

REVIEW

Celiac disease: diagnostic criteria in progress

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Until a few years ago, celiac disease (CD) was thought to be a rare food intolerance that was confined to childhood and characterized by severe malabsorption and flat intestinal mucosa. Currently, CD is regarded as an autoimmune disorder that is common in the general population (affecting 1 in 100 individuals), with possible onset at any age and with many possible presentations. The identification of CD is challenging because it can begin not only with diarrhea and weight loss but also with atypical gastrointestinal (constipation and recurrent abdominal pain) and extra-intestinal symptoms (anemia, raised transaminases, osteoporosis, recurrent miscarriages, aphthous stomatitis and associated autoimmune disorders), or it could be completely symptomless. Over the last 20 years, the diagnostic accuracy of serology for CD has progressively increased with the development of highly reliable tests, such as the detection of IgA tissue transglutaminase and antiendomysial and IgG anti-deamidated gliadin peptide antibodies. The routine use of antibody markers has allowed researchers to discover a very high number of 'borderline' cases, characterized by positive serology and mild intestinal lesions or normal small intestine architecture, which can be classified as potential CD. Therefore, it is evident that the 'old celiac disease' with flat mucosa is only a part of the spectrum of CD. It is possible that serology could identify CD in its early stages, before the appearance of severe intestinal damage. In cases with a positive serology but with mild or absent intestinal lesions, the detection of HLA-DQ2 and HLA-DQ8 can help reinforce or exclude the diagnosis of gluten sensitivity.

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INTRODUCTION

In recent years, our understanding of celiac disease (CD) has been rapidly growing because of significant advances in knowledge about its pathogenic, epidemiological, clinical and diagnostic aspects.^{1,2} CD, also known as celiac sprue or gluten-sensitive enteropathy, can be defined as a permanent intolerance to wheat gliadins and other cereal prolamins in the small bowel mucosa in genetically susceptible individuals. The main expression of the disorder is characteristic, though not specific, small intestine lesions that impair nutrient absorption and improve upon withdrawal of the responsible cereals. It is generally acknowledged that wheat (gliadins), rye (secalins) and barley prolamins (hordeins) are toxic for the intestinal mucosa of celiac patients due to their high glutamine (>30%) and proline (>15%) content, whereas prolamins of rice and maize are nontoxic due to a lower content of these two amino acids.³ Other studies have shown that oat prolamins (avenins), which have an intermediate glutamine and proline composition, are non-toxic, and only ingestion of a large amount of this cereal can provoke damage in the small bowel of celiac patients.^{4,5}

The genetic susceptibility to CD is confirmed by its high familial incidence (about 10% of first degree relatives of celiac patients are affected by the disease) and by its strict linkage with some human leukocyte antigen (HLA) class 2 alleles (up to 95% celiacs are HLA-DQ2 positive with the typical heterodimer DQA1*0501/DQB1*0201, whereas the remaining 5% are HLA-DQ8 positive HLA-DQB1*0302).^{6,7} Because about 20–30% of healthy people in Western countries display the same

HLA pattern, the presence of HLA-DQ2 and/or HLA-DQ8 must be considered an indispensable prerequisite for the disease but cannot alone justify the development of CD. Therefore, non-HLA genetic factors are likely to be required for the development of disease. An alteration in the terminal portion of chromosome 5 has been identified as a risk factor for both symptomatic and silent forms of CD, whereas a change in the terminal portion of the chromosome 11 possibly differentiates the two forms.⁸ Among the candidate genes, there is also a CD28/CTLA4 region on chromosome 2 that encodes receptors regulating T-lymphocyte activation.⁹ Recently, multiple genetic loci have been implicated in CD pathogenesis, but their impact on the development of the disease seems to be limited as compared to that of the HLA system.¹⁰

T-cell-mediated immune response plays a crucial role in the pathogenesis of the disease.¹¹ There is strong evidence that the mucosal lesions of gluten-sensitive enteropathy are initiated within the lamina propria and are due to major histocompatibility complex class 2-expressing activated macrophages that present gliadin peptides to α/β T-cell receptor CD4⁺ lymphocytes. This leads to increased production of cytokines (e.g., interleukin-15, interferon- γ and tumor necrosis factor- α), which recruit nonspecific effector cells responsible for initial tissue damage. The identification of tissue transglutaminase (tTG or TG2) as the predominant autoantigen of CD has allowed researchers to gain new insights into the pathogenesis of this disorder;¹² tTG belongs to a family of cytoplasmic calcium-dependent enzymes found in endothelial cells, erythrocytes, hepatocytes, lamina

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propria and small intestine epithelial cells. Damage to, or hyperpermeability of, the small intestine mucosa, caused by either toxic gluten fractions or other irritants, triggers the abundant extracellular release of cytosolic tTG. The following step is the crosslinking between the released tTG and gliadin, an excellent substrate for tTG, resulting in gliadin-tTG complexes and the creation of antigenic neoepitopes. Moreover, tTG selectively deamidates gliadin peptides, leading to a strongly enhanced T-cell-stimulatory activity.¹³

Epidemiological studies, performed by accurate serological screening in the general population, have radically changed our knowledge about CD prevalence, showing that the disease occurs worldwide much more frequently than previously thought (Table 1).^{14–21} The highest reported prevalence is in Europe: 1 in 99 in Finland, 1 in 122 in Northern Ireland and 1 in 175 people in Italy.^{16,20,21} Until a few years ago, gluten-sensitive enteropathy was erroneously considered uncommon in the United States, but serological screening in healthy blood donors has revealed a prevalence approaching that of Europe (1 in 250).²² Whereas CD is well documented in Asians from India and Pakistan,²³ it is rare among native Japanese and Chinese. The amazingly high CD prevalence in children of the Sahara (1 in 18) can be partially explained by the high amount of cereal (couscous) in the diet and by the particular genetic background of this population (i.e., high prevalence of HLA-DQ2/DQ8).²⁴

CD can manifest in any age group, from infants to the elderly. Retrospective analysis of clinical data shows that most adult celiacs had no sign of the disease during their childhood, thereby confirming that CD can develop in adulthood.^{25–28} About 20% of diagnoses occur in people over 60 years of age.²⁹ CD prevalence is higher in females than in males worldwide, with a mean F/M ratio of 2 : 1.³⁰

The clinical presentation of CD can be misleading because the symptoms vary tremendously from patient to patient and appear to depend largely on the length and the severity of small intestine damage (Table 2).³¹ Because of the heterogeneity among clinical signs and the lack of specificity of many presenting symptoms, the clinical diagnosis of CD is a challenge even for experts. Depending on the clinical, histopathological and immunological features, CD can be classified into the following forms: classical (typical), subclinical (atypical or mono-symptomatic), silent (asymptomatic) and potential/latent.³²

The classical form is characterized by the typical malabsorption syndrome with diarrhea, flatulence, weight loss, fatigue, vomiting,

abdominal pain and expression of severe intestinal damage affecting a large tract of small bowel. Thanks to the increased frequency of early CD diagnosis, this form is less and less often observed; however, some patients can still present with wasting cachexia characterized by muscle atrophy and cramps, severe hypoalbuminemia and electrolyte and metabolic disturbances, leading to hypocalcemic tetany and spontaneous bone fractures from marked osteoporosis.^{27,28,33}

In the subclinical form, gastrointestinal manifestations can be mild or absent and are often completely overshadowed by extra-intestinal symptoms, especially in those patients with a mild mucosal lesion confined to the proximal small intestine. Patients in this group have an isolated iron-deficient anemia,³⁴ unexplained folic acid deficiency and a hemorrhagic syndrome caused by vitamin K deficiency.³⁵ Failure to thrive is an important sign of CD in childhood, and short stature is a possible sign of CD in adults.³⁶ Dental enamel defects and aphthous stomatitis can suggest subclinical CD.^{37,38} Sometimes, CD patients have a gluten-sensitive dysmotility involving the whole gastrointestinal tract, and the clinical expression may be dyspepsia, reflux, dysphagia or, more frequently, severe constipation.³⁹ Irritable bowel syndrome, common in the general population, can hide a condition of gluten-sensitive enteropathy.⁴⁰ Atypical CD can also present with only psychiatric and neurological symptoms. In the former group, depression and anxiety have been reported,⁴¹ whereas in the latter there are a number of idiopathic neurological disorders, such as epilepsy with and without parieto-occipital calcifications, cerebellar ataxia, intellectual deterioration with attention/memory impairment, brain atrophy, peripheral neuropathy, multiplex myoclonus (Friedreich's disease) and multiple sclerosis.^{42–46} Reproductive system dysfunction may be a sign of CD in both sexes. In females, there is a trend to late menarche, amenorrhea, early menopause and infertility, which respond positively to gluten withdrawal.⁴⁷ Moreover, there is also a greater frequency of recurrent miscarriages (mainly in the first 3 months of pregnancy), stillbirth and neonatal death.⁴⁸ In males, impotence, decreased sexual activity, infertility, abnormalities of sperm morphology and motility may be expressions of CD.^{49,50} Another presentation of atypical CD is so-called celiac hepatitis, characterized by a gluten-dependent increase in serum transaminases without abnormality of any other liver functions.⁵¹ Both the serum transaminases and mild liver histological damage revert to normal after removal of gluten. Several disorders are associated with

Table 1 Epidemiology of celiac disease: serological screening in the general population confirmed by duodenal histology

Reference	Antibody testing	No. of cases	Age (years)	Celiac disease prevalence
Pittschieler K <i>Acta Paediatr</i> 1996	AGA	4615	18–82	1 : 513 (1.95‰)
Corazza GR <i>Scand J Gastroenterol</i> 1997	EmA	2237	20–87	1 : 559 (1.8‰)
Johnston SD <i>Lancet</i> 1997	EmA	1823	NR	1 : 122 (8.0‰)
Kolho KL <i>Scand J Gastroenterol</i> 1998	EmA	1070	NR	1 : 134 (7.5‰)
Ivarsson A <i>J Intern Med</i> 1999	EmA	1894	25–74	1 : 189 (5.3‰)
Riestra S <i>Scand J Gastroenterol</i> 2000	EmA	1170	2–89	1 : 389 (2.6‰)
Volta U <i>Dig Dis Sci</i> 2001	EmA	3483	12–65	1 : 175 (0.57%)
Maki M <i>N Engl J Med</i> 2003	tTGA	3654	7–16	1 : 99 ^a (1%)

Abbreviations: AGA, antigliadin antibodies; EmA: antiendomysial antibodies; NR, not reported; tTGA, antibodies to tissue transglutaminase.

^a 1 : 67 with positive serology, but without serological confirmation.

Table 2 Presenting symptoms of celiac disease

General	Weakness, lassitude, malaise, weight loss, short stature
Gastrointestinal	Diarrhea, anorexia, nausea and vomiting, flatulence and abdominal distension, abdominal pain, constipation, motility disturbance, glossitis/aphthous ulcers
Metabolic	Anemia features, bleeding tendency, edema, cramps/tetany, dental enamel hypoplasia
Musculoskeletal	Bone pain and fractures, myopathy
Neuropsychiatric	Depression, anxiety, paraesthesia, peripheral neuropathy, cerebrospinal degeneration
Reproductive	Menstrual irregularities, recurrent miscarriages, abnormalities of sperm morphology and motility
Skin	Variety of rashes, petechiae

gluten-sensitive enteropathy.^{52,53} The most well-known association is with dermatitis herpetiformis, a skin disease characterized by intensely pruritic papulovesicular lesions that occur symmetrically on the extensor surface of arms and legs and on the buttocks, trunk, neck and scalp.⁵⁴ All patients with dermatitis herpetiformis show gluten-dependent intestinal damage, which is indistinguishable from that of CD because it can present with mild clinical CD symptoms or with no symptoms at all. The withdrawal of gluten reverses not only the intestinal, but also the skin lesions in most dermatitis herpetiformis patients. Many other pathological conditions, such as autoimmune disorders (insulin-dependent diabetes mellitus type 1, thyroid disorders, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, alopecia, vitiligo, Addison's disease, Sjögren's syndrome, IgA nephropathy and IgA deficiency),^{55–65} idiopathic disorders (primitive dilated cardiomyopathy, atopy and inflammatory bowel disease)^{66–68} and chromosome disorders (Down, Turner and Williams syndromes),^{69–71} display a strong association with CD. The importance of diagnosing the subclinical form of CD associated with these disorders is twofold because a gluten-free diet not only prevents the clinical manifestations and complications of CD but also sometimes improves clinical symptoms of the associated disorders (Table 3).

The silent form is diagnosed in patients who do not complain of any symptoms. Examples of patients with this condition include first-degree relatives of celiac patients⁷² and subjects of the general population who are identified through serological screening.²⁰ It is common to find mild histological lesions usually confined to the proximal tract of the small intestine mucosa in these patients.

The potential form is a more and more frequently observed condition characterized by a normal villous architecture, but with some histological and immunologic features suggestive of the future development of CD. These features include an increased number of intraepithelial lymphocytes (IELs) (with an overexpression of γ/δ T-cell receptor lymphocytes); the presence of IgA and IgM gliadin antibodies (AGA) in the intestinal juices; and the presence of serum IgA antiendomysial antibodies (EmA), usually at low titer ($<1:40$).^{73,74} The potential form of the disease is considered the first step toward the flat mucosa characteristic of CD, and when the disease develops with the typical atrophy of small intestine mucosa, the condition is renamed 'latent CD'. Potential celiacs are frequently asymptomatic or may suffer from mild intestinal symptoms, such as abdominal pain, resembling those of irritable bowel syndrome.

DIAGNOSTIC CRITERIA

Small intestine biopsy

A long time ago, when CD was recognized as a new disease, its diagnosis was exclusively based on the finding of villous atrophy during a small intestine biopsy.⁷⁵ The most relevant feature of the disease was histological change, and histology became the gold standard for diagnosis. Despite substantial changes in the mode of presentation and the availability of new diagnostic tools, small bowel mucosal biopsy has remained the gold standard for CD diagnosis until now. In recent years, a progressive decline in the use of this diagnostic tool has been evident. First, standardized technical procedures, often neglected in many medical centers, have been identified; with regard to small

Table 3 Disorders associated with celiac disease

<i>Autoimmune</i>	<i>Idiopathic</i>	<i>Chromosomal</i>	<i>Miscellaneous</i>
T1DM	Dilated cardiomyopathy	Down syndrome	Female and male infertility
Hashimoto thyroiditis	Epilepsy with or without occipital calcifications	Turner syndrome	Depression
Graves' disease	Cerebellar ataxia	Williams syndrome	Psychiatric diseases
Autoimmune hepatitis	Peripheral neuropathy		Aphthous stomatitis
Primary biliary cirrhosis	Multiple myoclonus		
Primary sclerosing cholangitis	Multiple sclerosis		
Alopecia	Brain atrophy		
Vitiligo	Inflammatory bowel disease		
Psoriasis	Sarcoidosis		
Dermatitis herpetiformis	Atopy		
IgA deficiency			
Autoimmune atrophic gastritis			
Autoimmune hemolytic disease			
Sjögren's syndrome			
Myasthenia gravis			
Addison's disease			
IgA nephropathy			

Abbreviation: T1DM, diabetes mellitus type 1.

intestine histology, researchers have learned that when diagnosing CD, patchy and irregular mucosal lesions are just as relevant as continuous lesions.⁷⁶ Therefore, at least four biopsy samples, i.e., two from the duodenal bulb and two from the second third of the duodenum, should be taken. It is also essential that biopsy samples are correctly oriented to avoid tangential artifacts and spurious shortening or absence of villi.⁷⁷ Orientation is important not only for the evaluation of atrophic lesions but also for correct interpretation of minimal changes in small intestine mucosa. A well-oriented biopsy allows for a good evaluation of villi/crypt ratio ($\geq 3:1$ in mucosa with normal architecture) and, above all, an accurate count of IELs, which is difficult to obtain with transverse sections and/or convoluted villi. Provided that the orientation is correct, the pathological interpretation of an intestinal biopsy is a major pitfall in CD diagnosis, particularly in the presence of mild intestinal lesions.⁷⁸ Agreement between six different pathologists has been reported for the most extreme cases, such as normal mucosa and subtotal villous atrophy, whereas agreement was poor for cases of mild intestinal lesions (increased IELs and crypt hyperplasia), confirming the difficulty of getting a reproducible evaluation of non-atrophic lesions.⁷⁹ When an increase in IELs is suspected as the sole marker of intestinal mucosal damage, CD3 staining by immunohistochemistry is a mandatory adjunctive technique needed to count them.⁸⁰

It must also be emphasized that non-atrophic lesions of small intestine mucosa (Fig. 1a–b), characterized by an isolated increase in the number of IELs with or without crypt hyperplasia, indicate CD in only 10% of cases because many other conditions can be responsible for an increased number of IELs in the intestinal mucosa, including the following: food allergy, gastrointestinal infection (including *Helicobacter pylori* infection), Crohn's disease, ulcerative colitis, common variable immunodeficiency and autoimmune disorders.⁸¹ Therefore, pathologists should avoid overdiagnosing CD based only on an increased number of IELs. Immunohistochemical characterization of lymphocyte populations in the intraepithelial compartment using frozen sections of a duodenal biopsy may be useful for identifying gluten-sensitive patients among those with nonatrophic lesions. A high density of T cells with γ/δ receptors in the surface epithelium is a characteristic feature of gluten sensitivity. The mean proportion of γ/δ T-cells to IELs in gluten-dependent non-atrophic lesions ranges from 20% to 30%, but when non-atrophic lesions are not dependent on gluten, the proportion of γ/δ +T cells is about 2–3%. However, this technique has limited diagnostic utility due to the unavailability of formalin-fixed, paraffin-embedded tissue.⁸²

The predictive value of histology is much greater in the presence of villous atrophy (mild, partial or subtotal) (Figure 1c–d–e–f). However, it should be remembered that other disorders, including common variable immunodeficiency, autoimmune enteropathy, Whipple disease and eosinophilic gastroenteritis, can cause nongluten-dependent villous atrophy.⁸³

With its low degree of specificity, histology fails to be the gold standard of CD diagnosis, and it is time to recognize that for the majority of gluten-sensitive cases, histology alone cannot provide the diagnosis. Histology remains an important element in CD diagnosis, but pathological findings must be evaluated in the context of other relevant components, including clinical signs, serological markers and HLA haplotypes.⁸⁴

Serological tests

Ideas about CD have progressed, and currently there is a general consensus that it is a heterogeneous autoimmune disorder, the diagnosis of which relies not only on histological findings but also on increasingly important serological and genetic tests.

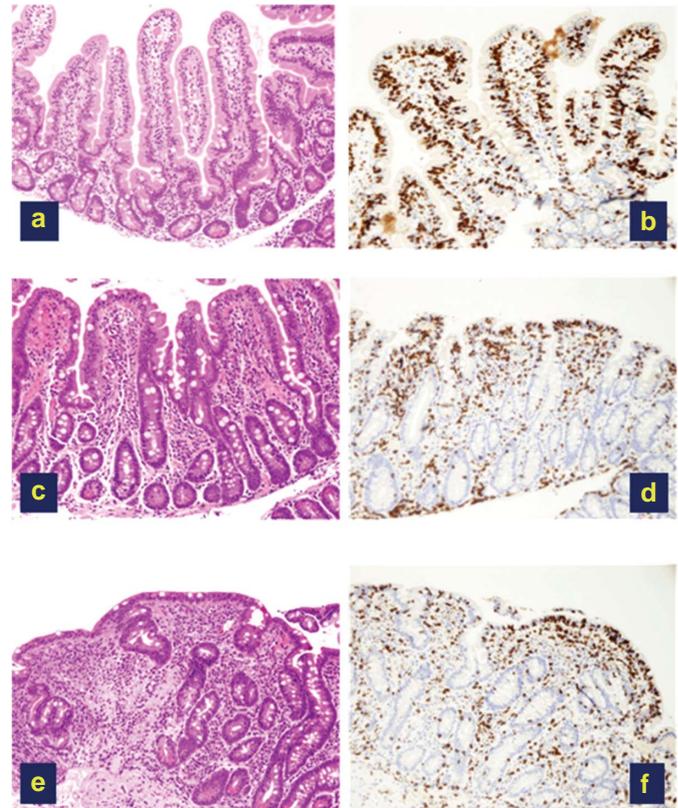


Figure 1 Different grades of small intestinal damage in coeliac disease patients: a–b normal villi and pathological increase of intraepithelial lymphocytes (IELs) (a–haematoxylin/eosin, b CD3 staining), c–d mild/moderate atrophy of villi and pathological increase of IELs (c–haematoxylin/eosin, d staining), e–f total villous atrophy and pathological increase of IELs (e–haematoxylin/eosin, f CD3 staining). Magnification x20.

Serology has become increasingly relevant to CD diagnosis.⁸⁵ The availability of immunologic tests that confirm symptoms to be strictly related to food intolerance has definitely changed the diagnostic algorithm for CD. CD-related antibodies have allowed researchers to confirm a great number of borderline cases in patients with mild intestinal lesions and positive serology, diagnosing the so-called potential CD. It is likely that serology could identify CD in its early stages, before the appearance of a severe intestinal damage. At present, the most widely used approach is to perform an intestinal biopsy, independent of serology results, only in patients with severe malabsorption; in individuals at risk for CD (those with first-degree relatives, iron-deficient anemics, and patients with unexplained osteoporosis, cryptogenic hypertransaminasemia, CD-associated autoimmune disorders, etc.), gluten-sensitive enteropathy can be excluded by the absence of CD-related antibodies, and only those with a positive serology test should undergo intestinal biopsy.

There is a general agreement that the best strategy for CD serological screening is the detection of IgA tissue transglutaminase antibodies (tTGA).⁸⁶ These antibodies are the most sensitive test for CD (up to 97%), whereas IgA EmA are employed as a confirmatory test in tTGA-positive cases due to their higher specificity (about 100% versus 91% of tTGA) (Table 4). 'False positives' for tTGA have been observed in patients with inflammatory bowel disease, food allergy, irritable bowel syndrome, giardiasis, other intestinal infections and autoimmune disorders. These 'false positives' cannot always be resolved by EmA because the results of EmA testing are reliable only in laboratories skilled in immunofluorescent assays.⁸⁷ The recognition of an

Table 4 Performance of serological markers for CD diagnosis

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic accuracy (%)
IgA tTGA	97	91	91	97	98
IgA EmA	94	100	100	94	97
IgA AGA	73	87	84	77	80
IgG AGA	73	77	75	75	75
IgA DGP-AGA	84	90	89	85	87
IgG DGP-AGA	84	99	98	87	92

Abbreviations: AGA, anti gliadin antibodies; CD, celiac disease; DGP-AGA, antibodies to deamidated gliadin peptides; EmA, antiendomysial antibodies; NPV, negative predictive value; PPV, positive predictive value; tTGA, antibodies to tissue transglutaminase.

EmA-positive pattern is sometimes difficult due to their resemblance to antismooth muscle antibodies.

IgA AGA is an obsolete test with low sensitivity and specificity; therefore, the search for these antibodies should be abandoned, except in very young children (under 2 years of age).⁸⁸ IgG tTGA should be used only for detecting CD in patients with IgA deficiency, a condition strictly related to CD.⁸⁹

A new antibody test has been introduced into the serological work-up of CD. This test consists of antibodies binding to deamidated gliadin peptides (DGP-AGA) (Table 4). Both IgG and IgA DGP-AGA show a lower sensitivity for CD than IgA tTGA, but IgG DGP-AGA displays a very high specificity for CD (higher than tTGA and similar to EmA); moreover, these antibodies allow for the identification of all CD cases in IgA-deficient patients with a very high sensitivity in young children (aged less than 2 years). In light of these promising results, it is possible to hypothesize a new serological protocol for CD that uses only two tests—IgA tTGA and IgG DGP-AGA—instead of the current four tests—IgA tTGA, IgA EmA, IgA AGA and IgG tTGA. This new procedure would reduce the number of tests required, thus providing an obvious advantage in terms of cost-efficiency (Figure 2).⁹⁰ Recent data have shown that IgA tTGA can be present in the intestine before the serum, thus predicting a forthcoming CD.⁹¹ These antibodies, detected by direct immunofluorescence on frozen sections of duodenal biopsies, display a high sensitivity for potential CD (78–100%), but their specificity is low because they are also present in a high proportion of patients with autoimmune disorders (diabetes mellitus type 1) or inflammatory bowel disease and in some controls.⁹² After improving their specificity, intestinal tTGA of the IgA class could be the best option for classifying non-atrophic intestinal lesions as gluten-dependent.

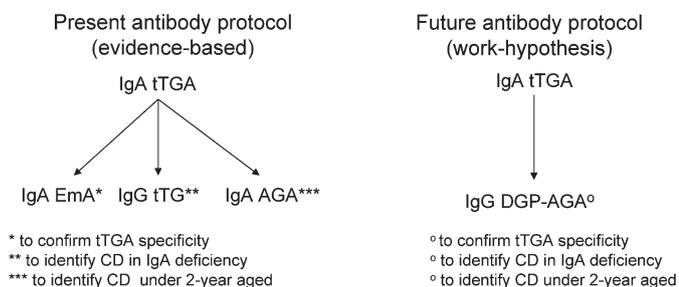


Figure 2 Comparison between the present and the new serological strategy for coeliac disease diagnosis. The combined search for IgG DGP-AGA to IgA tTGA in the diagnostic work-up of coeliac disease makes unuseful the detection of IgA EmA, IgG tTGA and IgA AGA. Abbreviations: tTGA, antibodies to tissue transglutaminase, EmA, antiendomysial antibodies, DGP-AGA, antideamidated gliadin peptide antibodies, AGA, anti gliadin antibodies, CD, celiac disease.

Genetics

The puzzle of diagnosing gluten sensitivity includes another relevant element, genetic testing. As generally acknowledged, CD is closely related to a well-defined HLA pattern, characterized by the presence of HLA-DQ2 and/or HLA-DQ8.^{6–8} HLA testing should not be routinely performed in all CD cases, but it is strongly indicated when CD diagnosis is controversial (because of a discrepancy between histology and serology results) and in first-degree relatives of CD patients. A positive test alone (finding HLA-DQ2-DQA1*05, DQB1*02- and HLA-DQ8-DQB1*0302) is never diagnostic for CD because about 30% of the general population displays the same HLA pattern as CD patients. The most important clinical impact of the test is when the result is negative, because the absence of HLA-DQ2, HLA-DQ8 and DQB1*02 excludes a diagnosis of CD (negative predictive value 100%). In patients with potential CD (positive serology with mild or absent histological lesions), HLA genotyping is useful to reinforce (when positive) or discount (when negative) the presence of the condition. In patients with villous atrophy and negative serology, HLA negativity should alert us to search for another cause of flat mucosa (common variable immunodeficiency, autoimmune enteropathy, Whipple disease, etc.). In patients with positivity for IgA tTGA at low titer without IgA EmA and IgG DGP-AGA a negative HLA test gives evidence that IgA tTGA readings are ‘false positives’.

CONCLUSIONS

There is no doubt that our understanding of CD has changed in its clinical, histological and autoimmune features, so that it seems to be a new disease as compared to that described in medical books from only 10 or 20 years ago. Therefore, it is time to change the historical dogma that uses histology as the gold standard for the detection of CD. Today, in light of the current knowledge and emerging complex clinical problems, we propose that the true gold standard for the final diagnosis of CD is the decision made by the clinician. The clinician is the only one who knows the patient and establishes the tests and their timing and is, consequently, the only one who can correctly interpret the panel of available data (clinical, serological, histological and genetic). The role of the pathologist is not diminished because he is always an important contributor in CD diagnosis. An accurate assessment of the morphology of the duodenal mucosa, while avoiding any clinical conclusions (which are often misleading), remains crucial for the final diagnosis of CD. A multidisciplinary team coordinated by the clinician, including specialists, pathologists and laboratory technicians, can pave the way for improving the quality of CD diagnosis by compiling all of the pieces needed to solve the CD puzzle.

A small intestine biopsy is still necessary for CD diagnosis, but it must be emphasized that with the improved diagnostic accuracy of serology and genetics, there is a trend toward non-invasive diagnosis of CD. The European Society of Paediatric Gastroenterology Hepatology and Nutrition has recently proposed new criteria for CD diagnosis, suggesting that in children with severe malabsorption, CD can be diagnosed on the basis of a positive serological test and the presence of a typical genetic pattern (DQ2 and/or DQ8), without the need for a small intestine biopsy. This is an early attempt to avoid duodenal biopsy for CD diagnosis, indicating that the diagnostic criteria for CD might change radically in the next few years.

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