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1

Celiac disease from a global perspective

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A B S T R A C T

Celiac disease (CD) is one of the commonest lifelong disorders in countries populated by individuals of European origin, affecting approximately 1% of the general population. This is a common disease also in North Africa, Middle East and India. The widespread diffusion of CD is not surprising given that its causal factors (HLA predisposing genotypes and consumption of gluten-containing cereals) show a worldwide distribution. Further studies are needed to quantify the incidence of CD in apparently "celiac-free" areas such as Sub-Saharan Africa and Far East. Several reports have shown that CD is increasing in frequency in different geographic areas. Genetic factors do not explain the rising incidence during the last decades; environmental or lifestyle factors may be responsible for these changes over time. The majority of patients with CD are still undiagnosed all over the world, leading to debate about the need of screening program.

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Introduction

Celiac disease (CD) is a systemic immune-mediated disorder caused by the ingestion of gluten-containing grains in genetically susceptible persons [1]. In the past, it was considered a rare disorder, mostly affecting individuals of European origin, and usually characterized by onset during the first years of life. Earlier investigations measured the incidence of CD, namely the number of "new" diagnoses in the study population during a certain period. One of the oldest epidemiologic studies on CD conducted in 1950 established that the cumulative incidence of the disease in England and Wales was 1/8000, whereas an incidence of 1/4000 was detected in Scotland [2]. The diagnosis at that time was entirely based on the detection of typical gastrointestinal symptoms. The awareness of the disease greatly increased in the 1960s when more specific tests for malabsorption and the paediatric peroral biopsy technique became available [3]. Consequently, an elevated incidence of the disease (which in the middle 1970s reached peaks of 1/450) was reported in studies from Ireland [4], Scotland [5], and Switzerland [6].

The availability of highly sensitive and specific serological tools, first the anti-gliadin (AGA) and later the anti-endomysium (EMA) and the anti-transglutaminase (tTG) antibodies, made it possible to evaluate the true prevalence of CD (number of affected persons in a population at a given time), showing an unsuspected frequency of clinically atypical or even silent forms of CD. Approximately twenty years ago Italy was the birth land of the new "era" of CD epidemiology, the one based on serological screening of general population samples. On a sample of 17,201 healthy Italian students it was shown that CD is much more common than previously thought and that most atypical cases remained undiagnosed unless actively searched by serological screening. The overall prevalence of CD (including known CD cases) was 1 in 184 subjects. The ratio of known (previously diagnosed) to undiagnosed CD cases was as high as 1–7 [7]. Using these sensitive serological tools for screening purposes, a huge number of further studies have shown that CD is one of the commonest, lifelong disorders affecting mankind all over the world, with a mean prevalence estimate of 0.9% [8].

Worldwide distribution of HLA and wheat consumption: the "evolutionary paradox of CD"

The widespread diffusion of CD is not surprising at all, given that its causal factors, HLA-predisposing-genotypes (DQ2 and DQ8) and consumption of gluten-containing cereals, show a worldwide distribution. We recently reviewed data on worldwide prevalence of CD, wheat consumption, and frequencies of HLA-DQ2 and HLA-DQ8 haplotypes and combined the three geographical maps to investigate their mutual relationship [8]. The global level of wheat consumption ranged between 21 and 564 g/person/day (Fig. 1); frequencies of HLA-DQ2 and HLA-DQ8 ranged between 0 and 28% and between 1 and 9%, respectively (Figs. 2 and 3). Interestingly, a significant correlation between the level of wheat consumption and the frequency of HLA-DQ2 or the sum of DQ2 and DQ8 was found worldwide (Fig. 4) [8]. Wheat consumption and HLA-DQ2 tended, indeed, to co-localize in different continents; in India wheat consumption is higher in Northern-Western states such as Punjab, Haryana, Delhi, Rajasthan, Uttar Pradesh, Bihar and Madhya Pradesh (so-called "celiac belt"). Likewise, the DQ2 allele frequency is higher in North (31.9%) than in South India (12.8% for Piramalai Kallars and 9% for Yadavas) [9]. In Africa the frequency of HLA-DQ2 is higher in the Northern populations consuming a gluten-rich diet, such as Saharawi (39%) [10], Libya (34%) [11], Algeria (28.3%) [12], Tunisia (23.4%) [12], Maroc (25%) [12], than sub-Saharan populations showing low frequency of DQ2 (Rwanda 15.5%, Tanzania 13.5%, Cameroon 7%) [12] and low level of wheat consumption [8].

We also observed a significant correlation between the frequency of HLA-DQ2 and the duration of wheat consumption according to the pattern of wheat culture spreading [8]. The history of CD is indeed related to the spreading of wheat cultivation after the agricultural revolution. Domestication of gluten-containing cereals began approximately 10,000 years ago in Neolithic settlements in the north-eastern (Turkey, Iran, and Iraq) and in the south-western (Palestine, Syria, and Lebanon) regions of the so-called Fertile Crescent area. Cultivation of wheat and barley slowly spread north-westward across Europe to reach Western countries, like Britain, "only" 4000 years ago [13]. The agricultural revolution paved the way to new diseases, such as CD. Since treatment with the GFD was not available in the