REVIEWS

Treatment Failure in Coeliac Disease: A Practical Guide to Investigation and Treatment of Non-responsive and Refractory Coeliac Disease

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Abstract

Coeliac disease is a common condition affecting up to 1% of the European adult population. Whilst the majority of patients will respond to a gluten free diet with resolution of symptoms and an improvement in histology, a significant minority have persistent problems. Refractory coeliac disease is a relatively uncommon cause of non-response to gluten free diet with potentially serious consequences of severe malabsorption and a high rate of progression to lymphoma. This review provides a practical guide to the investigation of patients who do not respond to a gluten free diet. We will highlight the differences between the more common non-responsive coeliac disease and the rare entity of refractory coeliac disease and discuss current management and treatment options for both non-responsive coeliac disease and refractory coeliac disease.

Key words

Celiac disease – non-responsive celiac disease – refractory celiac disease – refractory sprue – persisting symptoms – adherence.

Introduction

Coeliac disease is a common condition affecting up to 1% of the European adult population [1, 2]. Coeliac disease results from an inflammatory response to dietary gluten in the small intestine leading to villous atrophy in genetically predisposed individuals. Gluten is the umbrella term used to describe the alcohol solvent proteins found in cereals such as wheat, barley and rye. Villous atrophy leads to impaired absorption of nutrients in the small bowel. Historically, the symptoms of coeliac disease described are that of steatorrhoea. This is however a rare occurrence in contemporary presentation. However, recent consensus on the descriptive terminology suggests that "classical" coeliac disease is that of patients presenting with signs and symptoms of malabsorption or weight loss. "Non-classical" coeliac disease may represent patients presenting without these signs or symptoms [3].

Significant proportions of patients are asymptomatic/subclinical or are identified when the sequelae of coeliac disease such as anaemia or osteoporosis are diagnosed. Central to the diagnosis of coeliac disease is the histological and clinical improvement on institution of a gluten free diet (GFD). Treatment for coeliac disease is based on strict, life-long adherence to a GFD. In the majority of cases this will be sufficient to induce a clinical improvement in symptoms. However, a significant minority of patients will continue to be symptomatic. These patients can present a difficult diagnostic and therapeutic challenge. This review will concentrate on patients who either do not respond to a GFD (non responsive coeliac disease, NCD) or have refractory coeliac disease (RCD).

It is important to distinguish between true RCD disease and those who do not respond for other reasons. True RCD carries a significant burden of morbidity and mortality, mainly from malnutrition and lymphoma [4-7]. Early diagnosis and treatment of RCD, in some cases may prevent progression and reduce morbidity. It is therefore imperative that clinicians are aware of how RCD is diagnosed and possible differentials. This review will discuss the differences in diagnosis of RCD and NCD and the possible causes and treatments available for them.

Non responsive coeliac disease

The majority of patients with coeliac disease will respond to a GFD. Non-responsive coeliac disease (NCD) is defined as failure of symptomatic or histological improvement with a presumed GFD. This can be defined as primary if there

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has been no response to GFD after 12 months or secondary if after initial response symptoms relapse despite adherence to GFD. The time period is arbitrary but serves a purpose to highlight the long duration that may be required for a GFD to take effect. Causes of non-response include persistent gluten ingestion (the most common cause), an incorrect initial diagnosis and other causes of diarrhoea which may be associated or co-exist with coeliac disease. Finally RCD may also present in this manner – although this is an uncommon diagnosis.

Has the correct initial diagnosis been made?

Most cases are diagnosed on the basis of coeliac antibodies, duodenal histology and clinical response to GFD. If there is no clinical response to GFD, the serology and histology should be reviewed. In a case series of 55 patients referred to a tertiary centre, 6 of these patients, after reviewing histology and other evaluation, had their original diagnosis of coeliac disease disproved [8]. Recent evidence and clinical experience suggests that gluten can induce symptoms in those who do not have coeliac disease [9]. An initial response to gluten, therefore, does not necessarily confer a diagnosis of coeliac disease and all patients should have their primary diagnosis re-examined.

Histological evaluation although often straightforward can at times prove more difficult. This is particularly the case if orientation of the specimens is incorrect. Repeat evaluation by a specialist pathologist should be performed if there is any doubt as to the histological diagnosis and re-biopsy considered. Other supportive evidence of a diagnosis of coeliac, such as family history (attributable risk approx 10% for first degree relatives), functional hyposplenism and HLA genotyping may be useful [10]. The absence of HLA DQ2 or HLA DQ8 makes coeliac disease very unlikely [11, 12].

There are multiple other causes of small bowel villous atrophy which can be misinterpreted as coeliac disease; a comprehensive list is included in Table I. In a recent case series, Pallav et al retrospectively studied a cohort of 30 patients with non-coeliac enteropathy, 21 of whom had been previously misdiagnosed as having coeliac disease. They identified 10 different aetiologies as the cause with the most common being non-specific immune mediated enteropathy (33.3%), peptic duodenitis (16.6%), small bowel bacterial overgrowth (10%) and collagenous sprue (10%) [13]. Other differentials include Crohn's disease, AIDS enteropathy, adult autoimmune enteropathy, common variable immunodeficiency (CVID) and tropical sprue. These should all be considered as part of the differential diagnosis. If there is any doubt as to the initial diagnosis, repeat coeliac serology, endoscopic evaluation, histology and HLA genotyping should be undertaken. Immunoglobulins and anti-enterocyte antibodies can be useful in the diagnosis of CVID and autoimmune enteropathy [13-15].

Table I. Causes of small bowel villous atrophy and/or malabsorption

Agammaglobulinaemmia or hypogammaglobulinaemia
AIDS enteropathy
Allergies to proteins other than gluten eg. chicken, cows' milk, eggs, fish, soy.
Amyloidosis
Autoimmune enteropathy
Bacterial Overgrowth
Collagenous sprue
Crohn's disease
Eosinophilic enteritis
Giardiasis
Graft versus host disease
Intestinal lymphangiectasia
Intestinal lymphoma
Ischaemia
Mastocytosis
Tropical sprue
Tuberculosis
Radiation enteritis
Whipple's disease
Zollinger Ellison Syndrome

Non-adherence to GFD

Once the initial diagnosis of coeliac disease has been confirmed, the first step in the investigation of patients with ongoing symptoms is assessing for exposure to gluten. Estimated adherence to an effective GFD is in the region of 42-91% [16-18]. However, complete non-adherence is relatively uncommon at less than 5% in most studies with a range of 0-32%.[18] Patients with persistent gluten ingestion will remain positive for immunological markers of coeliac disease such as anti-TTG or endomysial antibody. They will have persistent changes present at small bowel biopsy. However it is important to note that although clinical improvement may occur within a few weeks of institution of a GFD histological changes can persist. In a histological follow up study, of 114 adults in whom a symptomatic and serological remission had been achieved, only 17.5% had achieved complete histological response at 2 years [19]. The distal small bowel is known to heal more quickly than the proximal small bowel and duodenal biopsies may not reflect this improvement [20-22]. Persistent symptoms should prompt re-evaluation rather than lack of histological improvement.

In series of patients with NCD the most common cause is of either deliberate or inadvertent exposure to gluten. In a review of patients referred to a tertiary centre in Minnesota 25 of 49 patients who remained symptomatic despite institution of GFD were found to have gluten contamination as the cause of their ongoing symptoms [8]. All of these patients had previously been given advice on GFD and felt that they were adhering to the regime. However after discussion with an expert dietician contaminant sources of gluten were identified. Common causes for inadvertent ingestion of gluten include inadequate knowledge of gluten

containing products, poor labelling of processed foods and frequent meals out [23]. Patients will tend to overestimate their adherence to a GFD diet however poor palatability and cost of gluten free products decrease adherence.

Most patients with coeliac disease can tolerate small amounts of gluten [24]. However there is evidence that even a modest ingestion of gluten can be enough to prevent mucosal healing [25]. Many patients with coeliac disease are asymptomatic but some patients are exquisitely sensitive to even small amounts of gluten in their diets. In a review of studies into gluten ingestion some patients required as little as 10 mg of gluten per day to induce development of intestinal mucosal abnormalities [24]. The average diet contains 13 grams of gluten per day [26]. In reality it is not possible to completely avoid gluten. The international standard for gluten free products is set by the Codex Alimentarius Commission. Until 2008 the Codex level to declare a product 'gluten free' was set at 200 mg of gluten per kilogram or 200 parts per million (ppm.) Since 2008 however the lower level of 20 ppm is required for gluten free products and a second level of 'very low gluten' has been set at 20-100ppm [10, 27].

A diagnosis of ongoing gluten exposure should be made after detailed dietary history including use of food diaries. This is best achieved with specialist dieticians. Improved understanding of the GFD, regular clinic attendance and membership of a coeliac advocacy group are all associated with improved adherence and should be encouraged [18, 28]. Patients in whom the diagnosis of coeliac disease is certain and are carefully adherent to a GFD may benefit from dietetic advice. This may result in a resolution of symptoms in patients who are supersensitive to gluten. However, for those with persisting symptoms further investigations to assess for RCD or other causes of ongoing diarrhoea are necessary.

Other causes for symptoms

When undertaking investigations in this group of patients it is essential that a systematic approach is adopted. Conditions that have been described in NCD include lactose malabsorption, small bowel bacterial overgrowth, exocrine pancreatic insufficiency and irritable bowel syndrome (IBS) [8]. Appropriate investigations including lactose hydrogen breath test, small bowel aspirates for culture and faecal elastase should be considered. Alternative diagnoses that are not directly associated but may occur in patients with coeliac disease include dietary allergy, protein losing enteropathies, anal sphincter dysfunction and Whipples's disease [8, 10, 29, 30].

Exocrine pancreatic insufficiency has been investigated in GFD adherent patients with chronic diarrhoea. This link was first described in 1957 and has been replicated in several subsequent studies [8, 30, 31]. In a recent study 20 of 66 patients were found to have concomitant pancreatic insufficiency on the basis of low faecal elastase levels [32]. It has been suggested that this is as a direct result of the level of villous atrophy. However, in the same study 13 of the 20 patients also consented to repeat duodenal biopsy; all of the patients had an improvement in the level of villous atrophy compared to their index biopsies. All of the patients improved symptomatically with the introduction of pancreatic enzyme replacement.

Secondary lactose or fructose intolerance may occur as a result of the mucosal surface damage in coeliac disease. In a study of 113 patients with NCD, lactose intolerance was identified as the cause of ongoing symptoms in 9 participants on the basis of a positive lactose hydrogen breath test [29].

There is a well documented link between microscopic colitis and coeliac disease and investigation for this eminently treatable condition should be sought where the predominant symptom is of diarrhoea [33, 34].

A link between small bowel bacterial overgrowth (SBBO) has also been identified. Tursi described 15 coeliac patients who remained symptomatic despite histological improvement of duodenal biopsies: 10 of these patients had positive lactulose hydrogen breath tests and were successfully treated with rifaximin [35]. Hydrogen breath tests are however less than ideal in diagnosing SBBO particularly in the setting of coeliac disease with a high number of false positives [36, 37]. In a further study of 79 patients with NCD 9 (11%) were found to have positive small bowel aspirates compared to none of the 23 asymptomatic treated coeliac disease patients [38]. However a more recent randomized study using rifaximin has failed to show any symptomatic benefit for coeliac patients with persisting symptoms. Nevertheless there is a paucity of published literature and further work is required to clarify the relationship between coeliac disease and small bowel bacterial overgrowth [39].

Many patients with coeliac disease will also fulfil the Rome III (or previously II) criteria for IBS and in cases where other causes of symptoms have been excluded this may be the most likely cause [40, 41]. A GFD is maybe low in fibre which may exacerbate constipation causing pain and bloating symptoms. It has been shown that patients with coeliac disease and IBS have worse SF-36 scores (a validated quality of life score) than those patients with only coeliac disease. This may suggest that clinicians should actively question for and treat symptoms of IBS [42].

An algorithm for the investigation of non response to GFD is provided in Fig. 1.

Refractory coeliac disease, ulcerative jejunitis and lymphoma

Once other causes of ongoing symptoms have been ruled out, a diagnosis of true RCD can be considered. True RCD is a rare condition defined as persistent malabsorptive symptoms and villous atrophy despite strict adherence to a gluten free diet (GFD) with negative serology for anti-TTG or EMA [12]. The cause and exact incidence of RCD is unknown but in patients investigated in specialist centres for NCD it is found to be the cause in 8-18%.[8, 29, 43]. In a recent review of patients in a 10 year period at a North American tertiary referral centre, the incidence of RCD

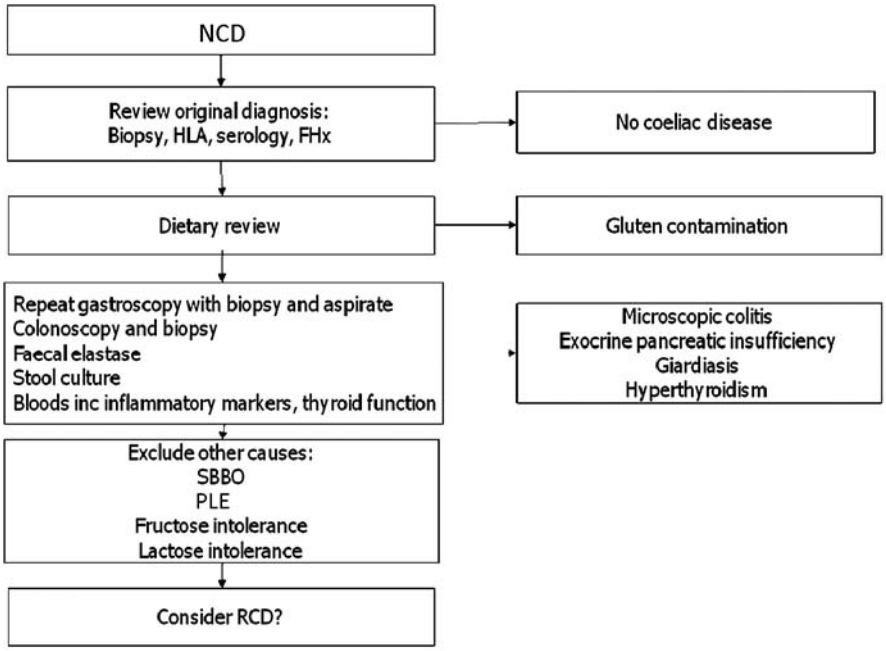

Fig 1. Diagnostic algorithm for NCD (FHx: family history; NCD: non-responsive coeliac disease; PLE: protein losing enteropathy; SBBO: small bowel bacterial overgrowth; RCD: refractory coeliac disease).

in patients referred with non-responsive disease was 8% (34/306), however only 1.5% (8/528) of patients whose primary diagnosis of coeliac disease was made at the centre developed RCD [43].

Persistent symptoms suggestive of malabsorption such as steatorrhoea and weight loss should prompt the clinician to consider a diagnosis of RCD. Refractory coeliac disease is an important diagnosis to make as it can carry such a poor prognosis. Earlier diagnosis may help to identify patients who will respond more favourably to treatment. Additional symptoms of fever, night sweats, abdominal pain, gastrointestinal bleeding and bowel obstruction suggest the possibility of underlying enteropathy associated T-cell lymphoma (EATL), ulcerative jejunitis or adenocarcinoma of the small bowel [12]. Ulcerative jejunitis (UJ) is defined by areas of multiple chronic ulcers with a benign appearance and in common is patients with type 2 RCD [4]. Ulcerative jejunitis can lead to small bowel structuring and subsequent small bowel obstruction and perforation. Patients with UJ respond poorly to treatment with GFD and have a poor prognosis [5]. EATL carries a dismal prognosis with an estimated 2 year survival of less than 30% [12].

Refractory coeliac disease can be subdivided into primary, where symptoms have persisted whilst maintaining strict GFD or secondary where there has been a recurrence of symptoms after apparent response to GFD for at least a year. It can be further subdivided into type 1 or type 2 diseases depending on the phenotypic appearances of the intraepithelial T-cell population. Type 2 RCD have a larger population of aberrant clonal T-cells and as such have a poorer response to treatment and an inferior prognosis with a higher level of progression to lymphoma. 5-year survival type 2 RCD is in the order of 50% compared to 90-100% in patients with type 1 disease [4, 6, 7]. Mortality occurs as a direct result of complications from malabsorption or progression to EATL.

Investigations

The diagnosis of RCD is primarily one of exclusion as detailed above. As well as ruling out other causes of non-responsive coeliac disease, evidence of malignancy should be sought. Refractory coeliac disease is part of a spectrum of disease including UJ and lymphoma. EATL most commonly involves the proximal jejunum, less frequently involves the rest of the small bowel stomach or colon and may also involve the liver, spleen and lymph nodes [44]. After oesophago-gastro-duodenoscopy, initial investigations should include non-invasive investigations of the small bowel such as MRI or barium follow-through to look for mucosal lesions. MR enteroclysis has recently been shown to have a diagnostic accuracy of 95% in the investigation of small bowel neoplasms [45]. CT scanning for lymphadenopathy may be helpful but its accuracy in diagnosing low grade small bowel obstructions is disappointing [46]. Positron Emission Tomography (PET) CT scan has recently been shown to have a high sensitivity for picking up EATL [47]. The same study did however show a number of false positive results and as a result histological diagnosis remains important. Small bowel capsule endoscopy is becoming more readily available and may be useful to identify lesions providing there is no evidence of stenosis on follow-through studies [48]. Double balloon enteroscopy may be useful to biopsy abnormal areas and confirm a histological diagnosis. Bone

marrow biopsy, lymph node biopsy and full thickness small bowel biopsy at laparotomy may be required.

As well as ruling out lymphoma, investigation of the small bowel is required to make a firm diagnosis of RCD. Small bowel biopsy is necessary to look for signs of persistent villous atrophy. It is also important to make the distinction between type 1 and 2 disease on the basis of this sample as this carries significant prognostic value [7, 43]. The normal intestinal intraepithelial lymphocyte (IEL) population consists of 80-85% CD8+ T-cell receptor (TCR) αβ cells and 15% CD8+ TCR γδ cells. IELs are thought to recognise bacterial proteins, preserve epithelial integrity and mediate antigenic tolerance. In uncomplicated coeliac disease IELs express CD3+ and CD8+ and there is an increase in γδ cells. Patients with type 1 RCD show a polyclonal expansion IELs on duodenal biopsy with less than 10% abnormal IELs; i.e. persistence of normal coeliac morphology [10]. Patients with type 2 RCD however have a monoclonal expansion of phenotypically abnormal IELs with TCR γδ chains, these cells also lose their normal surface markers of CD3, CD4 and CD8 [12]. Immunohistochemistry and PCR techniques are used to detect the abnormal intraepithelial lymphocytes (IELs) that are the basis for sub-classification. Normal TCR γδ cells have been shown to play an important role in mucosal homeostasis and possible suppression of inflammation. The clonal expansion, therefore, of abnormal TCR γδ may be a cause of the mucosal injury associated with RCD, ulcerative jejunitis and EATL [49].

Recent evidence has shown that the presence of an aberrant immunophenotype and monoclonality do not definitively confer a diagnosis of RCD however. A recent follow up study of patients with a spectrum of celiac disease has shown that the transient appearance of RCD type abnormalities is occasionally present in some patients with uncomplicated celiac disease. In each of these cases the aberrancy was detected during a period of non-adherence to GFD and all reverted to normal on reinstitution of an effective GFD. The patients in the study with RCD and EATL all had persistent changes and were adherent to a GFD throughout. Determination of adherence to GFD is imperative, therefore, to make a diagnosis of RCD. Patients with a higher level of abnormal IELs were also much more likely to progress to EATL suggesting that sequential biopsies in patients with aberrant IELs may be beneficial in predicting those who will go on to develop EATL and may facilitate earlier diagnosis [50]. Contrary to previous studies [7, 48] it does appear that RCD type 1 can progress to type 2 [50].

Management

True RCD is a rare condition and as such evidence is sparse and limited to small case series. Patients should be referred to a tertiary centre with an interest in RCD to initiate management. Patients will often present with signs of severe malabsorption with malnutrition and weight loss. Trace elements such as zinc and copper should be checked and corrected as well as routine investigations including haematinics, iron studies, full blood count, urea and electrolytes, albumin, magnesium and calcium [4]. The use of Total Parenteral Nutrition (TPN) feeding is required in 28-60% of patients to correct malnutrition [4, 6]. Special consideration should be taken to re-feeding syndrome for patients who have often been malabsorbing for some time. Some patients may be able to tolerate some form of enteral feeding whether by tube feeding or oral administration.

Once the patient's nutritional state has been addressed and support commenced treatment of the underlying condition can be considered. In a small number of cases nutritional support and maintenance of a strict GFD may be sufficient in patients with type 1 RCD [12]. Other nutritional therapies have also been tried. In a case series of ten patients with type 1 RCD, eight showed histological improvement with six patients improving symptomatically on a strict elemental diet [51]. Given the small numbers of patients with RCD evidence of effective treatment is limited to small case series. Treatment strategies have focussed on immunosuppression with the mainstay of therapy being glucocorticoids. Evidence for patients with type 1 RCD is encouraging with most patients achieving clinical remission and mucosal healing with steroids or a combination of steroids and azathioprine [12]. Many patients with type 2 RCD will also experience a clinical improvement in symptoms. Mucosal healing however is rarely achieved and treatment does not prevent progression to EATL [4, 6]. The majority of patients with RCD will be steroid dependant. Budesonide has a good side effect profile and may be preferable to prednisolone for long term maintenance due to its topical effect and reduced systemic absorption [52, 53]. Azathioprine has been studied as a logical steroid sparing agent with some success [54]. However these studies are small and a concern remains over the possible lymphoma-genesis potential of this treatment particularly in type 2 RCD where there is already a significant risk of development of EATL [12]. In an open labelled trial of 10 patients with RCD type 1, small bowel release mesalazine was given as monotherapy [4] or in combination with budesonide [6]. Half of patients had a full response and two were able to remain off steroids long term [55]. Cladribine, another purine analogue, has been shown to reduce populations of aberrant IELs and induce clinical remission in patients with type 2 RCD but probably does not prevent progression to EATL [56, 57]. Initial concerns over precipitation of overt lymphoma have limited its use. However, Tack et al have started to use Cladribine as first line therapy for type 2 RCD and have reported promising results [56]. Eighteen of 32 patients treated responded with 15 achieving complete histological remission. Follow up is ongoing but the 5 year survival in those who responded to treatment was 83% compared to 22% in those who did not. Cases of EATL were in line with previously reported rates. Autologous stem cell transplant has also shown some promising results in non-responders to Cladribine therapy. Within a year of transplant, 11 of 13 patients showed significant improvements in symptoms, performance status and body mass index. Treatment appeared relatively safe

with a single patient dying as a direct result of transplant. The 4 year survival was 66% progressing to EATL [58]. The role of TNF-α in mucosal inflammation has led to trials of Infliximab with case reports of successful treatment although numbers remain small [59-61]. Finally, translational research into IL-15 may in the future result in this as a potential target for novel therapy [62].

Conclusion

Most patients with coeliac disease will respond to treatment. The majority of non-responders will have other causes for their symptoms and may be classified as non-responsive coeliac disease rather than refractory. A structured approach to this group of patients is paramount and can result in an improvement in their symptoms.

Refractory coeliac disease remains a rare diagnosis despite an increase in detection rates for coeliac disease. As a result studies into potential treatments are limited but should focus on correction of malnutrition, strict gluten free diet, immunosuppression and early detection of lymphoma.

Conflicts of interest

No conflicts of interest declared.

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