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Review article

Current methods to diagnose the unresponsive and complicated forms of coeliac disease

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ABSTRACT

Coeliac disease is a common disorder. Due to the protean manifestations of the disease and the often mild but indolent course, the diagnosis is often missed. The method to diagnose this in principle reversible disease after the introduction of a gluten-free diet has attracted the attention of several scientific disciplines to find the simplest and most patient-friendly test. This has resulted in a noticeable impact on the clinical practice next to a general increased awareness of its existence, its pathogenesis, its course and recent evidence of increased mortality.

Amendments made in the diagnostic criteria of coeliac disease over the last half century have simplified the diagnosis. However, the aspect most relevant to the specialist in internal medicine is related to its grave consequences when the disease fails to respond to a gluten-free diet. These refractory cases may culminate in severe complications with sombre endings and malignancy. Fortunately, current technology can offer the specialist in internal medicine more facilities to diagnose the cause of the complicated cases in order to attempt to intervene in the course of disease and hopefully save these patients.

We review the available tools that now exist and their indications that can be practiced in a modern clinical setting for the diagnosis of the complicated forms of this disease.

1. Introduction

Coeliac disease (CD) affects 1% of the children and adults in the United States [1] and Europe [2] with similar prevalence rates in many other countries worldwide. The clinical and diagnostic features of CD and extraintestinal manifestation have been recently reviewed. Classical CD is dominated by symptoms and signs of gastrointestinal malabsorption. In the 'atypical forms', the extraintestinal features usually predominate, with few or no gastrointestinal symptoms [3]. The disease is characterized by structural changes of the proximal small bowel mucosa that are induced by immunological process in genetically susceptible individuals after exposure to derivatives of gluten from wheat, rye, and barley [4]. Gluten withdrawal from daily diet leads to symptomatic relief and recovery of the small bowel mucosa in most patients.

The diagnostic panel of CD was originally limited to small bowel histology obtained by the radiographically guided Cosby–Kugler suction capsule [5]. Because these techniques were uncomfortable or time consuming, the use of forceps via a fiberoptic flexible gastroduodenoscope was introduced as a practical method to obtain biopsy specimens from the duodenum [6,7].

2. The diagnosis of coeliac disease

There is no doubt that the more important point to make the diagnosis is to consider the possibility of this disease in the presence of unexplained symptoms and signs that point to a disease of the small intestine. Specific serum antibody tests are available to strengthen the level of suspicion. A positive family history, any of the protean manifestations and the known associated diseases are indications for antibody testing.

3. Serum antibody tests

Important for clinical practice has been the discovery and use of specific serum antibodies with high sensitivity and specificity such as antiendomysium (EMA) [8] and anti-tissue transglutaminase (tTGA) antibodies [9]. In fact, the presence of serum antibodies at the time of diagnosis and their disappearance after following a gluten-free diet confirm the diagnosis of CD according to the revised European Society of Pediatric Gastroenterology and Nutrition (ESPGAN) criteria [10].

Abbreviations: AGA, anti-gliadin antibodies; CD, coeliac disease; CT, computerized tomography; DBE, double-balloon enteroscopy; EATL, enteropathy-associated T-cell lymphoma; EMA, endomysium antibodies; FACS, flow cytometry; GFD, gluten-free diet; HLA, human leukocyte antigen; IELs, intraepithelial lymphocytes; MRI, magnetic resonance imaging; RCD, refractory coeliac disease; tTGA, tissue transglutaminase antibodies; TCR, T-cell receptor; VCE, video capsule endoscopy.

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Antigliadin antibodies (AGA) were used for a long time as a screening test, however studying the test prospectively in a clinical setting revealed low sensitivity (AGA–IgA: 42–46%; AGA–IgG: 61%) and specificity values (AGA–IgA: 85–88%; AGA–IgG: 82–84%) [11,12] rendering these tests outdated for current practice.

Although EMA is considered the gold serological standard in CD, results obtained in the research setting might be less accurate than those observed in the clinical practice due to the high prevalence in study populations [13]. Data from prospective studies revealed that sensitivity varied between 62 and 81% and specificity between 80 and 99% [11,12]. The EMA test has the disadvantage that it correlates with the degree of mucosal damage (mild cases are often negative) is semi-quantitative, time consuming, and operator dependent.

The enzyme tissue transglutaminase (tTGA), first recognized as autoantigen for EMA in 1997, belongs to a family of calcium-dependent enzymes that catalyse the crosslinking of proteins [9]. A wide range of kits measure tTGA quantitatively using guinea pig liver [14] as substrate. However, a superior performance has been achieved when human recombinant [15] or human red cell-derived transglutaminase [11] are used as antigen. The diagnostic performance of tTGA commercial kits in the clinical setting shows an overall sensitivity of 81–88% and a specificity of 84–99% [11,12].

EMA or tTGA are appropriate screening tests in primary care setting but tTGA has extra advantage for its technical capability [16]. Seroconversion after gluten restriction from diet can help to monitor response and patient compliance and hence represents a reasonable follow-up tool [16,17]. The routine measurement of serum IgA levels is currently replaced by testing for IgG isotypes of EMA or tTGA [18].

4. HLA–DQ typing

CD has a stronger genetic component than many other common complex diseases [19]. The spectrum of genetic candidates as in all multifactorial diseases is very wide. However, except from the coeliac specific HLA–DQ2 and HLA–DQ8 heterodimers, no convincing disease association has been found for other genetic test or the test did not find its way from the research field to clinical practice.

The HLA–DQ2 heterodimer is present in 90–95% of patients with CD and the remaining patients carry the HLA–DQ8 heterodimer [20,21]. However, approximately 25–40% of the general population in the United States and Europe carry either the HLA–DQ2 or HLA–DQ8 heterodimer [16].

HLA–DQ typing is a cost-saving first-line screening step to select candidates in high-risk group patients, such as those with the Down syndrome [22] and it can be a useful adjunct in an exclusionary sense when the diagnosis based on other test results is not clear. The absence of the HLA–DQ specific heterodimers could confidently exclude the diagnosis [12,16]. The clinical applicability is at present restricted by its limited availability.

5. Imaging studies

Although it has been suggested in many reports that imaging studies can be helpful in diagnosing CD, the diagnostic yield in uncomplicated disease is variable and inferior to that of other tests.

6. Barium studies

The radiographic signs described in patients with CD include the segmentation and flocculation of the barium column, loss of jejunal folds, oedema of the jejunal wall, dilatation of jejunum or ileum, a reversed jejuno-ileal fold pattern and an abnormal jejuno-ileal calibre [23]. However, the value of this technique is weakened by its low tolerance, poor ability to evaluate the bowel wall or extra-intestinal tissues next to the associated ionizing radiation. Finally, the diagnostic yield of the small bowel follow-through or enteroclysis has been overtaken by the development of more accurate techniques.

7. Abdominal ultrasound examination

During performing routine abdominal ultrasound examination several findings can be encountered that can suggest the presence of CD including a hyperdynamic mesenteric circulation, an abnormal small bowel structure, flaccid and dilated (2.5–3.5 cm) small bowel loops, diffusely thickened wall (3–5 mm), enlarged mesenteric lymph nodes, intraperitoneal fluid collection and intussusception [24].

8. Abdominal computerized tomography

Similarly to ultrasound, CT images can detect abnormalities as those described by barium or ultrasound studies in patients with CD [25].

9. Magnetic resonance imaging

Magnetic resonance imaging (MRI) of the small bowel is gaining an important place in the diagnosis of intestinal diseases and in the evaluation of CD. The technical approach has improved with the oral introduction of biphasic contrast “MR follow-through” or the administration of contrast medium through a naso-jejunal tube “MR enteroclysis”. Results initially described by ultrasound and CT scan could also be reproduced by MRI [26].

10. Gastro-duodenoscopy

The endoscopic features that are characteristically looked for in the descending duodenum after careful insufflation of air, include a reduced number of duodenal folds (Kerckring's folds), scalloping, mucosal fissures, visible submucosal vessels, cobblestone appearance (mosaicism), and erosions [27,28]. These endoscopic features are useful in the diagnosis of CD. But are not present in all patients and have a low sensitivity [29]. In a prospective study it was found that duodenal folds were absent or markedly decreased in 15 of 17 patients with subtotal villous atrophy and in 8 of 48 patients with partial villous atrophy or normal duodenal mucosa, giving a sensitivity of 88% and a specificity of 83%. All patients undergoing upper gastrointestinal endoscopy should be examined for the loss or reduction of duodenal folds and, should this be found, then duodenal biopsy specimens should be taken for histological diagnosis [30].

Even additional maneuvers to improve the sensitivity of standard endoscope techniques such as the water immersion technique, high-resolution magnifying endoscopy, chromoendoscopy, enhanced magnification endoscopy could not replace histology in its sensitivity and specificity of the diagnosis [31].

Ileal examination that is usually performed during colonoscopy to look for evidence of Crohn's disease can suggest the presence of CD by demonstrating digitate villi, flat mucosa, and convolutions [32].

11. Duodenal histology

The British physician, Paulley provided in 1954 the first description of the histological findings of jejunal mucosa in CD in surgical specimens [33]. The radiographically guided suction Crosby–Kugler capsule allowed the peroral taking of jejunal biopsies [5]. The taking of biopsy samples from the duodenum by using forceps via a fiberoptic or flexible endoscope was introduced later [6] as an alternative method. Duodenal biopsy specimens are fixed in 10% formalin for histological evaluation. Monoclonal anti-CD3 immunohistologic staining improve the assessment of the number of intraepithelial lymphocytes.

In 1992 Marsh [34] classified the histopathological architectural changes in the proximal duodeno-jejunal epithelium into a preinfiltrative

stage that is indistinguishable from the normal mucosa (Marsh 0), an infiltrative stage that is markedly infiltrated by intraepithelial lymphocytes (IELs) (Marsh 1), a hyperplastic stage describing enlarged crypts that are being infiltrated by an increase number of intraepithelial lymphocytes (Marsh 2), a flat destructive stage that exhibits the villous atrophy (Marsh 3) and an atrophic hypoplastic stage that represents the ultimate and irreversible lesion of the spectrum despite gluten withdrawal from the diet (Marsh 4). This classification was later modified by subdividing Marsh 3 into partial (Marsh 3a), subtotal (Marsh 3b), and total villous atrophy (Marsh 3c) [35]. A more simplified classification for duodenal pathology, based on 3 villous morphologies (A, non-atrophic; B1, atrophic, villous-crypt ratio <3:1; B2, atrophic, villi no longer detectable) and an intraepithelial lymphocyte count of >25/100 enterocytes gave a better interobserver agreement compared with the more cumbersome classifications of CD [36].

Gluten withdrawal from diet leads to quick and complete histological recovery in children but up to more than 2 years in adults [37].

Although histological diagnosis of CD is considered the gold standard, this method is not free of potential problems such as the failure to make a correct assessment when biopsy specimens have been poorly orientated or tangentially cut [38].

Intraepithelial lymphocytosis can be observed in cases of *Helicobacter pylori* infection [39]. Villous atrophy has been reported in cases of cow's milk allergy, giardiasis, Crohn's disease, HIV, tropical sprue, eosinophilic enteritis, common variable immune deficiency, autoimmune enteropathy [40]. These disorders should be considered when antibody tests are negative. To improve the diagnostic yield it is important that the endoscopist orient the biopsy specimens before fixing the samples. A fine brush help to handle the specimens and at least 4 specimens should be taken to maximize diagnostic accuracy.

12. Gluten challenge

The practice of gluten challenge, initially incorporated in the diagnostic algorithm of CD by the European Society of Pediatric Gastroenterology and Nutrition is now restricted to research settings. Although there is no consensus on the dose or the duration of gluten administration during the challenge, the use of 20–30 g/day for 3 months period can uncover hidden cases when biopsy specimens become abnormal or exclude confidently the disease when biopsy specimens remain normal [41]. A gluten challenge is helpful when specific serological tests are positive and a normal small intestinal biopsy is present.

13. The diagnosis of complicated forms of coeliac disease

The standard therapy in case of CD is a strict GFD since it restores the abnormal small intestinal mucosa and plays a protective role against malignancy [42]. But some patients do not improve with this diet and develop refractory CD (RCD), a disease of malabsorption due to persisting villous atrophy despite GFD for at least 12 months. This refractory state affects around 2–10% of all patients with CD and is suggested to be the link between CD and overt lymphoma [40,43]. RCD can evolve into ulcerative jejunitis [44] or enteropathy-associated T-cell lymphoma (EATL) [43,45] characterized by small bowel ulcerations with or without histological evidence of lymphoma but also by the development of gross tumour mass in advanced stages.

The prognosis and standard treatment of patients with EATL are unsatisfactory with only a few long-term survivors [46].

Until recently, the treatment of RCD, apart from a GFD, was experimental. Some patients respond more favorably after adding steroid therapy to the GFD. The outcome of studies investigating the role of immune modulating agents like azathioprine, cyclosporine, cladribine, and IL-10 have been disappointing [40]. Promising preliminary results have been reported in isolated cases of small series of patients with anti-TNF alpha therapy such as infliximab [47], alemtuzumab [48] and autologous hematopoietic stem cell transplantation [49]. Therefore, early detection of subjects with RCD is required. Additional immunohistochemical tests, imaging or endoscopic examinations are required. The choice of diagnostic tool should be based on individualized indications.

14. Imaging techniques

Currently a wide range of imaging studies with promising efficiency is available for the assessment of complicated forms a is discussed below.

15. Abdominal computerized tomography

CT is suitable for detecting the complications of CD by providing detailed images of mesenteric lymphadenopathy, lymphoma, carcinoma, ulcerative jejunoileitis, hyposplenism and cavitory lymph node syndrome (3–5 cm nodes with low density necrotic centers) [50,51]. It is important for the radiologist to be aware of the appearance of CD on CT when patients undergo this examination for other indications.

16. Magnetic resonance imaging

MR enteroclysis is helpful in detecting small bowel wall thickening and lymphadenopathy in complicated cases of CD [52]. However, the relative high costs and limited availability are as yet hampering factors to apply the use of MRI in routine clinical practice.

17. Nuclear imaging

Fluorine-18-2-fluoro-2-deoxyd-glucose positron emission tomography has been shown to be valuable for the diagnosis, staging, and follow-up of patients with malignant lymphomas [53]. Preliminary results suggest that this method is helpful in detecting EATL and is recommended as non-invasive screening method in patients with RCD [54,55].

18. Colonoscopy

In general lower gastrointestinal tract endoscopy and histological sampling is advocated for patients with RCD, particularly when villi have recovered in duodenal biopsy specimens. Microscopic colitis, comprising collagenous colitis and lymphocytic colitis, characterised clinically by chronic watery diarrhoea, a macroscopically normal colonic mucosa and abnormal histopathological features is also associated with CD and therefore has to be excluded [56], since the long-term prognosis of microscopic colitis is good and the risk of complications including colonic cancer is low [57].

19. Video capsule endoscopy

The video capsule endoscopy (VCE) allows a non-invasive endoscopic visualization of the entire small bowel, and has a superior sensitivity to radiologic imaging. VCE gained popularity in examining the small bowel in different entities including CD. Early reported VCE images could reveal flattened and scalloped mucosal folds [58]. However, VCE could not replace the histological diagnosis of CD [59]. VCE is more helpful in detecting complications like ulcerations suspicious for lymphoma [60].

20. Push enteroscopy

Push enteroscopy has been introduced to examine the proximal jejunum (50–120 cm) beyond the ligament of Treitz [61]. Investigators using this technique could reveal the presence of ulcerative jejunitis in some patients with RCD [44].

The examination is associated with 0.6–2% risk of complications such as perforation or pancreatitis.

21. Double-balloon enteroscopy

This technique has the potential for full-length examination of the small bowel, obtaining biopsies and performing endoscopic interventions [62]. The endoscope can be introduced orally (antegrade) or anally (retrograde). The procedure can be performed under conscious sedation. This technique is helpful to detect complications in patients with RCD such as ulcerative jejunitis and EATL [63,64]. Perforation or pancreatitis can occur in 1% [65].

Double-balloon enteroscopy (DBE) also has the capability to examine and obtain histological samples from distal segments of the small bowel and therefore seems to be a suitable method to detect complications in selected patients with RCD after being screened by non-invasive measures like VCE or an imaging examination. In a recent study performed in Germany, DBE had a diagnostic value of 42% in patients with malabsorption of unclear origin and was useful to rule out complications of long-standing CD such as ulcerative jejunitis or EATL. The authors advised that DBE should be reserved for patients with unexplained malabsorption [66].

22. Immunohistochemical studies

The increased infiltration of small intestinal epithelium by IELs is a typical histological change in patients with CD. These IELs however, are characterized by the abundance of T-cell receptor γδ+ [67]. In patients with RCD, IELs appear cytologically normal, but have a different phenotype that is characterized by the loss of surface CD3 and the development of cytoplasmic CD3 next to the loss of CD4, CD8, TCR-αβ and TCR-δγ from the surface [68]. Because the development of lymphoma is considered a multistep process in which subsequent genetic defects lead to a monoclonal lymphocyte proliferation with an abnormal phenotype, early recognition of pre-lymphoma stages with abundant aberrant T-lymphocytes may represent the window of intervention to improve the prognosis.

Molecular studies using polymerase chain reaction technique to detect monoclonal rearrangement of T-cell receptor-gamma (TCR-γ) gene, is one of the techniques to identify these abnormal T-lymphocytes [69]. Monoclonal TCR-γ genes rearrangements is considered to be highly predictive of T-cell lymphoma development in patients with RCD [43].

Monoclonal antibodies against CD3 and CD8 have been used for immunostaining to identify T-cell populations with abnormal phenotype characterized by the lack of CD8 [70]. The percentage of CD3+ cells without CD8 expression among IELs was statistically higher in RCD (48–98%) than in patients with CD (2–33%) and controls (0–42%).

Another method is the fluorescence-activated cell sorted (FACS) analysis. This technique characterizes the morphologically normal but phenotypically abnormal T-lymphocytes in duodenal specimens and allows the discrimination between intracellular and surface antigen expression, a feature that T-cell clonality and immunohistochemical studies are lacking [71]. The presence of 20% or higher of abnormal intraepithelial T-lymphocytes appeared to be of use in risk stratification, therapeutic options and subsequent follow-up of patients with RCD [72].

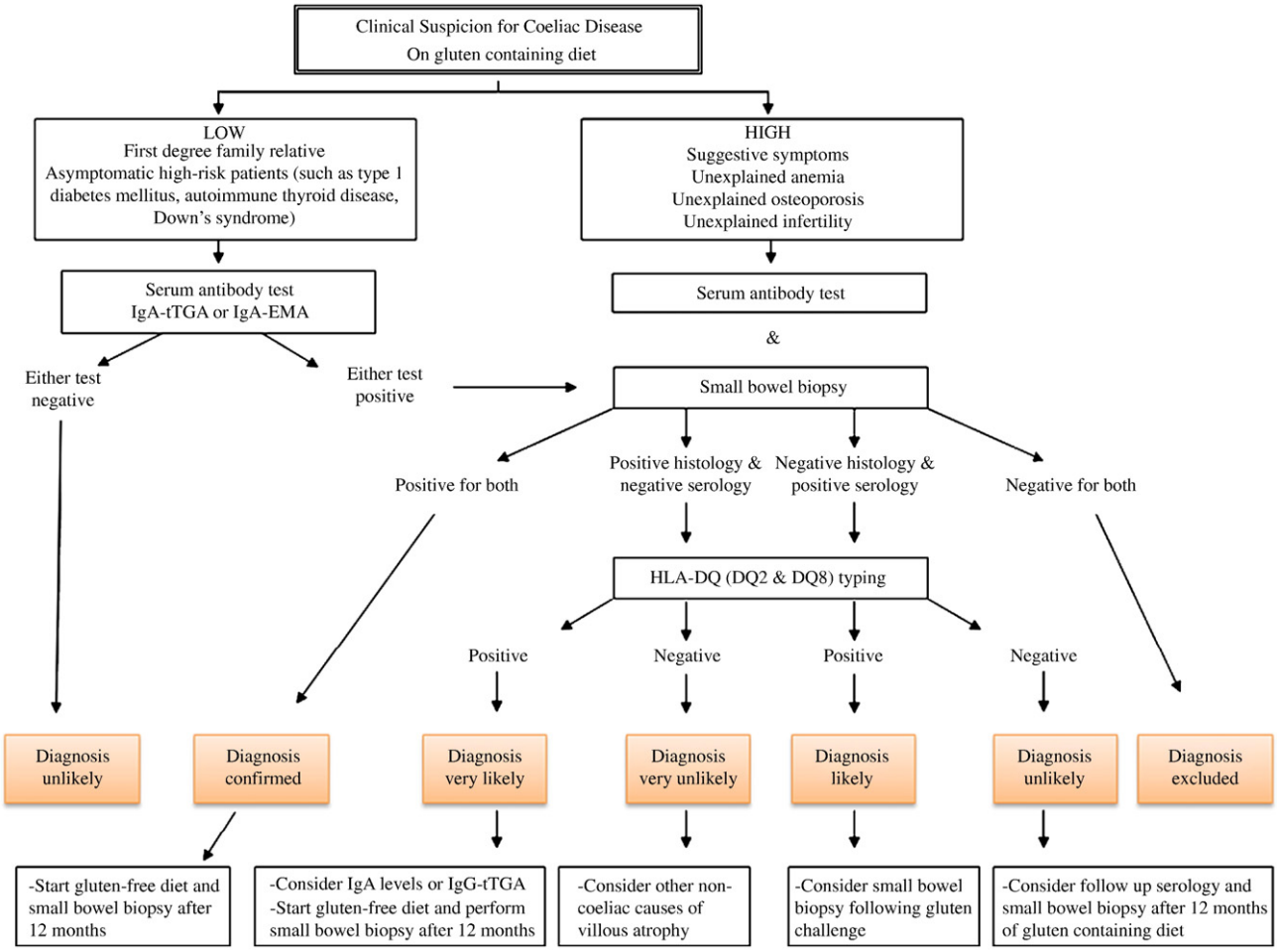

Fig. 1. Proposed algorithm to diagnose coeliac disease.

23. Discussion

In this review we describe the diagnostic tools that have been introduced thus far in clinical practice which can be subdivided into those addressing the establishment of the diagnosis of CD and those which are mostly useful in detecting severe complications of the disease. The majority of these methods have variable sensitivity and specificity. Most of the available data is not extracted from large populations or prospectively designed studies. Therefore the evidence for their value is for the time being based on guidelines generated by a group of experts and their application has to be personalized [73].

Small bowel (duodenal) mucosal changes appear to remain the cornerstone and the gold standard for diagnosing CD keeping in mind that this gold standard is not free from pitfalls [16]. Undergoing upper gastrointestinal endoscopy to obtain duodenal biopsy is criticized for its unpleasant experience especially in asymptomatic subjects or in children. Consequently, alternative tests are used in these cases to defer the procedure [74]. However, duodenal biopsy remains indicated for individuals when their clinical features are suggestive for CD since no reliable tool has yet emerged to replace it.

tTGA or less preferably EMA are the recommended initial tests to detect CD in primary care setting but duodenal histology remains recommended when clinical suspicion is high despite negative serological tests [16]. In unclear clinical situations duodenal biopsy appears to be advocated independently of serological results. tTGA (or EMA) can be used to monitor the response in CD to GFD especially in children. Duodenal histology, demonstrates recovery of the intestinal mucosa and identifies refractory cases in adult population [75].

HLA–DQ typing (abscence of HLA–DQ2 and–DQ8) is a rule-out test when there is high suspicion for CD [76]. This is exemplified in cases when serological and histological results are discrepant (Fig. 1). The rule-out character of the test can benefit asymptomatic individuals, such as first degree family members of patients with CD or patients with specific autoimmune disorders who are at increased risk for CD, by reducing the costs by avoiding repeated serological testing [76].

Although gluten withdrawal from daily diet leads to symptomatic relief and villous recovery in the majority of patients, a minority of patients maintains persistent villous atrophy despite strict restriction of gluten and develop refractory disease. Additional evaluation is required to stratify these patients according to their risk for development of severe complications such as EATL. The choice of diagnostic tool should be based on individualized indications. The understanding of the molecular basis for CD has improved and enabled the identification of targets for new therapies, although a strict gluten-free diet remains the mainstay of safe and effective treatment [77].

When the patient is not responding to the GFD an experienced dietician should perform a dietary evaluation. Positive specific serological tests may reveal indiscrete gluten ingestion, while HLA-typing can distinguish non-celiac causes of RCD [45]. Repeated duodenal histology examination complemented by molecular studies or flow cytometric studies to define the phenotypic characterization of isolated IELs from duodenal biopsies should be performed.

Imaging techniques such CT scan or fluorine-18-2-fluoro-2-deoxyd-glucose positron emission tomography are necessary non-invasive methods that should be restricted to refractory patients to identify EATL followed by small bowel endoscopical examinations with increased level of invasiveness according to the clinical status

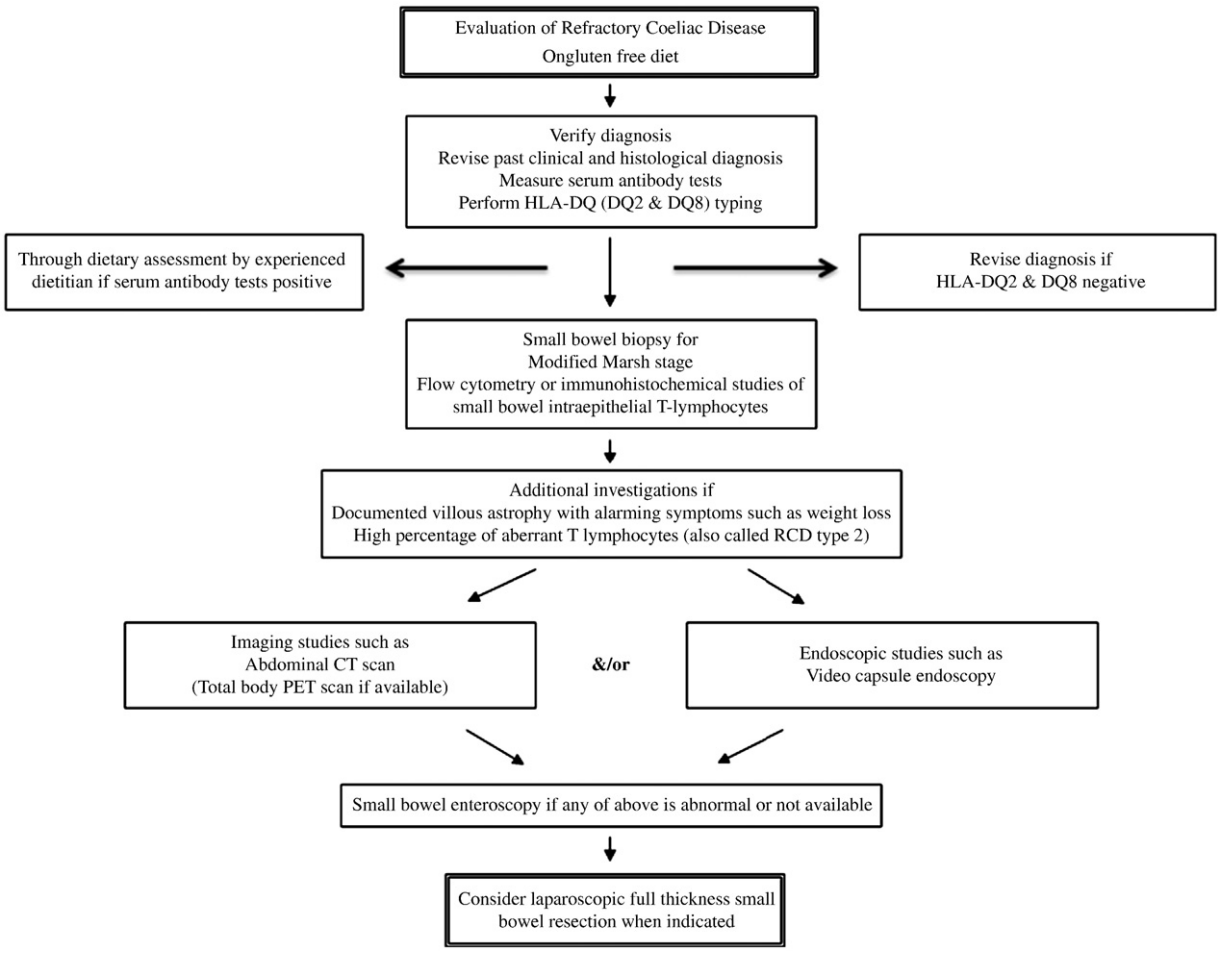

Fig. 2. Proposed algorithm to diagnose refractory and complicated forms of coeliac disease.

and results of other tools. Starting with VCE followed by more invasive techniques like push enteroscopy or DBE is a justified approach in the evaluation of this category of patients (Fig. 2).

As long as the drive remains to search for an alternative to endoscopy and duodenal biopsy, new tools to detect CD that are characterized by high performance, low costs, and least invasiveness will emerge hopefully in the future while other innovative or modified methods will develop to assess complicated forms. With our increased understanding of the disease, the diagnosis of CD appears to be more confident when initial as well as follow-up results of several tests are put together [78]. This consideration is applicable to the gold standard since as discussed earlier is not free of pitfalls.

The efforts to increase awareness of CD and its complications is justified because recent large studies have found that undiagnosed CD is associated with a nearly 4-fold increased risk of death [79]. High rates of complications and mortality have been reported in refractory CD [80]. A study in Sweden has examined mortality in CD according to small-intestinal histopathology and confirmed a modest increased risk of death among patients with CD, inflammation, or latent CD [81].

Learning points

- Coeliac disease is a common disease with an increased mortality. Due to its protean manifestations the diagnosis is often missed.
- Serological, genetic tests and small bowel biopsy specimens obtained through endoscopy allow an easy diagnosis to make in the majority of patients with uncomplicated form of celiac disease.
- The prognosis of these patients is very good provided they follow a strict-gluten free diet.
- Patients with complicated forms of the disease have a sombre prognosis.
- New technological advances in imaging, endoscopic and histological techniques facilitate the diagnosis of the complicated forms of the disease.

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