

EDITORIAL

## Extremely low prevalence of Celiac disease in Japan: Eternal silence or just the calm before the storm?

Celiac disease (CD) is an autoimmune enteropathy of the small intestine and causes malabsorption in genetically susceptible individuals. Fifty years ago, CD was considered to be an uncommon disease, affecting mainly children and limited to individuals of European ancestry. Subsequently, however, CD has been reported from most parts of world, including Asian countries.

The prevalence of CD varies from country to country. Although common in Europe and the United States, cases of CD have rarely been encountered in East Asia. In Japan, there has only been one report of the seropositive prevalence rate for anti-tissue transglutaminase IgA antibody (TTG). Of 2008 nonclinical subjects, 0.2% were positive for TTG, and only a single case (0.05%) was finally diagnosed with CD based on the histologic changes in duodenal mucosa.<sup>1</sup>

In this issue of *JGH OPEN*, Fukunaga *et al.*<sup>2</sup> explored the seroprevalence of CD by measuring TTG titers in 2055 healthy adults from a different cohort in Japan. Of the 2055 subjects, 4 (0.19%) showed a raised titer of TTG. The authors concluded that the prevalence of CD was likely quite low in Japan. As discussed by the authors, a limitation of their study was that serological testing targeted TTG only. Duodenoscopy with biopsy, testing for endomysial antibody (EMA), and HLA typing were not included in this retrospective study. The use of TTG is appropriate for screening in populations with a low incidence of CD because of the high quality and convenience of the assays. However, the specificity of TTG has been inferior to that of EMA.<sup>3</sup>

Numerous studies suggest that high levels of circulating TTG predict CD with high specificity.<sup>4</sup> Recent pediatric guidelines propose that duodenal biopsy may not be necessary for the diagnosis of CD in symptomatic patients if TTG titers are greater than 10 × the upper limit of normal (ULN) for the method.<sup>5</sup> Additional tests are optional, including a second TTG, EMA, and human leucocyte antigen (HLA) typing. In the current study, four patients were positive for TTG, but antibody titers were only slightly raised (ranging from 11.3 to 13.4 U/mL with an ULN 10 U/mL). In addition, none of the four had prominent digestive symptoms such as diarrhea or weight loss in a symptomatic survey. Thus, all patients would need duodenoscopy and biopsy for confirmation of CD. Indeed, it is likely that at least some are false positives and that the true prevalence of CD is lower than the prevalence of positive serology (0.19%) reported in this article.


Reasons for the low prevalence of CD in Japan include a low frequency of HLA types that predispose to CD and a relatively low intake of foods containing gluten. In Western countries, 99% of patients with CD carry at least one HLA-DQ2 or HLA-DQ8 haplotype. This compares with a frequency of 35–40% in unaffected Caucasian individuals. HLA-DQ2 has a

frequency of approximately 90% in CD and 20–30% in appropriate control populations. In contrast, the frequency of DQ2 in blood donors in Japan has been reported as only 0.3%.<sup>6</sup> For HLA-DQ8, the frequency in Japan and Caucasian populations appears to be similar at approximately 8–11%.<sup>7</sup> While HLA-DQ8 may seem a less compelling predisposing factor for CD, it accounts for almost all non-DQ2 cases. Furthermore, the absence of HLA-DQ2 or DQ8 has been used to exclude CD with a high negative predictive value. What seems clear is that a low frequency of HLA-DQ2 contributes to the low prevalence of CD in Japan. Another important factor is likely to be the intake of dietary gluten, mostly from wheat and wheat products. Historically, the population in Japan has had a low intake of wheat, but traditional rice-based diet are now being replaced by Western-style diets with a higher content of gluten.<sup>8,9</sup>

Another issue is whether CD is being overlooked by physicians and gastroenterologists in Japan. This seems unlikely as the endoscopic appearance of CD is well known, and endoscopy at low cost is widely practiced by well-trained endoscopists.

The final question is whether low prevalence of CD in Japan is set to continue or whether the prevalence will increase in the near future in a similar way to Western countries and India. If the major factor is a low frequency of HLA-DQ2, the prevalence may well continue to be low. However, the risk is that CD will increase in prevalence because of Western-style diets in individuals with HLA-DQ8. There may also be additional influences from non-HLA genes and environmental factors apart from gluten. The reality is that diet and lifestyle changes in Japan have been associated with increases in the prevalence of disorders such as non-alcoholic fatty liver disease and inflammatory bowel disease to levels comparable to that in Western countries. For CD, the current situation just might be the calm before the storm. In China, for example, a recent study found CD in 2.9% of 246 patients with an initial diagnosis of irritable bowel syndrome.<sup>10</sup> Only time will tell whether there will be similar experiences in Japan.

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