In 1888, Samuel Gee described a disorder of chronic maldigestion and malabsorption that affected individuals of all ages, particularly children 1 to 5 years of age, that he termed, "coeliac affection." Although he did not know the exact cause, he aptly suspected that the treatment was some form of dietary restriction, with a reduced allowance of "farinaceous foods," rich in starch or flour. More than a century later, we understand that celiac disease is an increasingly common disorder that occurs when genetically susceptible individuals are exposed to gluten, resulting in immune-mediated inflammation of the small bowel and a variety of clinical manifestations that need not be limited to the gastrointestinal tract.

As recently as 30 years ago, the disorder was thought to be relatively uncommon. In the 1980s, discovery of celiac-related antibodies and their use in serologic screening led to the identification of asymptomatic and mildly symptomatic cases. With current screening, the incidence approaches 1% of the general North American population, with higher frequencies in selected groups.

The Environmental Determinants of Diabetes in the Young (TEDDY) study is a multicenter, international research consortium charged with the goal of identifying genetic and environmental factors that contribute to the development of type 1 diabetes mellitus in children recruited from birth. In this issue, Agardh and colleagues present a subset of data that applies to clinical and serologic characteristics of study participants with genetic susceptibility for the development of celiac disease. Data presented in this study were acquired from the initial HLA antigen screening of more than 400,000 newborns across 6 centers in the United States, Finland, Germany, and Sweden. The investigators then followed more than 8000 children with genetic susceptibility (HLA DR3-DQ2 and/or DR4-DQ8) on a protocol that provided periodic screening for clinical symptoms and development of celiac disease-associated antibodies (anti-tissue transglutaminase immunoglobulin A).

The study presents several important findings, including a biopsy-confirmed incidence for celiac disease of 5% among these study subjects who were selected for HLA antigen susceptibility, as well as insights into the early natural history of celiac disease in young children. The data demonstrate that children who develop celiac disease antibodies may have early gastrointestinal or growth concerns, but by 3 to 4 years of age, most become asymptomatic and therefore may remain undiagnosed in the absence of protocol screening. Such findings, important toward devising diagnostic strategies, may only become evident from prospective, "big data" studies like TEDDY.

One of the larger questions that this study helps answer is the utility of population screening for celiac disease. Currently, screening is recommended for individual patients who present with a symptom that could be a manifestation of celiac disease, or when indicated by family history or coincident medical conditions like type-1 diabetes mellitus or Down syndrome. Ultimately, screening lies at the discretion of a clinician. Although screening with anti–tissue transglutaminase immunoglobulin A is
considered both sensitive and specific, it is not the gold standard test, and being seropositive does not absolutely implicate mucosal disease; in this study, 16% of seropositive children who underwent endoscopy did not have celiac disease. Given the clinical limitations of antibody screening and a required lifelong commitment to nutritional management, a confirmatory small bowel biopsy is still recommended.

Population screening for celiac disease has been considered in the past, but could not be justified, as all of the elements required to warrant generalized testing could not be fulfilled. Armed with emerging data that document a benefit from the dietary treatment of individuals with asymptomatic or mildly symptomatic celiac disease, a 2-tiered approach that includes newborn or early-life screening for genetic susceptibility, coupled with later screening for celiac-specific antibodies, has been proposed. It is this approach that is demonstrated by this study. By narrowing the testing pool to susceptible subjects, the diagnostic yield of a test is improved and better identifies children who will benefit from treatment from the earliest stages of the disease.

To quote Samuel Gee, “if the patient can be cured at all, it must be by means of diet.” With awareness and availability of gluten-free foods increasingly entrenched within the mainstream of the North American lifestyle, the burden lies on the identification of all children who may benefit from treatment. The prospective data from TEDDY effectively demonstrate the utility of 2-tiered screening and constitute a step forward in devising a population-screening strategy that best offers the appropriate treatment at a stage in life where it may yield the most lifelong benefit.

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