incidence of CD has been observed in areas that were previously considered CD-free due to global changes in the diet, mostly related to higher consumption of wheat-based products (eg, pasta, pizza).

In Western countries several recent studies evaluated the overall prevalence of CD in the general population, usually by counting the number of clinically diagnosed CD patients plus those detected by serological screening of a population sample. In Europe and the United States, the mean frequency of CD in the general population is approximately 1% (1,2), with some regional differences, the reasons for which remain elusive. The prevalence of CD is as high as 2% to 3% in Finland and Sweden, whereas it is only 0.2% in Germany, although these areas share a similar distribution of causal factors (level of gluten intake and frequency of HLA-DQ2 and -DQ8)(1,3). Although the incidence of clinically diagnosed CD cases is increasing, still the larger part of the “celiac iceberg” remains undetected, with a ratio of 1:3 to 1:5 between diagnosed and undiagnosed cases (1,3). A 6.4-fold increase in incidence has been recently described in Scotland from 1990 to 2009 and particularly classical cases of CD are increasing, indicating a true rise in the incidence of pediatric CD (4).

In Western countries the overall prevalence of CD is on the rise as well. A recent US study showed that CD prevalence was only 0.2% in the year 1975, and increased 5-fold during the following 25 years (5). The reasons for these changes are unclear, but have to do with the environmental components of CD (changes in the quantity and quality of ingested gluten, infant feeding patterns, the spectrum of intestinal infections, gut microbiota colonization, etc). Variation in the pattern of infant nutrition could influence the prevalence of CD at the population level, as suggested by the analysis of an epidemic of early-onset CD observed in Sweden during the 1980–1990s. The Swedish data indicated that the disease risk was substantially lower in infants introducing small amount of gluten when still breast-fed (3). The protective role of breast-feeding has been supported by other observational, retrospective studies and summarized in a meta-analysis (6). As far as weaning, an increased risk of CD has been reported in infants introducing gluten-containing food either before the age of 4 months or after 6 months, supporting the view of the “window” period of facilitated tolerance (4–6 months) (7). These observations have recently been challenged by a large epidemiological survey performed in Norway (8). The major results of this study performed on a large population sample (324 CD cases and 81,843 cohort controls), were somewhat shocking: (a) breast-feeding did not exert any protection against development of CD. Instead, mean duration of breast-feeding had been significantly longer in CD children (10.4 months) against development of CD. Instead, mean duration of breast-feeding has been supported by other observational, retrospective studies and summarized in a meta-analysis (6). As far as weaning, an increased risk of CD has been reported in infants introducing gluten-containing food either before the age of 4 months or after 6 months, supporting the view of the “window” period of facilitated tolerance (4–6 months) (7). These observations have recently been challenged by a large epidemiological survey performed in Norway (8). The major results of this study performed on a large population sample (324 CD cases and 81,843 cohort controls), were somewhat shocking: (a) breast-feeding did not exert any protection against development of CD. Instead, mean duration of breast-feeding had been significantly longer in CD children (10.4 months) than controls (9.9 months) and the disease risk was significantly higher in infants breast-fed for more than 12 months; (b) gluten introduction under continued breast-feeding was not protective; (c) in the adjusted analysis, only delayed (>6 months) but not early (<4 months) introduction of gluten was associated with an increased risk of CD8. The major limitation of the Norwegian study was that only children with clinically diagnosed CD were included in the analysis; therefore, any correlate (or lack of correlate) found in this study group does not necessarily apply to the overall celiac population (that is at least 3-fold larger). Another problem with this (and previous) case-control studies is the lack of an intervention arm. This situation will be clarified soon by 2 intervention, randomized, multicentre studies ongoing in Europe, both focused on large cohorts of at-family-risk infants prospectively studied since birth (9,10).

Apart from Europe and North America, the epidemiology of CD has been investigated in many other countries mostly populated by individuals of European origin (Fig. 1). The disease epidemiology reported from these areas largely overlaps with European and American data (11). CD is a common disorder in north Africa and
Middle East countries as well; however the diagnostic rate is still very low in these countries, mostly due to low availability of diagnostic facilities and poor disease awareness. In the Saharawis, an Arab population living in the western Sahara, the prevalence of CD in the general population is exceptionally high (5.6%) for reasons that are currently unclear. There are only anecdotal reports of CD in Sub-Saharan African countries.

In a recent study co-authored by David Branski, a serologic CD screening was performed in a representative sample of a young adult general population in Israel (12). The prevalence of overt CD diagnosed before recruitment was 0.12% (0.1% in men and 0.14% in women). The overall prevalence based on positive serology was 1.1%. Six of 9 subjects with positive serology underwent endoscopy, showing histological changes compatible with CD. The ratio of overt to silent CD was 1:8. These findings suggested that CD is highly prevalent in the young adult population in Israel.

The knowledge of the epidemiology of CD in the Asia Pacific region is still limited and mostly confined to India, where CD is being more frequently recognized, both in children and adults. However, as efficiently described by an Indian task force, CD in India is “submerged in an ocean of malnutrition.” The frequency of CD in India seems to be higher in the northern part of the country, so called “celiac belt,” a finding that is at least partially explained by the wheat-rice shift from the north to the south. The prevalence of CD amongst apparently healthy blood donors (n=1610) was 1:179 (0.56%) (13), a finding that overlaps with data from Western countries. In a large population sample (n=2879) Makharia and coworkers found CD prevalence to be 1.04% (1 in 96) and the prevalence of positive serological test (anti-transglutaminase antibodies) to be 1.44% (1 in 69) (13). Based on these data, it is estimated that 5 to 8 million people are expected to have CD in India. Of such a large pool of patients, only a few thousand patients have been diagnosed so far. If there is a real difference in the prevalence of CD in northern and southern parts of India, India may prove to be a model to subsequently the detection rate of this chameleonic disorder. These studies will also be instrumental to explain the dynamic of gene-environment interaction driving the current CD epidemic worldwide.

REFERENCES

Celiac Disease and Autoimmunity

*Riccardo Troncone and **Valentina Discepolo

ABSTRACT

Celiac disease (CD) has a multifactorial etiology with complex genetics and frequently occurs in association with other autoimmune disorders. Even though triggered by a dietary antigen, it shows many autoimmune features, the most peculiar being the presence of high titers of anti-tissue transglutaminase 2 autoantibodies, produced in the small intestinal mucosa since the early stages of the disease. More than 60% of CD-associated susceptibility loci are shared with at least another autoimmune condition, suggesting common pathogenic mechanisms. In particular, recognition of peptides by HLA molecules, posttranslational modifications required for optimal peptide binding and immune mechanisms leading to tissue damage have been found in CD as well as in other autoimmune diseases. This review briefly summarizes the main autoimmune features of CD, underlining the similarities with other autoimmune disorders, in particular with type 1 diabetes mellitus. Furthermore, the role of gluten and microbiome in driving autoimmunity is discussed.

Keywords: anti-tissue transglutaminase, celiac disease, gluten, type 1 diabetes

Increasing evidence supports the categorization of celiac disease (CD) as an autoimmune disorder. The association of CD with other autoimmune diseases is striking: type 1 diabetes mellitus, autoimmune thyroiditis, Sjogren syndrome, connective tissue disorders, and type 1 diabetes mellitus share genes and mechanisms. Similar to other autoimmune diseases, CD is a polygenic disorder with genes coding for the HLA class II molecules (DQ2.5 and DQ8) playing a major role. Interestingly, HLA-DQ2-DQ8 heterozygous show high risk for type 1 diabetes mellitus (T1D) development and in fact HLA-DQ8 transdimer has been shown to bind efficiently both gliadin peptides and peptides derived from GAD65 and IA-2 (8). The mechanisms governing the recognition of Celiac Disease and Type 1 Diabetes Mellitus Share Genes and Mechanisms

Similar to other autoimmune diseases, CD is a polygenic disorder with genes coding for the HLA class II molecules (DQ2.5 and DQ8) playing a major role. Interestingly, HLA-DQ2-DQ8 heterozygous show high risk for type 1 diabetes mellitus (T1D) development and in fact HLA-DQ8 transdimer has been shown to bind efficiently both gliadin peptides and peptides derived from GAD65 and IA-2 (8). The mechanisms governing the recognition of