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## Coeliac disease: changing diagnostic criteria?

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Coeliac disease (CD) is a chronic, multisystemic, autoimmune disorder, induced by gluten exposure, in genetically sensitive individuals (1-3). Its clinical presentation is extremely various, and changes considerably from full-blown malabsorption syndrome, seen in the classic childhood-onset disease, to subtle and atypical symptomatology, especially in the late-onset forms. The prevalence of CD varies widely in different parts of the world; however recent studies, employing new highly sensitive and specific serologic assays, have shown it to be a fairly common disease worldwide, about 1% in general population. This variability is most probably due to the differences in the diagnostic protocols used, the level of public health awareness, the nutrition habits (large use of gluten free cereals – i.e. rice, corn) and also, partially, to the true differences in the incidence of the disease (4). Until now, despite this clinical variability and the discover of new diagnostic tools, small bowel mucosal biopsy has remained the gold standard for CD diagnosis. Anyway recently the histological dogma is under criticism and new rules have been proposed. According to this changing of believe, European Society for Pediatric Gastroenterology,

Hepatology, and Nutrition (ESPGHAN) and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) released updated guidelines about the definition and diagnosis of CD in infancy (5-6). The wider definition of CD includes a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies (anti tissue transglutaminase – tTGA-, anti endomysial –EmA- and gliadin deamidated antibodies –DGP-AGA-), genetic markers (HLA-DQ2 and DQ8 haplotypes), and different grades of enteropathy. In these new criteria the importance of biopsy for CD diagnosis is decreased by including among CD patients symptomatic individuals who have positive serological and genetic tests, but normal intestinal mucosa; indeed it is well known that clinical and serological features of CD can precede histological changes by up to 2 years (7,8,9,10). The new concept of CD represents a radical change in thinking and it is still object of debate. The controversial issue of CD diagnostic criteria has become more intense after the discovery of a new gluten-related disorder, known as “gluten sensitivity” or “non-celiac gluten intolerance” (GS), characterized by a clinical picture similar to that of CD, frequent positivity for anti gliadin antibodies (AGA) (but absence of EmA, tTGA and DGP-AGA) and normal histology or microscopic enteritis (Marsh 0-II) (11,12,13). The uncontested power of intestinal biopsy as a gold standard for CD diagnosis has been recently

*Received:* 20 April 2012 *Accepted:* 4 May 2012

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reduced by the new ESPGHAN's criteria for CD diagnosis stating that intestinal biopsy can be omitted in symptomatic patients with high tTGA levels (>10 times above the upper normal limit), provided that they are also both EmA positive and HLA-DQ2 and/or -DQ8 positive.

It is also important to underline that intestinal biopsy by itself is not always diagnostic and may present many pitfalls. The number, size and site of the biopsy samples, and their orientation are all important factors that may confound the diagnosis of the disease (14). The mucosal histopathologic features are very variable, ranging from mild abnormalities, including intraepithelial lymphocytosis with intact villi, to completely flat mucosa, which nowadays represents only the tip of the iceberg (1, 15-20). In the majority of cases, the biopsy is not specific and we think that the pathologist is only a member of the multidisciplinary team involved in reaching CD diagnosis. In addition to this, we would like to underline that the "old CD" with flat mucosa is only a part of the spectrum of gluten related disorders; as a matter of fact the clinical profile of cases detected, because of positive serological tests, seems to be quite different compared to historical cases detected, based on severe malabsorption and histopathology only (total villous atrophy) (1).

The article by Rostami et al (21), published in this issue of the Journal, confirms that the relevance of duodenal biopsy for CD diagnosis is going down. The Authors aimed to assess the clinical picture of CD patients as well as the relationship between symptoms and the severity of intestinal mucosal lesions. Their study involved more than 100 cases of children with malabsorption and gastrointestinal symptoms. After the exclusion of other malabsorption causes subjects, included in the present study, were screened for EmA and an intestinal biopsy was performed. The first consideration which comes out from this study is that gastrointestinal and

extraintestinal symptomatology is surprisingly more prevalent in patients without villous atrophy (Marsh I) compared to those with atrophy (Marsh III). This finding may suggest that histology doesn't reflect the severity of disease and the degree of damage in intestinal mucosa might not be a reliable prognostic factor. In addition, symptomatology in CD does not seem to be related to the length of affected bowel, according to what observed by other authors (22, 23). The lack of relationship between pathology and symptoms might be explained by hypothesizing that malabsorption in CD is secondary to inflammation and cytokine stimulation. The sensitized mucosal lymphocytes or something else that correlates closely with that state of sensitivity might be the key factors, not only in pathogenesis, but also in the genesis of the symptoms. This theory would perhaps explain why Marsh 0-II patients with non-coeliac gluten sensitivity (GS) may behave like full blown CD (23), but further studies are necessary to verify this hypothesis. People with specific positive serology (EmA, tTGA, DGP-AGA) and microscopic enteritis (Marsh 0-II) should be evaluated with genetic testing for HLA-DQ2/-DQ8, whose positivity is the pre-requisite for confirming the diagnosis of potential CD. Potential CD patients should be put on a gluten free diet (GFD) when symptomatic, whereas they should be left on a gluten containing diet in absence of symptoms (10). This strategy is suggested by the demonstration of serology fluctuation or disappearance in patients on a gluten containing diet (24, 25).

Histology, nowadays, seems to be less important than in the past and this has been confirmed by other authors. Recently, Catassi and Fasano proposed five criteria for CD diagnosis: 1) symptoms suggestive for CD; 2) positivity of serum CD IgA class autoantibodies; 3) HLA DQ2 or DQ8 genotypes, 4) celiac enteropathy at the small intestinal biopsy, 5) response to the GFD. The diagnosis of CD is confirmed if at least 4 of

these 5 criteria are satisfied, so histology is only a part of the diagnostic puzzle and it can be quite normal if the other four elements are present (26). These simplified rules may be useful in clinical practice due to the wide variability of CD that can disorient gastroenterologists, above all in some borderline situations, such as the cited above potential CD or in seronegative CD characterized by clinical, genetic and histological signs of CD in patients lacking serum tTGA and EmA (27). Moreover, diagnosis may be difficult in CD patients with low levels of serum autoantibodies associated to a mild enteropathy at the intestinal biopsy (Marsh 0-II) and also in GS patients where are present changes to the epithelial barrier of the small intestine mucosa associated to microscopic enteritis (Marsh 0-II) (12). In these cases the detection of sub-epithelial IgA tTGA deposits can be determinant in the differential diagnosis between CD and GS (28, 29).

In conclusion, it is time to change the historical dogma that defines histology as the gold standard for the detection of CD. In light of the current knowledge and emerging complex clinical problems it is more and more evident that the true gold standard for the final diagnosis of CD is the decision made by the clinician. The role of the pathologist remains important in the diagnostic flow-chart since an accurate assessment of the morphology of the duodenal mucosa, while avoiding any clinical conclusion (which are often misleading), remains crucial for the final diagnosis of CD. A multidisciplinary team guided from the clinician, including immunologists, genetists, and pathologists, can pave the way for improving the quality of CD diagnosis by compiling all the pieces needed to solve the CD puzzle.

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