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Burden of persistent symptoms in treated coeliac disease: cause, aftermath or merely association?

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Coeliac disease (CD) is a common, immune-mediated enteropathy that can present at any age, in genetically susceptible individuals, and is treated with a strict, lifelong, gluten-free diet (GFD). While a strict GFD is highly effective in treating the enteropathy, a relatively understudied proportion of sufferers report persistent symptoms, and the restrictive diet itself can be associated with a high psychological burden, particularly in adolescent populations.[1] There is therefore an increasing interest in the development of novel and alternative treatment approaches for CD.

In this edition of *BMJ Open Gastroenterology*, in a longitudinal cross-sectional study with a median follow-up of 18 years postdiagnosis, Vuolle *et al* have reported on the long-term prevalence and associations of persistent symptoms in a large cohort of patients with CD following their transition from paediatric services into adulthood.[2] Interestingly, the prevalence of persistent symptoms (either gastrointestinal or extraintestinal) among 180 patients' adherent to a strict GFD was 18%. Overall, the majority (73%) of those that had refractory symptoms despite a strict GFD had gastrointestinal symptoms including abdominal pain, an altered bowel habit (constipation or diarrhoea) and dyspeptic symptoms, despite only 19% having a formal diagnosis of a gastrointestinal comorbidity (inflammatory bowel disease, irritable bowel sndrome, peptic ulcer disease or gastritis).[2] The prevalence of persistent diarrhoea, abdominal pain and dyspeptic symptoms was significantly higher in symptomatic individuals on a strict GFD even after adjusting for those with an existing gastrointestinal comorbidity diagnosis, strongly suggesting that many patients may have had an undiagnosed, overlapping, gastrointestinal condition. Importantly, those with persistent symptoms in this study had a much poorer general health and vitality score.[2]

One of the main limitations of the study by Vuolle *et al* is the lack of serological or histological follow-up as a measure of CD activity and as a surrogate marker of compliance with GFD. Notably, those with persistent symptoms in this study experienced more frequent everyday life restrictions with GFD than those without symptoms, and therefore, an objective measure of gluten exposure/CD activity would have been valuable.

Nonetheless, this study is an important reminder of the need for appropriate long-term follow-up and monitoring of CD, and the potential for refractory symptoms, refractory CD, and overlapping gastrointestinal disorders. This is particularly important as a recent multicentre secondary care study in the UK identified a worrying trend towards medical inertia, with over one-hird of gastroenterologists of the opinion that a doctor is not required for the management of CD.[3] The long-term follow-up strategy for CD is therefore an important, yet contentious issue with resource implications. Recent data suggests that patients with CD discharged back to primary care may be completely lost to follow-up without many aspects of their care needs being addressed,[4] which may have detrimental long-term outcomes.[5] While dietetics, or nurse-led follow-up, in secondary care may be appropriate for the majority of stable, asymptomatic patients with CD, established on a GFD, these recent data all suggest the importance of a safety netting mechanism for referral back to a gastroenterologist for symptomatic individuals.

After exclusion of active CD in the gastroenterology clinic, in the absence of alarm features, among the main differential diagnoses in those with persistent gastrointestinal symptoms such as those reported in the Vuolle *et al* study, would be a disorder of gut–brain axis (DGBI) such as irritable bowel syndrome (IBS) or functional dyspepsia. In

the study by Vuolle *et al*, the prevalence of extraintestinal symptoms including arthralgia and fatigue which affected over a third of those that were symptomatic, while unlikely to be a direct consequence of CD, are well-known somatic extraintestinal features of IBS.[6] Indeed, overlapping IBS symptoms are common, affecting over one-third of patients with CD,[7] and CD exclusion as an 'IBS mimic', is therefore strongly recommended when making an IBS diagnosis.[8]

Making an appropriate, 'positive' clinical diagnosis of a DGBI such as IBS or FD, in those that meet the symptom-based criteria for these conditions with quiescent CD, may help alleviate the burden of suffering, validating the patient's symptoms, and most importantly allowing access to evidence-based targeted medical, dietary and gut-specific behavioural interventions.[8] This positive approach may go some way towards improving general health and vitality which were significantly poorer in those with symptoms in the study by Vuolle *et al*.[2]

The pathophysiology of overlapping IBS in biopsy-proven quiescent CD has not been extensively studied and merits further study. Interestingly, the severity of gastrointestinal symptoms and extent of histological abnormalities at baseline were not predictive of persistent symptomatology at follow-up in the Vuolle *et al* study.[2] Despite this, it is plausible that changes in gastrointestinal neuromuscular function and visceral sensitivity as an aftermath of the previous enteric inflammation, akin to the well-studied pathophysiology of postinfective IBS, and IBS overlap in quiescent inflammatory bowel disease, which have been well described in the literature,[9] may be an important contributory factor, and this should be investigated in future studies.

The main take-home message from the Vuolle *et al* study is that clinicians should be vigilant of the high prevalence and burden of persistent symptoms in patients with treated CD. After proactively excluding active CD with updated biochemical and/or histological investigations and dietetics input, patients should be assessed for overlapping gastrointestinal co-morbidities, and commenced on appropriate evidence-based symptomatic treatments which may significantly improve quality-of-life and well-being.

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