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Conference on 'Malnutrition matters'

Symposium 1: Joint BAPEN and British Society of Gastroenterology Symposium on 'Coeliac disease: basics and controversies' Coeliac disease: optimising the management of patients with persisting symptoms?

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The vast majority of patients with coeliac disease will derive benefit from a gluten-free diet. However, some patients will not improve on the gluten-free diet or they will have a relapse of their symptoms. The present review will focus on this group of patients. Definitions for non-responsive coeliac disease and refractory coeliac disease will be provided. The most common reason for recurrent symptoms is continued gluten exposure. Other causes of persisting symptoms are discussed, including alternative causes of villous atrophy or co-existent pathology. Current literature is reviewed, including an initial investigation strategy for patients with persisting symptoms. A pragmatic management plan is described that can be initiated by any clinician. Finally, the current optimal investigational pathway for patients with refractory (or suspected refractory) coeliac disease is discussed and the reported effects of a number of therapeutic options are summarised. The aim of the present article is to provide clinicians with an up-to-date review of the literature in this clinical field and allow them to determine the most appropriate management strategy.

Refractory coeliac disease: Non-responsive coeliac disease: Persisting symptoms and adherence

Non-responsive coeliac disease

Definition and prevalence

Coeliac disease is the manifestation of an immune-mediated hypersensitivity reaction towards gluten in genetically-predisposed individuals. Treatment is with a lifelong gluten-free diet (GFD); indeed, part of the definition of coeliac disease is that it improves clinically and histologically on gluten withdrawal. However, a proportion of patients do not improve on a GFD, and it is these patients who will be the focus of the present review.

Non-responsive coeliac disease (NRCD) has historically been described as failure to respond to a GFD and can be manifest as primary NRCD (the individual never responds to a GFD) or secondary NRCD (a subsequent recurrence of symptoms after 1 year[1], although a recent study has suggested that an alternative timescale for secondary NRCD could be 6 months[2]). However, these definitions are all arbitrary. Furthermore, some studies have suggested that NRCD may not just be a failure to respond to a GFD but also the presence of persisting histological changes[1,3].

Historical studies estimate the prevalence of NRCD in the general population at 7–30%[4–6]. However, these estimates were based on small cohorts of patients. Contemporary clinical studies or patient-support-group surveys from the USA and UK have suggested that NRCD occurs in about 17–30%[7–9]. The majority of cases of NRCD are likely to be related to either inadvertent ingestion of tiny but clinically significant amounts of gluten or non-adherence[2,3,7].

Abbreviations: EATL, enteropathy-associated T-cell lymphoma; GFD, gluten-free diet; IEL, intraepithelial lymphocytes; NRCD, non-responsive coeliac disease; RCD, refractory coeliac disease; TCR, T-cell receptor.

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Table 1. Causes of malabsorption and/or villous atrophy[3]

Agammaglobulinaemmia or hypogammaglobulinaemia
AIDS enteropathy
Allergies to proteins other than gluten, e.g. chicken, cow's milk, eggs, fish, soyabean
Amyloidosis
Autoimmune enteropathy
Bacterial overgrowth
Collagenous sprue
Crohn's disease
Eosinophilic enteritis
Giardiasis
Graft *v.* host disease
Intestinal lymphangiectasia
Intestinal lymphoma
Ischaemia
Mastocytosis
Tropical sprue
Radiation enteritis
Whipple's disease
Zollinger Ellison syndrome

When determining whether a patient has NRCD it is important to be guided by symptoms rather than the histology alone. Clinical improvement may occur within days on a GFD but histological improvement continues for ≤2 years. The distal small bowel improves most rapidly and proximal biopsies may not reflect this improvement[1,10,11]. It has been demonstrated that after ≥1 year on a GFD less than one-quarter of patients with coeliac disease have normal endoscopic appearance or histology[12]. In the thirty-nine patients who were investigated normal histology was found after a mean of 8·5 (range 1–45) years in 21% (*n* 8) of patients, with partial villous atrophy in 69% (*n* 27) and total villous atrophy in 10% (*n* 4). More recently, persisting abnormalities have been demonstrated in 82·5% of adult patients with coeliac disease[13]. After a median of 2 (range 1–23) years on a GFD 17·5% of the 114 adult patients studied were found to have normal histology (Marsh grade 0; for details of the Marsh classification of lesions, see Marsh[14]), with 20·2% having raised intraepithelial lymphocytes (IEL; Marsh grade 1) and 30·7% and 31·6% having partial villous atrophy (Marsh 3a) and total villous atrophy (Marsh 3b) respectively. All patients were reported to have responded clinically to the GFD. It should be noted that the importance of raised IEL (in this context) without other histological change is still a matter of great debate.

Thus, it is recommended that classifying a patient as NRCD should be based primarily on persisting symptoms.

Does this patient really have coeliac disease?

In the patient with NRCD it is important to challenge the initial diagnosis of coeliac disease; in a report on one series of fifty-five patients referred for NRCD the original diagnosis of coeliac disease was disproved in six[3]. All previous diagnostic investigations including the serology and the original and subsequent duodenal biopsies should be reviewed. Biopsies should be well orientated and interpreted by a specialist gastrointestinal pathologist[3].

If the diagnosis of coeliac disease is uncertain then supportive evidence should be sought in the form of typical human leucocyte antigen status (DQ2 or DQ8), a positive family history of coeliac disease (with an attributable risk of approximately 10% for first-degree members), functional hyposplenism and the detection of IgA or IgG gliadin antibodies (historically), a raised endomysial antibody or tissue transglutaminase antibody[4].

Other causes of malabsorption and/or villous atrophy that should be ruled out are shown in Table 1[3].

Continued exposure to gluten?

The most common reason for NRCD is continued gluten exposure. This cause can be substantiated by a composite approach: (1) the patient describing symptoms; (2) a dietetic assessment for adherence; (3) persisting antibody titres (either tissue transglutaminase antibody or endomysial antibody), particularly if there is a baseline titre for comparison; (4) the persistence of histological changes on duodenal biopsy. In the group of fifty-five patients described earlier twenty-five of the fifty-nine with coeliac disease were identified as having gluten contamination responsible for their ongoing clinical and histological signs[3]. Inadvertent ingestion was found to usually occur in the form of commercially-packaged cereals derived from maize or rice that had contained malted barley. By recognising these sources as the reason for inadvertent gluten exposure it was shown that all patients improved symptomatically[3].

Adherence to a GFD is estimated to be approximately 50–70%[15–17]. Whilst it is true that patients overestimate their adherence, factors such as cost, poor availability and poor palatability of gluten-free foods decrease compliance. In addition, socialising and eating out may lead to inadvertent exposure to gluten[18]. Factors associated with improved compliance include understanding the GFD, membership of a coeliac disease advocacy group, attendance at a follow-up clinic and the perceived ability to maintain the diet in the course of everyday-life obstacles[19].

What are the other possible causes of persisting symptoms?

Having established the diagnosis of coeliac disease and adherence to a GFD, the next step in the patient with NRCD is to exclude other causes of symptoms.

This process can be subdivided into diagnoses that may be associated with coeliac disease, including microscopic colitis, pancreatic insufficiency, irritable bowel syndrome, small bowel bacterial overgrowth, thyroid dysfunction and secondary intolerances (as a result of mucosal surface damage, e.g. lactose or fructose intolerance)[2,7]. Less-common alternative diagnoses that are not associated with the condition but may occur in patients with coeliac disease include dietary allergies, other protein-losing enteropathies, complete malrotation of the gut, anal sphincter dysfunction and Whipple's disease[2,3,7].

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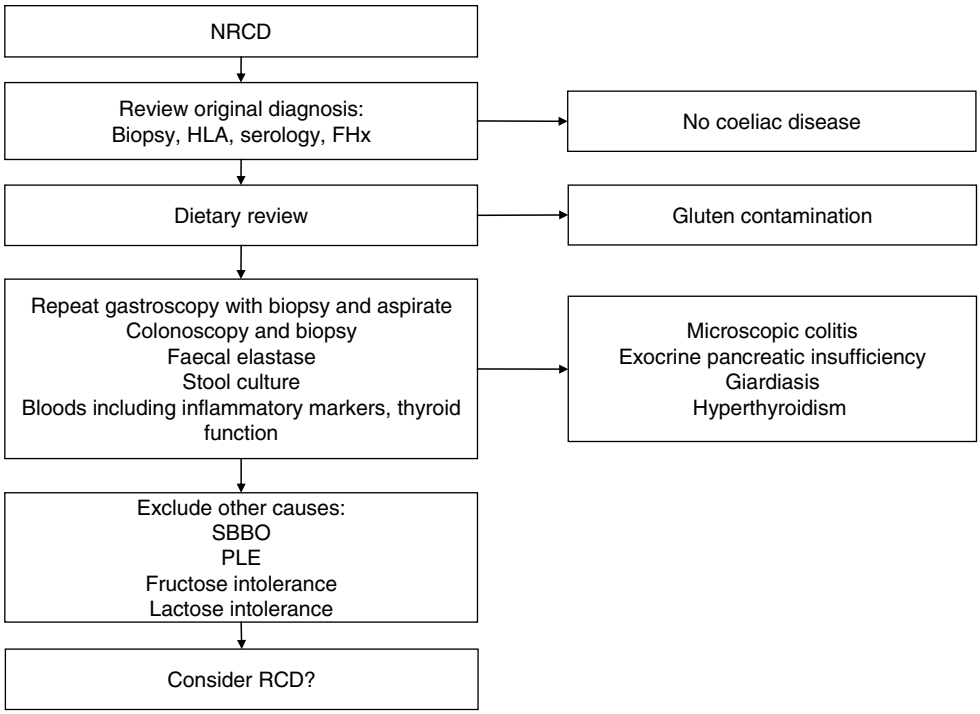

Fig. 1. Diagnostic algorithm for non-responsive coeliac disease (NRCD). HLA, human leucocyte antigen; FHx, family history; SBBO, small bowel bacterial overgrowth; PLE, protein-losing enteropathy; RCD, refractory coeliac disease.

Microscopic colitis is more common in patients with coeliac disease than in healthy controls; however, the recognition of this entity is only possible if random colonic biopsies are taken[20,21].

Pancreatic abnormalities have been noted historically in patients with coeliac disease[22–24]. More recently, it has been demonstrated that approximately one-third of those patients with coeliac disease who have chronic diarrhoea have low faecal pancreatic elastase levels. In addition, pancreatic supplementation confers some benefit, with a reduction in stool frequency[9].

Irritable bowel syndrome can mimic the symptoms of coeliac disease[25,26]. A report on 150 patients with coeliac disease, thirty of whom fulfilled the Rome criteria (diagnostic criteria used to make a positive diagnosis of functional bowel disorders, such as irritable bowel syndrome, based on clinical symptoms[27]), shows that patients with coeliac disease who have irritable bowel syndrome-type symptoms have a markedly lower quality of life than those without irritable bowel syndrome[25]. In addition, the quality of life of these individuals partly improves with improved adherence to a GFD. It was hypothesised that mucosal inflammation in coeliac disease may have a sensitising effect.

In a group of fifteen patients with coeliac disease who were all described as showing histological improvement on a GFD but remaining symptomatic, it was reported that ten were showing small intestinal bacterial overgrowth (assessed by a lactulose breath test). When these patients were treated with antibiotics (rifaximin) they were found after 1 month to be symptom free[28].

Adult autoimmune enteropathy is now recognised as a rare cause of villous atrophy. Patients have severe enteropathy unresponsive to any exclusion diet and are positive for enterocyte antibodies[29,30].

The clinical work up

Based on these data an initial work up, as shown in Fig. 1, is recommended. Routine blood tests, including haematinics (i.e. Fe, folic acid and vitamin B_{12}, which are necessary for Hb and erythrocyte production), should be undertaken. Repeat serological testing of tissue transglutaminase antibody and endomysial antibody, as well as human leucocyte antigen DQ typing, provide supportive evidence of coeliac disease. Blood tests including inflammatory markers and thyroid function tests are done to give supportive evidence of alternative diagnoses. Repeat gastroscopy with biopsy and small bowel aspirate should be performed. Colonoscopy with biopsies is done to exclude microscopic colitis. Faecal pancreatic elastase allows assessment of exocrine pancreatic function. Stools should be examined for giardia and other parasites. If these tests are normal, more unusual causes such as lactose or fructose intolerance or protein-losing enteropathy should be sought. In complicated cases with normal repeat duodenal biopsies faecal α-1-antitrypsin can be a useful marker to confirm that the patient has a protein-losing enteropathy.

Don't forget patients who are super-sensitive to gluten!

It is important to remember that even if these tests are normal and the patient still has persisting symptoms the individual could be super-sensitive to gluten. The typical gluten content of a GFD is 1 mg/d[31,32]; most patients with

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coeliac disease are able to tolerate ≤10 mg/d without adverse clinical or histological signs[33]. As a practical guide, a 30 g slice of wheat bread typically contains 4·8 g gluten and the average diet contains 13 g gluten/d[34,35]. In the UK naturally-occurring foods that contain <20 mg gluten/kg are considered 'gluten free' or 'naturally gluten-free'. Processed foods containing <100 mg gluten/kg are also considered gluten-free but the current exact labelling requirements are in the process of being clarified. Thus, patients could still have symptoms whilst adhering carefully to a GFD. Evidence of this outcome would be expected to be seen with the composite assessment made initially, but the use of a wheat-free diet and GFD may provide symptomatic benefit. However, this strategy is even more restrictive!

Refractory coeliac disease

Pathogenesis

The normal small intestinal IEL population comprises approximately 80–85% CD8+T-cell receptor (TCR) αβ cells and 15% CD8+TCRγδ cells[36]. IEL are derived from oligoclonal expansion of a relatively small number of αβ T-cell clones. IEL are thought to recognise bacterial proteins, preserve epithelial integrity and mediate antigenic tolerance. In uncomplicated coeliac disease IEL express CD3+ and CD8+ (T suppressor–cytotoxic phenotype) and there is an increase in γδ T-cells[36,37].

Coeliac disease may be considered to be refractory (RCD) when symptoms persist (primary) or recur (secondary) despite the adherence to a strict GFD and when other causes have been excluded[1]. RCD is subdivided into types I and II with a phenotypically normal or aberrant intraepithelial T-cell population respectively[37]. This type differentiation can be determined by using PCR analysis for the TCR gene rearrangement. RCD I is thought to yield a polyclonal product and in RCD II the gene rearrangement is clonal. Some authors have described a cut-off level in percentage terms as a means of differentiating RCD I from RCD II. Patients with RCD I have <10% aberrant (clonal) T-cells on duodenal biopsy[37].

This subdivision into RCD I and RCD II according to the percentage of aberrant T-cells has allowed investigators to infer differences in prognosis. RCD I is more likely to respond to immunosuppression, whereas RCD II seems largely resistant to treatment and transition to enteropathy-associated T-cell lymphoma (EATL) is common. In a group of ninety-three patients with RCD forty-three were reported to have RCD I, with none having coeliac-related mortality at 5 years. In the group with RCD II (*n* 50) the overall 5-year survival was reported to be 58%, falling to 8% in the twenty-six (52%) who developed EATL[38].

It is thought that T-cells bearing TCRγδ play a protective role in intestinal inflammation[39]. In RCD II there is an immunophenotypically-aberrant clonal intraepithelial T-cell population with monoclonal arrangement of the *TCRγ* gene[40,41]. The presence of these abnormal T-cells is correlated with lymphoma development[42]. Interestingly, in EATL the non-lymphomatous mucosa (adjacent mucosa) contains an identical monoclonal T-cell to the EATL, i.e. this condition could be cryptic lymphoma. The same observation has been made in ulcerated and non-ulcerated mucosa in ulcerative jejunitis. These observations could suggest that that RCD is a spectrum of disease ranging from the presence of monoclonal T-cells to ulcerative jejunitis and finally EATL. However, patients can present *de novo* at any point along this path without progressing through these stages.

Table 2. Initial work up for refractory coeliac disease (RCD)*[44]

1. T-helper:suppressor lymphocyte
2. IEL phenotyping; signs of cytotoxic monoclonality (PCR)
3. Mg, Zn and Cu
4. Small bowel radiology, capsule endoscopy, small bowel MRI enteroclysis, CT scan of abdomen, pelvis and thorax; looking for lymphoma
5. DEXA scan, bone densitometry study; looking for osteopaenia

IEL, intraepithelial lymphocytes; CT, computerised tomography; DEXA, dual-energy X-ray absorptiometry.
*Should follow the initial investigational pathway shown in Fig. 1 for patients in whom RCD is suspected.

A limited number of factors are predictive of RCD. In one series of patients weight loss was found to be predictive of RCD, with an OR of 31·1, and female patients were shown to have a decreased risk of RCD[2]. Patients who are homozygous for human leucocyte antigen DQ2 appear more likely to develop secondary EATL or *de novo* EATL[43]. Typically, RCD presents with severe malnutrition, malabsorption, hypoalbuminaemia and weight loss[41]. Ulcerative jejunitis can present similarly or as an emergency with perforation, obstructing stricture or bleeding. Lymphoma may present with local signs of abdominal pain and diarrhoea, or more systemically with weight loss, fever, sweats and skin rashes.

The clinical approach

A diagnostic approach to RCD is shown in Table 2[44]. The initial steps are to record the BMI and then exclude NRCD as outlined earlier. Coeliac serology, human leucocyte antigen typing, routine blood tests, haematinics, Ca, Mg, Zn and Cu should all be checked. Deficiencies in Zn and Cu have been identified as possibly contributing to RCD and there have been case reports of successful treatment with supplementation[42]. Duodenal biopsy should be assessed for T helper:suppressor cells, which is one way of initially differentiating patients with RCD from those who do not have RCD. It is worth specifically requesting the pathologist to assess the biopsy and comment on the ratio; a preponderance of T-helper cells suggests that RCD is more likely and a preponderance of T-suppressor–cytotoxic cells is consistent with normal coeliac disease and perhaps continued exposure to gluten. Specialist centres, including that of the authors, now offer assessment for aberrant clonal T-cell proliferation.

Following the initial work up delineated in Table 2 further exclusion or inclusion of lymphoma may require an opinion from an ear, nose and throat specialist[45,46], bone marrow aspiration, ultrasound scan of the neck, full-thickness small bowel biopsy and laparotomy with intraoperative enteroscopy. The initial small bowel investigations are generally available to most clinicians but it is worth considering several modalities.

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Newer techniques proving valuable in the assessment of RCD include positron emission tomography scanning, wireless capsule endoscopy and double-balloon enteroscopy. There are no large trials published to date, but in a small series of cases it has been shown that positron emission tomography has a high sensitivity for EATL and picks up some lesions missed on computerised tomography scanning[47]. However, false positive positron emission tomography results were also recorded in patients with RCD in the absence of EATL, which demonstrates the need to obtain histology. When wireless capsule endoscopy was performed in forty-seven patients with coeliac disease and a clinical suspicion of small intestinal malignancy, 87% were reported to have findings of coeliac disease with 60% having unexpected findings that included ulceration, cancer, polyps, stricture, submucosal mass and intussusception[48]. Furthermore, in fourteen patients with RCD who underwent wireless capsule endoscopy EATL was found in two patients with RCD II, one case of which had not been detected by computerised tomography or MRI[49]. Double-balloon enteroscopy can be used to obtain histology from lesions identified on MRI. In a group of twenty-one patients with RCD referred for double-balloon enteroscopy EATL was found in five patients, with another two having ulcerative jejunitis. EATL was excluded by double-balloon enteroscopy in four patients for whom there had been suggestive radiographic findings[50].

Based on these small studies it is now believed that in the presence of histopathological findings consistent with RCD II EATL should be aggressively sought. The justification for this approach is that historically this condition has been difficult to detect and the diagnosis has important prognostic implications for the patient.

Therapeutic options

The evidence for treatment of RCD is limited and amounts to little more than case series. Azathioprine and prednisolone have shown some benefit in RCD I. In nineteen patients with RCD treated with azathioprine and prednisolone eight of ten patients with RCD I were reported to have responded. Conversely, in those with RCD II six of eight patients developed EATL and seven patients died[51].

More recently, budesonide has also been used in this clinical scenario with reasonable effect[52]. There are case reports of the successful use of cyclosporine[53–55]. A single study assessing the use of IL-10 does not demonstrate benefit[56]. There is anecdotal use of total parenteral nutrition and albumin infusions but insufficient evidence to support their wider use.

Novel approaches to the treatment of RCD include anti-TNF[57,58], cladribine[59] and autologous stem-cell transplantation[60,61]. None has yet demonstrated clear benefit.

Conclusion

In conclusion, up to one-third of patients with coeliac disease will have persistent symptoms. The majority of cases will be related to adherence aspects of their GFD. It is important to differentiate between NRCD and RCD. This approach allows specific associated diseases to be diagnosed and treated. RCD I and II should also be clearly delineated, since differentiation allows the clinician an opportunity to provide the patient with important prognostic information as well as determine who may respond to immunosuppression (RCD I). Early nutritional supplementation is recommended and even enteral or parenteral nutrition if appropriate. The prognosis for RCD II remains poor but there are a number of novel therapies currently being evaluated.

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