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REVIEW
ΑΝΑΣΚΟΠΗΣΗ

The celiac iceberg
What textbooks do not clarify (and beyond)

Celiac disease was formerly considered to be a relatively rare malabsorption syndrome of childhood, whereas now is recognized as being a very common lifelong disorder that can present at any age. Although diagnosis is becoming more and more frequent, celiac disease is missed in most affected people. This review reassesses critical clinical and diagnostic aspects of celiac disease and, in a comparison with the current knowledge provided by leading internal medicine textbooks, illuminates the background to the widespread underdiagnosis of the disease.

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Το «παγόβουνο» της κοιλιοκάκης: Τι δεν διασαφηνίζουν τα ιατρικά συγγράμματα

Περίληψη στο τέλος του άρθρου

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1. INTRODUCTION

Celiac disease (or gluten sensitive enteropathy) was formerly considered to be a relatively rare malabsorption syndrome of childhood, but it is now recognized to be a very common lifelong disorder that can occur at any age.[1,2] Even though diagnosis is becoming more and more frequent,[3] celiac disease is missed in most affected people.[4] Current evidence suggests that for every adult patient that is diagnosed with the disease, at least 4–6 cases remain undetected.[4–9] This review reassesses the critical clinical and diagnostic aspects of celiac disease. Comparing the evidence with the current knowledge provided by leading internal medicine textbooks, an attempt is made to explain a possible contribution to the widespread underdiagnosis of the disease.

2. WHAT IS CELIAC DISEASE AND WHAT IS ITS PATHOGENETIC BASIS?

Celiac disease is a unique chronic systemic autoimmune disorder. Its onset is associated with a known environmental trigger, namely the ingestion of gluten-containing grains (wheat, barley, and rye), in genetically susceptible individuals.[10,11] This interplay between gluten, genetic, immune and environmental factors sets in motion a series of immunological events that lead to mucosal damage, primarily in the proximal small intestine, characterized by villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis.[11,12]

2.1. From gluten to autoimmunity

The precise mechanism of the mucosal injury remains

unclear, but there is no doubt that the disease is closely linked to certain human leukocyte antigen (HLA) genes. Almost all patients with celiac disease have alleles that encode for HLA-DQ2, and the rest for HLA-DQ8; however only a minority of people expressing DQ2/DQ8 present the disease.[13] Consequently, the presence of DQ2/DQ8 is necessary, but not sufficient for the manifestation of the disease.[12,14,15] Nevertheless, screening should be offered to first degree relatives of patients with celiac disease, the majority of whom will carry the HLA-DQ2/DQ8 allele;[16] hence, there is a high prevalence of the disease among these family members.

What appears to be central to the disease process, is the presence of aberrant intestinal CD4+ T cell populations in the lamina propria, which are the orchestrators of the adaptive arm of immunity. These cells recognise gluten peptides bound to HLA-DQ2/-DQ8 class II molecules on antigen-presenting cells, and subsequently drive the inflammatory cascade through cytokine production.[12,13]

2.2. "Open sesame!": Breaching the epithelial barrier

Under physiological circumstances, this interplay is prevented by the competent intestinal epithelial barrier, which normally prevents the gluten peptides (as all macromolecules) from gaining access to the microenvironmental milieu of the subepithelial region of the small intestine, which is suited for disease development. The loss of the intestinal barrier function, a key element of the innate arm of immunity, is possibly secondary to the dysfunction of the intercellular tight junctions, early in the development of celiac disease.[4,17,18] This pathway, which leads to the aberrant increase in gut permeability, is induced at least in part by direct exposure to gluten peptides, while other environmental factors (such as intestinal infections) appear to be possible culprits.[12]

The changes induced by gluten peptides through the innate immune system are even more widespread; from the loss of the intestinal barrier and the damage of epithelial cells, to increased expression of IL-15,[19] and activation of intraepithelial lymphocytes, with the participation of T(H)17 subset of cells.[19,20] It is now well recognized that the immunology of celiac disease goes beyond the gut, making it a true systemic disease.[21]

3. WHEN SHOULD THE DOCTOR SUSPECT CELIAC DISEASE?

3.1. Clinical manifestations – What the textbooks say?

In many renowned textbooks (ranging from Davidson[22] and Kumar & Clark,[23] to Harisson[24] and Cecil[25]) it is stated that the symptoms of celiac disease range from significant malabsorption with diarrhea and weight loss, to iron deficiency, anemia, and metabolic bone disease, even in the absence of gastrointestinal symptoms. Although not wrong, this approach is misleading, as it creates the false impression to the clinician that many of the patients with celiac disease will present overt symptoms of malabsorption; or at least that it is equally possible to encounter a patient with celiac disease who presents a typical malabsorption syndrome, as iron deficiency anemia, and other extraintestinal manifestations. This impression is further exaggerated by the fact that in the majority of academic textbooks "celiac disease" is described in the "malabsorptive syndromes" section; thus the medical student and future primary care physician is biased from the very beginning.

3.2. The celiac iceberg

Because of improvements in diagnostic methods for identifying celiac disease, a paradigm shift has occurred in the conceptual understanding, not only at the level of the epidemiology of the disease, but also in terms of its presentation (tab. 1). Adults with celiac disease now rarely present with classical manifestations such as diarrhea, gross symptoms of malabsorption, including steatorrhea and abdominal complaints. Far more commonly, they present with atypical (i.e. non-gastrointestinal) manifestations;[26,27] most notably, iron-deficiency anemia and chronic fatigue are often the presenting complaints.[28,29] If gastrointestinal symptoms do occur, they are non-specific and variable, including discomfort, bloating and altered bowel habit.

Thus, the clinical spectrum of celiac disease is well illustrated by an iceberg (fig. 1). The tip of the iceberg that is obvious represents what is now broadly described as the typical or classic form of the disease (i.e. any gastrointestinal presentation). The remaining, much larger, submerged part of the iceberg accounts for the up to ten times more frequent atypical and silent forms of the disease. The vast majority of the patients who present in this way (i.e. with no gastrointestinal symptoms) usually remain undiagnosed and thus carry a risk of long-term complications.[30]

At a conceptual level, the iceberg paradigm illustrates the fact that, although the small intestine may be one of the main targets of the disease, increasing evidence suggests that celiac disease can affect other organs, which transforms the clinical scenario from what was once considered an exclusively gastrointestinal disorder to a

Table 1. The range of symptoms, signs and associated conditions in adults with celiac disease. Celiac disease can affect every organ system. The most common presentation in adults is non-gastrointestinal, with iron deficiency anemia and chronic fatigue being the cardinal manifestations.

Non-gastrointestinal
Iron deficiency anemia*
Chronic fatigue*
Arthralgia ± arthritis
Skin rash
Dermatitis herpetiformis
Osteoporosis
Infertility
Abnormal liver biochemistry
Association with other autoimmune disorders (e.g. type 1 diabetes mellitus and autoimmune thyroid and liver disease)
Various neurologic symptoms
Depression
Gastrointestinal
Diarrhea
Steatorrhea
Abdominal pain
Bloating
Weight loss
Nonspecific gastrointestinal complains (e.g. discomfort, altered bowel habit)
Irritable bowel
Recurrent aphthous ulcers

* Most common

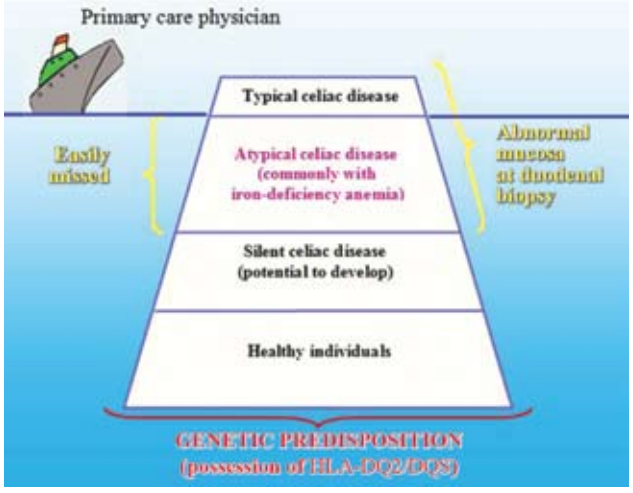

Figure 1. The adult celiac disease iceberg.

broader systemic disease.[31] Even the term "celiac disease" fails to illustrate this concept; the term "gluten sensitivity" may be more appropriate for reflecting the diverse extraintestinal gluten-dependent manifestations, which may be present even in patients with an apparently normal intestinal mucosa.[21,31]

3.3. Ironing out anemia in celiac disease and reducing the size of the submerged iceberg

Many of the patients with the hidden forms of celiac disease lying in the part of the iceberg below the waterline, may seek health care on numerous occasions, without celiac disease ever being considered.[32] In order to reduce the size of the submerged iceberg, it must be made clear that it is more probable to encounter celiac disease with non-intestinal manifestations. Furthermore, since iron deficiency anemia is the most common of these extraintestinal manifestations, the "common" patient with celiac disease would present with anemia and no other clinical clues of intestinal malabsorption.[33]

There is a clear tendency and higher predominance by twice or three times of women –most commonly in their 4th decade of life– than men who suffering from the disease.[12] To complicate things even more, in general, iron deficiency anemia, which prompts an investigation for celiac disease, is more often diagnosed in women than in men. Moreover, it must not be forgotten that iron deficiency anemia is considered a "red flag" symptom for the diagnosis of a malignancy.

If anemia is the common presenting feature of celiac disease, what is the chance of diagnosing celiac disease in patients presenting with iron deficiency anemia? Put differently, what is the prevalence of celiac disease in iron deficiency anemia? The results of studies focusing on this particular question revealed a 5–6% *de novo* diagnosis of celiac disease among patients presenting with symptoms of iron deficiency anemia.[34] The prevalence of celiac disease in asymptomatic iron deficiency anemia climbs to 10–15%.[35] The most characteristic feature of this form of celiac disease associated with iron deficiency anemia, is that it is completely refractory to oral iron treatment. As audits show that iron deficiency is underinvestigated, especially in premenopausal women, these reported percentages might be only a fraction of the actual prevalence of the disease.

Consequently, no degree of iron deficiency anemia should be ignored, and especially in the case of failure to respond to treatment, it should raise the suspicion of celiac disease.[33]

4. INVESTIGATIONS

4.1. What serological tests should be performed in the investigation of patients for celiac disease?

As stated in the textbooks of medicine,[22–25] the first line of investigation of a patient suspected of having celiac disease is measurement of serum IgA anti-endomysial, anti-gliadin or anti-tissue transglutaminase (tTG) antibodies. However, in clinical practice and especially in the primary care setting, tTG antibody testing is largely replacing the other tests. With a sensitivity of around 95%, a specificity reaching almost 100%, and being quicker to perform and less expensive, it is now the recommended single serologic test.[35–40] It is of interest that the tTG antibodies have not been linked to a pathogenetic mechanism, and at present it is not known whether they are primary or secondary to the tissue damage in celiac disease.

4.2. Biopsy and histological assessment remain the gold standard for diagnosis

While it has come to the forefront in recent years "celiac serology" alone is not adequate to establish the diagnosis of celiac disease. An endoscopic small bowel biopsy remains the gold standard, as it affords the most secure diagnostic information. Nevertheless, endoscopy is an invasive and costly procedure and in the face of the increasing sensitivity and specificity of antibody testing (tTG), the situation will probably be different in the future. Video Capsule Endoscopy is an emerging tool in the future armamentarium that is yet not mentioned in the internal medicine textbooks, but has proved to be valuable for the diagnosis of celiac disease.[41–45] It is not invasive, it images the entire small bowel length and is able to detect minute mucosal details.[45]

5. NO GRAIN, NO PAIN – THE MANAGEMENT PLAN

The lifelong elimination of wheat, rye and barley from the diet remains the cornerstone of treatment for celiac disease. However, a gluten-free diet can be a huge undertaking, especially for the newly diagnosed patient, although it will determine the overall status and significantly protect the individual from the long-term complications of the disease.

6. CONCLUSION

In conclusion, adult celiac disease is a common lifelong disorder, which has preserved the final riddle of its pathogenesis, presentation and true prevalence, puzzling us to this day, with many cases still remaining unrecognized. By far the most valuable diagnostic tools are a high index of suspicion, and a low threshold for serological testing. These, combined with the realization that the patients with celiac disease will probably present with extraintestinal manifestations, and most importantly with iron deficiency anemia, should lead to the significant change that is needed in clinical practice in order to reduce the size of the submerged iceberg of celiac disease in the community (tab. 2).

Table 2. In the diagnosis of celiac disease.

Key points
Celiac disease is a very common disorder that can occur at any age.
Celiac disease is a systemic autoimmune disorder that is precipitated by the ingestion of gluten-containing grains in genetically susceptible individuals.
The interaction between gluten and genetic, environmental and immune factors fuel the immune response which is mediated by both the innate and the adaptive arm of immunity.
In most affected people this condition is missed.
The most common adult mode of presentation is with no gastrointestinal symptoms and iron deficiency anemia is the commonest of these extraintestinal manifestations.
The first line of investigation is the measurement of serum tissue transglutaminase antibody.

ΠΕΡΙΛΗΨΗ

Το «παγόβουνο» της κοιλιοκάκης: Τι δεν διασαφηνίζουν τα ιατρικά συγγράμματα

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Η κοιλιοκάκη θεωρείτο ένα σχετικά σπάνιο σύνδρομο δυσαπορρόφησης που εκδηλωνόταν κυρίως στα παιδιά. Πρόσφατα, αναγνωρίστηκε ότι, ουσιαστικά, πρόκειται για μια χρόνια νόσο, η οποία μπορεί να εκδηλωθεί σε οποιαδήποτε ηλικία. Παρ' όλο που η συγκεκριμένη νόσος διαγιγνώσκεται όλο και πιο συχνά, εν τούτοις στους περισσότερους ασθενείς μπορεί να διαλάθει η διάγνωση. Στην παρούσα ανασκόπηση, συζητούνται και επαναπροσδιορίζονται σημαντικές πτυχές που αφορούν στην κλινική εικόνα και στη διάγνωση της κοιλιοκάκης. Επιπρόσθετα, οι πτυχές αυτές συγκρίνονται με την τρέχουσα γνώση που παρέχεται μέσω κορυφαίων συγγραμμάτων Παθολογίας, σε μια προσπάθεια να διαφωτιστεί η συνεισφορά τους στην υποδιάγνωση της νόσου.

Λέξεις ευρετηρίου: Γλουτένη, Ιστική τρανσγλουταμινάση, Κοιλιοκάκη, Φυσική ανοσία

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