges into a public health burden.^[18] On the other hand, if the studies turn out to show that low prevalence of CD is the reality, it would be interesting to explore the possible mechanisms or genes in Chinese people that make us tolerant to gluten. Through our active investigation, we believe that the hidden part of the “celiac iceberg” in China will gradually emerge in recent years.

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Conflicts of interest

None.

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