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OBSERVATION

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Risk factors in familial forms of celiac disease

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Abstract

Celiac disease has been reported in up to 2% of some European populations. A similar risk has been identified in the America and Australia where immigration of Europeans has occurred. Moreover, an increasing number of celiac disease patients are being identified in many Asian countries, including China and India. Finally, celiac disease has also been detected in Asian immigrants and their descendants to other countries, such as Canada. Within these so-called "general" celiac populations, however, there are specific high risk groups that have an even higher prevalence of celiac disease. Indeed, the single most important risk factor for celiac disease is having a first-degree relative with already-defined celiac disease, particularly a sibling. A rate up to 20% or more has been noted. Risk is even greater if a specific family has 2 siblings affected, particularly if a male carries the human leukocyte antigen-DQ2. Both structural changes in the small bowel architecture occur along with functional changes in permeability, even in asymptomatic first-degree relatives. Even if celiac disease is not evident, the risk of other autoimmune disorders seems significantly increased in first-degree relatives as well as intestinal lymphoma. Identification of celiac disease is important since recent long-term studies have shown that the mortality of celiac disease is increased, if it is unrecognized and untreated.

INTRODUCTION

Only a few decades ago, celiac disease was considered an uncommon disorder present mainly in Europe or in countries where Europeans had emigrated, including Canada and Australia[1]. In Ireland, and in particular, Galway in the West of Ireland, appears to have an especially high prevalence of celiac disease with an estimate of up to 1 in 300 persons[2]. Similar experiences have been noted in Scandinavian countries. In the United States, however, earlier reports suggest that the detection of celiac disease is surprisingly low[1,3]. With the emergence of modern serological screening tests for celiac disease and increased efforts to use these screening measures, celiac disease has become more readily detectable.

EMERGING RISK ESTIMATES

In recent years, changes have occurred with an estimate of overall prevalence rates increased in most countries, often in the region of about 1%-2%[4]. Interestingly, in a longitudinally-based study from Olmstead County in the United States over many decades, increased detection has been reported, in part, due to increased use of serological screening[5]. Recently, a report from Hangzhou in China has also suggested that the prevalence of adult celiac disease may be more common in China than previously appreciated[6]. Of note, celiac disease has also been

reported in immigrants to Canada from China, Japan and South Asia, particularly from the Punjab region of India[7]. Even in the United States, celiac disease is now generally believed to affect 0.5%-1.0% of the general population[8].

HIGH RISK GROUPS FOR CELIAC DISEASE

These reported numbers often reflect prevalence estimates, usually resulting from screening of selected groups, e.g. blood bank serum samples, thought to be representative of the entire population from a specific geographic area. Confirmatory small intestinal biopsies have often been done in sero-positive cases to provide an overall "minimal" estimate of population prevalence (since all sero-positive patients may not be available for biopsy). As shown in Table 1, there are also some high risk groups within the general celiac population, often without typical clinical symptoms, such as diarrhea or weight loss, that may have even higher prevalence rates. Among these factors that specifically denote a higher risk for celiac disease, the single most important is a familial history of biopsy-defined celiac disease with some estimates up to 20% or more of first-degree relatives. Diagnosis of celiac disease in all of these high risk groups, however, is especially important since failure to detect celiac disease coupled with failure to treat the disease may lead to an increased morbidity, and critically, a nearly 4-fold increased risk of mortality from celiac disease[9].

Table 1 High risk populations for celiac disease

Relatives, especially first-degree
Anemia, especially iron deficiency
Osteopenic bone disease
Insulin-dependent diabetes (type 1), especially children
Liver disorders, especially AIH and PBC
Genetic disorders, including Down and Turner's syndrome
Autoimmune endocrinopathy, especially thyroid disease
Skin disorders, particularly dermatitis herpetiformis
Neurological disorders, including ataxia, seizures, MG
Others, including IgA nephropathy

AIH: Autoimmune hepatitis; PBC: Primary biliary cirrhosis; MG: Myasthenia gravis.

Table 2 Evidence of familial risk

Biopsy and serological studies
Irish Setter dog model studies
Functional permeability studies
HLA marker studies
Genome wide expression/linkage studies

HLA: Human leukocyte antigen.

FAMILIAL RISK FACTORS

Evidence for a familial risk in celiac disease has been accumulated from many sources (Table 2), including biopsy and serological studies in families with known celiac disease[10-17], animal model studies in the Irish Setter dog[18,19], functional studies based on evaluation of intestinal permeability or other absorptive indices[20-23], human leukocyte antigen (HLA)-genotyping studies[24-26], and more recently, genome-wide expression and linkage studies[27].

Biopsy and serological studies

Early family studies using small intestinal biopsies have provided strong evidence for the familial nature of celiac disease[10,11]. A systematic review of these earlier studies using MEDLINE and EMBASE databases concluded that up to 20% of first-degree relatives of European descent may be at risk for celiac disease[12]. Similar results have been reported from non-European populations, including a recent report from the Punjab region of India[13]. In addition, more extensive studies in biopsy-defined celiac disease have further confirmed these findings, particularly in "at-risk" first-degree (1:22) and second-degree relatives (1:39), compared to a control "not-at-risk" group (1:133)[14]. This risk appears to be especially increased in families with at least 2 siblings diagnosed as celiac disease[15], and in this setting, more males were detected compared to females[16]. Particularly significant predictors of familial risk include carrying HLA-DQ2 and being a sibling of the proband[17].

Animal model studies

Animal studies have provided some indirect, but important evidence. Gluten-sensitive enteropathy has been reported in a family of Irish Setter dogs[18] along with the association of a canine major histocompatibility complex (MHC) DQ haplotype[19].

Functional studies

Earlier studies showed that an intentional increase in gluten intake may provoke jejunal mucosal architectural changes in some first-degree relatives along with reduced xylose absorption, even in those without clinically overt disease[20], suggesting that, in the genetically-predisposed, both structural and functional changes may be induced in familial celiac disease. Abnormal permeability to lactulose and mannitol in first-degree relatives also suggests that functional changes may occur in biopsy-defined disease[21] as well as in first-degree relatives with apparently normal small bowel biopsies[22]. Importantly, this familial risk in first-degree relatives is genetically-based and not related to their daily calculated gluten intake[23]. In other words, familial celiac disease is not due to a common environment with increased intake of gluten-containing foods, but has a definitive genetic basis.

Human leukocyte antigen marker studies

HLA markers have been popularly used for decades in clinical studies of celiac disease. These clinical studies have served to emphasize the strong genetic component involved in the development of celiac disease. In large part, possession of the HLA-DQ2 variant, necessary for presentation of dietary antigens to intestinal T-cells, is

critical. Non-HLA genetic factors are also increasingly recognized as a very important, and possibly even a more significant and critical risk factor in the development of familial celiac disease. Furthermore, a recent HLA-genotyping study (i.e. DQA1*0501, DQB1*0201, DRB1*04) with small bowel biopsies from Finland has suggested a practical means of exclusion of some first-degree relatives without celiac disease for screening purposes[24]. However, it has been reported that some asymptomatic first-degree relatives may show only minimal changes in intra-epithelial lymphocyte numbers[25]. In addition, with a prolonged follow-up, flat small bowel mucosal biopsies have been reported in familial disease without initially abnormal biopsies[26]. These findings are important and need to be confirmed as further longitudinal studies may be required in first-degree relatives without initial biopsy evidence of celiac disease.

Genome-wide studies

Most exciting are the recent genome-wide expression and genome-wide linkage studies done to explore a number of clinical disorders, including celiac disease. A recent meta-analysis of 8 genome-wide linkage studies in celiac disease permitted definition of both HLA and non-HLA chromosome regions that appear to predispose to celiac disease and suggested the possibility of different types of disease-predisposing variants[27].

RISK OF ASSOCIATED DISEASE IN RELATIVES

Of potentially even greater significance are reports on relatives without celiac disease at risk for other diseases, often associated with celiac disease. For example, a serological survey study of first-degree relatives of children with documented celiac disease suggested that autoimmune diseases may be increased in addition to biopsy-defined, but "sub-clinical" celiac disease[28]. In addition, first-degree relatives may also develop the closely linked dermatological disorder, dermatitis herpetiformis[29]. Moreover, patients with type-1 diabetes have an increased risk of celiac disease and biopsy-defined, but essentially asymptomatic and unrecognized celiac disease[30]. Finally, although lymphoma risk seems to have fallen in the past 4 decades, individuals with a sibling affected with celiac disease have an increased lymphoma risk[31]. These studies, then, have important implications for risk of familial forms of celiac disease in relatives, particularly first-degree, but also for a host of other genetically-related clinical disorders, even in the absence of celiac disease. In future, expression of different celiac disease phenotypes and their individual specific risks of different diseases may be more readily defined with precise genetic markers or more precise genetic signatures.

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