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AGA Clinical Practice Update on Diagnosis and Monitoring of Celiac Disease: Changing Utility of Serology and Histologic Measures: Expert Review

Steffen Husby^{#1}, Joseph A. Murray^{#2}, and David A. Katzka^{#2}

¹Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark

²Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota

These authors contributed equally to this work.

Abstract

Purpose: The purpose of this clinical practice update is to define key modalities in the diagnosis and monitoring of celiac disease (CD) in adults as well as in children and adolescents.

Methods: The recommendations outlined in this expert review are based on available published evidence, including cohort and case-control studies of the diagnostic process as well as controlled and descriptive studies of disease management.

Best Practice Advice 1: Serology is a crucial component of the detection and diagnosis of CD, particularly tissue transglutaminase-IgA (TG2-IgA), IgA testing, and less frequently endomysial IgA testing.

Best Practice Advice 2: Thorough histological analysis of duodenal biopsies with Marsh classification, counting of lymphocytes per HPF, and morphometry is important for diagnosis as well as for differential diagnosis.

Best Practice Advice 2a: TG2-IgA, at high levels ($> \times 10$ upper normal limit) is a reliable and accurate test for diagnosing active CD. When such a strongly positive TG2-IgA is combined with a positive endomysial antibody in a second blood sample, the positive predictive value for CD is virtually 100%. In adults, esophagogastroduodenoscopy (EGD) and duodenal biopsies may then be performed for purposes of differential diagnosis. **Best Practice Advice 3:** IgA deficiency is an infrequent but important explanation for why patients with CD may be negative on IgA isotype testing despite strong suspicion. Measuring total IgA levels, IgG deamidated gliadin antibody tests, and TG2-IgG testing in that circumstance is recommended.

Best Practice Advice 4: IgG isotype testing for TG2 antibody is not specific in the absence of IgA deficiency.

Correspondence: Address correspondence to Joseph A. Murray, M.D., Mayo Clinic, 200 First Street SW, Rochester, MN 55902. Telephone: 507-255-5713. Fax: 507-255-6318., murray.joseph@mayo.edu.

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Best Practice Advice 5: In patients found to have CD first by intestinal biopsies, celiac-specific serology should be undertaken as a confirmatory test prior to initiation of a GFD.

Best Practice Advice 6: In patients in whom CD is strongly suspected in the face of negative biopsies, TG2-IgA should still be performed and, if positive, repeat biopsies might be considered either at that time or sometime in the future.

Best Practice Advice 7: Reduction or avoidance of gluten prior to diagnostic testing is discouraged as it may reduce the sensitivity of both serology and biopsy testing.

Best Practice Advice 8: When patients have already started on a GFD prior to diagnosis, we suggest that the patient goes back on a normal diet with three slices of wheat bread daily preferably for 1–3 months before repeat determination of TG2-IgA.

Best Practice Advice 9: Determination of HLA-DQ2/DQ8 has a limited role in the diagnosis of CD. Its value is largely related to its negative predictive value to rule out CD in patients who are seronegative in the face of histologic changes, in patients who did not have serologic confirmation at the time of diagnosis, and in those patients with a historic diagnosis of celiac disease; especially as very young children prior to the introduction of celiac-specific serology.

Management: **Best Practice Advice 10:** Celiac serology has a guarded role in the detection of continued intestinal injury, in particular as to sensitivity, as negative serology in a treated patient does not guarantee that the intestinal mucosa has healed. Persistently positive serology usually indicates ongoing intestinal damage and gluten exposure. Follow up serology should be performed 6, 12 months after diagnosis, and yearly thereafter.

Best Practice Advice 11: Patients with persistent or relapsing symptoms, without other obvious explanations for those symptoms, should undergo endoscopic biopsies to determine healing even in the presence of negative TG2-IgA.

Keywords

celiac disease; histology; antibodies; management

Introduction

The concept of CD has undergone significant expansion in recent years. At one side, there is increased public concern about the effects of gluten on health and the trend of gluten sensitivity at large; and on the other side, an increasing awareness of the multifaceted symptomatology and systemic effects of CD. CD is strongly genetically dependent and particularly related to the presence of HLA-DQ2/DQ8¹. Furthermore, it is increasingly recognized as a common disease with a prevalence in a number of adult and childhood populations close to 1%^{1, 2}. The scope of this paper is to give a comprehensive update as to the options and uncertainties related to diagnosis and follow-up of CD. As CD may occur at all ages, a considerable portion of disease-compatible characteristics are universally applicable; whereas other aspects are specifically related to age groups. The diagnosis of CD is variably defined by four components: symptoms, the presence of HLA-DQ2/DQ8, celiac antibodies in serum, and duodenal histology. A crucial question³ is whether the diagnostic cornerstone, the duodenal biopsy with histological analysis, may be omitted in a proportion

of patients who fulfill other diagnostic criteria for CD. Two recent papers in *Gastroenterology* present evidence on this issue in children^{4, 5}.

The Role of Symptoms/Signs

Symptoms and signs are an important component of every diagnostic effort, as they bring the patient to the doctor's office and aid in preliminary problem sorting, even if symptoms are diffuse and multifaceted; as may be the case in CD. Symptoms of CD may be gastrointestinal (e.g., diarrhea or constipation) or extra-intestinal (e.g. dermatitis herpetiformis). The aim is to increase the prevalence of celiac disease in the tested population from 1%, which is the population prevalence, to 5–10% or above, where serologic testing and histologic analysis have an increased positive predictive value⁶. Do all symptoms seen with CD carry similar sensitivity and specificity for the disease? Probably not. Data with reporting of different symptoms in a recent pediatric prospective study suggests that malabsorption symptoms (including failure-to-thrive) increase the accuracy of antibody testing from 98–100%⁵. The co-existence of other diseases that are well known risk factors for CD further supports the likelihood of suspected diagnosis. These include: autoimmune diseases as type 1 diabetes, autoimmune thyroid disease, autoimmune liver disease; and chromosome abnormalities such as Down's and Turner syndrome. Such co-occurrence is of diagnostic value; as CD is present in 5–10% of children with type 1 diabetes⁷. Familial occurrence is common, as asymptomatic first degree relatives of celiac patients in a recent meta-analysis had a 7.5 % risk of CD⁸.

Serology

The discovery of transglutaminase-2 as the major autoantigen in CD⁸ led to the development of assays for IgA transglutaminase antibodies (TG2-IgA). Serological testing for TG2-IgA has become important in the diagnosis of CD based on increasing quality and convenience of assays such as ELISA, which are well-suited for automation and high-throughput testing. The IgA endomysial antibody test (EMA) based on fluorescence-testing on primate esophagus or human umbilical cord is based on antibody reactivity to tissue-bound TG-2. EMA is more labor-intensive and depends on personal judgement and experience. Assays for deamidated gliadin peptide (DGP), antibodies have been shown to have reasonably high accuracy⁸, although inferior to TG2-IgA. A multitude of commercial assays for TG2-IgA have been developed and standardized with laboratories encouraged to participate in quality control measures on a national or international basis. TG2-IgA has been employed as a screening test in multiple studies and in populations with a low incidence of CD⁸. EMA is well suited for second-line confirmatory testing, as EMA has a high specificity⁹. Point-of-care (POC) tests have been advocated for screening purposes and results comparable to conventional testing have been obtained¹⁰. However, POC tests may present difficulties with quality control when in the hands of inexperienced users and the advantage of rapid results is rarely decisive in the diagnosis of CD. Who should then be tested for CD and with what tests? A pretest probability of 5–10% seems advantageous to obtain significant accuracy⁶ which may be obtained by selecting patients with signs/symptoms consistent with CD or asymptomatic patients in the proper risk groups (e.g. type 1 diabetes or first degree

relatives). Population screening data suggests that even in the general population TG2-IgA assays may give reasonable results¹¹.

Significance of HLA-DQ2 and – DQ8

CD is strongly influenced by genetic factors as shown in twin studies¹, with most of the genetic dependence residing in HLA-DQ2 and – DQ8¹². A gene dose effect is present as the subtype HLA-DQ2.5 in a homozygous pattern, makes CD likely; whereas heterozygous HLA-DQ2.2, at the other side of the spectrum, makes CD unlikely. The absence of HLA-DQ2/DQ8 has primarily been used to exclude the disease with a high negative predictive value. Recent studies have shown that, in clinical practice, determination of HLA-DQ2/DQ8 is of no additional diagnostic value in cases with a high level of serum TG2-IgA antibodies^{5, 13}.

In conclusion, determination of HLA-DQ2/DQ8 may be reserved for second-line evaluation of patients where the diagnosis is doubtful (e.g. due to inconclusive celiac antibodies, histology, or prior GFD).

Biopsy and Histopathological Analysis

The analysis of duodenal biopsy specimens forms the classical diagnosis of CD, and represented an immense leap forward when it was introduced as the diagnostic criterion for CD in the 1950's. Today biopsies should be taken at EGD which allows the possibility of multiple biopsies from different parts of the duodenum. Biopsies from the bulb should be included, taking into account Brunner glands and other variants which may disturb the histologic interpretation^{14, 15}. The duodenal biopsy has been regarded as the reference standard for the diagnosis of CD, but lack of sampling quality has been suggested in several comparative studies^{15, 16}. Additionally, criticism has been raised as to the quality of duodenal biopsy interpretation¹⁷, particularly from non-specialized pathology departments. The process of placing the biopsy, the subsequent cutting and formalin fixation demands time and expertise - which is not always available or followed¹⁵. In practical terms, 5% of biopsies may lead to diagnostic uncertainty⁵. Description of the biopsies including positioning, Marsh classification, villus-crypt (VCr)-ratio and counting of lymphocytes (above 25 per HPF) to define lymphocytosis is recommended. CD3 staining for T-cells may be included¹⁸. Gamma/delta T-cell markers¹⁹ as well as IgA transglutaminase antibody deposits²⁰ may be supportive in the analysis.

Algorithms: Can diagnostic biopsy be avoided in selected cases?

The classical algorithm for the diagnosis of CD in children and adults is to perform a EGD with duodenal biopsies on the background of symptoms attributable to malabsorption or to conditions associated with CD. The development of reliable antibody tests has led to a combination strategy. In adults all guidelines including the ACG guidelines²¹ recommend screening with celiac antibody testing and, if positive, performing a biopsy in populations with a low-prevalence (<5%) of CD. The North American Society for Pediatric Gastroenterology Hepatology and Nutrition (NASPGHAN) guidelines from 2005²²

recommend performing a biopsy in all cases of suspected CD in children whereas the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guidelines from 2012²³ recommend using quantitative determination of TG2-IgA for first line screening. If the antibody titer is above x 10 ULN in a symptomatic patient, the guidelines give the option to perform further tests (TG2-IgA, EMA and HLA-DQ2/DQ8) in a second blood sample. If they all are confirmative, the child may be diagnosed with CD provided symptoms subside after the institution of a GFD. In practice, this strategy may reduce the need of EGD by 30–50%⁵. In unclear cases histological analysis is important, and even an approach with gluten challenge may be warranted. When patients have already started on a GFD prior to diagnosis we suggest that the patient goes back on a normal diet with three slices of wheat bread daily for 1–3 months followed by TG2-IgA determination, although even a shorter period of time has been advocated.

Management and Follow-up

The management and follow-up of patients with celiac disease (CD) is preferentially performed with a team-based approach in which the dietician has an important role in the practical advice on life-style and choice of foods²⁴. The majority of the patients will comply satisfactorily with a gluten-free diet (GFD) and experience relief of their symptoms, as well as decreasing celiac antibody levels. A reasonable follow-up schedule will be every 12 months. An open access or online service, perhaps aided with short message services (SMS), may improve adherence²⁵. In children and adolescents, a satisfactory increase in weight and height is an essential marker of the success of the GFD; whereas the adult patients may experience more subtle improvement. Lack of compliance in a GFD may lead to deterioration of quality of life²⁶. Long-term side effects of a GFD may be related to lack of vitamins and fiber in the diet. Lack of adherence to GFD may result in symptoms and complications of CD such as ongoing and worsening of malabsorption, anemia, and osteoporosis.

In practice, the majority of adult patients are not followed up, as shown in a study from Olmsted County where 35% of patients were adherent to follow up four years after diagnosis²⁷. Societal circumstances may affect this percentage, with national differences. Concordantly, the frequency of therapy-resistant CD occurs in a significant proportion of adults (20%)²⁸.

Maybe not surprising, teenagers are less satisfied with the impact of CD on their lives and even less adherent to a GFD. Whether the diagnosis of CD is based on symptoms or objective screening tests seemingly does not influence long-term adherence to GFD²⁹. Notably, children who are lost to follow up are more frequently non-adherent to GFD and are antibody-positive³⁰. As to malnutrition and growth, routine testing for vitamin and mineral deficiencies seems unnecessary in the large majority of children who attend registered follow-up and grow and develop normally without any symptoms³¹.

A key issue in the follow-up is the usefulness of serology; whether a decline in antibody levels is sufficient evidence for proper management. The usefulness of serology has been reported for children, best for EMA, and with a median time for mucosal healing of 2.2

years³². In a recent meta-analysis, the positive predictive value and sensitivity of persistently positive TG2-IgA determination was fairly low; with a sensitivity at 0.38 for adults, higher (0.70) for children. The negative predictive value of serology in adult patients on a GFD for 1 year or more was higher, with a specificity of 0.80 for adults, and 0.87 for children³³. It may be concluded that the usefulness of serology at follow-up is limited for adults and better for children. A refinement of the TG2-IgA determination utilizing the detectable levels below the upper normal limit may add in the identification of CD patients with mucosal healing³⁴.

The intestinal biopsies from an EGD are an important tool in the follow-up of CD. Histological evaluation is in essence an evaluation of mucosal healing. If damage equating to at least Marsh 2 changes are still present, another biopsy is required, after 12 months. However, the correlation between symptoms, mucosal healing, and later outcome of CD is not clear. In one study in adults factors predicting incomplete recovery were malabsorption (55% vs. 41%, $P = 0.003$), high EMA (46% vs. 25%, $P < 0.001$), and severe mucosal damage (total atrophy 32% vs. 19%, $P < 0.001$) at diagnosis³⁵. Symptoms did not reliably predict lack of mucosal healing and the majority of patients with lack of healing were without symptoms³⁶. However, in large studies the majority of adult patients did achieve complete mucosal healing³⁷. Irreparable damage in the mucosa may lead to the rare but serious appearance of refractory CD type 1 and type 2 with the latter having a considerable mortality after five years³⁸. While failure to heal the intestine was associated with an increased lymphoma risk, it was not associated with excess mortality. However, adequate studies where all patients have had follow up biopsies are inadequately powered to address long term risk of rare events²⁸. Even though data is conflicting for adults with lack of mucosal healing; the large majority do well, but with a small risk of non-responsive CD, which may lead to further complications.

Concluding Remarks

Significant changes have occurred in the diagnosis of CD in the last decade with serology gaining greater clinical importance based on better assay performance. The diagnosis of CD relies on a combination of symptom recognition, serology and histological analysis of duodenal biopsies. In children and adolescents, repeated serological testing with high TG2-IgA levels may render a gastroscopy with biopsy unnecessary. Cases with IgA-deficiency deserve special recognition. Treatment consists foremost of a GFD. It is important not to initiate a GFD before measurement of antibodies and biopsy. Follow-up secures the avoidance of long-term side effects of the GFD and aids the adherence to the GFD. The utility of serology vs. histology in follow-up has not been definitively settled.

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Abbreviations:

(CD)	Celiac Disease
(DGP)	Deamidated Gliadin Peptide
(EMA)	Endomysial Antibody
(ESPGHAN)	European Society for Paediatric Gastroenterology Hepatology and Nutrition
(GFD)	Gluten-Free Diet
(NASPGHAN)	North American Society for Pediatric Gastroenterology Hepatology and Nutrition
(POC)	point of care
(TG2)	transglutaminase-2

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Figure.
Suggested biopsy-avoiding diagnostic pathway for coeliac disease. On the right is the process for an asymptomatic or at-risk child. A positive anti-TG2 result should lead to biopsies and histological analysis for diagnosis. Potential celiac disease suggests further follow-up.