Diagnosis of Celiac Disease

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Introduction

In this chapter we review issues related to identifying the appropriate patient to test for celiac disease (CD), the performance characteristics of serological testing, the role of gene testing for Human Leukocyte Antigen DQ2 and DQ8 haplotypes, and issues related to the performance of small intestinal biopsy. The chapter concludes with a review of special diagnostic considerations in pediatric patients.

Identifying the Appropriate Patient to Test for Celiac Disease

Diagnoses of CD are increasing in the United States and worldwide. In a population-based study of individuals in Olmsted County, MN, the annual incidence of CD increased dramatically from 0.9 per 100,000 individuals in the years prior to the availability of serological tests (1950–1989) to 9.1 per 100,000 in the years 2000–2001.[1] Analysis of claims data from a national insurance company found that diagnoses of CD continued to increase through the year 2003, the last year of the analysis.[2]

Despite evidence of increasing rates of diagnosis, the majority of patients in the United States remain undiagnosed. Population based data are sparse, but inferences on the ratio of undiagnosed-to-diagnosed individuals can be made based on what is known regarding the seroprevalence of CD in the general population (0.8–1%).[3–5] In 2001, the point prevalence of diagnosed CD in Olmsted County was 0.04%.[1] If the seroprevalence of CD is 0.8%, then approximately 95% of patients with CD were undiagnosed at that time. While diagnosis

rates are increasing, the fact that the seroprevalence of CD is also increasing[4, 6] may result in a persistently high undiagnosed-to-diagnosed ratio. The high fraction of undiagnosed patients in the United States stands in contrast to parts of Europe, including Italy and Finland, in which the threshold to test for CD is lower and so the fraction of diagnosed patients is substantially higher.[7–8]

One approach to address the relatively low rates of CD diagnosis in the United States is to institute a program of population screening, in which all individuals regardless of symptoms undergo serological testing for CD, and those who screen positive subsequently undergo esophagogastroduodenoscopy (EGD) with small intestinal biopsy. Advocates for this approach note that CD meets World Health Organization criteria for diseases that warrant mass screening: early clinical detection is difficult; the condition is common; screening tests are highly sensitive and specific; effective treatment is available; and untreated disease can lead to complications.[9] Given the reduction in mortality risk that occurs in the years after diagnosis and institution of the gluten-free diet[10] and the reduced health care expenditures after diagnosis of CD,[2] screening for CD may be cost effective, and was found to be so in to three quantitative analyses.[11–13]

Despite calls for general population screening, problems with this approach have led to targeted case finding as the preferred method of increasing diagnosis rates. Apart from unresolved questions regarding the logistics of screening (such as deciding on the appropriate age and interval of screening) limitations of the currently available serological tests pose a significant problem. Given that the prevalence of CD in the general population is 1%, any test with an imperfect specificity will result in a large number of false-positives. Assuming that the specificity of tissue transglutaminase (TTG) IgA is 98%,[14] its positive predictive value when employed in the general population is only 34%; as a result, two thirds of screened individuals who have a positive result will undergo EGD with biopsy and not be diagnosed with CD; this false-positive rate may be reduced by only performing a biopsy on patients with dual positive serologies of TTG endomysial antibody (EMA), but difficulties with the latter serology (see below, Serological and Genetic Testing) makes this approach less than ideal.

In addition to the technical limitations of serological screening and its attendant false positive rate, one objection to routine screening for CD is based on the persistent uncertainty regarding the long-term prognosis of asymptomatic, undiagnosed CD. A major argument for screening is that CD is associated with an increased mortality risk, which declines in the years following diagnosis,[10] a decline that is attributed to the protective effects of the gluten-free diet. The evidence for a mortality risk in undiagnosed CD is less consistent. In an analysis of thawed serum, Rubio-Tapia, et al identified individuals with positive CD serologies (both TTG and EMA) in 14 out of 9,133 (0.2%) participants in the Warren Air Force cohort.[4] With a follow-up period of 45 years, the patients with seropositivity (who all remained undiagnosed) had a nearly four-fold risk of death compared to seronegative individuals (HR 3.9; 95% CI 2.0–7.5). In a second cohort study, healthy volunteers with a positive TTG had an increased mortality compared to seronegative subjects (HR 2.53; 95% CI 1.50–4.25).[15] But in four other studies in England,[16] Finland,[17] Ireland,[18] and individuals older than 50 in Olmsted county,[19] no increase in mortality was noted in undiagnosed

peripheral neuropathy, [25] migraines,[26] gastroesophageal reflux, [27] low bone density[28] and low levels of High-density lipoprotein.[29]

A recent study set at a health fair in Caspar, Wyoming sheds light on the fine line between case finding and screening the general population.[5] In this study, 3,850 individuals attending the health fair submitted a blood sample that was tested for TTG, and serum with positive results then underwent confirmatory EMA testing. These individuals also completed a questionnaire, querying respondents for gastrointestinal symptoms including bloating, abdominal pain, heartburn, nausea, diarrhea, and constipation. Of the 3,850 subjects, 34 had a positive TTG and EMA, yielding a prevalence of 0.8%. (31 out these 34 had not been previously diagnosed with CD, yielding an undiagnosed-to-diagnosed ratio of 10 to 1.) When comparing seropositive to seronegative individuals with regard to gastrointestinal symptoms, none of these symptoms were predictive of seropositivity. This null finding was due in part to the fact that these symptoms are quite common; more than 80% of all respondents had at least one such symptom. Thus, an aggressive case finding strategy may closely resemble a *de facto* mass screening approach.

At this time, there is no universally accepted threshold for testing for CD among physicians who have adopted this recommended strategy of case finding. Consensus statements from the United States and Europe broadly agree with the need to test for CD in scenarios such as chronic diarrhea and unexplained iron deficiency.[30–33] But there is less agreement on whether screening asymptomatic patients in high-prevalence groups (such as first degree relatives or patients with autoimmune thyroiditis) should be recommended [31–33] or merely offered with the caveat that the benefits of diagnosing asymptomatic patients are unclear.[30] Since a low threshold (i.e. a long list of symptoms that would prompt testing) may result in a testing a large proportion of patients seeking health care, it is imperative that physicians employing this strategy have a solid understanding of the performance characteristics of serological tests.

Serological and Genetic Testing

Serum Antibody Tests—CD is characterized by the presence of diverse antibodies in the serum that are made against 1) gliadin (conventional gliadin antibodies and deamidated gliadin peptide antibodies), a component of gluten, and 2) connective tissue components (tissue transglutaminase antibodies and endomysial antibodies). Overall, these tests are useful for the diagnosis of CD, although the diagnostic performance may be different for each test.

<u>Antigliadin antibodies:</u> Conventional gliadin antibodies are no longer recommended because of the lower sensitivity and specificity compared with other available serologic tests. However, there is considerable interest on the use of new generation deamidated gliadin peptide antibodies because these novel tests have improved diagnostic accuracy as compared to conventional gliadin antibodies.[34] In a recent review, the pooled sensitivity for IgA tissue deamidated gliadin peptide antibodies was 88% and specificity of 95%.[14] The role of deamidated gliadin peptide antibodies in diagnosing young children is discussed below (Diagnosis in Children).

Tissue transglutaminase antibodies: The enzyme tissue transglutaminase was recognized as the CD autoantigen. [35] This enzyme has many functions, including deamidation of gliadin peptides. [36] A wide range of kits with different characteristics measure tissue transglutaminase antibodies most often by quantitative enzyme-linked immunosorbent assay.[37] The substrates could be guinea pig liver (first generation assays), human red-cell derived and human recombinant. In general, specificity tends to be higher with human-based assays compared to first-generation assays.[38] The pooled sensitivity and specificity for human-based IgA tissue transglutaminase antibodies (TTG) are both 98%.[14] However, sensitivity (and to a lesser degree specificity) may vary among laboratories.[37] Because of its simplicity and overall good diagnostic accuracy, detection of IgA tissue transglutaminase antibodies is the serologic test of choice for the diagnosis of CD.[31, 39] False positive tests are unusual with human substrates, especially at high titers.[33]

Endomysial antibodies: Endomysial antibodies (EMA) have been available for diagnosis of CD for almost 30 years.[40] The antibodies could be measured using an indirect immunofluorescence technique using monkey esophagus, human jejunum, or human umbilical cord as substrate. [414243] The target antigen is tissue transglutaminase. The pooled sensitivity and specificity for IgA EMA were found to be 95% and 99%, respectively.[14] Specificity of IgA-EMA is similar for tests using either monkey esophagus or human umbilical cord substrates.[42] Despite the high specificity of this antibody, there are several test-related issues that may limit its use in clinical practice. It is semi-quantitative, time consuming, operator-dependent, and expensive. However, IgA EMA testing could be clinically useful if the result of the IgA TTG test is equivocal.[31] A positive IgA EMA test is strong evidence for celiac disease in patients with non-atrophic intestinal lesions (Marsh I–II).[44] An emerging indication for IgA EMA testing is to support a non-biopsy based diagnosis of celiac disease in symptomatic children with high titer of IgA TTG (see below, Diagnosis in Children).[33]

Clinical use of serologic tests: Serologic tests are useful to evaluate patients with suspected CD and may be helpful to monitor adherence to the gluten free diet (GFD). [39] Among adult patients with chronic abdominal symptoms, IgA TTG and IgA EMA have high accuracy for the diagnosis of CD.[45] The initial serologic test of choice for CD diagnosis is IgA TTG. Sequential testing (IgA TTG positive followed by IgA EMA) has been an effective strategy for detection of CD in large epidemiological studies but its accuracy in clinical practice may require further study, especially if the intention is to avoid an intestinal biopsy for confirmation of CD.[46] Testing for celiac disease is accurate only if the patient continues to follow a gluten-containing diet; therefore, it is important to inform patients that they should not start a gluten-free diet until the diagnostic process is completed.[39] Indeed, all serological tests could become negative after gluten withdrawal.[47] False negative serologic testing should be strongly considered in patients with selective IgA deficiency. In this scenario, cascade testing or alternatively concurrent measurement of total IgA should be considered. IgA deficient patients should be evaluated by measurement of IgG TTG, IgG DGP, and/or IgG EMA.[14] In addition, a false negative test result is more likely in young children (less than 2 years of age) and among patients with non-atrophic lesions.[39] Further assessment is needed when serology tests are negative but clinical suspicion of celiac disease is high;

approximately 10% of patients with celiac disease are seronegative. Intestinal biopsy to confirm or exclude celiac disease is indicated in people with 1) a positive serologic result from any TTG, deamidated gliadin antibodies, or EMA test and 2) seronegative patients if celiac disease is highly suspected and genetic testing is positive. A cascade testing algorithm used at Mayo Clinic for the diagnosis of celiac disease is summarized in Figure 1.

Genetic Testing—Almost all patients with CD are positive for either human leukocyte antigen (HLA) DQ2 (heterodimer DQA1*05/DQB1*02) or DQ8 (heterodimer DQA1*03/DQB1*0302).[48] HLA-DQ2 is carried in ~95% of patients with CD. Thus, the absence of these heterodimers has a high negative predictive value. Approximately 25%–30% of persons of European ancestry have one of these genotypes. [49–50] Thus, a positive result is of little diagnostic value. Of 1,008 European patients with CD, 61 were identified who neither carry the DQ2 nor DQ8 heterodimers but 57 encoded half of the DQ2 heterodimer.[51] Other non-HLA risk factors have been used to improve identification of high-risk individuals for CD but its role on clinical evaluation of patients with suspicion of celiac disease will require further study.[52] Routine addition of genetic testing (HLA-DQ testing) to TTG and EMA (or vise versa) does not increase diagnostic performance as either testing strategy alone.[53] Thus, HLA-DQ genotyping is not indicated in the initial evaluation of CD. Genetic testing could be useful to exclude the diagnosis of CD (negative genetic testing) in selected cases when diagnosis is uncertain (i.e., equivocal small bowel histology).[50] Genetic testing could be especially useful to exclude CD in patients already on a GFD because this test is not affected by gluten exclusion.

Small Intestinal Biopsy

Despite the diagnostic advances afforded by the availability of serological testing, the histological finding on small intestinal biopsy remains the gold standard for the diagnosis of CD, though in certain scenarios this may no longer be the case in pediatric patients (see below). Duodenal biopsy for the diagnosis of CD is most commonly performed after a patient is found to have a positive serologic test. But diagnostic biopsy may also be performed in the seronegative individual with signs and symptoms highly suspicious for CD, as none of the available serological tests has a sensitivity of 100%.

Biopsy can also be useful in the common (but less than ideal) scenario in which a patient already commenced a gluten-free diet prior to seeking medical care. The serologies in most patients with CD normalize after six to twelve months of adherence to the gluten-free diet, but the histopathological changes can persist for far longer; a recent study of patients with CD who underwent serial biopsy found that the median time to mucosal healing was 3.8 years.[54] Moreover, even those patients with confirmed mucosal healing often have persistent intraepithelial lymphocytosis in the context of a normal crypt-to-villous ratio.[55] Therefore, a patient with CD who is already adherent to the diet may have normal serologies but persistent histopathologic evidence of CD. However, it should be recommended not to start a GFD before completion of diagnostic investigations.

Endoscopic findings such as scalloping, fissures, a mosaic appearance, and decreased folds are often seen, but are neither sensitive nor specific findings in CD. In one study of 13

patients with scalloping of the duodenum but who ultimately were not found to have CD, alternative causes included Human Immunodeficiency Virus infection, eosinophilic enteritis, and giardiasis.[56] A study of 129 patients with newly diagnosed CD found that approximately one third of such patients had an endoscopic appearance that was entirely normal, despite histopathologic evidence of intraepithelial lymphocytosis and villous atrophy.[57]

Despite the imperfect sensitivities of serological testing, and the poor predictive value of a normal endoscopic appearance, many patients with symptoms consistent with CD undergo EGD but do not have a duodenal biopsy during the procedure. In an analysis of the Clincal Outcomes Research Initiative (CORI) national endoscopic database, Harewood, et al identified 3,992 patients who underwent EGD for the indications of diarrhea, iron deficiency, anemia, and weight loss during the years spanning 2000–2003. Of these 3,992 patients, all of whom had a normal appearing duodenum, biopsy was performed in only 438 (11%). [58] In a follow-up study of the CORI database spanning the years 2004–2009, the rate of duodenal biopsy during examinations with the same indication improved but remained low at 43%.[59] In this study, men were less likely to undergo biopsy than women (OR 0.81 95%CI 0.75–0.88), despite equal seroprevalence rates on screening,[3] and older individuals were less likely to undergo biopsy compared to younger patients (OR for 70 compared to 20–49 0.51 95%CI 0.46–0.57), despite the fact that CD can present at any age, including in elderly individuals.[60] The overall low rates of biopsy during EGD for symptoms that may be manifestations of CD indicate that endoscopist-related factors may be contributing in part to the under-diagnosis of CD.

Since the pathological findings in CD can be patchy and can affect areas of the duodenum with varying degrees of severity, multiple specimens from the duodenum should be submitted during biopsy to determine whether CD is present. Guidelines issued by the American Gastroenterological Association state that 4–6 specimens be submitted during duodenal biopsy.[39] This recommendation is based on the authors' understanding of the patchy nature of the disease, but was subsequently supported by the results of a study of CD patients, in which the sensitivity of biopsy for the diagnosis of CD declined when fewer than 4 specimens were submitted.[61]

In clinical practice in the United States, adherence to the standard of submitting 4–6 specimens during duodenal biopsy appears to be poor. An analysis of a national pathology database identified 132,352 patients who underwent duodenal biopsy during EGD's performed in the years spanning 2006–2009.[62] Of these 132,352 patients, 4 specimens were submitted during duodenal biopsy in only 45,995 (35%). Older patients were less likely to have 4 specimens submitted than younger patients (OR for age 80 versus <30 0.67; 95% CI 0.57–0.78), and patients with a procedure indication of diarrhea were more likely to have 4 specimens submitted than those with anemia (OR 1.20; 95% CI 1.10–1.30). The incremental diagnostic yield of adhering to this standard was high. The proportion of patients with a histological diagnosis of CD was only 0.7% when <4 specimens were submitted, as compared to 1.8% when 4 specimens were submitted. Even when the clinical indication was explicitly noted as suspected CD, adherence to this biopsy standard only occurred in 38.5% of all submissions. As the diagnostic yield for CD more

than doubled regardless of the indication for the procedure, the submission of   4 specimens during duodenal biopsy would likely substantially increase the rate of CD diagnosis.

Other factors that may impact the diagnosis rate of CD during EGD include failure to biopsy the duodenal bulb[63] and misinterpretation of subtle histopathology.[64] Issues related to histopathological interpretation of duodenal bulb specimens and of interobserver variability in the histopathological diagnosis of CD are covered in further detail in chapter 5, "Histopathology of Celiac Disease".

Thus, we propose that adequate sampling for CD diagnosis should include   4 specimens of the duodenum and include the duodenal bulb.

Because of the limitations associated with duodenal biopsy, some have advocated for diagnostic criteria that include, but do not entirely depend upon, biopsy results. Catassi and Fasano proposed a 5-point scoring system that incorporates 1) symptoms of CD (such as diarrhea, weight loss and iron deficiency anemia); 2) positive CD serologies at high titer; 3) the presence of a DQ2 or DQ8 haplotype; 4) characteristic histopathologic findings; and 5) a serological or histological response to the gluten-free diet.[65] The presence of four out of the five criteria (or three out of four, if gene testing is not performed) would meet diagnostic criteria for CD according to this proposed system, which has not yet been validated prospectively.

This algorithm would allow for patients who have signs and symptoms of CD but have borderline histology, or who refuse biopsy, to be classified as having CD. If this approach is widely adopted, patients meeting the four non-histological criteria for CD would not require a biopsy. But any gain in sensitivity in a non-invasive scoring system is done at the cost of specificity. The algorithm would consider patients to have CD if they are not HLA-tested but have symptoms and serologies that improve on a gluten-free diet. Given the imperfect specificity of currently available serologies and the known phenomenon of gluten sensitivity in the absence of CD,[66] a significant proportion of such patients may not have a positive HLA DQ2 or DQ8 and thus will likely not have CD as currently understood. Thus, an algorithm, as described above, that allows for a diagnosis of CD in adults without histologic evidence is not likely to be widely adopted by clinicians and investigators in the near future.

Diagnosis in Children

It is worth mentioning that the realm of diagnosing celiac disease historically has been solidly in the hands of pediatric gastroenterologists. It was in fact a meeting of the then just-created European Society for Pediatric Gastroenterology that established in 1969 the first diagnostic criteria, subsequently widely followed by adult as well as pediatric gastroenterologists worldwide. Essentially born in Europe with mostly biochemical research around the description of several new congenital disorders of digestion and absorption, pediatric gastroenterology soon emerged and became a powerful force in defining CD and in indicating how to diagnose it.

In the mid to late 60's, it had become clear that CD could be diagnosed with the peroral jejunal biopsy showing atrophy of the villi, but since there were many causes of that lesion

(and at that time especially chronic intestinal infections and milk protein allergy), a strong word of caution was exerted by the medical community not to diagnose CD until it could be proven that gluten was indeed the cause of the mucosal atrophy. Thus, not only was a clinical complete remission on gluten-free diet considered necessary, but this had to be followed by the documentation of the normalization of the lesion, and finally by its recurrence once gluten was reintroduced into the diet. These criteria were formalized in 1969 by a panel of experts in the then newly born European Society for Pediatric Gastroenterology (ESPGA, today ESPGHAN: European Society for Pediatric Gastroenterology, Hepatology and Nutrition).

These so-called "Interlaken criteria" (named for the area in Switzerland where this expert-only gathering took place) did not take into account another important discovery that had been made several years earlier: CD children possessed antibodies caused by the ingestion of gluten. The first category to be discovered were the anti-gliadin antibodies, detected and reported by Berger in 1964.[67] Seven years later, Seah et al. identified for the first time not an anti-food protein, but an actual auto-antibody in the serum of celiac children: the anti-reticulins. [68] It took, however, several years before their diagnostic utility was fully appreciated, and the real leap forward occurred in 1984 when the anti-endomysium antibodies (EMA) were described [69] that soon dominated the scene for their high specificity.

In the late 1980's, a large multicenter Italian study could demonstrate that by relying on strict clinical and laboratory criteria, and now also supported by EMA, a correct diagnosis of CD could be reached in 95% of cases by limiting to the one initial biopsy. [70] This plea for a change was soon followed by new diagnostic guidelines published the following year by ESPGHAN.[71] These guidelines have been widely followed worldwide, not only in pediatric, but also in adult gastroenterology. Even though they were not "evidence-based" in the strictest sense of the word as used today,[72] such recommendations still stemmed largely from the cited experience [70] and proved very useful not only in clinical practice but also as a reference for research.

The discovery in 1997 that tissue transglutaminase was the auto-antigen in CD led soon to the identification of a very sensitive marker: the tissue transglutaminase antibodies. Initially available as derived from guinea pigs (and hence with a good but not perfect sensitivity and specificity), the TTG antibodies were later developed from human origin and soon were shown to have extremely high sensitivity and good specificity. [73–75] North American pediatric gastroenterologists, in a plea to improve the poor diagnosis rates and long diagnostic delay (estimated to be higher than 10 years), were quick to understand the potential of TTG in the diagnosis, and in 2005 a panel of experts from NASPGHAN published evidence-based diagnostic recommendations directed at all physicians dealing with children who should be considered as possible CD patients.[32] This guideline provides algorithms that are essentially based on performing first the TTG assay in children at risk (groups at risk are defined on clinical presentations and/or belonging to categories where the prevalence of CD is known to be higher), and then proceeding with further work-up only on those who have a positive TTG titer, regardless of its value. It is unclear how widely followed these recommendations have been; but certainly we have witnessed a major

advance in the diagnosis rates in children over the past few years, in part due to an improving awareness of this condition, that has hit the media with a great impact.

Anti-deamidated gliadin peptides (DGP)

In pediatric age groups, there is evidence for a special role of the relatively new antibodies: the deamidated gliadin peptides. Antibodies from celiac disease patients have enhanced binding to deamidated gliadin peptides compared to controls.[76] The deamidation of gliadin peptides occurs via a reaction catalyzed by tissue transglutaminase. In 2004, antibodies against the deamidated gliadin peptides (DGP) were shown to be accurate indicators for celiac disease. [77] Thus, in recent years, many studies have been done to figure out what role these antibodies can play in the disease diagnosis and follow up in the pediatric population. In IgA-deficient subjects (i.e. patients having less than 20mg/dl of total IgA in their serum) DGP IgG has sensitivity and specificity similar to TTG IgG, so they have been proposed as a useful test in such patients. [78–79]

Even in patients with normal total IgA levels, TTG IgA and EMA are often negative in children with CD who are younger than two years. In the past, anti-gliadin antibodies (AGA) were used as non-specific marker of increased intestinal permeability to food proteins in young children but because of the low specificity for celiac disease (<80%) their use has been abandoned. However, the newer DGP do not suffer from such poor specificity, and--most importantly for pediatricians dealing with very young children--DGP has a high sensitivity in this patient population. Barbato, et al showed this in a study of 11 children under the age of 2 who had normal values of TTG and EMA but positive levels of DGP and subsequent histologic findings of celiac disease on endoscopy.[80] To further support the use of DGP in young children, Monzani, et al showed that DGP IgA and IgG had sensitivity levels of 100% in children younger than three years.[81] Similar results were also recently obtained by Mubarak et al[82] in an investigation in 212 children with suspected CD: when the analysis was restricted to the 41 children below 2 years of age, the DGP-IgG had a diagnostic accuracy of 100%.

But the peculiar place that DGP has in pediatric ages goes beyond their important role in screening: in fact, DGP appears to be especially useful in monitoring dietary compliance. In 2007 Liu, et al showed that after initiation of the GFD, these antibodies became undetectable sooner than TTG,[83] thus opening the way to further investigate their usefulness in this regard. Monzani, et al followed a population of 28 children and showed that DGP had a higher sensitivity than TTG IgA for monitoring compliance to the GFD;[81] in 106 children on GFD for more than 1 year, sensitivity to detect dietary lapses was 60% for DGP-IgA and 76% for DGP IgA+G, while TTG IgA sensitivity was much lower at 24%. Thus, while both IgA and IgG DGP's possessed higher sensitivity than TTG IgA, the combination of DGP IgA and DGP IgG performed better. Nachman, et al used a long-term prospective study to evaluate the predictive value of antibodies in monitoring compliance to the GFD in adults. [84] The study was on 53 adults recently diagnosed with CD and compared a complete set of antibodies including TTG IgA, EMA, DGP IgA and assays combining up to four different antibodies. The results showed that DGP IgA and TTG IgA were the most appropriate and consistent for monitoring compliance.

In addition to screening young children and to monitoring dietary compliance both in children and in adults, DGP may play a role in detection of "early cases" of celiac disease, defined as individuals with positive celiac autoantibodies who show mucosal changes of only Marsh 1 or 2 (i.e. no villous atrophy) but who subsequently develop villous atrophy (Marsh 3) when continuing to eat gluten. In a study on 42 adults proven to have early-stage CD despite normal small-bowel mucosal morphology (Marsh 1–2), and in 20 subjects with villous atrophy (Marsh 3), Kurppa et al. [85] found that sensitivity to detect early-stage CD was 79% for DGP vs. 64% for TTG.

In summary, in children the present evidence shows that TTG IgA and DGP IgA and IgG have superb and similar abilities to detect celiac disease, and that DGP IgG is also as good as TTG IgG in detecting IgA-deficient CD patients. In addition, DGP appears to have a unique and superior role in screening for celiac very young children, and may be superior to TTG in carefully monitoring dietetary compliance in diagnosed patients.

Diagnosis without a biopsy—Increased awareness and the 2005 NASPGHAN guidelines certainly allowed an improved diagnosis rate in North America, in spite of recent evidence of still inadequate utilization of a correct diagnostic approach by practicing gastroenterologists.[86] Could then these guidelines be simplified? Studies from both sides of the Atlantic began raising the possibility that an accurate selection of patients might allow avoiding altogether the biopsy. In fact, it was shown that a good correlation existed between intensity of the intestinal damage and levels of serum TTG [87] and that selecting patients with elevated titers of TTG could result in an extremely high positive predictive value, hence predicting the possibility of avoiding the intestinal biopsy.[88–91]

In addition, great emphasis has been placed by investigators on the diagnostic dilemma for patients presenting only minor or no changes at histological analysis of duodenal mucosa.[92–93] Do these patients have CD or not? Can we consider them as potential CD patients carrying a risk of developing the full-blown disease at a later stage? In essence: do they need to adhere to a GFD? Numerous speculations and proposed algorithms and scores have appeared,[65, 94] and certainly the issue is still evolving as advances are made. The rapid evolution of diagnostic criteria for CD is best exemplified by a simple analysis of papers listed in Medline (Pubmed.org): a search for "celiac disease diagnosis" in a 180 day period in 2011–2012 revealed 176 entries: nearly 1 paper published every day on the subject!

For these reasons, ESPGHAN convened a panel that was charged with the task of providing new, strictly evidence-based recommendations for the diagnosis of CD in children. Their conclusions have been recently published,[33] 22 years after the historical paper of 1990, and are expected to set the new, world-wide standard for such diagnosis. In brief, a panel of 17 experts defined CD and developed new diagnostic criteria based on the Delphi process. Two groups of patients were defined with different diagnostic approaches to diagnose CD: children with symptoms suggestive of CD (group 1) and asymptomatic children at increased risk for CD (group 2). In group 1, the guideline suggests that diagnosis of CD is based on symptoms, positive serology, and histology that is consistent with CD. If TTG IgA is high (this is defined as more than 10 times the upper limit of normal), and only when there is also additional evidence of a compatible HLA haplotype and of a positive titer of serum EMA,

then CD can be diagnosed without a duodenal biopsy. In group 2, the diagnosis of CD would be based on positive serology and histology, hence in all cases with the documentation of a positive biopsy.

Within weeks after publication of these guidelines a study whose results criticize them already appeared.[95] These authors analyzed retrospectively 145 consecutive celiac disease patients with positive TTG who had an intestinal biopsy. The positive predictive value (PPV) for different cut-off points of TTG levels for the diagnosis of celiac disease was assessed, and the authors performed a simulation in a setting of routine clinical practice so to calculate the post-test probability of celiac disease. They found that no cut-off level was associated with a PPV of 100%. The highest PPV value (98.6%) was associated to a cut-off of 80U/mL (11.4×upper normal limit). Furthermore, in the frequent clinical situations carrying a pre-test probability of less than 10%, the post-test probability after was not superior to 90% even with the highest levels of TTG. Thus, the need for a confirmatory intestinal biopsy may still be present.

In conclusion, it is important to note that the new ESPGHAN evidence-based guideline does not recommend skipping the biopsy in the selected cases mentioned above, but simply allows the physician to do so at his/her discretion. As in all cases in medicine, the diagnosis is essentially a contract that must be stipulated in each individual case between the doctor and his/her patient, and is based on one side on the physician's experience, knowledge of the literature and diagnostic acumen; and on the other on the patient's family understanding and fully informed consent, given without reservations. No guidelines, no matter how evidence-based, can possibly ever replace such mutual trust.

Acknowledgments

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1. Diagnoses of CD are increasing in the United States and worldwide.

2. Despite evidence of increasing rates of diagnosis, the majority of patients in the United States remain undiagnosed.

3. One approach to address the relatively low rates of CD diagnosis in the United States is to institute a program of population screening, in which all individuals regardless of symptoms undergo serological testing for CD, and those who screen positive subsequently undergo esophagogastroduodenoscopy (EGD) with small intestinal biopsy.

4. Despite calls for general population screening, problems with this approach have led to targeted case finding as the preferred method of increasing diagnosis rates.

5. The conflicting data with regard to mortality risk in undiagnosed CD are likely due to differences in age, definitions of seropositivity, and follow-up time, but given this residual uncertainty in magnitude of risk, if any, these data do not justify population screening.
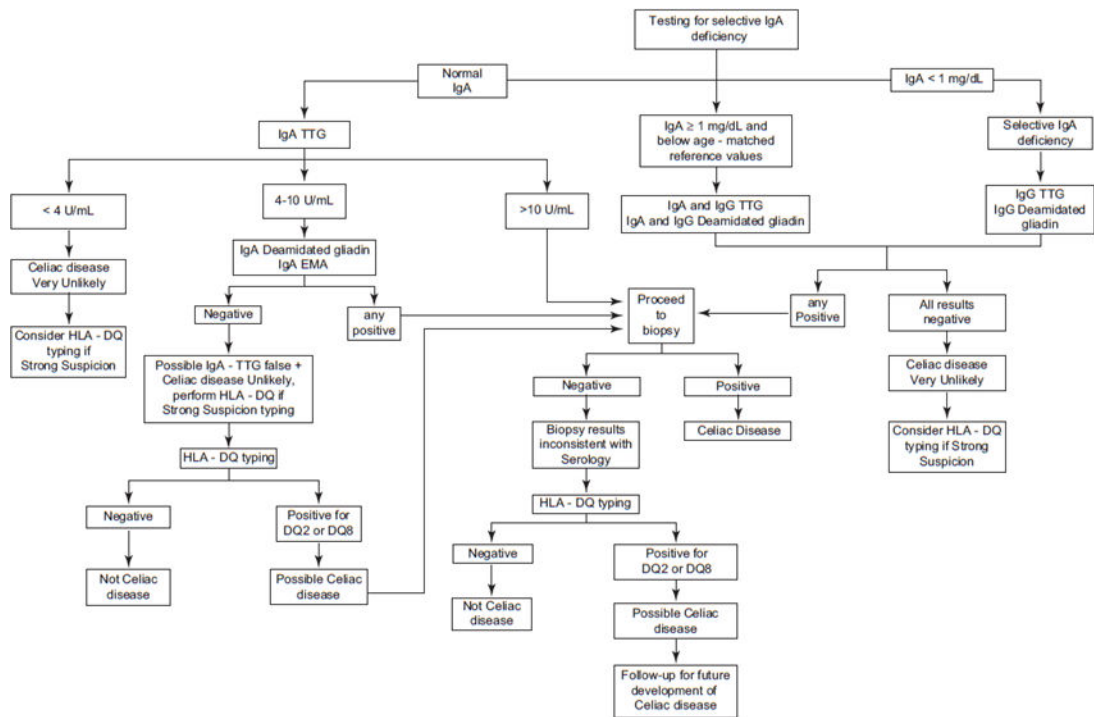
FIGURE 1.
Mayo Clinic Celiac Disease Diagnostic Testing Algorithm. Serology and genetic testing are part of an automated laboratory cascade testing, meaning that a sequence of tests driven by real time results is used to diagnose celiac disease using a single blood draw. This cascade testing is intended for adults on a gluten-containing diet. (Modified and used by permission of Mayo Foundation for Medical Education and Research. All rights reserved).