AGA Clinical Practice Update on the Evaluation and Management of Seronegative Enteropathies

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Abstract

Description: We aim to provide a consensus statement for the best approaches for diagnosis and management of patients with suspected enteropathy but negative results from serologic tests for celiac disease (seronegative enteropathy).

Methods: We collected findings from published cohort, case–control, and cross-sectional studies of diagnosis and case series and descriptive studies of management of patients believed to have celiac disease or other enteropathies unrelated to gluten but negative results from serologic tests.

Best Practice Advice: Best practice advice 1: review histologic findings with experienced pathologists who specialize in gastroenterology. Best practice advice 2: serologic tests are essential for an accurate diagnosis of celiac disease. For patients with suspected celiac disease but negative results from serologic tests, total immunoglobulin A (IgA) level should be measured; patients should also be tested for anti-tissue transglutaminase, IgA against deamidated gliadin peptide, and endomysial antibody (IgA). Patients with total IgA levels below the lower limit of detection and IgG against tissue transglutaminase or deamidated gliadin peptide, or endomysial antibody, should be considered to have celiac disease with selective IgA deficiency rather than seronegative celiac disease. Best practice advice 3: patients' diets should be carefully reviewed and duodenal biopsies should be collected and analyzed at the time of serologic testing, to determine exposure to gluten and accuracy of test results. Best practice advice 4: thorough medication histories should be collected from patients, with attention to angiotensin II receptor blockers such as olmesartan, along with travel histories to identify potential etiologies of villous atrophy. This will guide additional testing. Best practice advice 5: patients should be analyzed for disease-associated variants in human leukocyte antigen genes; results must be carefully interpreted. Negative results can be used to rule out celiac disease in seronegative patients. Best

practice advice 6: patients with suspected celiac disease who are seronegative but have villous atrophy and genetic risk factors for celiac disease must undergo endoscopic evaluation after 1–3 years on a gluten-free diet, to evaluate improvements in villous atrophy. A diagnosis of seronegative celiac disease can then be confirmed, based on clinical and histologic markers of improvement on the gluten-free diet. Best practice advice 7: seronegative patients with an identified cause for enteropathy should be treated accordingly; a follow-up biopsy may or may not be necessary. Best practice advice 8: patients with persistent signs and symptoms who do not respond to a gluten-free diet, and for whom no etiology of enteropathy is ultimately identified, should be treated with budesonide.

Conclusions: These best practice guidelines will aide in diagnosis and management of patients with suspected celiac disease but negative results from serologic tests.

KEY WORDS: GFD, coeliac, CeD, tTg

Abbreviations used in this paper: CeD, celiac disease; CVID, common variable immunodeficiency; DGP, deamidated gliadin peptide; EGD, esophagogastroduodenoscopy; EMA, anti-endomysial antibody ; GFD, gluten-free diet; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; IELs, intraepithelial lymphocytes; IgA, immunoglobulin A; tTG, anti-tissue transglutaminase

Introduction

Seronegative enteropathy, characterized by some degree of villous atrophy and negative tissue transglutaminase (tTG), deamidated gliadin peptide (DGP and anti-endomysial antibody (EMA), is a common clinical scenario encountered by gastroenterologists. While seronegative celiac disease (CeD) is one etiology and a frequent cause of seronegative enteropathy [1-3], villous atrophy is not specific for CeD. The differential diagnosis for seronegative enteropathy is broad and includes immune-mediated, infectious and iatrogenic causes, among others. The patient characteristics associated with seronegative enteropathy are difficult to describe, due to the heterogeneity of underlying etiologies. An accurate diagnosis of seronegative enteropathy may be complicated by challenges such as poorly oriented duodenal mucosa leading to misinterpretation of histological findings, the use of immunosuppressive agents masking serological findings, or inadequate or incorrect use of serology testing[4]. Previous work detailing the prevalence of seronegative CeD [5], diagnosis of seronegative villous atrophy [2, 6] and management recommendations for seronegative villous atrophy are available[1, 7-9]. However, there is limited evidence to guide clinicians regarding the minimal serological tests necessary, the role of the GFD in diagnosis and management, and the role of an expert pathologist in evaluating the diagnosis of seronegative enteropathy. Furthermore, the prognosis of seronegative enteropathy is poor when compared to patients with other causes of villous atrophy such as those with classic CeD, making accurate diagnosis and treatment of the utmost importance [3, 5, 10]. Furthermore, distinct therapy is available for many of the identifiable causes of seronegative enteropathy [1, 7, 8], and following an accurate diagnosis these treatments are highly effective. The purpose of this article is to provide a comprehensive and methodical approach for examining the differential diagnosis of and targeted treatment for seronegative enteropathy. Since seronegative CeD is a frequent cause of seronegative enteropathy here we discuss seronegative CeD in depth and separately from other etiologies of seronegative enteropathy. This expert review was commissioned and approved by the AGA Institute Clinical Practice Updates Committee (CPUC) and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA

membership, and underwent internal peer review by the CPUC and external peer review through the standard procedures of Gastroenterology.

Definition of Seronegative Enteropathy

Seronegative enteropathy is characterized by some degree of villous atrophy and negative tissue transglutaminase (tTG), deamidated gliadin peptide (DGP) and anti-endomysial antibody (EMA). Seronegative CeD is a common cause of seronegative. Seronegative CeD is defined as patients with or without gastrointestinal signs and symptoms of CeD in the presence of villous atrophy and compatible genetics and without IgA tTG, IgA DGP, and IgA EMA who show clinical and histological response to the GFD and for whom other etiologies have been examined. Patients with IgA deficiency, positive IgG based serology testing (IgG tTG, IgG DGP, and/or IgG EMA), and villous atrophy should be diagnosed with IgA deficiency associated with CeD, rather than seronegative enteropathy.

Histological Evaluation of Seronegative Enteropathy

A diagnosis of seronegative enteropathy requires an esophagogastroduodenoscopy (EGD) with duodenal and/or jejunal oriented biopsies showing villous atrophy. To establish an accurate diagnosis, a total of 4-6 biopsy specimens [11] should be submitted from the second portion of the duodenum and the duodenal bulb [12]. Histological findings should be reviewed with an experienced gastrointestinal pathologist to confirm that villous atrophy is present and to ensure that the biopsies are optimally oriented for evaluation [13]. Clinicians should consider using the Corazza-Villanacci classification to describe the histological findings in the duodenum [14]. In addition, while confirming a diagnosis of seronegative CeD by identifying tTG-specific, gluten-dependent deposits in the duodenal mucosa of patients has been described, it is not currently available for clinical purposes [15]. In all cases of seronegative enteropathy, clinicians should consider having experienced pathologists consult to confirm proper orientation of the duodenal tissue and to look for signs of other etiologies of enteropathy (Figure 1). These include the presence of granulomas, decreased goblet cells or absent/reduced plasma cells in the lamina propria, which may be suggestive of Crohn's disease, autoimmune enteropathy or common variable

immunodeficiency (CVID), respectively [13, 16]. When possible, experienced pathologists should review previous patient biopsies to compare disease progression or improvement of histological findings. Of note, patients who present only with increased intraepithelial lymphocytes (IELs) and normal villi should not be considered to have seronegative CeD or a seronegative enteropathy, as villous atrophy must be present [13, 17].

Evaluation for Celiac Disease

Seronegative CeD is the most common etiology of seronegative enteropathy. It represents up to one third of cases in Caucasians, and therefore, it should be considered early in the diagnostic work up [1-3, 5]. The definition for seronegative CeD is inconsistent in the literature. Some authors describe patients with IgA deficiency and positive IgG-based antibodies as having seronegative CeD [10], while others do not [4, 5]. Confusing the matter further, patients with only subtle duodenal findings, rather than villous atrophy, may be described as having seronegative CeD [18, 19]. Here, we define seronegative CeD as patients with or without gastrointestinal signs and symptoms of CeD in the presence of villous atrophy and compatible human leukocyte antigen (HLA) genetics, and without IgA/IgG tTG and IgA/IgG DGP and IgA/IgG EMA antibodies, who show clinical and histological response to the GFD and for whom other etiologies have been examined [6]. It comprises approximately 1.7-5 % of patients with CeD [4, 5]. Below we discuss the approach to using serology, HLA genetics and the GFD in determining whether seronegative CeD is the underlying etiology of seronegative enteropathy.

Serology

Serology is a crucial component in the diagnosis of CeD. Measuring serum total IgA and IgA tTG is recommended as the first step for patients suspected of having CeD, and detection of IgA EMA and/or IgA DGP may be indicated in specific cases [17, 20]. While discrepancy between these antibodies is common clinically, true seronegative CeD requires all IgA antibodies to present as negative. It is important to obtain or review serum total IgA levels in patients with possible seronegative CeD as selective or partial IgA deficiency occurs 10-15 times more frequently in patients with CeD compared to

healthy controls [21, 22]. If IgA deficiency is identified, patients should undergo serum IgG-based testing with IgG tTG and IgG DGP, and IgG EMA [17]. If IgG-based testing for CeD is positive and villous atrophy is present, a diagnosis of selective IgA deficiency associated with CeD, rather than seronegative enteropathy, should be made in the appropriate clinical setting inclusive of clinical and histological response to the GFD. Furthermore, it is essential to determine whether a patient has reduced or eliminated gluten or is on immunosuppressive therapy for another condition prior to testing, as serology results may be falsely negative [6].

HLA Genetics

In cases of suspected seronegative CeD, genetic testing should be performed to determine whether the patient carries an HLA genotype (DQ2 or DQ8) that is compatible with developing CeD. It is well described that up to 30% of the population may carry one or both of these genes, and yet only 2-3% of these genetically at-risk individuals will develop CeD during their lifetime [23]. Thus, HLA testing is most helpful for patients if results are negative, as this excludes the possibility of seronegative CeD as a diagnosis. However, compatible genetics infer that the patient has a risk of developing CeD, but these results cannot stand alone as a diagnostic criterion. HLA genetic testing may be particularly useful in cases when seronegative enteropathy is present, the diagnostic work-up for CeD is not complete, and the patient has already initiated a GFD and reports severe symptoms with gluten exposure [20]. In this case, a negative result for HLA DQ2 and DQ8 would confirm that CeD is not present. This would prevent the patient from undergoing a gluten challenge, an unnecessary trial of the GFD, and further diagnostic work-up for CeD. However, before confirming that HLA DQ2 and DQ8 are not present, results should be carefully interpreted. It is prudent that the gastroenterologist or CeD specialist review all alleles tested and reported (or obtain the alleles if not reported) by the lab, since commercial and academic labs may not report all possible alleles associated with CeD. Therefore, clinicians should carefully evaluate for HLA DQ2.5 (DQA1*0501, DQB1*0201), HLA DQ8(DQA1*03, DQB1*0302), HLA DQ 2.2 (DQA1*0201, DQB1*0202) and HLA DQ7.5 (DQA1*05, DQB1*0301) and review whether half heterodimers, which are compatible with CeD, are present before determining that a patient is HLA negative [24]. There is a

view that in the presence of a family history and a compatible HLA haplotype, mild enteropathy short of villus atrophy may be a form of CeD even in the absence of serologies [25]. However, given the uncertainty regarding the necessity of the gluten-free diet in this circumstance and the natural history of this condition, the optimal management of seronegative mild enteropathy in this context is unknown.

Gluten-Free Diet

Patients must not avoid gluten prior to diagnostic testing for CeD and reducing gluten should be discouraged, since these practices will limit the accuracy of both serological and histological results. It is imperative to discuss the amount of gluten in the patient's diet at the time of testing to determine whether the results are reliable. If gluten has been reduced or removed from the diet, additional or repeat testing should be completed after the patient consumes a regular diet that contains 1-3 slices of gluten-containing bread daily for 1-3 months to identify clinically meaningful endpoints [26, 27].

Evaluation of Other Conditions

There is a wide range of other conditions known to cause villous atrophy (Table 1). A thorough diagnostic work-up including a detailed medical history should be considered to evaluate for and guide the diagnostic work-up of other potential etiologies (Figure 1). Seronegative enteropathy has been linked to infectious etiologies such as parasitic infections and human immunodeficiency virus (HIV) [28], inflammatory conditions such as Crohn's disease and eosinophilic enteritis [2], immune- mediated etiologies such as autoimmune enteropathy and CVID [3, 29] and iatrogenic causes such as radiation enteritis or medications[1, 8, 28]. Clinicians should pay particular attention to obtaining a thorough medication history to determine whether a patient is taking an angiotensin II receptor antagonist, such as olmesartan, which has been described as causing enteropathy [8]. In some cases, this has led patients to be incorrectly diagnosed with refractory CeD [1]. Other medications including azathioprine [30] and mycophenolate mofetil [31], among others, also have been reported to cause enteropathy, which resolves with the discontinuation of the medication.

Conducting a detailed travel history is also necessary to identify risk factors associated with tropical sprue or Giardia, as these factors warrant additional testing. In addition, assessment of symptoms

such as fever, bloody diarrhea and weight loss may suggest Crohn's disease or a lymphoproliferative disorder [28], and signs such as a low total IgG, IgA and IgM may suggest common variable immune deficiency (CVID) [6]. In these cases, the role of additional testing such as computed tomography enterography, capsule endoscopy, and colonoscopy should be considered. Finally, in some cases no definitive etiology can be identified. These cases of idiopathic villous atrophy may be further categorized, based on clinical, histological and genetic characteristics, as due to transient conditions such as infection, immune-driven conditions or lymphoproliferative disorders [32]. A complete list of conditions other than seronegative CeD and the characteristic histological features, associated tests and treatments are described in Table 2.

Management and Treatment of Seronegative Enteropathy

Seronegative CeD

Once a diagnosis of seronegative CeD has been confirmed, patients should meet with a dietician to learn about the GFD frequently in the first year to ensure they have an adequate understanding of the GFD. Thereafter, annual meetings with a dietitian should be scheduled for follow-up care. Since serological markers cannot be used for follow-up in the case of seronegative CeD, clinical and histological improvement on a GFD is required to ultimately confirm the diagnosis of seronegative CeD. Duodenal biopsies should be obtained during EGD in the same manner as described above. Histology should be reviewed by a gastrointestinal pathologist to compare the initial and follow-up biopsies and comment on whether improvement or resolution has occurred. The timing of the follow-up biopsy will depend on the patient's clinical status and adherence to the GFD, but it may occur approximately 12 months after diagnosis [27] or sooner in those with severe illness. Patients should meet with a dietician before a repeat endoscopy is performed in order to ensure they are following the GFD correctly. If seronegative CeD is suspected, but the patient does not respond to the GFD, clinicians should consider referring the patient to a celiac disease center for consideration, work-up and treatment of refractory CeD [33]. Refractory CeD may be a complication of CeD or seronegative CeD. Patients may or may not have positive serology and therefore whether it is classified as a seronegative enteropathy is dependent on the clinical case. If

refractory type 2 CeD is considered a possibility, flow cytometry and T-cell gene rearrangement studies should be performed [33]. Clinicians should consider the open capsule budesonide protocol, starting at 9mg daily, be used as a first line treatment for refractory CeD [34]. The length of the treatment course will depend on the patient's symptoms, and budesonide should be tapered slowly over a 9-month period [34]. Alternative medications to consider include prednisone and azathioprine, among others, pending the patient's clinical status and treatment response [35].

Other Etiologies of Seronegative Enteropathy

Patients who have an identified etiology of seronegative enteropathy should be treated accordingly (Table 2). In cases where an underlying cause was identified, a follow-up EGD with biopsy may not be indicated according to the etiology identified, treatment, and clinical status. In other cases, no underlying etiology may be identified. For example, in a study of 200 cases of SNVA, Aziz et al. found that they were unable to identify an underlying etiology in 18% of cases [3]. However, 72% of these idiopathic cases had resolution of villous atrophy without intervention 9 months following the initial biopsy suggesting a transient atrophy [3]. Based on this, for patients who are stable and for which the etiology of seronegative enteropathy cannot be determined, repeating an endoscopy after a period of time without intervention may be considered. Ultimately, follow-up endoscopy and the timing at which they are performed should be determined in response to the patient's underlying etiology, treatment and clinical condition. In other cases, patients with seronegative enteropathy for which no etiology has been identified may be clinically unstable. In these cases, clinicans may consider budesonide, starting at 9mg daily, as a first line treatment followed by prednisone or azathioprine based on the patient's clinical status and response to treatment [34, 35].

Conclusion

Seronegative enteropathy is a histological finding that may be identified in accordance with a wide-range of etiologies. In cases where seronegative enteropathy is suspected, it is of utmost importance that biopsies are reviewed by an expert pathologist to determine and confirm whether enteropathy is present.

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A thorough medical history with careful attention to medication and travel history is necessary to determine possible causes of seronegative enteropathy, as distinct treatment is available. Seronegative CeD is the most common cause of seronegative enteropathy. However, diagnosis can be complicated by misinterpretation of histological findings, insufficient serological testing, IgA deficiency, and initiation of the GFD before testing is complete. Confirmation of seronegative CeD requires compatible HLA genetics, clinical improvement on a GFD, and a follow-up endoscopy with biopsy to ensure mucosal improvement after sufficient time on a GFD.

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Table 1: Etiologies of Seronegative Villous Atrophy

Immune Mediated
Serongative CeD
Common variable immune deficiency
Autoimmune enteropathy
Intestinal lymphoma
Sarcoidosis

Infectious
Parasitic infections (Giardia lamblia)
Tropical sprue/Environmental enteropathy
Whipple's disease
Small intestinal bacterial overgrowth
Tuberculosis
HIV enteropathy

Iatrogenic
Medications
- Olmesartan
- Azathioprine
- Mefenic acid
- Methotrexate
- Mycophenolate mofetil

Chemotherapy
Graft vs. host disease
Radiation enteritis
Transplanted small intestine

Inflammatory
Crohn's disease
Collagenous sprue
Eosinophilic enteritis

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Table 2: Conditions, Characteristics and Treatment of Potential Etiologies of Seronegative Enteropathy

Condition	Pertinent history	Histology findings	Other Tests	Treatment
Giardiasis [27]	Diarrhea, abdominal pain, weight loss	Identification trophozoites on villi	PCR from duodenal aspirate, positive stool specific immunoassay	Metronidazole
Tropical sprue [34]	Travel to endemic areas, B12 and folate deficiency	Increased plasma cells and eosinophils in LP, changes in duodenum. Jejunum and ileum	-	Tetracycline or doxycycline + folic acid
Collagenous sprue [10]	Diarrhea, abdominal pain, weight loss	Subepithelial collagen deposition	-	GFD +/- Immunosuppression (budesonide, prednisone, azathioprine)
CVID [9]	Onset after age 2, poor response to vaccines, recurrent infections, persistent diarrhea	Absence of plasma cells, polymorphonuclear infiltrate	IgG < 5g/L+ low IgA or IgM	Budesonide
Autoimmune enteropathy [9]	Intractable diarrhea and weight loss	Few IELs, lymphoplasmacytic infiltrate in LP, decreased goblet cells, neutrophilic cryptitis	Anti-enterocyte antibody	Immunosuppression (steroids, azathioprine, infliximab etc)
Intestinal lymphoma [9]	Diarrhea, abdominal pain, fever, weight loss, bleeding, signs of obstruction, perforation	Monoclonal population of T cells	Inflammatory markers, CT scan, capsule endoscopy, PET scan	Hematology consultation
SIBO [27]	Anatomical abnormalities, poor motility, other predisposing conditions	Increased IELs and neutrophils, increased plasma cells in LP	H_2-glucose breath test, duodenal aspirate	Antibiotics
Crohn's disease [35]	Bloody diarrhea, fever, weight loss	Aphthous ulceration, skip lesions, granulomas	Elevated ESR, CRP	Immunosuppression, biologic agents
Eosinophilic gastroenteritis [27]	Multiple allergies, atopy	Massive eosinophilic infiltration	Peripheral hyper eosinophilia	dietary therapy, glucocorticoids
HIV enteropathy [36]	Presence of opportunistic infections	Decrease CD4+ T lymphocytes, increase in CD8 + T lymphocytes	HIV antibody test	Antiretroviral therapy
Tuberculosis [35]	Cough, ascites, night sweats	Granulomatous disease	Interferon-gamma release assay, CT, ascitic fluid analysis	Anti-tuberculous therapy

Whipple disease [27]	Joint inflammation, hyperpigmentation of sun exposed skin	PAS^+ macrophagic infiltration of the lamina propria	Positive PCR for *T. Whipplei*	Ceftriaxone or penicillin G then TMP/SMX hydroxychloroquine and doxycycline
Radiation enteropathy [37]	History of radiotherapy	Lamina propria fibrosis	-	-
Graft vs. Host Disease [38]	Diarrhea, abdominal pain, nausea, vomiting, anorexia, PMH of bone marrow transplantation	Crypt cell necrosis, loss of epithelium	-	prednisone or budesonide

Abbreviations: HIV: human immunodeficiency virus, SIBO: small intestinal bacterial overgrowth, CVID: common variable immune deficiency, IEL: intra-epithelial lymphocytes, LP: lamina propri

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