HLA Testing for Coeliac Disease in Ireland?

Abstract:

Recent studies have shown a worldwide prevalence of coeliac disease (CD) of around 1 in 100 and one of the highest prevalence rates in Ireland. Coeliac disease is a genetic disease and its prevalence appears to be increasing. For example, a greater than 6-fold increase over a 20 year period was evident in a recent retrospective Scottish study. Children with selective IgA deficiency, Down syndrome, Type I diabetes mellitus and autoimmune diseases are at increased risk of CD. Those with a family history are particularly vulnerable with as many as 1 in 10 first-degree, and 1 in 40 second-degree relatives affected. The most commonly described symptoms include diarrhea, excessive flatulence, weight loss, failure to thrive, abdominal distension, pain, bloating, vomiting and anorexia. Irritability is a particularly consistent finding in asymptomatic children. However, it must also be remembered that the vast majority of affected individuals manifest few or no symptoms at all.

The reference standard for the diagnosis of coeliac disease has been the demonstration of histological changes of villous atrophy, crypt hyperplasia and increased intraepithelial lymphocytes in the small intestinal mucosa, as defined by the Marsh criteria. However, the diagnostic criteria for CD have evolved over the past two decades with the availability of newer and better serological assays. The necessity for a confirmatory biopsy in all situations recently has been challenged. The European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPAGHN) guidelines continue to recommend IgA anti-TG (tissue transglutaminase) antibodies as the first line test in all symptomatic children. However, ESPAGHN now propose that in a genetically (HLA) susceptible symptomatic child with tTG of at least 10 times the upper limit of normal, with a positive anti-endomysial antibody (EmA) result and a history of a first-degree relative with CD, a confirmatory small intestinal biopsy is no longer needed. HLA testing (for the HLA-DQ2-DQ8 and DQ8-DQ8 haplotype) is more frequently in non-symptomatic at-risk patients also is recommended in the absence of these haplotypes, coeliac disease is very unlikely. Some national bodies have already introduced these criteria into their CD diagnostic pathway.

Against this background, the findings of a large multinational prospective study on the risk of coeliac disease for children with risk HLA haplotypes by Liu et al is of some interest. The TEDDY (The Environmental Determinants of Diabetes in the Young) study group was formed in 2007 for follow up of children at high genetic risk of Type 1 diabetes (T1DM) who were prospectively enrolled at birth in Sweden, Finland, Germany and the USA. Development of CD was a secondary outcome in the TEDDY study as the major HLA genotypes that confer risk of T1DM also impart a similar risk for CD. More than 6000 children carried one of the four HLA genotypes and had serological screening with tTG. The authors calculated cumulative risks for development of CD autoimmunity (ie. positive tTG antibodies) and overt coeliac disease by 5 years in those with two copies of HLA DR3-DQ2 were 26% and 12%, respectively. Similarly, the risks were 11% and 36% respectively for those with a single copy of that HLA DQ2 haplotype. Both these results were highly statistically significant (p<=0.001).

The findings of this study are not truly novel but rather confirm and extend those of previous studies regarding the effects of HLA on the risk of coeliac disease. The authors propose that their results might help inform future studies on population screening. Given that 25% of the children homozygous for DR3-DQ2 in the study cohort developed CD before 5 years of age, on the face of it this suggestion appears unreasonable. It is important to remember that this study did not address many fundamental factors around the appropriateness and effectiveness of population screening. For example, it did not compare the relative effects of the various risk HLA haplotype combinations on the development of coeliac disease within a normal population and did not address issues such as cost effectiveness, efficacy of HLA-based screening compared with other tests or the acceptability of gluten exclusion for screen-positive asymptomatic patients.

HLA-based stratification for screening purposes would pose particular challenges for Irish children because HLA DQ2 and DQ8 are very frequently found in our population. In fact, many practitioners, including our group at the National Referral Centre for Paediatric Gastroenterology, do not use HLA testing in our algorithm for testing in coeliac disease. However, we use tissue transglutaminase antibodies (TG) for initial testing and total IgA (the latter to exclude the false negative results in coeliac patients who have IgA deficiency) where there is clinical suspicion and in at-risk groups. Although CD diagnosis without resorting to biopsy may be considered in very limited clinical circumstances we await the results of prospective studies underway to confirm the reliability of non-biopsy based diagnosis of coeliac disease before embracing this approach more widely.

References