Chapter 16

Celiac Disease and Gastrointestinal Functional Disorders

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Abstract

Celiac disease (CD) is one of the most frequent genetic disorders diagnosed in the adult population and it may present a wide spectrum of gastrointestinal symptoms, which bear a large degree of overlap with functional dyspepsia, irritable bowel syndrome (IBS) or functional diarrhea. It has been demonstrated that CD, as diagnosed by positive serology and villous atrophy, is more frequent in patients with functional dyspepsia (1.2-6.2%) and IBS (4.7-11.4%) than in the general population. This prevalence may be higher if we consider the whole spectrum of gluten-dependent mucosal histopathological lesions, including lymphocytic enteropathy. Consequently, patients with these gastrointestinal symptoms might be misdiagnosed with a functional bowel disorder if the diagnostic approach does not include CD-specific antibody tests and duodenal biopsies. This fact might bring, as a result, a delay in CD diagnosis and treatment, with important consequences in terms of morbidity and quality of life. Non-celiac gluten sensitivity is a clinical condition characterized by symptoms that improve after gluten withdrawal, negative celiac serology and absence of enteropathy, which may be involved as a trigger in some functional bowel disorders such as IBS.

1. Introduction

The European Society of Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) recently defined celiac disease (CD) as a systemic immune-mediated disease caused by gluten in genetically predisposed individuals, characterized by the presence of a variable combination of gluten-dependent clinical manifestations, specific antibodies, HLA-DQ2 or DQ8 haplotypes and enteropathy.[1] Classically, the CD diagnosis needed the presence of villous atrophy in duodenal biopsies, however, recent evidence shows that patients with mild forms of enteropathy (Marsh I or II lesion) may present gastrointestinal and extraintestinal symptoms with the same frequency as patients with atrophy.[2-4] The diagnosis of CD in these patients, who often have a negative serology, is not easy and requires the presence of an HLA-DQ2 or DQ8-compatible haplotype as well as the demonstrating that its symptoms and enteropathy are gluten-dependent.[5,6]

The clinical expression of CD is quite variable, ranging from very serious forms with diarrhea and dehydration to oligosymptomatic or asymptomatic forms (silent CD). In adults, its most frequent presentation is oligosymptomatic with digestive and/or extradigestive symptoms.[7] Some of the gastrointestinal symptoms, such as dyspepsia, recurrent abdominal pain or diarrhea, are very prevalent in gastroenterological practice and may be erroneously attributed to a functional gastrointestinal disorder if the diagnostic study is not completed with CD-specific antibody tests and duodenal biopsies. Since the sensitivity of serology is less than 30% in mild enteropathy, it is recommended to carry out a fuller diagnostic study with duodenal biopsies in those cases where there is a high index of clinical suspicion.[8] The use of additional immunohistochemical staining with monoclonal antibodies for CD3 lymphocytes facilitates visualization of intraepithelial lymphocytes (IELs) and thus the diagnosis of mild enteropathy forms.[9]

Functional dyspepsia, irritable bowel syndrome or functional diarrhea are some of the functional gastrointestinal disorders, which have been associated with celiac disease or non-celiac gluten sensitivity, a clinical entity of recent appearance.

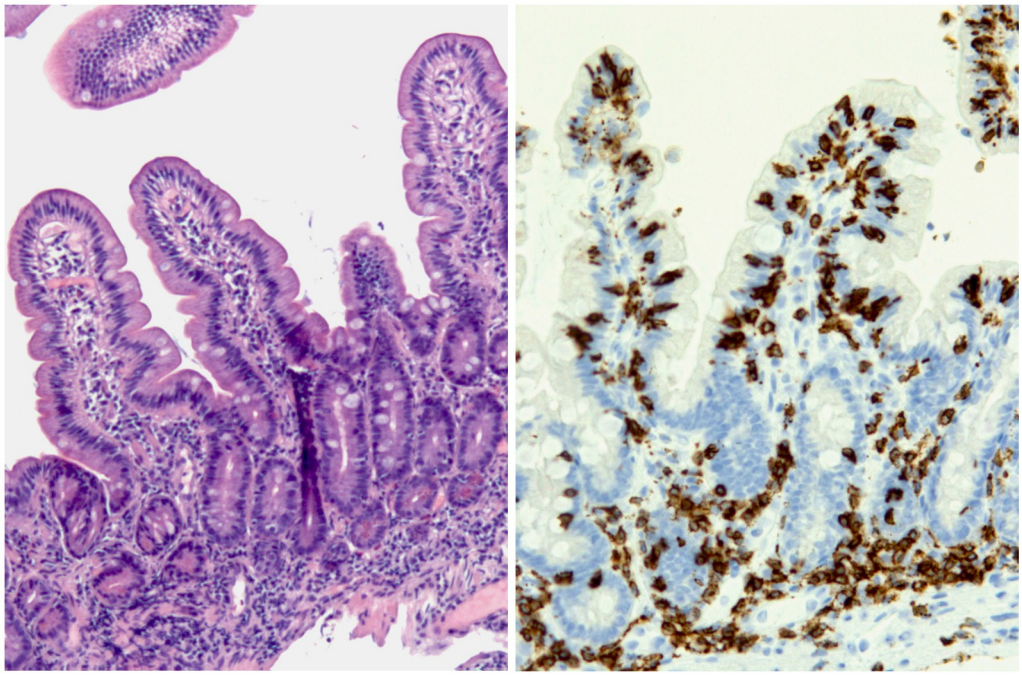

Figure 1. Immunohistochemistry with monoclonal antibodies for CD3 lymphocytes facilitates visualization of intraepithelial lymphocytes and the diagnosis of mild forms of enteropathy. Left: apparently normal villi after hematoxylin-eosin staining. Right: significant increase in intraepithelial lymphocytes after performing CD3 (+) lymphocyte immunostaining (Courtesy Dr. Vera, Department of Pathology, Hospital San Jorge, Huesca).

2. Functional Dyspepsia

Functional dyspepsia, according to the Rome III criteria, is characterized by the presence, for at least three months, of one or more of the following symptoms:

1) postprandial fullness,

2) early satiety,

3) epigastric pain,

4) epigastric burning and the absence of structural alterations in upper endoscopy that could explain these symptoms.

It could be concluded, therefore, that functional dyspepsia is a diagnosis of exclusion which is established when, in a patient with symptoms attributable to the gastroduodenal tract, there is evidence of neither structural damage (negative endoscopy) nor of biochemical damage which can explain the symptoms. This is a highly prevalent entity, which, although not serious, causes a significant impact on the quality of life of patients.[10]

Dyspepsia is also a common symptom in CD patients; it may be present in 40-60% of the cases at the time of diagnosis. Ciacci et al.,[11] in a retrospective study that analyzed 195 adult CD patients, observed how many patients presented, at the time of diagnosis, nonspecific gastrointestinal symptoms such as dyspepsia (40%), abdominal pain (35%) and meteorism (31%). Zipser et al.[12] evaluated, by means of a questionnaire, the presentation symptoms in patients diagnosed with CD between 1993 and 2001, describing how 77% of them had abdominal discomfort, 73% flatulence, and 46% nausea and/or vomiting. Esteve et al.,[2] in a study conducted in Spain in 221 first-degree relatives of 82 CD patients, observed how those relatives with enteropathy more often presented symptoms like abdominal pain (39.1% vs 23.5%), abdominal distension (52.2% vs 21.8%) and flatulence (65% vs 39%).

Several trials have evaluated the prevalence of CD in patients with dyspepsia. Although these studies are very heterogeneous in methodology and definition of dyspepsia, they show a prevalence generally superior to that of the general population, with figures ranging between 1.2% and 6.2%.[13] A meta-analysis and systematic review of these studies also shows a higher frequency of positive celiac serology (7.9% vs 3.9%) as well as of CD diagnosed by duodenal biopsy (3.2% vs 1.3%) in dyspepsia patients compared to the control population, although these differences were not statistically significant.[14]

Year	Author	Country	Study type	Patients	Diagnosis dyspepsia	Diagnosis CD	CD (%)
1999	Dickey[15]	Ireland	Case series	119	Medical criterion	Biopsy	7 (5.8)
2000	Bardella[16]	Italy	Case series	517	Medical criterion	Biopsy	6 (1.2)
2003	Vivas[17]	Spain	Cases and controls	92	Rome II	Serology + biopsy	3 (3.3)
2004	Locke[18]	USA	Population study	34	Questionnaire	Serology	2 (5.9)
2004	Cammarota[19]	Italy	Case series	396	Medical criterion	Biopsy	7 (1.7)
2005	Lima[20]	Brazil	Case series	142	Medical criterion	Biopsy	4 (1.4)
2006	Lecleire[21]	France	Cases and controls	75	Rome II	Biopsy	1 (1.3)
2007	Ozaslan[22]	Turkey	Case series	196	Rome II	Serology + biopsy	3 (1.5)
2007	Hadithi[23]	Netherlands	Case series	167	Medical criterion	Biopsy	3 (1.6)
2008	Giangreco[24]	Italy	Case series	726	Rome II	Biopsy	15 (2)
2009	Rostami-Nejad[25]	Iran	Case series	415	Medical criterion	Biopsy	28 (6.2)

Table 1. Celiac Disease prevalence studies in patients with dyspepsia.

Previous studies assess the prevalence of CD, based on positive celiac serology and the presence of villous atrophy in patients with dyspepsia. If we consider the whole spectrum of histological CD lesions, including forms of mild enteropathy, this prevalence could be even higher. A retrospective study in Spain which investigated 142 patients with dysmotility-like dyspepsia (postprandial distress) and negative duodenal endoscopy, found different histological lesion degrees in 35% of the cases. Those patients with positive tissue transglutaminase antibodies (t-TGA) (6.7%) or else HLA DQ2 and/or DQ8 haplotypes (84.1%) were invited to undergo a gluten-free diet (GFD) for a period of not less than 1 year. This strategy resulted in relief or disappearance of dyspeptic symptoms in 91.9% and in histological damage regression or

improvement by 81%, establishing a final CD diagnosis in 28 of them (19.7%). It must be pointed out that the duodenal histopathological study included immunohistochemistry with CD3 lymphocyte monoclonal antibodies.[26]

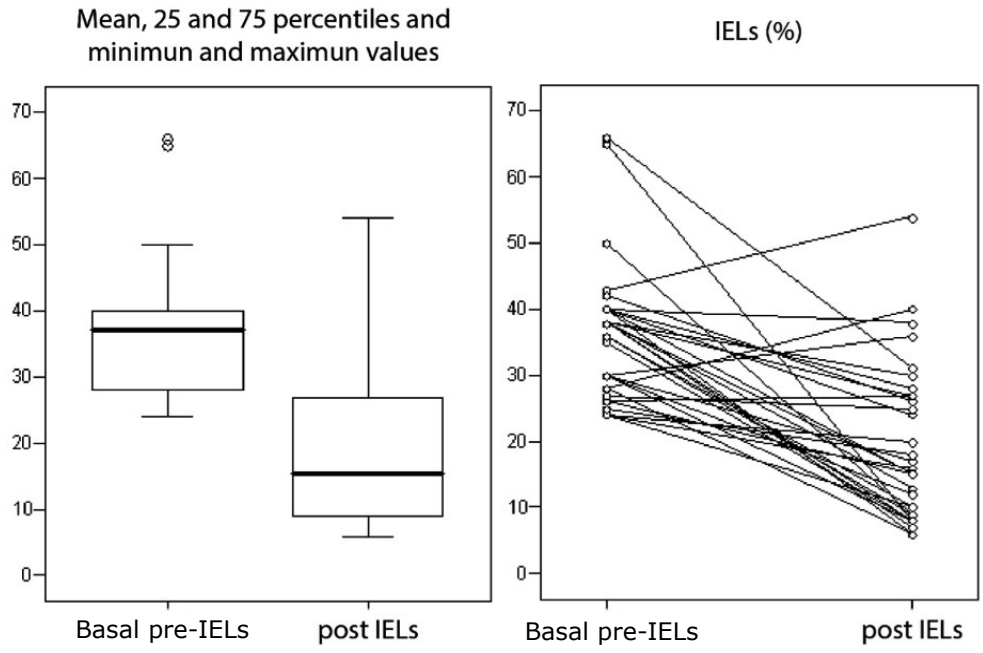

Figure 2. Intraepithelial lymphocytes (IELs) before and after starting a gluten-free diet in 32 patients with dysmotility-type dyspepsia with enteropathy in duodenal biopsies, which also had a positive serological result (t-TGA) and/or a compatible HLA-DQ2 or DQ8 genetic study.[26]

Therefore, CD can be a frequent, often unsuspected, cause of dyspepsia which could be erroneously misdiagnosed as functional dyspepsia if the diagnostic work is not completed with duodenal biopsies. The cost-effectiveness of duodenal biopsies requires well-designed studies for the purpose of excluding the presence of intestinal histological lesions that can explain the nature of the symptoms before making a functional dyspepsia diagnosis. Meanwhile, it seems reasonable to indicate duodenal biopsies in the presence of a reasonable clinical scenario and/or indicative of CD. This recommendation acquires more consistency when the patient has an HLA DQ2- or DQ8- compatible haplotype. A general analysis, including t-TGA determination, should be included as well in the initial assessment of patients with dyspepsia.[13]

3. Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by the presence of abdominal pain or discomfort associated with changes in the frequency of and/or stool consistency. Following the Rome III recommendations, IBS is divided according to IBS stool consistency, constipation-predominant (IBS-C), diarrhea-predominant IBS (IBS-D), IBS with an alternating pattern or IBS with an undefined pattern. It is a common disorder, with a prevalence of 5-15% and, although it is not serious, it can significantly reduce the quality of life of patients. Currently the mechanisms by which IBS occurs are unknown, although it has been associated with digestive function abnormalities, especially in motility and sensitivity and there is increasing evidence supporting the existence of microinflamatory phenomena and changes in intestinal immune function.[27]

CD can frequently present with symptoms that are also characteristic of IBS, including abdominal pain (77%), bloating (73%), diarrhea (52%), constipation (7%) and an alternating bowel habit pattern (24%).[12] This means that IBS is often the initial diagnosis in many patients before the discovery of CD many years later. Other features common to both diseases include female predominance, the fact that symptoms may be precipitated by a stressful life event and the frequent concomitance of dysthymia, depression, chronic fatigue, fibromyalgia and other manifestations characteristic of functional gastrointestinal disorders, such as pyrosis and dyspepsia. Several case-control studies have evaluated the prevalence of positive celiac serology as well as CD diagnosis based on the presence of villous atrophy, in patients with IBS, demonstrating a higher prevalence (4.7-11.4%) in relation to the control population.[18,28,29]

Author	Dx	N	Serology	Biopsy	p
Sanders[28] (2001)	AGA + EMA Biopsy	Cases: 300 Controls: 300	66/300 (22%) (11 EMA+) 44/300 (15%) (2 EMA+)	14/300 (4.7%) 2/300 (0.7%)	=0.004 OR, 7 (1.7-28)
Shahbazkhain[29] (2003)	EMA Biopsy	Cases: 105 Controls:105	12/105 (11.4%) 0/105	12/105 (11.4%) 0/105 (0%)	=0.0003 OR, infinite
Locke[18] (2004)	t-TGA	Cases: 50 Controls: 78	2/50 (4%) 2/78 (2.6%)	-	NS

Table 2. Case-control studies which have evaluated the risk of celiac disease in IBS patients (AGA: antigliadin antibodies; EMA: endomysial antibodies; t-TGA: tissue transglutaminase antibodies; OR: odds ratio).

A recent systematic review and meta-analysis including 2278 patients with IBS diagnostic criteria showed they had a higher prevalence of IgA anti-gliadin antibodies (AGA) (4%; CI 95% 1.7-7.2), endomysial antibodies (EMA) or t-TGA (1.6%, CI 95% 0.7-3) as well as CD demonstrated by duodenal biopsy (4.1%, CI 95% 1.9-7). The risk of positive AGA results (OR 3.4, CI 95% 1.6-7.1), EMA or t-TGA (OR 2.9, CI 95% 1.3-6.3) and CD demonstrated by duodenal biopsy (OR 4.3, CI 95% 1.8-10.6) was also higher in IBS patients when compared to the control population.[30] However, a recent prospective study undertaken in the United States found no difference in CD prevalence

as demonstrated through duodenal biopsy in 492 IBS-D patients (0.4%) and 458 asymptomatic controls (0.4%). Although statistically not significant, patients with IBS-D tested positive for celiac serology (AGA, t-TGA or EMA) in 7.3% of cases versus 4.8% in the control group.[31]

All these studies refer to patients with positive celiac serology or CD results based on the existence of villous atrophy. If we consider the whole spectrum of histological CD lesions and include all patients who have some degree of enteropathy, regardless of serological outcome, along with an HLA-DQ2 or DQ8 genetic study and gluten-dependence criteria, the prevalence of CD in IBS patients could be higher. In this sense, there is a study which evaluated the whole CD lesion spectrum in 102 patients with IBS-diarrhea and negative celiac serology (t-TGA), which showed how as much as 23% of them exhibited some degree of enteropathy and, the presence of t-TGA in the duodenal aspirate in 30%. For 26 enteropathy patients with t-TGA in the duodenal aspirate and HLA-DQ2 (+), GFD was recommended, with improvement in diarrhea and intestinal serology in all of them.[32]

Currently, the American College of Gastroenterology recommends screening for CD in patients with IBS-D and alternating pattern IBS by determining serum t-TGA. This recommendation is based on studies in which the CD diagnosis was based on finding positive celiac serology (t-TGA and EMA) and on the presence of villous atrophy in duodenal biopsies.[33] However, as previously described, patients with mild forms of enteropathy (Marsh I or II lesion) may show gastrointestinal symptoms characteristic of IBS with a frequency similar to that of patients with villous atrophy, but often, unlike the latter, the result of celiac serology is frequently negative. For this reason, duodenal biopsies in IBS patients with negative celiac serology should still be considered when there is a clinical scenario suggestive of CD, such as those patients with a family history of CD, autoimmune diseases or a previous history of growth retardation, infertility, and osteoporosis or iron deficiency anemia of unknown origin. In these cases, the HLA-DQ2 or DQ8 haplotype determination can help to reach a decision regarding the need to complete the study with duodenal biopsies.[34]

4. Functional Diarrhea

A functional diarrhea diagnosis is established in those cases in which diarrhea, often watery, is not accompanied by alarming symptoms/signs, no abnormalities in routine blood and stool tests and normal sigmoidoscopy. However, there may be different entities, such as bile acid malabsorption, disaccharide (lactose, fructose or sorbitol) malabsorption or CD, which may equally manifest an apparently functional watery diarrhea.[35]

A Spanish study prospectively evaluated the presence of CD, bile acid malabsorption and disaccharide malabsorption in 62 consecutive patients with chronic watery diarrhea and Rome II criteria for functional diarrhea or IBS-diarrhea diagnosis. The diagnostic study included the sequential performance of:

1) genetic HLA-DQ2-DQ8 study;

2) Duodenal biopsies in patients with positive HLA-DQ2 or DQ8;

3) SeHCAT test (selenium 75-tagged tauroselcholic acid scintigraphy),

4) Hydrogen breath test (lactose and fructose-sorbitol),

when all previous tests were normal or when the patient related a possible clinical sugar intolerance. According to these diagnostic test results, the patients were treated with either a gluten-free diet, the removal of dietary sugars or else with cholestyramine. With this diagnostic strategy 28 (45.2%) patients were diagnosed with bile acid malabsorption, 10 (16.1%) with CD, 10 (16.1%) with disaccharide malabsorption, 2 (3.2%) with bile acid and disaccharide malabsorption and only 12 (19.4%) patients were diagnosed with functional diarrhea. All patients diagnosed with CD had mild enteropathy and negative celiac serology (t-TGA and EMA).

It must be pointed out that the duodenal histopathological study included immunohistochemistry with CD3 lymphocyte monoclonal antibodies and CD diagnosis was based on clinical and histological response after the GFD.[36]

5. Non-Celiac Gluten Sensitivity

In recent years, the concept of non-celiac sensitivity to gluten (NCGS) has been introduced to refer to those patients with gluten-dependent symptoms but who do not have in serum positivity for t-TGA or EMA, with absence of enteropathy in duodenal biopsies. It has been hypothesized that unlike patients with CD, in which an adaptive immune response with antibody production is triggered, in NCGS there is only an innate response to gliadin which determines the appearance of microinflamatory changes in the intestinal mucosa reflected in increased IEL expression and the release of cytokines and other inflammation mediators.[37,38]

	Celiac disease	**Non-celiac gluten sensitivity**
Prevalence	Around 1%	Suspected to be around 5-6%
Pathogenesis	Adaptive immune response to gluten peptides	An innate immune response to gluten has been implied
HLA-DQ2 and/or DQ8	Present and necessary	Not necessary
Serology	T-TGA and EMA (+)	t-TGA and EMA (-). Sometimes AGA (+)
Villous atrophy	Present	Absent

Table 3. Differences between celiac disease and non-celiac gluten sensitivity (AGA: antigliadin, EMA: endomysial antibodies; t-TGA: tissue transglutaminase antibodies). Adapted from Di Sabatino.[39]

NCGS can cause gastrointestinal symptoms such as diarrhea, recurrent abdominal pain and flatulence, as well as non-gastrointestinal symptoms such as ataxia, headache, attention deficit, hyperactivity or asthenia and has been implicated as a possible cause of some functional gastrointestinal disorders. Two studies have evaluated the prevalence of NCGS in IBS patients using a double-blind methodology by comparing gluten with placebo. Biesiekierski et al.[40] evaluated a total of 34 patients with IBS in whom a CD diagnosis had been excluded and had improved clinically after performing a GFD. The patients were randomized regarding gluten (16 g/day) or placebo intake for 6 weeks. Thirteen (68%) of the 19 patients who received gluten

showed poor control of digestive symptoms, compared with only 6 (40%) of 15 patients receiving placebo (p=0.0001). In a visual analog scale, patients receiving gluten presented, since the first week, worse scores in terms of overall symptoms, abdominal pain, flatulence and satisfaction with stool consistency and asthenia. No differences between the two groups were observed regarding the determination of fecal lactoferrin, serum t-TGA and AGA, high-sensitivity CRP or intestinal permeability determined by a dual lactulose-rhamnose test. Carroccio et al.[41] retrospectively evaluated 276 patients with IBS, out of a total of 920, according to the Rome II criteria, who had previously responded clinically to the withdrawal and subsequent dietary wheat overload with a double-blind placebo-controlled methodology. These patients were further classified into 2 groups: isolated wheat sensitivity (group 1, 70 patients) and wheat sensitivity associated with multiple food hypersensitivity (group 2, 206 patients). This classification was performed following a withdrawal and overload of cow's milk proteins, eggs, tomatoes and chocolate with a methodology similar to that employed with wheat. Patients in group 1 had anemia more frequently (70%), a family history of CD (14%), HLA-DQ2 or DQ8 haplotype (75%) and the presence of EMA in cultured duodenal mucosa (30%), while group 2 patients presented a more frequent coexistence of atopy (35%), IgG anti-betalactoglobin antibodies (39%), basophil activation determined by flow cytometry (80%) as well as increased eosinophils in the duodenum and colon. In relation to a control group of patients with IBS without wheat sensitivity criteria, patients in both groups had a higher frequency of anemia (24%), weight loss (35%), atopy coexistence (29%), a childhood history of food allergy (18%) as well as lymphocytic enteropathy in the duodenal mucosa (present in 96% of group 1 patients and 90% in group 2). These results, according to the authors, confirm the existence of a non-celiac wheat sensitivity and suggest that, within the same, there could be two different groups: one with features similar to CD (group 1) and one with features closer to food allergy (group 2).

These studies demonstrate the existing relationship between gluten and the occurrence of gastrointestinal symptoms in patients with a previous functional gastrointestinal disorder diagnosis such as IBS, but they also highlight the heterogeneity of NCGS. The lack of well-defined diagnostic criteria and the absence of characteristic biological and morphological parameters may turn NCGS into a "hodgepodge" in which to include all those patients with functional gastrointestinal symptoms that respond clinically to a GFD and present neither villous atrophy nor positive celiac serology.[42] It will be necessary to conduct further prospective and controlled studies to evaluate the evolution of patients with mild enteropathy, an HLA-DQ2 and/or DQ8 genetic study, but negative t-TGA to determine if these patients actually a constitute separate clinical entity or if they are part of the evolutionary spectrum of CD. The determination of subepithelial IgA deposits against tissue transglutaminase by immunofluorescence or performing an intraepithelial lymphocytes subsets characterization (IEL lymphogram) by flow cytometry could help diagnose patients who are part of the CD spectrum, but these techniques have a certain level of complexity and they are not straightforward to use routine clinical practice.[43,44]

6. Gluten and Gastrointestinal Motility Disorders

It has been shown that patients with CD may have motility disorders along their entire digestive tract, such as a decrease in lower esophageal sphincter pressure, slow small intestinal transit, delayed gallbladder emptying and accelerated colonic transit. Moreover, all these alterations tend to normalize months after starting a GFD.[45]

Motility disorders of the upper gastrointestinal tract may explain the appearance of symptoms such as postprandial fullness, bloating, flatulence, nausea, vomiting, regurgitation and pyrosis. Rocco et al.[46] evaluated gastric emptying by ultrasonography and an octanoic hydrogen test in 20 CD patients and 10 controls. They observed that CD patients showed delayed gastric emptying (252 ± 101 minutes) compared with control patients (89 ± 16 minutes) and that it became normal one year after starting a GFD (97 ± 14 minutes). Bassoti et al.[47] studied antroduodenojejunal motility using manometry in 11 patients with untreated CD, 12 CD patients treated with GFD for at least one year and 33 control patients. They found that CD patients showed interdigestive (fasting) and postprandial motility disorders relative to control patients. In the fasting period a decrease in the interdigestive migrating motor complex frequency was observed, with phase I and phase II shortening, and a lower phase III propagation velocity. These changes improved once the GFD was begun although they failed to disappear completely, a fact, which the authors attributed to the persistence of mild enteropathy signs in some patients.

The pathophysiology of these motor alterations in CD is not well known and it has been explained by the existence of complex interactions between the malabsorption of certain nutrients, the existence of an autonomic nervous system dysfunction and, finally, changes in the secretion of certain gastrointestinal hormones.[45] The presence of unabsorbed fats in the small intestine may favor a delay in gastric emptying and slowing of orocecal transit time. On the other hand, the immune response generated by gluten in the intestinal mucosa, along with the increase of inflammatory cells in the lamina propria and the secretion of various cytokines and inflammatory mediators could affect the nerve cells of the intestinal nerve plexus and cause an extrinsic autonomic neuropathy with subsequent gastrointestinal dysmotility.[48] Finally, alterations have been described in the gastrointestinal secretion of certain hormones, which (among other functions) may alter gastrointestinal motility. Several studies have demonstrated the existence of a decrease in postprandial cholecystokinin secretion and an increase in plasma levels of neurotensin, peptide YY and somatostatin.[49-51] As is the case with gastrointestinal motility changes, the secretion of these gastrointestinal peptides tend towards normalization once a GFD is initiated.[45]

On the other hand, it has been shown that gluten, especially gliadin, may have a direct toxic effect on the intestinal mucosa which is not mediated by an adaptive immune response and which, therefore, does not require the HLA-DQ2 and DQ8 heterodimers. This direct action of gluten on intestinal epithelium, along with the activation of an innate immune response, has been implicated in the production of gastrointestinal and extraintestinal symptoms in patients diagnosed with NCGS.[37] The pathogenic mechanisms involved in the direct response to gliadin include increased intestinal permeability secondary to zonulin release, apoptosis induction, increased oxidative stress and cholinergic nervous system stimulation by opioid receptor activation.[37,52] The activation of an innate immune response with IL-15 release and IEL stimulation can also lead to a microinflamatory response and involvement of the nerve cells of the enteric nerve plexus, resulting in gastrointestinal dysmotility.[53] Finally, fructans present in

cereals and fermentation of gluten peptides by sulfate-reducing bacteria increase the production of ammonia and hydrogen sulfide, gases which can also cause gastrointestinal and non-gastrointestinal symptoms such as asthenia.[54]

7. Summary and Conclusions

CD is one of the most frequent genetic disorders diagnoses in population, which is increasingly being diagnosed with more frequency in adults. Its clinical presentation often being including gastrointestinal symptoms that may overlap with those described in functional dyspepsia, IBS or functional diarrhea.

A higher frequency of CD, based on positive serology results and villous atrophy, has been shown in patients with functional dyspepsia and IBS compared to the general population. If we consider the whole spectrum of histological CD lesions, including milder forms such as lymphocytic enteropathy, this frequency could be even greater.

The diagnosis of mild enteropathy form is not easy since often the result of celiac serology is negative. In these cases it is necessary to demonstrate the presence of an HLA-DQ2 or DQ8 compatible haplotype and confirm that the symptoms and enteropathy are gluten-dependent. The determination of subepithelial IgA deposits against tissular transglutaminase or the performance of an IEL lymphogram could help diagnose patients who are part of the CD spectrum but these techniques are not straightforward to use in routine clinical practice.

Patients with gluten-dependent digestive symptoms, negative celiac serology and absent or mild enteropathy have been included in a new clinical entity called non-celiac gluten sensitivity. At present, there are no well-defined diagnostic criteria for this condition and some of these patients could be part of the evolutionary spectrum of CD.

The existence of alterations in motility in the upper gastrointestinal tract, such as delayed gastric emptying or abnormal motor activity, could explain the appearance of symptoms such as postprandial fullness, bloating, flatulence, nausea, vomiting, regurgitation and pyrosis. Characteristic IBS symptoms in CD patients may be caused by effects on the digestive function derived from direct toxic gluten effect on the intestinal epithelium and the activation of an innate immune response.

CD could be a frequent, often unsuspected, cause of very prevalent symptoms, such as dyspepsia, IBS or seemingly "functional" diarrhea. Patients with these symptoms may be erroneously diagnosed with functional gastrointestinal disorder study if the diagnostic study is not completed with CD-specific antibody tests and the performance of duodenal biopsies. This fact might bring, as a result, a delay in CD diagnosis and treatment, with important consequences in terms of morbidity and of the patient’s quality of life.

It will be necessary to conduct well-designed prospective studies evaluating the cost-effectiveness relationship of duodenal biopsies in patients with dyspepsia, IBS and functional diarrhea. Meanwhile it seems reasonable to include a t-TGA determination in these patients’ initial assessment and to indicate duodenal biopsy when there is a clinical scenario suggestive of CD (including HLA-DQ2 and DQ8 genetic testing).

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