INTRODUCTION

Epidemiological data provide strong evidence of a steady rise in autoimmune disease throughout westernized societies over the last decades. Celiac disease (CD), being an autoimmune disease, is not an exception. Currently, we are witnessing a diffused ongoing epidemic of CD of great scale. The prevalence of the disease is increasing constantly and has increased over fourfold in the last half-century. The prevalence of “suspected” celiac disease varies from 1 in 87 to 1 in 500 individuals in western countries. The majority of patients are undiagnosed since diagnosed cases of CD have a much lower prevalence being somewhere between 1 in 500 and 1 in 9000 individuals. In high risk populations, the average risk of CD can reach 5-10%. The generally reported incidence of CD in the western world is around 1%, however, 2 to 5.6% were reported in Northern European countries and in the Sahara desert region in North Africa respectively. Even in the Far East, where rice is the main staple food, increased incidence of CD is being reported, whereby India is a good example.

The geoepidemiological distribution of the autoimmune diseases, the world-wide North-South gradient and the West-East gradient in Europe related to the socioeconomic status, the rapid increase in developed countries and population migration observations are indicative of an environmental impact, rather genetic factors, driving these rapid and recent evolutionary processes. Among others, two major environmental factors, strongly related to socioeconomic status are suspected to drive these phenomena: infections and nutrition. Nutrition plays a pivotal factor in CD induction. Gluten, which is the storage protein of wheat, and its alcohol-soluble gliadins, are the primary offending inducers of the disease. Most recently, the hypothesis that the industrial food additive enzyme microbial transglutaminase, used in the food processing as a protein glue, is a newly recognized environmental inducer of CD, was forwarded.

*Corresponding author: Aaron Lerner
Pediatric Gastroenterology and Nutrition Unit, Carmel Medical Center, B. Rappaport School of Medicine, Technion-Israel Institute of Technology, Haifa, Israel
Multiple publications exist, describing past or actual incidences/prevalence of CD, at single points in time, however, long term longitudinal follow-up studies, on selected populations are scarce. The present review will concentrate on such studies. The aims being to calculate the % increases per year of CD incidence worldwide, analyze the differential increases of CD per country and identify geoepidemiological trends.

METHODS

A systematic review was performed to identify incidences of CD. Studies from the last 6 decades (1950-2011) were identified using Medline, Google, and Cochrane Library databases. Only long-term regional or long-term follow-up studies are reported. Studies on high risk populations and material from hospital archives, were excluded. A diploid statistical analysis was employed: Assessments were made using the reported incidences and used to calculate the average annual percent changes in incidence rates. Diploid statistical analysis used the Software MedCalc® and involved performing a t-test for the comparison of two independent means (p<0.05 was considered statistical significant).

RESULTS

The mean ± s.d. of the net increased %/year in the overall incidence of CD worldwide is 9.77±8.27. Allocating these annual net % increases in individual countries, in a decreasing order: The Netherlands had the highest increase while the USA exhibited the lowest one, as shown in figure No 1. The No 1 summarizes the past and the more recent incidences of CD, and the time gap between the surveys, in specific countries, where follow up studies were available. The highest/lowest %/year increased incidences were depicted in Canada/Estonia (33.3, 2.5, respectively). Comparing the differences between the overall means: s.d. of the old vs new calculated incidences, the surge was highly significant (p<0.0211). In order to normalize for the periods of time, so as to minimize environmental influences, all the incidence surveys carried out between 1976-2001, in countries where more than 2 or more comparative studies were performed, were compared (shown in Figure 2). A clear upward trend of CD incidence is shown, throughout these 2.5 decades (r²=0.968 p<0.019). The mean ± s.d. net %/year increases in children were comparable to those depicted in adult populations: 6.6±7.9, 5.2±4.0, respectively, p=0.664.

The North/South and West/East trends in CD incidence surges are shown in Figure 3. The increases were higher in Northern/Southern countries than in Western/Eastern ones, reaching significant levels, (11.3±9.0, 5.2±3.4, 11.8±9.3, 6.4±3.7, p<0.002, p<0.007, respectively).

DISCUSSION

Population-based estimates of the incidence of CD in different countries are crucial for investigating possible etiologies or influencing environmental factors or underlining risk factors. Quantification of the likely healthcare burden and the planning of future strategies to face the ongoing epidemic of CD is of no less importance.

The beneficial aspects of early recognition of CD are well known. The CD related complications of stunted growth, failure to thrive, nutritional deficiencies, osteoporosis, anemia, increased risk of malignancy, infertility, hepatic transaminasemia and association with other autoimmune diseases are all potentially reversible on a gluten free diet, when the disease is diagnosed early enough. The increased awareness responsible for the surge in diagnosed patients' needs to continue together with a lower threshold for screening high risk populations using a cheap, non-invasive and reliable antibody biomarker to prevent delays in diagnosing such a common but preventable disease.

In the present review the increased incidences of CD worldwide, in the last decades are described. The mean of the net increased %/year incidence of CD worldwide is quite high at 9.77%. Differences between old vs new frequencies, in the counties where the information was available, were highly significant.

The net increased incidences of CD in the Northern and Western countries, compared to the Southern and Eastern ones follows the global geoepidemiological trends of autoimmune disease. Reviewing available literature, it can be deduced that incidences of CD have increased significantly over the last 60 years. The recent outbreak of autoimmune diseases in industrialized countries has brought into question the factors contributing to this increased incidence. Given the constancy of genetics, growing attention has focused on environmental factors, and in particular, the western lifestyle. Indeed, over the last few decades significant changes in western dietary habits, such as an increase in the consumption of refined grains, have been described.

Figure No 1: The annual net % increases/year, in individual countries, in an increasing order. (adapted from references:6,7,15-41)
Several explanations can be what the reasons for such a fold increase in the rate.

The brain gut axis is involved in many gastrointestinal disorders, suggesting that life events associated with increases in global wheat consumption, supporting the hygiene hypothesis. However, the list of infections associated with CD is increasing constantly, as is the case with other autoimmune diseases. Infections are major inducers of autoimmunity. Molecular mimicry, epitope spreading, bystander activation, and stimulation of pattern recognition receptors, as well as persistent infection and polyclonal activation of B cells, are suggested as mechanisms. Most recently light was shed on the interaction between host genetics and microbiota composition in relation to CD development. Expression of the HLA-DQ2 is a strong risk factor for the development of CD. Children with this haplotype have an altered microbiota composition prior to clinically apparent disease.

Stress: The brain gut axis is involved in many gastrointestinal conditions and stressful events affect multiple functions of the digestive tract. The stress load is increasing alongside modern life, thus impacting gut physiology. Multiple animal studies have shown how stressful stimuli breach intestinal functional integrity. Prior to diagnosis, the number of stressful events in celiac disease has been found to be more frequent than in the control group suggesting that life events may favor the clinical appearance of celiac disease or accelerate its diagnosis.

E. Gastrointestinal microbiome

Alterations in small intestinal microbial composition have recently been associated with autoimmune diseases including active CD, indicating a possible role for the microbiota in CD evolution. One of the potential mechanisms appears to be increased intestinal permeability. Since intestinal disbiosis is environmentally driven and heavily nutrient dependent, the changing environment in the later decades can explain the recent surge in CD incidence.

F. Increased intestinal permeability by disbiosis and food industrial additives

Various dietary components are also known to regulate epithelial permeability by modifying expression and localization of tight junction proteins. More so, formula milk-feeding in conjunction with CD HLA-DQ genotype plays a role in establishing the infants gut microbiota, whereas, breast-feeding reduced the genotype-related differences in microbiota composition. Recently, HLA-DQ2 was described as a high risk genetic factor in the altered microbiota composition prior to clinically apparent CD. Chronic...
inflammatory diseases of the intestine, such as celiac disease, are characterized by a leaky intestinal barrier. Tight junctions are not static barriers but highly dynamic structures that are constantly being remodeled due to interactions with external stimuli, such as food residues and pathogenic and commensal bacteria. In fact, commonly used industrial food additives abrogate human epithelial barrier function, thus, increasing intestinal permeability through the opened tight junction, resulting in entry of foreign immunogenic antigens and activation of the autoimmune cascade. The hypotheses that microbial transglutaminase, a common food industrial additive, is a new environmental inducer of CD, was recently suggested. Taken together, the modern period surge in process food consumption, in conjunction with the dynamic CD disbiosis increasing intestinal permeability, can present one piece of the puzzle of CD incidence increase in the western world.

G. Increased public and professional awareness.

There has been a marked increase in both the public's, and physician's awareness (and also in the restaurant kitchen) of gluten related disorders. Despite this, under awareness and under diagnosis are still prevalent. The studies emphasize the need for educating the public, patients, restaurant chefs and physicians in both the prevalence of celiac disease and the importance of early diagnosis, as well as the wide availability of serological tests on the market.

H. Improved diagnosis.

Multiple serological tests exist on the market. The first reliable one was found in the early 1980s but the most frequently used one is IgA-tissue transglutaminase (tTG). Several combinations of CD related auto antibodies have been studied but not accurately compared with each other. The most frequently combined tests used are anti IgG-deaminated gliadin peptide and IgA-tTG, however, the new generation anti neo-epitope tTG combining tTG docked gliadin IgG-IgA is very reliable and is increasingly being used. Since only the tip of the CD iceberg is above the waterline and the much larger portion of the CD iceberg remains undetected underwater, it can be expected that the prevalence of the disease will continue to increase. An active case-finding strategy in the primary care setting was shown as an effective means to improve the diagnostic rate of CD in North America. The need for a wider availability of the serological tests that can facilitate the diagnosis of celiac disease is obvious.

Several biases exist in the present review. Despite thorough review, some longitudinal follow ups could have been missed. The incidence analyses were done at large intervals, using different experimental designs, and different serological biomarkers and, during the last decades the knowledge, awareness, biomarkers, inclusion and exclusion criteria, as well as CD diagnostic guidelines, have changed extensively. These are the reasons why the present inclusion/exclusion criteria are so stringent. More specifically, in order to normalize for the periods of time, in order to diminish environmental influences, all the incidence studies done within a well-defined period, in countries where more than 2 or more comparative studies were performed, are displayed in Figure No 2.

In Summary, reviewing available literature, it can be deduced that incidences of CD have increased significantly over the last 60 years. The net increased incidences of CD in Northern and Western countries, compared to Southern and Eastern ones, were higher. No differences were observed between the adult and pediatric CD patients. The concrete explanation for the described surge of CD incidences is unknown, as multiple environmental changes have taken place over the last decades. These observations point to a stronger influence of environmental factors as opposed to genetic factors on CD development.

No grant supported and no competing interests

References

8. Chatenoud L, You S, Okada H, Kuhn C, Michaud B, Corfe BM. Occurrence of celiac disease in the Canterbury...


How to cite this article: Aaron Lerner et al., The World Incidence Of Celiac Disease Is Increasing: A Review. International Journal of Recent Scientific Vol. Vol. 6, Issue, 7, pp.5491-5496, July, 2015

******